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PROF. DR. HASAN AKGÜL

PROF. DR. ENGİN ŞAHNA

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Chapter 1

THE PELVIC ANATOMY IN CESAREAN SECTION: A SURGICAL ROADMAP

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Introduction

The cesarean section (CS) is among the most commonly executed major surgical operations globally. Although frequently contextualized within obstetrical urgency or fetal indication, its successful implementation is essentially an application of surgical anatomy (Myers et al., 2001). Surgeons operate on the pelvis, a complex channel of bones and soft tissue designed for childbirth. A deep comprehension of the layered anatomy, the dynamic physiological alterations throughout pregnancy, and the prevalent anatomical variances is not only theoretical; it constitutes the foundation of secure and effective surgical practice (De Araujo et al., 2018). This knowledge directly affects how surgeons make decisions, from the first cut in the skin to the last closure of the uterus. It affects important outcomes, including the length of the surgery, the amount of blood lost, the prevention of damage to the organs, and the mother's long-term recovery (Patel et al., 2021). The pregnant pelvis is a dynamic structure. Hormonal impacts, particularly relaxin and progesterone, cause substantial alterations, such as ligamentous laxity, heightened vascularity, and soft tissue edema. These modifications, although promoting vaginal birth, may obscure normal anatomical planes and heighten tissue susceptibility during surgical procedures (Bhatia & Chhabra, 2018). Consequently, the obstetric surgeon must operate with a cognitive framework that incorporates both the conventional anatomical relationships and their alterations during pregnancy.

This chapter offers a comprehensive, step-by-step examination of the pelvic anatomy observed after a cesarean section. The procedure will progress from the epidermis and subcutaneous tissues, through the fascial and muscular layers of the abdominal wall, into the peritoneal cavity, ultimately reaching the central focus: the pregnant uterus and its surrounding structures. Particular attention will be directed to anatomical landmarks that assist the surgeon, potential hazards where harm is most probable, and the functional justification for prevalent surgical approaches. This chapter seeks to combine anatomical knowledge with surgical application, providing the surgeon with the insights required to navigate this intricate field with assurance and accuracy.

1. The Abdominal Wall: The Gateway to the Uterus

The exploration of the pelvis commences with the abdominal wall. The selection of incisions and the method of navigating these layers establish the foundation for the entire surgery. The two principal incisions for cesarean section are the Pfannenstiel (suprapubic transverse) and the midline vertical incision. Each presents unique anatomical benefits and considerations (Wylie et al., 2010).

1.1 Superficial Layers: Skin and Subcutaneous Tissue

The skin of the lower abdomen receives innervation from cutaneous nerves originating from the anterior rami of T10 (umbilical region) to L1 (suprapubic region). A Pfannenstiel incision involves a curvilinear transverse cut made around 2-3 cm superior to the pubic symphysis, situated within the pubic hairline. This site utilizes natural skin tension lines (Langer's lines), facilitating enhanced cosmetic healing (Joshi et al., 2016). The incision must be sufficiently long, generally 15–17 cm, to provide proper operating exposure without excessive traction, which is a frequent source of extension into the lateral muscles or blood vessels (Sentilhes et al., 2013). Subcutaneous tissue, mostly consisting of adipose tissue (Camper's fascia) and a deeper membranous layer (Scarpa's fascia), is located beneath the skin. The thickness of this layer varies considerably among people, is affected by body composition, and is frequently markedly elevated during pregnancy. Precise hemostasis in this layer is essential, as hematoma development frequently leads to postoperative wound problems (Bonanni et al., 2025). The superficial epigastric arteries, which are branches of the femoral artery and vein, traverse this layer and may be located laterally; they must be identified and ligated if severed.

1.2 The Anterior Rectus Sheath and the Linea Alba

Below the subcutaneous layer lies the strong, fibrous aponeurosis of the anterior rectus sheath. At the midline, the sheaths from both sides converge to create the linea alba, an avascular plane that serves as the target for a Pfannenstiel incision (Kriener, 2023). The primary anatomical procedure involves locating and incising the anterior rectus sheath. The surgeon creates a small transverse incision in the midline, then extends it laterally with precision, either bluntly or with scissors, while curving slightly upward to align with the initial skin incision. It is essential to stay near the sheath to prevent excessive undermining of the subcutaneous tissue, which may compromise the vitality of the skin edges (Hofmeyr, 2008). The structure of the rectus sheath alters inferiorly. The traditional account states that the aponeurosis of the internal oblique muscle bifurcates to encase the rectus abdominis muscle, with the anterior layer merging with the aponeurosis of the external oblique to create the anterior sheath, and the posterior layer uniting with the aponeurosis of the transversus abdominis to establish the posterior sheath. This configuration is seen solely above the arcuate line (linea semicircularis of Douglas), generally situated at the midpoint between the umbilicus and the pubic symphysis. Inferior to the arcuate line, the aponeuroses of all three muscles traverse anteriorly to the rectus muscle. Thus, underneath this line, there exists no authentic posterior rectus sheath; only the transversalis fascia and peritoneum separate the muscle from the intra-abdominal contents (Loukas, 2008). This anatomical detail is crucial; during entrance, particularly if the incision is prolonged or the patient

possesses a low arcuate line, the peritoneum may be adherent or in close proximity, heightening the danger of unintentional enterotomy.

1.3. The Rectus Abdominis and Pyramidalis Muscles

Upon incising the anterior rectus sheath, the bilateral rectus abdominis muscles are observed. The strap-like muscles are divided at the midline by the linea alba. In a Pfannenstiel technique, the rectus muscles are not incised but are instead split along the midline and retracted laterally. This distinct separation is feasible due to the muscles being linked to the anterior and posterior sheaths by tendinous crossings, allowing them to be displaced. The diminutive pyramidalis muscle, frequently located just superior to the pubic symphysis, is situated anterior to the rectus muscles and serves as a reference for the midline. The lateral retraction of the muscles reveals the underlying transversalis fascia and peritoneum. At times, the linea alba may be misaligned, or there may be considerable diastasis recti (separation of the rectus muscles) resulting from pregnancy, which can disrupt midline alignment and necessitate meticulous dissection to prevent lateral deviation (Skręt-Magierło et al., 2015).

1.4 The Peritoneum: Entering the Abdominal Cavity

The ultimate layer of the abdominal wall is the parietal peritoneum. Prior to incision, the surgeon must delicately palpate to confirm that no underlying bowel or omentum is attached. The peritoneum is elevated with forceps, and a tiny incision is made to permit air passage and establish a cavity. The incision is then elongated both superiorly and inferiorly, generally employing blunt dissection with fingers or scissors. Precautions are taken inferiorly to prevent injury to the bladder dome. The visceral peritoneum enveloping the bladder is typically more opaque and vascular than the parietal peritoneum of the front abdominal wall, serving as a visual indicator. The surgeon has accessed the abdominal cavity and encounters the pregnant uterus, typically with the larger omentum and loops of small intestine positioned superiorly. The initial anatomical evaluation involves identifying the lower uterine segment and its association with the bladder (Fangmann et al., 2022).

2. The Pelvic Cavity and the Gravid Uterus

The pregnant uterus dominates the pelvic and abdominal landscape. Its anatomical relationships shift dramatically as gestation progresses, fundamentally altering the surgical approach.

2.1 The Peritoneal Coverings: The Vesicouterine Pouch

The vesicouterine pouch, also known as the anterior cul-de-sac, is a crucial anatomical area in the female reproductive system. This is a fold of peritoneum that extends from the anterior surface of the uterus to the

posterior superior surface of the bladder. In non-pregnant women, this region constitutes a profound recess. As the uterus expands, the lower uterine segment extends and thins, while the peritoneal reflection is elevated. During the third trimester, this reflection is generally positioned several centimeters above the pubic symphysis (Takeda et al., 2020). The formation of the bladder flap involves a purposeful surgical dissection of the peritoneal reflection. The loose areolar connective tissue in this region is relatively avascular; however, it houses a network of tiny veins. The objective of the dissection is to displace the urinary bladder inferiorly, distancing it from the intended uterine incision, thus safeguarding it from damage and creating a clear zone for uterine closure. The dissection must be either acute or blunt, but it must be executed in the appropriate tissue plane. An overly superficial dissection may entrap the bladder dome, whereas an excessively deep dissection may directly incise the uterine wall, resulting in considerable bleeding from the cervical and vaginal branches of the uterine arteries that anastomose in this area (Tuuli et al., 2018).

2.2 The Lower Uterine Segment: The Surgical Focal Point

The lower uterine segment is the section of the uterus located between the anatomical internal os and the histological internal os. During pregnancy, it experiences significant transformations, a process referred to as the development of the lower segment. As the upper uterus undergoes myometrial hypertrophy, the lower segment becomes thinner and more passive, facilitating labor and cervical dilation. This thinning serves as the physiological justification for its application in CS; it is simpler to incise, exhibits reduced bleeding, and demonstrates superior healing compared to the thicker, more muscular upper portion. The lower part is anatomically less vascular than the uterine corpus. The arcuate arteries, which traverse circumferentially in the outer part of the myometrium, are diminutive in this area. The primary uterine arteries traverse laterally at the internal os, rendering them vulnerable if the uterine incision extends excessively laterally. The shift from the more robust top segment to the slender lower segment is frequently discernible as a ridge, serving as a valuable reference for the surgeon (Rao et al., 2022).

2.3 The Uterine Incision: Types and Anatomical Correlates

- **Low Transverse Incision (Kerr Incision):** This incision, located in the lower uterine region, is the most prevalent type. The advantages include its positioning in a relatively avascular region and its postoperative coverage by the bladder, which may assist in containing any potential dehiscence. The primary anatomical consideration is its positioning. It needs to be central and curved. If set too low, it may encroach into the cervix, which predominantly consists of fibrous tissue and exhibits limited healing

capacity. If positioned excessively high, it encroaches upon the contractile top section, which is more vascular and susceptible to inadequate repair and rupture in subsequent pregnancies. Lateral extension represents the most prevalent problem. The incision must not surpass the visible limits of the lower section to prevent severing the uterine arteries and veins, located roughly 2 cm lateral to the uterus at this juncture (Dodd et al., 2014).

- **Classical Incision:** This procedure is a vertical incision in the superior uterine body. It is utilized in particular circumstances where the lower segment is either inaccessible or underdeveloped (e.g., extreme preterm, substantial lower segment fibroids, some instances of transverse lying). This incision anatomically crosses the dense, highly vascular myometrium of the top portion, resulting in increased blood loss. Moreover, due to its location in the active contractile segment of the uterus, it presents a markedly elevated risk of rupture in future pregnancies when compared to the low transverse incision (Thompson et al., 2022).

- Low Vertical Incision: This incision spans from the lower segment to the higher segment. This is a compromise employed when greater space is required than what a transverse incision provides; however, a complete classical incision is not preferred. The anatomical issue lies in managing the superior apex of the incision, which may expand unpredictably into the top segment if not meticulously maintained (Kan, 2020).

3. Critical Adjacent Structures: The Anatomical Pitfalls

A safe CS requires not only knowledge of the target organ (the uterus) but also a vigilant awareness of the surrounding structures that are at risk of injury.

3.1. The Urinary Bladder

The bladder is the most commonly injured structure during cesarean section. Its anatomical position is directly anterior to the lower uterine region and the cervix. In a non-pregnant condition, it is classified as a pelvic organ; however, when the uterus expands, it transitions into an abdominal organ. During labor, the descent of the fetal head into the pelvis displaces the bladder anteriorly and superiorly, often resulting in significant edema, particularly following prolonged labor or restricted descent. The vascular supply of the bladder is pertinent to the surgeon. It receives branches from the internal iliac artery, chiefly the superior and inferior vesical arteries. These veins approach the bladder from its lateral sides. Lateral dissection during the formation of the bladder flap or while managing the lateral extension of a uterine incision may compromise these arteries. Identifying bladder injury is crucial; the presence of clear urine at the site or a discernible defect necessitates repair, usually performed in two layers using absorbable sutures (Manidip et al., 2020).

3.2 The Ureters

The ureters are more susceptible in some situations, including a cesarean section conducted for a wide ligament hematoma, a severely damaged fetal head, or during a cesarean hysterectomy. Their trajectory is misleadingly proximal to the uterus. They descend retroperitoneally along the medial side of the psoas major muscles, traverse the bifurcation of the common iliac arteries, and subsequently proceed along the pelvic sidewall. At the ischial spine, they curve anteromedially to traverse beneath the uterine arteries ("water under the bridge") roughly 1.5–2 cm lateral to the cervix, prior to entering the bladder trigone. The left ureter is typically positioned nearer to the cervix than the right ureter. The ureters remain unobserved during surgery unless intentionally dissected. The principle for their protection is to remain medial and next to the uterus when clamping or suturing lateral structures. In cases of uncertainty regarding their placement, especially in deformed anatomy, deliberate identification through broad ligament incision or palpation for the distinctive peristaltic "snap" may be required (Selçuk et al., 2018).

3.3 The Uterine Arteries and Venous Plexus

The uterine artery, a branch of the internal iliac artery, serves as the primary blood supply to the uterus. It traverses medially along the base of the wide ligament, arriving at the uterus at the level of the internal cervical os. It thereafter ascends convolutely along the lateral border of the uterus, anastomosing with the ovarian artery. The venous outflow corresponds to the arterial supply, creating a dense, thin-walled plexus (the uterovaginal plexus) that is particularly susceptible to rupture. The lateral expansion of uterine incision can swiftly cause a rupture of these veins, leading to a life-threatening hemorrhage that may retract into the wide ligament and result in a hematoma (Drake et al., 2019). Control typically necessitates meticulous dissection, clamping, and ligation of the ascending branch of the uterine artery at the site of the laceration.

3.4 The Bowel

The small intestine and sigmoid colon are often retracted into the upper abdomen following peritoneal access. Nevertheless, individuals may be at danger in instances of adhesions resulting from past surgeries, such as a prior cesarean section or other abdominal interventions. Adhesions between the omentum or colon and the anterior abdominal wall or the uterus may result in unintentional enterotomy during entrance or uterine delivery. Adhesiolysis must be executed with precision, employing precise dissection under direct visualization to prevent serosal lacerations or complete bowel perforation (Standring, 2020).

4. Anatomical Considerations in Special Situations

4.1 The Obese Patient

Obesity poses significant anatomical problems. The panniculus (abdominal fat apron) can be massive, obscuring landmarks and making the Pfannenstiel incision technically difficult. The subcutaneous layer is frequently very thick, heightening the risk of seroma and wound infection. Various variations may be utilized. The skin incision may be positioned higher (supraumbilical) or may utilize a Joel-Cohen or modified Misgav-Ladach incision, characterized as a straight, transverse incision situated superior to the Pfannenstiel incision. Placement of a subcutaneous drain or standard closure of the subcutaneous tissue layer (if thickness surpasses 2 cm) is advised to mitigate wound problems (Zoorob et al., 2020). Intraoperatively, the enlarged uterus and omentum may complicate exposure, frequently necessitating specialist retractors and assistance.

4.2 The Patient with a Previous Cesarean Section

A previous cesarean section substantially modifies the anatomy. Adhesions frequently occur, especially between the front uterine wall, the bladder, and the parietal peritoneum. The "bladder flap" from the prior surgery may exhibit extensive adhesions, rendering its dissection perilous. The initial abdominal penetration poses an elevated risk of bowel or bladder damage in the presence of adhesions. The uterine scar may be thin or dehiscent (uterine window), and the lower section may be inadequately delineated. The surgeon must foresee these alterations, contemplate a superior first incision, and be ready for a potentially more challenging and protracted dissection (Awonuga et al., 2011).

4.3 The Deeply Impacted Fetal Head

Delivering a deeply engaged fetal head through a standard low transverse incision can be exceedingly challenging and poses a risk of severe extension of the incision and harm to maternal arteries. Various anatomical manipulations can provide assistance. The surgeon may utilize reverse breech extraction, wherein the fetus is delivered feet first. Alternatively, an assistant might exert upward pressure on the head through the vagina (push technique). An alternative is to employ specialized equipment, such as a Paterson's knife or a fetal pillow, to disimpact the head from beneath. From an anatomical standpoint, these procedures seek to alter the relationship between the fetal head and the mother's bony pelvis, employing the available space in the sacral hollow to rotate and elevate the head (Gq Peak et al., 2023).

5. Anatomical Basis for Hemostasis and Closure

Comprehending vascular anatomy is essential for bleeding management. Hemorrhage from the edges of the uterine incision predominantly originates from the radial branches of the arcuate arteries. These are optimally managed with timely clamping and ligation. Diffuse oozing from the placental bed (atony) is addressed with pharmaceutical interventions and surgical methods like compression sutures (e.g., B-Lynch), which exert physical pressure on the uterine vascular arcades. In instances of placenta accreta spectrum, when the placenta infiltrates the myometrium and its vascular supply, the architecture is severely modified, necessitating sophisticated surgical planning, frequently involving vascular occlusion methods or hysterectomy (Li et al., 2021). The closure of the uterus must realign the myometrial layers to facilitate maximum healing. A single-layer closure may suffice; however, a double-layer closure is sometimes employed to guarantee effective hemostasis and proper layer-to-layer apposition, potentially diminishing the chance of scar dehiscence in subsequent pregnancies. The visceral peritoneum (uterovesical peritoneum) is frequently left open, since research indicates this minimizes adhesion formation without elevating other dangers (Di Spiezio Sardo et al., 2017). The closure of the abdominal wall must adhere to its layered anatomy. The rectus muscles are permitted to return to their original position. The anterior rectus sheath is sutured closed with a continuous, slowly absorbable suture to ensure enduring strength. Inadequate closure of this layer is a key contributor to incisional hernia. The subcutaneous tissue is sutured if it exceeds 2 cm in thickness to reduce dead space, and the skin is closed using sutures or staples (Gurusamy et al., 2017).

Conclusion

The cesarean section is a technique fundamentally based on anatomical research. Each phase, from positioning the skin incision to concluding the suture, relies on understanding the layered anatomy of the abdomen and pelvis, the dynamic physiology of gestation, and the interrelations between the uterus and adjacent organs. By using this comprehensive mental map, the surgeon becomes more adept at avoiding problems, addressing unforeseen discoveries, and improving outcomes for both mother and child. As technology advances, this fundamental knowledge remains the foundation upon which surgical excellence is established. The ongoing examination of pelvic anatomy, with its variations and pathological alterations, is essential for obstetrical education and practice.

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Chapter 2

MICRORNAS IN PREGNANCY MONITORING

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INTRODUCTION

Cells release exosomes to transfer essential molecules, including proteins and miRNAs (Jin et al., 2024). Small (18-25 nucleotides) non-coding RNA molecules encoded by endogenous genes, called microRNAs (miRNAs) are involved in the regulation of post-transcriptional gene expression in plants and animals (Bartel, 2004). miRNAs are initially transcribed from genes as long precursor RNAs by RNA polymerase II. These pri-miRNAs are processed by the Drosha-DGCR8 complex in the nucleus to give rise to pre-miRNAs. Once in the cytoplasm, these pre-miRNAs are cleaved by the enzyme Dicer into mature, single-stranded miRNAs. These in turn bind to target mRNAs, which are then degraded or prevent further protein synthesis (Bidarimath et al.,2014). miRNAs post-transcriptionally modulate gene expression. Generally, miRNAs have been discovered to dock to the 3'-UTR of target mRNAs. This binding depends on the RNA-induced silencing complex (RISC) and leads to the degradation of the mRNA. Binding may cause full mRNA degradation or inhibit protein translation. The interaction is a function of the complementarity level of the miRNA and its target mRNA; with perfect complementarity resulting in mRNA cleavage and nonapeutide synthesis and partial complementarity generally leading to translational suppression. Consequently, one miRNA can regulate many mRNAs (Bidarimath et al.,2014; Place et al.,2008; Bartel, 2009).

It has been showed to that miRNAs are involved in numerous biological processes including cell proliferation, differentiation, apoptosis and development (Gilad, 2008). The miRNAs are highly stable in different body fluids (blood, urine, saliva) and can be readily extracted and measured. Indeed, it has previously been demonstrated that miRNA levels can serve as sensitive biomarker for physiologic and pathologic status (Gilad, 2008; Thind and Wilson, 2016).

The association between miRNAs and tumors has been extensively studied in the literatures of recent past years. MicroRNAs (miRNAs) are key gene-regulators in various biological processes. These small molecules are important control elements in normal and abnormal cell growth and differentiation. It has been described that such molecules can regulate genetic and epigenetic profiles in cancer cells and can impact the formation, growth, dissemination and response to treatment of tumors (Bartel, 2009; Bracken et al.,2016). More than one thousand miRNAs have been discovered in humans in recent years, and their function has been demonstrated in the regulation of cell proliferation and apoptosis in the pathophysiology of cancer (Zhang et al., 2007; Friedlander et al., 2014).

MiRNAs have a great potential for diagnosis and follow-up in gynaecology and obstetric. Especially in pregnancy-related diseases (e.g., preeclampsia, gestational diabetes, preterm delivery), miRNA signatures mirror defective

placental function and metabolic alterations. Likewise, abnormal expression of miRNA in gynecological cancers, including ovarian and cervical cancer, have illustrated the tumorigenesis and progression. MiRNAs are also involved in the pathophysiology of inflammatory diseases such as endometriosis. Thus, circulating miRNA levels are emerging as important markers for early disease detection, therapy response monitoring, and personalized medicine strategies (Gilad et al., 2008; Enquobahrie et al., 2011; Masete et al., 2022). Their miRNAs could be potential-biomarkers to diagnose-perinatal diseases. Recent investigations have demonstrated that this non-invasive method has good potential for early diagnosis and monitoring of diseases, such as fetal growth restriction and Down syndrome (Jin et al., 2024).

The present review intends to cover the current knowledge about the application of microRNAs in pregnancy surveillance.

1. The Role of miRNAs in Pregnancy Physiology

The mother-foetus boundary plays an important role in the success of pregnancy, and many miRNAs are tissue specific for these things. Their expression status in normal comparison to problem pregnancies suggests their possible involvement in pregnancy related processes. Nevertheless, even with intense investigations in pregnancy, the mechanisms of miRNA, are still not thoroughly elucidated (Morales&Markert, 2011; Bidarimath et al.,2014).

Successful pregnancy rely on mother-foetus interface and acceptance of foetus by the mother immune system. In the tissues, immune cells, e.g. NK, T and macrophages, which accumulate in the uterus in early pregnancy support placentation, and fetal tolerance. However, their retention and functions in the uterus are not completely understood (Bidarimath et al., 2014).

The placenta is a transient organ with rapid development and more than 600 miRNAs (Xu et al.,2021). miRNAs such as let-7a and miR-518b regulate trophoblast cell proliferation, while others, such as miR-34a and miR-210, control the invasive differentiation of trophoblasts. However, most of these studies are performed in vitro and in vivo studies remain scant(Liu et al., 2018;Xu et al.,202). C19MC, the largest known miRNA cluster in the human genome, is highly expressed in placenta, promoting pregnancy by sustaining trophoblast cell proliferation (Bortolin-Cavaille et al., 2009). Gene expressions are regulated by microRNA, and the healthy pregnancy is involved in the regulation of placental development at various stages during the pregnancy (Jin et al., 2022).

Placental miRNAs modulate the behaviour of trophoblast cells and are also secreted into the maternal circulation in exosomes leading to hormone-like cross-talk between the mother and foetus. This property renders miRNAs

a possible diagnostic tool (Xu et al., 2021). The schedule and site of miRNAs expression shift during the course of pregnancy and their roles in placenta are temporary and cell specific. We found i.e. that miR-18a was expressed at high levels during early pregnancy and was expressed in invasive EVTs (extra villous trophoblast), being likely that it is involved in the regulation of the trophoblast invasion by targeting the TGF-β / Smad2 signaling pathway. This indicates that miRNAs play a dual role in placenta (Xu et al.,2020).

Regulation of miRNA expression in human trophoblast cells is involved in the physiological and pathological processes of pregnancy. Among these causes, hypoxia (lack of oxygen) is better known; in hypoxic conditions, miRNAs are upregulated, such as miR-210. Furthermore, environmental disruptors like phthalates, bisphenol A and phenol can also modulate the expression of trophoblast miRNAs; for example, miR-155-5p is up-regulated by phthalates and miR-146a is increased by bisphenol A. These include upregulated expression of placenta- specific miRNA clusters, such as C19MC, which are controlled by epigenetic regulation, especially methylation. Lastly, genetic factors, such as single nucleotide polymorphisms), can influence the expression of miRNAs, including miR-126 and miR-143, and consequently alter the trophoblast function (Jin et al., 2022).

Hypoxia-regulated miR-210 is expressed in various human and murine trophoblast cell subpopulations in early pregnancy. By acting on multiple genes, it helps to regulate trophoblast cell proliferation, invasion, apoptosis, syncytialisation, and angiogenesis (Anton et al., 2013; Wang et al., 2020).

2. The role of miRNAs in pregnancy complications

Exosomes, which are released from the placenta into the maternal circulation and are detectable from week 6 of pregnancy, might be implicated in the pathogenesis of preeclampsia. In preeclampsia patients, plasma concentration of exosomes is increased as compared to healthy pregnant women, and they are of bigger average diameter. qRT-PCR analysis further revealed higher content of the microRNAs miR-153-3p and miR-325-3p in these exosomes. These results indicate that exosomes could be potential markers for diagnosing preeclampsia, but the biological functions of the miRNAs contained in them require further investigation (Li et al.,2020). miRNA, specific to placenta, are the important molecules involved in placental development and functions and any change in expression of these miRNAs is associated with complications of pregnancy. These modified miRNAs have been described to be putative biomarkers for these disorders. The placenta specific miRNAs can also be found in the maternal blood and their levels are altered in women with pregnancy complications However, these findings must be confirmed in prospective, large-scale trials before they can be used in the clinic (Lycoudi et al., 2015).

Dysregulation of miRNAs leads to the progression of pregnancy complications such as preeclampsia, foetal growth restriction and gestational diabetes. Thus, clarifying the roles of placental miRNAs could provide insights to potentially achieve new drugs in the future to prevent and treat those diseases (Jin et al.,2022).

Affecting cell proliferation and differentiation, miRNAs are related to the occurrence of pregnancy complications including, but certainly not limited to, preeclampsia and intrauterine growth restriction. Thus, a large number of studies have shown that miRNAs could be reliable biomarkers for the prediction of placenta-related disorders (Wu m/a/.1.,2012; Xu et al.,2021; Spataro et al., 2024).

2.1.1. The role of miRNAs in preeclampsia

Preeclampsia is a hypertensive pregnancy disorder, which leads to generalized endothelial dysfunction in the maternal circulation (Murphy et al., 2015). Preeclampsia occurs in 2-7% of all pregnancies and is one of the most common complications associated with illness and death in the mother and the foetus. It is a condition marked by a sudden increase in blood pressure (hypertension) and protein in the urine in pregnant women who previously did not have high blood pressure after 20 weeks of pregnancy. There may be exacerbations with even further elevation in blood pressure, which can be associated with pulmonary oedema, seizures, or oliguria (Sibai, 2003). MiR-210 has also been noted to deviated from the norm in the blood of those at risk of preeclampsia 8–12 weeks before the onset of clinical symptoms (Lycoudi et al. 2015).

The study of Hromadnikova et al indicated that the expression of C19MC miRNAs, including miR-516-5p, miR-517, miR-520a, miR-525 and miR-526a, was significantly upregulated in the serum of preeclampsia subjects. The findings of this investigation showed that the elevation of these miRNAs is a specific marker for confirmed PE and, also, the miRNAs levels correlated with CPR measurements. 133 4) However, similar changes of those miRNAs were not found in the gestational hypertension and fetal growth restriction groups (Hromadnikova et al., 2013).

Eighty-seven unique circulating miRNAs in first trimester have been reported to be associated with placental disorders (preeclampsia, IUGR, preterm birth) [43]. There were seven specific miRNAs (miR-125b, miR-518b, miR-628-3p, miR-365a-3p, miR-520h, miR-374a-5p, miR-191-5p) that were observed to be obviously related to these complications in more than one literature. These results imply that these miRNAs might be valuable for early detection and monitoring (Subramanian et al.,2023). Wu et al., 2012) miR-574-5p, miR-26a miR-151-3p, miR-130a and miRs 181a, 130b, 30d, 145, 103, 425, 221 and 342-3p as well as miR-24 were up-regulated while miR-144 and

miR-16 were down-regulated in the serum of women with severe preeclampsia when compared to that of healthy control: miR-pro-files. Seven of these fifteen miRNAs including miR-24, miR-26a, miR-103, miR-130b, miR-181a, miR-342-3p, and miR-574-5p were validated to be upregulated in PE women through quantitative RT-PCR (Wu et al.,2012).

The objective of the present study was to investigate the plasma miRNAs expression profiles of delivery and 1 year postpartum in patients with severe preeclampsia. Among these, miR-98-5p, miR-222-3p, miR-210-3p, miR-155-5p, miR-296-3p, miR-181a-5p, and miR-29b-3p, were also found to be significantly increased in the blood plasma of women with severe preeclampsia. There were no differences in these miRNAs in mild preeclampsia patients. The majority of these miRNA changes in women with preeclampsia reverted to normotensive levels one year post-partum, whereas the decline in miR-221-3p levels remained. This implies that there is potentially chronic inflammation during postpartum in patients with history of preeclampsia. These results support circulatory miRNAs as potential candidates biomarkers for monitoring of the impact of preeclampsia on maternal systems as they have been linked to longterm risk (cardiovascular diseases) post preeclampsia (Murphy et al.,2015). Lip et al. (Lip et al.,2020) also compared miRNA levels in blood plasma from women with early-onset PE to healthy pregnant and non-pregnant women. 24 distinct miRNAs were found whose plasma levels were altered in women with preeclampsia. In further tests on three targeted miRNAs with the highest increasing levels and lowest FDR (miR-574-5p, miR-1972, and miR-4793-3p), we found these miRNAs suppressed the proliferation, migration and tube formation of endothelial cells. It is, therefore, indicated that miR-574-5p and miR-1972 may represent as vasoactive anti-angiogenic factors that contribute to the development of preeclampsia by inducing endothelial dysfunction (Lip et al., 2020). In 2025, a study was conducted to explore the contribution of miR-155-5q to preeclampsia development. This finding indicates miRNA hinders the normal placental trophoblast activities by regulating its target gene PIK3R1 and is involved in the pathogenesis of the disease (Zhou& Xu,2025). The work of Zhou et al., reveals the role of miR-513c-5p in the pathogenesis of preeclampsia, demonstrating that this miRNA can suppress LRP6, and in turn impair biological functions of trophoblast cells including invasion, migration and proliferation, thus contributing to the disease development (Zhou et al.,2021). Another research demonstrated that the overexpression of miR-193b-5p in preeclampsia and intrauterine growth restriction downregulates the mobility of trophoblast cells by targeting APLN and FGF13. These data indicate that miR-193b-5p may contribute to the trophoblast dysfunction in these pregnancy complications (Awamleh& Han,2020).

miRNA-210 is hypoxia-responsive miRNA and is associated with the pathogenesis of preeclampsia. This molecule is involved in the disease by

handicapping trophoblast cells, which allow the placenta to anchor in the uterus. And thus miRNA-210 is suggested as a potential candidate for use in pregnancy monitoring(Jaszczuk et al., 2022).

Preeclampsia is closely related to future HF. During pre-eclamptic pregnancies, the left ventricle undertakes concentric remodelling, persisting after delivery. This defect is also associated with a molecular signature that is proposed to predispose to heart failure, including in expression of miRNAs. In a review, miRNAs that are commonly increased (miR-18 miR-21, miR-125b, miR-195, miR-499-5p) and decrease (miR-1, miR-30) are found in cardiac remodelling and preeclampsia. Furthermore, a few miRNAs, including miR-29b and miR-181b, were increased in one condition and decreased in the other. These results are regarded as crucial progress in the search for potential indicators of adverse pregnancies and to understand preeclampsia's association with cardiovascular diseases (Mohseni et al., 2018).

2.1.2. The role of miRNAs in foetal growth restriction

Fetal growth restriction (FGR, previously IUGR) is a pathological condition in which there is failure in utero to reach the foetal growth potential as genetically determined. This is typically a fetal weight below the 10 th percentile for gestational age. FGR can result in low birth weight and severe complications in newborns. Placental insufficiency, wherein the placenta is unable to supply the fetus with sufficient nutrients and oxygen, is one of the most common etiologies of this condition (Dumolt et al.N/AMARTINIAMGA, 2021; Kamphof et al.n/A). Genetic and maternal life style factors, environmental factors, and condition of inflammation, alone or in combination, are those which artificially have an explanation for to the associated risk of FGR (Malhotra et al., 2019). In another report, authors measured miRNA in the blood plasma of FGR-pregnant female members. The study revealed that the pregnancy status was able to up-regulate and down-regulate the concentration of placental-specific miRNAs in plasma and found that in FGR, the expression level of the miRNAs detected in plasma was about twofold of that in controls. Notably, the same miRNAs were found to be downregulated in the placenta of fetuses diagnosed with FGR (Mouillet et al., 2010).

In a separate investigation miRNA and gene expression were assessed in placenta samples from women with early-onset PE and FGR. The analysis results based on next-generation sequencing revealed 6 miRNAs and 22 genes as differentially expressed in all the patients (classified as 3 groups: preeclampsia early onset, preeclampsia associated with intrauterine growth restriction, and patients with both diseases). Additional analyses indicated that several miRNAs might regulate genes of significance such as APLN, CSF1, and FZD5 by changing gene expression (Awamleh et al., 2019).

A recent systematic review indicates that miRNAs including miR-210 and miR-424 (up-regulated in fetal growth restriction (FGR)), and miR-518b and miR-519d (downregulated in FGR) impact on angiogenesis and growth signalling pathways. These results imply that miRNAs could possibly be used as biomarkers for the early detection of FGR (Kochhar et al.,2022).

Based on the findings of a recently published study with 48 foetuses, miR-25-3p, miR-185-5p and miR-132-3p miRNAs are upregulated in the cord blood of late-onset foetal growth restriction foetuses. Such miRNAs influence events like heart and neuron death. These miRNAs are proposed to be potential biomarkers for diagnosis and treatment of late-onset FGR (Loscalzo et al.,2021). In a separate study including 25 foetuses, the miRNA profiles in the cord blood of foetuses with late-onset FGR were analyzed. From the analyses, miR-25-3p and specifically miR-148b-3p were found to be upregulated in FGR fetuses. Several of these miRNAs related to processes of biochemistry such as neuronal plasticity and energy metabolism, may not only contribute to but also help to explain the pathophysiology of late-onset FGR (Morales-Roselló et al.,2020).

Another study investigated miRNAs screening in maternal blood to identify FGR. For the four miRNAs (miR-16-5p, miR-103-3p, miR-107-3p, miR-27b-3p), elevated plasma levels during the early pregnancy months and decreased ones during the very last gestational trimester were found. These data indicate that assessing miRNAs in maternal blood might be in the future explored as diagnostic tool for FGR and its associated fetal hypoxia (Tagliaferri et al.,2021).

One systematic review on the role of miRNAs in the blood of mothers with FGR reported 48 distinct miRNA that were differentially expressed. Especially, the expression of miR-16-5p, miR-590-3p and miR-206 miRNAs was consistently upregulated and it has been documented that these miRNAs suppress angiogenic genes including VEGF and PIGF, perturbing angiogenesis and pregnancy outcome. These miRNAs could serve as candidate biomarkers in the early detection of FGR (Kolawole et al.,2025).

