Current Approaches in Natural and Health Sciences

EDITORS

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SERÜVEN YAYINEVİ

Genel Yayın Yönetmeni / Editor in Chief • Eda Altunel

Kapak & İç Tasarım / Cover & Interior Design • Serüven Yayınevi

Birinci Basım / First Edition • © Haziran 2025

ISBN • 978-625-5897-20-6

Serüven Yayınevi / Serüven Publishing
Türkiye Adres / Turkey Address: Kızılay Mah. Fevzi Çakmak 1. Sokak
Ümit Apt No: 22/A Çankaya/ANKARA
Telefon / Phone: 05437675765
web: www.seruvenyayinevi.com
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Baskı & Cilt / Printing & Volume
Sertifika / Certificate No: 42488

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Chapter 1

NATURAL SGLT-2 INHIBITORS: A PROMISING APPROACH TO DIABETES MANAGEMENT

Omer Faruk SONAR[1], Sevgi Nese AYIRKAN[2], Hatice DUNDAR[3], Omer VAROL[4], Yasemin KORKMAZ[5], Ahmet Gokhan AGGUL[6]

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1. Introduction

Diabetes mellitus, often referred to as diabetes, is a chronic metabolic disorder characterized by high blood glucose levels. This occurs due to either inadequate insulin production or the body's resistance to insulin (Antar et. al., 2023). Despite advancements in treatment methods, a definitive cure for the disease remains elusive. Current therapies primarily focus on managing symptoms rather than eliminating the disease itself. This ongoing challenge has led to an increased emphasis on developing new therapeutic agents. Among these, Sodium-Glucose Co-Transporter-2 (SGLT-2) inhibitors have become significant, not only for their role in lowering blood glucose levels but also for addressing various complications related to diabetes. SGLT-2 is a key transporter responsible for glucose reabsorption in the kidneys, making it a valuable target for innovative antidiabetic strategies (Wilding et. al., 2018).

At the same time, there is a growing interest in using natural bioactive substances for diabetes management, primarily due to their potential effectiveness and lower risk profiles. In this context, the current study investigates the SGLT-2 inhibitory potential of compounds found in olive oil, including oleuropein, luteolin, apigenin, tyrosol, and hydroxytyrosol, using *in silico* techniques. SGLT-2 inhibitors work by blocking the renal reabsorption of glucose, which helps expel glucose through urine and lowers systemic glucose levels. The findings of this study could significantly improve diabetes treatment by highlighting the potential of plant-based molecules as alternative or complementary therapeutic options.

2. General Information

2.1. Definition of Diabetes Mellitus

Diabetes Mellitus is a common and chronic metabolic disease characterized by elevated blood glucose levels. This condition occurs either due to a complete lack of insulin production or because the body cannot respond effectively to the hormone insulin (American Diabetes Association, 2014). Under normal physiological conditions, insulin facilitates the entry of glucose into cells, where it is utilized for energy production. When insulin is insufficient or ineffective, glucose remains in the bloodstream, resulting in chronic hyperglycemia. Over time, this glucose imbalance can cause progressive damage to multiple organ systems and increase the risk of life-threatening complications. (Alam et al., 2021).

2.2. Diabetes Epidemiology

Diabetes has become one of the most pressing public health issues of the 21st century; however, its significant social and economic conse-

quences are often underestimated globally. This underrecognition contributes to the steady rise in its prevalence and hinders the development of comprehensive management strategies. Since the early 2000s, the International Diabetes Federation (IDF) has conducted extensive research to emphasize how diabetes affects populations of all ages and socioeconomic backgrounds in every region of the world.

According to the International Diabetes Federation (IDF), diabetes and its complications significantly contribute to global healthcare costs, currently leading to an increase of more than 10% in total medical expenditures. The ongoing growth of urban areas, rising sedentary lifestyles, and the continuous increase in the global population are expected to worsen this economic burden. Findings from the Eleventh Edition of the IDF Diabetes Atlas indicate that approximately 588 million people were living with diabetes worldwide in 2024. This number is projected to rise to 852 million by 2050. Additionally, nearly 50% of adults with diabetes are still undiagnosed, highlighting a significant gap in early detection and care (IDF, 2025).

