INTERNATIONAL COMPILATION OF RESEARCH AND STUDIES IN CHEMISTRY

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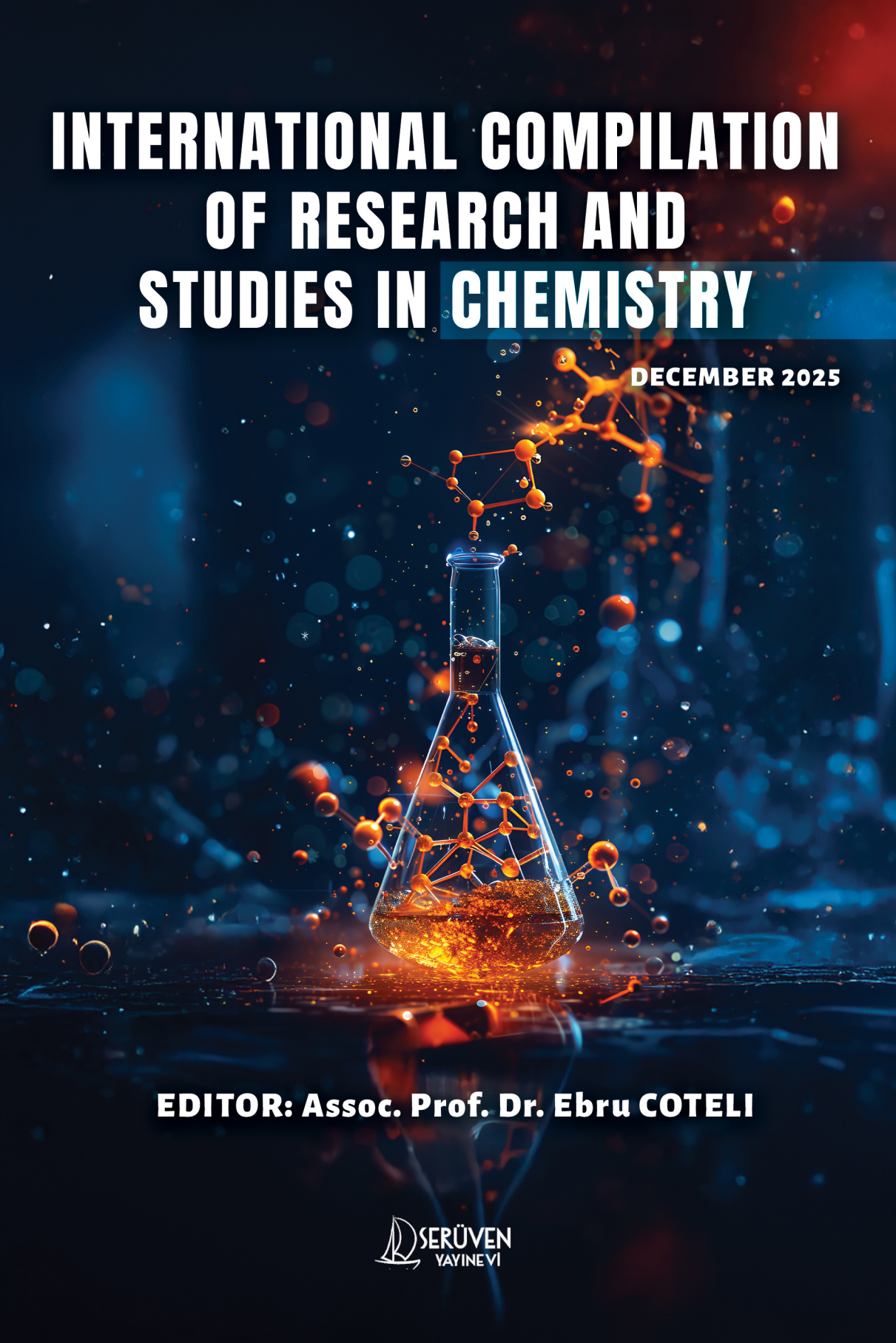

EDITOR: Assoc. Prof. Dr. Ebru COTELI

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CONTENTS

Chapter 1

IMPORTANT CAROTENOID: LUTEIN AND ITS BIOCHEMICAL ACTIVITIES

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1. INTRODUCTION

Carotenoids are synthesized by plants and microorganisms, but not by humans. Therefore, lutein, an important carotenoid, must be metabolized exogenously through the diet. The most important sources of lutein are green leafy vegetables and egg yolks. It is also a yellow xanthophyll found quite commonly in foods such as peas, cabbage, lettuce, and spinach (Ranard et al., 2017). Carotenoids are pigments found in the structures of red, yellow, orange, and dark green vegetables and fruits. These are natural, fat-soluble antioxidants that give plants their color (Thomas & Johnson, 2018). Due to its chemical structure, lutein has important biological functions in preventing eye diseases and maintaining retinal functions (Li et al., 2020). Lutein is one of the carotenoids found in high concentrations in the human retina because of its anti-inflammatory properties (Buscemi et al., 2018; Li et al., 2020).

1.1. CHEMICAL AND PHYSICAL STRUCTURE OF LUTEIN

Carotenoids are divided into two groups: carotenes and xanthophylls. Carotenes are composed of carbon and hydrogen, while xanthophylls contain a hydroxyl group in their structure (Thomas & Johnson, 2018). There are two types of xanthophylls: lutein and zeaxanthin. Literature studies have shown that lutein and zeaxanthin supplements have protective and healing effects on metabolic processes (Okur, 2019). Lutein is a lipophilic pigment that participates in metabolism through the same absorption pathway as dietary lipids and is absorbed by the small intestine (Rodriguez-Amaya, 2015).

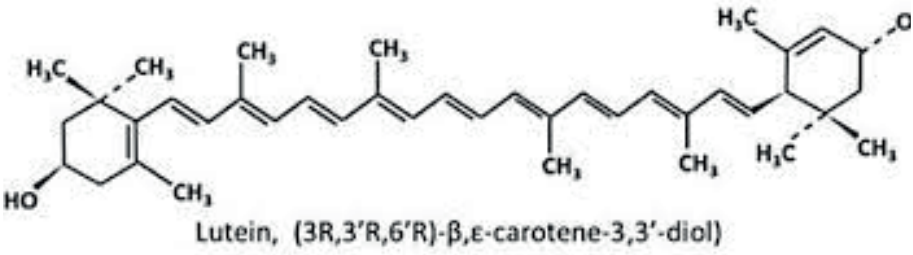
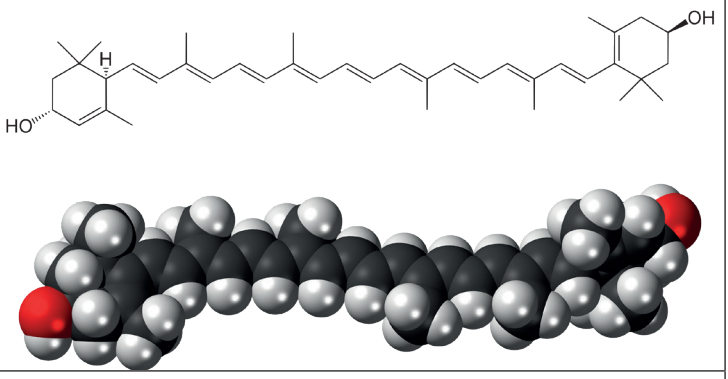


Figure 1. *The chemical formula for lutein*

The physical properties of lutein are shown in Table 1.

Table 1. Physical properties of lutein (El-Raey et al., 2013).

Closed Formula	$C_{40}H_{56}O_2$
Open Formula	
Systemic Name	(3R,3'R,6'R)-b,e-Carotene-3,3'-diol
Other Names	Lutein Trans-lutein Xanthophyll
Mol. Wt (average)	568.871 g/mol
Melting point	183-185 °C
Resolution	Insoluble in water, soluble in oil. It is also soluble in ethanol, methanol, ethyl acetate, hexane, THF (tetrahydrofuran), and methylene chloride.

1.2. LUTEIN SOURCES

One study determined that 90% of the petal color of a flower of the Tagetes genus is lutein. Microalgae, in particular, have also been found to have high lutein content. One of the most important sources of lutein is egg yolk. Due to the fat content of egg yolk, lutein is easily absorbed by the body (Becerra et al., 2020). Additionally, the amount of lutein in foods is affected by factors such as exposure to acid, heat, and light during food processing. These factors, like lutein, also cause the long-chain conjugated double bonds in the structure of other carotenoids to break down (Ramirez, 2016). Lutein is stored in the body, primarily in the eyes, brain, skin, breast, and cervix. Because lutein is poorly soluble in water, it is found in the inner core of cell membranes or bound to proteins. It is the first defense molecule that protects cell membranes against oxidative damage (Hammond et al., 1997). Foods containing lutein are shown in Figure 2.

Figure 2. *Foods containing lutein*

Lutein, in particular, is used in the coloring of foods, medicines, and cosmetic products. The leaves of the marigold plant contain high levels of lutein. Studies have shown that as the color of the leaves of this plant becomes darker, the lutein content increases (Lin et al., 2015). Microalgae are another source of lutein. They are a good source of lutein because they have a higher growth rate than plants (Yen et al., 2013; Lin et al., 2015). Lutein can be extracted from plants using a variety of organic solvents, including methanol, acetone, diethyl ether, hexane, and isopropanol. The choice of solvent is crucial when extracting lutein from plants. Acetone and ethanol, especially those with water solubility, are frequently used to obtain lutein from plant material (Saini & Keum, 2018). Lutein is a phytochemical of plant origin. The synthesis of lutein in plants occurs through several mechanisms. Lutein synthesis in plants is made from lycopene and α-carotene. This synthesis is shown in Figure 3.

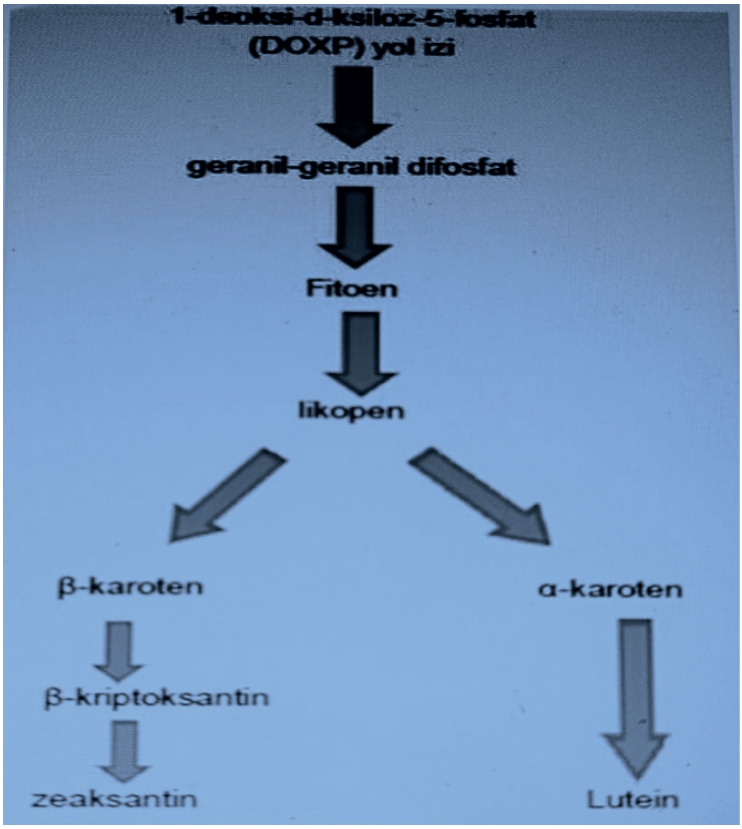


Figure 3. *The synthesis of lutein in plants*

1.3. FUNCTIONS OF LUTEIN IN METABOLISM

1.3.1. Lutein and Antioxidant Effect

The numerous conjugated double bonds in lutein's structure and the polarity of these bonds provide it with the capacity to scavenge free radicals and enhance antioxidant enzyme systems in metabolism. This is why lutein has the capacity to resist oxidative stress in the body. In particular, the conjugated double bonds in the structure of lutein and the two hydroxyl groups at both ends make lutein stronger than other carotenoids in terms of antioxidant power. The conjugated double bonds in the structure increase electron-donating power, while the hydroxyl groups increase radical-scavenging power. Therefore, it is the most powerful antioxidant among carotenoids. Lutein has the capacity to prevent and eliminate damage caused by oxidative stress (Sindhu et al., 2010; Sheng et al., 2020).

1.3.2. Lutein and Cardiovascular Health

Oxidative stress and resulting inflammation in metabolism contribute to cardiovascular disease. Studies have shown that lutein, thanks to both its antioxidant properties and its ability to inhibit inflammation, may have cardiovascular disease-preventive properties (Thomas & Johnson, 2018). A study has shown that dietary lutein intake prevents stroke and cardiovascular disease (Leermakers et al., 2016; Perrone et al., 2016). The most important cause of cardiovascular disease is atherosclerosis. This disease is caused by chronic inflammation of artery walls (Kobiyama & Ley, 2018). LDL, in particular, produced as a result of oxidative stress, plays a significant role in the development of atherosclerosis. Therefore, lutein and other carotenoids play an important role in preventing this disease (Maria et al., 2015). The formation of atherosclerotic lesions, in particular, is an important sign of aging in the vascular system. In this environment, reactive oxygen species production occurs, and ruptures occur (Suzuki et al., 2013). Increasing plasma lutein levels in metabolism and increasing lutein intake will increase antioxidant capacity and reduce lipid peroxidation, thus eliminating the risk of cardiovascular disease (Koh et al., 2011). In one study, decreases in the amount of carotenoids such as lutein, zeaxanthin, lycopene, α-carotene, and β-carotene were observed in cases of coronary artery disease (Lidebjer et al., 2007). Studies have shown that lutein is protective against myocardial infarction and is necessary for a healthy cardiovascular system (Zou et al., 2014). One study reported that the risk of stroke and coronary heart disease was very low in animals fed high amounts of lutein (Perrone et al., 2016).

1.3.3. Lutein and Eye Health

People who consume insufficient amounts of green leafy vegetables and fruits are at risk of developing AMD (age-related macular degeneration). This condition causes vision loss and, in the long run, blindness. It has been reported that dietary lutein prevents this visual impairment. Near the retina of the eye is a yellow spot called the macula (Ramirez, 2016). The yellow macula is located in the back and middle portion of the retina. Photoreceptors responsible for high-resolution vision are abundant here. These contain substances called lutein and zeaxanthin. These carotenoids in the macula absorb light in the blue range. These carotenoids protect the eye from harmful rays. Lutein screens these harmful rays and prevents them from damaging this layer of the eye. Consuming lutein through fruits and vegetables is important for eye health (Koushan et al., 2013). Carotenoids, in particular, have antioxidant properties because they scavenge free radicals and prevent the oxidation of phospholipids in cell membranes. Lutein is responsible for protecting the eye from light-induced oxidative damage (Ma & Lin, 2010). Research shows that factors such as oxidative stress, ultraviolet light, diabetes, and aging cause the

eye disease called cataracts. Studies indicate that lutein plays an important role in preventing cataracts (Manayi et al., 2016).

1.3.4. Lutein and Diabetic Retinopathy

One of the most serious diseases in the world is diabetes. It occurs as a result of a deficiency of the hormone insulin in the body. The most significant negative effect of diabetes is diabetic retinopathy. This disease causes significant vision loss, especially in adults. It manifests itself through vascular abnormalities in the retina (Wang & Lo, 2018). In particular, carotenoid supplementation has been reported to improve visual functions in patients with retinopathy. One study determined that dietary lutein intake prevents diabetic retinopathy due to its antioxidant and anti-inflammatory properties (Sahli et al., 2016).

1.3.5. Lutein and Brain Health

The brain is structurally rich in unsaturated fatty acids. Therefore, it is vulnerable to free radical attacks and requires protective systems. Lutein's most important role in metabolism is to protect tissues from phototoxic damage. It serves this role due to its anti-inflammatory, antioxidant, and light-filtering properties. Lutein has excellent free radical scavenging properties due to the number of conjugated double bonds in its structure and its high polarity. Furthermore, all carotenoids, like lutein, share these properties. These properties demonstrate the importance of lutein for brain health (Madaan, et al., 2017). Lutein may also function through various other mechanisms in regulating brain function. For example, lutein complements its role by altering the functional and physicochemical properties of membranes. DNA damage and gene regulation occurring in the cell nucleus negatively affect cell viability. These events lead to the aging process. This can be corrected by taking lutein. Myelin, which acts as a sheath on axons, is crucial for maintaining neural communication. Dysfunction in this system can lead to memory and thought disorders. It is of vital importance. Lutein within the myelin sheath regulates the structure of the myelin, ensuring smooth communication between neurons (Erdman et al., 2015).

1.3.6. Lutein and Parkinson's Disease

PD (Parkinson's disease) is generally seen in people over the age of 50 in the world. This disease has become increasingly common recently. Studies show that lutein is particularly important in both the prevention and treatment of the disease by protecting brain cells (Juturu, 2015). Studies have also shown that lutein affects the pathological pathways of inflammatory cytokines such as interleukin 6 (IL-6) and angiotensin II signaling. Furthermore, lutein plays an important role in preventing neurodegeneration caused by oxidative stress

in metabolism and the resulting diseases like Alzheimer's and Parkinson's (Ozawa et al., 2012). One study showed a significant association between lutein intake and the risk of PD (Takeda et al., 2013). Such studies are important because there is no definitive cure for this disease.

1.3.7. Lutein and Cancer

All xanthophylls are particularly effective in preventing mechanisms that lead to cancer formation. They achieve this effect through multiple mechanisms, including preventing oxidative damage, inhibiting angiogenesis, reducing cell differentiation, and modulating the immune system (Ribaya-Mercado & Blumberg, 2004). It has been reported that people who consume large amounts of fruits and vegetables, in particular, have a reduced risk of metabolic cancer due to increased serum carotenoid levels. Carotenoids, which are natural antioxidants, prevent free radicals from causing cell damage. Thanks to this feature, lutein has an important place in the prevention of many diseases, such as ovarian, prostate, breast, and lung cancers (Madaan et al., 2017). A study has shown that lutein has significant effects on the differentiation of esophageal cancer cells. It has been reported that lutein inhibits the proliferation of these cells (Pei et al., 2007). Lutein, in particular, has been reported to selectively induce apoptosis in transformed breast cells, but this mechanism is absent in normal breast cells (Sumantran et al., 2000). Another study showed that people who consume foods rich in carotenoids, especially lutein, have a very low risk of developing premenopausal breast cancer (Freudenheim et al., 1996). Studies have shown that lutein, in particular, induces cell death and significantly inhibits the growth of breast cancer cells (Gong et al., 2018). Another study showed that increasing lutein intake was protective against the development of early atherosclerosis (Dwyer et al., 2001).

1.3.8. Lutein and Skin Health

Prolonged exposure of our skin to UV light causes premature aging. This is a worrying situation for human beings. To prevent this situation, the human body creates a protective barrier against these factors. Especially if there are no protective barriers on the skin, free radical reactions begin in the skin, and skin aging and even cancer risk occur. Antioxidants, especially in the body and in cosmetic products, act to prevent and repair skin damage caused by UV rays. Lutein, in particular, has the ability to distinguish blue light (high-energy photons) from the visible light spectrum. Substances containing lutein protect the skin against these harmful rays. Because of its powerful antioxidant properties, lutein both protects the skin and prevents skin aging. Lutein has a lipophilic structure and is found in the lipid portion of cell membranes. Therefore, lutein acts as a chain breaker in lipid peroxidation reactions, eliminating the effects of free radicals. A study shows that taking 10

mg of lutein daily with the diet makes significant contributions to maintaining skin health (Shegokar & Mitri, 2012).

CONCLUSIONS AND RECOMMENDATIONS

Free radicals are reactive species that carry an unshared electron pair. Free radicals cause damage by affecting biologically important molecules such as lipids, DNA, carbohydrates, and proteins during metabolism. Substances that prevent and eliminate these harmful effects of free radicals are called antioxidants. The antioxidant, anticancer, and anti-inflammatory effects of carotenoids, in particular, have made them important. The double bonds in the carotenoid structure prevent and eliminate the harmful effects of free radicals. Lutein, one of the most important carotenoids, has a distinctive structure, distinguishing it from other carotenoids with its hydroxyl groups. Studies have indicated that lutein plays a significant role in reducing oxidative damage and regulating the immune system. Lutein, an important xanthophyll, has been the subject of scientific research in recent years. Lutein's antioxidant activity and ability to protect metabolism against oxidative stress make it a biologically important molecule. Further studies on lutein's biological activities are needed. Furthermore, its inclusion in people's diets is crucial. It is important to discover natural foods containing lutein and use them in daily nutrition. Public awareness on this issue is essential.