2.1.3. The role of miRNAs in gestational diabetes

Gestational diabetes mellitus (GDM) is a frequent complication in the second half of pregnancy, which is associated with long-term insulin resistance. It is generally diagnosed in late second or third trimester of pregnancy. Because of the heterogeneity of the diagnostic criteria among countries, its incidence varies from 1.8% to 31%. It can have a range of negative effects for mothers and babies. There is also increased rate of preeclampsia, caesarean section and shoulder dystocia in mothers with this complication (McIntyre et al.,2019; Metzger et al.,2019).

Irregularly expressing miRNAs influence not only maternal metabolic adaptation, but also the function of pancreatic beta cells. This leads to GDM by insulin resistance and deficiency of insulin secretion (Liu, et al., 2021).

Juchnicka and Kuzmicki analysed the miRNAs in blood as potential GDM diagnostic tools. miR-132/29a/222 were significantly downregulated in sera of patients with GDM as compared to healthy pregnancy in sera of weeks 16-19. In particular, miR-29a and miR-222 were reliably validated in several series of samples. The investigators declared that these miRNAs may be used as an early and non-invasive diagnostic approach for GDM (Juchnicka & Kuzmicki, 2021).

Another research has also analyzed the relationship between circulating miRNAs and GDM susceptibility in early and middle gestation. Levels of miR-155-5p and miR-21-3p were correlated with GDM in the study. An important result was stronger associations, particularly for female carriers of male fetuses, among pre-pregnancy overweight/obese women. These findings indicate that circulating miRNAs represented a promising marker for the early diagnosis of GDM, (Wander et al. 2017).

Yoffe et al.' Russo and various other miRNAs [8 Y.Y._pet al. Growth retardation of fetal rats exposed to maternal gestational diabetes mellitus in early pregnancy is associated with inhibition of IGF-1 expression. A logistic regression model based on these two miRNAs showed 91% accuracy in predicting GDM (AUC 0.91). It is implied that circulating miRNAs may serve as biomarkers of GDM in early gestation and that an early non-invasive test may be developed for early diagnosis of GDM (Yoffe et al. 2019).

Studies analyzing the effects of maternal diabetes (pre-gestational and gestational) in pregnancy complications and the involvement of miRNAs in this context were assessed in a recent review. It was observed that all the included studies were exclusively based on GDM and no profiling of miRNA was carried out in the pre-gestational types of diabetes. Interestingly, the majority of GDM studies investigated miRNAs in the characteristic of potential biomarkers. This implies that profiling of miRNA needs to be undertaken in all diabetes types to decipher the link between maternal types of diabetes and pregnancy complications (Masete et al., 2022).

2.1.4. The role of miRNAs in Spontaneous Abortion

Spontaneous abortion is the natural loss of a pregnancy 20 weeks before. Chromosome differences are to blame for half of those cases. Diagnosis is by ultrasound and management can be expectant or by medication or surgery as indicated (Griebel et al. 2005).

Research on circulating miRNA profiles in both unexplained recurrent spontaneous miscarriage (URSA) and a normal pregnancy. Twenty-five miRNAs (miR-146b-5p, miR-320b, miR-221-3p, miR-559 and miR-101-3p) were determined to be differentially expressed in URSA compared to the control. These miRNAs are believed to play a role in apoptosis and immune responses. The findings hint that circulating miRNAs may play a role in URSA and the circulating miRNAs is a potential new diagnostic biomarker for URSA (Qin et al., 2016).

A study by Zhao et al. detected down-regulation of miR-146a-5p in the endometrial tissue of URSA patients. It had been proposed that this state is capable of contributing towards miscarriage through induction of immune tolerance in the feto-placental interface (Zhao et al. By contrast, research conducted by Zhang et al. (Zhang et al.) also found that miR-184 level was high in the endometrial tissue and peripheral doners of recurrent miscarriage. This miRNA was shown to induce death (apoptosis) of the placental cells (trophoblasts) causing a woman to soon after naturally abort. These two studies showed that various miRNAs are involved in the pathogenesis of RSM, which may serve as potential diagnostic and therapeutic targets (Zhao et al., 2018; Zhang et al., 2019).

MiRNA gene variants (SNPs) including miR-499a, miR-149, miR-125a, and miR-10a were indicated by a recent meta-analysis to contribute to the risk for recurrent spontaneous miscarriage. These miRNA variants may be candidate bio-markers for screening of high-risk women (Wang et al., 2023).

Conclusion

MicroRNAs have been shown to play a complicated and vital role in the physiology and pathology of pregnancy in recent investigators. These molecules are crucial for the maintenance of a normal pregnancy through the coordination of placental growth, trophoblast activities as well as maternal-fetal immune responses. Pregnancy complications such as preeclampsia, fetal growth restriction, gestational diabetes and spontaneously fetal loss identified specific alterations in the circulation miRNA profiles. The altered expression implies the miRNAs might be the potential biomarker for these diseases.

In the future, miRNA-based diagnostic devices could accelerate the early diagnosis of pregnancy complications and promote the formulation of individualized therapeutic regimens. Studies in this field show that miRNAs are a promising instrument to monitor the maternal and fetal health and to manage pregnancy disorders.

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Chapter 3

EXTERNAL EAR ANATOMY

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INTRODUCTION

The external ear (auris externa) constitutes the first part of the auditory system and is meanly divided into two parts: the auricle (pinna) and the external acoustic meatus (external auditory canal). The auricle is located on the side of the head and serves to collect sound vibrations. The external acoustic meatus is a pathway that transmits these vibrations to the eardrum. The auricle also protects the middle and inner ear from the physical, chemical, and biological effects of the external environment (1-3).

The external ear is not only the starting point of the auditory system but also holds value as a significant aesthetic and social element. As with most facial anthropometric measurements, variations in the outer ear have been reported based on age, gender, race, and ethnicity. It also plays a role in receiving, selecting and directing sound waves for hearing and provides support for glasses, headphones, ear defenders, earplugs and hearing aid devices (4).

EMBRYOLOGY OF EXTERNAL EAR

The ear is an anatomical unit that provides both hearing and balance in adults. It consists of three parts of different origins that function as a single functional unit.

The pinna develops from six mesenchymal proliferation zones located at the dorsal ends of the first and second pharyngeal arches and surrounding the first pharyngeal cleft during the 6th week. In the 11th-12th weeks of intrauterine life, these hillocks fuse to form the auricle, and the tragus, crus helicis, helix, antihelix, antitragus and earlobe originate from these hillocks. The earlobe is the first structure to develop in the external ear (5-7). With the development of these buds, first the outer ear and then the earlobe are formed. These prominences, located three on each side of the external auditory canal, later fuse to form the permanent pinna. The formation of cartilage begins in the seventh week with the origin of the concha from the ectoderm of the first brachial groove (7, 8). Since the fusion of the auricle prominences is a very complicated process, developmental disorders of the auricle are quite common. Initially, the external ear is located in the lower region of the neck and with the development of the mandible it rises towards the sides of the head to the level of the face.

The external auditory canal develops from the dorsal part of the first pharyngeal cleft. At the beginning of the third month, epithelial cells at the base of the external auditory canal proliferate, forming a solid epithelial structure called the meatal plug. By the seventh month, this plug dissolves, and the epithelium lining the meatal floor contributes to the formation of the

permanent eardrum. Sometimes, failure of the meatal plug to dissolve before birth results in congenital deafness (5,6).

The auricular cartilage, which forms the external ear, has incredible flexibility during the first few days of life due to circulating maternal estrogens. It is hypothesized that hyaluronic acid, a major component of ear cartilage, is increased by circulating estrogen and is responsible for the neonatal pinna's development into a flexible structure (9).

AURICULA (PINNA)

The auricle is a structure largely composed of fibroelastic cartilage. This cartilage is connected to the surrounding structures via extrinsic ligaments and muscles. It is connected to the external acoustic meatus by fibrous tissue. The skin covering the pinna is thin and firmly adherent to the underlying cartilage. Its surface is covered with thin skin and contains fine hairs and sebaceous glands, most abundant on the auricular concha and scapha (2). The only exception is the lobule auriculae, which forms the lower part, and this part has no cartilage; it consists of connective tissue, vessels and fat tissue. The hairs (tragi) on the tragus and antitragus are numerous and thick. The skin of the pinna is continuous with the skin of the external auditory canal. The pinna, with its concha, allows sound waves to be directed into the external auditory canal. In addition, the indentations and protrusions of the auricula play an important role in the directional localization of frequencies (1).

The pinna, resembling an ellipse with a broad apex, is concave overall, despite showing many indentations and protrusions, with this surface facing outward and slightly forward. The edge that externally borders the pinna is called the helix and is the most prominent anatomical structure in the ear. The helix terminates as the crus of helix just above and behind the ear opening and joins the earlobe below, called the auricular lobule. A small protrusion (auricular tubercle, "Darwin's tubercle") is often seen in the middle of the helix, extending forward. This protrusion is very prominent until the sixth month of intrauterine life but gradually diminishes thereafter. Additionally, two other protrusions are visible on the cartilage when the ear skin is lifted. The protrusion anterior to the crus of helix is called the spin of helix, and the protrusion at the end of the helix closest to the earlobe is is prolonged downward as a tail-like process, the cauda helicis. The shallower protrusion located in front of and parallel to the helix is called the antihelix. The antihelix originates from the antitragus, extends anteriorly and upwards, and divides into two crura (crura of antihelix). The depression between these crura is called the triangular fossae. The sulcus between the helix and the antihelix is called the scapha. The depression bounded posteriorly by the antihelix is called the auricular concha. The superior-anterior end of the crus of helix divides the

auricular concha into two. The superior portion is called the cymba concha, and the inferior portion is called the cavitas (cavum) concha (2).

The prominence located anterior to the cavitas concha and anterior to the external auditory canal is called the tragus. The bulge opposite the tragus is called the antitragus, and the notch between the two is called the intertragic incisure. The soft, noncartilaginous portion at the lower end of the auricle is called the auricular lobule and is composed of skin, areolar connective tissue, and fatty tissue. Its shape varies from person to person (2).

On the cranial surface of the auricle, instead of the pits we see on the outer surface, there are prominences, and instead of prominences, there are depressions and grooves. The structures here are called antihelical fossae, eminentia conchae, eminentia scapulae, eminentia fossae triangularis, groove of crus of helix (1, 2).

The auricular cartilage is a single piece, pinna-shaped, and not found on the earlobe and between the tragus and helix. In addition to the structures we can see as indentations and protrusions when covered with skin, the tail of helix is present at the lower end of the helix. The notch between the tail of helix and the antihelix is called the fissura antitragohelicina. The groove on the cranial surface of the cartilage between the eminentia conchae and the eminentia fossae triangularis is called the sulcus antihelicis transversus. This groove fits into the lower extension of the crura of antihelix on the outer surface. There is a vertical edge called ponticulus in the eminentia conchae, to which the posterior auricular muscle attaches. The auricular cartilage has two notches. The first of these is the terminal notch of auricle, located on the anteroinferior aspect of the crus of helix, and the second is the intertragic incisure (intertragic notch), located between the tragus and antitragus.

Ligaments of Auricle (Ligamenta Auricularia, Ligament of Valsalva)

The auricular ligaments consist of two parts: extrinsic and intrinsic. The extrinsic ligaments connect the auricle to the temporal bone, and the intrinsic ligaments that connect the various parts of the auricular cartilage to each other (2).

The extrinsic ligaments are divided into two types: anterior and posterior. The anterior auricular ligament extends from the tragus and spine of helix to the base of the zygomatic process of the temporal bone. The posterior auricular ligament extends from the auricular concha to the lateral surface of the mastoid process. One of the two intrinsic ligaments extends between the tragus and helix, completing the external auditory canal. The other, an insignificant ligament, extends between the tail of helix and the antihelix on the cranial side (1, 2).

Auricular Muscles

These are two groups of muscles: extrinsic and intrinsic, which extend between the pinna, the skull, and the skin, as well as between various parts of the pinna.

Extrinsic Muscles: These muscles are located between the auricle and the skull and scalp. Their function is to move the auricle and are rudimentary in humans. These muscles are the anterior auricular muscle, the superior auricular muscle, and the posterior auricular muscle.

Anterior auricular muscle: This very thin and inconspicuous muscle originates from the anterior part of the temporal fascia and inserts into the protrusion on the anterior side of the helix.

Superior auricular muscle: This thin, fan-shaped muscle originates from the galea aponeurotica and inserts into the superior aspect of the auricle as a thin, flat tendon.

Posterior auricular muscle: This muscle, shaped like two or three bundles, originates from the mastoid process via a short aponeurosis and inserts into the posterior inferior aspect of the auricle.

Functions: The anterior auricular muscle pulls the pinna forward, the superior auricular muscle upward, and the posterior auricular muscle backward. These muscles lose their importance in humans and, working in conjunction with the occipitofrontalis muscle, move the scalp rather than the ear itself. However, some individuals can move their pinnae slightly with these muscles.

Nerves: Anterior and superior auricular muscles are innervated by the temporal branch of the facial nerve; posterior auricular muscle is innervated by the auricular posterior branch of the facial nerve.

Intrinsic Muscles: These muscles are located between the skin and cartilage in the auricula. These muscles; helicis major muscle, helicis minor muscle, tragicus muscle, antitragicus muscle, transverse muscle of auricle and oblique muscle of auricle.

The helicis major muscle: This is a small muscle that runs vertically along the anterosuperior aspect of the helix. It originates from the spine of helix and inserts into the helix just above.

The helicis minor muscle: This is a small muscle that covers the crus of helix and extends obliquely.

The tragicus muscle: This is a short muscle located lateral to the tragus.

The antitragicus muscle: This muscle originates from the lateral aspect of the antitragicus and inserts into the antihelix and tail of helix.

The transverse muscle of auricle: This muscle is located on the cranial surface of the auricular cartilage and consists of transverse fibers extending from the eminentia conchae to the eminentia scaphae. A portion of the muscle consists of connective tissue fibers.

The oblique muscle of auricle: This muscle is also located on the cranial surface of the auricle. It extends between the eminentia conchae and the eminentia fossae triangularis.

Nerves: They are innervated by the facial nerve. (The muscles on its outer surface are innervated by the temporal branch, and the muscles on its inner surface are innervated by the auricular branch.)

Arteries of the Auricle

The posterior auricular artery (branch of the external carotid artery), auricular artery (branch of the occipital artery), anterior auricular artery (branch of the superficial temporal artery).

Veins of the Auricle

They are companions to the arteries of the same name. Numerous arteriovenous anastomoses occur in the skin of the auricle. They drain into the external jugular vein.

Sensory Nerves of the Auricule

The greater auricular nerve, the lesser occipital nerve (branches of the cervical plexus); the auricular nerve "Arnold's nerve" (branch of the vagus nerve); the auriculotemporal nerve (branch of the mandibular nerve), and the posterior auricular nerve (branch of the facial nerve).

Lymphatics of the Auricle

They drain into the parotid nodes, the deep cervical nodes, and the mastoid nodes (1, 2).

The Importance of the Auricle

The pinna is one of the most distinctive features of the face (10, 11). It is considered the most prominent and defining structure of the face. It is the part of the external ear consisting of the helix-antihelix complex, the conchal complex, and the lobule. It has an irregular surface. Its shape and size are influenced by age, gender, and ethnicity (12-14). Furthermore, the literature

also indicates that chromosomal disorders and psychiatric disorders can affect the ear structure (8, 11).

It is known that determining the ear's biometry and characteristics is important for person identification, gender, and age estimation (9). Due to its fixed position on the side of the face and its larger size than other facial parts such as the retina and iris, it has been used as a key feature in forensic medicine applications (13). The auricle, in particular, is an important subject of study in anthropology, forensic medicine, and plastic surgery, as its morphological structure varies among individuals. Furthermore, auricular morphometry is one of the key parameters used in biometric research, in age, gender, and identification determination in forensic medicine studies, in the diagnosis of syndromes characterized by morphological abnormalities in genetic counseling, and in determining treatment approaches in plastic and reconstructive surgery (15, 16). It has demonstrated relative stability in shape and orientation compared to facial expression. Furthermore, it is believed that external ear characteristics are unique to an individual, meaning they can be used as supporting evidence. The external ear's relative size ratios reach their final form in the fourth month of intrauterine life. However, the ear continues to grow in size after birth until the individual reaches adulthood. Aging is another factor that causes significant changes in auricle size, and in older individuals, greater values in ear length compared to width are more pronounced; this length has been attributed to changes in lobules and elastic fibers. Conversely, lobule width is inversely proportional to age (13). The earlobe is considered an important feature of beauty in many societies (17).

The auricle reaches its width between ages 5 and 11, and its length between ages 12. and 16. (18). The auricle reaches its adult size by puberty, and although its dimensions increase with age, the ratio between these measurements remains constant. Studies have found that the auricle's morphometric measurements are longer and wider in males than in females. Recent studies in the literature have reported a positive correlation between auricular morphometry and height, and that auricular dimensions can be used in linear equation models for height estimation (16).

The natural and beautiful shape of the pinna (auricula), separate from the outer ear (auris externa), is also important from an aesthetic perspective. Both ears play a vital role in creating a natural, harmonious appearance and an aesthetically pleasing facial appearance (19). Because its size, shape, position, protrusion, and symmetry all influence a person's appearance, it is an important organ that contributes significantly to facial aesthetics (4). The shape, size, and orientation of each pinna are as unique as fingerprints. The appearance and symmetry of the pinna contribute to facial aesthetics (9, 11, 17). Morphometric and morphological information about the ear is as

important for facial symmetry and is as unique to the individual as biometric datas such as fingerprints, iris, and voice. Like fingerprints, earprints are also unique to each individual and vary from person to person. No two ears are alike. The primary reason for this is the development of six protruding segments on either side of the head, beginning in the fourth and fifth weeks of pregnancy, and the completion of ear formation. These growing protrusions then fuse together. While the phenotypic state of the outer ear depends on inherited genes, conditions in the womb also have a significant impact on ear shape. Ears do not change shape after forming in the womb before birth, but they do undergo changes in volume and appearance with age (7). However, some generalizations are possible: men have larger ears than women, both the length and width of the ears increase with age, and overall ear size varies by ethnic group. (11, 15). Ear morphology and morphometry are more important than typical biometric features such as facial recognition because they are rarely affected by aging. However, they are not affected by changes in facial expression. Therefore, the ear is widely used as a forensic tool for individual identification due to its permanence and distinctiveness in individuals from birth to adulthood (15).

EXTERNAL ACUSTIC MEATUS

It extends from the auricular concha to the tympanic membrane. It is approximately 4 cm long from the tragus and 2.5-3 cm long from the base of the auricular concha. The external auditory canal is not a straight tube, but rather a curved tract shaped like a flat "S". The external auditory canal courses from the outside inward, first inward and slightly upward (pars externa), then inward and slightly upward (pars media), and finally inward and slightly downward (pars interna) again (1, 2). The external auditory canal, which appears oval in cross-section, has its widest diameter at the entrance of the canal (external acoustic pore), extending obliquely posteriorly and downward, and horizontally at the base of the canal. Normally, there are two narrowing points. The first of these is located at the end of the cartilaginous portion of the canal, and the second is located in the bony portion (isthmus) 2 cm from the bottom of the auricular concha. The bottom of the canal is covered by the obliquely placed tympanic membrane (1, 20). The external auditory canal is covered by a thin layer of skin tightly adherent to the cartilage and bone. This skin continues only as the epidermis over the tympanic membrane (2).

The outer 1/3 of the external acoustic meatus consists of cartilage (pars cartilaginea) (8 mm), and the inner 2/3 consists of bone (pars ossea) (16 mm) (1, 2, 20).

Cartilage of External Acoustic Meatus (Pars Cartilaginea): The cartilage part of the external ear canal begins at the base of the auricular concha,

extends to the external acoustic pore, and attaches to the bone via connective tissue. It is approximately 8 mm long, and the cartilage forming this section is called the cartilago meatus acustici. Externally, it is continuous with the auricular cartilage. Its medial end is firmly attached to the bony portion of the temporal bone. This cartilage part is not completely tube-shaped and lacks cartilage in its posterior and superior portion. This area is covered by a fibrous membrane. Anteriorly, it has two or three deep notches (notch in cartilage of acoustic meatus) (1, 2).

Bony of External Acoustic Meatus (Pars Ossea): The bony part of the external auditory canal is approximately 16 mm long, twice the length of the cartilaginous part, but narrower. It extends from the external acoustic pore to the tympanic membrane. Its anteroinferior and posteroinferior parts are formed by the tympanic part of the temporal bone. In the fetus, this part is only a tympanic ring. Its posteroinferior part is formed by the squamous part of the temporal bone. This part, narrower than the cartilaginous part, extends medially, anteriorly, and somewhat inferiorly. At the end of the canal, there is a bony ring called the annulus tympanicus, to which the tympanic membrane attaches (2).

The pars ossea, which has a slight convexity from posterior to superior, extends inward, forward, and slightly downward. The inner opening of the bony canal is narrower than the outer opening and is obliquely oriented, resulting in an anterior wall that extends 4 mm further medially. The upper part of the inner opening contains a notch called the tympanic notch (Rivinus' notch). The remaining part contains a groove called the tympanic sulcus, to which the eardrum attaches. The outer opening is wide and notched, and a cartilaginous portion is attached here. When examining the external auditory canal with a speculum, the cartilage pars should be aligned as closely as possible with the pars ossea. To achieve this, the pinna should be pulled upward, backward, and slightly outward (20). This allows the external auditory canal and most of the tympanic membrane to be seen. The skin covering the external auditory canal is a continuation of the skin of the pinna and also covers the outer surface of the tympanic membrane. This very thin skin lacks papillae and is tightly adherent to the underlying cartilage or bone. Inflammation in this area can cause the skin to stretch, preventing it from expanding. This can be very painful. The subcutaneous connective tissue in the pars cartilage is thick and contains numerous ceruminous glands. Their secretions mix with shed epithelium and dust entering the ear to form earwax, also known as cerumen. This secretion has a protective function in the external ear canal (1, 2, 3). Normally, the external ear canal is well protected and self-cleaning. Ear cleaning not only causes trauma to the external ear canal, but also contributes to infections due to the lack of cerumen, which has protective properties such as physical protection, antimicrobial activity, maintaining a low pH, and

lysosomal activity (20). The skin on the cartilaginous portion of the external ear canal contains hairs called tragi (2).

Adjacences of the External Acoustic Meatus

The head of the mandible is located anterior to the external auditory canal. It is directly adjacent to the bony portion. A section of the parotid gland lies between it and the cartilaginous portion. Therefore, movement of the mandible can partially affect the lumen of the cartilage. Posterior to the osseous portion are the mastoid cells, separated only by thin lamellae of bone. This is clinically significant.

Arteries of the External Acoustic Meatus

Posterior auricular artery (branch of the external carotid artery); Profundus auricular artery (branch of the maxillary artery); Anterior auricular artery (branch of the superficial temporal artery).

Veins of the External Acoustic Meatus

They are companions to the arteries of the same name. They drain into the external jugular vein, maxillary vein, and pterygoid venosus plexus.

Sensory Nerves of the External Acoustic Meatus

Auriculotemporal nerve (branch of the mandibular nerve) (distributes on the anterior and superior walls); auricular nerve (Arnold's nerve, branch of the vagus nerve) (distributes on the posterior and inferior walls).

Lymphatics of the External Acoustic Meatus

They drain into the parotid nodes, the deep cervical nodes, and the mastoid nodes (1, 2).

CONCLUSION

The external ear is critical for the initiation of auditory function and the protection of the middle and inner ear. A detailed understanding of its anatomical, histological, and embryological characteristics is essential for otorhinolaryngology and surgical practice. Furthermore, the anthropological and social significance of the auricle demonstrates that the external ear is not only a hearing organ but also a crucial component of individual identity.

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Chapter 4

CHILDREN WITH SPECIAL NEEDS AND NURSING APPROACH

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Introduction

The prevalence of children with special needs is increasing worldwide. Banks and McCoy (2011) report that approximately 25% of school children worldwide have special needs. According to research conducted in 30 countries across Europe, the rate of identifying children with special needs in schools ranges from 1.06% to 20.50%, with an overall average of 4.44%. According to the results of this study, 21% of school children in the United Kingdom (England) (Scotland), 16% in Iceland, 13% in Lithuania, 12% in Slovakia, 6% in Germany, 5% in Denmark, and 3% in England are students with special needs (European Agency for Special Needs and Inclusive Education, 2018). The prevalence of children with special needs was 13% in the United States between 2015 and 2016, 22.9% in Japan, 17% in elementary school students in Canada, and 27% in middle school students (People for Education, 2018; ABD, National Center for Education Statistics, 2016). Chronic illnesses among children in inclusive education include chronic diseases such as asthma, diabetes, cancer, or kidney failure, or physical disabilities such as visual, hearing, or orthopedic disabilities (Milli Eğitim İstatistikleri Orgun Eğitim National Education Statistics, Formal Education, 2017). These children with chronic illnesses, physical disabilities, or disabilities may have various health needs within the school system. Primary health care needs include medication use, emergency intervention in the event of a crisis or seizure, intervention in the event of falls and injuries, provision of walking support, and provision of self-care support (Juonala et.al., 2011). Meeting these needs during school, which plays a crucial role in a child's life, is crucial for not only healthy growth and development but also for educational success. This is important for the approach of nurses.

What is a Special Needs Child?

Children with special needs should be evaluated and appropriate interventions planned to maximize community and individual health. The child and their family should be considered holistically. The addition of a new family member causes many functional, structural, social, and economic changes. Problems arise when the new family member has special needs or when someone in the family experiences a long-term illness. The literature indicates that a child experiencing a long-term illness, a disability, or special needs from birth has many emotional, social, developmental, physical, and psychological impacts on parents (Arakelyan, Maciver, Rush, O'hare & Forsth, 2019).

Unlike individuals with normal development, individuals with mental, visual, hearing, physical disabilities, language and speech disorders, attention deficit and hyperactivity problems, learning difficulties, autism or gifted individuals are defined as individuals with special needs (Varış and Hekim, 2017).

Children with special needs are defined as those with mental, visual, hearing, orthopedic disabilities, language and speech disorders, attention deficit and hyperactivity problems, learning difficulties, autism, or gifted individuals whose developmental processes differ from those of normal individuals (Varış and Hekim, 2017).

Individuals with special needs are generally classified into the following groups:

Intellectual Disability (Down syndrome, Autism etc.)

Specific Learning Disability

Physical Disability, Chronic Illness, and Orthopedic Disability

Speech and Language Disability

Hearing Impairment

Visual Impairment

Attention Deficit Hyperactivity Disorder (ADHD)

Pervasive Developmental Disorder (Ayyıldız, 2007).

Health Needs of Children with Special Needs and Problems

Among children with special needs, it is known that children with intellectual disabilities have more physical and mental health problems than healthy children, (Storrie et.al., 2011; Janicki et.al., 2002) and that 20–25% may also have comorbid epilepsy (Forsgren et.al., 1990). Children with intellectual disabilities are more likely to experience visual impairment, obesity, seizures, and hearing problems than their healthy peers, and they may exhibit problem behaviors 3–5 times more frequently than their peers (Admiraal and Huygen, 1999). Therefore, activities that improve the mental health of children with special needs, in addition to improving their physical health, are very important.

Another group included in inclusion students are children with autism spectrum disorders. Children with autism spectrum disorders may face health risks such as sensory problems, seizures, mental health problems, and injuries, as well as physical, cognitive, and behavioral developmental delays. Children with autism spectrum disorder may have food intake restrictions due to certain substances (intolerances and allergies to wheat, milk, or gluten-containing foods), and they may experience difficulties due to lack of self-care (Evenhui, 2001). Primary health needs can be addressed as follows: medication use, emergency intervention in case of crisis or seizure, intervention in cases

of falls and injuries, provision of walking support, and provision of self-care support. Meeting these needs during school, which plays a crucial role in a child's life, is crucial for ensuring healthy growth and development, as well as for educational success (Juonala et.al., 2011).

In a study investigating the health needs of mainstreamed primary school students, Kabasakal et al. (2018) evaluated 404 mainstreamed students. According to the research findings, 13.4% of the mainstreamed children had a chronic disease, and 9.5% had a health problem that could develop urgently (epileptic seizure, fainting, falling, etc.). The proportion of mainstream students who usually or occasionally have health needs during school hours is 39.9%. For 49% of students, any health problem that arose during their time at school was met. Of those who met the health needs of these children during school, 74.8% were teachers, and 19.7% were parents. Furthermore, in this study, 50.2% of parents found school personnel's health information inadequate. 21.8% of families reported that their children needed health care at school in the week preceding the survey.

In another study conducted by Roizen and et.al. (2014) to identify health problems in 440 children with Down syndrome, 55% of the children had heart disease, 39% had vision and hearing problems, 32% had asthma/reactive airway disease, and 27% had thyroid disease. Surgery was required in 58% of children with heart disease at an average age of 9 months. In a study conducted by Tenenbaum et al. (2014) on 162 hospitalized children with Down syndrome aged 0-16, it was reported that 49% of these children had been hospitalized three or more times, and respiratory tract infections were the leading cause of hospitalization at 39.6%, followed by surgical procedures at 22.3% and heart failure at 8%.

Recommendations for the Health Needs of Children with Special Needs

Nurses fulfill seven fundamental roles to enhance children's lifelong health outcomes and educational success. These roles include providing direct care, leading the delivery of health services, screening and referral for health conditions, providing an emotionally safe environment, planning, implementing, and evaluating health promotion activities, leading health policies and programs, and facilitating communication, connection, and coordination among school staff, families, and healthcare professionals. In line with these roles, school health nurses are expected to gather information about children with special health needs, monitor their development, evaluate the process in collaboration with the multidisciplinary school team, and implement these into routines (Lee et.al., 2014).

Children with Special Needs and Nursing Approach

By communicating with individuals, nurses can become aware of their feelings, needs, and problems and plan care accordingly. The ability to communicate with individuals is one of the core competencies of nurses (Ghazavi et.al., 2010). Positive health indicators will be achieved when nurses effectively use their educational and counseling roles in maintaining health (Özpulat, 2010). One of the roles of nurses that helps protect and improve individual, family, and community health, prevent illness, and develop coping skills is the role of educator (Ergün et.al., 2016). Nurses, who play many important roles such as providing care, counseling, and education, can participate in the planning and implementation of family education programs (Tambağ and Öz, 2014). A study conducted with families of children with visual and intellectual disabilities found that education provided to families to develop positive parenting skills increased their ability to support their children and their self-efficacy (Platje et.al., 2018). Another study implemented a family support education program addressing the challenges faced by mothers of children with intellectual disabilities. It was determined that after the training, families' knowledge and awareness levels increased and families shared their experiences (Aksoy and Demirli, 2020).

The nursing approach to surgery for children with special needs focuses on patient safety. For example, precautions should be taken to limit neck manipulation in children with Down syndrome. The child's neck should be secured in a balanced position with a soft neck collar to avoid extension, rotation, or excessive neck flexion Due to the frequency of airway anomalies, it is important to have a variety of airway devices available to effectively manage respiratory complications. During surgery, the nurse should be ready to assist the anesthesiologist in applying cricoid pressure in the event of rapid and serial induction of a child with a history of gastroesophageal reflux and vomiting (Meitzner and Skurnowicz, 2005).

For example, autism is often diagnosed by family members, nurses, physicians, or other health professionals who monitor the child's development (Sayan and Durat, 2007). In this context, pediatric nurses can assist in early diagnosis through physical examinations during child care and growth and development monitoring (Ocakçı ve Karakoç, 2013). For early diagnosis, the nurse must be familiar with the normal growth and development process for children aged 0-6 and be able to recognize abnormalities. When the nurse notices that something is wrong with the child's development, they must take action (Sayan and Durat, 2007). In this regard, it would be appropriate for the nurse to make a nursing diagnosis within the scope of the process, initiate appropriate interventions and referrals, and provide guidance to the family. Nurses should emphasize the importance of mother-baby interaction from

the newborn period onward for early diagnosis and the need to take children for regular health checks until they are one year old (Ocakçı ve Karakoç, 2013; Sayan and Durat, 2007).

A nurse working in a unit caring for children diagnosed with autism must have the knowledge to apply the principles and techniques of behavioral, auditory, and educational therapy used in care. For example, children diagnosed with autism do not like being touched or hugged, but they are quite interested in music and rhythmic rocking (Pektaş, 2016). The nurse can help the mother and child bond by having the mother touch and caress the bare parts of the child's body, accompanied by music and rocking (Ocakçı ve Karakoç, 2013). It has been observed that when children are provided with the necessary educational support, they largely overcome this problem and can continue to integrate with their peers and society for the rest of their lives (Vuran and Turhan, 2012). Delay in language development is often the first symptom noticed by families of children diagnosed with autism. Initially limited to speech and language disorders, the disorder has now been broadened to encompass disorders of the communication process. Children diagnosed with autism have serious deficiencies in using language for social communication (Birkan, 2012).

Additionally, it is particularly necessary for the child health nurse to include typically developing siblings in the assessment and care process within the context of a family-centered and holistic approach to care (Hockenberry and Barrera, 2011). The child health nurse is defined in the nursing regulations as "the nurse responsible for the healthy physical, cognitive, emotional, and social growth and development of children aged 0-18 within the family and community, their protection from illness, and their maximization of health, in accordance with universal children's rights and professional nursing roles". The development of initiatives to protect, maintain, and improve the health of typically developing children aligns with the philosophy of care and defined roles of pediatric nursing (Kaya et.al., 2020; Yüzer Alsaç & Yiğit, 2018).

Differences between siblings should be explained based on the child's age and stage, questions should be asked about how they perceive the situation, and communication and interaction processes between siblings should be maintained and maintained in accordance with the illness, and parents' attitudes should be evaluated to ensure their understanding of their effects on the child (Vatne, 2017; Emerson & Giallo, 2014). Nurses are responsible for creating and implementing relevant practices within the scope of their roles as educators, counselors, advocates, health promoters, rehabilitators, comforters, and communicators and coordinators (Hockenberry & Barrera, 2011).

Conclusion

Early diagnosis should guide the work of nurses within the framework of primary health care services for children with special needs. Furthermore, developmental disorders can be identified early through risk assessment and influencing factors. Referring the family to appropriate units, confirming the diagnosis, and initiating therapy early are crucial for reducing the child's problems and supporting their development. A comprehensive multidisciplinary approach is required. Physicians, nurses, speech and occupational therapists, social workers, physical therapists, and psychologists should work collaboratively.

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Chapter 5

APPLICATIONS OF METAL NANOPARTICLES IN DRUG DELIVERY SYSTEMS

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1. INTRODUCTION

Nanotechnology, whose foundations were laid for the first time in Richard Feynman's 1959 speech titled "There's Plenty of Room at the Bottom," with the argument that it is possible to produce structures at the atomic level, is based on the principle of studying, designing, and functionalizing materials between 0.1 and 100 nanometers (Nikolova M. et al., 2020).

The emergence of nanotechnology has revolutionized the field of modern medicine by offering innovative solutions to overcome the limitations of traditional drug delivery systems. Nanoparticles, defined as particles with at least one dimension in the range of 1-100 nm, possess unique physical, chemical, and biological properties that differ significantly from their larger counterparts. These properties, such as a large surface area-to-volume ratio, high reactivity, tunable optical and magnetic properties, and ease of functionalization, have made nanoparticles an indispensable platform for designing next-generation therapeutic systems. Among various classes of nanomaterials, metal nanoparticles (MNPs) have garnered significant interest due to their potential in targeted, controlled, and effective drug delivery applications. (Chandrakala et al., 2022). Metal nanoparticles such as gold (Au), silver (Ag), iron oxide (Fe_3O_4), zinc oxide (ZnO), and platinum (Pt) are among the most extensively studied due to their biocompatibility, stability, and multifunctionality. These metal nanoparticles exhibit distinctive properties that make them superior carriers compared to traditional drug delivery systems such as liposomes, polymeric nanoparticles, and micelles. Their optical, electrical, and magnetic properties enable them to be used not only as passive carriers but also as active components in stimulus-responsive or multifunctional drug delivery systems. For example, gold nanoparticles (AuNPs) exhibit strong surface plasmon resonance, enabling photothermal and photodynamic therapy, while iron oxide nanoparticles (Fe_3O_4) can be guided by external magnetic fields for magnetic targeted drug delivery and imaging (Jahangirian et al. 2019).