Table 1: IDF's global estimates for 2024 and 2050 years

Global Overview	**2024**	**2050**
Population		
Total world population	8.1 billion	9.7 billion
Adult population (20-79 years)	5.3 billion	6.6 billion
Diabetes (20-79 years)		
Global diabetes prevalence	11.1%	13.0%
Number of individuals with diabetes	588.7 million	852.5 million
Number of deaths attributed to diabetes	3.4 million	-
Diabetes-related healthcare expenditures (20-79 years)		
Total healthcare expenditures (2021, USD)	1.015 trillion	1,043 trillion

Source: IDF Diabetes Atlas-11th Edition, 2025

Diabetes is a major metabolic disease resulting from either a complete lack of endogenous insulin or the body's reduced responsiveness to it at the peripheral level. Recognized as a chronic illness requiring ongoing clinical management, diabetes mellitus is associated with high rates of disease and death worldwide, affecting populations in both industrialized and developing nations. Beyond its serious health consequences, diabetes places severe social and economic burdens on millions, significantly impacting their well-being. It remains one of the leading causes of global mortality (Magliano, Boyko, & Atlas, 2021).

2.3. Oral Antidiabetic Drugs in Diabetes Management

Oral antidiabetic agents are crucial for managing blood glucose levels, particularly in individuals diagnosed with type 2 diabetes mellitus. Administered orally, these medications target various metabolic pathways to achieve glycemic control. Their mechanisms include enhancing insulin secretion, improving cellular insulin sensitivity, and inhibiting glucose production and absorption. Unlike injectable insulin therapies, oral antihyperglycemic drugs provide a non-invasive treatment alternative and are often the first choice for newly diagnosed cases of type 2 diabetes. Among these, biguanides, especially metformin, are the most commonly prescribed. Metformin primarily works by reducing hepatic glucose production and increasing insulin sensitivity, which enhances glucose uptake and utilization. Other classes of oral antidiabetic agents exhibit various mechanisms of action. Sulfonylureas stimulate pancreatic beta cells to increase insulin secretion. DPP-4 inhibitors prolong the activity of incretin hormones, enhancing insulin release and suppressing glucagon production. Thiazolidinediones improve insulin sensitivity, particularly in adipose tissue and skeletal muscle. Alpha-glucosidase inhibitors slow the digestion and absorption of carbohydrates in the intestine, helping to reduce postprandial glucose excursions. Meglitinides promote a rapid and short-acting release of insulin from pancreatic beta cells (Piragine et al., 2023).

2.4. SGLT2 Inhibitors in Diabetes Management

SGLT-2 inhibitors have emerged as a valuable class of oral antidiabetic medications, known for their unique mechanism and various health benefits. Drugs such as ertugliflozin, canagliflozin, dapagliflozin, and empagliflozin—approved by the FDA—are commonly prescribed for adults with type 2 diabetes mellitus. These medications are typically recommended in conjunction with lifestyle modifications, such as a balanced diet and regular physical activity, to enhance glycemic control. SGLT-2 inhibitors block glucose reabsorption in the renal proximal tubules, which increases urinary glucose excretion. This action not only aids in effective blood sugar regulation but also offers cardioprotective and nephroprotective benefits, which are especially crucial for individuals with type 2 diabetes mellitus who face a higher risk of heart and kidney diseases. Moreover, these agents help reduce body weight and systolic blood pressure, enhancing their therapeutic significance (Baghel et al., 2024).

Oral antidiabetic medications, including SGLT-2 inhibitors, are commonly prescribed when lifestyle modifications alone fail to achieve target glycemic levels. These agents can be used as monotherapy or in combination with other glucose-lowering medications or insulin. However, due to

their insulin-independent mechanism of action, SGLT-2 inhibitors are not suitable for individuals with type 1 diabetes, which requires exogenous insulin administration (Wilding et. al., 2018).

Despite significant advances in the understanding and management of diabetes, a definitive cure remains elusive. Current therapeutic strategies are primarily aimed at controlling hyperglycemia and preventing long-term complications. This persistent gap in curative treatment has intensified scientific and clinical interest in natural therapeutic approaches, particularly those involving antioxidant-rich compounds that may alleviate oxidative stress in diabetic patients. Consequently, many individuals are exploring plant-based or naturally derived alternatives as complementary approaches to standard diabetes care.