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Chapter 2

ZINC: BIOCHEMICAL FOUNDATIONS, PHYSIOLOGICAL FUNCTIONS. AND ITS ROLE IN HUMAN HEALTH

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1. INTRODUCTION

The total amount of zinc in the human body is approximately 2–3 grams. Most of this element is stored in muscles (60%), bones (30%), and the remainder in organs such as the skin, liver, kidneys, retina, and prostate (Roohani et al., 2013). While zinc is not an element that can be stored in the body, it is in a dynamic balance that requires constant intake. Therefore, adequate zinc intake through diet is essential for maintaining physiological functions (Institute of Medicine [IOM], 2002). In biological systems, zinc primarily functions as a cofactor for metalloenzymes. More than 3,000 proteins and enzymes identified to date contain zinc (Maret, 2013). The structural integrity of enzymes such as DNA and RNA polymerase, superoxide dismutase, carbonic anhydrase, and alkaline phosphatase, in particular, depends on zinc. This property makes zinc an indispensable element in the fundamental molecular mechanisms of life (Vallee & Falchuk, 1993). Inadequate dietary zinc intake poses serious public health problems, particularly in developing countries. Zinc deficiency can manifest as numerous clinical symptoms, including growth retardation, immunodeficiency, skin lesions, and decreased sense of taste and smell (Wessells & Brown, 2012). Conversely, excess zinc can have toxic effects, particularly with long-term and high-dose supplementation (Plum et al., 2010).

Recent studies have revealed that zinc plays a crucial role not only in basic biochemical processes but also in broader systemic processes such as neurological health, aging, metabolic diseases, and immune responses (Chasapis et al., 2012; Maares & Haase, 2016). As such, zinc stands out as an element that is being carefully studied in modern medicine for both preventive and therapeutic approaches.

1. BIOCHEMICAL AND PHYSIOLOGICAL ROLES OF ZINC

Zinc is a key regulator of numerous biochemical and physiological processes in the human body. Found in the structures of more than 3,000 proteins, this element plays catalytic, structural, and regulatory roles (Andreini et al., 2006). At the cellular level, zinc participates in numerous vital functions, including enzyme activity, protein synthesis, gene expression, cell division, apoptosis, and oxidative balance (Maret, 2013; Haase & Rink, 2014).

1.1. Enzymatic Functions

Zinc serves as a cofactor in approximately 10% of enzymes and is essential for maintaining catalytic activity. Some of the most well-known zinc-containing enzymes include:

- Carbonic anhydrase: Regulates acid-base balance by catalyzing the conversion of carbon dioxide to bicarbonate (Coleman, 2020).

- Alkaline phosphatase: Plays a role in bone mineralization and phosphate metabolism (Millán, 2006).
- Superoxide dismutase (Cu/Zn-SOD): An important antioxidant enzyme that combats oxidative stress (Fridovich, 1995).
- DNA and RNA polymerases: Dependent on zinc for the replication and transcription of genetic material (Vallee & Falchuk, 1993).

These enzymatic activities demonstrate the central role of zinc in maintaining vital functions at the biochemical level.

1.2. Structural Roles

Zinc is important not only for catalytic but also for maintaining structural integrity. It plays a role in DNA and RNA binding, particularly in protein motifs known as "zinc fingers" (Figure 1). These motifs ensure the structural stability of transcription factors and are critical for regulating gene expression (Klug, 2010; Nakaseko, 1992; Neuhaus, 1992).

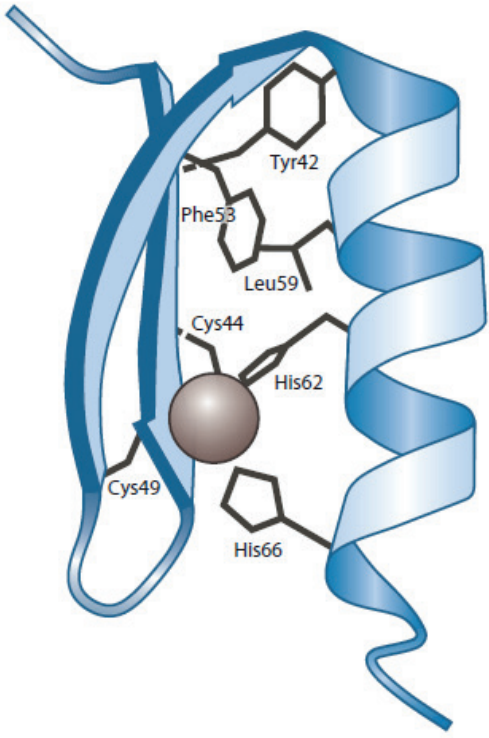

Figure 1. *The structure of a zinc finger from a twodimensional NMR study of a two-finger peptide in solution. The same study showed that the linker between the two modules is highly flexible.*

Therefore, zinc indirectly affects the activity of thousands of genes in the functional readout and regulation of the genome (Andreini & Bertini, 2012).

1.3. Cellular Functions and Signal Transduction

Zinc acts as a "second messenger" in cellular signaling. Zinc ions interact with intracellular calcium and magnesium signaling to regulate processes such as neuronal excitability, insulin secretion, and immune cell activation (Yamasaki et al., 2007; Haase & Rink, 2014). Furthermore, zinc transporters in cell membranes—the ZIP (Zrt-/Irt-like Protein) and ZnT (Zinc Transporter) families—maintain intracellular zinc homeostasis. ZIP proteins transport zinc into the cell, while ZnT proteins transport zinc out or to organelles (Kambe et al., 2015). The balance of these transporter systems is critical for cell metabolism, immune response, and neurological functions.

1.4. Antioxidant Defense and Cell Protection

Zinc indirectly limits the formation of reactive oxygen species (ROS). This effect provides antioxidant capacity through the Cu/Zn-SOD enzyme and stabilizes sulfhydryl groups, thus maintaining cellular membrane integrity (Powell, 2000). Zinc also contributes to the neutralization of free radicals by stimulating metallothionein synthesis (Coyle et al., 2002). With these properties, zinc plays an important role in preventing many diseases associated with oxidative stress and slowing the aging process.

1.5. Effects on Hormones and Metabolic Regulations

Zinc is present in the crystal structure of insulin, regulating its storage and release in pancreatic β-cells (Chausmer, 1998). It also plays a role in the synthesis and release of various hormones, including thyroid hormones, growth hormone, testosterone, and melatonin (Marreiro et al., 2017). Therefore, zinc deficiency can lead to widespread metabolic disorders in the endocrine system.

2. ZINC AND THE IMMUNE SYSTEM

The immune system plays a fundamental role in the body's defense against infections and foreign agents. Zinc is an essential trace element for the effectiveness of both innate and adaptive immune responses (Haase & Rink, 2014; Maares & Haase, 2020). Zinc deficiency results in significant impairments in both cellular and humoral immune functions, increasing susceptibility to infections (Prasad, 2008).

2.1. Effects on Innate Immunity

Innate immunity constitutes the organism's first line of defense and includes phagocytic cells (neutrophils, macrophages), natural killer (NK)

cells, and epithelial barriers. Zinc is essential for maintaining functions such as chemotaxis, phagocytosis, and cytotoxic activity of these cells (Wintergerst et al., 2007). Zinc deficiency impairs neutrophil and macrophage function, hindering pathogen clearance (Bonaventura et al., 2015). Furthermore, zinc protects mucosal barriers from damage by maintaining epithelial integrity (Shankar & Prasad, 1998). Zinc also plays a key role in regulating the inflammatory response. It inhibits the activation of the NF-κB (nuclear factor kappa B) pathway, preventing excessive cytokine production and playing a role in regulating the inflammatory response (Wessels et al., 2013). This mechanism suggests that zinc supports not only immune stimulation but also the limitation of inflammation.

2.2. Effects on Acquired Immunity

The adaptive immune system orchestrates specific immune responses via T and B lymphocytes. Zinc is essential for the maturation and activation of T cells (Rink & Haase, 2007). The thymus gland utilizes this element in the synthesis of thymulin, a zinc-dependent hormone. Zinc deficiency reduces thymulin activity, negatively impacting T cell proliferation and cytokine production (Dardenne, 2002). Similarly, zinc deficiency impairs the function of $CD4^+$ T helper cells, impairing antibody production. Zinc, which also acts on B cells, plays a role in regulating antibody (especially IgG and IgA) synthesis (Maywald et al., 2017). Thus, zinc deficiency suppresses both cellular and humoral immune responses, reducing defense against infections.

2.3. Zinc Deficiency and Susceptibility to Infections

Zinc deficiency is one of the most common micronutrient deficiencies in developing countries, and its effects on the immune system are particularly pronounced in children. According to World Health Organization (WHO) data, zinc supplementation reduces the frequency and severity of illnesses such as diarrhea, respiratory infections, and malaria in children (WHO, 2021). Furthermore, studies in adults have reported that zinc supplementation shortens the duration of colds (rhinovirus) and alleviates symptoms (Hemilä, 2017). These findings suggest that zinc may positively impact the course of viral infections by optimizing the immune response.

2.4. Homeostatic Role in Regulation of Immune Response

During the immune response, zinc levels change rapidly; during infection or inflammation, plasma zinc levels decrease while intracellular storage increases. This dynamic process, called nutritional immunity, provides a defensive advantage by limiting pathogens' access to zinc (Hood & Skaar, 2012). Zinc transporter proteins (ZIP and ZnT) actively participate in this process, regulating the activity of immune cells (Kambe et al., 2015).

Therefore, zinc deficiency not only weakens the immune system but also disrupts the inflammatory balance. Maintaining optimal zinc levels is critical for maintaining immune homeostasis.

3. CONSEQUENCES OF ZINC DEFICIENCY

Zinc deficiency is a significant health problem that disrupts many biological processes and manifests in a wide range of clinical symptoms. The severity of the deficiency can lead to mild, moderate, or severe clinical manifestations. This condition becomes particularly pronounced during periods of rapid growth (infancy, childhood, adolescence) and during periods of increased physiological zinc requirements, such as pregnancy and breastfeeding (Prasad, 2013).

3.1. Effects on Growth and Development

Because zinc is essential for cell proliferation and protein synthesis, its deficiency is closely associated with growth failure (Roohani et al., 2013). Children may experience slower height growth, delayed skeletal development, and delayed puberty. These effects increase childhood morbidity and mortality, particularly in countries where low-zinc diets are common (Black, 2003).

3.2. Immune System Disorders

Zinc deficiency results in decreased T lymphocyte activation, impaired cytokine production, and reduced phagocytosis capacity (Maares & Haase, 2020). This results in frequent infections, particularly diarrhea and respiratory illnesses, and prolonged illness duration (Shankar & Prasad, 1998). Zinc supplementation administered to children in developing countries reduces diarrhea rates by up to 15% (WHO, 2021).

3.3. Dermatological and Wound Healing Disorders

Because zinc is essential for keratinocyte proliferation and collagen synthesis, its deficiency causes dermatitis and eczema-like skin lesions, excessive hair loss, and delayed wound healing (Maret, 2013). Acrodermatitis enteropathica, which occurs in severe deficiency, is a rare but important disease that can be life-threatening.

3.4. Loss of Taste and Smell

Zinc plays a role in the synthesis of taste receptor proteins. Its deficiency can cause hypogeusia and anosmia (reduced sense of taste and smell) (Sandstead, 2012). This condition exacerbates nutritional deficiencies, especially in older individuals.

3.5. Effects on Reproductive Health

Zinc plays a role in testosterone synthesis and sperm production. Its deficiency increases the risk of hypogonadism, decreased sperm quality, and infertility in men (Chasapis et al., 2012). In women, it negatively impacts ovarian function and pregnancy health, and is also known to increase the risk of miscarriage and preterm birth (King et al., 2015).

3.6. Neuropsychiatric Symptoms

Zinc deficiency can affect neurotransmitter functions, leading to learning difficulties, attention deficits, and behavioral changes (Sandstead, 2012). It is also thought that low zinc levels may contribute to conditions such as Alzheimer's and depression (Maares & Haase, 2020).

4. ZINC AND ITS RELATIONSHIP WITH DISEASES

Zinc is an element that acts as a cofactor for numerous enzymes and regulates fundamental mechanisms such as cellular defense, gene expression, and oxidative stress control. Therefore, disruptions in zinc homeostasis play an important role in the pathophysiology of many acute and chronic diseases (Maares & Haase, 2020; Chasapis et al., 2012).

4.1. Immune System and Infectious Diseases

Zinc is essential for the integrity of both the innate and adaptive immune systems. Mechanisms such as T and B lymphocyte differentiation, phagocytosis, and cytokine synthesis depend on zinc availability (Haase & Rink, 2014).

In cases of zinc deficiency:

- T cell activity decreases,
- Interleukin-2 (IL-2) production is suppressed,
- Phagocytosis capacity decreases.

Consequently, susceptibility to viral and bacterial infections increases (Shankar & Prasad, 1998). Diarrhea, pneumonia, malaria, and respiratory tract infections, especially in children, are closely associated with zinc deficiency (Black, 2003). Zinc supplementation shortens the duration of symptoms and reduces mortality in these diseases (WHO, 2021).

4.2. Diabetes Mellitus

Zinc is a trace element necessary for the synthesis, storage, and secretion of insulin (Chausmer, 1998). Insulin granules in the β-cells of the pancreas

are found in complex with zinc. Therefore, zinc deficiency is characterized by decreased insulin secretion, impaired glucose metabolism, and increased oxidative stress (Jansen et al., 2009). Plasma zinc levels have been reported to be low in patients with type 2 diabetes, and zinc supplementation can improve glycemic control (Maares & Haase, 2020).

4.3. Cardiovascular Diseases

Zinc, a component of antioxidant enzymes (e.g., superoxide dismutase), prevents free radical damage. Increased oxidative stress in zinc deficiency leads to damage to the vascular endothelium and increases the risk of atherosclerosis (Chasapis et al., 2012). Furthermore, zinc insufficiency may contribute to the progression of cardiovascular disease through LDL oxidation and inflammation (Krebs, 2013). However, it has also been reported that excessive zinc intake can lower HDL cholesterol levels and pose a cardiovascular risk (Plum et al., 2010). Therefore, a balanced intake is important.

4.4. Neurological and Psychiatric Diseases

Zinc is found in high concentrations in nerve cells and plays a role in neurotransmitter release, synaptic plasticity, and neuronal signal transmission (Takeda, 2001). Its deficiency results in neurological dysfunction, learning disabilities, memory impairment, and behavioral disorders (Sandstead, 2012). Furthermore, research suggests that low zinc levels may be associated with the pathogenesis of conditions such as depression, Alzheimer's disease, and epilepsy (Grabrucker, 2014). There is also evidence that zinc supplementation in the treatment of depression may increase antidepressant efficacy (Nowak et al., 2005).

4.5. Oxidative Stress and Cancer

Zinc plays a role in DNA repair and cell cycle control, protecting genetic integrity. Its deficiency makes DNA vulnerable to oxidative damage, increasing the risk of mutation (Prasad, 2013). Some epidemiological studies have reported that zinc deficiency may increase the risk of prostate, esophageal, and colon cancer (Costello et al., 2006). Zinc also maintains the structural stability of the p53 tumor suppressor protein. Therefore, disruptions in zinc homeostasis may promote tumor development (Franklin & Costello, 2009).

4.6. Aging and Chronic Diseases

With aging, zinc absorption decreases, plasma levels decrease, and immune function weakens. This phenomenon is described as "immunocenescence" (Haase & Rink, 2014). Zinc supplementation may strengthen the immune response in older individuals, reduce the frequency of infections, and improve quality of life (Prasad et al., 2007).

5. ZINC SOURCES AND DAILY INTAKE RECOMMENDATIONS

Zinc is found in both animal and plant-based foods; however, animal sources are generally more bioavailable. The richest sources of zinc include red meat, liver, eggs, and seafood (especially oysters, crab, and mussels) (King et al., 2015; Gibson et al., 2008). In plant-based sources, zinc is found in whole grains, legumes, nuts, and seeds. However, the phytate (phytic acid) content in these foods significantly reduces zinc absorption. Phytate forms insoluble complexes with zinc, preventing its absorption from the intestines (Gibson et al., 2010). Therefore, individuals on a vegetarian diet are at higher risk of zinc deficiency (Wessells & Brown, 2012). Traditional processes such as fermentation, sprouting, or soaking are recommended to reduce phytate levels (Hotz & Brown, 2004). The recommended daily intake of zinc for adults is 8 mg for women and 11 mg for men (IOM, 2001). This requirement increases during pregnancy, lactation, growth spurts, and conditions requiring infection or tissue regeneration (Maares & Haase, 2020).

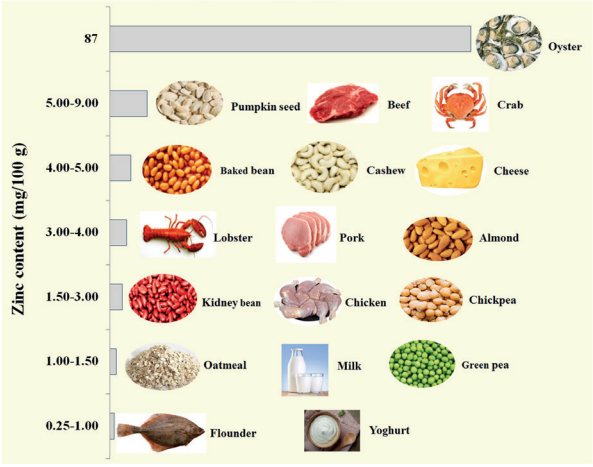

Figure 2. *Examples of foods rich in zinc (data obtained from NIH [2021]).*

5.1. Factors Affecting Zinc Absorption

Zinc absorption occurs primarily in the jejunum and ileum regions of the small intestine. Absorption occurs through both active transport and passive diffusion. The primary transporter proteins involved in absorption are membrane proteins belonging to the ZIP (Zrt- and Irt-like Protein) and ZnT (Zinc Transporter) families (Lichten & Cousins, 2009). ZIP proteins facilitate zinc entry into the cell, while ZnT proteins transport zinc out of the cell or to organelles. The rate of absorption generally varies between 15–40%, depending on the amount of zinc consumed and its composition (Plum et al., 2010). Elements such as phytate, fiber, calcium, and iron can reduce absorption, while amino acids (especially histidine and cysteine) and organic

acids (citric and malic acid) can increase it (Lonnerdal, 2000). Absorbed zinc is transported by binding to plasma proteins such as albumin and transferrin and is stored primarily in the liver, muscle, and bone tissues. Homeostatic regulatory mechanisms primarily excrete zinc through the intestines, urine, and sweat (Maret, 2013). These feedback mechanisms are crucial for maintaining body zinc levels.

Absorption enhancers:

- Animal proteins (meat, dairy products)
- Organic acids (citric acid, malic acid)
- Low phytate content

Absorption reducers:

- Phytic acid (in whole grains and legumes)
- High calcium and iron intake
- Alcohol consumption
- Chronic gastrointestinal diseases (e.g., celiac disease, Crohn's disease) (King et al., 2000)

5.2. Excessive Intake and Toxicity

Zinc can be toxic if taken in excess of the recommended daily intake. The upper safe intake level (UL) has been set at 40 mg/day for adults (Food and Nutrition Board, 2001).

Possible effects of excessive zinc intake:

- Decreased copper absorption → hypochromic anemia
- Immune system suppression
- Nausea, vomiting, diarrhea
- Decreased HDL cholesterol levels (Plum et al., 2010)

While these effects are reversible with short-term high-dose supplementation, long-term high intakes can lead to permanent metabolic disorders.

5.3. Evaluation of Zinc Status

Plasma or serum zinc concentration is generally used to assess zinc levels. Normal values are generally between 70–120 µg/dL (King et al., 2000). However, serum levels alone are not diagnostic because they can be affected by infections, stress, fasting, and hormonal status. Therefore, biochemical tests should be evaluated in conjunction with clinical findings.

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Chapter 3

CHEMISTRY OF THE RESVERATROL MOLECULE AND ITS FUNCTIONS IN METABOLISM

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1. INTRODUCTION

Free radicals are unstable groups of atoms or molecules that have unpaired electrons. Free radicals are highly reactive due to their unpaired electrons and attack atoms and molecules in their environment. However, despite their short lifespan, they can also react with other substances, transforming them into free radicals. A series of reactions continues in this manner (Gülçın et al., 2003; Akkuş, 1995). Antioxidants are compounds that delay the start of the oxidation process of substances that can auto-oxidize or reduce the rate of oxidation. Thousands of substances, both natural and artificial, are known to exhibit antioxidant properties (Gülcin, 2012). One of the polyphenolic antioxidants is resveratrol (Yılmaz, 2010). Resveratrol (3,4,5-trihydroxystilbene) is a natural antioxidant compound with a polyphenol structure that is found in high amounts in fruits such as grapes, peanuts, strawberries, and cherries (Aydogan et al., 2007). Resveratrol increases the level of glutathione and traps free radicals through glutamate-cysteine ligase enzymes (Turkmen et al., 2005). Additionally, studies have indicated that resveratrol has anti-carcinogenic, anti-inflammatory, immunomodulatory, anti-mutagenic, and antifungal effects. Its antioxidant properties, in particular, prevent oxidative damage by binding reactive free radicals and promoting metal chelation (Dundar & Aslan, 2000).

1.1. RESVERATROL SOURCES

Studies have reported that resveratrol is found in foods such as grapes, grapevines, peanuts, blueberries, blackberries, strawberries, pistachios, cranberries, and purple grape juice (Tian & Liu, 2020; Udenigwe et al., 2008). Resveratrol is found in high amounts, especially in the skins of colored grape varieties (Keskin et al., 2009).

It has also been reported that the concentration of the trans-isomer, the form of resveratrol in red wine, varies between 0.1 and 15 mg/L (Frémont, 2000). A study investigated the amount of resveratrol in peanuts and wine. The results indicated that the amount of resveratrol in peanuts was half that in wine (Venugopal & Liu, 2012). Sources of resveratrol are shown in Figure 1.