One of the most significant advantages of MNPs in drug delivery is their ability to increase bioavailability and site-specific drug accumulation. Traditional systemic drug delivery often suffers from rapid clearance, low selectivity, and high toxicity to healthy tissues. Through surface modification with polymers (e.g., PEG, PVA), ligands, peptides, antibodies, or aptamers, metal nanoparticles can be tailored to recognize specific biological targets, such as overexpressed receptors on cancer cells or inflamed tissues. This active targeting approach maximizes efficacy by enabling preferential accumulation of therapeutic agents at the disease site while minimizing off-target effects. Furthermore, the large surface area of metal nanoparticles allows for high drug loading capacity, and controlled release can be

achieved via external triggers such as pH, temperature, magnetic fields, or light irradiation (Chandrakala et al., 2022). Additionally, MNPs serve as versatile platforms for therapeutic applications by combining therapeutic and diagnostic functions into a single nanostructure. For example, gold and iron oxide nanoparticles can simultaneously carry drugs and act as contrast agents for imaging modalities such as MRI, CT, or fluorescence imaging. This type of multifunctional nanocarrier facilitates real-time monitoring of drug distribution, release kinetics, and treatment outcomes, paving the way for personalized and precision medicine (Abdelkawi et al., 2023). The ability to track treatment processes in the body makes metal nanoparticles one of the most promising materials in modern nanomedicine, increasing treatment efficiency and safety.

In summary, metal nanoparticles represent a groundbreaking approach to drug delivery, offering controlled release, targeted therapy, and combined diagnostic capabilities. The ability to modify physicochemical and biological properties allows for precise adjustment of pharmacokinetics and pharmacodynamics. Despite ongoing challenges in clinical translation and safety verification, continued interdisciplinary research continues to improve the design, functionality, and therapeutic index of nanoparticles. As nanotechnology advances, the application of metal nanoparticles in drug delivery systems is expected to play a significant role in the future of personalized medicine, oncology treatment, and non-invasive therapeutic strategies.

2. METAL NANOPARTICLES IN DRUG DELIVERY SYSTEMS

The integration of metal nanoparticles into drug delivery systems offers various advantages compared to conventional treatments. MNP-based systems can increase therapeutic efficacy by providing region-specific delivery while minimizing systemic toxicity and side effects. Furthermore, their ability to respond to external stimuli such as magnetic fields, light, or pH changes improves pharmacokinetics and patient compliance by enabling controlled and sustained release of drugs. Additionally, the surface of these nanoparticles can be easily modified with polymers, ligands, or antibodies to enable targeted recognition of specific cells or tissues, such as tumor regions or inflamed areas (Sathish Sundar et al., 2016; Chandrakala et al., 2022).

Recent advancements in the synthesis and surface engineering of metal nanoparticles have expanded their applications to various therapeutic areas, including oncology, antimicrobial treatment, cardiovascular diseases, and neurological disorders. However, despite their potential, challenges remain regarding their long-term safety, biological distribution, and clearance mechanisms. Ongoing research aims to optimize the design of

metal nanoparticle-based carriers to strike a balance between efficacy and biocompatibility (Chandrakala et al., 2022).

Overall, the application of metal nanoparticles in drug delivery systems represents a promising frontier in the field of nanomedicine, offering innovative solutions for precise, efficient, and personalized treatment strategies.

Gold Nanoparticles

At the nanoscale, AuNPs, which exhibit properties such as localized surface plasmon resonance (LSPR), are utilized in optical sensors, Raman spectroscopy, and biological detection systems due to their light absorption and scattering capabilities (Guan et al., 2022; Bansal et al., 2020; Kesharwani et al., 2023). AuNPs synthesized in sizes ranging from 1-100 nm exhibit color changes depending on pH and temperature; absorption bands in UV-Vis spectra differ according to size and shape (Bansal et al., 2020). Although AuNPs are not directly toxic, some coating and solvent materials used in their synthesis can cause toxicity. Cetyltrimethylammonium bromide (CTAB), particularly used in nanorod synthesis, can be toxic even at low doses. Cytotoxicity depends on particle size, surface coating, and concentration. While AuNPs smaller than 2 nm can cause mitochondrial damage, particles around 15 nm are generally non-toxic. Especially biocompatible coatings (such as PEG) and green synthesis methods reduce toxicity (Bansal et al., 2020).

The most common chemical method used in the synthesis of gold nanoparticles (AuNPs), the Turkevich method, is based on the reduction of $HAuCl_4$ using sodium citrate. Citrate acts as both a reducing and stabilizing agent. With this method, particles with a size of 10–20 nm are obtained; however, when polyphenols such as tannic acid are used, smaller particles (3.5 nm) can be produced (Bansal et al., 2020; Nejati et al., 2022). Gold nanocrystals in the shape of rods, stars, and cubes can be produced using seed-mediated methods. In this method, small seed cores are used as growth centers, and controlled growth is achieved using reducing agents such as ascorbic acid or hydroxylamine. The Brust-Schiffrin method, on the other hand, enables particle synthesis in the 1–6 nm range in a two-phase system, with sodium borohydride acting as the reducing agent. Physical methods include laser ablation, arc discharge, microwave-assisted synthesis, and electrochemical production, while biological methods feature environmentally friendly approaches using plant extracts, bacteria, and fungi (Nejati et al., 2022).

AuNPs are important carriers for tumor targeting and controlled release of chemotherapy drugs. Nanocafes and nanoshell structures can destroy only tumor cells by providing local heating with infrared rays, thus protecting healthy tissues. It also has the potential to be used in combined therapies that integrate chemotherapy, radiotherapy, and gene therapy. AuNPs

increase drug solubility, facilitate accumulation in target tissue, and enable controlled release. In biosensor applications, DNA, proteins, and ions play a role in color-change-based systems for detection, as well as in sensors that increase sensitivity for miRNA detection. AuNPs obtained through green synthesis exhibit antibacterial activity against Gram-positive and Gram-negative bacteria, which is based on their free radical scavenging capabilities. Additionally, it supports plant development by promoting seed germination, leaf growth, and increasing chlorophyll content, which highlights its potential for use as a yield-enhancing agent in agriculture (Hammami et al., 2021).

Faid et al. (2022) used AuNPs as a drug delivery system to enhance the transport of doxorubicin (DOX) to tumor cells, thereby reducing systemic toxicity. These nanocomposites, analyzed by UV-Vis spectroscopy, TEM, FTIR, and photoluminescence spectroscopy, generally have a spherical morphology with a diameter of 10-12 nm and be stable. Surface plasmon resonance (SPR) changes and spectroscopic findings indicate that DOX successfully interacted with gold nanoparticles and loading occurred. Studies on the MCF7 breast cancer cell line have shown that the cytotoxicity of DOX is increased when loaded onto AuNPs compared to free DOX. Additionally, AuNPs enhance therapeutic efficacy by allowing for more effective drug accumulation within cells through endocytosis, as they can be transported into cells more efficiently. This mechanism is particularly advantageous in cancer types where multidrug resistance (MDR) has developed. For this reason, AuNP-based drug delivery systems are actively being evaluated not only in anticancer treatments but also in the delivery of antibacterial, antifungal, and antiviral agents (Faid et al., 2022).

In the study conducted by Ghosh et al. (2021), gold nanoparticles smaller than 5 nm were synthesized using thioglucose to improve the therapeutic efficiency of amphotericin B, which has low solubility in water and high toxicity. The nanoparticles were found to have a hydrodynamic diameter of 10–20 nm and a zeta potential of –30 mV as determined by DLS analysis, while UV and FTIR analyses confirmed that the drug was successfully conjugated via EDC/Sulfo-NHS coupling. The research results demonstrated that these conjugates were effective against parasitic diseases such as Leishmania mexicana and fungal infections such as *Cryptococcus neoformans*. AmpoB@AuNP exhibited strong antifungal activity against both planktonic and biofilm forms of *C. neoformans*, and showed significant efficacy even in intracellular infections where conventional amphotericin B was insufficient. Moreover, flow cytometry confirmed that ATTO dye-labeled AuNPs were internalized by macrophages. Toxicity analyses revealed that AmpoB@AuNP showed no significant cytotoxic effects on either erythrocytes or murine macrophage cells; on the contrary, compared with conventional amphotericin B, cell viability was largely preserved at concentrations up to 16 μg/mL. In

conclusion, this nanoformulation was reported to provide a drug delivery system with enhanced aqueous solubility, reduced toxicity, and improved therapeutic efficacy (Ghosh et al., 2021).

Sulaiman et al., (2020) developed a gold nanoparticle (AuNP)-based system for the delivery of hesperidin (Hsp), which has low bioavailability. Hsp loaded onto AuNPs synthesized with glutathione and NaBH4 reducing agents were found to be spherical in morphology (10–50 nm), stable (–29 mV), and biocompatible. Drug release was rapid at pH 5.04 (89%) and slower at pH 7.4 (60%), indicating the system's potential for selective activity against tumor cells. In MDA-MB-231 breast cancer cells, Hsp-AuNPs provided higher cytotoxicity (88% cell death) compared to free Hsp and free AuNPs, while showing no significant toxicity in normal cells. Low hemolytic effect was detected in hemolysis tests (<6%), and biological safety was confirmed. Additionally, Hsp-AuNP treatment increased macrophage phagocytosis, reduced pro-inflammatory cytokine release, and supported immune-mediated anticancer activity. These findings indicate that the Hsp-AuNP system holds promise as a biocompatible, tumor-selective, and effective drug carrier, particularly in the treatment of breast cancer (Sulaiman et al., 2020).

In the study by Zhang S. et al. (2020), programmable DNA strips derived from long-chain DNA molecules were designed and synthesized using the Rolling Circle Amplification (RCA) method. Cancer cell-recognizing aptamers, fluorophores, and chemotherapeutic agents can bind to the created DNA strands (RDL1 and RDL2). The RDL2 form has gained a more robust structure with the addition of complementary short DNA sequences, and the rate at which the strips fold and shape correctly has increased (Zhang S. et al., 2020). DNA strands were coated with AuNPs to form core-shell model nanocomposites. These structures have functions such as recognizing cancer cells, effective entry into cells, traceability (with fluorescence), and pH-sensitive drug release. Specific targeting of breast cancer cells was achieved using the AS1411 aptamer, and the anticancer drug DOX was loaded onto a high-density DNA coating. In the experiments conducted, these DNA/AuNP composites, named Au-R2A, demonstrated both a high drug loading capacity (~7.6×10^5 DOX molecules/particle) and controlled release properties at low pH (such as inside cancer cells). Additionally, intracellular uptake tests performed using fluorescence microscopy and flow cytometry have shown that these structures provide higher penetration into breast cancer cells and lead to effective cell death. The specificity of the targeting mechanism has been confirmed by aptamer mutations and receptor blocking experiments. In conclusion, this DNA strand/gold nanoparticle-based system stands out as an alternative, innovative, and effective nanocarrier to traditional DNA origami systems due to its punch-free DNA folding, targeted drug delivery, biological stability, and high drug loading properties. This method can also be adapted

for different types of cancer by reprogramming with different aptamers, making it a versatile and clinically suitable system.

Hydrophobic photosensitizers used in photodynamic therapy, such as hypericin, have low solubility and limited cellular uptake, which restricts treatment effectiveness. Hypericin was physically adsorbed onto sonicated PEG-COOH functionalized ~10 nm AuNPs to make photodynamic therapy more effective and safe, while preserving its chemical structure, as reported by Mokoena et al. (2022). UV-Vis and FTIR analyzes confirmed the binding of hypericin's functional groups to the AuNP surface; HR-EM and DLS results showed that the particles were uniform (~10 nm), non-agglomerated, and stable. Zeta potential (ZP) has shown that the compound is stable in colloidal solution and can provide biocompatibility in circulation. In cellular localization studies, it was determined that the hypericin-AuNP complex provided rapid accumulation in MCF-7 cells, especially in lysosomes and mitochondria, while free hypericin showed lower and delayed uptake. In PDT application (594 nm, 10 J/cm^2), the hypericin-AuNP complex induced apoptosis-predominant cell death; neither the laser nor the conjugate alone caused significant toxicity. In conclusion, hypericin-AuNP conjugation overcomes the limited effectiveness of hydrophobic photosensitizers like hypericin, accelerating cellular uptake, increasing bioavailability, and enhancing the efficacy of photodynamic therapy. This approach offers more effective results compared to traditional photosensitizer applications, particularly due to the advantages of passive targeting (EPR effect) in the tumor microenvironment and the ability to remain stable in circulation. Cell death occurred primarily through apoptosis. The study shows that AuNP-based carrier systems are promising in photodynamic therapy, and it is recommended that in vivo experiments be conducted in advanced stages to thoroughly investigate intratumoral targeting, biodistribution, long-term safety, and clinical applicability (Mokoena et al., 2022).

Kadkhoda et al., (2022) developed PEG-coated and MUC1 aptamer-functionalized gold nanoparticles (AuNPs) for targeted delivery of paclitaxel (PTX). It was determined that the dimensions increased to 50-100 nm after coating and loading, and the structure maintained colloidal stability for 14 days. The release of PTX, which achieved 86% encapsulation efficiency, was accelerated in a tumor-like acidic environment and under 808-810 nm NIR light, providing dual-stimuli controlled release. In conclusion, the PEG-coated and MUC1 aptamer-targeted AuNP system offered a more effective strategy than chemotherapy and photothermal therapy by enhancing the controlled release of PTX and selective cytotoxicity, and was considered a promising candidate for in vivo applications (Kadkhoda et al., 2022).

El-Ghareb et al. (2020) synthesized gold nanoparticles (GA-AuNP) using the gallic acid reduction method to combine cancer diagnosis and treatment

on the same platform. They loaded these with doxorubicin (DOX) and labeled them with technetium-99m (99mTc). Gallic acid served as both a reducing agent and a stabilizer. TEM analysis reported that the particles were spherical and homogeneous, with the size increasing from ~14 nm to ~50 nm; loading efficiency of 91% and labeling efficiency of 93% were achieved. Drug release tests showed that the system is pH-sensitive; rapid release of up to 93% occurred at pH 5.3, DOX-loaded GA-AuNPs exhibited four times stronger cytotoxicity in MCF-7 cells compared to free DOX. While limited accumulation was observed in tumor tissue after intravenous injection in animal studies, intratumoral administration provided high selectivity, achieving an accumulation of ≈56 target/neighboring tissue with an ID/g of 86.7%. In conclusion, 99mTc-DOX-loaded GA-AuNPs have been evaluated as a promising theranostic candidate due to their pH-sensitive release, enhanced anticancer activity, high intratumoral accumulation, and imaging capability (El-Ghareb et al., 2020).

Alshammari et al., (2021) synthesized gold nanoparticles by evaluating ceftriaxone as both a reducing and capping agent, addressing the rapidly increasing resistance to third-generation cephalosporins like ceftriaxone, particularly during the COVID-19 pandemic, due to the misuse and overuse of antibiotics in recent years. In UV-Vis analysis, it was determined that the absorption band of GNPs at 520 nm in ceftriaxone-loaded CGNPs shifted to 536 nm and an additional band formed at 241 nm. DLS results showed that the particle size increased from 51.6 nm to 95 nm, and the zeta potential values changed from -16.6 mV to -25.7 mV. SEM and TEM images confirmed the spherical morphology, with core sizes found to be ~10 nm and ~21 nm, respectively. FTIR analysis supported the drug-gold interaction, and UV-Vis and HPLC determined an 80% loading efficiency. In antibacterial tests, CGNPs showed lower MIC50 values (0.9-1.6 μg/mL) against E. coli, S. aureus, S. abony, and K. pneumoniae compared to pure ceftriaxone, while pure GNPs were ineffective. The strong effect is explained by the fact that nanoparticles can carry more drugs due to their high surface area, increase the permeability of bacterial cell membranes, and saturate and neutralize resistance enzymes. In conclusion, loading ceftriaxone onto gold nanoparticles approximately doubled the drug's antibacterial potential and presented a promising method for addressing the issue of resistance. However, it is stated that in-vivo distribution and toxicity studies are needed for these nanoformulations to be translated into clinical practice (Alshammari F. et al., 2021).

Silver Nanoparticles

Silver, used for antimicrobial purposes for approximately 5000 years, exhibits properties such as high electrical/thermal conductivity in bulk form, but shows differences as the size decreases, including a lower melting

point, UV-Vis band broadening, and increased surface reactivity. Surface charge (zeta potential), factors such as chemical composition (e.g., Ag, Ag_2O, Ag_2S), and shape directly affect the behavior of these particles in a biological environment (Pryshchepa et al., 2020; Panja et al., 2021). AgNPs exhibit strong antioxidant properties due to their ability to neutralize free radicals, and with these properties, they can provide protective effects against aging, inflammation, cancer, and neurodegenerative diseases. The flavonoids and polyphenols contained in AgNPs synthesized with plant extracts support their antioxidant activities. They are also effective against parasitic infections; they can prevent the multiplication of parasites such as helminths and Leishmania species by arresting their cell cycle. They are also evaluated as anti-inflammatory, antidiabetic, as an acetylcholinesterase inhibitor in Alzheimer's treatment, and as an infection preventive in wound dressings and implants (Mikhailova, 2020). In wound healing, they promote angiogenesis by supporting tissue regeneration and reducing scar formation (Jaswal and Gupta, 2023).

In the chemical synthesis of AgNPs, Ag^+ ions are converted to Ag^0 using reducing agents such as sodium borohydride, ascorbic acid, or citric acid; stabilizers like PVP and CTAB prevent agglomeration. Photochemical, electrochemical, microwave-assisted, and sonochemical methods are sub-techniques (Jaswal and Gupta, 2023). Physical methods include microwave, laser ablation, electric arc discharge, ball milling, and evaporation-recondensation. Although solvent-free pure particles can be obtained, high energy consumption and the need for special equipment are limiting factors (Nie et al., 2023). In the biological synthesis of AgNPs, *Fusarium* species can be used with cell wall enzymes, while *Bacillus* and *Penicillium* species can be used in extracellular synthesis (Dawadi et al., 2021). Plant extracts are also effective in reduction and stabilization; for example, AgNPs obtained with *Cestrum nocturnum* leaf extract showed strong antioxidant potential due to their small size and surface properties (Keshari et al., 2020).

The increasing number of bacteria developing resistance to antibiotics has drawn attention to the use of AgNPs with antibacterial effects as drug delivery systems, as an alternative solution to enhance targeted delivery. In the study conducted by Kaur et al. (2019), silver nanoparticles were synthesized using the chemical reduction method with trisodium citrate, and vancomycin was loaded onto the surface of these nanoparticles. Citrate acted as both a reducing agent and a stabilizer. The shift in surface plasmon resonance in UV-vis analysis, the observation of new functional groups in FTIR, small changes in crystal structure in XRD analysis, and the surface morphology in TEM images indicate that vancomycin is bound to AgNPs. In the agar diffusion tests performed, vancomycin-coated AgNPs showed higher antibacterial activity against both Gram-positive (*Staphylococcus aureus*) and Gram-negative

(*Escherichia coli*) bacteria. Even in E. coli strains where vancomycin alone is ineffective, an antibacterial effect was observed when used in combination with AgNPs. This is also an important indicator of the synergistic effect. The underlying mechanisms of this effect include the binding of silver ions to the cell membrane, disrupting DNA and protein functions, and the destruction of cell structures through the production of ROS. Additionally, in cytotoxicity tests conducted, these nanocomposites were shown to be non-harmful to mammalian cells at specific concentrations. In conclusion, this study demonstrates that vancomycin-coated silver nanoparticles can serve as an effective alternative to antibiotics against antibiotic-resistant bacteria and can be safely utilized as a drug delivery system. The developed Van@citrate-AgNP system can be utilized in targeted antibacterial therapy applications with modifications (Kaur et al., 2019).

Nikolova et al. (2023) used silver nanoparticles (AgNP) for the safe and controlled delivery of phenindione. It was determined that the phenylindione-loaded AgNPs synthesized by the galactose reduction method are spherical, 20-30 nm in size, and stable. DFT calculations revealed a weak hydrogen bond-based interaction between phenindione and AgNPs, indicating that this structure facilitates controlled release. In drug release experiments, it was confirmed that the nanoparticle system released phenindione slowly and steadily. In antimicrobial tests, AgNPs loaded with phenindione were effective against Gram-positive bacteria, while in cytotoxicity analyzes, they exhibited a moderate antiproliferative effect on leukemia cells. In anticoagulant tests, free phenindione carries an excessive bleeding risk, while phenindione-loaded AgNPs showed a safer anticoagulant profile by prolonging PT and APTT times by approximately 1.5 times. Ex vivo smooth muscle experiments confirmed the controlled release of phenindione from nanoparticles and showed a delayed but sustained spasmolytic effect compared to the free form. These results indicate that fenindione-loaded AgNPs offer a promising drug delivery system with anticoagulant, antimicrobial, and spasmolytic properties (Nikolova et al., 2023).

Stoyanova et al. (2025) used silver nanoparticles (AgNPs) as drug carriers for the targeted delivery of mebeverine to the colon in the treatment of irritable bowel syndrome (IBS). AgNPs synthesized by the fructose reduction method were loaded with mebeverine and its analog. TEM analysis showed particle sizes in the range of 84-95 nm, while DLS and zeta potential revealed that stable structures were obtained. In cytotoxicity tests performed on HepG2 cells, AgNPs without the drug showed the highest toxicity, while mebeverine-loaded AgNPs exhibited lower toxicity. In the genotoxicity analysis, mild DNA damage and an increase in oxidative stress were detected, especially in AgNPs loaded with the analog, after 72 hours of exposure. Molecular docking studies have shown that mebeverine analog-loaded AgNPs have the

strongest binding affinity for the VEGFR2 protein. In conclusion, mebeverine and its analog-loaded AgNPs hold promise as targeted drug delivery systems for the treatment of IBS. However, it is emphasized that the cytotoxic and genotoxic effects should be carefully evaluated depending on duration and dose (Stoyanova et al., 2025).

Due to the serious side effects and development of resistance caused by methotrexate (MTX), Rozalen et al. (2020) developed a study as an alternative approach. In this study, AgNP-MTX (silver nanoparticles loaded with methotrexate) were synthesized by controlling temperature and pH using $NaBH_4$ and trisodium citrate (TSC) as reducing agents, resulting in spherical AgNPs with a narrow size distribution of approximately 13 nm. FTIR and XPS analyses confirmed that MTX binds to AgNPs via its carboxyl group, with a loading rate of 28-40%. In drug release tests, free MTX followed first-order kinetics, while AgNP-MTX release was found to fit the Higuchi model and showed diffusion-controlled release. In cytotoxicity tests, AgNP-MTX provided a higher effect at a lower dose compared to free MTX, especially in colorectal cancer cells (HTC-116). The activity in lung cancer cells (A-549) remained at a lower level. It was thot that the increased activity in HTC-116 cells could be related to folate receptors. In zebrafish (Danio rerio) tests, free MTX caused toxic effects, cardiac edema, and morphological abnormalities in early-stage embryos, while AgNP-MTX formulations showed significantly lower toxicity at the same concentrations. In embryos treated with AgNP-MTX, the mortality rate decreased, there was no change in heart rate, and developmental abnormalities remained at a minimal level. This study demonstrated that methotrexate can be released in a controlled manner with the aid of AgNPs, reducing its toxicity and increasing its efficacy against cancer cells. This system can widen the therapeutic window of MTX, offer effective treatment with lower doses, and carry a lower risk of systemic side effects during chemotherapy (Rozalen et al. 2020).

Hussein-Al-Ali et al. (2022) synthesized alginate-coated AgNPs to increase the bioavailability of low-solubility ciprofloxacin (Cipro) and achieve controlled release, and developed a new nanocomposite by loading Cipro onto their surfaces. XRD analyzes showed that both AgNPs and Cipro-AgNPs have a crystalline structure, and the particle size increased from 85 nm to 100 nm after loading. FT-IR results confirmed that Cipro binds to AgNPs via hydrogen bonds mediated by alginate. In TGA analyzes, Cipro-AgNPs showed a three-stage mass loss, and the Cipro content was calculated to be approximately 22%. The zeta potential of Cipro-AgNPs is +6.5 mV, indicating suspension stability. SEM images showed needle-like and nodular structures prone to clustering, while TEM images revealed spherical shapes with an average size of 96 nm. The drug loading capacity was found to be 26.3%, a two-stage profile was obtained in the release experiments, and 98% release occurred after 770

minutes. This process followed the Hixson-Crowell kinetic model, and the dissolution time was calculated to be 407.5 minutes. According to the MTT assay results, neither AgNPs nor Cipro-AgNPs showed any toxic effect on 3T3 cells. In conclusion, it was found that Cipro-AgNP nanocomposites offer a safe drug delivery system with a crystalline structure, an average size of 100 nm, a high drug loading capacity, sustained and controlled release, and no toxicity. These features make the nanocomposites in question a promising candidate for pharmaceutical applications, particularly for increasing the bioavailability of antibiotics with low solubility (Hussein-Al-Ali et al., 2022).

Although colistin (Col) is a potent antibiotic against Gram-negative bacteria, its clinical use is limited due to nephrotoxicity. Muenraya et al. (2022) loaded colistin onto silver nanoparticles to achieve a stronger antibacterial effect and reduced toxicity. Col-AgNPs were synthesized by reducing silver nitrate with $NaBH_4$, using sodium dodecyl sulfate (SDS) as a stabilizer. Analyzes have shown that AgNPs contain a crystalline silver core and their size increases with the colistin coating. Formulation F3 provided small, homogeneous, and long-term stable particles; the drug loading rate varied between 10-20%. In antimicrobial tests, Col-AgNPs exhibited lower MIC/MBC values and wider inhibition zones against *E. coli, K. pneumoniae*, and *P. aeruginosa* compared to plain AgNPs and free colistin. In mechanism studies, it was determined that bacteria disrupt the membrane structure to form pores, leading to cytoplasmic leakage and DNA damage. In safety tests, Col-AgNPs were found to be safe in the range of 0.5-16 μg/mL, and although toxicity increased at 32 μg/mL, they were less harmful compared to bare AgNPs. The coating structure has limited silver ion release and oxidative stress. In conclusion, Col-AgNPs enhanced the efficacy of colistin by combining its target binding property with the antimicrobial effects of silver, and were found to be safe at low-to-moderate doses. Although high-dose toxicity and low drug loading rate pose limitations, it is a promising candidate against resistant bacteria (Muenraya et al., 2022).

Steckiewicz et al. (2022) developed two new drug delivery systems by conjugating silver nanoparticles (AgNP) with chlorhexidine (CHL) and metronidazole (MET to overcome the limitations of existing treatments: AgNP-CHL and AgNP-PEG-MET. Nanoparticles synthesized by the sodium borohydride reduction method were found to have diameters of ~13 nm and ~4 nm, respectively, in TEM analyzes. DLS and TGA data showed that CHL provided a thick stabilization layer, while MET stabilized by PEG adhered strongly to the silver surface. Both conjugates exhibited strong antimicrobial activity against Gram-positive/negative bacteria and *Candida albicans*. While AgNP-CHL is effective at low concentrations, especially against *Staphylococcus epidermidis*, AgNP-PEG-MET has been found to be more advantageous against Gram-negative bacteria and fungi. Cytotoxicity tests

revealed that AgNP-CHL is safe in the range of 0-0.5 μg/mL, while AgNP-PEG-MET is biocompatible in the range of 0-10 μg/mL. Both structures have been shown to reduce levels of inflammatory cytokines (IL-1β, IL-6, TNFα) as well as MMP3 and MMP8, thus potentially contributing to the prevention of tissue destruction in the treatment of periodontitis. In conclusion, AgNP-CHL offers a stronger antimicrobial effect, while AgNP-PEG-MET provides higher biocompatibility, and further in vivo studies are needed to clinically validate these findings (Steckiewicz et al., 2022).

While current treatments for ulcerative colitis include sulfasalazine (SSZ) and anti-TNF-α drugs, their efficacy is limited and side effects are observed. Therefore, Asgharzadeh et al. (2021) aimed to develop a more potent and tolerable treatment approach by loading sulfasalazine onto silver nanoparticles (SSZ-AgNP). In the study, silver nanoparticles were synthesized using ascorbate and citrate, then their surfaces were functionalized with APTES, and sulfasalazine was bound via DCC/NHS. FT-IR analysis showed characteristic peaks for citrate, Si-O-Si, and drug binding; PXRD confirmed the face-centered cubic silver phase. FESEM images showed a spherical morphology and an increase in particle size with drug loading. EDX results showed a homogeneous distribution of Ag, Si, and S elements. In preclinical evaluation, the application of SSZ-AgNPs in a colitis model induced by dextran sodium sulfate (DSS) reduced disease activity index by decreasing weight loss, diarrhea, and rectal bleeding. Colon shortening was prevented, the colon weight/length ratio improved, and histologically, inflammatory cell infiltration, edema, and crypt loss were reduced. At the molecular level, SSZ-AgNP treatment suppressed oxidative stress; increased thiol levels, catalase, and SOD activities; and decreased MDA levels. Additionally, the expression of TNF-α, IFN-γ, and profibrotic genes was suppressed, and the spleen-to-body weight ratio decreased. As a result, the SSZ-AgNP structures showed a stronger anti-inflammatory and antifibrotic effect compared to free sulfasalazine. Improvements in clinical, histological, and molecular parameters indicate that this nano-drug system is a promising candidate for ulcerative colitis treatment and should be supported by future clinical studies (Asgharzadeh et al., 2021).

Zinc Oxide Nanoparticles

Zinc oxide nanoparticles (ZnO-NPs) exhibit a wide variety of morphologies, ranging from spherical structures to three-dimensional flower, hedgehog, and snowflake shapes (Jiang et al., 2023). ZnO exhibits semiconductor properties, remains stable at high temperatures, is effective at neutral pH, and has antimicrobial effects (Al Jabri et al., 2022). Its chemical stability, broad light absorption, and strong electrochemical bonding capacity make it versatile. ZnO-NPs can be produced by chemical, physical,

and biological methods. The most commonly used substrates in biological synthesis are plants; leaf, root, seed, and fruit extracts reduce and stabilize Zn(II) ions with compounds such as phenolic acid, flavonoids, and saponins (Bandeira et al., 2020). Increasing the amount of plant extract and zinc acetate reduces particle size and increases yield (Gnanasekaran et al., 2024). While enzymes and proteins in bacteria carry out reduction, some species trigger the formation of $Zn(OH)_2$ and $[Zn(NH_3)_4]^{2+}$ by producing ammonia. In intracellular synthesis, ions are taken up and reduced by the cell; however, cell lysis is required to obtain nanoparticles (Bandeira et al., 2020). Algae, on the other hand, perform reduction with hydroxyl and carboxyl groups (Elrefaey et al., 2022). While laser ablation is a physical method for producing homogeneous-sized ZnO-NPs, mechanical grinding is low-cost but has poor size control. The one-step solid-state method relies on the sintering of zinc salts at high temperatures. Among chemical methods, direct precipitation forms $Zn(OH)_2$ and annealing yields ZnO-NP; homogeneous precipitation allows for controlled crystal growth. The hydrothermal method is advantageous for controlling size and crystal structure. The sol-gel method produces ZnONPs through the hydrolysis of alkoxides or salts; in its environmentally friendly versions, natural resources like black tea can be used. Additionally, deposition using templates and liquid phase methods offers advantages in functionalization and porous structure. Zinc oxide nanoparticles are used in biomedical, optoelectronic, sensor, and photocatalysis applications due to their high surface area, biocompatibility, and low toxicity properties (Jiang et al., 2023). By altering the permeability of the cell membrane, the ZnONPs that enter the cell cause oxidative stress within the cell, leading to the death of the bacteria. Their effectiveness against pathogens such as *Listeria*, *E. coli*, and *S. aureus* has been proven. It extends shelf life by inhibiting microbial growth, especially in products like fruit juice and sauces (Mwafy et al., 2023). In medicine, ZnO-NPs, due to their small size, penetrate tumors and exhibit selective effects, and are used for biomarker delivery and imaging. ZnO-NPs coated with polymethyl methacrylate are successful in detecting low-density biomarkers (Mandal et al., 2022). It also offers alternative treatments for antibiotic-resistant bacteria, supports immunity in animal feed, and prevents infection. It improves quality by preventing taste and aroma loss in foods and providing controlled release (Zhou X.-Q. et al., 2023).

To overcome the low bioavailability of curcumin, Perera et al. (2020) synthesized different ZnO morphologies (spherical, rod, spear, short and long leaf) and loaded curcumin onto their surfaces. The highest loading rate was achieved in long-leaf ZnO nanocomposites due to their large surface area. In antibacterial tests, ZnO-curcumin nanocomposites (ZNP-C) provided strong inhibition against both Gram-positive and Gram-negative bacteria, and were found to be more effective compared to using ZnO or free curcumin

alone. The global (SZNP-C) and rod (RZNP-C) forms showed the strongest antibacterial effect. In MTT assays performed on a rhabdomyosarcoma cell line, ZNP-C was found to have lower EC50 values compared to free curcumin and bare ZnO nanoparticles, indicating higher anticancer activity even at lower doses. The most effective results were obtained in spear and spherical forms. Cytotoxicity analyzes performed on HEK293 healthy kidney cells revealed that ZNP-Cs were less toxic than drug-free ZnO nanoparticles. The lowest toxicity was observed in the global form, which proved to be the most effective structure against cancer cells while having the least impact on healthy cells. In conclusion, ZnO-curcumin nanocomposites stand out as a promising nanoformulation with synergistic properties, enhancing both antibacterial and anticancer activity. This system holds potential as an antibiotic-free treatment and as a supportive agent in cancer therapy (Perera et al., 2020).

Although cisplatin (Cp) and gemcitabine (Gem) are potent anticancer agents, their high toxicity limits their clinical use. With the ZnO-NP(Cp/Gem) system developed by Hu and Du (2020), these drugs were loaded onto ZnO nanoparticles simultaneously, resulting in spherical structures with a diameter of approximately 20 nm. DLS analysis showed that the particles remained stable for 48 hours. According to the MTT results, the ZnO-NP(Cp/Gem) group showed higher cytotoxicity against A549 lung cancer cells compared to Cp, Gem, or their combinations alone. Intracellular ROS levels reached their highest level in this group, while GSH levels significantly decreased. This situation indicates that DNA damage and apoptosis are triggered through oxidative stress. In vivo experiments on immunosuppressed mice showed that the ZnO-NP(Cp/Gem) group maintained tumor development at the lowest level compared to all other groups. The solubility of ZnO nanoparticles in acidic environments, their biocompatibility, and the EPR effect allow them to accumulate in tumor tissues, making them advantageous for targeted drug delivery. In conclusion, the ZnO-NP(Cp/Gem) system provided a synergistic anticancer effect by enhancing the efficacy of chemotherapy drugs under both in vitro and in vivo conditions, and triggered cell death through oxidative stress and apoptosis. These findings indicate that ZnO-NP-based systems offer a promising nano-drug carrier platform for lung cancer treatment (Hu and Du, 2020).