2.5. Natural Antioxidants

The olive tree (*Olea europaea* L.) has been valued for its health-promoting properties for a long time and has played a central role in traditional medicine for centuries. This plant is a rich source of bioactive compounds known for their antioxidant, anti-inflammatory, and therapeutic effects. Key constituents include oleuropein, luteolin, hydroxytyrosol, tyrosol, diosmetin, and rutin, among others (Benavente-Garcıa et al., 2000). The chemical structures of these natural compounds are illustrated in Figure 1.

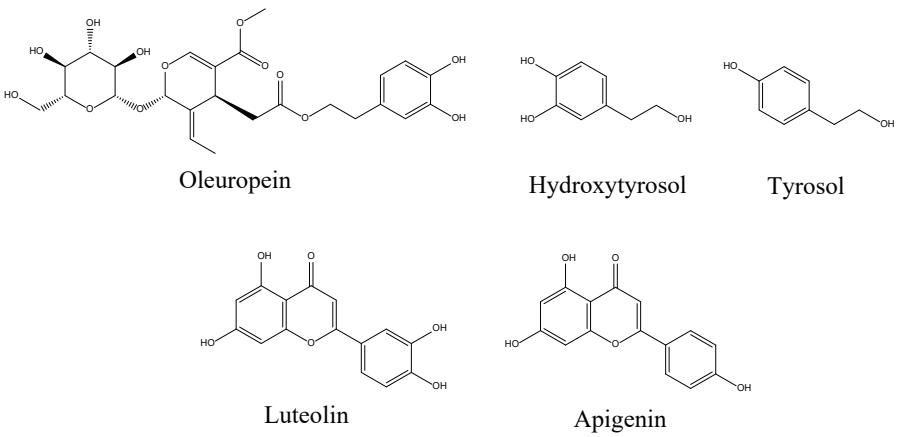

Figure 1: Structures of the natural compounds from olive oil

Among these, oleuropein stands out as a significant secoiridoid compound that is especially abundant in olive leaves and unprocessed olive fruits. Its molecular structure contains a combination of elenoic acid, hy-

droxytyrosol, and glucose units, which together contribute to its powerful antioxidant and anti-diabetic properties (Aggul et al., 2020).

Oleuropein is one of the main phenolic compounds found in olives and olive-derived products, known for its wide range of pharmacological benefits. It demonstrates potent antioxidant activity by neutralizing free radicals and boosting endogenous antioxidant defense systems. Moreover, oleuropein exhibits anti-inflammatory, antimicrobial, cardioprotective, neuroprotective, and anticancer effects, making it a molecule of increasing interest in the field of natural therapeutics (Aggul et al., 2020).

In the context of metabolic disorders, oleuropein has shown potential antidiabetic activity by enhancing insulin sensitivity, lowering blood glucose levels, and modulating lipid metabolism. It also influences key enzymes and pathways involved in oxidative stress and inflammation, which are closely linked to the pathogenesis of type 2 diabetes mellitus. Additionally, studies suggest that oleuropein may support pancreatic β-cell function and reduce hepatic glucose production, indicating its potential role as a complementary agent in diabetes management (Da Porto et al., 2021)

2.6. Molecular Docking Analysis

Molecular docking is a widely used computational approach for investigating the interactions between ligands and their biological targets, usually proteins. This method involves positioning a ligand within the binding site of a receptor—often a protein with a known three-dimensional structure—to estimate the most favorable interaction pose. Docking techniques not only offer insights into the geometry and orientation of ligand-receptor complexes but also facilitate the prediction of binding affinities.

In the present study, Maestro 12.9 from the Schrödinger Molecular Modeling Suite was used to conduct all *in silico* simulations. Two primary scoring systems were employed: EmodelScore, which identifies the most stable conformation of a ligand within the receptor, and GlideScore, which evaluates and ranks ligands based on their binding strength. The crystal structure of the SGLT-2 enzyme (PDB ID: 2XQ2) was retrieved from the RCSB Protein Data Bank and prepared using Schrödinger's Protein Preparation Wizard.