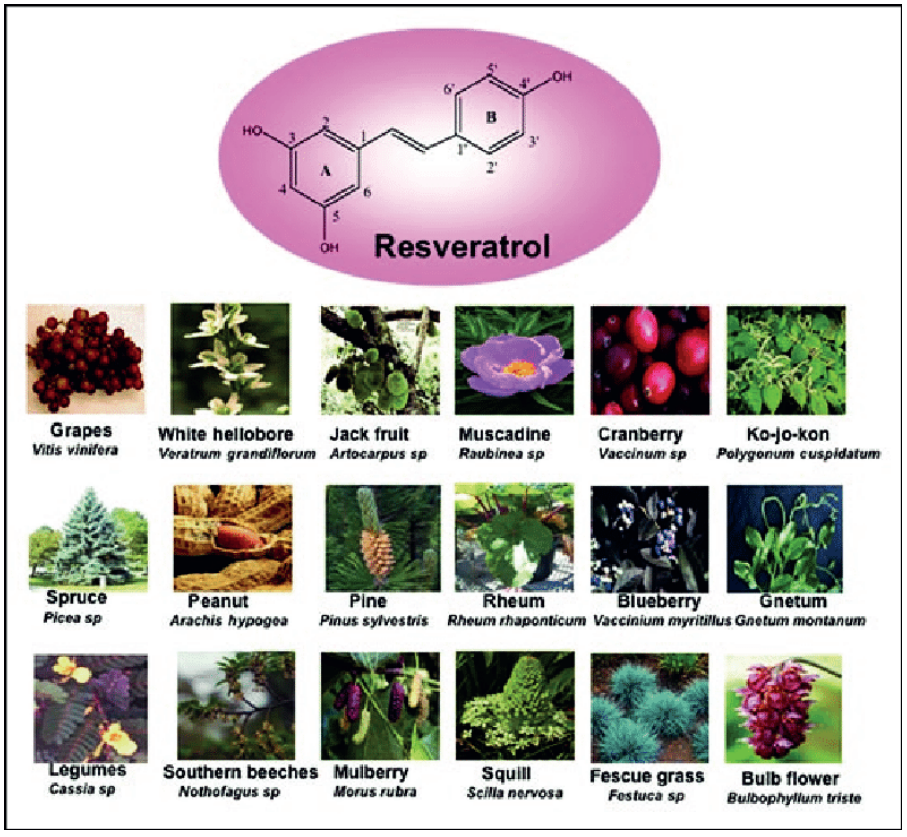
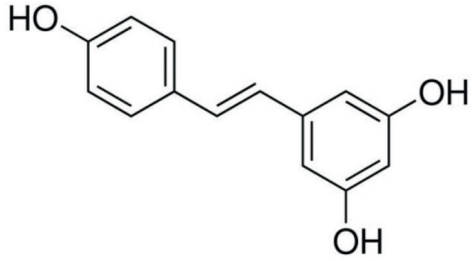


Figure 1. *Sources of resveratrol (Harikumar & Aggarwal, 2008).*

1.2. CHEMICAL AND PHYSICAL STRUCTURE OF RESVERATROL

Resveratrol, with its closed formula $C_{14}H_{12}O_3$ and molecular weight of 228 g/mol, has a melting temperature of 253°C. It is also a plant polyphenol and has a 14-carbon skeleton. It is quite soluble in ethanol but only very slightly soluble in water. Polyphenols are natural chemicals formed by the combination of a large number of phenol units. This group constitutes a large part of phytochemicals (Table 1). These components are chemically divided into two groups: flavonoids (flavonols, flavones, flavan-3-ols, proanthocyanides, anthocyanides, and isoflavones) and non-flavonoids (hydroxycinnamic acids, ellagitannins, gallotannins, and stilbenes) (Kaleci, 2018).

Table 1. *Physical Properties of Resveratrol (Türkoğlu, 2019).*

Closed Formula	$C_{14}H_{12}O_3$
Open Formula	
Systemic Name	5- [(E)-2-(4-hidroksifenil-etenil]benzen-1,3 diol
Other Names	Trans-resveratrol Trans-3,5,4'-trihidroksistilben 3,4',5 sistilbentriol (E)-5-(p-hidroksistil)resorsinol 3,5,4'-trihidroksi-cis-stilben 3,5,4'-trihidroksi-trans-stilben
Molecular Weight	228.25 g/mol
Boiling point	253-255 °C
Physical Structure	White-Solid
Resolution	Soluble in water, methanol, and acetone.

The resveratrol molecule has two different forms: trans-resveratrol and cis-resveratrol. These forms are shown in Figure 2.

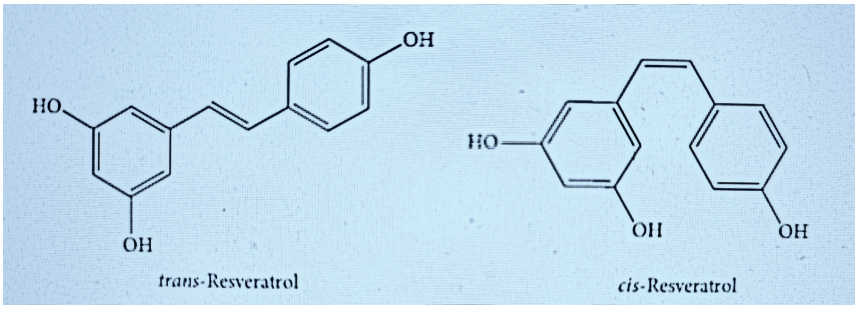


Figure 2. *Forms of the resveratrol molecule.*

1.3. FUNCTIONS OF RESVERATROL IN METABOLISM

1.3.1. ANTIOXIDANT EFFECT

Polyphenols are a family of antioxidants that include anthocyanins, flavonoids, phenolic acids, and stilbenes. Resveratrol (3,4',5-trihydroxystilbene) is a subgroup of stilbenes and a polyphenolic compound found in grapes, wine,

peanuts, and blueberries (Li et al., 2006). The function of resveratrol as a natural antioxidant is explained by three different antioxidant mechanisms. One of these mechanisms is to compete with coenzyme Q and reduce the oxidative chain complex at the site of ROS formation. The second is to capture the superoxide radical formed in the mitochondria, and the third is to inhibit lipid peroxidation induced by the products of the Fenton reaction. It has been reported that resveratrol can capture both superoxide and hydroxyl radicals. Studies have shown that resveratrol, in particular, has a weaker effect on scavenging reactive oxygen species (ROS) in vitro, while acting as a potent antioxidant in vivo. The reason for resveratrol's high antioxidant properties in vivo is its ability to increase nitric oxide synthesis. Resveratrol's in vivo antioxidant effect, in particular, is due to its ability to capture nitric oxide and superoxide radicals. Resveratrol also maintains intracellular concentrations of antioxidants in metabolism (de la Lastra & Villegas, 2007). Resveratrol has been reported to increase the amount of glutathione in human lymphocytes, counteracting the damage caused by hydrogen peroxide. Additionally, it has been reported that resveratrol causes increases in the levels of enzymes such as glutathione peroxidase, glutathione reductase, and glutathione-S-transferase in human lymphocytes (Das & Maulik, 2006).

1.3.2. ANTI-INFLAMMATORY EFFECT

Inflammation is a multistage mechanism. It is a multistage biological process that involves multiple cell types and intermediary signals (Lugrin et al., 2014). Inflammation, in particular, is an adaptive response in metabolism generated by various danger signals such as microorganism invasion and tissue damage (Medzhitov, 2008). In vivo and in vitro analyses have shown that resveratrol has anti-inflammatory properties and inhibits the production of anti-inflammatory factors (Gao et al., 2001). Studies have reported that resveratrol strongly suppresses NO production in macrophages. Specifically, it has been found to strongly reduce the amount of nitric oxide synthase (iNOS) protein (Tsai et al., 1999). Specifically, resveratrol has been found to dose-dependently inhibit the production of TNF-α, IL-1α, and IL-6. It has also been found to reduce mRNA expression and protein secretion of IL-17 in vitro (Fuggetta et al., 2016). In addition, studies have reported that resveratrol suppresses the activation of the proinflammatory mediator Nrf2/HO-1 pathway and the expression of IL-8. Thus, it has been found to reduce H. pylori-induced gastric inflammation (Zhang et al., 2015).

1.3.3. ANTIVIRAL EFFECT

There are numerous in vitro and in vivo studies on the antiviral activity of resveratrol. It is the most important polyphenolic compound studied in this field. Specifically, resveratrol's antiviral activity is possible through inhibition of gene expression, viral replication, protein synthesis, and nucleic acid synthesis. For example, in influenza virus infection, resveratrol has been shown to inhibit nuclear-cytoplasmic translocations of viral ribonucleoproteins in MDCK cells. It has been found that it reduces the expression of viral proteins, especially by inhibiting protein kinase C pathways (Abba et al., 2015). Studies have indicated that resveratrol inhibits HSV (Herpes Simplex Virus) infection both in vivo and in vitro. This substance, in particular, has been found to exhibit potent anti-HSV activity (Docherty et al., 1999). Additionally, resveratrol increases histone acetylation reactions, thus regulating HSV-2 infection (Ding et al., 2020). Varicella-zoster virus (VZV) belongs to the Herpesviridae family and is the most important cause of chickenpox, a common childhood disease (Andrei & Snoeck, 2021). In vitro studies have shown that resveratrol reduces VZV replication in a dose- and time-dependent manner (Docherty et al., 2006). Pseudorabies virus (PRV) is a type of herpesvirus found in pigs. It is the cause of Aujeszky's disease (AD) in pigs. This disease is caused by PRV infection in pigs. This infection results in stillbirths and abortions in pigs. Resveratrol treatment prevents the effects of this virus and restores serum progesterone levels (Su et al., 2016).

1.3.4. CYTOTOXIC EFFECT ON CANCER CELLS

Studies have indicated that resveratrol inhibits metabolic events in tumor cells, such as cell growth, transcription, tumor cell proliferation, stimulating hormone signaling, and inhibiting angiogenesis. (Amini et al., 2023; Gielecińska et al., 2023; Karkon-Shayan et al., 2023; Song et al., 2023; Kumar et al., 2022).

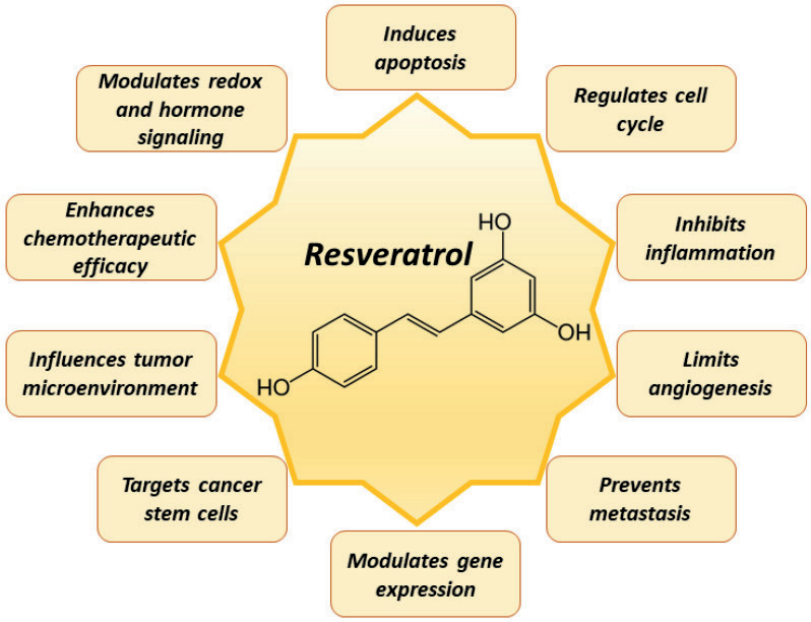


Figure 3. *Cytotoxic effects of resveratrol on tumor cells in metabolism (Kopustinskiene et al., 2023).*

Resveratrol induces apoptosis-mediated cell death and arrests the cell cycle through three basic mechanisms. These mechanisms are of three types: initiation, proliferation, and metastasis (Sheth et al., 2012). It has been shown to have a growth inhibitory effect on various cancer cells in vitro. Resveratrol has also been reported to have growth-inhibiting effects on various cancer cells in vitro, including breast (Gomes et al., 2019), colon (Schneider et al., 2000), lymphoma and leukemia (Schmitt et al., 2002), and prostate (Sheth et al., 2012; Selvaraj et al., 2016). In a study conducted on mice, resveratrol supplementation was found to inhibit the proliferation and development of pancreatic cancer cells (McCubrey et al., 2017).

1.3.5. EFFECT ON NEURODEGENERATİVE DİSEASES

Studies suggest that oxidative and inflammatory damage occurring in the central nervous system contributes to neurodegenerative diseases, such as stroke and Alzheimer's disease. Resveratrol, in particular, has potent antioxidative and anti-inflammatory properties, suggesting its potential use in the treatment of neurodegenerative diseases. It has been reported that resveratrol regulates the activities of metabolic regulators in the onset of neurodegenerative disorders (Berman et al., 2017). Studies have reported that resveratrol reduces the production of ROS (reactive oxygen species) in the

brain and periphery due to its anti-inflammatory effect (Yang et al., 2021). Resveratrol, in particular, is thought to prevent Parkinson's disease by reducing oxidative stress. The formation of free oxygen species in metabolism leads to harmful chemical reactions, such as DNA damage and LDL peroxidation. By inhibiting these radicals, resveratrol also prevents the formation of such reactions (Kung et al., 2021).

1.3.6. ANTIDIABETIC EFFECT

Resveratrol has important effects on diabetes because it lowers blood sugar and protects the beta cells in the pancreas, which secrete insulin (Yücel et al., 2018). Studies have determined that resveratrol provides glycemic control in metabolism and has antioxidant activities (Berman et al., 2017; Hausenblas et al., 2015). It also affects the glycolysis mechanism by affecting skeletal muscle and insulin sensitivity. Due to this feature, it is thought that resveratrol may be important in preventing the decrease in skeletal muscle and insulin sensitivity that occurs in diabetes (McCubrey et al., 2017). In a study conducted on elderly patients with impaired glucose tolerance, it was determined that the use of resveratrol delayed postprandial glucose levels and reduced the level of insulin released after meals (Berman et al., 2017). In a study conducted on 283 people with type 2 diabetes, it was determined that high-dose resveratrol (≥100 mg/day) intake brought fasting blood plasma glucose values to normal limits (Tain & Hsu, 2018). Recent studies have indicated that resveratrol is important in preventing diabetes and alleviating some diabetic complications. Resveratrol has been found to reduce plasma glucose and triglyceride concentrations and improve metabolic parameters in diabetic rats (Cai et al., 2005; Kim et al., 2004).

1.3.7. ANTI-AGING EFFECTS

Resveratrol has been reported to have numerous health benefits and help prevent aging. The primary purpose of the effects of natural products like resveratrol is to prevent cell death or aging, diabetes, cardiovascular disease, and other illnesses. Studies have shown that resveratrol can increase human lifespan by activating sirtuins and SIRT1 molecules (Zhang et al., 2021). Studies have shown that the Klotho gene functions as an aging-suppressing gene. In particular, stimulating the expression of this gene is thought to be a potential treatment for age-related diseases (Chen et al., 2021). Resveratrol is used both in cosmetic products and as a food supplement for its anti-aging effects. Studies have also shown that resveratrol is a tyrosinase inhibitor, regulating the inflammatory process in keratinocytes, the melanocyte cells responsible for melanin production, and protecting melanocytes from oxidative damage (Doğru, 2021). Resveratrol, in particular, has been reported to prevent normal skin aging by inhibiting nitric oxide. It has also been determined to

have anti-aging properties because it reduces the expression of inflammatory and skin-aging genes (Lee et al., 2010).

CONCLUSION AND RECOMMENDATIONS

As a result of the literature studies, it has been reported that resveratrol is effective on cancer, obesity, diabetes, cardiovascular diseases, non-alcoholic fatty liver disease, and neurodegenerative diseases. Cancer has been on the rise, especially recently. Cancer has become one of the most common illnesses affecting people in society and is a leading cause of death. Resveratrol has multifaceted effects in the treatment of cancer. Therefore, it has the potential to be used in oncological interventions. Resveratrol, in particular, plays a significant role in cancer treatments because it affects mitochondrial functions in cancer cells and plays a role in apoptosis and energy production mechanisms. As more studies are conducted on this topic, resveratrol has the potential to be used in future cancer prevention and cancer treatments. Resveratrol is a biologically important molecule, especially because of its antioxidant activity and its ability to protect the metabolism against oxidative stress. In fact, many of the medicinal effects of resveratrol are mainly due to its antioxidant effect. Further studies are needed on the biological activities of resveratrol.

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Chapter 4

BIOLOGICAL PROPERTIES AND STRUCTURE-ACTIVITY RELATIONSHIPS OF HYDRAZONE COMPOUNDS

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1. INTRODUCTION

Hydrazones, with the general structure R1–R2C=NNH2 (where R1 and R2 represent alkyl and/or aryl substituents), are obtained through the reaction of aldehydes or ketones with hydrazines or hydrazides in an acidic medium using various solvents. They are characterized by the presence of a three-atom azomethine unit (–C=N–N–). The general formation scheme of hydrazones is shown in Figure 1.

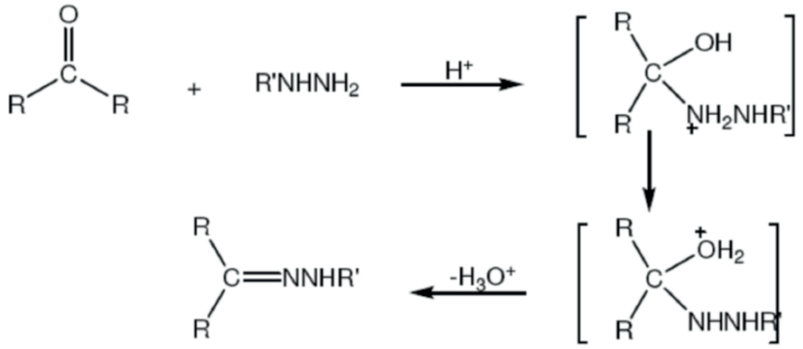


Figure 1. *The general formation mechanism of hydrazones*

The N=C bond in hydrazones interacts with the lone electron pair of nitrogen. In hydrazones, the nitrogen exhibits nucleophilic behavior, while the carbon atom can display both electrophilic and nucleophilic characteristics (Corey & Enders, 1976). The combination of the hydrazone moiety with different functional units imparts unique physical and chemical characteristics to the structure, thereby conferring a broad range of distinctive biological and pharmacological properties to these compounds (Khan, 2008). In recent years, the increasing prevalence of drug-resistant microbial infections has emerged as a growing public health concern.

Therefore, the design and development of new antibacterial agents, as well as the investigation of their mechanisms of action and structure–activity relationships, have become a critical biomedical necessity (Dikio et al., 2017). Schiff bases containing hydrazide– hydrazone moieties with the −(C=O) NHN=CH structural motif have been demonstrated to serve as important pharmacophoric frameworks in the design and development of biologically active molecules (Battin, 2019; El-Medani et al., 2020; Gryboś et al., 2018). The fact that hydrazone-containing compounds constitute an important class in drug lead design has prompted researchers to tune the electronic and structural properties of hydrazones by modifying their substituents and to synthesize new hydrazone Schiff bases (Lahinakillathu et al., 2025).

Studies have shown that the synthesized hydrazone compounds exhibit significant biological activities, including notable antimicrobial (Vicini et

al., 2002; Vinuelas-Zahinos et al., 2008), antituberculosis (Kaymakçıoğlu & Rollas, 2002), anticonvulsant (Ragavendran et al., 2007; Vicini et al., 2002), anti-inflammatory (Bezerra-Netto et al., 2006; Rollas & Güniz Küçükgüzel, 2007) and antitumor effects, and that their anticancer potential is particularly promising (Singh et al., 2022; Yadav et al., 2021). Hydrazones are known to function as herbicides, insecticides, nematicides, rodenticides, and plant growth regulators (Lei et al., 2015; Liu et al., 2010). These advantages of hydrazones have accelerated the synthesis of new compounds and the investigation of their antimicrobial properties These advantages are driving intensive research into hydrazone compounds.

2. ISOMERISM IN HYDRAZONES

Hydrazones readily undergo keto–enol tautomerism. These ligands predominantly exist in the keto form in the solid state; however, once in solution, they tend to exhibit an equilibrium distribution between the keto and enol forms (Rauf et al., 2015)**.**

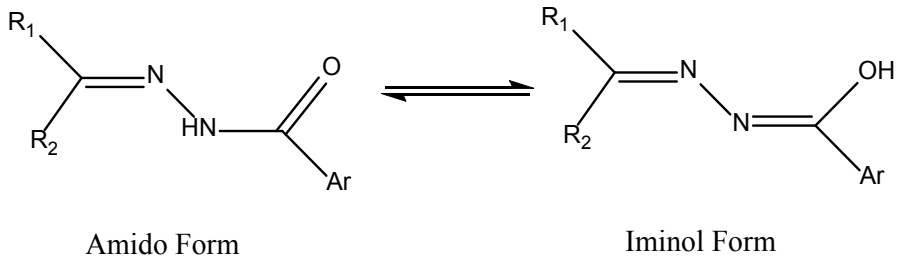


Figure 2. *Keto-Enol tautomer of hydrazones*

In hydrazones, the restriction of rotation around the C=N double bond results in the formation of E and Z geometric isomers in their iminol forms. (Knapp et al., 1981; Palla et al., 1986; Ragavendran et al., 2007). In hydrazides, an equilibrium exists between the two isomeric forms, meaning that both forms are present in the compound at certain proportions. The shift of the equilibrium toward a particular isomer is governed by the steric effects of the groups surrounding the bond, the electrostatic repulsion between the oxygen and nitrogen atoms, and the molecule's potential to form hydrogen bonds (Patil et al., 2018). Moreover, due to the free rotation around the HN–C(O) bond within the molecule, each of these isomers can further give rise to corresponding cis/trans forms (Purandara et al., 2019).