Due to the colonization of pathogenic bacteria, leading to fever and septic shock, and further complicating the healing process, Saddik et al. (2022) developed an azithromycin (AZM)-loaded zinc oxide review to address the need for pharmaceutical materials that accelerate the healing of infected wounds. ZnONPs were synthesized by combining precipitation and calcination methods; subsequently, AZM was adsorbed onto their surfaces. The average diameter of pure ZnONPs was determined to be 34 nm, while the diameter of AZM-loaded ZnONPs was 39 nm. It was concluded that

adsorption occurs in multiple layers on heterogeneous surfaces, based on the Freundlich isotherm model. The maximum loading capacity was found to be 160.4 mg/g. In in vitro release experiments using dialysis, it was observed that AZM-ZnONP formulations released the drug rapidly and in a controlled manner. It has been found that the loading efficiency and release amount increase, especially at high AZM concentrations. The optimal production conditions were determined using a Box-Behnken design. It was found that AZM-ZnONP formulations showed superior antibacterial activity against both Staphylococcus aureus (MRSA) and *Escherichia coli* compared to free AZM and ZnONPs, as determined by diffusion and minimum inhibitory concentration (MIC) tests. MIC values were found to be significantly lower for AZM-ZnONP. In studies on a wound model in rats, the hydrogel formulation containing AZM-ZnONP provided faster wound closure, lower bacterial load, and better tissue regeneration compared to other treatments. In histological analyzes, the increase in epidermal thickness and collagen fibers was significantly improved in the group treated with AZM-ZnONP. In conclusion, AZM-loaded ZnONPs have the potential to be an alternative to conventional treatments due to their advantages, such as high antibacterial activity, rapid tissue regeneration, and low toxicity (Saddik et al., 2022).

Akbarian et al. (2020) synthesized ZnO nanoparticles using an environmentally friendly method with *Camellia sinensis* extract to increase the bioavailability of low-resolution PTX and loaded PTX by coating it with chitosan (Ch). XRD analysis showed a pure hexagonal crystal structure and a size of ~11 nm; FESEM and TEM confirmed the spherical morphology and chitosan coating. TGA results revealed chitosan degradation and the presence of PTX; FTIR analyzes showed OH, NH, and amide groups. Drug release tests have shown that over 90% of PTX is released within the first 2 hours. Morphological alterations, apoptosis, and vacuolization were observed in MCF-7 breast cancer cells, while limited effects were seen in fibroblasts at the same doses. MTT analysis showed that ZnO-Ch-PTX structures were more potent against MCF-7 cells and less toxic to fibroblasts compared to free PTX. Apoptosis assays increased early and late apoptosis in cancer cells while producing no significant changes in fibroblasts. In conclusion, ZnO-Ch-PTX nanocarriers produced by green synthesis showed a strong cytotoxic and apoptotic effect on cancer cells and reduced side effects on healthy fibroblast cells. This biodegradable ZnO and chitosan-based system holds promise as a safe anticancer drug delivery platform by increasing the efficacy of PTX (Akbarian et al., 2020).

Iron Oxide Nanoparticles

Iron oxide nanoparticles (IONPs) are widely used in biomedical applications due to their biocompatible structure. Iron oxides can exist in various polymorphs of which α- Fe_2O_3 (hematite), γ-Fe_2O_3, β-Fe_2O_3 (maghemite),

and γ-Fe_2O_3, Fe_3O_4 (magnetite) are crystalline (Ezealigo et al., 2021). γ- $Fe_2O_3$is ferrimagnetic and is used as an MRI contrast agent, for drug delivery, and in hyperthermia, while α- $Fe_3O_4$is evaluated in catalysis and sensors due to its high corrosion resistance. Fe_3O_4, on the other hand, stands out for its ferrimagnetic structure; it exhibits superparamagnetic properties at sizes below 6 nm (Kumar et al., 2021). Sensing methods determine size, shape, and magnetic properties (Ogebzode et al., 2023). Especially, IONPs with a size of 3-15 nm offer significant advantages in targeted drug delivery and therapy due to their transient magnetization properties under an external magnetic field (Samrot et al., 2021). Chemical techniques are the most common methods for producing iron oxide nanoparticles; physical and biological methods are used more sparingly. The sol-gel method relies on the evaporation of water to cause the colloidal solution to gel, and it typically produces particles with a size of 15-50 nm. The main starting materials are iron alkoxides and iron salts. In the co-precipitation method, ferric and ferrous ions are mixed in a basic medium; non-toxic particles suitable for biomedical applications in the range of 5-40 nm are obtained. Although suitable for mass production, size control is difficult (Hernandez-Hernandez et al., 2020). Sonochemical methods allow for the control of core size and magnetic properties in the production of IONPs using ultrasonic radiation (Lüdtke-Buzug and Penxová, 2019). Biosynthesis, on the other hand, produces environmentally friendly and biocompatible nanoparticles from phytochemicals of bacterial and plant origin (Kumar et al., 2021). IONPs can be used as theranostic agents, providing both diagnosis and treatment simultaneously. While MRI contrast agents are widely used, particle size and shape play a significant role in their ability to penetrate and target tissues. They are particularly effective in targeted therapies as drug delivery systems, especially in cancer treatment (Rahman, 2023). Antifungal agents nystatin and miconazole, when functionalized with chitosan-coated IONPs, provide controlled and sustained release through electrostatic interactions (Arias et al., 2020). Fluorescently labeled IONPs can be used for protein detection and biological analysis, while silica or polymer coatings increase stability, reduce toxicity, and facilitate biological distribution.

Curcumin triggers DNA damage in HeLa cells and activates p53 and H2A. It facilitates the translocation of Xser140 proteins from the cytoplasm to the nucleus. However, due to curcumin's low bioavailability and rapid metabolism, it is difficult to completely eliminate tumor cells. Alternatively, Farani et al. (2022) are attempting to enhance the suppressive effect of curcumin on cancer by developing curcumin-loaded iron oxide nanoparticles. The ability of folic acid to bind to folate receptors, which are highly present in cancer cells, allows these nanoparticles to interact more effectively with tumor cells. Therefore, HPG@Fe_3O_4 nanoparticles modified with folic acid to target cancer cells increased curcumin loading capacity and showed higher

cytotoxicity against cancer cells. HeLa cells were examined using the MTT assay, and it was observed that nanoparticles loaded with curcumin led to higher toxicity compared to free curcumin. Additionally, the effectiveness of these nanoparticles was also evaluated in MRI tests, and an increase in T2-weighted signal intensity was observed. This indicates that folic acid-modified nanoparticles hold potential for cancer diagnosis. In conclusion, folic acid-modified HPG@Fe_3O_4 nanoparticles, curcumin, and other therapeutic agents stand out as promising tools for cancer treatment and diagnosis. These nanoparticles may contribute to the development of targeted therapies and serve as a potential therapeutic agent in the treatment of cervical cancer (Farani et al., 2022).

In order to transport DOX, which has limited efficacy in the treatment of glioblastoma multiforme (GBM), to brain tissue, Norouzi et al. (2020) developed iron oxide nanoparticles stabilized with EDT (EDT-IONP). Thanks to the negatively charged carboxyl groups, DOX was loaded and release was controlled. The average core size is ~4.7 nm, while the hydrodynamic diameter reached 75.5 nm after loading. TEM, FTIR, EDX, and XRD analyzes confirmed the structural integrity of the magnetite/maghemite phase. In vitro results showed that DOX-EDT-IONPs were taken up 2.8 times more by U251 GBM cells compared to free DOX, and the application of a magnetic field increased uptake. This structure has overcome P-gp-mediated drug resistance, suppressed DNA repair genes (Top II, Ku70), and activated apoptosis and tumor suppressor genes (Caspase 3, p53, MEG3, GAS5). ROS production, DNA damage (increased γ-H_2AX), and actin disruption were among the mechanisms. Drug release showed a sustained release lasting 4 days at neutral pH, and a rapid release reaching 64% early on in an acidic environment. In the BBB-GBM common culture model, better barrier penetration was achieved compared to free DOX; in the combination of transient barrier opening with ADTC5 peptide and magnetic field support, penetration and cytotoxicity were significantly increased. In conclusion, the DOX-EDT-IONP system offers a promising nano-drug delivery platform that could serve as an alternative to traditional chemotherapy in GBM treatment, with properties that facilitate BBB passage, controlled release, and magnetic guidance (Norouzi et al., 2020).

To reduce the side effects associated with high-dose phenytoin (PHT) use, Ghane et al. (2024) developed a "core-double shell" nanoparticle system consisting of silica and gelatin-coated superparamagnetic Fe_3O_4 cores. This structure offered both pH-sensitive controlled release and magnetic field targeting properties, and also showed potential as an MRI contrast agent. The nanoparticles were produced with an average size of 41 nm, FTIR and XRD analyzes provided structural confirmation, and VSM results showed that superparamagnetic properties were preserved. Zeta potential measurements confirmed the successful formation of layers and biological stability. The PHT

loading capacity was found to be 2.01%, and the encapsulation efficiency was 10.05%. In the 24-hour release, 84% of the drug was released at physiological pH and 89% at acidic pH, indicating that this could lead to faster drug delivery in epileptic foci. The release kinetics were found to be consistent with Fickian diffusion. MTT analysis determined that the nanoparticles did not exhibit cytotoxicity for up to 3 days. In conclusion, the superparamagnetic nanoparticle system with a core-double shell structure developed in this study stands out as a potential carrier system that can achieve targeted, pH-sensitive, controlled drug release and is MRI-traceable, making it suitable for the treatment of brain diseases such as epilepsy (Ghane et al., 2024).

To reduce the side effects and increase the efficacy of tamoxifen (TMX), Rostami et al. (2022) loaded the drug onto L-lysine-coated magnetic Fe_3O_4 nanoparticles. Cores approximately 9-30 nm in size were stabilized with L-lysine, while TMX was bound to the surface thru hydrogen bonds and adsorption. The hydrodynamic diameter is ~154 nm, and the magnetic properties are preserved. In drug release tests, free TMX dissolved rapidly, while F-Lys-TMX showed controlled release, exhibiting slow release at pH 7.4 and accelerated release under acidic conditions. In biological tests, F-Lys-TMX exhibited a stronger antiproliferative effect with lower IC_{50} values compared to free TMX, increased apoptosis (58.6%), arrested the cell cycle at G0/G1, and elevated Caspase-3/9 activation. In conclusion, F-Lys-TMX nanoparticles are more effective at lower doses compared to free TMX, and their controlled release and biocompatible magnetic structure make them a promising drug delivery platform for breast cancer treatment (Rostami et al., 2022).

Copper Oxide Nanoparticles

Copper oxide (CuO) exhibits semiconductor properties and, due to its physical characteristics, has applications in many fields such as field emission, high-temperature superconductors, catalysts, sensors, and batteries (Sarfraz et al., 2020). The high surface-to-volume ratio of CuO makes it very reactive and allows it to interact easily with other materials. Additionally, the moderate band gap, good catalytic activity, and high optical transparency of CuO further expand its industrial applications (Keabadile et al., 2020). In recent years, CuO nanoparticles have shown antimicrobial activity and the ability to cross biological membranes and reach target organs (Sarfraz et al., 2020). Copper, a cheap and highly efficient reactive catalyst, is an essential element for humans and is also found in enzymes such as superoxide dismutase, cytochrome oxidase, and tyrosinase. For these reasons, copper and/or copper oxide nanoparticles are attracting significant interest in terms of their biological activity research and synthesis (Kolahalama et al., 2022). Copper nanoparticles (CuNPs) are synthesized using methods such as chemical reduction, sol-gel, laser ablation, and electrical discharge (Salman M. et al.,

2025). Among physical methods, pulsed laser ablation in liquid relies on the vaporization of a copper metal target by high-energy laser pulses, producing high-purity and controlled-size CuO-NPs in a liquid medium. This method is important in optical, electronic, and biotechnological applications due to particle size and shape control (Naderi-Samani et al., 2024). Gelation is achieved by heating a solution of copper (II) nitrate and NaOH, followed by drying and calcination, to obtain CuO-NPs chemically (Patel et al., 2022). This type of CuO-NPs is used in cancer treatment, radiotherapy, and diagnostic applications (Salman et al., 2025). In biosynthetic methods, plants, fungi, algae, and bacteria act as reducing/stabilizing agents. Plant extracts reduce Cu^{2} ions thru flavonoids, phenols, proteins, and terpenoids, providing rapid, simple, and homogeneous-sized production (Chakraborty et al., 2022). For example, CuO-NPs synthesized with *Solanum nigrum* leaf extract are effective in photocatalytic and biomedical applications (Muthuvel et al., 2020). CuO nanoparticles exhibit antibacterial activity against bacterial strains such as *Staphylococcus aureus*, *Bacillus circulens* BP2, *Escherichia coli*, and *Pseudomonas aeruginosa* (Sarfraz et al., 2020; Balcucho et al., 2020). CuO nanoparticles are used in the detection of biomolecules such as cholesterol and DNA sequences, and in the analysis of HIV drugs. (Safraz et al., 2020; Tavakoli and Hashemzadeh, 2020). CuO nanoparticles selectively induce apoptosis in tumor cells and inhibit the growth of cancer cells. These nanoparticles are used in various types of cancer, including prostate, eye, breast, liver, brain, kidney, and lung (Sarfraz et al., 2020; Dey et al., 2020).

In a study conducted by Mohammadhassan et al. (2022), CuO nanoparticles were synthesised using a chemical method, combined with MTX, and coated with bovine serum albumin (BSA) to obtain the CuO@ BSA-MTX structure. TEM images showed that the average diameter of the nanoparticles was 23.78 nm and that they exhibited spherical, uniform morphological structures. AFM analysis showed that the BSA-MTX coating successfully bound to the CuO surface and the particle thickness increased from 13 nm to 44 nm. FT-IR and UV-vis spectra also confirm the interaction between CuO and BSA-MTX. Drug release studies showed that after 96 hours, 75% of MTX was released in the presence of proteinase K enzyme, while only 25% was released in its absence. These results indicate that the system is enzyme-responsive and provides controlled release. Cytotoxicity analyses revealed that the CuO@BSA-MTX structure exhibited a stronger anticancer effect on the MDA-MB-231 human breast cancer cell line compared to free MTX, while drug-unloaded CuO was non-toxic. This study demonstrates that CuO@BSA-MTX nanoparticles are a promising drug delivery system with controlled drug release and enhanced anticancer effects, and that their therapeutic benefit may be even more pronounced in vivo (Mohammadhassan et al., 2022).

Dutta et al. (2024) developed a 5-Fluorouracil (5-FU)-loaded pectin/xanthan gum-based gel (PXFCu6) using CuO nanoparticles (CuONP) produced by a green synthesis method with *Trichosanthes dioica* seed extract. The average size of the nanoparticles was found to be 26 nm, with a zeta potential of –23.7 mV and a spherical morphology. FTIR, viscosity, spreadability, pH, and stability tests confirmed the suitability of the formulation for vaginal application. In-vitro release tests have shown that the addition of xanthan gum extends drug release for up to 8 hours. In MTT cytotoxicity assays, PXFCu6 gel showed 3.62 and 1.63 times higher anticancer activity compared to free CuONPs and 5-FU, respectively. In antibacterial tests, an inhibition zone of 52.05 ± 1.37 mm was obtained against *E. coli*. While the gel remained stable at 4°C, slight degradation was observed at 25°C. The results indicate that the biocompatible and biodegradable carrier system can both induce apoptosis in HeLa cells, thereby increasing anticancer efficacy, and reduce the risk of infection during treatment due to its antibacterial properties. These findings indicate that the PXFCu6 gel formulation is a promising candidate for the local treatment of cervical cancer (Dutta et al., 2024).

Palladium Nanoparticles

Palladium (Pd) is classified as a Platinum Group Metal (PGM) along with platinum (Pt), rhodium (Rh), ruthenium (Ru), iridium (Ir), and osmium (Os). The elements in this group generally exhibit similar chemical properties, with Pd being the element with the lowest density and melting point within this group (Joudeh et al., 2022).

PdNPs are synthesized using chemical, physical, and biological methods. To prevent agglomeration, support materials such as metal oxides, silica, polystyrene, and carbon nanotubes are used; alloying with Cu, Ru, Ni, and Co increases catalytic activity and reduces costs. Techniques such as physical vapor deposition and laser ablation provide particle size control (Alaqarbeh et al., 2023; Salman et al., 2023). In the chemical reduction method, stabilizers (e.g., PVP) play a critical role in size control (Ortega-Murcia et al., 2020). Sonochemical methods provide reduction through ultrasonic cavitation, while shape and size control can be achieved with agents like PVP and N-BCNT (Prekob et al., 2020; Alaqarbeh et al., 2023). Additionally, the production of PdNPs with sizes of 5-6 nm is possible through supercritical fluid nucleation and the sol-gel method (Alaqarbeh et al., 2023). In biological synthesis, plants, bacteria, algae, and fungi are used as reducing/stabilizing agents. Polyphenols, alkaloids, terpenoids, and flavonoids found in plant extracts affect nanoparticle morphology. Successful syntheses have been reported with *Cinnamomum camphora*, *Anacardium occidentale*, *Glycine max*, and *Catharanthus roseus* (Manjare et al., 2021). In bacteria, hydrogenase enzymes of the *Desulfovibrio desulfuricans* species play a critical role in the reduction

process (Macaskie et al., 2021). Additionally, the production of PdNPs is possible with algae and fungi; for example, the synthesis of PdNPs with sizes of 2-7 nm using *Botryococcus braunii* and 13-18 nm using *Agaricus bisporus* has been reported (Arya et al., 2020; Mohana and Sumathi, 2020). Due to their effective catalytic properties, Pd nanoparticles provide less catalyst usage compared to traditional catalysts in various organic reactions such as hydrogenation, carbon-carbon bond formation (Heck and Suzuki reactions), and petroleum cracking (Joudeh et al., 2022) Additionally, Pd nanoparticles are used in the electronic and biomedical fields in fuel cells, hydrogen sensing and storage systems, sensors, and photothermal applications, exhibiting strong antibacterial effects against bacteria such as *Staphylococcus aureus* and *Escherichia coli*, as well as an anticancer effect on human breast cancer cells (MCF7) (Alaqarbeh et al., 2023).

In a study by David and Sing (2025), the use of PdNPs as drug carriers was evaluated to reduce the off-target toxicity and side effects of chemotherapeutic agents such as DOX and 5-FU. DOX and 5-FU, previously encapsulated in a chitosan matrix, were loaded onto PdNPs synthesized by reducing a solution of dihydrogen tetrachloropalladate (H_2PdCl_4) with sodium borohydride and sodium citrate. Subsequently, targeted nanocomplexes were obtained by adding the transferrin protein. In the NTA analysis, the sizes of the chitosan-coated nanocomplexes were found to be between 98-174 nm. Zeta potentials were found to be above +15 mV, indicating high colloidal stability. The encapsulation efficiencies of DOX and 5-FU were calculated to be 74.81% and 72.63%, respectively. Controlled and pH-sensitive release was observed in an acidic environment (pH 4.2 and 5.2); the release rate of all drugs significantly increased compared to physiological pH. Dual drug-loaded nanocomplexes significantly increased ROS generation and apoptosis, particularly in HeLa cells. In HEK293 cells, low toxicity was observed. The dual system has shown a stronger anticancer effect compared to single-drug systems. Blocking T_f receptors resulted in a significant reduction in the uptake of nanocomplexes, which confirmed the T_fR-mediated cellular uptake mechanism. The transferrin-targeted PdNP-based dual drug delivery system synthesized within the scope of this study demonstrated high drug encapsulation capacity, pH-sensitive controlled release, effective anticancer activity, and low toxicity to healthy cells. This system, which targets Tf receptors, is considered a promising approach, especially in the treatment of cervical cancer (David and Sing, 2025).

PdNP and melatonin (MLT), which possess pro-oxidant and antioxidant properties, have the potential to increase chemotherapeutic efficacy. Gurunathan et al. (2020) reported that PdNPs synthesized via resveratrol (~10 nm, cubic crystal structure) reduced cell viability in A549 lung cancer cells in a dose-dependent manner when co-administered with MLT and doxorubicin

(DOX), while not causing significant toxicity in normal cells. Combination therapy has been shown to disrupt membrane integrity, with increased LDH leakage and elevated dead cell protease activity; and to increase oxidative stress, with elevated markers of ROS, MDA, LHP, NO, and oxidative DNA damage. In parallel with this, a decrease was observed in the antioxidant defense system (GSH, TRX, CAT, SOD, GPx, GST). Mitochondrial dysfunction was confirmed by decreased ATP levels, MMP loss, and reduced gene expression of PGC-1α, NRF2, and TFAM. Apoptosis was supported by AO/EB staining, DNA fragmentation, and increased expression of p53, p21, Bax, cytochrome c, and caspase-3 genes; Bcl-2 decrease and elevated caspase-9/-3 activities were particularly evident in the combination group. In conclusion, the combined use of PdNP and MLT offers a promising approach to lung cancer treatment thru the induction of oxidative stress and apoptosis (Gurunathan et al., 2020).

CONCLUSION

The studies examined have shown significant potential for metal and metal oxide-based nanoparticle drug delivery systems (palladium, copper oxide, iron oxide, zinc oxide, silver, and gold nanoparticles) in terms of increasing the effectiveness of chemotherapeutic drugs, reducing off-target toxicities, providing antibacterial effects, and offering controlled release mechanisms. When evaluated comparatively, each system has its own unique advantages and limitations.

Palladium nanoparticles (PdNPs), with transferrin targeting, achieved high encapsulation efficiency and pH-sensitive release of DOX and 5-FU, demonstrating a strong anticancer effect in HeLa cells. Melatonin-loaded PdNPs have created synergy through oxidative stress and apoptosis. While PdNPs are advantageous in terms of biocompatibility, long-term safety data are limited. Copper oxide nanoparticles (CuO NPs) produced stronger cytotoxicity with enzyme-responsive release in BSA-coated systems loaded with methotrexate compared to free drug; 5-FU-loaded gel formulations combined anticancer and antibacterial effects in local treatments. However, CuO NPs carry the risk of cytotoxicity at high doses, requiring biocompatibility optimization. Iron oxide nanoparticles (IONPs) stand out for their theranostic potential. Folic acid-curcumin systems increased cytotoxicity and MRI contrast; DOX-EDT-IONPs crossed the blood-brain barrier and were targetable with magnetic guidance. Structures loaded with phenytoin or tamoxifen have also provided controlled release. Nevertheless, production costs and bioaccumulation risks remain problematic. Zinc oxide nanoparticles (ZnO NPs) are attracting attention for their antibacterial and anticancer activities. Curcumin-loaded composites enhanced antimicrobial activity, while cisplatin and gemcitabine-loaded systems exhibited potent tumor suppression. Azithromycin-loaded ZnO NPs accelerated wound

healing, while paclitaxel-loaded green synthesized systems were effective against cancer cells. However, rapid release profiles necessitate long-term controlled release. AgNP and AuNP-based systems have different strengths. AgNPs inherently possess antibacterial properties and exhibit synergy with antibiotics, but genotoxicity and low loading percentage are limiting factors. AuNPs, on the other hand, stand out for their high biocompatibility, surface functionalization, and theranostic integration; in examples of DOX, paclitaxel, and hypericin, they have provided selective, pH-sensitive, and imaging-assisted release. However, liver/spleen accumulation and production scalability are obstacles to clinical use.

In conclusion, despite their immense potential, some challenges and safety concerns need to be addressed for MNP-based systems to be widely adopted in clinical settings. Among the fundamental topics are biocompatibility, cytotoxicity, biodistribution, metabolism, and excretion. The physicochemical properties of nanoparticles, such as size, shape, surface charge, and coating, play a critical role in determining their interactions with biological systems, including cellular uptake, immune response, and elimination pathways. The accumulation of metal nanoparticles in vital organs or their prolonged residence in the body can lead to oxidative stress, inflammation, or organ toxicity. Therefore, comprehensive toxicological assessments and long-term in vivo studies are necessary to determine safety profiles and regulatory approvals. As nanotechnology advances, the application of metal nanoparticles in drug delivery systems is expected to play a significant role in the future of personalized medicine, oncology treatment, and non-invasive therapeutic strategies.

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Chapter 6

PAIN MECHANISMS AND POSTOPERATIVE PAIN CONTROL IN BREAST SURGERY

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1.Introduction

Breast surgery is one of the most frequently performed surgical procedures for the treatment of both benign and malignant pathologies. Despite high success rates, procedures such as mastectomy, lumpectomy, axillary dissection, or reconstructive surgery may cause significant postoperative pain. Pain is not merely a physiological response but a complex phenomenon that also encompasses psychological, social, and behavioral components. Inadequate pain control can prolong the patient's recovery period, increase the risk of postoperative complications, and predispose to the development of chronic pain. Therefore, understanding the pathophysiological mechanisms of pain following breast surgery and implementing effective control strategies constitute an essential part of surgical success.

2.Epidemiology of Pain in Breast Surgery

Postoperative pain following breast surgery has been reported at remarkably high rates in the literature. Acute postoperative pain occurs in almost all patients, and in approximately 30–50% of cases, this pain becomes chronic (1). Postmastectomy pain syndrome (PMPS) is defined as pain persisting for more than three months after surgery, typically neuropathic in nature, and occurs in 20–50% of patients. The intensity and duration of pain vary depending on the surgical technique, extent of nerve injury, the patient's psychological condition, history of radiotherapy, and the effectiveness of pain management strategies. In patients for whom adequate analgesia is not achieved in the early postoperative period, the likelihood of chronification increases significantly.

3.Pathophysiological Mechanisms

Pain following breast surgery is a complex process involving the simultaneous contribution of nociceptive, inflammatory, and neuropathic components. After surgical trauma, an inflammatory response begins in the tissues, leading to the release of proinflammatory mediators such as prostaglandins, bradykinin, histamine, serotonin, and cytokines. These mediators increase the sensitivity of peripheral nerve endings, resulting in peripheral sensitization. Peripheral sensitization facilitates the transmission of low-threshold pain signals to the central nervous system (2). This process activates dorsal horn neurons through Aδ and C-type afferent fibers. Over time, the increased synaptic transmission at the dorsal horn level leads to central sensitization, which causes pain to become more widespread and results in the perception of normally non-painful stimuli, such as light touch, as painful (allodynia).

4. Nerve Injury and Neuropathic Processes

In breast surgery, the intercostobrachial nerve, thoracic intercostal nerves, and supraclavicular branches are particularly at risk. Injury to these nerves during axillary dissection or sentinel lymph node biopsy is one of the major causes of neuropathic pain. Neuromas that form following nerve transection can generate ectopic impulse discharges, leading to spontaneous pain. In addition, due to central plasticity, the perception of pain may induce lasting changes in the dorsal horn of the spinal cord (3). This mechanism contributes to the persistence of neuropathic pain and makes its treatment more challenging.

5. Chronification and Postmastectomy Pain Syndrome

In breast surgery, the intercostobrachial nerve, thoracic intercostal nerves, and supraclavicular branches are particularly vulnerable. Injury to these nerves during axillary dissection or sentinel lymph node biopsy represents one of the principal causes of neuropathic pain. Neuromas that form following nerve transection may generate ectopic discharges, resulting in spontaneous pain. Furthermore, central plasticity can induce long-term alterations within the dorsal horn of the spinal cord (3), thereby contributing to the persistence of neuropathic pain and complicating its management.

6. Postoperative Pain Control

Postoperative pain control in breast surgery is of great importance not only for ensuring patient comfort but also for maintaining respiratory function, promoting early mobilization, accelerating wound healing, and preventing the development of chronic pain. Inadequate pain management can lead to shallow breathing, pulmonary complications such as atelectasis and pneumonia, an increased risk of deep vein thrombosis, and an exacerbated stress response. Moreover, uncontrolled pain during the acute period can trigger central sensitization, playing a key role in the development of postmastectomy pain syndrome (PMPS). For this reason, current approaches are based on the principle of multimodal analgesia. Multimodal analgesia achieves more effective and safer pain control by synergistically combining drugs and techniques that act through different mechanisms. This strategy reduces opioid consumption, decreases the incidence of side effects (e.g., nausea, vomiting, sedation, respiratory depression), and contributes to earlier discharge.

Pharmacological therapy constitutes the cornerstone of pain management in breast surgery. These include paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, gabapentinoids, and local anesthetics.

Paracetamol exerts its analgesic effect by inhibiting the cyclooxygenase enzyme in the central nervous system, thereby suppressing prostaglandin synthesis. It can be effective as a single agent for mild to moderate pain but is more commonly used in combination with other agents within multimodal regimens. Intravenous formulations are preferred in the early postoperative period because of their rapid onset of action and high bioavailability.

NSAIDs reduce tissue inflammation—one of the major causes of postoperative pain—by suppressing the peripheral inflammatory response. Ibuprofen, ketorolac, and diclofenac are among the most frequently used agents in breast surgery. These drugs inhibit prostaglandin synthesis, thereby reducing pain and edema. COX-2 selective inhibitors (e.g., parecoxib, celecoxib) demonstrate fewer gastrointestinal side effects; however, they should be used cautiously due to their potential effects on bleeding risk and renal function (4).

Opioids are effective for the control of moderate to severe pain. Morphine, tramadol, and oxycodone are commonly preferred agents. By binding to μ-opioid receptors, opioids produce central analgesic effects. However, because of adverse effects such as respiratory depression, nausea, vomiting, constipation, and sedation, they should be used at the lowest effective dose and for the shortest possible duration. Nowadays, patient-controlled analgesia (PCA) systems allow for individualized dose adjustments, thereby reducing the risk of overdose.

Gabapentinoids (gabapentin, pregabalin) are particularly effective in postoperative pain with neuropathic components following breast surgery. They block voltage-gated calcium channels, reducing synaptic neurotransmitter release and suppressing central sensitization. When initiated preoperatively and continued postoperatively, these agents lower pain scores and reduce opioid requirements (1).

Local anesthetics can be administered as infiltration into the surgical field or as wound-site infusion. Applications with long-acting local anesthetics such as bupivacaine or ropivacaine directly block impulse transmission at peripheral nerve endings. Particularly in extensive dissection cases, adding these methods to multimodal analgesia significantly strengthens pain control.

In conclusion, pharmacological management of postoperative pain following breast surgery should be planned in accordance with multimodal analgesia principles. The combination of different drug classes not only reduces pain intensity but also decreases the risk of complications, accelerates patient mobilization, and helps prevent the development of chronic pain.

7. Regional Anesthesia and Nerve Blocks

Regional anesthesia techniques are increasingly used in breast surgery and are key components of multimodal analgesia. They aim to block nociceptive transmission from the surgical site to the central nervous system, reducing both acute and chronic pain.

7.1. PECS Blocks (Pectoral Nerve Blocks)

PECS I involves local anesthetic infiltration between the pectoralis major and minor muscles, blocking the lateral and medial pectoral nerves. PECS II adds injection between the pectoralis minor and serratus anterior muscles, blocking additional structures such as intercostal and intercostobrachial nerves, providing a broader analgesic effect.

Randomized controlled trials have shown that PECS II provides longer analgesia, lower opioid use, and lower pain scores in the first 24 hours compared to PECS I (5). Meta-analyses confirm that PECS blocks are associated with fewer side effects (nausea, vomiting, respiratory depression) and faster recovery (6).

7.2. Erector Spinae Plane (ESP) Block

ESP block involves injection of local anesthetic between the erector spinae muscle and the thoracic transverse process, providing widespread thoracic analgesia. It is simple, safe, and effective in reducing pain and opioid use.

7.3. Serratus Anterior Plane (SAP) Block

SAP block involves injecting local anesthetic between the serratus anterior and latissimus dorsi muscles, providing sensory blockade for the lateral thoracic wall and axillary area (7). Compared to PECS II, SAP offers longer analgesia and broader dermatomal coverage but carries a small risk of pleural puncture.

Integrating PECS, ESP, and SAP blocks into multimodal analgesia protocols significantly reduces postoperative pain scores, opioid consumption, and hospital stay. ESRA and ASRA guidelines (8, 9) strongly recommend regional anesthesia for breast surgery and emphasize preemptive use to prevent chronic pain development.

8. Multimodal and Preemptive Analgesia

Multimodal analgesia combines agents acting at different levels of pain physiology, ensuring effective control with fewer side effects. Preemptive analgesia, achieved by administering analgesics or local anesthetics before surgical trauma, prevents sensitization and reduces postoperative pain and opioid requirements.

9. Surgical Technique, Rehabilitation, and Psychosocial Approaches

Surgical technique is a key determinant of postoperative pain. Nerve preservation, minimal tissue trauma, and proper hemostasis reduce pain severity. Early mobilization, physiotherapy, and posture exercises accelerate recovery. Psychological factors such as anxiety and depression lower pain thresholds, whereas patient education and psychosocial support improve outcomes.

10.Conclusion

Pain following breast surgery is multifactorial and requires multidisciplinary management. Surgical technique, regional anesthesia, pharmacological therapy, and psychosocial support are complementary components. Early and effective pain control not only enhances comfort but also prevents chronic pain development. Coordination between surgeons, anesthesiologists, and nurses is fundamental for optimal management.

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Chapter 7

POTENTIAL ROLE OF NEUROINFLAMMATION AND OXIDATIVE STRESS IN EPILEPSY

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Introduction

Epilepsy is a common neurological disorder affecting approximately 65 million people worldwide. Approximately 35% of patients are symptomatic and accompanied by a functional impairment in the central nervous system (CNS) (Soltani Khaboushan et al., 2022). Current treatment primarily targets the termination of seizure activity, often neglecting to address underlying causes. Overall, one-third of patients are resistant to treatment (Perucca et al., 2023). Studies indicate that factors such as genetic disorders, infections, metabolic defects, immunological disorders, and nitric oxide (NO) and serotonergic signaling disorders are implicated in the etiology of epilepsy (Soltani Khaboushan et al., 2022; Gunes et al., 2017, 2025; Ozdemir, 2025; Sahin et al., 2022). However, the etiology of approximately half of epilepsy cases remains undetermined.

Numerous mechanisms have been proposed for the development of resistance to epilepsy treatment (Löscher et al., 2020). Recent experimental studies have helped to better understand the pathophysiological mechanisms underlying drug resistance in epilepsy (Perucca et al., 2023). Current data on antiepileptic drugs have led to revisions in the development of specific drugs for various etiologies. Accumulating evidence has revealed that when selecting an antiepileptic drug in the clinic, drug resistance should be considered in addition to the patient's medical history, comorbidities, and previous drug responses. Numerous theories have been put forward regarding drug resistance in epilepsy. In particular, oxidative stress, a key factor in regulating synaptic transmission, and neuroinflammation link theories of the development of epileptic drug resistance. Any triggering factor, such as brain inflammation, inadequate regulation of the body's own anti-inflammatory processes, and oxidative stress can lead to the development of epilepsy. It should never be forgotten that other mechanisms besides neuroinflammation may also play a role in drug resistance in epilepsy (Alvim et al., 2021; Campos-Bedolla et al., 2022). Therefore, more research is needed on biomarkers of neuroinflammation and oxidative stress in epilepsy. During the epileptogenic process, numerous plastic, visible, technological, and structural changes occur in the brain, including frequent diseases, cell death, and neurotransmitter dysfunction. These consist of a wide range of pathological mechanisms, such as regulated and oxidative stress (Mohapatra et al. 2025).

The aim of this review is to elucidate the molecular mechanisms of neuroinflammation and oxidative stress in epilepsy and to evaluate the potential sources of new drugs for patients with treatment-resistant epilepsy based on recent data. Furthermore, this review highlights the importance of novel neuroinflammatory biomarkers in seizure pathophysiology and offers recommendations for future research.