The active binding site was established using the Receptor Grid Generation module in Maestro. Ligand structures were initially created with the built-in 2D sketching tool and then imported for further processing. Known clinical SGLT-2 inhibitors—dapagliflozin, canagliflozin, and em-

pagliflozin—were obtained from PubChem for comparative analysis. All ligand structures underwent energy minimization and geometry refinement using the LigPrep module. Subsequently, molecular docking was performed using the Glide XP (extra precision) protocol. Docking results were assessed based on the lowest binding energy conformations, and interaction diagrams illustrating key receptor-ligand interactions were produced with Maestro 12.9.

3. Results

The results of the molecular docking analysis demonstrated that oleuropein displayed a strong inhibitory interaction with the SGLT2 enzyme, surpassing several clinically used reference compounds. Among the tested molecules, oleuropein achieved some of the lowest binding free energy values, indicating a high binding affinity for the active site of the target protein. The calculated binding free energy for oleuropein was −6.088 kcal/mol, reflecting its potential as an effective natural SGLT2 inhibitor. A detailed comparison of docking scores and binding affinities is presented in Table 2.

Table 2: Docking scores and binding energies of the compounds for SGLT2

Protein	Compounds	Docking Score	XP GScore	Glide Emodel
SGLT2 (PDB: 2XQ2)	Oleuropein	-6,088	-6,090	-33,919
	Luteolin	-6,059	-6,059	-28,958
	Apigenin	-4.427	-4.475	-21,257
	Tirosol	-3.759	-3.759	-21,599
	Hidroksitirosol	-3.555	-3.557	-19,625
	Dapagliflozin[a]	-7,875	-7,875	-42,543
	Canagliflozin[a]	-7,875	-7,875	-42,543
	Empagliflozin[a]	-7,956	-7,956	-48,940