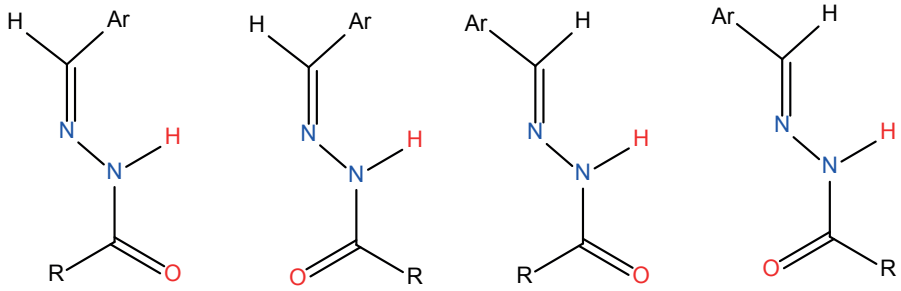


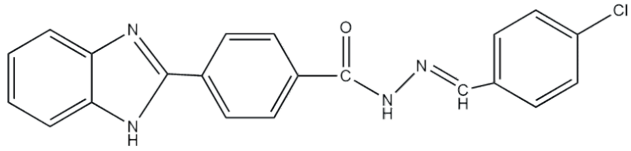
Figure 3. *Isomers of hydrazone derivatives*

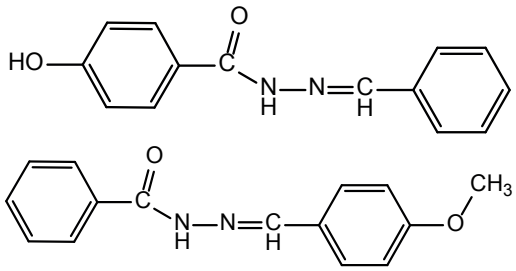
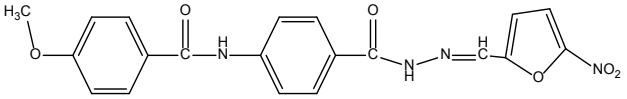
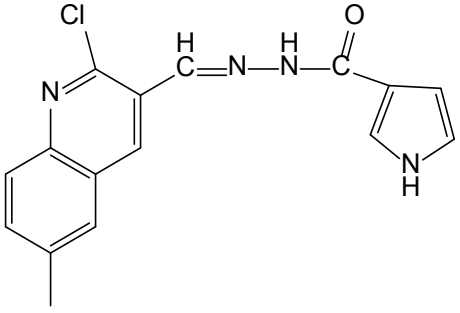
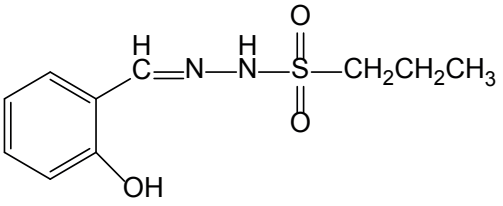
3. BIOLOGICAL AND PHARMACOLOGICAL PROPERTIES OF HYDRAZONES AND THEIR STRUCTURE-ACTIVITY RELATIONSHIPS

3.1. ANTIMICROBIAL ACTIVITY

Bacillus subtilis, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *pneumococci* are significant pathogenic microorganisms that can cause severe infections in humans and are sometimes associated with serious complications and mortality. Today, the emergence of antibacterial-resistant bacterial strains due to the improper use of antibacterial and antimicrobial drugs has prompted researchers to develop new antibacterial agents (Bayrak et al., 2009; Özkay et al., 2010). Hydrazones are among the most extensively studied compounds for their antimicrobial activity and are known to exhibit strong antimicrobial effects. Examples of hydrazone compounds reported in the literature to possess antimicrobial activity are provided below (Table 1) (Bawa et al., 2009; Jankulovska et al., 2019; Küçükgüzel et al., 2002; Özkay et al., 2010; Özmen & Olgun, 2008)

Table 1. Selected hydrazone compounds with antimicrobial properties.

Structure	Referance
	(Özkay et al., 2010)

	(Jankulovska et al., 2019)
	(Küçükgüzel et al., 2002)
	(Bawa et al., 2009)
	(Özmen & Olgun, 2008)

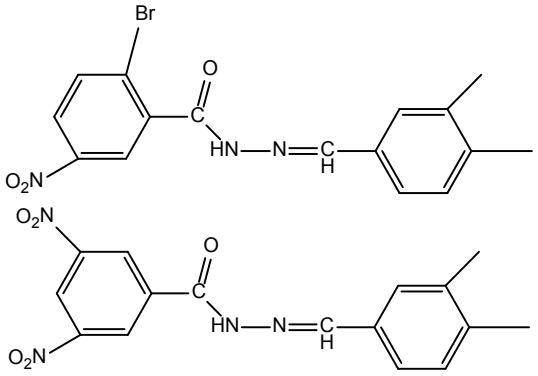
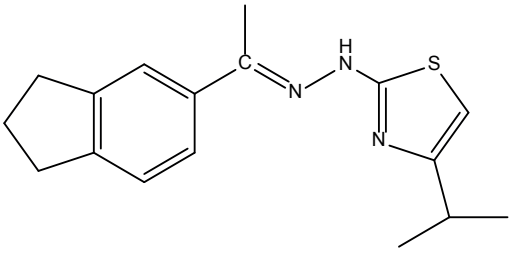
In structure-activity studies, it has been observed that structural changes in Schiff bases containing electron-donating or electron-withdrawing groups are crucial in determining their biological effects (Koopaei et al., 2022; Korcz et al., 2018). In general, hydrazone compounds bearing OCH_3, NO_2, or halogen substituents at the para position, as well as those containing nitrogen-based heterocyclic rings, have been found to exhibit strong antimicrobial activity (Jankulovska et al., 2019; Kumar et al., 2009; Özkay et al., 2010). When comparing electron-withdrawing groups (NO_2, –Cl, –Br), it becomes evident that halogen substituents on the aromatic ring play a critical role in conferring antibacterial activity. Moreover, the introduction of an electron-withdrawing halogen onto a second aromatic ring is thought to further enhance the antibacterial potential of these compounds (Kumar et al., 2008).

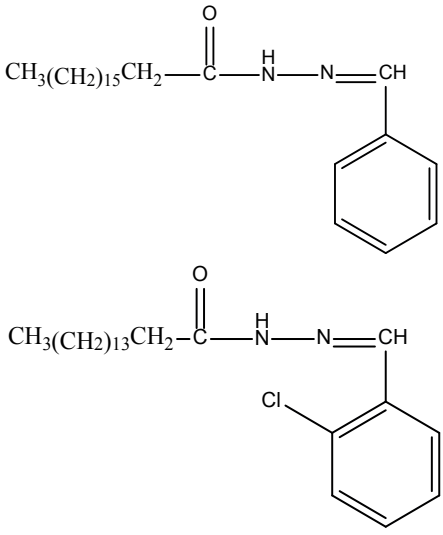
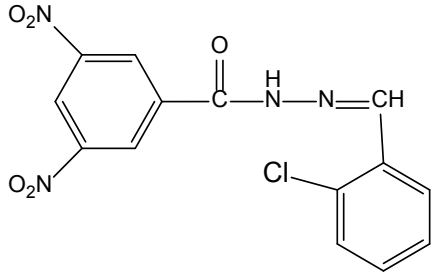
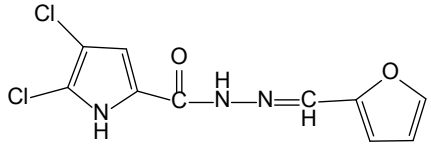
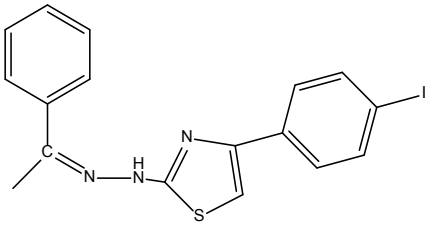
The incorporation of an OH group into the aromatic ring has been observed to markedly enhance antimicrobial activity, attributed to the ability of this substituent to form hydrogen bonds with the target biomacromolecule (Narang et al., 2012).

3.2. ANTIFUNGAL ACTIVITY

Fungal infections can occur as superficial or systemic diseases affecting humans, animals, and plants. The antimicrobial activities of many synthesized hydrazone compounds have been investigated, and they have been reported to exhibit strong antifungal activity. Hydrazone derivatives are therefore highly important in the development of new antifungal agents. Examples of hydrazone compounds reported in the literature to possess antifungal activity are provided below (Table 2) (D. Kumar et al., 2010; Kumar et al., 2009; Maillard et al., 2013; Rane & Telvekar, 2010; Secci et al., 2012).

Table 2. *Selected hydrazone compounds with antifungal properties.*

Structure	Referance
	(Kumar et al., 2009)
	(Maillard et al., 2013)

	(D. Kumar et al., 2010)
	(D. Kumar et al., 2010)
	(Rane & Telvekar, 2010)
	(Secci et al., 2012)

Structure–activity studies have shown that antifungal activity increases in compounds bearing a chloro group at the ortho position and electron-withdrawing groups at the para position (Güven et al., 2007; Jankulovska et al., 2019; Kumar et al., 2009; Sharma et al., 2004). When electron-withdrawing groups attached to the aromatic ring are compared, the highest antifungal activity has been observed in the presence of a nitro substituent (Kumar et

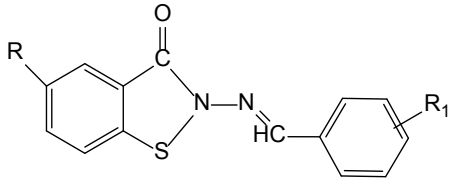
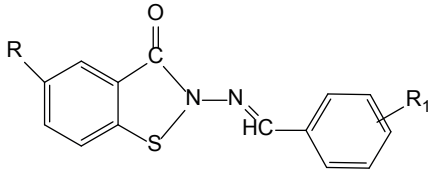
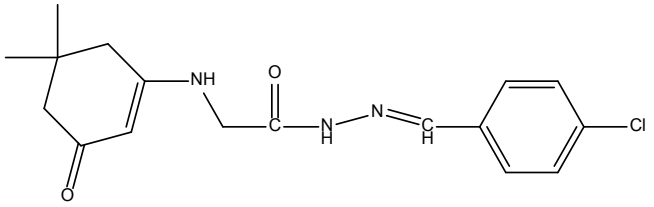
al., 2008). Additionally, it has been observed that in hydrazone compounds derived from carboxylic acids, the biological activity increases as the chain length of the acid moiety increases (D. Kumar et al., 2010; Narasimhan et al., 2007).

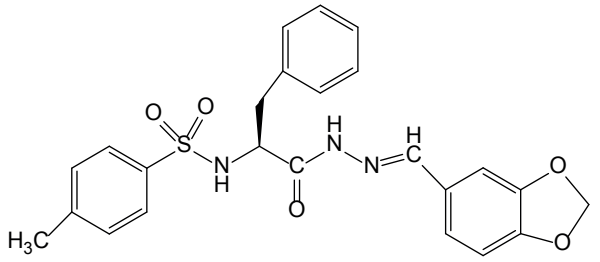
3.3. ANTIVIRAL ACTIVITY

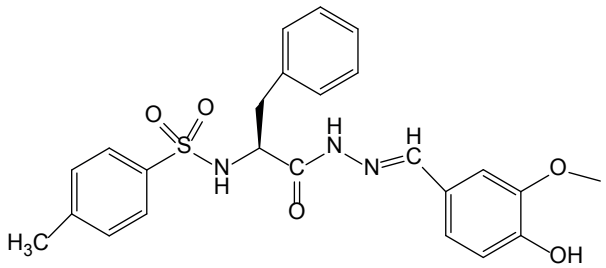
Viruses are extremely small infectious agents that replicate only by utilizing the cellular machinery of a living host and are capable of infecting a wide range of organisms, including humans, animals, and even plants. Human immunodeficiency virus (HIV) infection has claimed approximately 33 million lives to date. Therefore, developing effective treatment options for this virus is a significant public health concern (Jin et al., 2010; Tian et al., 2009). Extensive research has been conducted on hydrazones for the synthesis of antiviral agents, and many hydrazone derivatives have been found to possess significant antiviral activity (Che et al., 2019; Vicini et al., 2009).

Several acylhydrazone compounds have been found to exhibit effective antiviral activity against a wide range of viruses (El-Sabbagh & Rady, 2009; Tian et al., 2009). Various Studies on hydrazones containing pyridine, phenanthroline, and quinolone have shown that these compounds reduce the activity of the Epstein–Barr virüs (Prasad & Joseph, 2020). Some hydrazone compounds reported to have antiviral activity are shown in Table 3.

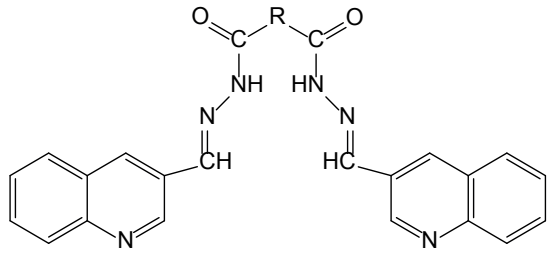
Table 3. *Selected hydrazone compounds with antiviral properties.*

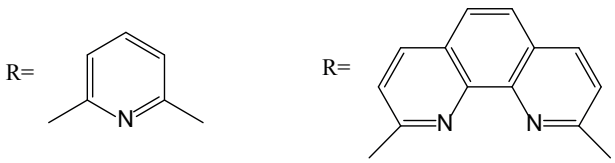
Structure	Referance
 R: H R_1: H (1) R_1: 3-F (2) R_1: 4-Cl (3) R_1: 3-NO_2 (4)	(Vicini et al., 2009)
 R: CH_3 R_1: 4-F (5) R_1: 4-Cl (6) R_1: 3-NO_2 (7) R_1: 3-OH (8)	
	(El-Sabbagh & Rady, 2009)





(Tian et al., 2009)





(Prasad & Joseph, 2020)

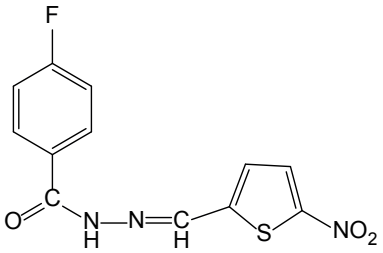
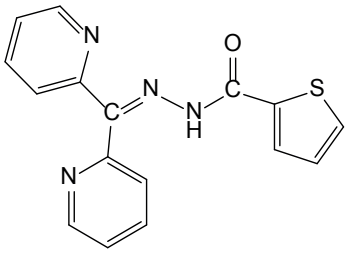
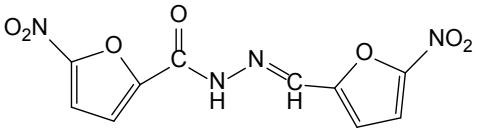
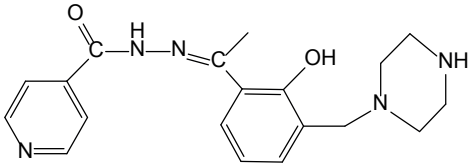
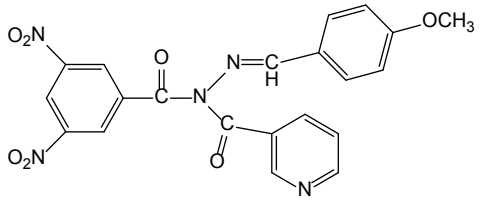
Structure–activity studies of hydrazone derivatives have generally shown that the presence of Cl and S substituents enhances their antiviral activity (El-Sabbagh & Rady, 2009; Vicini et al., 2009).

3.4. ANTITUBERCULAR ACTIVITY

The treatment of tuberculosis has become increasingly challenging due to the rising prevalence of multidrug-resistant mycobacterial strains. In this context, the search for new compounds that exhibit potent tuberculostatic activity while maintaining a low toxicity profile has emerged as an ongoing scientific necessity (Bedia et al., 2006). Many hydrazone derivatives are known to have widespread use in the treatment and control of tuberculosis. Therefore, numerous hydrazone compounds with antituberculosis activity have been reported (Camus et al., 2002; P. Kumar et al., 2010; Pavan et al.,

2010; Sriram et al., 2005; Sriram et al., 2010). Some hydrazone compounds reported to have antitubercular activity are shown in Table 4.

Table 4. *Selected hydrazone compounds with antitubercular properties.*

Structure	Referance
	(Camus et al., 2002)
	(Sriram et al., 2010)
	(Pavan et al., 2010)
	(Sriram et al., 2005)
	(P. Kumar et al., 2010)

Structure–activity studies have shown that electron-withdrawing substituents on the aromatic ring generally enhance antitubercular activity, and that electron-withdrawing halogen groups are more effective in increasing this activity compared with electron-withdrawing nitro groups (Kumar et al., 2008). Moreover, these studies highlight the important role of nitrogen-containing heterocyclic moieties in further improving this activity (Özkay et al., 2010).

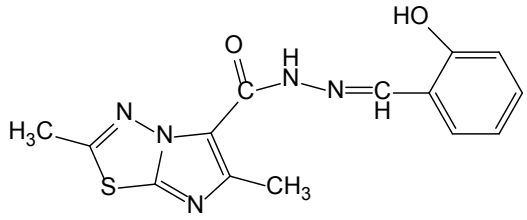
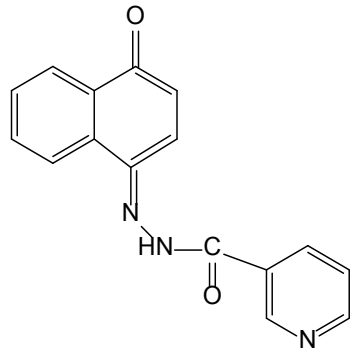
3.5. ANTICANCER ACTIVITY

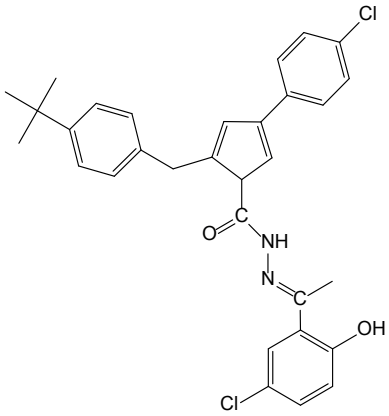
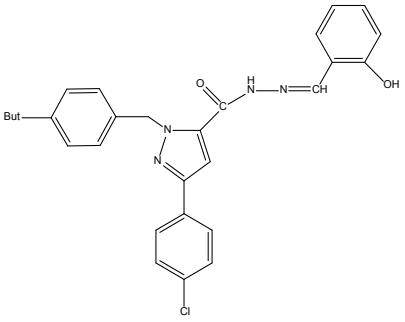
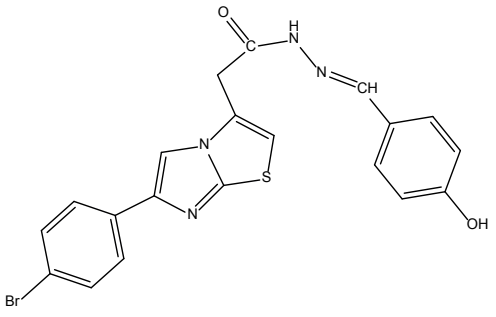
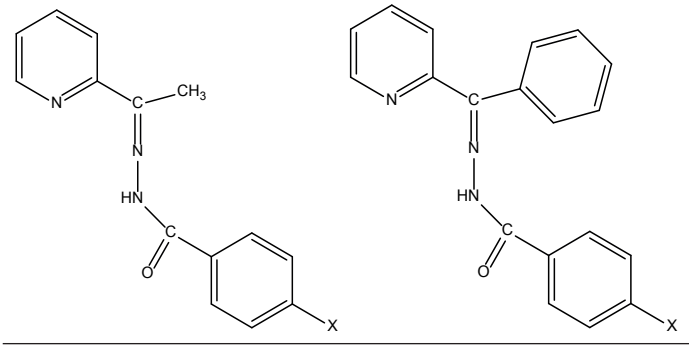
The World Health Organization defines cancer as the formation of abnormal cells that proliferate rapidly beyond normal tissue boundaries, invade adjacent structures, and metastasize to distant organs. Hydrazone compounds have emerged as noteworthy targets in antitumor drug research due to their demonstrated efficacy against various tumor cell lines.