Neuroinflammation in Epilepsy

Data from clinical and experimental studies demonstrate the relationship between neuroinflammation and epilepsy (Campos-Bedolla et al., 2022). Drug-resistant epilepsy has been identified in various diseases associated with neuroinflammation, such as cerebral inflammation, tuberous sclerosis (Boer et al., 2010), cortical dysplasia (Lyer et al., 2010), and hippocampal sclerosis (Crespel et al., 2002). Numerous evidence suggests that levels of proinflammatory cytokines are increased in patients with epilepsy (Campos-Bedolla et al., 2022) (Table 1). Elevated levels of the proinflammatory cytokines interleukin (IL)-1β and interleukin-6 (IL-6) have been found in patients with temporal lobe epilepsy. However, one year after surgical treatment, proinflammatory cytokine levels decreased, and epileptic seizures were alleviated. This demonstrated the importance of suppressing neuroinflammation in reducing seizures (Lorigados et al., 2018). Essentially, neuroinflammation refers to damage to microglia (M) and astrocytes in neuronal tissue, resulting in increased levels of inflammatory cytokines and excessive release of reactive oxygen species (ROS). This exacerbates the degeneration of dopamine neurons in the brain, ultimately leading to progressive neuronal death (Li et al., 2022).

Table 1. *Effects of pro-inflammatory cytokines on epilepsy*

Aspect	Model	Findings and Observations	References
Central IL-6 modulation	Wistar rats	Intranasal IL-6 administration increased central IL-6 levels	(Kalueff et al. 2004
IL-6 overexpression and seizures	Transgenic mouse model	IL-6 overexpression increased seizure susceptibility	(Alapirtti et al. 2009)
Maternal immune activation	C57BL/6 Mice	Elevated IL-6 levels in offspring linked to epilepsy	(Pineda et al. 2013)
IL-6 and peripheral immune system	C57BL/6J mice	Abnormal IL-6 levels trigger seizures without CNS viral replication	(Cusick et al. 2017)
IL-6 and Posttraumatic Epilepsy (PTE)	Human	Significant correlation between high IL-6 levels and PTE	(Choudhary et al. 2021)
IL-6 Receptor Inhibition	Human	Inhibition of IL6R decreases epilepsy occurrence	(Yu et al. 2024)
HMGB1/TLR4 Axis and Calcium Permeability	Rodent seizure model	HMGB1/TLR4 axis modulates receptor phosphorylation	(Terrone et al. 2020)
Targeting RAGE and TLR4 Pathways	C57BL/6 mice and RAGE knockout	Blocking RAGE/TLR4 reduces posttraumatic epilepsy	(Ping et al. 2021

Box-1 Mitigates Cognitive Decline	Adult zebrafish	Reduced HMGB1, TLR4, and NF-κB mRNA levels and neuroprotection	(Paudel et al. 2021)
Novel Treatments: Exosome-Based Delivery of miR129-5p	C57BL/6J mice	Exosomes reduce HMGB1/ TLR4- mediated inflammation	(Liu et al. 2024)
Caspase-1 Inhibition	Sprague-Dawley rats	Reduced IL-1β secretion and seizures	(Ravizza et al. 2006)
Mechanistic Insights	Rodent model	IL-1β modulates inflammation via Nrf2/HO-1/NLRP3 signaling pathway	(Wu et al. 2023)
IL-6 in autoimmune Epilepsy	Human cohort	IL-6 implicated in GADA-associated autoimmune epilepsy	(Basnyat et al. 2023)
TNF-α induced astrocyte dysfunction	C57B6/J mice	Microglia derived TNFα disrupted astrocyte activity	(Henning et al. 2023)
Purinergic Signaling and TNF-α in Temporal Lobe Epilepsy	Male and female C57BL/6 mice	Inhibition of TNFα-driven purinergic signaling with P2Y1 receptor blockers normalizes synaptic activity and reduces glutamate release	(Nikolic et al. 2018)
mPGES-1 and Chemoconvulsant-Seizures	C57BL/6 mice	Reduced PGE2 levels and neuronal damage with mPGES-1 inhibitors	(Yasmen et al. 2023)
Neuroinflammatory Markers in Epilepsy	Human	Elevated CCL11 and PGE2 correlate with increased seizure frequency and severity	(Gakharia et al. 2022)

Neuroinflammation is triggered by multiple factors and causes a series of inflammatory responses in the central nervous system (CNS) (Campos-Bedolla et al., 2022). This inflammatory response induces microglia, astrocytes, and endothelial cells in the blood-brain barrier (BBB), resulting in increased levels of pro- and anti-inflammatory molecules. While neuroinflammation is associated with neuronal hyperexcitability and seizures, frequent seizures can also trigger a series of neuroinflammatory reactions, creating a vicious cycle that leads to intractable epilepsy (Li et al., 2023). Chronic neuroinflammation can lead to persistent neuronal loss and persistent neuronal hyperexcitability. Proinflammatory molecules that increase neuronal hyperexcitability can lead to increased seizure activity, leading to excitotoxic damage in the brain and subsequent permanent changes in synaptic connections (Campos-Bedolla et al., 2022). Increased levels of proinflammatory factors induce the expression

of various surface receptors and stimulate immunity. Activation of cytokine receptors in brain cells increases their excitability through modifications of receptor-bound ion channels or voltage-gated channels and also leads to presynaptic changes in synaptic transmission (Campos-Bedolla et al., 2022). Proinflammatory mediators also induce transcriptional gene activation, leading to a long-lasting immune response and molecular plasticity changes that trigger epileptogenesis. Discovery of a molecule that contributes to neuroinflammation could be a potential drug for the treatment of epilepsy (Ma and Li. 2021).

An experimental study showed that IL-1β rapidly increases in activated microglia and astrocytes in the forebrain of rats during an acute seizure, and IL-1β levels do not return to normal levels even after the seizure subsides (Ravizza et al., 2006). Inflammatory responses are essential for wound healing, but prolonged neuroinflammation can impair neuronal function and lead to epileptogenesis (Hollis et al., 2025). Furthermore, increased IL-1β release increases the paracellular permeability of the BBB, facilitating leukocyte recruitment and the degradation of tight junction proteins (Labus et al., 2014). In addition, IL-1β signaling increases Ca2+ conductance by activating the NMDA receptor. Consequently, this leads to elevated intracellular Ca2+ levels, which elevate neuronal hyperexcitability. Another proinflammatory cytokine, IL-18, is linked to epileptogenesis and has been shown to be elevated in epileptic patients (Mochol et al., 2020).

The Roles of Microglia and Astrocytes in Neuroinflammation

Any damage to neuronal tissue primarily causes functional changes in the endothelium of blood vessels. Immune cells migrate from the bloodstream to the affected brain tissue, activating astrocytes and microglia.

Microglial cells are tissue-specific resident macrophages of the brain and are classified as glial cells. Resting microglial cells (M0) transform into an active form when stimulated and play a crucial role in maintaining cellular homeostasis. When activated, microglial cells transform into two forms (Hollis et al., 2025):

1) M1 subpopulation: Classically activated macrophages with proinflammatory properties.

2) M2 subpopulation: Alternatively activated macrophages with anti-inflammatory properties.

The balance between M1 and M2 microglia can be disrupted depending on regulatory factors and internal and external factors. Disruption of the M1/M2 balance can lead to the development of inflammatory-mediated diseases

(Feng et al., 2025) (Figure 1). Experimental evidence has shown that activated microglial cells in animals with induced epilepsy increase seizure frequency (Devinsky et al., 2013). Activated microglia secrete cytokines and chemokines, initiating further inflammatory processes (Yu et al., 2023). In addition, microglial cells can secrete nitric oxide (NO) by activating nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. NO can potently trigger the release of proinflammatory mediators (TNF) (Li et al., 2023). Microglia also activate astrocytes, causing them to secrete cytokines that trigger their proliferation.

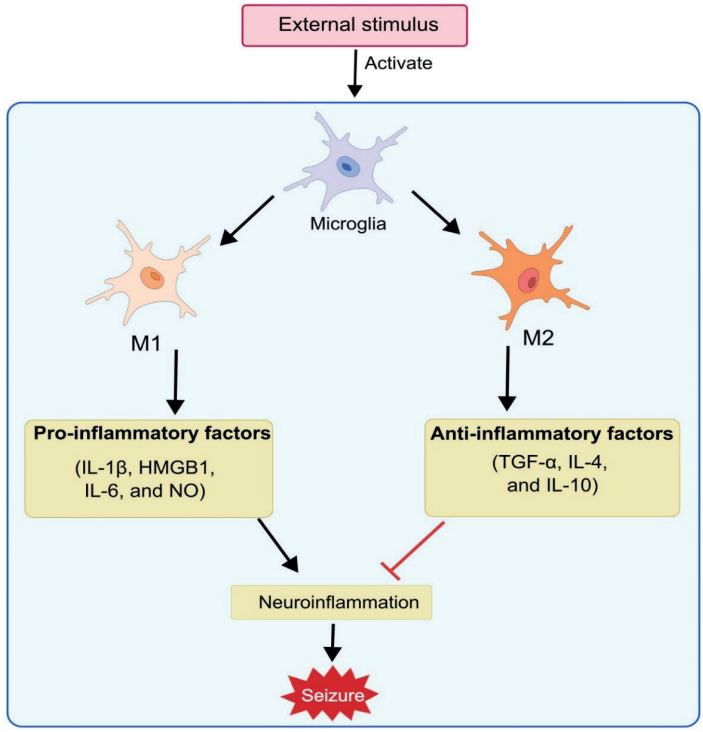

Figure 1. *Transformation of activated microglia cells into M1 and M2 forms and the mechanism by which M1 glia release proinflammatory factors to induce seizures (Feng et al., 2025).*

Astrocytes are glial cells and play important roles in maintaining neuronal function and homeostasis. Astrocytes participate in the regulation of neuronal excitability by controlling glutamate reuptake and extracellular potassium levels during an epileptic seizure (Sun et al., 2023). The roles of astrocytes in seizure pathophysiology are extensive and include ion homeostasis, energy metabolism, neurotransmitter regulation, and interactions with other glial cells. Activation of astrocytes by microglia releases proinflammatory molecules such as interleukin-1 beta (IL-1β), high mobility group box 1 (HMGB1), and nuclear factor Kappa-beta (NF-κB) (Li et al., 2023).

Role of Oxidative Stress and Neuroinflammation in Epilepsy

Oxidative stress is a condition that has detrimental effects on the body and occurs when the balance between oxidative processes, which produce high amounts of ROS and free radicals in cells, and their antioxidant capacity is disrupted. Keeping ROS levels low is crucial for maintaining normal neuronal cell function. Excessive ROS production can have undesirable consequences in tissues. It can lead to the destruction of protein components, mitochondrial dysfunction, and severe damage to lipid membranes, ultimately leading to cell death (Borowicz-Reutt and Czuczwar, 2020).

Superoxide (O_2–) is produced in high amounts as a byproduct of mitochondrial metabolism through various biochemical pathways, such as oxidative phosphorylation. This makes mitochondria the center of ROS production within the cell. Free radical production and scavenging processes maintain the physiological ROS balance. During the development of epilepsy, excessive ROS production occurs in the mitochondria of brain cells, leading to oxidative damage. Furthermore, various enzymatic activities in mitochondria lead to ROS production, including G-3-PDF, CYP-450, monoamine oxidase, and Cyt-b5 reductase (Mishra et al., 2024).

The balance of GABAergic and glutamatergic signals is disrupted due to the interaction between oxidative stress and neuroinflammation. Decreased GABAergic signaling leads to decreased GABA receptor activation, which in turn inhibits inhibitory neurotransmission. At the same time, increased glutamate release and signaling through N-methyl-D-aspartate receptors (NMDARs) leads to increased calcium ion (Ca^{2+}) concentrations, which induce excitotoxicity and oxidative stress (Phoswa et al., 2023) (Figure 2). Reactive oxygen species such as superoxide (O_2–) and hydrogen peroxide (H2O2) exacerbate oxidative stress. This is then accompanied by antioxidant responses such as glutathione peroxidase (GPx), superoxide dismutase (SOD), and nuclear factor erythroid 2-related factor 2 (Nrf2). Ultimately, the physiological functions of mitochondria are impaired. Abnormal astrocyte function is accompanied by a decrease in glutamate transporter-1 (GLT-1). GLT-1 dysfunction impairs glutamate reuptake and leads to exacerbation of excitotoxicity. Additionally, increased astrocyte activity leads to increased levels of molecules such as interleukins (IL-6 and IL-1β), TNF-α), NF-κB, toll-like receptor 4 (TLR4), and cyclooxygenase (COX), exacerbating neuroinflammation and ultimately leading to cell death (Borowicz-Reutt et al., 2020).

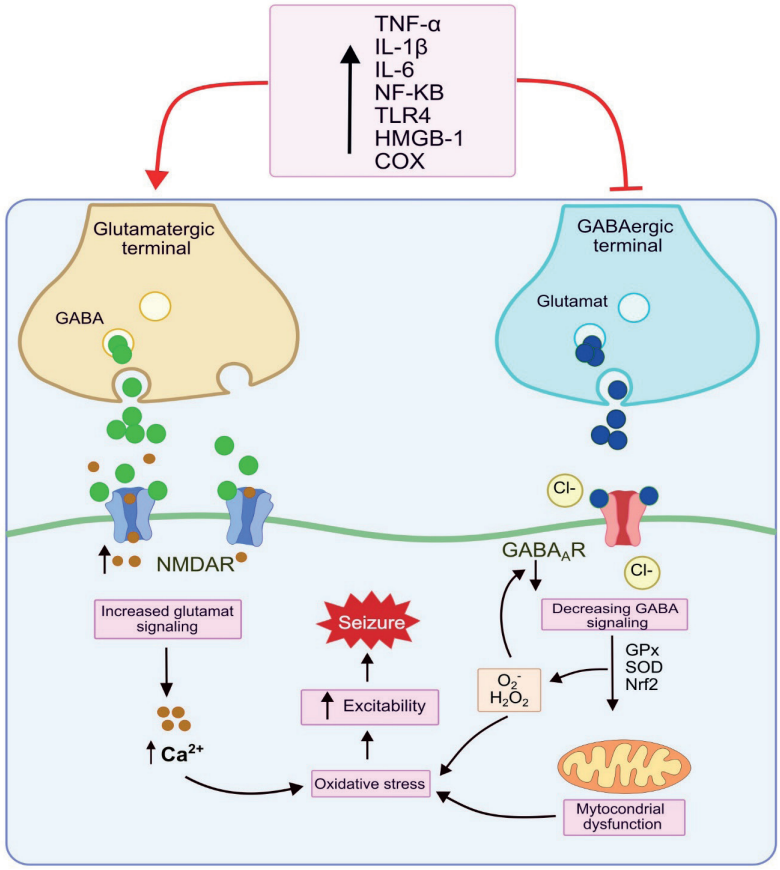

Figure 2. *Schematic representation of the mechanism of seizure induction by the effects of proinflammatory cytokines on glutamate and GABA release in neuronal cells and by increasing mitochondrial oxidative stress (Phoswa et al., 2023).*

Inflammatory molecules in neuroinflammation

HMGB1 is a chromatin-binding protein that can be found intracellularly and extracellularly. It participates in the regulation of gene transcription within the cell. Its extracellular form is triggered by neuroinflammatory factors and acts as a "danger signal" within the brain. Microglia, glial cells, and neurons can actively secrete HMGB1. Toll-like receptor 4 (TLR4) is another molecule detected in microglial cells. TLR4 and the advanced glycation end-product receptor (RAGE) are activated by HMGB1, thereby activating the proinflammatory IL-1R/TLR4 cascade. Ultimately, proinflammatory cytokines are synthesized, leading to neuronal hyperexcitability (Chen et al., 2023).

Activation of NF-κB molecules is also mediated by the proinflammatory IL-1R/TLR4 cascade. Activated NF-κB molecules are transported to the nucleus for transcription of genes involved in the immune response, such as adhesion

molecules, cytokines, and chemokines. NF-κB, HMGB1, the TLR receptor, and RAGE are potential biomarkers of epilepsy due to their important roles in neuroinflammation (Yu et al., 2023). One study demonstrated significantly higher HMGB1 levels in the blood of patients with drug-resistant epilepsy compared to healthy controls (Walker et al., 2022). In an experimental study in mice, the use of anti-HMGB1 antibodies reduced inflammation-related factors and BBB permeability, and lowered the seizure threshold (Fu et al., 2017). In an animal model of epilepsy, TLR4 expression was found to be upregulated, providing important evidence that TLR4 plays a role in ongoing inflammatory processes (Paudel et al., 2020). Injection of TLR4 antagonists reduced seizures in mice induced by intrahippocampal injection of kainic acid and bicuculline.

The Role of Cytokines

Interleukin-1

The interleukin-1 family is divided into three subgroups: IL-1α, IL-1β, and IL-33 (Hu et al., 2016). This family participates in the regulation of innate immune responses. It binds to IL-1R receptors and activates the NF-kB and mitogen-activated protein kinase (MAPK) pathways, leading to cell apoptosis (Dong et al., 2024). Among the IL-1 cytokine family, the role of IL-1β in epileptogenesis has been the subject of further investigation. Among the interleukins, IL-1β is the best-known proinflammatory cytokine. Studies indicate that IL-1β is not found in cerebrospinal fluid (CSF) under physiological conditions. However, in any inflammatory state (e.g., due to brain injury), IL-1β is detected in abundance in activated microglia and astrocytes. IL-1β, along with IL-6 and TNF-α, is involved in the pathophysiology of epilepsy. Increased levels of IL-1β have been detected in brain samples from patients with drug-resistant epilepsy (Dong et al., 2024). A study in the pediatric population also observed elevated levels of IL-1β in CSF and serum (Shi et al., 2017).

IL-1β is a versatile molecule that acts on various pathways and is critical in epileptic seizures. It stimulates neuronal hyperexcitability by increasing NMDA receptors. It also causes a 30% decrease in γ-aminobutyric acid (GABA) signaling (Rana et al., 2018). Furthermore, IL-1β can activate voltage-gated Ca2+ channels in the cell membrane, increasing Ca^{2+} influx and decreasing K^{+} efflux. It plays a role in BBB disruption by activating oxidative stress responses via nitrogen oxides. Anakinra, an IL-1β antagonist, has proven effective in patients with drug-resistant epilepsy (Dong et al., 2024). Consequently, IL-1β is a molecule that plays a key role in the vicious cycle of epileptogenesis. Epileptic seizures increase IL-1β levels, which further exacerbates neuroinflammation and neuronal hyperexcitability. Interleukin-1α (alpha) activates similar intracellular pathways as IL-1β, but is elevated not only during inflammation but also in the absence of inflammation.

Interleukin-6

IL-6 is known as one of the important proinflammatory cytokines, and its expression is frequently increased during seizures in cases of refractory status epilepticus (Girardin et al., 2023). IL-6 increases glutamate levels and GABA transporter proteins (GAT-1 and GAT-3), leading to decreased extracellular GABA levels. These changes lead to decreased inhibitory signaling and increased neuronal excitability, ultimately leading to seizures. High IL-6 levels in brain tissue are a consequence of increased BBB permeability. Evidence suggests significant increases in IL-6 levels during recurrent epileptic seizures (Ethemoglu et al., 2021). The combined use of tocilizumab (an IL-6 receptor antibody) and anakinra in febrile infection-associated epilepsy syndrome has been found to reduce seizures (Grebenciucova et al., 2023). Similarly, decreased IL-6 levels have been shown in the serum of patients treated with valproic acid.

Interleukin-2

IL-2 is a regulatory cytokine secreted by activated T cells and is required for the differentiation of Treg cells, a subpopulation of regulatory CD4+ lymphocytes. Treg cell dysfunction is implicated in the pathophysiology of autoimmune diseases. Recent studies indicate that low-dose IL-2 therapy, which activates Treg, treats autoimmune encephalitis by restoring the balance between regulatory and effector T cells (Lim et al., 2016). Furthermore, IL-2 cytokines regulate the function of both B cells and NK cells by binding to the IL-2R receptor. In addition, IL-2 cytokine administration has been reported to cause microglial activation. Some evidence has shown that serum IL-2 levels are increased in epilepsy (Guo et al. 2014).

Interleukin-4

The IL-4 cytokine is secreted by basophils, eosinophils, and mast cells. It promotes the differentiation of M2 microglia in the brain; therefore, it exerts anti-inflammatory effects on neuronal tissue (Gadani et al., 2012). Accumulating evidence has shown that IL-4 cytokine produces anti-epileptic effects by reducing inflammation and decreasing excitability in neuronal cells. Additionally, lower levels of IL-4 cytokine have been detected in postoperative tissue sections from patients with epilepsy (Dong et al., 2024).

Interleukin-10

IL-10, a cytokine secreted by astrocytes and microglia in brain tissue, exhibits anti-inflammatory activity. Furthermore, it has been shown to exert protective effects against apoptosis and inflammation in cells (Ouyang et al., 2019). Decreased serum IL-10 levels have been found in patients

with hippocampal temporal lobe epilepsy during the development of drug resistance. Furthermore, IL-10 increases GABAA receptor activity and exhibits neuroprotective effects (Ruffolo et al., 2022).

Tumor necrosis factor alpha (TNF-α)

TNF-α is released into the extracellular fluid by microglia and astrocytes in brain tissue, particularly when glutamate levels are low. TNF-α is a proinflammatory molecule and therefore increases neuronal excitability, leading to increased seizure frequency. High levels of TNF-α molecules have been detected in the serum and CSF of epilepsy patients. Furthermore, TNF-α cytokine levels have been observed to be higher in patients with drug-resistant epilepsy than in other patients (Sinha et al., 2008). Treatment with anti-TNF-α monoclonal antibodies in patients with Rasmussen disease has been shown to reduce seizures (Soltani et al., 2022).

Interferons (IFN)

Interferon gamma (IFN-γ) is a proinflammatory cytokine that activates the transcriptional activator (JAK/STAT) pathway and acts by binding to its receptor (IFN-γR) (Sun et al., 2023). Activation of this pathway reduces the concentration of GABA receptor subunit alpha-1 (GABAARα1), leading to excessive neuronal hyperexcitability. Elevated IFN-γ levels have been demonstrated in the hippocampus of rat epilepsy models and in the CSF and serum fluid of epileptic patients (Sin ha et al., 2008). Studies have found that IFN-γ levels are significantly elevated in epileptic patients compared to controls. All this evidence suggests that IFN-γ may be a biomarker for seizure prognosis in epilepsy (Gao et al. 2017).

Transforming Growth Factor Beta (TGF-β)

TGF-β participates in immune regulation and plays a role in many physiological processes, such as cell growth and differentiation. TGF-β activates TGF-βR1 and TGF-βR2 receptors to activate intracellular signaling pathways. TGF-β blocks glutamate transporters in glial cells and reduces glutamate reuptake, leading to increased arousal and hyperexcitability (Mukhtar et al., 2020).

Experimental evidence has demonstrated that the TGF-β cytokine exacerbates seizures by inducing neuronal hyperexcitability. Furthermore, TGF-β cytokine levels are upregulated in patients with drug-resistant epilepsy (Yu et al., 2014). Furthermore, TGF-β signaling leads to NMDA receptor-mediated neuronal hyperexcitability and seizure-like activity. Furthermore, stimulation of TGF-β signaling reduces the expression of GABAergic genes and increases glutamatergic stimulation, which in turn increases seizure activity (Cacheaux et al. 2009).

Prostaglandins

Prostaglandins (PGs) are produced primarily by astrocytes and microglial cells and participate in seizure pathophysiology by regulating neuronal excitability. Prostaglandin E2 (PGE2) interacts with its receptors (EP1, EP2, EP3, and EP4), resulting in increased neuronal activity. Stimulation of EP3 receptors on glial cells increases glutamate release and leads to neuronal hyperexcitability. PGE2 antagonists reduce seizure severity and neurological damage in experimental epilepsy models. Blocking the cyclooxygenase-2 enzyme reduces the production of anticonvulsant prostaglandins such as prostaglandin D2 (PGD-2), leading to increased seizure frequency (Rana et al., 2018).

Complement

The complement system consists of a complex network of proteins that enhances the ability of macrophages to eliminate pathogens. The underlying mechanisms and how complement dysfunction may contribute to diseases such as epilepsy are not yet fully understood (Kobylarek et al., 2019). Clinical study findings have revealed that untreated epilepsy patients have significantly higher serum C3 levels compared to controls (Başaran et al., 1994). These results suggest that the complement system plays an important role in the management of seizures.

Future Directions in Epilepsy Treatment

Given the important role of oxidative stress and inflammation in the development of epilepsy, antioxidant and anti-inflammatory therapies may be promising for epilepsy treatment. A large body of evidence suggests that targeting neuroinflammation is an important therapeutic approach to prevent the development of epilepsy. Experimental studies demonstrate that anti-inflammatory therapies targeting specific molecules successfully prevent epileptic seizures. In clinical trials, broad-spectrum anti-inflammatory interventions, particularly approaches such as ketogenic diets or steroid therapy, have yielded positive results (Li et al., 2023).

Antibody-based therapies specifically modulate immune responses by neutralizing proinflammatory cytokines. Therefore, targeting neuroinflammation in epilepsy therapy is promising. Experimental models and human case reports have demonstrated that the use of anti-IL-6 receptor antibodies, anti-TNF-α antibodies, and anti-IL-1β antibodies (kanakinumab) reduce neuroinflammation and seizure frequency in patient groups (Costagliola et al., 2022). Further experimental and clinical studies are needed to investigate new therapies targeting specific antioxidants and proinflammatory cytokines. A detailed understanding of the roles of neuroinflammation and oxidative stress in the causation of epileptic seizures and appropriate therapeutic

approaches against such seizures are essential. Further research and further understanding of the pathophysiology of epilepsy are needed to prevent and treat epilepsy, and to develop alternative antiepileptic therapies.

Conclusions

Clinical and experimental studies demonstrate the important role of oxidative stress and neuroinflammation in epilepsy. They reveal that levels of oxidative stress markers and proinflammatory cytokines are elevated in epilepsy. Accumulating evidence demonstrates that proinflammatory cytokines and oxidative stress play a significant role in increasing neuronal excitability, increasing the frequency of epileptic seizures, and maintaining chronic neuroinflammation in the CNS. This is associated with the chronic activation of numerous signaling pathways, leading to damage to the blood-brain barrier. Numerous studies are necessary to identify and validate biomarkers of oxidative stress and neuroinflammation in epilepsy and to utilize them in the treatment of epilepsy. Molecular studies are needed to monitor serum biomarker dynamics during the progression of epilepsy and to obtain detailed information about their temporal significance. Advanced imaging techniques such as functional MRI and PET can provide important clues in correlating biomarker activity with neuroinflammatory and oxidative stress processes. A better understanding of the role of the relationship between oxidative stress and neuroinflammation in epilepsy could lead to the development of new therapeutic approaches, thereby improving treatment management and outcomes in patients with epilepsy. Oxidative stress plays a critical role in the development of epileptic seizures. Early effects of ROS during seizures include lipid peroxidation, reactive gliosis, and mitochondrial DNA damage. DNA damage is followed by neurodegeneration, neuronal circuit reorganization, hyperexcitability, and increased seizure frequency. Combining antiepileptic drugs with anti-inflammatory agents or antioxidants may enhance epilepsy treatment and reduce epileptic seizures.

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Chapter 8

NUTRIGENOMICS-BASED PERSONALIZED NUTRITION INTERVENTIONS: EFFICACY AND ETHICAL-CLINICAL DIMENSIONS

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1. Introduction

The pursuit of personalized nutrition has emerged from decades of frustration with population-level dietary recommendations that yield heterogeneous results across individuals (Ordovas, Ferguson, Tai, & Mathers, 2018). Nutrigenomics, the study of gene nutrient interactions and their impact on health, provides a scientific foundation for tailoring dietary interventions based on an individual's genetic makeup (Fenech, El-Sohemy, Cahill, Ferguson, & Milner, 2019). The promise of this field lies in its potential to predict dietary responses, optimize nutrient intake, and prevent chronic diseases through personalized guidance (Corella, Coltell, Macian, & Ordovás, 2018). By integrating data from genomics, epigenetics, transcriptomics, metabolomics, and microbiomics, nutrigenomics enables a shift from one-size-fits-all dietary recommendations to individualized strategies grounded in biological variability (Zeevi et al., 2015).

Recent empirical studies have reinforced this concept, providing evidence that multi-omic integration enhances the precision and efficacy of dietary interventions (Bonnafous, Legrand, & Palierne, 2022). For instance, nutrigenomic profiling now enables prediction of individual lipid responses to specific fatty acid compositions, improving cardiometabolic outcomes in randomized controlled trials (Horne, Gilliland, O'Connor, & Madill, 2021). Similarly, personalized nutrition approaches leveraging genetic and metabolic data have improved adherence to dietary recommendations over time, suggesting that genetic feedback reinforces motivation and behavioral change (Celis-Morales, Livingstone, Marsaux, & Mathers, 2020).

Beyond behavior, nutrigenomics also advances mechanistic understanding of metabolic heterogeneity. In obesity management, gene variants in APOE, FTO, and PPARγ have been shown to significantly modify responses to fat-rich or carbohydrate-restricted diets (De Toro-Martín, Arsenault, Després, & Vohl, 2017). More recent evidence shows that multi-omic integration especially inclusion of gut microbiome and metabolome data enables prediction of dietary glycemic responses with unprecedented accuracy (Wang, Liu, & Zhu, 2023). A 2024 randomized clinical trial demonstrated that individuals who received personalized nutrition advice based on microbiome and metabolomic profiles experienced greater improvements in insulin sensitivity and lipid metabolism than those given general dietary guidance (Kim, Wang, & Wu, 2024).

Moreover, nutrigenomics has expanded into early life nutrition and pediatric contexts. A 2025 multi-omics analysis of plant-based diet indices (PDIs) in children revealed that higher adherence to PDIs was associated with beneficial gut microbial signatures and metabolomic profiles influencing

short-chain fatty acid production, highlighting the interplay between diet quality, microbiota, and host genetics (Zheng, Xu, & Li, 2025). These findings indicate that dietary interventions informed by genomic and microbial data can have long-term developmental benefits.

Cognitive health research has similarly benefited from nutrigenomic perspectives. A longitudinal study involving 1,670 adults found that APOE ε4 carriers with long-term omega-3 supplementation exhibited slower cognitive decline and reduced conversion to Alzheimer's disease, illustrating a gene nutrient interaction with tangible clinical impact (Abid, Navaj, & Vishwakarma, 2025). These outcomes emphasize how personalized nutrition can extend beyond metabolic health to neurological protection and aging.

However, enthusiasm for nutrigenomics must be balanced with caution. Despite positive findings, systematic reviews have shown variability in the reproducibility and clinical magnitude of reported effects (Livingstone, Celis-Morales, & Mathers, 2022). While nutrigenomic interventions often improve intermediate outcomes such as dietary adherence or metabolic biomarkers there is limited evidence of significant effects on hard endpoints such as disease incidence or mortality (Ordovás, Ferguson, Tai, & Mathers, 2022). Additionally, commercial genetic tests have proliferated without adequate clinical validation, raising concerns about overinterpretation and potential misinformation (Blumfield, Saadeh, & Collins, 2022).

In response, leading institutions advocate for stringent clinical trials, transparent data-sharing frameworks, and ethical oversight to ensure safe translation of nutrigenomics into public health and clinical practice. The field now stands at a critical juncture balancing technological innovation with methodological rigor, ethical accountability, and equitable accessibility.

The overarching objective of this chapter is to synthesize current evidence on the efficacy of nutrigenomics-based personalized nutrition interventions, while critically analyzing their ethical and clinical dimensions. By examining empirical findings, predictive modeling approaches, and real-world clinical pathways, the discussion seeks to clarify both the transformative potential and the limitations of this emerging domain.

2. Scientific Foundations of Nutrigenomics and Multi-Omic Integration

Nutrigenomics encompasses a suite of interconnected disciplines nutrigenetics, nutriepigenomics, and nutrimetabolomics that collectively explore how nutrients interact with the genome to influence physiological processes and disease susceptibility (Fenech et al., 2019). Nutrigenetics focuses on genetic variants that modulate individual responses to dietary

factors, such as the FTO polymorphism's influence on obesity risk or the MTHFR C677T variant's effect on folate metabolism (Livingstone et al., 2022). Nutrigenomics proper investigates how diet regulates gene expression through transcriptional and epigenetic mechanisms, such as histone acetylation or DNA methylation patterns induced by dietary methyl donors (Milagro, Martínez, & Corella, 2023). Nutrimetabolomics, in turn, uses metabolite profiling to map downstream biochemical consequences of nutrient-gene interactions, capturing real-time metabolic phenotypes (Abid et al., 2025).

Multi-omic integration has become indispensable to understanding the full scope of nutrigenomic influence (Bashiardes, Zilberman-Schapira, & Elinav, 2018). For example, combining genomic and microbiomic data reveals how host genotype and gut microbiota jointly determine metabolic outcomes (Calder, 2019). Transcriptomic and metabolomic integration can identify specific pathways by which nutrients alter gene regulation, such as polyphenol-induced modulation of the Nrf2 pathway in oxidative stress defense. Such approaches provide a systems-level perspective on nutritional physiology, enabling computational modeling that predicts responses with increasing precision (Kapellou, Salata, Vrachnos, Papailia, & Vittas, 2025).

The integration of multi-omics data with machine learning represents a significant methodological advance. Predictive algorithms can incorporate SNPs, dietary intake, microbiome profiles, and clinical variables to forecast glycemic or lipid responses to specific meals (Nisa, Kirthi, & Sinha, 2025). By continuously refining these models through large-scale datasets, the field moves closer to evidence-based personalization. However, methodological limitations persist: many studies remain small, lack replication, or rely on convenience samples of predominantly European ancestry (Andonotopo et al., 2025). Consequently, current prediction models may not generalize across diverse populations.

Biological plausibility for nutrigenomic interventions is further supported by mechanistic studies linking dietary components to gene expression pathways. For instance, omega-3 fatty acids activate PPAR-α and modulate transcriptional networks associated with lipid metabolism (Almoghrabi et al., 2025; Blumfield, Nowson, & Abbott, 2022). Similarly, dietary polyphenols regulate gene expression through epigenetic modulation of histone deacetylases and microRNAs. These mechanistic insights provide the molecular scaffolding necessary for precision dietary interventions aimed at metabolic optimization and disease prevention (Horne et al., 2021; Martinez, Lewis, & Romero, 2021).

3. Evidence of Efficacy: Clinical Trials and Interventional Data

Clinical evidence evaluating nutrigenomics-guided dietary interventions has expanded substantially over the past decade, though results remain mixed (Bray, Heisel, & Isasi, 2021). Early randomized controlled trials (RCTs) assessing genotype-based diets found modest improvements in weight loss or metabolic outcomes compared to standard advice, but many were limited by short duration and small sample sizes (Celis-Morales et al., 2020; Livingstone et al., 2022). For example, the Food4Me trial the largest of its kind demonstrated that personalized nutrition based on genetic, phenotypic, and lifestyle data led to more favorable dietary behavior changes than generic recommendations. However, genotype information contributed minimally beyond phenotypic personalization, suggesting that the added clinical value of nutrigenomics remains incremental(Celis-Morales et al., 2020).

In more recent years, several RCTs and longitudinal studies have sharpened this evidence. A 2023 randomized trial in individuals with overweight/obesity compared high-monounsaturated fat versus saturated fat reduction in diets stratified by APOE genotype; APOE ε4 carriers showed greater reductions in LDL-cholesterol when saturated fat was reduced, compared to non-carriers, with effect sizes (Cohen's d) of ~0.35 over 24 weeks. Another trial (2024) investigated omega-3 supplementation in hypertriglyceridemic subjects stratified by FADS1 genotype: individuals with the "fast desaturase" allele reduced triglycerides ~20% more than those with the alternative allele when given high-dose EPA/DHA (V. Singh, 2023; Y. Singh, Sinha, Likhita, Arya, & Verma, 2025). These trials suggest genotype-diet interactions with clinically relevant lipid endpoints.