[a] *A clinically used SGLT2 inhibitor*

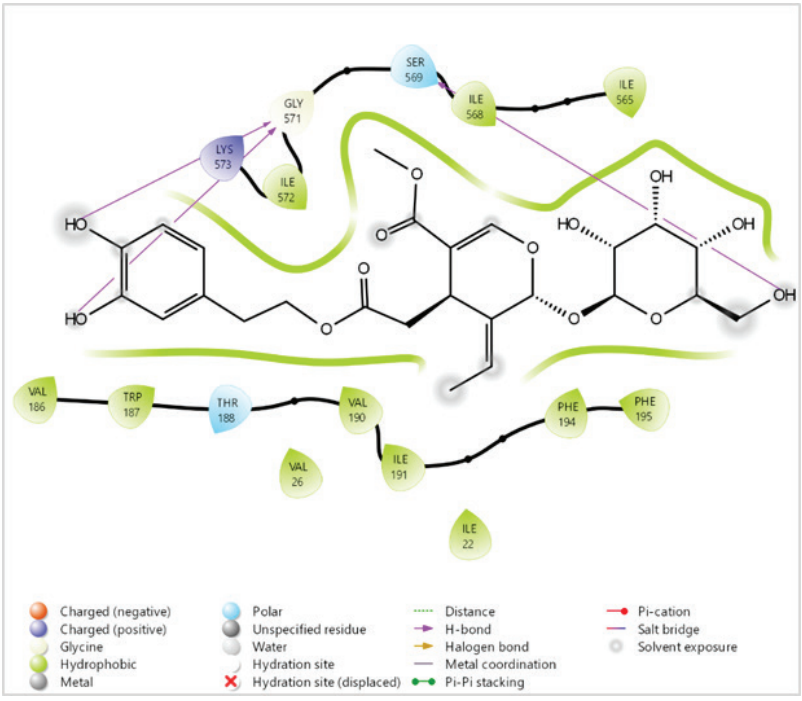

Figure 2: Two-dimensional (2D) interactions of oleuropein with the SGLT2 protein

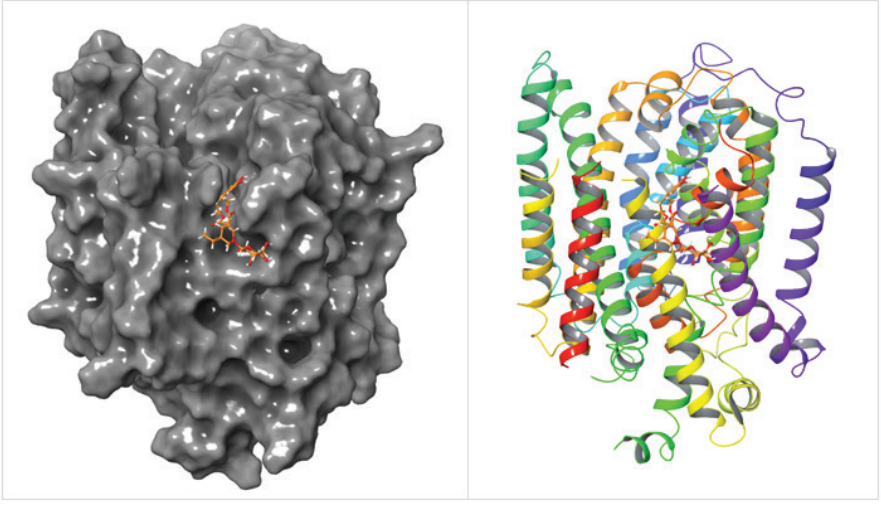

Figure 3: Three-dimensional (3D) docking poses of oleuropein with SGLT2 protein

(Oleuropein is represented in orange spheres and stick modeling)

Oleuropein formed hydrogen bonds with the amino acid residues SER569 and GLY571. Additionally, the compound exhibited hydrophilic interactions with multiple residues, including ILE22, VAL26, VAL186, TRP187, VAL190, ILE191, PHE194, PHE195, ILE565, ILE568, and ILE572. Moreover, it interacted with two hydrophobic residues—THR188 and SER569—within the active site, as shown in Figures 2 and 3.

In summary, preliminary findings suggest that oleuropein may provide a promising natural alternative to some existing SGLT-2 inhibitors, showing comparable or even superior inhibitory activity. Among the evaluated compounds, oleuropein revealed the most favorable interaction profile with the SGLT2 receptor. As a major phenolic glycoside abundantly found in olive leaves, oleuropein has a unique chemical structure that appears to enhance its capacity to modulate glucose transport by inhibiting SGLT-2 activity.

This inhibition mechanism not only facilitates urinary glucose excretion, aiding glycemic control, but it may also offer cardiovascular and antioxidant benefits important for the overall management of type 2 diabetes. The results support the potential of oleuropein as a candidate for developing next-generation SGLT-2 inhibitors derived from natural sources. However, further in vitro, in vivo, and clinical investigations are necessary to fully clarify its therapeutic role and validate its efficacy and safety in the context of diabetes management.

Acknowledgement

The authors would like to express their sincere gratitude to the Faculty of Pharmacy at Agri Ibrahim Cecen University for their valuable support and contributions throughout this research. This work was conducted as part of undergraduate thesis projects.

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Chapter 2

BUTYRYLCHOLINESTERASE (BChE) AS A THERAPEUTIC TARGET IN ALZHEIMER'S DISEASE

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1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, memory impairment, and behavioral disturbances (DeTure & Dickson, 2019). While the exact cause of AD remains unclear, cholinergic dysfunction is widely recognized as a key factor in its pathophysiology (Chen et. al., 2022). Current pharmacological treatments primarily aim to enhance cholinergic neurotransmission by inhibiting acetylcholinesterase (AChE). However, as the disease progresses, AChE activity significantly declines, whereas butyrylcholinesterase (BChE) activity remains stable or may even increase. This change in enzymatic activity has renewed interest in BChE as a potential therapeutic target (Greig, Lahiri & Sambamurti 2002).

Historically overshadowed by AChE, BChE has gained prominence due to its role in both cholinergic signaling and β-amyloid plaque formation (Darvesh et. al., 2025). Recent studies suggest that selectively inhibiting BChE may provide cognitive benefits with fewer side effects, particularly in the later stages of Alzheimer's disease. Moreover, advancements in medicinal chemistry and natural compound screening have led to the identification of novel BChE inhibitors with promising pharmacological profiles (Sun et. al., 2024).

In this context, this study aims to reassess the therapeutic relevance of BChE by exploring its biochemical properties, the pathological significance in Alzheimer's disease, and the potential of inhibiting it as a developing strategy for treating Alzheimer's disease.