The anticancer activity of numerous synthesized hydrazone compounds has been investigated. Research has shown that hydrazones exhibit anticancer activity against various cancer types, including breast cancer (Dandawate et al., 2012; Öztürk et al., 2025), lung cancer (Xia et al., 2008; Zheng et al., 2009), and ovarian cancer (Terzioglu & Gürsoy, 2003). Additionally, thiazole-based hydrazides have been reported to exhibit anticancer activity against prostate cancer, while hydrazones derived from acetylpyridine and benzoylpyridine have been found to act as antitumor agents against brain tumors (Despaigne et al., 2012; Gürsoy & Güzeldemirci, 2007).

Examples of hydrazone compounds reported in the literature to possess anticancer activity are provided below (Table 5).

Table 5. *Selected hydrazone compounds with anticancer properties.*

Structure	Referance
	(Terzioglu & Gürsoy, 2003)
	(Dandawate et al., 2012)

	(Zheng et al., 2009)
	(Xia et al., 2008)
	(Gürsoy & Güzeldemirci, 2007)
	(Despaigne et al., 2012)

In structure-activity studies, electron-withdrawing groups in the meta position of the phenyl ring near the hydrazone have been reported to have a positive effect on anticancer activity (Aboelmagd et al., 2019; Jęśkowiak et al., 2019). The presence of heterocyclic moieties in hydrazone compounds has been shown to enhance anticancer activity (Tadić et al., 2021).

4. CONCLUSION

The fact that hydrazone derivatives constitute an important class in drug active substance design has prompted researchers to modulate the electronic and structural properties of these compounds by introducing various substituents and to synthesize new hydrazone-based molecules. The biological activity of hydrazones stems from their ability to react with nucleophiles such as thiol and amino groups and to form strong hydrogen bonds with target biomolecules (Zhang et al., 2012). Many of the antimicrobial effects are thought to stem from the highly lipophilic properties of hydrazone compounds, which allow them to more easily penetrate microbial membranes (Malhotra et al., 2012). Structure activity results indicate that structural changes involving electron-donating or electron-withdrawing groups in hydrazone compounds have a decisive effect on their biological activities (Koopaei et al., 2022; Korcz et al., 2018).

In summary, the biological effects of hydrazones and their related structure-activity relationships highlight the importance of these compounds as versatile therapeutic candidates. Ongoing research in this field contributes to a better understanding of these relationships and is increasingly expanding the applications of hydrazones in pharmaceutical and medicinal chemistry.

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Bayrak, H., Demirbas, A., Demirbas, N., & Karaoglu, S. A. (2009). Synthesis of some new 1, 2, 4-triazoles starting from isonicotinic acid hydrazide and evaluation of their antimicrobial activities. *European journal of medicinal chemistry*, *44*(11), 4362–4366.

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Chapter 5

USING ESSENTIAL OILS AS SUSTAINABLE FOOD PRESERVATIVES: THEIR CHEMICAL STRUCTURE AND SAFETY CONSIDERATIONS

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1. INTRODUCTION

Consumers are choosing more additive-free and natural goods these days since they are more conscious of their diet and health. Investigating natural alternatives to chemical additives is therefore essential. These substitutes have the potential to revolutionize the food sector. The use of essential oils (EOs) as a natural alternative has grown in popularity in recent years. These extremely volatile, aromatic, and lipophilic compounds are referred to as secondary metabolites of plants and offer defense against attacks by herbivores and microbes (El Omari et al., 2024). The biological features of EOs are often determined by their principal constituents (Aanniz et al., 2025; El Omari et al., 2023; Elhrech, Aguerd, El Omari, et al., 2025; Paventi et al., 2020). Strong antibacterial and antifungal activity has been observed by a number of EOs and EOCs, including cinnamaldehyde, thymol, carvacrol, and eucalyptol against a range of microorganisms, especially foodborne bacteria and fungi like, *Penicillium spp*., *Shigella spp*., *Salmonella spp*., *Campylobacter jejuni*, *Aspergillus flavus*, *Listeria monocytogenes,* and other species that are important in food decomposition (Barbieri et al., 2022; Goli et al., 2024; Kačániová et al., 2023; Touhtouh et al., 2024). Furthermore, the antioxidant qualities of plant EOs and their constituents have been extensively demonstrated in the literature (Konfo et al., 2023). However, according to research conducted by Aanniz et al. (2024) and Ben-Fadhel et al. (2024), the use of encapsulation technology to protect bioactive EOCs from external factors using a variety of techniques, such as gelled emulsion, nanoemulsion, and nanoliposomes, demonstrated a great potential to blend the strong aroma of the EO while maintaining biological functions and to strengthen its resistance to outside stresses in the food matrix for a longer period of storage (Anvar et al., 2023; Bilen et al., 2024; Emadzadeh et al., 2021). Few research have looked at the potential toxicological profile of EOs, despite the fact that many have looked at their use as food preservatives. This is because each EO's chemical makeup varies greatly and is heavily influenced by phenological fluctuations, extraction techniques, plant positioning and part usage make it challenging to identify any EO's unique toxicological profile.

This study provides a comprehensive analysis of EOs and its main components as food industry preservation. It examine the effectiveness of their antioxidant, antifungal, and antibacterial qualities in their natural and encapsulated types, in addition to the current status of studies on their chemical compositions. In contrast to previous research, this study highlights the crucial interactions that can greatly impact the preservation effects of EOCs with dietary ingredients as lipids, proteins, and carbohydrates. The review also addresses important needs for commercial application by combining data on toxicological safety and consumer sensory appeal. This paper provides a thorough and updated perspective on the prospects and practical challenges related to EO-based food preservation by looking at these interrelated issues.

2. THE CHEMISTRY OF ESSENTIAL OILS THAT ARE MOSTLY UTILIZED IN THE FOOD SECTOR

Plants create as secondary metabolism products, EOs are intricate blends of low molecular weight substances. According to their biosynthetic pathways, these volatile compounds can be divided into three groups: (i) the terpenoid pathway produces terpenes, terpenoids, and their oxygenated derivatives; (ii) the shikimate system produces aromatic compounds and phenylpropanoids; and (iii) the fatty acid pathway produces esters and aliphatic chemicals. Using a variety of extraction methods, such as the use of steam distillation, hydrodistillation (HDE), microwave-based extraction, free of solvent microwave extraction (SME), and two- step ohmic-assisted hydrodistillation, essential oils could be acquired with varying yields from various parts, such as seeds, stems, leaves, and flowers (Aanniz et al., 2025; El Omari et al., 2024). The Terpenes and the terpenoids, including erpinen-4-ol (20.23%), sabinene (20.18%), and 1,8-cineole (16.69%), along with camphor (45.01%) and (16.29%) of the Moroccan *A. odorata* Subsp. Pectinata and *S. officinalis*, as well, are the primary components of A. speciosa EO (Assaggaf et al., 2022; Benali et al., 2020).

Furthermore, chemicals originating from the shikimate pathway predominated in numerous EOs. In particular, carvacrol was present in the EOs of *O. Onites, O. vulgare*, and *O. minutiflorum* from Turkiye (67.86%, 52.01%, and 81.35%) (Tekin et al., 2025). Different extraction techniques on the same plant material can result in notable differences in the amounts of key EOCs, according to Narayanankutty et al. (2021) and his team. According to the same study, β-myrcene was the main EOC extracted from Indian *C. amada* rhizomes by microwave-assisted extraction, ultrasound-assisted extraction, steam distillation, and HDE at 43.20%, 37.40%, 30.80%, and 25.50%, respectively. Furthermore, because it alters the disappearance or appearance of specific chemicals, the extraction technique variation has an impact on the EO composition both numerically and subjectively. Notably, monoterpenes are known to undergo chemical modifications as a result of steam distillation (Tahir Saleh et al., 2023).

The chemical makeup of the EO can also be significantly influenced by the location of the plant. For instance, α-terpinene (20.4%) and γ-terpinene (17.4%) made up the majority of the essential oil (EO) isolated from Brazilian *M. alternifolia* leaves (J. C. da Silva et al., 2025). In contrast, α-pinene accounted for 21.64 percent of the EO isolated from Indian *M. alternifolia* (Sevik et al., 2021). Another element affecting the chemical composition is the plant organ employed in the extraction of EO (X. Liu et al., 2023). Being aware that different plant sections, such as seeds, stems, leaves, flowers,

bark, or roots, manufacture and store EOs. Each component frequently has discrete secretory glandules, which result in different compositions of secondary metabolism (Butnariu, 2021). Furthermore, every geographic area has distinct soil and climate features, such as differences in pH, temperature, humidity, light exposure, altitude, and nutrient availability.

As a result, plants belonging to the same species that grow in different places may have distinct environmental adaptations. The plant's metabolic pathways may be impacted by these adaptations and environmental stressors, leading to differences in the composition of metabolism in secondary, such as EOs (Asres et al., 2024; X. Liu et al., 2023; Tahir Saleh et al., 2023). Temperature, for example, has a major impact on the release of terpenes, such as isoprene and monoterpenes, from fragrant plants. Because high temperatures increase the activity of the enzymes that produce volatile organic compounds, the emission of EOs is typically more noticeable in warm weather (Aćimović, 2025). Regarding the different extraction method used, have shown while HDE can partially degrade thermolabile components, steam distillation may result in the hydrolysis of certain compounds (Gumustepe et al., 2023; Tahir Saleh et al., 2023)

Furthermore, a wider variety of EOCs, including some non-volatile compounds that would not present in steam-distilled EOs, are captured by solvent extraction. On the other hand, because of its lower working temperatures and special solvent characteristics, the supercritical CO_2 extraction maintains a composition that is comparable to the plant's natural profile (Hegazy et al., 2025). The concentration and composition of EOs can be affected by additional factors, such as the time of harvest and the stage of plant growth. For example, the optimal time to harvest is when the calyces are just beginning to form at the tips of the stems, and *M. piperita* EO reaches its maximum EO content right before flowering (Łyczko et al., 2020).

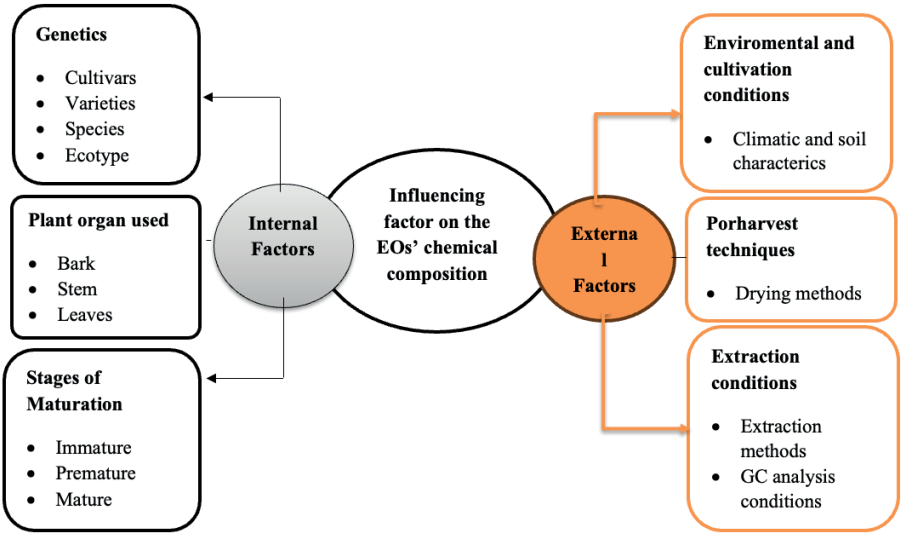

Figure 1. *Factors influencing EOs' chemical makeup, both quantitatively and qualitatively.*

3. EOS' ANTIOXIDANT POTENTIAL AND MECHANISMS

Lipids, proteins, vitamins, and pigments are all harmed by oxidative processes, a chemical kind of food deterioration (Bensid et al., 2022). Reactive oxygen and nitrogen species (RONS), a group of highly energetic free radicals and non-radical molecules, are responsible for this oxidation (Elhrech et al., 2024). Nitric oxide (NO), nitrite (NO_2), alkoxyl radicals (RO), peroxynitrite (ONOO), hydroperoxyl radicals (HO_2), peroxyl radicals (ROO), and hydroxyl radicals (OH) are the most frequently detected RONS in food matrices (Parcheta et al., 2021). Food undergoes harmful physicochemical changes as a result of oxidation, which reduces food shelf life. These changes cause the food product's nutritional value and organoleptic qualities to deteriorate, making it unfit for human consumption or in violation of legal requirements.

The application antioxidants various is essential to mitigate, avert, or potentially remedy damage associated with oxidation by either inhibiting the formation of free radicals or curtailing their spread (Goyal et al., 2025). It can be performed by direct application or integration with packaging processes, especially in the food industry (Basavegowda & Baek, 2021; Parveen et al., 2025). Among these anti-free radicals, synthetic antioxidants commonly added to food include butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), and tert-butylhydroquinone (TBHQ), as well as tocopherols and plant-based phenolic compounds such as flavonoids, phenolic acids, and diterpenoids. But according to recent studies, synthetic chemicals might be harmful to people's health (Hoang & Park, 2024). Because of growing concerns

about the long-term health risks of synthetic antioxidants, researchers and businesses are focusing on natural antioxidants, such as substances derived from plants including tocopherols, essential oils, and polyphenols, which are widely recognized for their antioxidant qualities (Ciobanu et al., 2024; Parveen et al., 2025).

The antioxidant qualities of plant EOs and their constituents have been extensively demonstrated in the literature. Studies on the potential of several EOs used in food as antioxidants, examined using diverse techniques, are compiled in Table 4. Several molecular processes underlie the EOCs' antioxidant action. By giving hydrogen atoms to lipid peroxyl radicals (ROO), phenols like thymol and eugenol function as radical scavengers, stabilizing the radicals and stopping the lipid peroxidation chain process. By preventing the spread of radicals or producing new antioxidant molecules, additional EOCs like terpenes aid in this defense (de Sousa et al., 2023).

4. THE FOOD INDUSTRY'S USE OF EOS' ENCAPSULATION STRATEGY

Even though EOs and related constituents have a range of biological qualities, like antibacterial, antioxidant, and antifungal capabilities, they are nevertheless used as stabilizers for food (Benali et al., 2025; Konfo et al., 2023). Because of their unstable and delicate physicochemical characteristics, EOs' use in vivo is frequently restricted. These include strong flavor, low water solubility, photothermal sensitivity, and notably high volatility (Fakhariha et al., 2025). In order to preserve and improve their effectiveness in the food systems, numerous delivery techniques have been created over the last ten years (Y. Zhang et al., 2025). One of the best delivery techniques is encapsulation technology. It works by encasing EOCs (also called the core material) in biocompatible carriers (also called wall material).

This procedure improves EOs' dispersion in food, increases their long-term stability, and allows for targeted controlled release without materially altering the meal's organoleptic qualities (Aanniz et al., 2024; Reis et al., 2022). The efficiency of the encapsulation technique is greatly influenced by the included agent, the exterior wall material, the preparing process, and the technological goal of the application (Ben-Fadhel et al., 2024). As a result, selecting the right encapsulation techniques minimizes any adverse effects while increasing efficacy. In the food business, for example, nanoencapsulation methods—specifically, nanoemulsions, nanoliposomes, and polymer-based nanocarriers—are becoming more well-known. By shielding EOCs from environmental elements including heat, light, and oxygen, these techniques successfully increase their stability, dispersibility, and controlled release (Aanniz et al., 2024; Maurya et al., 2024). Additionally, lecithin, cyclodextrin,

gelatin, chitosan, starch, and alginates are examples of wall materials used in delivery systems that have demonstrated efficacy in boosting efficiency of encapsulating and maintaining biochemistry (Ben-Fadhel et al., 2024).

Still, based on emulsions methods—such as spray-drying and freeze-drying of nanoemulsions— are the most extensively used to convert encapsulated EO into a stable powder, frequently for food applications (Banožić et al., 2025; Maurya et al., 2024). Furthermore, membrane emulsification is increasingly acknowledged as a viable option due to its capacity to accurately control droplet size and distribution and its potential to function as a single-step encapsulation solution (Reis et al., 2022). The extensive application of these encapsulation methods in numerous actual food systems attests to their effectiveness (Biswas et al., 2022).

Numerous studies have demonstrated that the bioactivity, sensory perception, and physicochemical stability acceptability of essential oils and related constituents in various food compositions are enhanced by nanoemulsions, nanoliposomes, and biopolymer-based carriers. By maintaining food's nutritional, physicochemical, and microbiological stability, these technologies assist prolong its shelf life (Roselló et al., 2024).

5. EOS' INTERACTION WITH FOOD INGREDIENTS

The type and qualities of the nutrition, that are dependent on inherent elements such water activity, salt, redox potential, pH levels, nutritional content, and other used components, impact the choice of food preservative (Cox et al., 2021). When employing EOs or their bioactive components as a conservative agent, these requirements are crucial. According to Gómez-Llorente et al. (2024), the kind and concentration of food molecules determine the antimicrobial action vanillin once administered in a liquid food matrix. Vanillin's antibacterial activity is hampered by proteins, lipids, and carbohydrates, but enhanced by organic acids and alcohols. When proteins are present, EOs' antibacterial efficacy is changed. This is because proteins can attach to the phenolic chemicals in the EOs, preventing the hydroxyl groups antibacterial properties (Ju et al., 2022). Lipids prevent microbes from coming into contact with the functional groups of the EO by forming a protective layer surrounding the bacterial membrane (Babic et al., 2021). Additionally, different carbohydrates affect the EOCs in different ways (Maurya et al., 2021).

On the other hand, organic acids, such as citric acid, can permeate and change the permeability of bacterial membranes, intensifying the bactericidal impact. Additionally, alcohols preserve or enhance antibacterial action (Gómez-Llorente et al., 2025). The pH values of the food matrix determine how effective EOs are against microorganisms. This is because EOs become

more hydrophobic at low pH, which facilitates their breakdown in the phospholipid membrane of the target bacterium (Nourbakhsh et al., 2022). Furthermore, when lipids are present such as protein and sunflower oil such as Serum albumin from cows, the antibacterial action of thymol and carvacrol whenever used a preservative for food to stop E. coli from growing was either fully and partially halted (Gómez-Llorente et al., 2025).

Staphylococcal inhibitors action of Vanillin and cinnamonaldehyde in milk are predominantly regulated by the proteins and lipids included in milk (Hou et al., 2022). Therefore, to attain the same antibacterial activity in food as in vitro investigations, greater quantities of the bioactive components are required. This also explains why low-fat milk exhibits a stronger bactericidal impact from cinnamonaldehyde than high in fat dairy (Babic et al., 2021). Because lipophilic EO's nature makes it easy for it to become stuck during the lipid phase, which makes challenging for the essential oils get to target bacterium in the medium based on water (Hou et al., 2022; Y. Liu et al., 2021).

The microbiological effectiveness of EOs is not directly impacted by water activity (aw). However, merely lowering the aw in food systems can greatly reduce the proliferation of germs. The interaction of EOs with food may impair their ability to preserve food and extend its shelf life.constituents, notably for organoleptic perception (Ellouze et al., 2024). As a result, excessive EO concentrations may cause unfavorable alterations in flavor and scent, which may have a detrimental impact on customer approval (Angane et al., 2023).

6. EOS' POSSIBLE TOXICITY TO CONSUMERS' SAFETY

The safety of EOs is not always assured by their "natural" origin. Based on a single-dose oral toxicity assessment in mice, the median lethal dose (LD_{50}) of *B. cinerea* essential oil (EO)—defined as the amount required to induce 50% mortality—was estimated at 507.5 mg/kg body weight. This toxicity may largely be attributable to the considerable proportion of *β-thujone* (46.80%) present in the EO, given that the LD_{50} of *β-thujone* has previously been reported as 442 mg/kg b.w. (Ben Moussa et al., 2025). Findings suggest which EO's toxicity and chemical makeup are related. Furthermore, a recent Phase I clinical research shown that healthy people tolerated daily 1-2 mg/kg of carvacrol for a thirty-day period (Ghorani et al., 2021). These results, however, are at odds with evidence of the genotoxic and cytotoxic effect of carvacrol greater dosages. Notably, human blood cells have shown cytotoxicity at dosages higher than 0.15 mg/mL (Konig et al., 2024). Additionally, carvacrol injection at concentrations less than 0.00015 mg/mL may cause endocrine abnormalities, which could be harmful to the development of the embryo (X. Zhang et al., 2021). Because larger quantities

can produce oxidative stress, genotoxicity, and cytotoxicity, even when low amounts may be harmless, these discrepancies emphasize the significance of dosage before administration.

Another investigation reported that the acute oral toxicity of free *C. pulegiodorus* essential oil (EO) in mice exhibited an LD_{50} of 460.42 mg/kg body weight (Monteiro dos Santos et al., 2024). Furthermore, even at sublethal doses (50 and 250 mg/kg), the EO induced notable changes in biochemical and hematological profiles, as well as alterations in liver and kidney tissues, while producing no evidence of genotoxicity. Similarly, another species of the same plant material has been investigated by Oliveira et al. (2024). However, when given to mice at a single dose of 2000 mg/kg, it did not result in any harmful effects or damage to DNA. Another study found that the cytotoxicity of EOs from *C. limon*, *E. globulus*, and *R. officinalis* reduced measured cell viability, and the mean half-maximal inhibitory concentration (IC_{50}) ranged from 0.08 to 0.17 per cent. With an IC50 of 0.08 ± 0.06%, *R. officinalis* EO has the most hazardous potential. Additionally, every EO that was evaluated had a high risk for irritating mucosal membranes at 0.5% (Lanzerstorfer et al., 2021). *T. algeriensis* essential oil is harmless to use in the pharmaceutical industry, since oral assessment at an acceptable dosage of 2000 mg/kg body weight of free *T. algeriensis* might exhibit clear toxic effects that go away after 4 hours and don't harm the kidney or liver tissues in any way. These results validate the use of encapsulating for a safe and efficient package method that increases the durability and biological activity of EOs in a variety of sectors.