Glycemic control studies have also progressed. Firstly, a 2022 longitudinal cohort study of over 2,500 prediabetic participants incorporated genetic risk scores (GRS), diet quality indices, and physical activity; those in the highest GRS tertile showed greater benefit from a Mediterranean diet in delaying type-2 diabetes onset ("Application of machine learning algorithm incorporating dietary intake in prediction of gestational diabetes mellitus," 2024; Hazelton, Chanson, Nguyen, Patel, & Thompson, 2022). Similarly, a 2023 intervention trial combining dietary counseling with gut microbiome profiling used multi-omic data to tailor carbohydrate quality; postprandial glucose spikes were reduced by ~15% relative to control after 12 weeks (Wang et al., 2023). Such evidence underscores that models integrating genetics + microbiome + diet can outperform simpler interventions.

Behavioral outcomes are likewise improving. A 2021 RCT involving overweight adults compared standard diet advice vs. nutrigenomic-informed advice (including FTO, MTHFR, FADS genes) plus behavioral counseling;

the nutrigenomics group had significantly greater improvements in dietary fat quality, fruit & vegetable intake, and reported self-efficacy after 6 months ($p<0.01$). Retention rates were higher as well, suggesting participant engagement is enhanced when personalized genetic feedback is delivered (Martinez et al., 2021). Despite these promising findings, limitations remain. Many recent trials still have relatively short follow-up (<12 months), which limits assessment of long-term outcomes like incidence of cardiovascular disease or diabetes. There is also variability in the genetic panels used, sometimes lacking replication or validated clinical utility (V. Singh, 2023; Y. Singh et al., 2025). Effect sizes, while statistically significant, are often moderate; moreover, publication bias toward positive findings may overestimate true benefits. Meta-analyses published in 2022-2023 conclude that nutrigenomics-guided advice often yields improvements in intermediary markers (lipids, glucose, diet quality) but that strong evidence for reduction in hard endpoints is still limited (J. Li, Cheng, & Huang, 2022).

In summary, studies from the past five years provide increasing support for nutrigenomics-guided interventions, especially for lipid metabolism and glycemic control, and point toward enhanced behavioral adherence when personalized feedback is used. However, consistent translation into long-term clinical endpoints remains to be proven, and standardization of genetic testing, larger sample sizes, longer follow-ups, and inclusion of diverse populations are needed.

4. Clinical Implementation Pathways

Implementing nutrigenomics into clinical practice requires multidisciplinary collaboration across dietetics, genetics, bioinformatics, and clinical medicine. A structured implementation framework begins with patient selection and informed consent, followed by validated genetic testing, interpretation by trained professionals, and integration of findings into personalized nutrition care plans (Almoghrabi et al., 2025; Fayyaz et al., 2025). Genetic testing must meet the three classic criteria of analytic validity, clinical validity, and clinical utility before recommendations are made. Clinical guidelines emphasize the need for rigorous quality assurance and transparency regarding test limitations to prevent misuse or overinterpretation of genetic results (Almoghrabi et al., 2025; Phugat & Goel, 2025).

In practice, integrating nutrigenomics into healthcare systems entails the creation of electronic health record (EHR) modules capable of storing and interpreting genetic data securely (Bhattacharjee & Mohapatra, 2025). Clinical decision-support tools can prompt clinicians with gene diet interaction alerts and evidence-based dietary guidance. However, such

systems demand robust data governance and professional training to ensure accurate use. Educational curricula for dietitians and physicians must now incorporate genomic literacy, ethical reasoning, and communication strategies tailored to discussing probabilistic genetic information (Miller & Kelly, 2025). Without these competencies, clinicians risk providing either oversimplified or misleading advice to patients. The success of nutrigenomics-based interventions also depends on patient engagement and behavior change. Evidence shows that when genetic information is presented in an empowering, non-deterministic way, adherence to dietary recommendations increases significantly (Arshad et al., 2025). Conversely, when communicated poorly, genetic feedback can evoke anxiety or fatalism (Stewart-Knox, Bunting, & Kuznesof, 2016). Therefore, effective implementation must integrate motivational interviewing, digital self-monitoring tools, and culturally sensitive counseling to ensure patient-centered outcomes(Ramos-Lopez et al., 2025).

Real-world implementation studies remain limited. Pilot programs integrating nutrigenomic testing in primary care report high patient satisfaction but modest clinical improvements in metabolic biomarkers (Kavya, Krishna, Rameshkumar, & Srivignesh, 2025). Scaling these efforts requires standardized reporting frameworks and cost-effectiveness analyses to determine whether personalized approaches yield meaningful public-health benefits compared to population-level interventions (Y. Singh et al., 2025).

5. Data Science and Predictive Modeling in Personalized Nutrition

The integration of nutrigenomics with data science and machine learning remains one of the most dynamic frontiers in precision health. Predictive modeling harnesses high-dimensional datasets including genomic variants, transcriptomic profiles, gut microbiota composition, dietary intake records, wearable sensor data, and metabolomic signatures to forecast individual metabolic responses, such as postprandial glycemic responses or susceptibility to type 2 diabetes (J. Li et al., 2022; Z. Li et al., 2025). In recent years, models that incorporate diet, microbiome, host genetics, and lifestyle data have shown improved prediction of disease progression and metabolic phenotypes compared to models using only one or two data types (J. Li et al., 2022). Supervised learning methods, such as extreme gradient boosting (XGBoost), LightGBM, and random forests, have been successfully employed in recent studies to predict progression from prediabetes to type 2 diabetes when dietary indicators are included as feature. For example, the study from the Henan Rural Cohort used dietary indicators like whole grains, red meat, nuts, and eggs along with clinical variables to build XGBoost models that achieved high discrimination in predicting T2DM

progression (Ghosh, 2024). Similarly, in gestational diabetes mellitus (GDM) prediction, models combining dietary features with sociodemographic and clinical data showed higher AUCs using LightGBM and XGBoost compared to models without dietary data, indicating that dietary variables improve predictive performance (Ebadi & Selamoglu, 2025).

Unsupervised learning clustering techniques continue to identify "metabotypes" or microbiome-driven phenotypes that share similar metabolic response profiles. A 2025 study of children's plant-based diet indices (PDIs) used multi-omics (microbiome + metabolome) to cluster children into groups with differing production of short-chain fatty acids (SCFAs), bile acids, and related metabolites; dietary quality gradients corresponded to metabolic health markers (Panagoulias, Tsihrintzis, & Virvou, 2025). Such clustering aids in stratifying individuals who might respond differently to the same dietary intervention. Deep learning frameworks are increasingly being explored to combine genetic and clinical data for risk prediction. A recent systematic review of models for predicting T2DM found that combining SNP-based genetic data with clinical features and other biomarkers led to higher AUCs than either domain alone; though gains are often modest, these additive models signal the value of integrating multiple data streams (Mugisha Emmanuel). Nevertheless, computational performance gains still face limitations in clinical translation. Many new models, while achieving promising AUCs or accuracies, rely on retrospective datasets from homogeneous populations, often East Asian or European, limiting generalizability (Guizar-Heredia et al., 2023). Model interpretability remains a challenge: the "black-box" nature of deep learning techniques can make it difficult for clinicians to understand which features (genes, microbiome taxa, dietary items) drive predictions, complicating clinical decision-making. To mitigate this, methods such as SHAP values or LIME for feature importance, and simpler tree-based models, are increasingly used to increase transparency (Rajoriya, Gupta, Vengurlekar, & Jain, 2025).

Data integration across modalities also poses challenges harmonizing dietary intake assessments, standardizing microbiome and metabolomic measurement protocols, handling missing data, and dealing with time-series data from wearables or continuous glucose monitoring (CGM). Privacy and ethical issues are also front of mind: federated learning and privacy-preserving ML methods are being explored more intensively to allow collaborative model development without centralized sharing of sensitive data (Priyadarshini, Nair, & Nandan, 2025).

Several studies over the past few years have pushed the boundary by implementing predictive systems in real-world clinical settings. One example is a nutrition education clinic for people with type 2 diabetes, where

an XGBoost model incorporating lifestyle, self-reported dietary control, medication compliance, and sociodemographics was used to predict one-year glycemic control; the model achieved AUC ~0.74, suggesting modest but meaningful predictive utility (Mugisha Emmanuel). In another study of prediabetes progression (2215 individuals), dietary indicators plus non-dietary clinical variables in machine learning models showed improved calibration and discrimination (Mahdavi, 2025).

In sum, while recent advances reinforce that integrating diet, microbiome, and genomics data with modern machine learning methods significantly improves the prediction of metabolic outcomes, clinical relevance is still constrained by issues of generalizability, interpretability, and prospective validation. Future work must focus on large, diverse longitudinal cohorts, incorporation of dynamic data (time-series, CGM, wearables), and ethically robust models that maintain privacy and fairness.

6. Ethical and Legal Considerations

Nutrigenomics raises complex ethical, legal, and social questions surrounding privacy, equity, consent, and commercial exploitation. Genetic data are inherently sensitive, with implications not only for individuals but also for biological relatives (Ceriani et al., 2023). Ensuring confidentiality, secure storage, and responsible data sharing is therefore paramount. The General Data Protection Regulation (GDPR) and similar frameworks set legal standards for data processing, but compliance remains inconsistent across regions (Wheatley, 2024).

Informed consent must evolve beyond a one-time signature to a dynamic, continuous process reflecting the longitudinal nature of genomic data use. Participants should understand the potential for incidental findings, data reuse, and future reinterpretation of results (Adetunji et al., 2023). Clinicians bear the ethical obligation to communicate genetic risk in a balanced manner avoiding both alarmism and false reassurance (Rahman & Muhammad, 2023). Commercialization further complicates the ethical landscape. The proliferation of direct-to-consumer (DTC) nutrigenetic tests often blurs the boundary between wellness and clinical applications. Many DTC companies lack rigorous validation and regulatory oversight, potentially misleading consumers with non-evidence-based recommendations (Chapman, Manders, & Parnell, 2016). Professional societies emphasize the need for clinician-mediated interpretation of test results to safeguard against misinformation and inequitable access.

Equity concerns are central to ethical implementation. Genomic research has historically underrepresented non-European populations, risking interventions that are less accurate or effective for diverse groups

(Burgess, Rankin, & Turvey, 2020). Additionally, cost barriers may exacerbate socioeconomic disparities in access to precision nutrition (Fenech et al., 2019). Addressing these inequities requires policy frameworks promoting inclusivity in research design, equitable data sharing, and subsidized access to validated genomic testing.

Finally, there are legal considerations regarding liability and clinical responsibility. When genetic data inform dietary advice, clinicians assume partial accountability for test interpretation and patient outcomes. Therefore, national professional boards and regulatory agencies must establish scope-of-practice guidelines delineating roles for dietitians, physicians, and genetic counselors in nutrigenomics-based care.

7. Clinical Challenges and Future Directions

Despite technological progress, numerous clinical and operational barriers hinder the widespread adoption of nutrigenomics. Among them are the lack of standardized testing panels, variable quality of genetic interpretation, and absence of consensus on clinical endpoints (V. Singh, 2023). Many trials rely on surrogate biomarkers rather than hard outcomes such as cardiovascular events or mortality. Additionally, the polygenic and multifactorial nature of diet disease relationships limits the explanatory power of single genetic variants(Bahinipati, Sarangi, Mishra, & Mahapatra, 2021) . Future research should prioritize large-scale, longitudinal cohort studies integrating genomics, metabolomics, and microbiome data to capture complex causal pathways. Randomized controlled trials using adaptive designs and digital phenotyping will enable continuous refinement of personalized dietary algorithms (Shaman, 2024). Incorporating behavioral science into nutrigenomics is also essential; sustained dietary change depends on motivation, social support, and habit formation as much as genetic predisposition (Hosseiniara & Hosseini Zijoud, 2024). Clinically, the future may lie in hybrid precision-nutrition models that combine genomic insight with traditional risk assessment tools. For example, integrating nutrigenetic risk scores with conventional cardiovascular risk calculators could enhance dietary counseling accuracy (Roosan et al., 2023). Furthermore, combining nutrigenomics with pharmacogenomics termed "nutri-pharmacogenomics" may allow co-optimization of diet and medication regimens for metabolic diseases(Morais, Maciel, Duarte, Lais, & Lima, 2024).

Advances in digital health wearable biosensors, mobile apps, and tele-nutrition platforms will play a critical role in implementing these models at scale (Kassem et al., 2023). However, technological innovation must proceed alongside ethical governance to maintain patient trust and data integrity (Blumfield, Nowson, et al., 2022). Building interdisciplinary networks that

unite clinicians, geneticists, ethicists, and policymakers is vital to ensure nutrigenomics evolves responsibly.

8. Conclusion

Nutrigenomics represents a paradigm shift in nutrition science one that integrates molecular biology, data analytics, and clinical practice to deliver individualized dietary interventions. The evidence to date suggests that while genetic personalization can modestly enhance dietary adherence and metabolic outcomes, its clinical utility is context-dependent and remains under investigation. The translation of nutrigenomics into routine healthcare requires validated testing, trained professionals, ethical oversight, and equitable access frameworks.

Moving forward, the field's success will depend on transparent research, interdisciplinary education, and robust public engagement. When implemented responsibly, nutrigenomics holds the potential to bridge the gap between biological individuality and public-health nutrition transforming preventive care into a more precise, ethical, and patient-centered discipline.

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Chapter 9

THE EFFECTS OF SOCIAL MEDIA ADDICTION IN ADOLESCENCE

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Introduction

Adolescence represents a pivotal developmental stage in which personality gains a social dimension, identity exploration intensifies, and individuals strive to balance autonomy with responsibility. In this period, social media plays a significant role in meeting developmental tasks such as expanding peer networks, fostering a sense of belonging, and shaping identity (Avci et al., 2025; Digital Wellness Lab, 2024). However, uncontrolled and excessive engagement with social media may impair adolescents' physical, psychological, and social functioning, aligning with the characteristics of behavioural addictions. Social media addiction is typically defined by difficulties in regulating use, experiencing restlessness when disconnected, and disruptions in academic, interpersonal, or daily life activities (American Psychiatric Association, 2025). Empirical evidence indicates that such problematic use is linked to sleep disturbances, reduced academic performance, social withdrawal, and heightened risks of anxiety and depression among adolescents (Kılıç, 2019; Özer and Özden-Yıldırım, 2023; Primi et al., 2021; Van der Eijnden et al., 2021). Moreover, the persistent urge to remain online and reliance on social comparison mechanisms can erode self-esteem and adversely influence both family (Ekşi and Ümmet, 2013) and peer relationships (Lin et al., 2023). Consequently, examining the multifaceted effects of social media addiction during adolescence is critical for informing preventive and protective strategies at both individual and societal levels.

The purpose of this study is to investigate the physical, psychological, academic, and social consequences of social media use in adolescence. Additionally, it seeks to highlight the adverse outcomes of social media addiction and to discuss protective approaches that may assist adolescents in coping with these challenges. In doing so, the study aims to contribute to the development of interventions that foster healthy and balanced digital media practices in academic and social contexts.

Social Media Addiction and Its Effects

The concept of social media encompasses digital environments that allow interactive engagement and participation (Vidal et al., 2020). It includes diverse online networks through which individuals can communicate both verbally and visually. Nearly half of the global population, about 49%, actively use social media platforms (Kemp, 2020). These platforms cover a wide range of tools, such as e-mail, instant messaging, blogs, online forums, dating sites, entertainment and gaming applications, and social networking services. In the last decade, platforms developed to facilitate communication and information sharing have become widespread across societies. Notably, adolescents constitute more than 80% of the users registered on platforms such

as Facebook, YouTube, Instagram, and Tumblr (Statcounter, 2020). This rapid increase in social media usage has brought about significant consequences, generating both beneficial and detrimental effects on young people as well as the general population (Victor et al., 2024).

Adolescents use social media for various relational, academic, and entertainment-based purposes, such as expressing their feelings and thoughts, establishing and maintaining social relationships, enjoying online content (such as videos, short stories, blog posts, or reels), and collaborating on school assignments and projects (Cheng et al., 2021). Social media enables young people to continue interacting with their families and peers, make new friends, and socialise through photo sharing (Hong et al., 2014). In addition, communication and idea sharing established through group work can contribute to adolescents' learning processes (Alimoradi et al., 2022; Ruckwongpatr et al., 2022). While these functions are important for adolescents, it is also noted that prolonged use of social media platforms carries the risk of developing addiction (Pornsakulvanich, 2018).

Social media addiction is defined as a form of behavioural dependency that develops when individuals engage in uncontrolled and excessive use of social networking platforms. Adolescents are considered the most at-risk group for this condition, as their developmental stage makes them more susceptible compared to other user populations (Doan et al., 2022). Lenhart et al. (2015) demonstrated that with the widespread adoption of smartphones, 71% of adolescents aged 13–17 were active on more than one social media platform, while 24% reported being online almost continuously throughout the day. Similarly, Özer and Özden-Yıldırım (2023) revealed that 31.3% of children between the ages of 6 and 15 primarily use the internet for accessing social media. In another study, İnce and Yılmaz (2020) indicated that 94.5% of adolescents are daily users of at least one social media platform. Collectively, these findings highlight that online engagement begins at an early age and that problematic or addictive use can emerge during the initial phases of adolescence (İnce and Yılmaz, 2020).

The negative effects of problems experienced in the online environment on adolescents are quite diverse. These effects include anxiety, depression, loneliness, and social isolation on an emotional level; substance use, aggressive tendencies, and cyberbullying on a behavioural level; insomnia in relation to sleep; low academic achievement, absenteeism, or dropping out of school; as well as difficulties in relationships with peers and family members (Dong et al., 2022; Mascia et al., 2020).

Social media addiction can have significant negative effects on adolescents' physical health. In particular, prolonged screen exposure causes eye problems,

headaches, fatigue, disrupted sleep patterns (Primi et al., 2021), disruption of biological rhythms, and reduced physical activity. Korkmaz et al. (2023) found that social media addiction negatively affects sleep quality and reduces life satisfaction. A study conducted by Smahel et al. (2015) conducted a study with children aged 9–16 in nine European countries and reported that digital media use not only negatively affects physical health indicators (e.g., eye problems, headaches, loss of appetite, and fatigue) but also triggers aggression and sleep problems shortly after use. A longitudinal study examined the relationship between adolescents' frequency of social media use and bedtime and sleep quality; heavy social media use in the evening was associated with delayed sleep onset and poor sleep quality (Van der Eijnden et al., 2021). Furthermore, the decrease in physical activity alongside the increase in time spent on social media (Ardesch et al., 2023; Buda et al., 2021) may reinforce a sedentary lifestyle, leading to long-term negative consequences such as obesity (Byun et al., 2024), musculoskeletal problems, and overall poor health. These findings indicate that social media addiction poses serious risks to physical health. Considering that sleep patterns and physical activity are critical for healthy development, particularly during adolescence, it is clear that protective and preventive strategies need to be developed to reduce these risks.

One of the most frequently discussed consequences of social media addiction is its negative impact on individuals' mental health (Vidal et al., 2020). A meta-analysis study conducted by Cunningham et al. (2021) reported that an increase in the time spent on social media and frequency of use could trigger both problematic social media use and various mental health issues. Research conducted specifically on adolescents indicates that social media addiction is associated with decreased attention span (Primi et al., 2021), low self-esteem (Fernandes et al., 2020; O'Day & Heimberg, 2021), depressive symptoms (Bányai et al., 2017; Primi et al., 2021; Victor et al., 2024), anxiety, feelings of loneliness, and sleep disorders (Alonzo et al., 2020; Dagher et al., 2021; Luo et al., 2021). Indeed, social media use has been highlighted as a potential reason for the increase in depression and suicide rates observed during adolescence (Twenge et al., 2018; Vidal et al., 2020).

Nevertheless, scholars emphasise the need for caution when interpreting the association between social media use and mental health outcomes (Beeres et al., 2020). Current findings do not provide definitive evidence regarding a direct causal relationship between social media engagement and adolescents' psychological well-being (Heffer et al., 2019; Nesi et al., 2021). Theoretically, the connection between problematic social media use and adverse mental health indicators has been supported by both empirical and longitudinal research; yet, the strength and direction of this association appear to vary according to contextual factors, individual differences, and patterns of use (Beeres et al., 2020; Victor et al., 2024). Importantly, social media should

not be viewed solely as a risk factor, since for some adolescents it may also serve as a source of support. Positive contributions such as enhancing peer relationships, fostering social connectedness, and promoting psychosocial resilience have been documented in the literature (O'Reilly et al., 2023; Senekal et al., 2023). Nonetheless, these benefits may shift into harmful outcomes when use becomes excessive or addictive. For this reason, more comprehensive longitudinal investigations—considering cultural contexts, psychosocial characteristics, and motivations for use—are essential to clarify the complex relationship between social media use and adolescent mental health.

Social media addiction has significant negative effects on adolescents' academic lives. Firstly, it can directly disrupt the learning process by leading to shorter study periods and weakened concentration abilities. Indeed, studies have shown that social media addiction negatively affects students' academic achievement and overall school performance (Dagher et al., 2021; Luo et al., 2021). Furthermore, distractions during lessons, delayed homework submissions, and declining exam performance are among the outcomes frequently reported in the literature. These findings indicate that social media addiction may pose long-term risks not only in psychosocial but also in cognitive and academic domains.

Social media addiction can have multidimensional effects on adolescents' psychosocial development. It can have particularly negative effects on identity development (Keskin and Demirbaş, 2024) and may lead to a decline in face-to-face communication skills. Furthermore, it has been noted that addiction can create disconnections in family (Kumar, 2024) and peer relationships (Andrianie et al., 2024) and may increase the likelihood of exposure to cyberbullying (Pirimi et al., 2021). It has also been reported that social media use may negatively affect young people's ability to empathise (Kumar, 2024).

Literature reviews reveal that family support, communication patterns, and friendships play a critical role among the determining factors of social media addiction (Vossen et al., 2024). In particular, healthy communication and supportive environments within the family enable adolescents to manage their social media use in a more conscious and balanced manner, thereby reducing the risk of addiction. Similarly, it is stated that young people who can establish strong friendships are able to use the time they spend on social media in a more controlled and purposeful manner, and are therefore more resistant to social media addiction. These findings show that social media addiction is shaped not only by individual characteristics but also by social environment and family dynamics. Therefore, the supportive role of families and educational environments is critical in regulating adolescents' social media use and minimising its negative effects. Future research examining the interaction between social environment and individual psychosocial

factors on addiction in a more comprehensive manner could contribute to the development of intervention strategies.

Protective Factors and Prevention Strategies

There are numerous protective factors that reduce the risk of social media addiction in adolescents. Research indicates that family support and effective communication play a critical role in this process (Capa-Luque et al., 2025; Huang et al., 2023; Leijse et al., 2023). Parental guidance and constructive supervision support the controlled use of social media (Lu et al., 2025), while encouraging family activities and offline social events helps balance adolescents' digital behaviour. Research indicates that parents' active and supportive attitudes positively influence adolescents' online behaviour and reduce the risk of social media addiction (Demers et al., 2024). In this context, it is possible to state that regular communication and clear rules within the family constitute an important mechanism for limiting social media use.

Having strong and supportive peer relationships in adolescents' social circles is also considered an important protective factor in preventing social media addiction (Pazdur et al., 2025). A study by Lin et al. (2023) indicated that peer relationships have a positive effect on the satisfaction of adolescents' basic psychological needs and that these effects play a role in preventing social media addiction. Furthermore, it is stated that face-to-face interactions and developed social skills can reduce dependence on online platforms. In this context, contributing to the prevention of social media addiction can be achieved by developing adolescents' social skills and increasing their face-to-face interactions. These findings indicate that adolescents having strong and supportive peer relationships in their social environment is an important protective factor in preventing social media addiction.

Adolescents with high psychosocial resilience and a well-developed sense of self-efficacy are more resistant to negative stimuli received through social media and have a lower risk of developing addiction. In particular, strong self-control and emotional regulation skills make it easier for adolescents to maintain a more conscious and limited level of social media use. The literature shows that psychological resilience plays a mediating role in the relationship between loneliness and social media addiction (Yam et al., 2024). Furthermore, it is emphasised that adolescents have limited ability to regulate their social media use according to their emotional state and that developing these skills is critical for maintaining controlled use (Dreier et al., 2024). These findings suggest that interventions aimed at enhancing adolescents' psychosocial resilience and emotional regulation capacities may be effective in reducing the risk of social media addiction.

Additionally, school-based education and awareness programmes can

raise adolescents' awareness of digital literacy, time management, and the psychosocial effects of online behaviour. Meta-analyses and systematic reviews examining school-based programmes report that these interventions reduce the socio-economic burden of primary prevention while broadening the scope of the target audience (Cañas and Estévez, 2021; Lopez-Fernandez and Kuss, 2020; Romero Saletti et al., 2021).

Psychological counselling and cognitive behavioural interventions are particularly effective methods for adolescents showing signs of excessive use or addiction; these interventions enable adolescents to recognise their digital behaviours, develop self-control skills, and acquire alternative coping strategies. Cognitive behavioural therapies have been shown to be effective in reducing symptoms of internet addiction and improving psychological well-being in adolescents (Malinauskas and Malinauskiene, 2019). Such preventive and intervention-focused approaches, when implemented early on, can significantly reduce the risk of social media addiction. These strategies encourage adolescents to establish healthy and balanced relationships in the digital world and support their overall psychosocial development.

Conclusions and Recommendations

This study examined the multidimensional effects of social media use during adolescence and found that it can lead to various negative consequences at the physical, mental and social levels. Social media addiction is associated with negative psychosocial outcomes in adolescents, such as reduced attention span, sleep disorders, poor academic performance, anxiety and depression. However, it is noted that family support, effective communication, strong friendships, psychosocial resilience, and a sense of self-efficacy function as protective factors in reducing the negative effects of social media addiction. In this context, approaches that help adolescents manage their social media use in a balanced and conscious manner are becoming increasingly important. Families can strengthen communication by adopting warm, supportive, and guiding attitudes, encouraging offline activities and shared family activities. In the school environment, the implementation of digital literacy and social skills programmes can contribute to adolescents developing conscious usage habits. Furthermore, cognitive behavioural interventions and psychological counselling programmes are recommended for adolescents who overuse social media or show signs of addiction. These multi-faceted strategies can both strengthen adolescents' psychosocial development and minimise the risk of social media addiction by supporting them in establishing healthy and balanced relationships in the digital world.

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Chapter 10

RADIOLOGICAL MAP OF ANATOMY: MEASUREMENT TECHNIQUES FROM IMAGING

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Introduction

Anatomical structures can be evaluated quantitatively through linear, angle, area, volume and tractography-based measurements on medical images. These measurements enable the determination of gender, age-related structural changes, and the collection of important data for clinical research.

Linear Measurements

Linear measurement refers to the distance measurement between two anatomical structures. Point-to-point linear distance calculations between specified dental anatomical structures have been studied up-to-date. For example, calculations such as the distance between the right and left infraorbital foramen were made. This method allows for quantitative analysis of jaw anatomy and may be useful in applications such as isurgical planning, prosthesis design or clinical evaluation (Ersalıcı et al., 2025).

In the study of Torimitsu et al. (2018), perpendicular length from the most anterior margin of the hyoid body to the line connecting the most distal points of the greater hyoid horns and the linear distance between the most lateral edges of the hyoid body measurements were made (Figure 1). And these measurements have been proven to contribute significantly to gender determination. The data obtained from the study may be an important indicator for forensic cases.

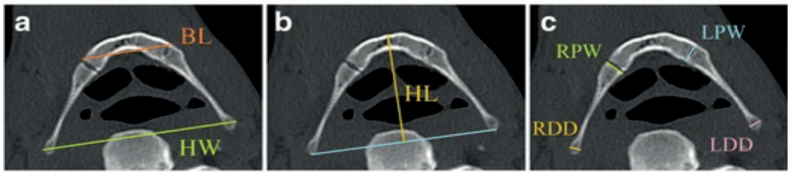

Figure 1. *Two-dimensional computed tomography images showing measurements in the sagittal plane: (a) hyoid width (HW) and body length (BL); (b) hyoid length (HL); (c) width of the left proximal end (LPW), width of the right proximal end (RPW), diameter of the left distal end (LDD), and diameter of the right distal end (RDD) (Torimitsu et al., 2018).*

In a study on femur measurements, gender determination equations in the literature were tested on the obtained linear measurement data. They suggested that population-specific femoral measurements obtained with CT are more reliable than those obtained directly with osteometry and that the femur has a high sexual dimorphism with relevant forensic applications (Ujaddughe, Haberfeld, Bidmos, & Olateju, 2025).

Angular Measurements

The angle between the roof of the femoral notch and the long axis of the femur was defined as the alpha angle. The relationship between the anterior cruciate ligament (ACL) and this angle was examined. While several anatomical factors and alpha angle affect the risk of ACL injury in women, only alpha angle was found to be a determining factor in men. The alpha angle has been shown to be a significant risk factor in both genders (Barnum, Boyd, Vacek, Slauterbeck, & Beynnon, 2021).

Condylar path (CP) angle and lateral guidance (LG) angles measured flatter on the affected side in all participants. The results of this study, conducted on individuals with chronic, unilateral temporomandibular joint disorder (TMD) pain and untreated, natural occlusion, shows that the habitual chewing side may contribute to ipsilateral chronic TMD pain and this condition can be diagnosed by measuring the CP and LG angles (Santana-Mora et al., 2021).

Area Measurements

Peritoneal surface area in a living body was measured to provide baseline data for clinical applications. Abdominal computed tomography images of adult individuals were analyzed. The peritoneal surface was segmented and three-dimensionally modeled using artificial intelligence-assisted medical imaging software. Additionally, the peritoneal surface area of male individuals was found to be 3.7% larger than that of females (Choi, Park, Jeon, Lee, & Baek, 2024).

A recent surface area measurement study targeted the psoas major muscle. Muscle surface area measurement was performed in two stages. Muscle thickness measurements were made with an ultrasound (US) device and an inertial measurement unit (IMU) consisting of a gyroscope, accelerometer and magnetometer was used to increase the accuracy of these measurements. Thanks to the IMU, the angle of the ultrasound probe is fixed, making the measurements more consistent and increasing the reliability of the study. A significant and highly positive correlation was found between muscle thickness measured by ultrasound and anatomic cross-sectional area (ACSA) measured by magnetic resonance imaging (MRI). ACSA estimation was made reliably through regression analysis and it was stated that this approach may be useful in the early diagnosis and follow-up of conditions related to muscle mass loss such as sarcopenia (Ito et al., 2024).

Each talus and calcaneus were photographed from a fixed distance using a professional camera with a tripod and a millimetric ruler. Morphometric measurements were made on the photographs using the Imagej® image

analysis program (Version date: 2023, USA). Metric measurements, angular measurements and joint surface area measurements were made on these bones. It is thought that the study data can guide surgical interventions by providing a good knowledge of the anatomical structure of the region (İpek, Gümüş, & Akdoğan, 2025).

Volumetric Measurements

Horos software was used as the reference method for 3D planimetric volume measurement of pituitary adenomas. In addition, a practical alternative called the Ellipsoid formula was also implemented, but it was suggested not to be preferred because it showed lower volumetric data trends than the horos software. They also stated that they preferred the Horos software system because it works similarly to OsiriX (de Figueiredo et al., 2023).

Measure®, FSL-FIRST v.5.0.4, volBrain v.1.0, FreeSurfer v.5.1 and ITK-SNAP v.1.8 were used. The nucleus caudatus and hippocampus regions were studied to evaluate the accuracy levels of these software in different morphological difficulties. Automatic segmentation methods are sufficiently accurate for easy structures (e.g. caudate), but for difficult structures (e.g. hippocampus) they only correlate with volume but fail to approximate the true value. Therefore, manual or stereological volume measurement should be preferred especially in studies requiring small samples and high sensitivity. The number of structures examined, expertise and time can also be taken into consideration when selecting the segmentation technique (Akudjedu et al., 2018).

Intracranial and ventricular volumes were evaluated by the researchers using 3D Slicer (v5.0.2) on CT data of healthy individuals and hydrocephalus patients (including those with missing skulls). Two tools in 3D Slicer—Swiss Skull Stripper and Segment Editor—were used for these calculations. Although volumetric differences were observed according to gender and age, no statistically significant relationship was found with the disease. This open-source approach was recommended by the authors for future studies in terms of accuracy and consistency (Huang, Huang, Guan, Liu, & Que, 2025).

While the software programs 3D Slicer, FreeSurfer, and volBrain are free, reliable, and do not require complex programming, they do have certain limitations and important differences. VolBrain and 3D Slicer provide a completely automatic, visually accurate and easy method. T1 MRI-derived FreeSurfer may overestimate the true value even when high-quality 3D T1 scans are used in ICV calculations. While FreeSurfer and volBrain only use T1 MRI scans, 3D Slicer can work with more scan types (Harkey, Baker, Hagen, Scott, & Palys, 2022).

ImageJ software allows the application of planimetry technique used to calculate the volume of anatomical structures. In this technique, ROI boundaries are determined manually. The total volume (V) was calculated by multiplying each cross-sectional area (Σa) by the cross-sectional spacing (t) ($V = \Sigma a \times t$). In the study, a significant difference was found between genders in the volume of Medulla Oblongata (MO). MO volume was found to be larger in males compared to females. A gradual decrease in MO volume has been reported in healthy individuals between the ages of 20–40 (Mohamed et al., 2023).

Volume comparisons were made on incisors according to measurement methods. The volumes of the teeth were calculated using manual segmentation techniques in 3D Doctor and ImageJ (Fiji) programs, manual and automatic segmentation methods in ITK-Snap program, and automatic segmentation methods in 3D Slicer program. Measurements made with manual segmentation in ITK-Snap and ImageJ programs, gave the closest results to the physical volume measurements of the teeth. Automatic segmentation method in ITK-Snap and 3D Slicer programs are an easy to use and less time consuming method. In 3D Doctor software, volume measurements tended to increase with larger voxel size (Aydogdu, Adisen, & Ertas, 2024).

VolBrain-HIPS data pipeline was preferred for automatic segmentation on MRIs of healthy individuals. The HIPS pipeline, a special tool of the VolBrain system, divides the hippocampal subfields and the hippocampus into segments and processes MRIs in the Neuroimaging Information Technologies Initiative (NIFTI) format. The researchers converted sagittal 3D-T1 DICOM format image files to NIFTI format and uploaded them to VolBrain. Gender and right-left comparisons of hippocampal data are presented not only with absolute measurements but also for volumetric data. They reported that hippocampus-tuned volume information should also be taken into account when analyzing VolBrain data and making clinical or anatomical decisions. Alternative methods have been used to adjust volumetric data, including total hippocampal volume. They stated that they accepted the asymmetry index as an indicator of the magnitude of asymmetry and made the negative asymmetry index data positive. They performed regression modeling based on age and gender for comparisons of asymmetry magnitude. They suggested that in the asymmetry data generated by VolBrain, asymmetry be considered as a magnitude scale in individuals with a right or left dominant hippocampus or hippocampus subfield. They introduced alternative meaningful regression models in their study to observe how the volumetric numerical composition of hippocampus subfields changes with age. They thought that the asymmetry data reported by VolBrain needed to be discussed and may contain errors (Özen et al., 2025).

VolBrain software was developed for automatic segmentation and volume measurement of brain structures. The researchers used this method because this system's online accessible pipeline called Vol2Brain which provides volumetric data of regions such as subcortical structures, brainstem, cerebellum and intracranial space without requiring advanced technical knowledge from the user.

In their study, they found that volume reduction in structures such as nucleus accumbens, nucleus caudatus, putamen and thalamus was higher in the right hemisphere in male individuals over 35 years of age. The findings from their studies show that there are some subcortical structures that are more sensitive to the aging process and that hippocampal changes occur later (Peric, Romčević, Mastilović, Starčević & Boban, 2025).

Voxel-Based Morphometry is a method that allows for the comparison of gray matter volume between groups; Stalter et al. used this method in their study and found significant gray matter loss in certain regions of the cerebellum in older individuals compared to younger individuals and thus, it has been concluded that aging leads to significant structural changes in cerebellar structures (Stalter, Yogeswaran, Vogel, Sörös, Mathys, & Witt, 2023).

TotalSegmentator is a system developed for the segmentation of many anatomical structures working with CT data sets and used for volumetric calculations (Wasserthal et al., 2023).

Various software tools have been developed to perform anatomical measurements, segmentation, and volumetric analysis using radiological imaging techniques. Some of the most commonly used ones are shown in Table 1.

Table 1: *Commonly Used Software Tools for Anatomical Measurement and Segmentation from Radiological Imaging*

Software / System	Area of Application	Technology / Features	Access
VolBrain	The volume of brain structures	Automatic segmentation (MRI-based)	Web-based (free)
FreeSurfer	Cortical, subcortical volumes	Surface modeling, volume measurement, brain analysis	Open source
Horos	General medical volume measurement	DICOM image reading and volume measurement	Open source (MacOs)
OsiriX	Clinical imaging and volumetric analysis	DICOM-supported, advanced volume measurement module	Open source (MacOs)
3D Slicer	All body structures (brain, bones, organs, etc.)	Modular structure, segmentation, 3D modeling	Open source
ITK-SNAP	Brain, tumor, organ volume	Semi-automatic segmentation	Open source
ImageJ (FIJI)	Histological and medical images	Area-volume calculation, 3D support with special plugins	Open source
Voxel-Based Morphometry	Analysis of brain volume differences	Gray matter volume comparison in MRI images	MATLAB add-on (free)
TotalSegmentator	Automatic 3D segmentation	Deep learning with 100+ structure segmentation	Open source

Tractography / DTI Measurements

Diffusion tensor imaging (DTI) is becoming increasingly important in the evaluation of brain metastases (BM) in terms of revealing microstructural changes. A systematic review has demonstrated that DTI can distinguish BMs from both primary brain tumors and different metastatic sources. The relationship between tractography and BMs is better understood. This technique is an imaging technique that models and visualizes the three-dimensional pathways of nerve fibers in the brain using DTI data. This can contribute to surgical planning and radiotherapy strategies. The integration of both quantitative DTI measurements and tractographic information into multidisciplinary decision-making processes contributes significantly to early diagnosis and treatment planning (Ghaderi, Mohammadi, & Fatehi, 2024).

Dauleac, Mertens, Frindel, Jacquesson, and Cotton (2025) in their studies, using the anterior commissure (AC) and posterior commissure (PC) lines as a reference, they mapped the brain's projection pathways in healthy

individuals in three dimensions using DTI and tractography methods. For each projection path, specific ROI coordinates defined relative to this reference line were used and the road network has been visualized using tractographic data obtained from these regions (Figure 2). Thus, the anatomical locations of the projection pathways have been precisely determined. They have stated that this coordinate-based approach could be useful in clinical and research applications, particularly in terms of distinguishing projection pathways at the spinal cord level (Dauleac, Mertens, Frindel, Jacquesson, & Cotton, 2025).

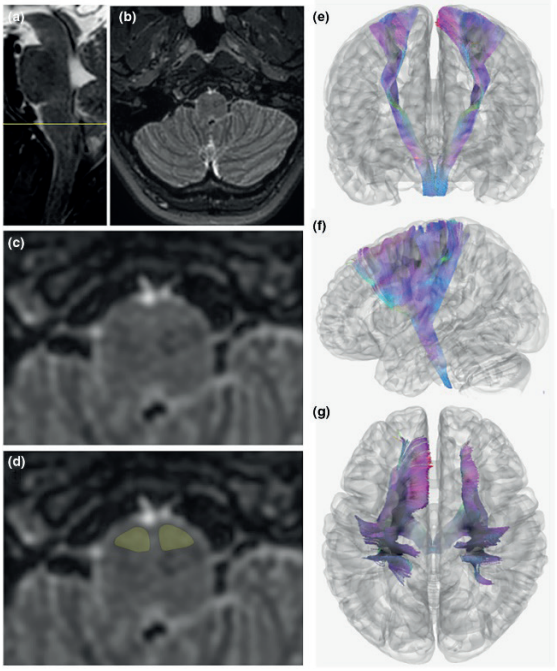

Figure 2. *ROI design and 3D tractography representation of the corticospinal tractus. (a) Sagittal T2-weighed image of the brainstem; the yellow line is located at the level of the pyramids, in the medulla, and represents the axial section plane of the image in panel b. (b) Axial T2-weighed image through the pyramids, just above the decussation. (c) Enlargement of the image in panel b, centered on the medulla. (d) ROIs defining the pyramids are highlighted. Coronal (e), sagittal (f), and axial (g) views allow to follow corticospinal fiber (Dauleac, Mertens, Frindel, Jacquesson, & Cotton, 2025).*

Elastography-Based Measurements

In the study by Shan et al. (2025), they examined the mechanical separation between the skull and brain in individuals exposed to repetitive head injuries (RHI) using elastography measurements based on the skull-brain interface obtained using the magnetic resonance elastography (MRE) method. Controlled 60 Hz vibrations were transmitted to the brain via a passive driver. The 3D displacement data generated by the impact was recorded using an Spin

Echo – Echo Planar Imaging-based Dual-Sensitivity Displacement Mapping Magnetic Resonance Elastography pulse sequence. The study monitored the severity of tissue deformation, movement transmission at the interface, and potential integrity losses in the PAC (pia-arachnoid complex) structure. High levels of RHI exposure have caused an increase in these parameters. Researchers have stated that elastography-based biomarkers may be useful for neurotrauma monitoring and treatment approaches.

3D Reconstruction Measurements

In a study conducted by Ruican et al. (2021), histological heart sections from five fetuses terminated at 12–13 weeks of gestation were scanned microscopically, corrected using MATLAB, and reconstructed in 3D using Amira–Avizo software. They reported that cardiac measurements ranged from 14/5/3.5 mm to 17/7/4 mm, and that the AV septum, ventricular outflow tracts, aorta and pulmonary artery trunk, and veno-atrial connections could be safely visualized. Although natural morphological deformations were observed, this did not prevent the evaluation of anatomical structures. The authors emphasize that 3D reconstructions obtained from histological sections are a viable method for detailed examination of early fetal heart anatomy and reliable measurements (Ruican et al., 2021).

Conclusion

Various software programs, it is possible to evaluate hard and soft tissues of human anatomy. This serves as a guide for the early diagnosis of diseases and treatment planning.

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Chapter 11

TRANSURETHRAL RESECTION (TUR) SYNDROME: AN ANESTHESIOLOGICAL PERSPECTIVE ON PATHOPHYSIOLOGY, RECOGNITION, AND MANAGEMENT

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Introduction

Anesthetic management plays a pivotal role in the safety and success of urological surgeries, which often involve significant fluid shifts, bleeding risks, and physiologic stress responses. The anesthesiologist must balance hemodynamic stability, fluid management, and optimal surgical conditions while remaining alert to unique complications such as irrigation fluid absorption and electrolyte disturbances. Close coordination between the surgical and anesthesia teams ensures early recognition of adverse events and improves perioperative outcomes. In procedures like transurethral resection of the prostate, where intravascular absorption of irrigation fluid may occur, the anesthesiologist's vigilance is vital for preventing life-threatening complications such as TUR syndrome.

A broad range of transurethral, hysteroscopic, and percutaneous procedures utilize large volumes of irrigating or distending fluids to clear blood and tissue, maintain visualization, and expand the operative field. Typical examples include transurethral resection of the prostate (TURP) and transurethral resection of bladder tumors (TURBT), hysteroscopic diagnostic and therapeutic procedures (e.g., submucosal leiomyoma resection), percutaneous nephrolithotomy, arthroscopy, and other minimally invasive interventions. Among these, TURP remains a gold-standard therapy for bladder outlet obstruction secondary to benign prostatic hyperplasia, with high efficacy rates when appropriately selected.

The TUR syndrome is a potentially life-threatening complication driven by systemic absorption of irrigating solutions, leading to dilutional hyponatremia, hypo-osmolality, fluid overload, and—depending on the solute—specific toxicities. Although modern energy modalities (e.g., bipolar resection) and isotonic saline irrigation have decreased its frequency, anesthesiologists must recognize early signs, guide intraoperative prevention, and coordinate prompt treatment when it occurs (Mamoulakis et al., 2009; Sinha et al., 2022).

This chapter synthesizes the pathophysiology, risk factors, clinical picture, diagnostic approach, and anesthetic management of TUR syndrome, integrating practical algorithms and contemporary guidance on the use of hypertonic saline for symptomatic hyponatremia

Irrigation Fluids and Electrosurgery Modalities

· Monopolar TUR and Non-electrolyte Fluids

During monopolar transurethral resection of the prostate (TURP), irrigating solutions that contain electrolytes—such as normal saline or Ringer's lactate—are contraindicated because they conduct electrical current and interfere with the dispersion of monopolar cautery energy. Instead, non-

electrolyte and non-conductive irrigants have traditionally been employed to ensure clear visualization and safe resection. Among these, the most commonly used are 1.5% glycine, 3% sorbitol, and 5% mannitol. Each solution possesses distinct physicochemical properties, osmolarity, and metabolic profiles that influence both surgical visualization and systemic effects when absorbed into the circulation.

1.5% glycine, with an osmolarity of approximately 200 mOsm/kg, is markedly hypo-osmotic relative to plasma and completely non-electrolytic. When absorbed in significant quantities, it can lead to dilutional hyponatremia as well as metabolic disturbances such as hyperglycinemia and hyperammonemia, the latter resulting from hepatic metabolism of glycine to ammonia. In some cases, excessive glycine absorption has been linked to visual disturbances or transient blindness, attributed to its neurotransmitter-like inhibitory effects on the retina and central nervous system.

Similarly, 3% sorbitol is also hypo-osmotic and, upon systemic absorption, can raise blood glucose concentrations, posing a particular hazard in diabetic or insulin-resistant patients. 5% mannitol, by contrast, is nearly iso-osmotic with plasma (approximately 275–285 mOsm/kg) but remains non-electrolytic. Mannitol absorption tends to cause osmotic diuresis and intravascular volume shifts, potentially aggravating fluid imbalance or hypotension in vulnerable individuals (Mamoulakis et al., 2009).

Because these hypo-osmotic non-electrolyte irrigants lack the buffering and ionic capacity of plasma, their large-volume absorption during surgery may result in profound dilutional hyponatremia, hypo-osmolality, and subsequent neurological or cardiovascular complications—the hallmark features of classic TUR syndrome. Consequently, careful monitoring of irrigation pressure, operative duration, and total fluid volume is crucial whenever monopolar techniques and such solutions are used.

- **Bipolar TUR and Isotonic Saline**

Bipolar transurethral resection (TUR) systems have revolutionized endoscopic urologic surgery by enabling the use of isotonic saline (0.9% NaCl) as an irrigating medium instead of non-electrolyte hypotonic solutions required in monopolar techniques. The isotonic nature of saline prevents the conduction of electrical current between the active and return electrodes, confining energy delivery to the tissue between the bipolar loop and the return electrode on the resectoscope (Mamoulakis et al., 2009; Sinha et al., 2022). This technology markedly reduces the risk of classic TUR syndrome, as the absorption of isotonic saline does not produce the same degree of dilutional hyponatremia or hypo-osmolality that characterizes monopolar glycine or sorbitol-based resections.

Nevertheless, the shift to saline irrigation has introduced a different spectrum of physiological disturbances. The absorption of large quantities of isotonic saline—particularly during prolonged or high-pressure resections—can still lead to intravascular volume overload, elevated right-sided cardiac pressures, and pulmonary congestion. In some cases, excessive saline absorption has been associated with the development of hyperchloremic metabolic acidosis due to chloride retention and subsequent bicarbonate dilution (You et al., 2021). Furthermore, elderly or cardiac-compromised patients may not tolerate rapid changes in circulating volume, predisposing them to heart failure or respiratory distress.

Although bipolar technology has significantly mitigated the incidence of electrolyte-related complications, it has not completely eliminated the hemodynamic and metabolic risks linked to irrigant absorption. Therefore, strict intraoperative vigilance—particularly regarding irrigation pressure, operative time, and early recognition of volume overload—remains essential for maintaining patient safety and minimizing postoperative morbidity (Mamoulakis et al., 2009; Sinha et al., 2022; You et al., 2021).

Osmolality, Serum Osmolality Formula and Determinants

Normal serum osmolality is approximately 280–310 mOsm/kg. A practical estimate of serum osmolality can be calculated using the following formula:

Serum Osmolality (mOsm/kg) = $(2 \times [Na^+])$ + (Glucose (mg/dL) / 18) + (BUN (mg/dL) / 2.8)

Serum sodium concentration is the principal determinant of plasma osmolality. Even modest reductions in serum sodium can lead to clinically significant hypo-osmolality, particularly when the decline occurs rapidly. Understanding the determinants of serum osmolality is crucial for anesthesiologists, as even minor deviations can profoundly influence cellular water balance and cerebral function during perioperative care (McPherson & Pincus, 2023).

Pathophysiology of TUR Syndrome

Systemic absorption of irrigant occurs via open prostatic venous sinuses or mucosal breaches. The absorbed volume is proportional to:

- Hydrostatic pressure of the fluid column (bag height),
- Number and size of opened venous channels, and
- Duration of resection/irrigation.

Typical absorption during TURP has been reported around 10–30 mL/min of resection time, with wide variability (Aziz et al., 2015; Bapat et al., 2007). As a rough clinical rule, ~1 liter of absorbed hypo-osmotic fluid may reduce serum Na^+ by ~5–8 mmol/L, with symptoms escalating as Na^+ falls below 125–120 mmol/L.

The consequences include:

1. Dilutional hyponatremia & hypo-osmolality: Systemic absorption of hypo-osmotic irrigating solutions leads to a rapid decline in serum sodium concentration, resulting in dilutional hyponatremia and decreased plasma osmolality. As extracellular osmolality falls, water moves intracellularly, particularly into neurons and glial cells, producing cerebral edema. This process increases intracranial pressure and manifests clinically as nausea, vomiting, headache, restlessness, confusion, seizures, and, in severe cases, coma due to brain swelling and neuronal dysfunction.

2. Volume overload: The intravascular uptake of large volumes of irrigant expands plasma volume and can overwhelm cardiac compensatory mechanisms. Depending on the patient's baseline cardiovascular status, this may present as hypertension, reflex bradycardia (Cushing's triad in response to raised intracranial pressure), or hypotension if cardiac decompensation occurs. When fluid accumulation exceeds the heart's pumping capacity, pulmonary edema and congestive heart failure may develop, especially in elderly or cardiac-impaired patients.

3. Solute-specific toxicity: Each irrigating solute carries unique metabolic and toxicological properties that contribute to the clinical presentation.

- **Glycine:** Absorption can result in elevated serum glycine and ammonia levels (hyperglycinemia, hyperammonemia), which may cause transient visual disturbances, blurred vision, or even temporary blindness due to retinal and cortical inhibitory neurotransmission.
- **Sorbitol:** When absorbed systemically, sorbitol is metabolized to fructose and glucose, potentially leading to hyperglycemia and metabolic stress, particularly in diabetic patients.
- **Mannitol:** Although nearly iso-osmotic with plasma, mannitol absorption can induce osmotic diuresis and rapid intravascular volume shifts. This may lead to hypotension, electrolyte imbalance, or dehydration during the postoperative period.

4. Hemolysis: The sudden exposure of erythrocytes to markedly hypo-osmotic solutions can cause red blood cell lysis. Intravascular hemolysis exacerbates anemia and reduces oxygen delivery to tissues, while free hemoglobin may precipitate renal tubular injury and pigment nephropathy. These effects further complicate the clinical course and contribute to multi-organ dysfunction if not promptly recognized and corrected.Thermal energy and tissue handling further open venous channels, and patient factors (e.g., cardiac reserve) modulate clinical impact.

Risk Factors

- Prolonged operative time exceeding approximately 60 minutes substantially increases the risk of irrigant absorption, since prolonged resection maintains open venous channels and extends mucosal exposure to fluid influx.
- Elevated irrigation pressure, whether due to excessive bag height or the use of pressurized infusion systems, augments hydrostatic forces that drive irrigant directly into the prostatic venous plexus and systemic circulation.
- A larger prostate gland with a rich venous network facilitates greater vascular absorption, predisposing the patient to significant fluid and solute shifts during prolonged transurethral resection.
- Performing monopolar TUR with hypo-osmotic non-electrolyte fluids such as glycine, sorbitol, or mannitol markedly elevates the likelihood of classical TUR syndrome through rapid systemic absorption of these solutions.
- Trendelenburg positioning increases pelvic venous congestion, and when combined with poor bladder drainage or obstructed outflow, it enhances the probability of intravascular fluid entry.
- Under general anesthesia, early neurologic manifestations of hyponatremia—including confusion, agitation, or visual disturbances—may remain unnoticed, delaying diagnosis and intervention.
- The presence of comorbid conditions such as impaired cardiac reserve, renal insufficiency, or pre-existing hyponatremia reduces physiological tolerance to acute volume and electrolyte changes, thereby amplifying the clinical severity of absorbed irrigant effects.

Clinical Manifestations of TUR Syndrome	
Early / Often Subtle Signs	**Progressive / Severe Manifestations**
Perioral, facial, or neck paresthesias and burning sensations.	Marked hyponatremia (<125–120 mmol/L) and hypo-osmolality.
Restlessness, headache, nausea, or vomiting.	Neurological symptoms progressing from confusion to seizures and coma.
Visual disturbances, especially following glycine absorption.	Pulmonary edema and hypoxemia.
Hypertension accompanied by bradycardia, chest tightness, or dyspnea.	Electrocardiographic abnormalities such as QT prolongation or arrhythmias.
	Hemolysis presenting with dark urine and anemia.

Table 1. *Clinical Manifestations of TUR Syndrome (Symptoms can begin within 15 minutes of resection onset but may also present up to 24 hours postoperatively, especially if absorption was unrecognized intraoperatively)*

Diagnosis and Monitoring

Maintain a high index of suspicion for TUR syndrome, particularly when non-electrolyte irrigants are used, the duration of surgery is prolonged, or postoperative recovery is slower or atypical. Continuous vigilance and structured monitoring can allow for early detection and prompt intervention. Recommended actions include;

- Immediate laboratory evaluation: Serum sodium and serum osmolality should be measured without delay to assess for dilutional hyponatremia and hypo-osmolality. Additional parameters such as plasma glucose, blood urea nitrogen (BUN), creatinine, arterial blood gases (ABG) to evaluate acid–base balance, and hematocrit levels provide essential information about metabolic disturbances, renal handling of absorbed fluid, and degree of hemodilution.

- Comprehensive hemodynamic and cardiorespiratory monitoring: Continuous ECG tracing and pulse oximetry are indispensable for detecting arrhythmias, QT interval prolongation, and hypoxemia, which may signal significant electrolyte shifts or pulmonary involvement. Capnography assists in evaluating ventilation adequacy, and in hemodynamically unstable patients, invasive arterial pressure monitoring is advised to guide fluid therapy and vasoactive support precisely.

- Focused respiratory and chest examination: Auscultation for crackles, assessment of oxygen saturation trends, and observation for

respiratory distress are necessary to identify pulmonary edema at an early stage. Portable chest imaging may be warranted in symptomatic or high-risk patients to confirm interstitial fluid accumulation and guide diuretic therapy.

- Differential diagnostic evaluation: When intraoperative or postoperative deterioration occurs, the clinician should also consider other potential causes such as excessive anesthetic depth, hypercapnia, residual neuromuscular blockade, pharmacologic side effects, or acute endocrine disturbances. Distinguishing these entities from true fluid absorption–related pathology is essential to avoid delayed recognition and inappropriate management.

Anesthetic Management

Choice of Anesthesia

Regional (spinal) anesthesia remains the preferred technique for most transurethral procedures, as it enables the anesthesiologist to recognize early neurological and cardiovascular manifestations of TUR syndrome without the masking effects of general anesthetic agents. Establishing a sensory block to approximately the T10 dermatome provides sufficient anesthesia and muscle relaxation for cystoscopic or transurethral resection (TUR) operations while preserving patient consciousness and cooperation. During regional anesthesia, the onset of restlessness, visual disturbances, or sudden nausea can alert the clinician to early systemic absorption of irrigant fluid before severe biochemical derangements occur.

By contrast, general anesthesia, though necessary in certain situations such as uncooperative patients or prolonged procedures, may obscure the initial neurological indicators of fluid overload and hyponatremia. Under general anesthesia, the earliest warning signs are typically hemodynamic or respiratory in nature. Sudden fluctuations in blood pressure—whether abrupt hypertension due to increased intravascular volume or hypotension secondary to myocardial depression—should raise suspicion. Similarly, bradycardia, arrhythmias including widened QRS complexes or ventricular tachycardia, and unexpected hypoxemia may all represent indirect evidence of irrigant absorption and volume expansion. In some cases, delayed emergence or agitation upon recovery from anesthesia can serve as a late but critical clue to underlying electrolyte imbalance.

Ultimately, the choice between regional and general anesthesia should be individualized based on the patient's comorbidities, anticipated surgical duration, and the surgeon's experience. Regardless of technique, continuous vigilance for hemodynamic instability and careful correlation of intraoperative

changes with potential irrigant absorption remain essential to prevent delayed recognition and ensure timely management of developing TUR syndrome (Bah, 2018).

Intraoperative Monitoring and Prevention

During transurethral procedures, intraoperative monitoring and preventive strategies play a decisive role in minimizing the risk of TUR syndrome and its related complications. The irrigation pressure should always be kept as low as possible while still maintaining adequate visualization of the surgical field. Ideally, the irrigation bag should not exceed a height of 75 cm above the pubic symphysis, since higher pressures markedly increase hydrostatic force and promote fluid entry into the venous system. Pressure-assisted irrigation devices are best avoided because they can generate uncontrolled flow and accelerate systemic absorption of irrigant fluid.

Frequent bladder decompression is another essential preventive step. Continuous or intermittent drainage prevents overdistension of the bladder, which otherwise raises intravesical pressure and encourages transurethral absorption of irrigation solution. The surgical team should regularly verify the patency of the outflow channel, and in situations involving large resections or poor drainage, a suprapubic catheter can be inserted to maintain low pressure and clear visibility throughout the operation.

Whenever possible, bipolar resection systems using isotonic saline should be preferred, as they substantially reduce the likelihood of dilutional hyponatremia compared to the non-electrolyte fluids employed in monopolar techniques (Mamoulakis et al., 2009; Sinha et al., 2022). Nevertheless, even isotonic saline can cause hypervolemia or metabolic acidosis when absorbed in excessive quantities; thus, vigilant hemodynamic and volume monitoring remains essential.

The total operative time should also be minimized to reduce cumulative exposure to irrigating fluid. Surgical duration beyond 60 minutes increases the probability of venous absorption, and for very large prostates or complex resections, staging the operation into two or more sessions may be a safer alternative. Similarly, the degree of Trendelenburg positioning should be minimized, as steep head-down tilt elevates pelvic venous pressure and encourages systemic uptake of the irrigant.

Early coagulation of bleeding surfaces is an equally critical measure. Prompt and effective hemostasis limits venous sinus exposure, reduces oozing, and thereby prevents ongoing absorption of hypotonic or isotonic fluids. Using appropriate electrosurgical settings and maintaining a steady rhythm of resection and coagulation can significantly limit the total absorbed volume.

Finally, in prolonged or high-risk cases, periodic measurement of serum sodium concentration should be considered to detect early biochemical evidence of irrigant absorption. A gradual decline in serum sodium during surgery may precede clinical symptoms and serve as an early indicator of evolving dilutional hyponatremia, allowing the anesthesiologist to initiate corrective measures before severe manifestations develop.

Estimating Absorbed Volume

When both preoperative and postoperative serum sodium concentrations are available, a rough estimation of the total volume of absorbed irrigating fluid can be made using basic distribution principles. Because extracellular fluid represents roughly 20 % of total body weight, the magnitude of serum sodium dilution can serve as a clinical surrogate to infer approximate absorption volume. Although this calculation provides only a broad approximation, it remains useful for contextualizing the degree of risk and determining the intensity of postoperative monitoring required in patients undergoing transurethral resection.

Despite the convenience of this approach, several experimental and clinical studies have shown that tracer-based methods provide a more precise quantification of irrigant absorption. Described the use of ethanol as an indicator substance, where small amounts of ethanol are added to the irrigating fluid and breath alcohol concentrations are periodically measured. The rise in ethanol detected in exhaled air directly correlates with the amount of fluid absorbed during surgery, enabling real-time monitoring of systemic uptake. Such techniques have proven particularly valuable in preventing severe dilutional hyponatremia and related neurologic complications (Zhang, 2020).

In practice, while ethanol dilution monitoring is considered the gold standard in research settings, simplified clinical models based on changes in sodium concentration and estimated extracellular distribution volume still offer a pragmatic alternative for routine intraoperative and postoperative evaluation. The combined application of both physiologic estimation and tracer-based monitoring represents the most comprehensive strategy currently available for assessing irrigant absorption in transurethral surgery (Hahn, 2016).

Acute Management Algorithm

- **Immediately discontinue the surgical procedure**: The very first and most crucial step upon recognizing signs of TUR syndrome is to halt the transurethral resection at once. Continuing resection not only prolongs patient exposure to the irrigant source but also sustains open venous sinuses through which additional fluid can rapidly enter the circulation. Early surgical cessation helps limit further

absorption, stabilize hemodynamics, and allows the anesthesiologist to shift focus toward resuscitative and corrective measures without ongoing fluid influx.

- **Secure the airway and optimize oxygenation:** Maintenance of airway patency and adequate oxygen delivery must follow immediately. Hypoxemia is a common manifestation of pulmonary edema and cerebral dysfunction resulting from fluid overload or hyponatremia. Supplemental oxygen should be provided promptly, and if the patient exhibits reduced consciousness, uncontrolled seizures, or respiratory distress, endotracheal intubation should be performed early. Controlled mechanical ventilation not only safeguards oxygenation but also facilitates precise control of carbon dioxide levels, which is critical in patients with altered intracranial dynamics.

- **Stabilize circulation and manage blood pressure alterations:** Hemodynamic instability may manifest as either hypertension due to intravascular volume expansion or hypotension secondary to myocardial depression and vasodilation. Continuous blood pressure monitoring—preferably with invasive arterial access in unstable patients—guides appropriate intervention. Hypertension can often be managed with short-acting vasodilators or deepening of anesthesia if sympathetic overactivity is suspected, while hypotension requires cautious administration of fluids and vasoactive support to maintain organ perfusion. The objective is to preserve coronary and cerebral circulation without exacerbating volume overload.

- **Address volume overload and pulmonary congestion:** When clinical or radiologic signs of pulmonary edema are present, diuretic therapy is indicated to promote renal excretion of excess intravascular volume. Intravenous loop diuretics, such as furosemide 20–40 mg, are typically effective provided that blood pressure remains adequate and renal perfusion is not compromised. Diuretic response should be carefully monitored by tracking urine output and hemodynamic parameters. In refractory cases or patients with significant renal dysfunction, more advanced interventions—such as ultrafiltration or hemodialysis—may be necessary to restore volume balance.

- **Manage hyponatremia based on clinical severity, sodium concentration, and serum osmolality:** The therapeutic approach to hyponatremia in TUR syndrome must be individualized according to both the degree of biochemical disturbance and the patient's neurological presentation. Mild or asymptomatic hyponatremia—characterized by a small reduction in serum sodium (≤5 mmol/L)—

often resolves spontaneously as the absorbed irrigant is excreted by the kidneys and the fluid-electrolyte balance is naturally restored. In such patients, supportive care with vigilant observation and optimization of renal perfusion is generally sufficient. However, when serum sodium levels fall below approximately 125–120 mmol/L and neurological manifestations such as confusion, restlessness, seizures, or decreased consciousness appear, immediate intervention with hypertonic saline becomes mandatory. The European Society of Endocrinology (ESE) recommends administration of 150 mL of 3% sodium chloride over 20 minutes, repeated once within the first hour if symptoms persist (Arshad et al., 2022; Ball, 2016). This bolus strategy provides rapid osmotic correction and alleviates cerebral edema, but it must always be performed under strict biochemical monitoring.Frequent serum sodium measurements—ideally every 2 to 4 hours during the first postoperative day—are essential to avoid overcorrection. The general target correction rate should not exceed 1–2 mmol/L per hour, with a maximum rise of 10–12 mmol/L within the first 24 hours. Rapid or excessive elevation of sodium concentration carries a significant risk of osmotic demyelination syndrome, especially in patients who develop brisk water diuresis after initial stabilization. For this reason, careful titration of therapy and close interdisciplinary communication between the anesthesiology, urology, and critical care teams are vital. Concurrent management must address associated complications that aggravate neurological dysfunction. Seizures should be promptly controlled using benzodiazepines such as midazolam (2–4 mg IV); if convulsions persist, additional anticonvulsant therapy such as phenytoin (10–20 mg/kg IV) may be administered. In patients who exhibit severe or refractory symptoms despite appropriate saline therapy—particularly those with renal failure, uremia, or persistent solute retention—hemodialysis can be a life-saving measure. Dialysis not only corrects hyponatremia and restores osmolality more efficiently but also facilitates removal of absorbed solutes such as glycine, sorbitol, and mannitol while alleviating concurrent volume overload.

Ultimately, management of hyponatremia in the context of TUR syndrome requires a delicate balance between rapid symptom relief and the prevention of overcorrection-related complications. Anesthesiologists play a central role in coordinating this process by initiating timely treatment, ensuring continuous monitoring, and tailoring corrective strategies to the individual patient's physiological response. Vaptans (tolvaptan/conivaptan) are not recommended for acute symptomatic hyponatremia in this setting by ESE guidance (Ball, 2016).

Postoperative Care and ICU Indications

Patients who develop moderate to severe manifestations of TUR syndrome require vigilant postoperative observation, often best achieved in an intensive care or high-dependency unit setting. Individuals presenting with marked electrolyte disturbances—particularly hyponatremia—pulmonary edema, prolonged or recurrent seizures, or hemodynamic instability should not be managed in standard recovery areas. These patients benefit from continuous invasive or noninvasive hemodynamic monitoring, serial neurological evaluations, and frequent laboratory assessments including serum sodium, osmolality, renal function, and arterial blood gases. Such close surveillance enables timely detection of delayed complications, such as worsening cerebral edema, arrhythmias, or progressive respiratory compromise. Even after initial stabilization and apparent clinical improvement, latent or secondary deterioration may occur several hours postoperatively, typically within the first 24 hours. Therefore, cautious postoperative management should include controlled fluid administration, oxygen therapy, and judicious diuretic use under direct monitoring. In cases with persistent neurological symptoms, cranial imaging and consultation with neurology or critical care specialists may be warranted to rule out osmotic demyelination or cerebral edema. Early identification and correction of recurrent electrolyte imbalances are essential. Serum sodium levels should be re-evaluated every few hours until normalization is achieved, and the correction rate must remain within safe limits to prevent neurological injury. If the patient exhibits ongoing pulmonary congestion, supplemental oxygen or noninvasive ventilation may be required, and in refractory cases, invasive mechanical ventilation should be considered. Moreover, renal function should be closely monitored, as both hypo-osmotic stress and diuretic therapy can transiently impair renal perfusion and urine output.

Discharge from the intensive or monitored unit should only be considered once the patient demonstrates sustained hemodynamic stability, normal mental status, and consistent electrolyte balance over at least 24 hours. Even then, delayed discharge from the hospital is advisable in high-risk individuals—particularly elderly patients, those with cardiac or renal comorbidities, or those who required hypertonic saline therapy—since late recurrence of neurological or cardiopulmonary manifestations has been documented. A structured postoperative follow-up plan, involving urology, anesthesiology, and critical care teams, ensures comprehensive recovery and reduces the likelihood of overlooked sequelae related to fluid absorption during transurethral surgery.

Evolving Technologies and Impact on Incidence

Technological advances—including bipolar systems, laser enucleation (e.g., HoLEP), and procedure-specific refinements—have reduced the incidence and severity of classic TUR syndrome while maintaining efficacy (Bapat et al., 2007; Sinha et al., 2022). Nevertheless, prevention principles (lower pressure, shorter duration, early coagulation, adequate drainage) remain the cornerstone, and anesthesiologist-led vigilance continues to be decisive.

Conclusion

TUR syndrome continues to represent a potentially serious yet largely preventable complication of endoscopic urologic surgery. Although its incidence has declined substantially with the adoption of bipolar energy systems and isotonic saline irrigation, the syndrome persists as an important clinical concern for anesthesiologists and urologists alike. In modern practice, two distinct forms can be recognized. The first, the "classic" variant, arises during monopolar resection when non-electrolyte hypo-osmotic irrigants such as glycine or sorbitol are absorbed in significant quantities, leading to dilutional hyponatremia, hypo-osmolality, cerebral edema, and neurological deterioration. The second, increasingly encountered with bipolar techniques, is dominated by volume overload and metabolic complications, including hyperchloremic acidosis secondary to excessive isotonic saline absorption. Both variants share the potential for abrupt hemodynamic instability, respiratory compromise, and severe metabolic derangement. From an anesthesiological standpoint, vigilance and prevention remain the most effective strategies. Key preventive measures include minimizing irrigation pressure, maintaining low bag height, ensuring continuous bladder drainage, promptly coagulating venous sinuses, and limiting operative duration whenever feasible. The preference for bipolar systems and isotonic saline has markedly reduced the risk of hyponatremia, yet volume management must still be approached cautiously, particularly in elderly or cardiac-compromised patients. Careful intraoperative monitoring of hemodynamics, urine output, and—when indicated—serum sodium levels can detect early deviations before they progress into full-blown TUR syndrome. Recognition of early warning signs is equally crucial. Under regional anesthesia, subtle neurological cues such as agitation, restlessness, nausea, or visual disturbances may herald the onset of fluid absorption. Under general anesthesia, anesthesiologists must instead rely on cardiovascular and respiratory indicators—sudden hypertension, bradycardia, arrhythmias, or unexplained hypoxemia—to identify the syndrome's evolution. Once suspected, immediate cessation of surgery, airway stabilization, and correction of hemodynamic and electrolyte imbalances are mandatory. Treatment hinges on the prompt administration of hypertonic saline for symptomatic hyponatremia, while diuretics such

as furosemide help relieve pulmonary congestion in volume-overloaded patients. In refractory or severe cases, particularly those complicated by renal dysfunction or persistent metabolic derangements, renal replacement therapy provides an effective means of correcting both fluid and solute disturbances. Postoperatively, patients with moderate or severe presentations require intensive monitoring, serial laboratory evaluation, and supportive therapy to prevent delayed complications such as recurrent hyponatremia or neurological injury. The interdisciplinary cooperation of anesthesiology, urology, and intensive care teams is fundamental to achieving safe outcomes.