7. EOS USE IN THE FOOD SECTOR

Foods are subjected a variety of degradation causes during storage, such as microbial activity, ambient conditions, and chemical reactions. Food preservatives therefore serve to keep from spoiling and maintain its nutritious value for a longer shelf life. Consumers today choose more healthy foods options, like minimally processed and unprocessed meals and foods free of chemical additives. Because EOs have potent antibacterial and antioxidant qualities, a number of studies have examined the idea of replacing chemical preservatives with natural ones (Brandt et al., 2023; Goli et al., 2024; Sindhu et al., 2023). EOs can prolong the food's stability period and efficiently maintain its nutritional, physicochemical, and microbiological stability (Benali et al., 2020; Kačániová et al., 2025)

7.1. Baked Products

EOs have studied agents of conservatism. In fact, bread's shelf life has been successfully extended to 90 days by applying *T. vulgaris* EO encapsulated in Zein nanocapsules (Gonçalves da Rosa et al., 2020). This effect likely results from a combination of the bioactive properties of *T. vulgaris* essential

oils—particularly their antioxidant and antimicrobial capacities—and the barrier function of the encapsulating microparticles, which confer enhanced environmental stability and enable controlled release over the storage period.

7.2. Beverage and Fruit Juices

Applying *M. officinalis* (42.7% geranial and 28.4% neral) to fresh watermelon juice effectively preserves its microbiological stability for seven days at 4 °C, demonstrating strong antimicrobial efficacy against strains of *L. monocytogenes* and preventing virulence-related characteristics like biofilm formation and quorum sensing (Carvalho et al., 2023). Furthermore, applying *C. sinensis* EO (95.1% limonene) free or encapsulated in chitosan nanoemulsion at a concentration of 0.2 µL/mL in combination with mild heat (52 °C) to fresh orange and apple juices has demonstrated more beneficial antibacterial effects against *E. coli* O157:H7 Sakai than using EO treatment alone (Bento et al., 2020).

7.3. Dairy Goods

Effective antioxidant and antibacterial properties have been demonstrated by *M. communis* EO in lactic butter conservation (0.02% direct application), heat treatment (70 and 80 °C for 15 s), and light-shielded storage (4 °C for 50 days). According to Keceli and Mertoglu (2024), *M. communis* EO can therefore serve as a stabilizer to prolong the lactic butter's expiration period. In the yogurt product, Abed et al. (2022) revealed an antifungal activity of *C. citratus* (DC.) EO when directly administered against the mold and yeast strains responsible for yogurt deterioration, attaining 80-100 % inhibition at 5 °C for up to 90 days of conservation.

Compared to dietary products, EOs have a stronger antibacterial action in vitro (Boukhatem et al., 2020). The availability of more nutrients in food matrices than in laboratory culture medium could be the cause of this phenomena. This promotes cellular component turnover and aids in bacterial repair, which may boost bacterial resistance to a variety of stressors (Abebe, 2020).

7.4. Vegetables and Fruits

A therapy containing encapsulated *P. cablin* (Blanco) Benth. EO in chitosan nanoemulsion was used to prevent potato sprouting during storage. Das and Chaudhari (2025) found a 100% anti-potato sprouting activity at 25 ± 2 °C for up to 60 days. The coated potato tubers start to germinate at day 70, and by day 90, 23.68% of them have sprouted. Therefore, the prolonged *P. cablin* EO supply in the aliment over 70 days of storage is made possible by nanoemulsion coating, thereby preserving potato storage quality. Z. Wang

et al. (2025) have successfully increased the shelf life of cherry tomatoes and maintained their quality. With a half-maximal effective dose of 0.18 mg/mL, adding *O. vulgare* EO to gelatin/carrageenan has shown exceptional conservation ability against *B. cinerea* for six days. Furthermore, after seven days, complete antifungal protection against *A. alternata*, *B. spicifera*, *B. fuckeliana*, *C. hawaiiensis*, and *P. italicum* was demonstrated with 100% healthier fruits when *Thymus serpyllum* L. EO (at 300 µg/mL) was added to water/Tween 20/agar (Roselló et al., 2024).

7.5. Meat

Nowadays, a key strategy for guaranteeing beef imports and exports is long-term frozen storage. However, compared to fresh meat, thawed meat has a far lower shelf life. Alginate-based edible coatings with 0.05% *T. vulgaris* EO have demonstrated an excellent, preserved coloring during meat exposure and significantly decreased lipid oxidation (Guerrero et al., 2020). Coating materials fused with EO can be applied in conjunction with other conservation procedures. Chen et al. (2021) successfully extended the stability period of roast duck meat when stored at 2 ± 2 °C for more than 21 days by using *O. vulgare* EO (0.15%) or *C. zeylanicum* EO (0.60%) in a chitosan edible coating combined with modified atmosphere packaging (30% CO_2 and 70% N_2). This is because EOs have a bactericidal effect on spoilage microorganisms, and modified environment packaging has the ability to both prevent lipid oxidation and preserve the desired vivid beef color (Kandeepan & Tahseen, 2022).

7.6. Sea Food

Shi et al. (2025) showed that *O. basilicum* EO microemulsions at 0.8% greatly improved the cooking quality, flavor, and general acceptance of snakehead fillets in addition to their resistance to microbial contamination. *S. putrefaciens*, *A. hydrophila*, and *Pseudomonas spp*. were among the foodborne bacteria that showed exceptional microbial activity when *Litsea cubeba* EO and *O. vulgare* EO were combined at a 6:4 ratio. Additionally, the nanoemulsion coating method greatly increases the shelf life of the grass carp fillets by preventing fat oxidation, preserving lower levels of thiobarbituric acid (TBA) and total volatile basic nitrogen (TVB-N), improving physical texture, encouraging a strong muscle structure, and producing a acceptable odor (M. Yang et al., 2024).

8. CONCLUSION

Nowadays, people are choosing more natural and additive-free products since they are more conscious of their eating habits and health. Due to their strong biological properties, especially their antibacterial, antifungal, and antioxidant effects, which allow for the efficient control of food spoilage

and prolong the food's shelf life, essential oils (EOs) have become more and more popular in recent years as a natural substitute for chemical preservatives in the food industry. The current understanding of the use of EOs in the food business is compiled in this review. It assesses the chemical makeup, antioxidant, antibacterial, and antifungal properties of EOs in both free and encapsulated forms, as well as the interactions between EOCs and the food matrix—a topic that has not received enough attention in earlier reviews—and how these interactions affect the biological efficacy of these constituents. Furthermore, the examination of consumer acceptance and safety offers a thorough and current viewpoint on the useful application of EOs to enhance food stability. The physicochemical weaknesses of EOs in food applications have been addressed by encapsulating technology, however there are still issues with customer acceptability, regulations, and the economy. In order to translate laboratory results into commercially viable products, future research should concentrate on elucidating the molecular mechanisms of interactions between EOs and food components in their free and encapsulated forms as well as performing more thorough safety and sensory assessments in actual food matrices using multidisciplinary techniques.

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Chapter 6

SCHIFF BASES IN MODERN TECHNOLOGY: APPLICATIONS AND DEVELOPMENTS

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1. INTRODUCTION

German-born scientist Hugo Schiff created a novel class of organic molecules in the nineteenth century, later termed Schiff bases, which were crucial to the advancement of coordination chemistry (Abo Dena, 2014). Schiff bases are a type of chemical compounds characterized by the presence of an azomethine (-N=CH-) or imine linkage. Schiff bases are often synthesized by a condensation process between primary amines and aldehyde or ketone carbonyl derivatives (Dalia et al., 2018; Yernale et al., 2014). Schiff bases have the potential to act as versatile ligands that can coordinate with metal ions and form stable complexes (Kostova & Saso, 2013). In recent years, coordination chemistry has received huge in terest owing to its link with the production of more effective, less dangerous, and tailored metal-based drugs related to nutrition and the study of metabolism (Fricker, 2007). The most intriguing area of bioinorganic chemistry is the study of Schiff bases formed from a primary amine and a carbonyl compound through dehydration to produce an imine compound (Anacona et al., 2016). Schiff bases have been extensively researched for their diverse applications, particularly as corrosion inhibitors, catalytic supports, thermostable materials, metal ion complexing agents, and in biological systems. Moreover, their liquid crystal and intriguing optical, optoelectronic, and electrical capabilities are extensively studied. Additionally, Schiff bases demonstrate efficiency in both photoluminescence and electroluminescence, while the polymeric variant of this material group reveals notable nonlinear optical characteristics (Trivedi et al., 2002).

1.1. MODERN APPLICATIONS

1.1.1. GREEN CHEMISTRY

Green chemistry is a branch of chemistry that uses tools, methods, and technologies. It helps scientists and chemical engineers to produce more efficient and environmentally friendly products in research, development, and production (Ahluwalia & Kidwai, 2004).

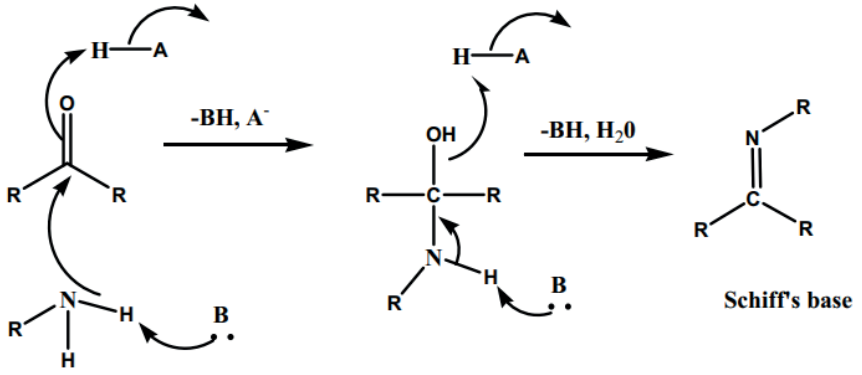

Figure 1. *Mechanistic method illustrating the synthesis of Schiff base*

Green chemistry is widely accepted as a significant methodology in synthetic chemistry, offering a revolutionary perspective on organic synthesis and drug design. It provides significant ecological and financial benefits compared to traditional synthetic processes. It enhances selectivity via Schiff bases (Figure 1), reduces reaction times, and increases the efficiency of conventional methods by streamlining separation and purification processes (Ahluwalia & Kidwai, 2012). A study by Mahmood (Mahmood, 2021) identified numerous environmentally friendly synthetic approaches for the synthesis of Schiff bases, enabling better results in a shorter time. Therefore, the technologies used include microwave irradiation, natural acid catalysis, ultrasonic processing, milling, and water as a green solvent. Microwave irradiation has been considered the most effective method, followed by ultrasonic, naturally acid-catalyzed, and grinding techniques, respectively. Conventional methods frequently include toxic solvents and chemicals, jeopardizing human health and the environment (Mir & Banik, 2025). The advent of more eco-friendly alternatives, including solvent-free reactions, microwave-assisted synthesis, and renewable starting materials, presents intriguing methods to mitigate environmental effects. Figure 2 provides an overview of the researcher's significant advancements in the microwave-assisted synthesis of Schiff base compounds over the last 20 years (Jain & De, 2022). The synthesis of Schiff-based ligands in environmentally sustainable settings is an emerging area of research with considerable implications for sustainable chemistry and the development of more eco-friendly chemical processes.

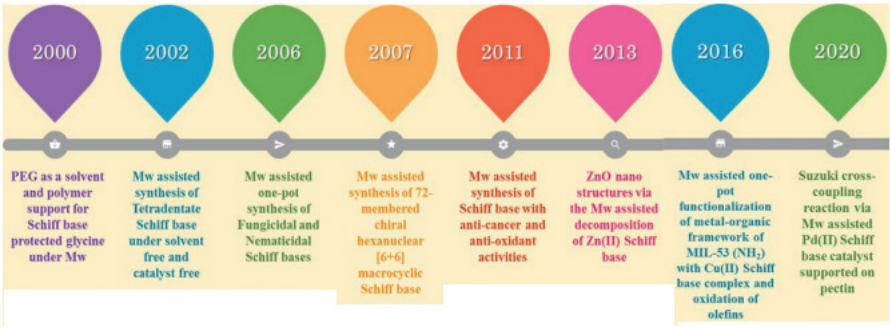

Figure 2. *Advancements in microwave-assisted Schiff base compounds over the past two decades years (Jain & De, 2022).*

1.1.2. MATERIALS SCIENCE AND NANOTECHNOLOGY

Although Schiff base complexes are well-known for their chemical, biological, and electronic versatility, comprehending their mechanical properties is crucial for enhancing their application in flexible electronics, implantable systems, and intelligent bioelectronic coatings, where durability and biocompatibility are critical (Mousa et al.., 2025). The significance of Schiff-based ligands arises from their capacity to interact with metal ions, creating complex structures that may be meticulously designed without experiencing irreversible changes. In addition to their considerable biological importance, Schiff-based metal complexes are widely utilized as corrosion inhibitors, pigments, electrochemical sensors, intelligent precursors for nanooxide production, and polymer stabilizers (Upendranath et al., 2022).

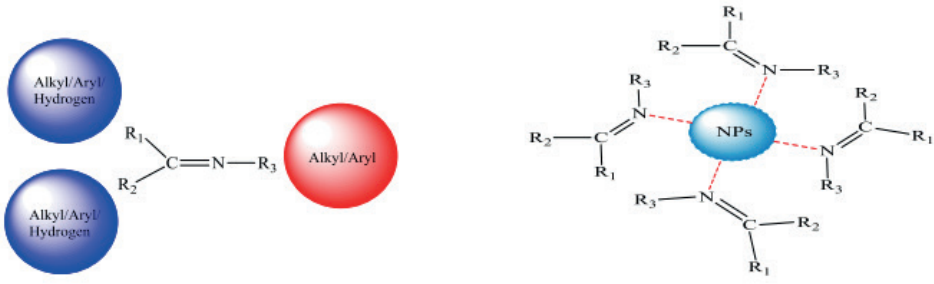

Figure 3. *Basic chemical structure of Schiff bases and functionalized Schiff base nanoparticles (Khan et al.,2023).*

Modern advances research in Nanoscience has focused on enhancing the application of nanoparticles (NPs) by modification or functionalization. As shown in Figure 3, nanoparticles have used organic, inorganic, and metal complexes, as well as Schiff base ligands. Functionalized nanoparticles

have been used as sensors to detect extremely low amounts of heavy metals, herbicides, biomolecules, as well as enzyme inhibitors and potential antioxidants. Schiff base functionalized NPs have recently gained popularity due to their environmental friendliness, huge surface/volume ratios, versatility, and great durability (Hamrahian et al., 2018). These nanoparticles have numerous applications in nanoscience, particularly in the pharmaceutical industry. Schiff base functionalized NPs inhibit microorganisms due to the Schiff base in the nanocomposite and the different functional groups present in the NPs (Elemike et al., 2016), found that the nanomaterial was effective against bacteria that damage macromolecules like DNA, RNA, and proteins . Furthermore, the most distinguishing property of SB functionalized NPs is their use as catalysts in a variety of chemical processes, including oxidation and hydrogenation.

1.1.3. PHARMACEUTICAL TECHNOLOGIES

Schiff bases and their metal complexes have been discovered to possess antibacterial and antifungal properties, with potential applications in cancer prevention and herbicide development (Silva et al., 2011). In a study by Mushtaq et al., as shown in Figure 4, it was discovered that antibacterial drugs derived from Schiff bases showed significant activity against bacteria through structural modifications, while antifungal drugs were primarily effective in treating skin diseases (Mushtaq et al., 2024).

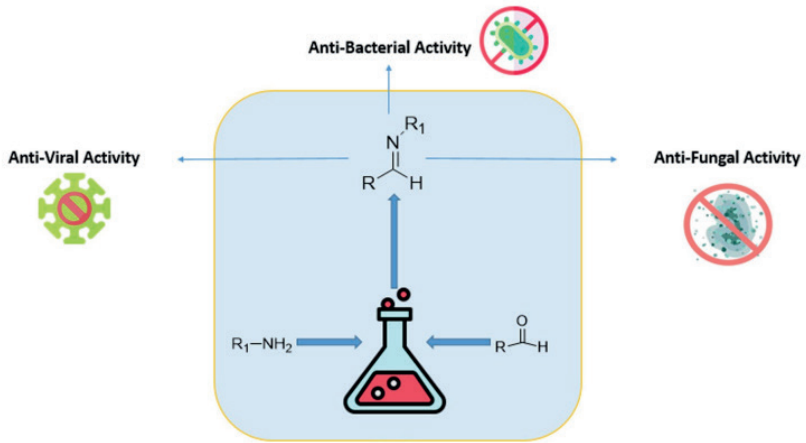

Figure 4. *The significance of Schiff bases within the pharmaceutical framework (Xu et al., 2020).*

Amino acid Schiff bases, generated through the condensation of simple amino acids like isatin with glycine, valine, phenylalanine, cysteine, leucine, and alanine, demonstrate significant antibacterial properties. Additionally, cellulose-derived Schiff bases have shown antibacterial efficacy against

Escherichia coli, Enterococcus faecalis, and Staphylococcus aureus (Xu et al., 2020). For example, as shown in Figure 5, the synthesis and biological activities of numerous compounds featuring two azomethine groups have been reported by medicinal chemists (Gul al., 2024). Schiff bases modified with nitro, halogen, and dimethoxy groups have been found to exhibit significant anticancer activity. These anticancer agents specifically inhibit protein kinases, induce apoptosis, and function as tubulin-targeting and polymerizing agents. Furthermore, Schiff base compounds exhibit antimalarial activity, anti-schistosomal activity, and a strong inhibitory effect against Alzheimer's disease. Researchers want to investigate and identify compounds with improved enzyme inhibitor properties via the synthesis of novel Schiff bases derivatives, perhaps resulting in the development of more effective pharmaceuticals.

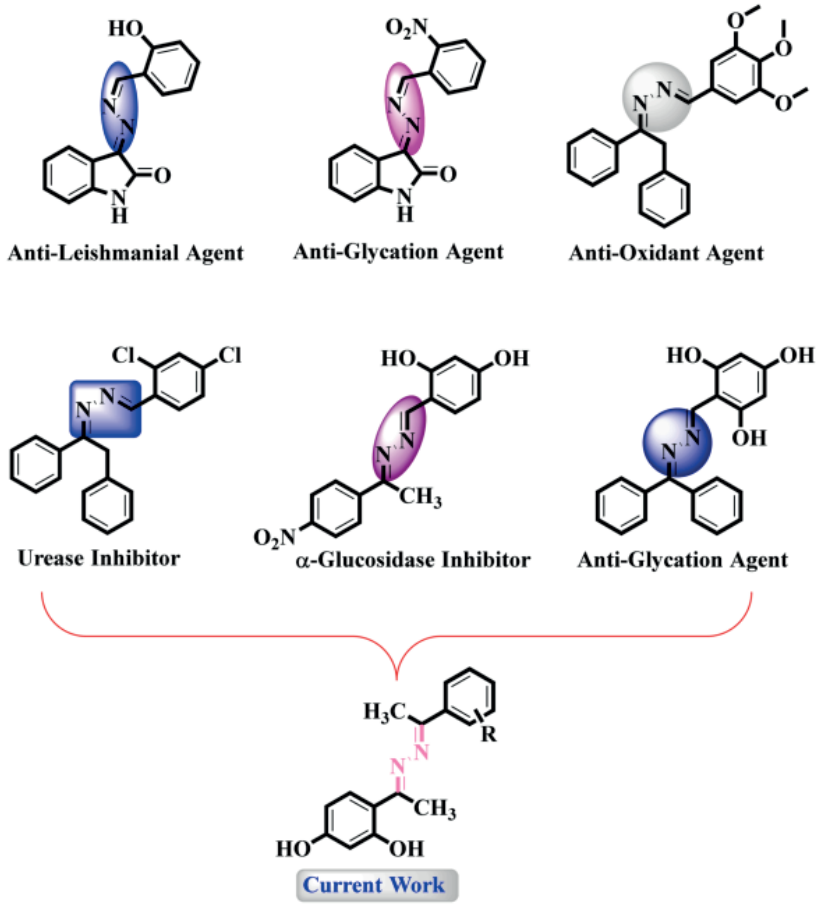

Figure 5. *Various bis-Schiff base derivatives exhibiting diverse biological activity (Gul al., 2024).*

1.1.4. ENERGY AND ELECTRONIC APPLICATIONS

Schiff bases and their complexes with transition metals are significant for their applications in nonlinear optics, molecular and metal ion sensing, dye-sensitized solar cells, molecular magnetism, and photoluminescence (Sek et al., 2013). In particular, it is widely used in the production of OLEDs to change the emission color and improve the efficiency of the device (Kagatikar &Suni, 2021). Similarly, Kagatikar et al. devices producing various colors, including blue, green, red, and white, are fabricated from Schiff bases and their complexes by adjusting the emission wavelength through the incorporation of diverse substituent groups and metal atoms; this renders the devices highly luminescent and thermally stable.

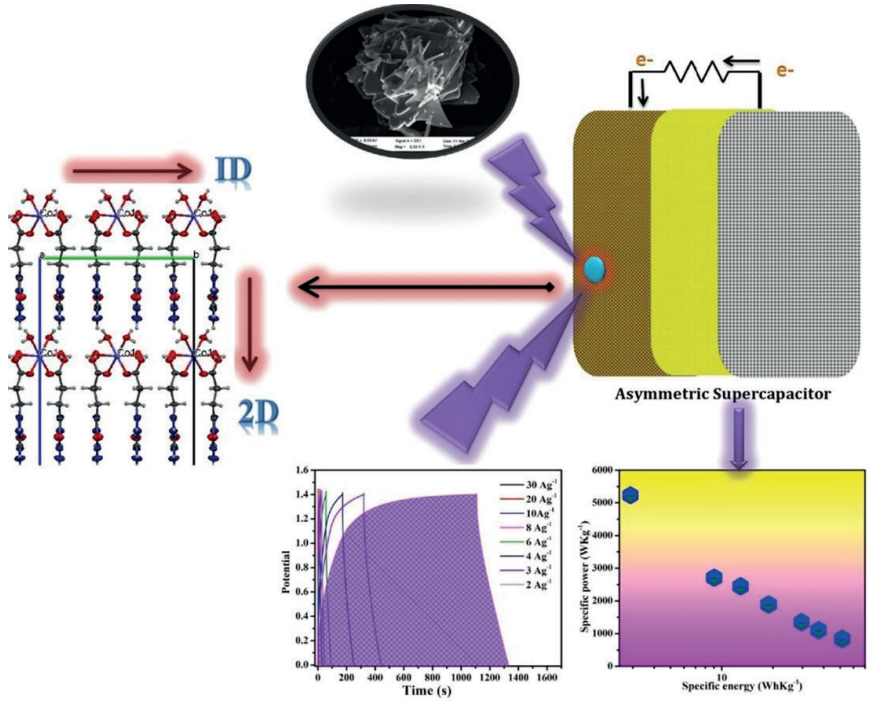

Figure 6. Schiff base complex utilized as a battery-type electrode for supercapacitor applications (Parveen et al.,. 2025)

Composites of Schiff bases and transition metal complexes have played a crucial role in investigating their electrochemical behavior and potential applications in energy storage systems, such as lithium-ion, sodium-ion, and redox flow batteries, as well as supercapacitor electrodes (Fig. 6). Numerous Schiff base composites, including carbon-based materials, COFs, ImCOFs, SNWs, and MCPs, have been employed as energy storage devices (Yadav & Kumar Rao, 2024).

1.2. RECENT DEVELOPMENTS

Recent studies have revealed that flexible organic crystals with Schiff bases—such as rubber organic crystals, plastic organic crystals, and flexible organic crystals combining elasticity and plasticity—are used in versatile applications like optical waveguides, optoelectronic devices, biomimetic soft robots, and organic photonic integrated circuits (Xue et al., 2024). An addıtıonal development, biosilica-reinforced Schiff-base structures, featuring a triazine core and functionalized with GPTMS, have been created for applications requiring excellent thermal stability, flame retardancy, and corrosion resistance (Anusri et al., 2025). This advancement is regarded as a revolutionary notion in heterocyclic core-based benzoxazine chemistry for high-performance corrosion-resistant applications. Taha et al., discovered Schiff base sensors for detecting and identifying poisonous and dangerous ions using basic analytical procedures, highlighting its significance in several industries. Schiff base sensors will be beneficial in biological imaging of different metal ions from diverse cell lines used in medical diagnostics, as well as environmental studies for detecting and mapping toxic metal ions (Taha et al., 2024). Different Schiff bases and their homo- and hetero-binuclear metal complexes exhibit potential bioactive cores and can be utilized in the development of imaging methods for the detection of metal medicines and cisplatin-DNA adducts, cell cycle arrests, DNA repair, and apoptosis (Deepa & Angappan, 2023). Elucidating evoked-state dynamics and photo-induced transformations is crucial in photochemistry and vision research, and basic investigations on model Schiff base systems (such as retinal protonated Schiff base analogs) contribute to this goal. That is the deciding factor in whether or not they live up to their potential as effective therapies for retinal degenerative diseases (Pashandi and Jastrzebska,2025).

CONCLUSION

Through continued research and innovation, comprehensively reveal the role of Schiff bases and metal complexes in coordination chemistry and the synthesis of innovative molecules with remarkable structures and properties. Schiff-based ligands have attracted significant interest due to their versatile coordination characteristics and potential applications in medical, industrial, and biological fields. The pharmacological relevance of Schiff bases has garnered much interest and is anticipated to produce favorable outcomes in this domain in the future. Anticancer multinuclear complexes have emerged as one of the multidisciplinary research areas and have future potential for exploration by the scientific community. Advancing the application of Schiff-based anticancer metal drugs represents significant developments in the design, synthesis, and mechanism studies of anticancer metal drugs. Simultaneously, Schiff-based metal complexes possess the capacity to revolutionize metal-

based medicines and offer remedies for substantial health issues. The utilization of Schiff bases and metal complexes in nonlinear optical devices, catalytic agents, medicinal agents, metal ion detection, metal ion extraction from aqueous solutions, dyes, and industrial applications is significantly important for contemporary and future technologies.

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Chapter 7

CHEMISTRY OF ANTIMICROBIAL PEPTIDES: MOLECULAR INNOVATIONS AND MEDICAL APPLICATIONS

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1. INTRODUCTION

The discovery of penicillin reduced the severity and mortality of infections, and immunosuppressive drugs and surgical interventions improved the safety of other treatments. However, antimicrobial resistance (AMR) has become more common in recent years due to the misuse of antifungals and antibiotics (Friedman et al., 2016). According to the World Health Organization (WHO), antimicrobial resistance (AMR) is a significant global public health threat, potentially causing approximately ten million deaths annually by 2050 (Wozniak, et al., 2023).

The approval of only eight new antibiotics by the US FDA between 2011 and 2016 indicates a stagnation in new antibiotic development (Bohlmann et al., 2018). The fact that AMPs act through a wide variety of mechanisms reduces the risk of resistance and offers opportunities for treatment processes. Combination therapies can be used in conjunction with AMPs and antibiotics; this strategy can prevent the development of resistance, particularly against bacteria such as *E. coli, P. aeruginosa,* and *S. aureus.* (Rodrigues et al., 2022). Peptides offer a broad spectrum of activity against bacteria, fungi, viruses, and parasites, and are noted for their clinical applicability and potential as an alternative to traditional antibiotics. However, their low stability and toxicity to human cells hinder their widespread use (Alzain et al., 2025).

The goal of this review is to shed light on the molecular advancements, chemical characteristics, and modes of activity of peptides that are antimicrobial (AMPs), that have continued to be active over the past few years. This research also aims to discuss the existing and potential medicinal applications of AMPs in order to give a foundation for methods of therapy.

2. CLASSIFICATION OF ANTIMICROBIAL PEPTIDES

Antimicrobial peptides (AMPs) are classified using four criteria: source, activity, structural features, and amino acid-rich species (Figure 1).

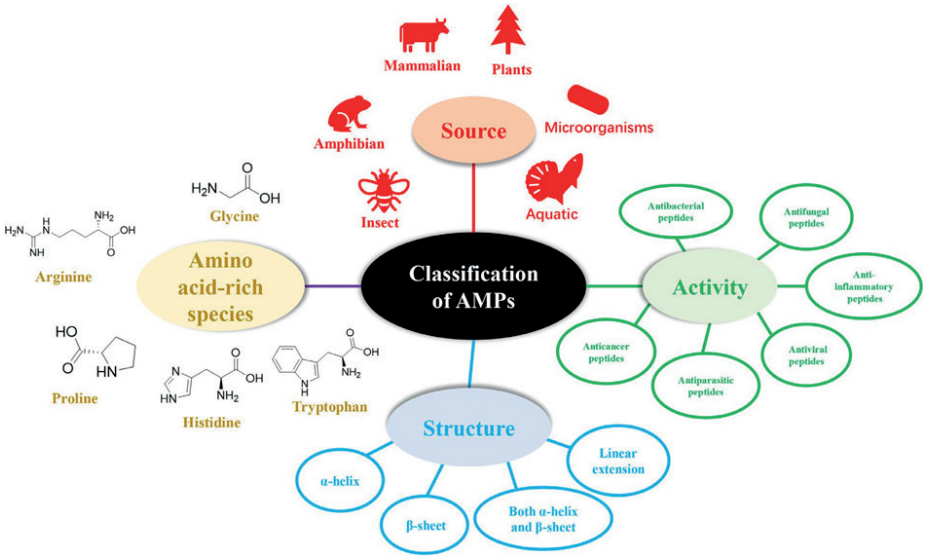

Figure 1. *Classification of antimicrobial peptides (Huan et al., 2020).*

2.1. CLASSIFICATION OF ANTIMICROBIAL PEPTIDES BASED ON SOURCES

AMPs are classified into major classes according to their biological nature, source, and structural. AMPs are characterized structurally as α-helical, β-sheet, extended and loop and can be discovered in humans, animals, insects, microbes, and plants. They are categorized as antiviral, antibacterial, antifungal, antiparasitic, and anticancer peptides (Saeed et al., 2022).

2.1.1. MAMMALIAN ANTIMICROBIAL PEPTIDES

Humans and other vertebrates have mammalian antimicrobial peptides (AMPs), mainly cathelicidins and defensins, among others. Disulfide bond configurations are used to classify defensins into α-, β-, and θ- kinds. Human beta-defensin 2 (hBD-2) is prominent in the elderly, while cathelicidin LL-37 is prevalent in neonates (Gschwandtner et al., 2014). The levels of human host defense peptides (HDPs) varies during time. HDPs are found all over our bodies and play a major role in nursing, especially with casein 201 peptides in colostrum (Zhang et al., 2017). Enzymatic hydrolysis is used for extracting AMPs from milk and milk products, which include peptides like α-lactalbumin and β-lactoglobulin. HDPs are involved in healing wounds, apoptosis, and immunological modulation in addition to their antimicrobial roles (Akalın, 2014).

2.1.2. ANTIMICROBIAL PEPTIDES FROM AMPHIBIANS

The pathogenicity of bacteria is significantly influenced by peptides that are antimicrobial (AMPs) (Huan et al., 2020). Amphibian peptides, such as dermaseptins and magainins, are abundant in frogs (Soltaninejad et al., 2021). Magainins, a 23-amino acid, are naturally antibacterial and prevent both Gram-positive and Gram-negative bacteria from growing (Lin et al., 2022). Antimicrobial peptides (AMPs) are abundant in the skin productions of frogs belonging to the genus Xenopus, Silurana, Hymenochirus, and Pseudhymenochirus (Conlon & Mechkarska, 2014).

2.1.3. INSECT DERIVED ANTIMICROBIAL PEPTIDES

Antimicrobial peptides (AMPs) have a significant impact on bacteria, causing them to mutate and spread (Huan et al., 2020). Defensins, sekropins, and drosomisin are commonly found in AMPs. This product has a variety of antimicrobial ingredients, making it a viable alternative to antibiotics. According to Dutta et al. (2019), cecropin inhibits AMP signaling. In the 1950s, AMPs were introduced, and today, they are widely used. According to Zahedifard et al. (2020), Jellein peptides play a crucial role in the microorganization of the body.

2.1.4. PLANT ANTIMICROBIAL PEPTIDES

Plants exhibit potent antimicrobial properties against pathogenic microorganisms, including anticancer and anti-inflammatory activities, and possess several antimicrobial peptides (AMPs) (Lei et al., 2019). While AMPs derived from plants share similarities with those derived from animals, insects, and microorganisms, common plant AMPs, such as defensins, are notable for their amphipathic nature and rich cysteine content (Wu et al., 2018). However, in the case of hevein-like peptides, some plant-derived AMPs differ from their animal counterparts (Józefiak & Engberg 2017). Currently, although many plant AMPs have been identified, none are approved for clinical use.

2.1.5. MICROORGANISMS-DERIVED ANTIMICROBIIAL PEPTIDES

Antimicrobial peptides (AMPs), which are produced by microorganisms and bacterial cells, have antimicrobial properties. According to Cao et al. (2018), bacteria such as gramicidin are present. Biological expression of AMPs is attracting increasing attention due to high costs; It is produced using systems such as *Pichia pastoris, S.s cerevisiae* and *E. coli* (Parachin et al., 2012). Myticusin-beta and pardaxin are examples of AMPs that can be used as alternative antibacterial and antiviral treatments (Oh et al., 2020).

3. CLASSIFICATION BASED ON ACTIVITY

AMPs are biological molecules found in all organisms, from prokaryotes to humans, that play a role in defense against infections (Hancock, 2000). As bacteria synthesize AMPs to eliminate competitors, these molecules exert both direct antimicrobial effects and can influence host responses. Decreased AMP synthesis leads to diseases such as atopic dermatitis (Hassan et al., 2012). The Antimicrobial Peptide Database (ADP3) categorizes AMP biological activities into: anti-tumor, anti-parasitic, anti-viral, antifungal, antibacterial, and anti-HIV.

3.1. ANTIBACTERIAL PEPTIDES

Antibiotics (AMPs) can inhibit VRE, *A. baumannii,* MRSA, and other clinical pathogens such as *S. aureus, L. monocytogenes, E. coli, Salmonella*, and *V. parahaemolyticus.* This article discusses the negative effects of some bacteria on the body. Defensins, cecropins, and nisin, for example, prevent the development of Gram-positive and Gram-negative bacteria. *Aristicluthys nobilia* interferon-I-based AMPs P5 and P9 suppress MRSA activity (Li et al., 2019). There is no doubt that the stability and antimicrobial peptides are beneficial to medicine.

3.2. ANTIFUNGAL PEPTIDES (AFPs)

Antifungal medications are used to treat and prevent fungal infections through several mechanisms (Neelabh **&** Rani 2016). This mechanism involves the activation of enzymes and the inhibition of DNA and RNA (Van der Weerden et al., 2013). Antifungal medications are effective against *Aspergillus* and *C. albican.* Brevinin, ranatuerin, and aurin 1.2 are present. However, their toxicity to human cells poses a significant challenge in clinical applications (Van Eijk et al., 2020).

3.3. ANTIVIRAL PEPTIDES (AVPs)

Antiviral medications and viruses have potential therapeutic benefits. In this case, viral tagging and integration prevents the detection of specific viruses. Antivirals are effective against both RNA and DNA viruses, and membrane instability leads to viral infection. HIV-1 and HSV-2 are not the only viruses that can cause a rash. Fuzeon belongs to the group of anti-HIV medications that include Maximin 3, Magainin 2, and Dermaseptin. Antiviral medications improve gene expression profiles and increase cytotoxicity potency (Goodsell, 2015).

3.4. ANTIPARASITIC PEPTIDES

Animal-to-human or contact between individuals, the environment, and nutrition are only a few of the ways that parasitic protozoa may infect both people and animals (Chalmers et al., 2020). Novel methods for therapy are required when parasite resistance to drugs rises. Antiparasitic drugs work well against parasites including leishmaniasis and malaria. In addition to katelis and temporins, Epi-1, a form of AMP, may also be utilized for the treatment of Trichomonas vaginalis (Neshani et al., 2019). Leishmania parasites have been successfully demonstrated to be inhibited by Jellein and KDEL (lysine, aspartic acid, glutamic acid, and leucine) peptides via a number of methods (Zahedifard et al., 2020).

3.5. ANTICANCER PEPTIDES (ACPs)

Anticancer peptides target tumor cells, activate immune cells, inhibit angiogenesis, and activate proteins that affect gene transcription. Tricrypticin and its derivatives are harmful to Jurkat cells, while puroindoline A and indolicidin exhibit anticancer activity (Arias et al., 2020). The effectiveness of anticancer peptides is determined by the balance between hydrophobicity and net charge. Furthermore, peptides such as human LL-37, insect defensins, and melittin can be toxic to both cancer and normal cells (Mai et al., 2001). Toxicity is a significant concern in clinical applications.

4. CHEMICAL FOUNDATIONS OF ANTIMICROBIAL PEPTIDES

AMPs are found in plants, mammals, insects, and marine invertebrates, and the majority are cationic peptides (Table 1). These peptides exhibit amphipathic properties when interacting with membranes. AMPs serve as drug transporters, antimicrobial and antitumor agents, mitogenic and contraceptive agents, and in signal transduction. A thorough understanding of their antimicrobial and therapeutic potential offers insights into the multifunctional properties of AMPs and their potential for enhanced bioavailability. Additionally, AMPs act as signals in communication processes, as well as mitogenic drugs, anticancer drugs, preventive substances, and drug distribution systems (Kamysz et al., 2003).

Table 1. *Various sources of Antimicrobial Peptides (AMPs)* **(***Pushpanathan et al., 2013)*

Source of AMPs	AMPs	References
Insect	abaecin, apidaecin, Alo3, attacins, cecropin A, ceratotoxin, coleoptericin, drosomycin, drosocin, diptericin, defensin A, formaecin, gallerimycin, heliomicin, lebocin, melittin, metchnikowin, ponericin G2, pyrrhocoricin, royalisin, sarotoxin IA, sapecin, spinigerenin, smD1, stomoxyn, termicin, thanatin	(Bulet et al., 1999; Bulet et al., 2005)
Amphibians	brevinin-20a, distinctin, japonicin-1, japonicin-2, maximin-1, nigrocin-1, nigrocin-2, pseudin-2, temporin-1Od, tigerin-1	(Rinaldi 2002)
Echinoderms	Betathymosins, centrocins, filamin A, Strongylocins	(Li, 2010)
Crustaceans	arasin, armadillidin, astacidin 2, Callinectin, crustin, hemocyanin derived peptides, hyastatin, homarin, penaeidin, scygonadin, stylicin	(Rosa and Barraco 2010)
Plants	lipid transfer proteins, plant defensins, thionins, ,	(Castro and Fontes 2005)
Mammals	defensin, histatin, LL-37, indolicidin, protegrin, lactoferricin	(Jenssen et al., 2006)
Bacteria	bacillomycin, Iturin, nikkomycins, syringomycin, syringostatins, syringotoxins,	(Sorensen et al., 1998)
Fungi	aculeacins, aureobasidin, echinocandins, FK463, helioferins, leucinostatins, mulundocandins	(De Bolle et al., 1996)
Fishes	Chrysophsin, HFIAP, misgurin, oncorhyncin II and III, pardaxins, parasin pleurocidins,	(Ravichandran et al., 2010)

4.1. SIGNIFICANT OF ANTIMICROBIAL PEPTIDES PHYSICOCHEMICAL PROPERTIES

4.1.1. LENGTH

The length of AMPs is critical for cytotoxicity. For beta-sheet AMPs, it should be at least 8 amino acids, for alpha-helical AMPs, it should be at least 22, and for amphipathic structures, it should be 7-8 amino acids (Westerhoff et al., 1989). Shortened peptides exhibit lower toxicity than the originals, underscoring the importance of length in the design of new synthetic peptides (Park et al., 2007).

4.1.2. NET CHARGE

The main element in the first approach to negatively energized cellular membranes is the net electrical charge of AMPs, which is the total of all ionizing charges of the peptide and can range from negative to positive. For

instance, V13K's hemolytic ability increased when its positive negative charge was increased from +8 to +9, however its efficacy against *P. aeruginosa* was eliminated when its net electrical charge was lowered down +4 (Jiang et al., 2008).

4.1.3. HELICITY

Helicity refers to the spin structure of AMP (antimicrobial peptides) and is more important for activity than other factors. However, toxicity plays a critical role in eukaryotic cells (Huang et al., 2010). In addition, the modification of α--helical peptides to d-amino acids leads to decreased hemolytic activity. This type of modification leads to increased AMP levels and hemolytic activity in the body. Peptides must be flexible and able to change their conformation during membrane insertion (Jenssen et al., 2006).

4.1.4. HIDROFOBISITE

Hydrophobicity affected the activity and selectivity of AMP molecules; 50% of the amino acid sequences of natural AMPs consist of hydrophobic residues (Tossi et al., 2000). Antimicrobial properties might be increased by enhancing the degree of hydrophobicity on the positively charged surface of AMPs beneath a certain value (Huang et al., 2010) and decreased by minimizing it (Lee et al., 2002). Every AMP amount is ideal for staying hydrated (Chen & Harrison 2007).

4.1.5. AMPHIPATHICITY

Amphipathicity is an important feature that enables AMPs to interact with microbial membranes. According to Fernandes-Vidal et al. (2007), the hydrophobicity of microbial membranes is highly critical. Synthetic AMPs are characterized by amphipathic behavior.

4.1.6. SOLUBILITY

For AMPs to affect membranes of lipids, they must be soluble in aqueous solutions. Hybrid AMPs frequently form dimer chains, which lowers hemolytic efficiency, and AMP compounds lose an ability for interacting with cell membranes. Additionally, interaction to microbial membranes is increased when dimer formation is lost. It might also emphasize the significance of structure minimization and dissolution (Chen et al., 2005).