In summary, although technological advances have significantly reduced its incidence, TUR syndrome remains an ever-present risk inherent to endoscopic surgery. Its prevention and management rely on meticulous intraoperative technique, early recognition of physiological disturbances, and adherence to evidence-based treatment protocols. Through comprehensive perioperative planning, judicious monitoring, and coordinated multidisciplinary response, anesthesiologists can minimize morbidity, prevent life-threatening sequelae, and preserve the considerable therapeutic benefits that transurethral resection continues to offer in modern urologic practice.

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Chapter 12

GREEN NANOTECHNOLOGY IN ANTIMICROBIAL TREATMENT: ECO-FRIENDLY NANOFIBERS

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1. INTRODUCTION

Nanofibers are nanomaterials that have gained significant interest in recent years due to their unique physicochemical properties and characteristics. The cross-sectional diameters range from tens to hundreds of nanometers, making it an attractive choice for a series of advanced applications due to its very high surface area-to-volume ratio (Lim, 2017; Maryam et al., 2016). Nanofibers are also unique in their ability to form porous network structures similar to natural biological tissues (Leung and Ko, 2011). They can be produced from natural and synthetic polymers, carbon-based materials, semiconductors, and composites (Lim, 2017; Hassanzadeh et al., 2013). In recent years, thanks to rapid advances in the synthesis and characterization of nanofibers, they have attracted attention in a wide variety of fields, including water and environmental purification, tissue engineering, the food industry, the textile industry, clean energy applications and storage, protective materials, biosensors, healthcare, and biomedical engineering (Wang and Hsiao, 2016; Qamoshi and Rasuli, 2016; Ramakrishna et al., 2010; Lim, 2017).

Today, nanofiber technology is attracting attention in biomedical studies as a potential solution to current challenges such as burn and wound care, organ repair, osteoporosis, and the treatment of various diseases (Huang et al., 2003; Bedeloğlu et al., 2017; Demirel, 2016). Some of the reasons why these studies are attracting attention are that nanofiber arrangements can be customized to a great extent due to the very high surface area and surface energy of nanofibers, and their properties, such as flexibility. Despite being made of the same materials, nanofiber wound dressings, tissue engineering scaffolds, and drug carriers perform significantly better than their micro- or macro-scale counterparts, as demonstrated by numerous in vitro studies (Leung and Ko, 2011). The porous structure of nanofibers enables drug particles to pass through the matrix more efficiently, facilitating wound healing (Ghajarieh, 2021).

The concept of sustainable products was first introduced by the United Nations in 1987 and refers to meeting current needs without compromising the ability of future generations to meet their own. For a material to be considered sustainable, it must be obtained from a renewable source and be biodegradable (Fouad and Farag, 2019). In this context, the availability of materials that can be produced and used sustainably, without harming the environment, is of great importance (Johnston et al., 2007).

Global issues in the energy and environmental fields are increasing interest in sustainable materials. The limited availability of fossil fuels and their release of greenhouse gases such as carbon dioxide, methane, and nitrous oxide during use, leading to global warming, increases the need for clean energy solutions (D'Amato, 2002). Water and air pollution are other critical environmental problems that are rapidly growing worldwide. It is projected that

by 2025, more than half of the world's countries will experience clean water scarcity, and this proportion will reach 75% by 2075 (Veleirinho et al., 2008).

For many years, petroleum-based polymers and their derivatives have been widely used in daily life due to their attractive properties such as low cost, processability, and ease of use. Polymers are found in almost every aspect of life, from textiles to electronics, from biomedical products to food packaging (Vilela et al., 2014; Voirin et al., 2014; Miller, 2014). However, a large portion of petroleum-based polymers is not recyclable. Approximately 95% of single-use polymers remain in the environment without degrading. Therefore, petroleum-based polymers do not meet sustainability criteria. The main reason for this is that these polymers are produced from fossil-based raw materials such as ethylene, propylene, and benzene (Vilela et al., 2014; Voirin et al., 2014; Miller, 2014). In contrast, natural polymers are obtained from living organisms and their production relies on renewable resources. Natural polymers such as collagen, alginate, gelatin, starch, and chitosan have gained significant interest in recent years due to their environmentally friendly nature, ease of modification, biocompatible structures, and excellent biodegradability (Zhao et al., 2016).

In recent years, the use of biomaterials based on renewable polymers has been rapidly increasing, especially in biomedical applications. Thanks to advancements in properties such as bioactivity, biocompatibility, and mechanical strength in these materials, a wide range of potential applications has emerged in fields like tissue engineering, implant technologies, and controlled drug delivery systems. Similarly, in the field of nanotechnology, research is focused on the synthesis of nanomaterials using sustainable, environmentally friendly methods for the future (Malik et al., 2021). Nanofibers from renewable sources are attracting attention for their biocompatible, non-toxic, and biodegradable structures compared to nanofibers produced by conventional methods. These nanofibers, produced from biomaterials such as collagen, gelatin, chitosan, and cellulose, can be placed in the human body without causing any adverse reactions and can be naturally degraded and removed from the body after completing their tasks (Hernández-Rangel et al., 2021; Campiglio et al., 2019; Nazrin et al., 2020). These features make environmentally friendly nanofibers highly suitable for various biomedical applications, including tissue regeneration and drug delivery systems (Berdimurodov et al., 2023). Considering the increasing environmental pollution in recent years and the growing need for environmentally friendly resources, the development of technologies for clean energy production, storage, and the reduction of environmental pollution is of great importance. Materials with nanofiber morphol ogy offer promising solutions in both energy and environmental applications due to their high surface areas, porous structures, and functionalizability (Thavasi et al., 2008).

Antibacterial agents are indispensable pharmaceutical substances used in the treatment of bacterial infections. Antibacterial agents aim to control infections by inhibiting the growth of bacteria or killing them. In their early years of discovery, they were seen as a great victory for humanity and a revolution in the fight against bacterial diseases. Antimicrobial agents have been a cornerstone of modern medicine throughout history, playing a critical role in a wide range of applications, from surgical interventions to intensive care practices (Leekha et al., 2011). However, their uncontrolled and widespread use over the years has led to a rapid increase in antibiotic resistance, making it one of the most serious global health threats today. When a bacterium becomes resistant to a specific antibiotic, it means that treatment is no longer effective against infections caused by that bacterium.

Antimicrobial resistance (AMR) is a major global health crisis that threatens the effectiveness of treating infectious diseases (Williams-Nguyen, et al., 2016). Factors such as the overuse and misuse of broad-spectrum antibiotics, non-compliance with prescribed treatments, and uncontrolled antibiotic use in agriculture and animal husbandry have contributed to the rapid spread of resistance and led to the easy transfer of resistant strains between humans, animals, and the environment (Tenover, 2006). The slowdown in the development of new antibiotic classes is also deepening this crisis, and searching for urgent, innovative solutions is imperative (Zhou et al., 2015).

Since AMR arises from the rapid evolution of bacteria against antibiotics, it has the potential to render existing treatment methods fundamentally ineffective (Khameneh et al., 2016). While antibiotics have played a critical role in medical advancement throughout history by reducing mortality rates, their indiscriminate use has paved the way for the emergence of resistant pathogens (Read, 2014). The inadequacy of new antibiotics further exacerbates the problem of resistance (George, 2018). The indiscriminate use of these medications not only threatens the health of individual patients but also the microbial balance of society and future treatment options (Leekha et al., 2011). Therefore, combating antimicrobial resistance should not only focus on discovering new drugs; comprehensive strategies addressing the root causes of the problem must also be developed. The growing problem of antibiotic resistance is driving researchers to explore new treatment approaches beyond traditional antibiotics. The scarcity of new drug classes and the increasing ineffectiveness of existing options clearly highlight the need for innovative and unconventional strategies in treating bacterial infections (Theuretzbacher and Piddock, 2019). Alternative treatment approaches include antimicrobial peptides, bacteriophages, immune system modulators, and new-generation small molecule antibiotics that can overcome traditional resistance mechanisms (Ahmad et al., 2021; Salam et al., 2023).

In this direction, nanotechnology-based therapeutic systems have been developed to address the problems caused by antibiotic resistance. Among these developments, drug-loaded renewable nanofibers are particularly noteworthy. These nanofibers offer significant advantages such as controlled drug release, high drug loading capacity, high encapsulation efficiency, simultaneous release of multiple drugs, simplicity of the production process, and cost-effectiveness for pharmaceutical and biomedical applications. Therefore, renewable nanofibers are seen as promising innovative platforms for the development of antibacterial drug delivery systems (Ulubayram et al., 2015).

2. ECO-FRIENDLY NANOFIBERS AND THEIR USE IN HEALTH

Recent advancements in nanotechnology have significantly increased the use of environmentally friendly nanofibers in the healthcare field. Environmentally friendly nanofibers have various applications in the healthcare field, including tissue engineering, drug delivery systems, gene therapy, antibacterial treatment, wound healing, and tissue repair (Shaikh and Shaikh, 2024). Nanofibers derived from natural biopolymers offer a strong environmental and biological alternative to traditional synthetic polymers due to their superior physicochemical properties, such as biocompatibility, biodegradability, hydrophilicity, and enhanced cell interaction (Krishnan et al., 2012). These biopolymers are natural polymers such as alginate, cellulose, chitosan, silk fibroin, and gelatin, and they can be converted into nanofiber form and used in a wide variety of biomedical applications (Lee et al., 2009). These polymers are derived from different sources such as brown algae, plants, microbes, and animals, and exhibit varying molecular behaviors depending on seasonal changes, source locations, and processing methods. (Krishnan et al., 2012).

The nanofiber structures obtained with these polymers offer a suitable microenvironment for cell growth and tissue regeneration due to their high surface area and porosity (Malik et al., 2021). It holds remarkable potential in the field of tissue engineering, particularly due to its numerous properties such as smaller size, good mechanical properties, excellent chemical and molecular structures, and surface functionalization capability (Peng et al., 2014). It has been observed that nanofibers guide cellular organization in the regeneration of musculoskeletal tissues and promote myotube formation by supporting the alignment of muscle cells. (Malik et al., 2021) This situation presents a promising approach for skeletal muscle tissue engineering. Additionally, it has been determined that chitosan-gelatin-based three-dimensional nanofiber scaffolds enhance cell proliferation and mineralization by mimicking the natural composition of bone tissue. These types of nanofiber systems offer significant advantages in terms of both mechanical strength and biocompatibility as tissue engineering scaffolds (Zadehnajar et al., 2020).

Environmentally friendly nanofibers are also used as drug delivery systems and controlled release platforms (Berner et al., 2019; Manish and Abhay, 2012). The prepared non-toxic biopolymer-based nanofibers have also shown promising results in non-viral gene delivery systems. Positively charged biopolymers such as chitosan, gelatin, and cellulose form complexes with nucleic acids, enabling the controlled release of therapeutic genes. These systems offer a significant alternative in the fields of gene therapy and tissue regeneration by eliminating the safety risks caused by viral vectors (Nguyen et al., 2017; Che et al., 2015).

Environmentally friendly nanofibers are also effectively used in wound healing and tissue repair applications. Cellulose and collagen-based nanofibers function as hemostatic wound dressings, accelerating the blood clotting process; gelatin nanofibers loaded with silver nanoparticles or chlorhexidine, on the other hand, reduce the risk of infection and provide controlled antimicrobial release. These nanofiber structures shorten the bleeding time compared to traditional gauze and prevent foreign body reactions due to their biocompatible nature (Choi et al., 2008; Ranjbar-Mohammadi et al., 2016; Abrigo et al., 2014). Gelatin and cellulose nanofiber dressings also support wound healing by accelerating epithelialization in burn treatment, while maintaining moisture balance. This prevents further tissue damage caused by contact with dry surfaces (Gao et al., 2021; Chen et al., 2017).

Another important application area is implant technologies. Nanofiber composites made from a mixture of polycaprolactone and collagen promote the growth of osteoblast cells while maintaining mechanical strength during bone regeneration. Similarly, gelatin/hydroxyapatite scaffolds are used as biodegradable structures to support cartilage tissue formation (Wang et al., 2020; Chen et al., 2021; Jia et al., 2021; Eldurini et al., 2021). Unlike traditional metal or plastic implants, these biocomposites biodegrade over time, preventing chronic foreign body reactions (Berdimurodov, 2023). While biopolymers have beneficial biomedical applications, they are not stable in biological fluids and can exhibit toxicity in some cases. Recent advancements in nanotechnology, particularly the conversion of biopolymers into nanofibers for use in a variety of biomedical applications, have increased its importance in various fields (Jeevanandam et al., 2022).

In conclusion, environmentally friendly nanofibers represent a rapidly growing research area in the healthcare field. The conversion of natural biopolymers into nanofibers offers significant advantages in terms of both environmental sustainability and biological safety. These nanofiber systems hold high potential in many areas, including tissue engineering, wound healing, drug and gene delivery, biosensors, and implant applications. (Jeevanandam et al., 2022). In the future, with the further development of green production

technologies, the integration of environmentally friendly nanofibers into clinical applications will accelerate, paving the way for sustainable solutions in the biomedical field (Patel et al., 2025; Berdimurodov et al., 2023).

3. ECO-FRIENDLY NANOFIBERS AND ANTIBACTERIAL EFFECT

Antibacterial resistance has become one of the most serious global health problems of our time, significantly limiting the effectiveness of current treatment strategies. Additionally, traditional routes of antibiotic administration-oral, intravenous, topical, or inhalation-often lead to rapid drug release, systemic toxicity, tissue irritation, and prolonged treatment duration. The long-term use of these methods accelerates the tendency of bacteria to develop resistance and reduces treatment success. Therefore, significant research is being conducted to develop new generation drug delivery systems for controlled, targeted, and sustainable delivery of the drug (Ulubayram et al., 2015).

In recent years, produced nanofibers have shown significant potential for encapsulating and delivering antibacterial and therapeutic agents to target sites (Tottoli et al., 2020; Wang et al., 2022). These nanostructures also show promise in accelerating wound healing. Along with these treatment approaches, not harming the ecological environment is also of great importance. For this reason, biopolymer-based environmentally friendly nanofibers have come to the forefront as environmentally sensitive and biocompatible alternative drug carriers (Berdimurodov et al., 2023). Additionally, hybrid structures obtained from the combination of these biopolymers with synthetic polymers such as polycaprolactone (PCL) or polyvinyl alcohol (PVA) enhance mechanical strength while also improving antibacterial efficacy (Li et al., 2021; Karolina Pierchala et al., 2021; Rahmani Del et al., 2020; Wang et al., 2021). Thus, environmentally friendly biopolymer-based nanofibers not only provide a sustainable alternative but also exhibit superior performance compared to traditional methods in antibacterial treatment. Thanks to both biocompatible and environmentally friendly production processes and effective drug delivery and controlled release capabilities, it offers promising innovative solutions in the field of antibacterial treatment (Berdimurodov et al., 2023).

3.1. Chitosan Nanofibers

Chitin is the second most abundant natural polysaccharide in nature after cellulose. Chitin, a structural component found in the exoskeletons of arthropods and the cell walls of fungi, is typically obtained from waste products of the seafood industry, such as crab and shrimp shells (Jayakumar et al., 2010; Rinaudo, 2006). However, since chitin is not soluble in common solvents, it is mostly converted to its more deacetylated derivative, known as

chitosan, for industrial applications. (Pillai et al., 2009). Additionally, chitosan can be obtained naturally from fungi (Roberts, 1992; Kalantari et al., 2019).

Chitosan is a positively charged biopolymer with a repeating glucosidic structure, containing one amino and two hydroxyl groups. (Agrawal et al., 2010; Raafat et al., 2017). Chitosan, classified as a green polymer due to its natural, renewable, and biodegradable structure, has been extensively used in biomedical applications in recent years after being converted into nanofiber form using the electrospinning method (Kalantari et al., 2019; Desai et al., 2008; Doğan, Özyıldız et al., 2013; Elsabe et al., 2012; Geng et al., 2005; Homayoni et al., 2009; Kriegel et al., 2009; Pakravan et al., 2011; Rieger et al., 2016; Ziani et al., 2011). Chitosan nanofibers (CNFs) produced by electrospinning have significant potential in areas such as drug delivery, cell culture, wound healing, gene therapy, food, tissue engineering, and water filtration (Greiner and Wendorff, 2007; Ardila et al., 2016; Ignatova et al., 2009; Jayakumar et al., 2010; Haider and Park, 2009; Martínez-Camacho et al., 2011).

Chitosan-based nanofibers also exhibit effective antimicrobial activity, making these properties an environmentally friendly alternative in antibacterial treatment (Muzzarelli et al., 1988; Shahidi et al., 1999; Papineau et al., 1991; Sudarshan et al., 1992; Young et al., 1982). The antimicrobial effect of chitosan stems from its polycationic structure (Islam et al., 2017). Chitosan's positively charged amino groups interact with the negatively charged cell membranes of bacteria, disrupting membrane integrity, leading to permeability changes, and ultimately triggering cell death (Islam et al., 2017; Zheng & Zhu, 2003). Additionally, the interaction of chitosan with proteins and lipids on the surface of microorganisms disrupts cellular physiological activities, thereby inhibiting bacterial growth. As the degree of deacetylation (DD) increases, the positive charge density of chitosan rises, which contributes to enhanced antibacterial activity (Kong et al., 2010).

In a 2017 study conducted by Arkoun et al., it was reported that chitosan nanofiber mats prepared in different thicknesses (1 cm^2 and 2.5 cm^2) exhibited strong antibacterial effects against the bacteria *Escherichia coli*, *Salmonella Typhimurium*, *Listeria innocua*, and *Staphylococcus aureus*. A reduction of over 99% in bacterial growth was observed, particularly in *E. coli*, *L. innocua*, and *S. aureus*. Increasing the chitosan content has enhanced this activity to the point of completely stopping it. These results confirm that chitosan nanofibers can exhibit a broad-spectrum effect against both Gram-negative and Gram-positive bacteria (Arkoun et al., 2017). Additionally, loading natural agents like plant extracts (e.g., thyme oil, turmeric, aloe vera) into chitosan nanofiber matrices synergistically enhances the natural antibacterial activity of these structures. Curcumin, a hydrophobic polyphenol derived from turmeric root, exhibits anticancer, anti-inflammatory, antioxidant, and antibacterial effects.

Castellano and his colleagues prepared curcumin-coated chitosan/collagen nanofibers using an electrospinning process. In conclusion, it was observed that curcumin-loaded chitosan/collagen nanofibers have a high inhibitory ability against *E. coli* and *S. aureus* when examined under in vitro conditions (Castellano, et al., 2023). Therefore, chitosan-based nanofibers stand out among environmentally friendly nanotechnological solutions due to both their biocompatible and biodegradable structures and their high antibacterial activity.

3.2. Cellulose Nanofibers

Cellulose is a biopolymer obtained from natural sources such as wood and cotton pulp through various chemical and physical processes, possessing high mechanical strength, biodegradability, biocompatibility, and non-toxicity (Nagarajan et al., 2019). One of the fastest-growing applications of cellulose nanofibers (CNF) is in systems where they are used as carriers for active agents or antimicrobial compounds. Cellulose nanofibers can be easily functionalized or combined with metal nanoparticles (such as silver, copper, or zinc oxide), essential oils, chitosan, or other bioactive substances due to their abundance of hydroxyl groups, resulting in hybrid nanocomposites with enhanced antibacterial properties. These types of composites exhibit broad-spectrum antibacterial activity, long-lasting effects, and reduced toxicity compared to traditional antibiotics or synthetic polymers (Van and Coburn 2019; Pettignano et al., 2019; Gopi et al., 2019). While the primary source of cellulose is plants, it exists in two forms: plant cellulose and bacterial cellulose. Because bacterial cellulose is formed by converting glucose into cellulose polymers through bacterial metabolism, it causes less environmental pollution (Iguchi et al., 2000). However, bacterial cellulose (BC), synthesized by bacteria such as *Acetobacter xylinum*, although notable for its high surface area-to-mass ratio and high purity, exhibits limited antibacterial and antioxidant properties in its natural state (Eslahi et al., 2020; Torres et al., 2019). Therefore, the use of cellulose modified with various substances such as silver nanoparticles, zinc oxide, or natural plant extracts has become important for increasing antibacterial activity (Ludwicka et al., 2019). Additionally, CNF-based materials can be produced in the form of films, hydrogels, wound dressings, and nanofiber mats suitable for various biomedical and health applications. Their biocompatibility, moisture retention capacity, and mechanical flexibility make them particularly suitable for wound healing and infection prevention, offering an environmentally friendly and effective alternative to synthetic antimicrobial materials (Xi et al., 2020).

Silver-loaded cellulose nanofibers are used in wound dressings to reduce the risk of infection by showing resistance to pathogens such as *S. aureus*, *S. pneumoniae*, and *E. coli*. In a study examining chloramphenicol (CAP)-

loaded bacterial cellulose and 2,3-dialdehyde cellulose hydrogel (DABC) membranes, it was reported that the DABC structure increased fibroblast cell adhesion and proliferation on the surface (Çaylı and Kahraman, 2023). This situation demonstrates the therapeutic potential of cellulose-based nanofibers as both antibacterial and biocompatible platforms. Additionally, nanocellulose systems functionalized with plant-derived biopolymers offer environmentally friendly antibacterial alternatives. For example, NC/PE fibers obtained by impregnating natural extracts like propolis into cellulose nanofibers provided complete growth inhibition against *S. aureus* and MRSA strains (Bhuyan et al., 2021; Takaisi-Kikuni et al., 1994). SEM analysis showed that the addition of propolis was homogeneously distributed on the surface of the nanofibers, and the structure became denser, increasing antibacterial performance (Oprică et al., 2023). Similarly, $CuSiO_2$/BC composites obtained with Cu nanoparticles and a SiO_2 coating exhibited long-term antimicrobial activity against both *E. coli* and *S. aureus*. This system offers a permanent antibacterial effect due to its resistance to the oxidation of metal ions (Ma et al., 2016).

Cellulose-based eco-friendly nanofibers are emerging as promising materials for antibacterial therapy due to their biodegradable structures, biocompatibility, and sustainable production methods. Cellulose nanofiber systems functionalized with silver, zinc oxide, propolis, or other natural agents can provide long-lasting antibacterial activity without harming the environment and offer innovative solutions for combating pathogens resistant to conventional antibiotics.

3.3. Soy Protein Isolate Nanofibers

Soy Protein Isolate (SPI) is an environmentally friendly, natural plant protein that is commercially used as a food component and stands out for its low cost, biodegradability, biocompatibility, non-toxicity, availability, long-term storage, and stability. (Silva et al., 2003; Chien et al., 2013; Li et al., 2004) Soy protein isolate (SPI) is naturally obtained from soybeans by removing carbohydrate and fat components (Kumar et al., 2002; Pan et al., 2015).

SPI, which is considered a safe alternative to animal-derived proteins, reduces the risk of infection and offers a use free from cultural and ethical issues. Additionally, due to its biologically active regions that support cell adhesion and migration, it holds significant potential in tissue regeneration and blood clotting processes (Santin et al., 2007; Merolli et al., 2010). These features make SPI particularly prominent in applications such as orthopedic biomedical applications, bone regeneration, skin renewal, bone filling, and biomedical coatings (Zhijiang et al., 2019).

It has been reported that SPI-based membranes enriched with antibiotics or antimicrobial agents show promising results in wound dressings due to

their biodegradable structures (Peles and Zilberman 2012). However, the limited mechanical performance of SPI nanofibers and the lack of strong antibacterial properties in their pure form are significant factors that restrict their biomedical applications. Therefore, it is often reinforced by creating hybrid structures with other biopolymers such as chitosan, cellulose, or gelatin, or combined with silver nanoparticles or natural extracts to gain antimicrobial properties, and used in this way. (Fahimirad et al., 2021) A recent study focused on the production of composite SPI/HEC (hydroxyethyl cellulose) nanofibers. These structures have been enriched with the mineral clay halloysite and the drug diclofenac sodium to enhance their bioactivity. The resulting drug-loaded nanofibers were found to be effective in inhibiting both Gram-positive (*B. subtilis*) and Gram-negative (*E. coli*) bacteria. This result indicates that SPI-based nanofibers are not only biocompatible but also a flexible platform that can exhibit strong antibacterial properties (Ullah et al., 2022). Similarly, it has been reported that nanofibrous mats produced from chitosan-soy protein-cellulose combinations exhibit strong antibacterial effects, particularly against Gram-positive *S. aureus* (Pan et al., 2015). These findings indicate that the integration of plant-based components with SPI-based nanofibers enhances antibacterial efficacy.

Various studies show that SPI-based nanofibers are supported with natural components to enhance their antibacterial effectiveness. For example, combining SPI/gelatin nanofibers with essential oils from *Zataria multiflora* and *Cinnamomum zeylanicum* provided 100% inhibition against Gram-positive bacteria (*S. aureus, B. cereus*, and *L. monocytogenes*) and 70%-63% inhibition against Gram-negative bacteria (*E. coli* and *S. Typhimurium*) (Raeisi et al., 2021).

Overall, SPI's natural abundance, biodegradability, non-immunogenicity, and lack of toxic effects make it a significant candidate for the development of environmentally friendly nanofibers. Additionally, thanks to its polymer combinations and support with bioactive agents, it overcomes mechanical limitations and provides broad-spectrum antibacterial activity. Considering all these features, it can be said that SPI-based nanofibers are promising environmentally friendly materials for biomedical applications in antibacterial treatment.

3.4. Alginate Nanofibers

Alginates are polysaccharides formed in the cell walls of brown seaweed, consisting of (1,4)-β-D-mannuronic acid and (1,3)-α-L-guluronic acid chains (Safi et al., 2007). It is widely used in biomedical applications due to its biological origin, biocompatibility, biodegradability, non-toxicity, hydrophilicity, high solubility, low cost, and good structural integrity (Shalumon et al., 2011). Sodium alginate (SA) is used in biomedical applications as a wound dressing, drug

carrier, and tissue engineering scaffold (Safi et al., 2007). Although sodium alginate (SA) is a suitable material for producing nanofibers, its mechanical stability and structural integrity in pure form are limited. Therefore, it is improved by interacting with polymers such as PVA or polyethylene oxide (PEO), which imparts the desired mechanical and biological properties (Safi et al., 2007). Pure alginate is not antibacterial; however, it can be used as an antimicrobial wound dressing when combined with silver nanoparticles or synthetic polymers (Ding et al., 2004; Caykara et al., 2005). Additionally, alginate lacks cell recognition properties; therefore, its use in the biomedical field can be improved by blending it with protein-based polymers such as collagen, gelatin, elastin, and silk fibroin to enhance cell adhesion (Wongkanya et al., 2017). In this context, nanofibers were developed by combining SA and soy protein isolate (SPI). Wongkanya et al. tested the antibacterial activities of electrospun SA/PEO/SPI fibers against *S. aureus* (Gram-positive) and *E. coli* (Gram-negative) and observed that they only inhibited the growth of Gram-positive *S. aureus*. This situation arises because vancomycin is only effective against Gram-positive bacteria. The composition of polymer blends significantly affects fiber morphology and drug release behavior, making electrospun SA/PEO/SPI nanofibers suitable for evaluation as biomedical devices with advantages such as controlled release, antibacterial activity, and biocompatibility (Wongkanya et al., 2017).

In another study, synthetic polymers such as PVA and polyethylene oxide were added to aqueous SA solutions. Polyvinyl alcohol (PVA) is a biocompatible and non-toxic synthetic polymer; it is used in wound dressings due to its chemical and thermal stability and high water absorption capacity (Üstündağ et al., 2010). When combined with SA, it can absorb exudate and promote wound healing due to its hemostatic properties and superabsorbent structure (Barnett et al., 1987). For example, in one study, polyvinyl alcohol/sodium alginate (PVSA) nanofibrous mats were prepared as an AMOX (amoxicillin) release system via electrospinning. PVSA/AMOX (Amoxicillin) nanofibrous mats have been shown to exhibit antibacterial activity against *S. aureus* and *E. coli* (Cerçi et al., 2025). Similarly, SA/PVA/ZnO nanofibrous mats showed strong inhibition against *S. aureus* while having a slightly lower effect on *E. coli* (Shalumon et al., 2011). To enhance the functionality of biomaterials, nanofibers are enriched with various antibacterial agents. For example, double-layered films integrated with electrospun nanofibers of SA/GG (gellan) and PVA/carrageenan have been found effective against S. aureus, E. coli, and P. aeruginosa, and have enhanced the tissue engineering potential of wound dressings. The addition of silver nanoparticles and antibiotics to SA-based nanohydrogels increased antibacterial activity against both Gram-positive and Gram-negative bacteria (Abdollahi and Asl, 2024).

Overall, alginate-based nanofibers, polymer combinations, cross-linking strategies, and the addition of antibacterial agents make these systems promising as multifunctional and environmentally friendly solutions in tissue engineering and wound healing.

3.5. Gelatin Nanofibers

Gelatin, a natural polymer obtained by partial hydrolysis of collagen, is biodegradable, biocompatible, non-toxic, and non-immunogenic (Ki et al., 2005). Collagen makes up approximately 30% of vertebrate body proteins and is found in high concentrations in skin, bones, and tendons. Due to its biological origin, gelatin has a wide range of applications, from the food industry to pharmaceutical fields, particularly in tissue engineering and regenerative medicine. Gelatin's easy gelling ability provides an advantage in controlled drug delivery systems and the production of smart hydrogels (Klotz, et al., 2016; Sahoo et al., 2015; Duconseille et al., 2015; Curcio et al., 2010). Additionally, due to its liquid-loss prevention properties, it is widely used in biomedical engineering and wound healing applications. However, gelatin alone does not possess antibacterial properties, which poses a significant limitation in wound dressing applications. To address this deficiency, various antimicrobial compounds are added to gelatin to enhance its biological performance. For example, nanofibers prepared by adding a quaternary ammonium functionalized methacrylate polymer (METAK) to gelatin functioned as an effective antibacterial wound dressing (Stopiglia et al., 2012). Similarly, the addition of essential oils also enhanced antimicrobial activity. In a study conducted by Unalan et al., PCL/GEL nanofiber mats loaded with clove oil (CLV) were prepared. Poly(ε-caprolactone) (PCL), a synthetic polymer widely used in wound healing applications, is attracting attention due to its high mechanical strength, good biocompatibility, and processability. However, the biodegradability of PCL and its effects on cell adhesion/proliferation are limited (Abedalwafa et al., 2013). To overcome these disadvantages, combination with gelatin (GEL), a natural polymer containing molecular components found in the extracellular matrix, is preferred. Gelatin increases biocompatibility by promoting cell adhesion and proliferation (Gaspar-Pintiliescu et al., 2019). Looking at the study results, it has been reported to be effective against both Gram-positive *S. aureus* and Gram-negative *E. coli* bacteria (Yao et al., 2016; Ramalingam et al., 2019). In the study by Fallah et al., curcumin (CUR)-loaded electrospun PCL/GEL nanofibers were developed, and it was observed that the addition of CUR increased antibacterial activity against both Gram-positive and Gram-negative bacteria (Fallah, et al., 2016; Unalan et al., 2019).

Loading antibiotics into gelatin is also emerging as an important strategy. Safdari et al. reported that ceftazidime-loaded silk/gelatin nanofibers showed

significant antibacterial activity against *Pseudomonas aeruginosa* (Safdari et al., 2016). Similarly, chloramphenicol-loaded gelatin nanofibers developed by Nada et al. exhibited strong antimicrobial activity against *S. aureus*, *P. aeruginosa*, and *Candida albicans* (Nada, et al., 2016). Additionally, structures obtained by adding silver ions to gelatin nanofibers have shown high antibacterial activity, particularly against resistant bacteria commonly found in burn wounds. In the study by Rujitanaroj et al., it was reported that silver ion-loaded gelatin nanofibers were effective against *P. aeruginosa*, *E. coli*, and methicillin-resistant *S. aureus* (Rujitanaroj et al., 2008). In another study, nanofiber mats of PVA/G/BAC (Benzalkonium chloride) aqueous solutions were prepared. Nanofibers with high mechanical strength have shown antibacterial activity against Gram-negative (*E. coli* and *P. aeruginosa*) and Gram-positive (*B. subtilis* and *S. aureus*) bacteria. Therefore, it is thot that medical applications such as roll bandages can be used. (Yüksek et al., 2019) These findings indicate that gelatin-based nanofibers offer an environmentally friendly option for antibacterial treatment. Although gelatin nanofibers are not antibacterial on their own, when modified with essential oils, antibiotics, or metal ions, they hold significant potential for multifunctional wound dressings and drug delivery systems.

3.6. Silk Fibroin Nanofibers

Silk fibroin, a natural protein derived from the *Bombyx mori* silkworm, has garnered significant interest as a biomaterial due to its unique combination of mechanical strength, biodegradability, and biocompatibility. Silk fibroin in nanofiber form provides a highly porous, extracellular matrix (ECM)-like structure that can serve as a carrier for antibacterial agents or act as an active antibacterial scaffold (Vepari and Kaplan Silk 2007; Malik et al., 2021).

Silk fibroin (SF), a fibrous protein obtained from *Bombyx mori* cocoons, has emerged as a versatile biopolymer for biomedical use. The amino acid composition, dominated by glycine, alanine, and serine, provides a highly ordered β-sheet crystal structure, resulting in exceptional tensile strength and chemical stability. SF is also suitable for wound dressings, tissue scaffolds, and drug delivery systems due to its excellent oxygen and water vapor permeability, minimal immunogenicity, and controlled degradation properties. When processed into a nanofibrous form, silk fibroin gains additional advantages such as a high surface area-to-volume ratio, interconnected porosity, and surface modifiability, enabling effective interaction with biological tissues and antimicrobial agents (Vepari and Kaplan Silk 2007; Lu et al., 2011). Today, silk fibroin is successfully applied in many areas, including materials used for wound healing, artificial blood vessels, surgical sutures and repair materials, and the delivery of antimicrobial agents (Calamak et al., 2015). Additionally, new processing techniques developed for silk fibers and proteins have

increased the biomedical potential of these molecules (Zhang et al., 2012).

Silk-based nanofibers are promising carrier systems, especially for the delivery of antibacterial agents. In some of the studies conducted, it has been reported that silver nanoparticle-loaded silk fibroin nanofibers exhibit antibacterial activity against Gram-positive bacteria (*S. aureus, S. epidermidis*) and Gram-negative bacteria (*P. aeruginosa*) (Calamak et al., 2015). Similarly, it has been reported that nanofibrous membranes obtained by loading silver sulfadiazine onto the top layer of silk fibroin sponges via electrospinning exhibit strong antibacterial activity against *S. aureus* (Çakır et al., 2018).

All these findings indicate that silk fibroin-based nanofibers are not only effective in antibacterial treatments but will also hold a significant place among future environmentally friendly biomaterials due to their biocompatible and sustainable properties.

CONCLUSION

The rise of antimicrobial resistance has created a pressing need for sustainable, biocompatible, and highly efficient materials in modern antibacterial therapy. Within this framework, green nanotechnology provides a promising avenue for developing eco-friendly nanofiber systems that combine environmental sustainability with therapeutic functionality. Environmentally friendly nanofibers produced from natural biopolymers such as chitosan, cellulose, alginate, gelatin, soy protein isolate, and silk fibroin have demonstrated significant potential in combating bacterial infections while minimizing ecological impact. Their biodegradability, biocompatibility, high surface area, and tunable porosity make them superior candidates for applications in wound healing, tissue regeneration, and drug delivery systems.

These natural nanofibers not only act as structural scaffolds that mimic the extracellular matrix but also serve as effective carriers for antibacterial agents, enabling controlled and sustained drug release directly at the infection site. Moreover, hybridization with synthetic polymers and functionalization with metallic nanoparticles, natural extracts, or antibiotics enhances their mechanical strength and antimicrobial activity. Such multifunctional nanofibers represent a new generation of antibacterial materials that effectively address clinical needs while adhering to the principles of green chemistry and sustainability.

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