4.2. THE RELATIONSHIP BETWEEN PHYSIOCHEMICAL PROPERTIES OF ANTIMICROBIAL PEPTIDES

There are many factors and interactions that influence AMP activity. In AMP design, these parameters must be considered together, as changes in

one parameter can affect others (Giangaspero et al., 2001). A simple sequence change can have significant consequences on AMP activity and the effects on target cells. Predicting the consequences of AMP modifications or the functions of synthetic peptides is difficult.

4.3. AMP MODIFICATIONS

Many AMPs need after translation changes to carry out their tasks, even though they are often produced in their active states. Phosphorylation, d-amino acid addition, methylation, amidation, glycosylation, and proteolytic cleavage are among the alterations that naturally formed AMPs go through (Rifflet et al., 2012). The modifications could be crucial when creating novel chemical AMPs. Although peptides synthesized that have these alterations can be produced using recombinant cell lines, a chemical process is needed to synthesize artificial amino acids (Bommarius et al., 2010).

4.3.1. MODIFICATION OF AMPS WITH COVALENT BONDS

Covalent modification can lead to significant changes in the antimicrobial activity of AMPs. The addition of a disulfide bond to sakacin P increased the antimicrobial activities, while rendering it inactive against HSV. In other studies on indolicidin derivatives, the addition of a disulfide bond to CP-11 and the trp-trp cross-link to indolicidin provided higher protease stability without any change in their antimicrobial activity (Osapay et al., 2000).

4.3.2. MODIFICATION OF ANTIMICROBIAL PEPTIDES BY CHANGING AMINO ACID CONTENT

Antimicrobial peptides (AMPs) can be modified by amino acid substitutions; these changes can affect AMP activity, target selectivity, and membrane penetration. The presence of certain amino acids, particularly proline, can affect membrane permeability. Furthermore, modifications such as the removal of neutral amino acids and the addition of positively charged residues have been made to human AMP LL37 to reduce cytotoxicity; this method has yielded P60.4, which is effective against MRSA (Goblyos et al., 2013).

4.3.3. MODIFICATION OF ANTIMICROBIAL PEPTIDES BY AMIDATION

AMPs can now incorporate particular chemical groups or artificial compounds because to developments in free peptide production. The peptides' ends were altered by an inclusion of amide groups, which led to complete membrane placement, quick communication with Gram-negative bacteria, and an over ten-fold improvement in cellular absorption (Kim et al., 2011).

Additionally, amidated peptides showed enhanced penetration of membranes. Antimicrobial peptides can also be made more stable by C-terminal alterations; a free acid-modified Api88 version, for instance, demonstrated a 15-fold rise in protease resistance.

5. CURRENT PROGRESS AND APPLICATION OF ANTIMICROBIAL PEPTIDES

5.1. MEDICINE

Antimicrobial peptides (AMPs) have biological functions that include regulating proinflammatory reactions, promoting cell proliferation, and promoting wound healing (de la Fuente-Núñez et al., 2017). AMPs are used as treatments in dentistry, surgical infections, and ophthalmology, but only gramicidin, daptomycin, and colistin have received FDA approval (Guaní-Guerra et al., 2010). AMPs, which offer alternative therapeutic options for dental health, are effective in burn wounds and surgical infections. However, their ophthalmological applications are still theoretical. Pharmaceutical applications of AMPs require reducing cytotoxicity and improving stability, and new formulation methods and targeting mechanisms have been developed.

5.2. FOOD

Because food preservatives can harm human health, there is an increasing interest in natural preservatives. Antimicrobial peptides (AMPs) effectively inhibit common bacteria and fungi and are resistant to high temperatures, acids, and alkaline conditions. Therefore, AMPs are considered a promising alternative. Nisin is a bacteriocin obtained from L. lactis subspecies and is generally recognized as safe (GRAS) by the FDA. However, currently, only nisin and polylysine are FDA-approved food additives (Khan **&** Oh, 2016).

5.3. ANIMAL HUSBANDRY AND AQUACULTURE

The ban on the use of growth promoters in feed has created a need for new antibacterial strategies, according to the European Union, 2006. Antimicrobial peptides (AMPs) have the potential to improve performance, support immunity, and improve intestinal health in poultry, pigs, and aquaculture (Cote et al., 2020). SIAMP is effective in treating IBV in chickens, while porcine intestinal AMPs provide high daily gain and feed efficiency in broilers (Hu et al., 2017). Furthermore, some peptides exhibit inhibitory activity against important viruses in fish farming (León et al., 2020). According to Cheng et al. (2017), AMP in soybean meal fermented with *B. subtilis* E20 is effective against *V. parahaemolyticus and Vibrio alginolyticus*, while increasing the resistance of *Litopenaeus vannamei* to this bacterium.

5.4. AGRICULTURE

In agriculture, bacteria and fungi, known as plant pathogens, cause significant losses. Infections caused by *Aspergillus flavus,* green mold caused by *Penicillium digitatum* on citrus fruits, gray mold caused by Botrytis cinerea on strawberries, and Geotrichum citri-aurantii on citrus fruits all damage the growth and yield of agricultural crops (Liu et al., 2019). Research suggests that some antifungal peptides (AFPs) may be effective in combating these pathogens.

CONCLUSION

There are significant challenges in the research and application of antimicrobial peptides (AMPs) that urgently need to be addressed. Interdisciplinary interactions can contribute to the development of potential AMPs. Various computational simulation methods are being used to study the mechanisms of AMPs, but experimental designs need to be improved. Animal experiments are important for testing the effects of complex physiological conditions.

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Chapter 8

A REVIEW ON UTILIZATION OF BORON WASTES IN INDUSTRIAL APPLICATIONS

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1. INTRODUCTION

Boron (symbol B) is a semi-metallic element with an atomic number of 5 and an atomic weight of 10.81. It belongs to group 3A of the periodic table. Boron does not occur in its free state in nature. It is widely found in boric acid and various forms of borates or boron silicates (Wang et al., 2014). It is estimated that the average boron content varies from 1 to 500 mg kg^{-1} in the Earth's crust, from 2 to 100 mg kg^{-1} in soil and from 0.5 to 9.6 mg L^{-1} in the ocean (Bhagyaraj et al., 2021).

Boron is mostly found in the structure of about 230 minerals bearing sodium, calcium or magnesium salts. Tincal, colemanite, ulexite, kernite, boracite, pandermite, hydroboracite, and szaybelite are the major boron minerals with commercial importance(Najid et al., 2021; Kim et al., 2023). 73% of the world's boron mineral reserves are found in Türkiye in the deposits of Kütahya-Emet, Balıkesir-Bigadiç, Bursa-Kestelek and Eskişehir-Kırka with an annual refined boron production capacity of 2.7 million tons (Eti Maden, 2019).

Alteration of minerals to effective products comes true with the enrichment and grinding processes (Bulut et al., 2025). During these ore treatment and refining processes, huge amounts of clay wastes and pond wastes were generated with the high B_2O_3 content of 11-20 wt%. (Kavas et al., 2011; Cengizler, 2022).

Tinkal mineral at Kırka contains grey clays containing dolomite and montmorillonite in similar quantities, as well as dolomite-rich white clays and calcite. The Bursa-Kestelek and Kütahya-Emet-Hisarcık boron plants produce wastes containing paramagnetic minerals such as montmorillonite, calcite, chlorite and biotite. The Bigadiç waste in Balıkesir contains montmorillonite, calcite and gypsum (Oruç et al., 2004). Boron is found in these clay deposits, and the production processes result in waste clays containing B_2O_3 at high content that make the tailings economically valuable (Vapur et al.,2021).

Today, the increasing rate of consumption has led to an increase in production capacities, and accordingly, the evaluation of wastes, which are seen as alternatives to raw material sources, has gained importance. Recycling boron waste in various industries also has several advantages. Primarily, it reduces production costs and environmental impact. It also reduces the problem of waste storage and, consequently, storage costs. Furthermore, products manufactured using waste maintain or even enhance product quality when the dosage and process controls are managed correctly (Oruç et al., 2004).

2. THE USE OF BORON WASTES IN INDUSTRIAL APPLICATIONS

Boron-containing waste clays and sludges have found a broad use in the construction sector, such as ceramic, cement and concrete, brick, and road material industries (Çelik, 2015; Topaloğlu Yazıcı and Çetinkaya, 2018; Aldakshe et al., 2020).

2.1. In the Ceramic Production

In the ceramic industry, kaolinitic clays are one of the main raw materials. Boron waste clays with a high B_2O_3 content are used as an alternative to raw materials, with the advantage that B_2O_3 is an effective flux material in ceramic production, for example, in mud production, frit and glaze preparation, and tile production. Also, B_2O_3 acts as a glass former, enabling the formation of a glassy phase with reduced viscosity at low temperatures. (Hernandez et al., 2022; Goltsman and Yatsenko, 2024). Additionally, reducing temperatures can offer several benefits, including energy savings and enhanced material properties. For example, it has been found that lower temperatures can reduce water absorption and porosity in stoneware and porcelain tiles (Özdemir and Kıpçak, 2016; Zanelli et al., 2019).

Taşkıran et al. (2025) investigated the usability of boron mining wastes (containing 7.3 wt% % B_2O_3) in the wall tile production in combination with the other industrial by-products such as marble and limestone cutting wastes, fly ashes of coal-burning thermic power plants and sand wastes of the glass industry. These wastes were used at a ratio of 50 % at different body compositions at production. The most proper recipe was tried to reveal. The results pointed out that these formulations with the proper combination of selected residues show similar firing behaviour and technical properties to traditionally industrial compositions.

Cengizler (2022) investigated the effects of using raw colemanite waste in wall tile production. The waste with the 11.24 % B_2O_3 content calcined at 800 ˚C and subsequently sintered at 950 ˚C was used in the production of tile wall at the percentage of 40 %. The study resulted in 64% increased strength at these optimum conditions.

Karadağlı and Çiçek (2020) added boron waste (16-31wt % B_2O_3) at the percentages of 3–10 wt % to a formulation of commercially produced porcelain tiles. They observed that the sintering temperature reduced from 1233°C to 1195°C. It was seen that the results of the study encourage the utilisation of boron wastes in the production of porcelain tiles.

In another study, boron waste (containing 7.5 wt % B_2O_3) was used in the production of monticellite-based ceramic powders, and the bioactivity characteristics of these powders were evaluated. According to the research, the synthesis of boron-containing ceramic powder occurred at a low temperature of 800 ˚C, and it was observed that the surface of the powders exhibited bioactive properties and that a bone-like apatite layer formed on the surface within 15 days (Koroglu et al., 2017).

In the study by Cicek et al. (2014), a colemanite enrichment waste (19.7wt % B_2O_3) from Eti Bor Bigadiç deposit (open pit), located in the Marmara region in Turkey, was used together with meat bone and meal ash from the Glanford Power Station (Scunthorpe, UK) and recycled soda lime silica glass by Sasıl Life (Biella, Italy) in the glass-ceramics at the ratio between 30-40 wt% %. The microstructure evolution and mechanical properties of the produced glass-ceramics were found to be significantly influenced by rapid sintering, the particle sizes of the selected wastes, the amount of glass-ceramic forming oxides, and the sintering cycle. The boron wastes act as a flux, creating a liquid phase at approximately 950°C and enabling densification.

2.2. In Cement and Concrete Production

Boron wastes are versatile and effective additives for use in cement and concrete, offering performance and sustainability benefits. In addition, using these wastes as additives helps to reduce environmental issues while improving the properties of these materials.

The reason for adding boron wastes to cementitious materials is generally attributed to their positive effect on enhancing the fire resistance and durability of composites, and sometimes their mechanical strength. For instance, the addition of up to 10% colemanite waste or 5–7% ulexite can enhance the compressive strength and durability of cementitious composites, although higher amounts may diminish performance (Özdemir and Öztürk, 2003; Yildirim and Al-Mashhadani, 2023; Baştürk et al., 2025) In addition, boron residue has been demonstrated to reduce water absorption and augment resistance to external factors (Yildirim and Al-Mashhadani, 2023).

The earlier studies that use boron waste as cement and aggregate replacement mainly investigated the effects of wastes on properties such as compressive and bending strengths, hydration heat, setting time, and volume expansion (Zhang et al.,2016). It is found that B_2O_3-containing wastes generally, at higher amounts, more than 10 % decrease strength parameters and increase setting times of cement-based materials (Sevim and et al., 2019).

Ünal and Cambaz (2025) investigated the possibility of using colemanite concentrator waste of Kütahya-Emet Eti Maden Company (27.80 % B_2O_3)

and fly ash as a cement and concrete additive. Cement was replaced with colemanite waste at the ratios of 5 %, 10 %, 20 % and fly ash at 10 %, 20 %. The results showed that use of these additives enhanced workability, density, and microstructural integrity but had a negative impact on compressive strength at high replacement levels. As a result, the specimen with 5% colemanite concentrator waste showed the best mechanical properties.

Tincal-derived boron waste from borax processing was utilized to produce geopolymer mortar. For this purpose 10%, 20%, 30% and 40% tincal waste (9.83 % B_2O_3) was replaced with ground blast furnace slag. The samples were cured at room temperature and 60˚C, after which they were exposed to high temperatures (200-600˚C). The samples' unit weight, compressive strength, ultrasonic pulse velocity, and mass loss values were measured. The results exhibited that tincal waste added up to 20 % enhanced the sample properties before and after high temperature implementation (Çelik and et al., 2024).

The impact of using boron waste on the mechanical properties, durability, and radiation absorption properties of cementitious systems was investigated by Mardani et al. (2023). As the amount of boron waste in the mixture increased, some properties such as radiation absorption, resistance to high temperatures and freeze-thaw resistance improved. However, the fresh water requirement and the setting time of the mixtures were affected negatively by the addition of boron waste. Examining the effects of boron waste on compressive strength revealed that adding up to 10% waste increased strength, whereas adding more than this amount decreased it.

Boron waste was also used as part of the pumice aggregate in lightweight concrete production. It is substituted with pumice aggregate at the ratios of 1%, 3%, 5%, 7%, 9% by weight. With increasing boron-waste content up to 9%, physical and mechanical properties improved compared to reference lightweight concrete. The results showed that pumice aggregate with boron waste can produce lighter, but still viable, concrete (Aldakshe et al., 2020).

In the study by Kunt et al. (2015) calcined and non-calcined borogypsum at the ratios between 1% - 7% were added to cement mortar. The effects of these wastes on the cement properties were examined, and also setting time and consistency analyses were applied to fresh mortar. In addition, strength tests of 3, 7 and 28 days were performed according to the Turkish Standard (TS EN 196-1). The optimum results were obtained for both calcined and non-calcined borogypsum at a ratio of 3%.

2.3. In Brick Production

There are many articles in the literature about the reuse of boron-containing industrial wastes in fired-clay bricks, perlite/lightweight bricks, and

geopolymer bricks. The effects of the wastes on the physical and mechanical properties of bricks were evaluated.

In the study of Çağlar (2023), the effect of silica aerogel produced from boron waste (25.5 % B_2O_3) on the compressive strength and thermal performance of bricks was investigated. Firstly, aerogel was produced and then substituted into the brick structure at different ratios by volume (15% - 45%). Brick samples were produced by firing them at 900 ˚C and 1000 ˚C. After that, compressive strength and heat transfer coefficient determination tests were applied to the samples. The results showed that compressive strength and heat transfer coefficient value decreased with the increasing amount of aerogel at both temperatures.

Murathan (2023) prepared different types of brick samples by adding waste casting sand at the ratios 20-80 % and waste boron at 10-20 % (33.1 % B_2O_3) to clay-based bricks and tested them for their bulk density, drying shrinkage, water absorption, compressive strength, and frost resistance. Firing temperature of the composite bricks was 800ºC. The produced brick exhibited higher compressive strength, bulk density, and resistance to frost, and lower drying shrinkage and water absorption compared with standard bricks. This suggests that boron waste (together with other industrial wastes) can enhance the quality of fired clay bricks.

In the study by Al Amara and Çağlar (2023), geopolymer bricks were produced by using Eskişehir Kırka region boron waste (25 % B_2O_3) and Seyitömer thermal power plant fly ash. They kept the fly ash at 10% and varied the boron waste from 10% up to 60%. It was found that as the amount of boron waste increased, porosity, water absorption, and heat-transmission coefficients decreased, but Compressive strength improved up to 50% substitution; beyond that, flexural strength decreased. The study concluded that using boron waste and fly ash in brick production at certain rates is feasible and environmentally friendly.

Çimen et al. (2020) produced bricks by mixing perlite at a constant rate of 5% and boron wastes (22.9 % B_2O_3) at varying rates between 5% and 20 %. The firing temperature was chosen as 900 °C. Physical and mechanical tests showed that with proper proportions, boron waste improved the brick's performance.

In the study, the author aimed to produce more durable bricks by using boron waste (25% B_2O_3) from the Kırka region of Eskişehir and fly ash from the Seyitömer thermal power plant, in terms of physical and mechanical properties (freezing and thawing resistant, thermal insulation properties). For this purpose, 10 % boron waste was used and kept constant near the varying percentages of fly ash (10%, 20%, 30%). The produced samples were fired at 800, 900, and 1000 °C. As a result of physical and mechanical tests, it was determined that the usage of fly ash and boron waste together in brick production at certain rates had no disadvantage and the optimum temperature was 900 °C (Çağlar, 2021).

2.4. In Road Materials Production

Using boron wastes as a component in road materials offers a promising way to both recycle industrial by-products and reduce demand for natural resources while increasing the material's performance under proper conditions.

Kara (2021) produced stone mastic asphalt and concrete pavement by using boron wastes (27-35 % B_2O_3) in varying sizes between 0.1-16 mm. After performing relevant tests, the results showed the unsuitability of boron waste as aggregate in stone mastic asphalt. To increase the strength of concrete pavements, steel fibre should be used in the mixture and the obtained concrete should be exposed to curing methods, including both soaking in water for 3 days and keeping in the oven at 200°C (following the water application).

Keskin and Karacasu (2019) investigated the effects of three types of boron-containing additives, such as crushed boron waste (11.84 % B_2O_3), borax pentahydrate (47.90 % B_2O_3) and anhydrous borax (69.30 % B_2O_3) in asphalt concrete. Marshall specimens were prepared by adding crushed boron waste and borax pentahydrate at ratios between 5-15 %, and anhydrous borax at 5-10 %. According to Marshall test results, it was found that these three materials meet the specification limits, and creep tests showed that crushed boron waste material extended asphalt specimens service life.

Zhang et al. (2016) used boron waste as an additive in road base material by stabilizing the waste mixture with lime and cement. When stabilized with lime, boron waste can achieve sufficient unconfined compressive strength for use in road bases when the content of lime is greater than 8 % but due to its poor frost resistance, lime-stabilized boron waste can only be used in non-frozen regions. Lime-cement-stabilized boron waste mixtures showed higher compressive and tensile strengths than those of a lime-stabilized one. At the same time, the drying shrinkage coefficient of lime-cement-stabilized boron waste mixtures was smaller than lime-stabilized boron waste. Also, it was found that a lime-cement-stabilized boron waste mixture was suitable for frozen regions.

Gürer and Selman (2016) investigated the properties of asphalt concrete containing boron waste (12.20 % B_2O_3) as mineral filler. For this purpose, they added 4%, 5%, 6%, 7% and 8% boron waste as well as a 6% limestone filler as the control sample to the asphalt concrete samples. After the relevant tests were performed on the samples, it was found that boron waste can be used in medium and low-traffic asphalt concrete pavements.

3. CONCLUSION

This review comprehensively evaluated the utilization of boron-containing industrial wastes in construction materials, with a particular focus on ceramics, cement and concrete, bricks, and road materials. The findings

reported in the literature clearly demonstrate that boron wastes, which are generated in large quantities during ore beneficiation and refining processes, possess significant potential as secondary raw materials due to their high B_2O_3 content and favorable mineralogical composition.

In ceramic production, boron wastes primarily act as effective fluxing agents, promoting liquid-phase formation and enabling sintering at lower temperatures. This leads to reduced energy consumption while maintaining or improving key properties such as densification, water absorption, and mechanical strength. Similar benefits are observed in glass-ceramic and porcelain systems, where appropriate boron waste additions contribute to improved microstructure and thermal efficiency.

In cementitious systems, boron wastes have been shown to enhance certain durability-related properties, including fire resistance, radiation shielding, and resistance to environmental degradation, when used at controlled replacement levels. However, excessive amounts may adversely affect setting time and mechanical strength, emphasizing the importance of optimizing dosage and mix design. In geopolymer and lightweight concrete applications, boron wastes contribute to improved thermal stability and reduced density, supporting their suitability for sustainable construction practices.

For brick production, including fired-clay, lightweight/perlite, and geopolymer bricks, boron wastes improve sintering behavior, reduce porosity and water absorption, and can enhance compressive strength and thermal insulation when used at appropriate ratios. These improvements enable the production of energy-efficient and durable units while simultaneously reducing the consumption of natural clay resources.

The application of boron wastes in road materials further demonstrates their versatility, particularly as mineral fillers or stabilized base materials. While limitations exist regarding their direct use as aggregates in certain asphalt mixtures, studies confirm their feasibility in asphalt concrete, stabilized road bases, and low- to medium-traffic pavements when proper formulation and stabilization methods are applied.

Overall, the reuse of boron-containing wastes in construction materials offers environmental, economic, and technical advantages, including waste minimization, conservation of natural resources, reduced production costs, and, in many cases, enhanced material performance.

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