2. General Information

2.1. Alzheimer's Disease

AD is a progressive neurodegenerative disorder characterized by memory loss, cognitive dysfunction, and behavioral changes. Its multifactorial pathophysiology involves β-amyloid plaque accumulation, tau protein hyperphosphorylation, oxidative stress, synaptic degradation, and neuroinflammation (Querfurth & LaFerla, 2010).

AD is the leading cause of dementia worldwide, accounting for 60–70% of all dementia cases. According to the World Health Organization (2021), over 55 million people live with dementia globally—a number projected to rise to 139 million by 2050 due to aging populations. The prevalence of AD doubles approximately every five years after the age of 65, with women disproportionately affected (Prince et. al., 2016). This increasing burden places a significant strain not only on patients and families but also on healthcare systems and economies.

2.2. Role of Cholinesterases in Alzheimer's Disease

Two key enzymes hydrolyze acetylcholine (ACh) in the synaptic cleft: acetylcholinesterase (AChE, EC 3.1.1.7) and butyrylcholinesterase (BChE, EC 3.1.1.8). Under normal physiological conditions, AChE predominates in the brain, while BChE plays a secondary role. However, in AD, AChE levels decline significantly, whereas BChE activity increases, especially in areas of amyloid deposition. This dynamic shift in enzyme activity suggests a more prominent role for BChE in the later stages of the disease. Furthermore, BChE has been found in association with amyloid plaques and neurofibrillary tangles, implicating it not only in neurotransmitter regulation but also in the pathogenesis of AD itself (Sun et. al., 2024).

2.3. Cholinesterase Inhibitors

Cholinesterase inhibitors are the primary class of drugs approved for symptomatic treatment of mild to moderate AD. These agents act by inhibiting the degradation of ACh, thereby enhancing cholinergic neurotransmission. Among them, donepezil is a selective, reversible AChE inhibitor approved for all stages of AD. It is favored for its once-daily dosing and relatively mild side-effect profile (Rogers & Friedhoff, 1996). Rivastigmine inhibits both AChE and BChE. Its dual mechanism is particularly advantageous in moderate-to-severe stages when BChE becomes more dominant. It is available as an oral capsule and a transdermal patch, the latter offering better gastrointestinal tolerability (Birks et. al., 2015). Galantamine selectively inhibits AChE and also modulates nicotinic ACh receptors, enhancing endogenous ACh release and synaptic plasticity (Wilkinson et. al., 2002).

2.4. BChE Inhibitors

AChE inhibitors have long been considered the first-line treatment for AD. However, their clinical application is often limited by dose-dependent side effects and restricted long-term efficacy. Recent studies have highlighted the potential of BChE inhibitors, as well as dual AChE/BChE inhibitors, which show improved therapeutic outcomes and a more favorable safety profile compared to selective AChE inhibitors. Consequently, dual cholinesterase inhibitors have emerged as a promising focus in developing novel anti-AD agents. Newer approaches focus on selective BChE inhibitors, which may prove more beneficial in advanced AD when BChE levels increase. Notably, selective BChE inhibitors are preferred because they result in fewer side effects (Zhou & Huang, 2022).

3. Conclusion

This paper presents a comprehensive overview of the structural characteristics, functional roles, and clinical relevance of BChE, with particular emphasis on its therapeutic potential in the context of Alzheimer's disease.

Cholinesterases—particularly BChE—play a crucial role in the progression and potential treatment of AD. While AChE has long been the primary target of pharmacological intervention, the increasing activity of BChE in advanced AD suggests its growing importance. BChE contributes not only to the breakdown of ACh when AChE levels decline but also to amyloid plaque formation and neuroinflammation. Therefore, targeting BChE may be particularly beneficial in the later stages of AD.

Future therapeutic strategies should consider the stage-specific enzymatic environment of the AD brain. Selective BChE inhibitors, or dual inhibitors such as rivastigmine, offer promising avenues for addressing the evolving cholinergic landscape in AD. Moreover, the integration of personalized medicine—guided by biomarkers, genetic profiling, and imaging—could optimize treatment efficacy and safety. Continued research into the biological functions, distribution, and pharmacological modulation of BChE will be essential for developing more targeted, stage-specific, and effective interventions against Alzheimer's disease.

Acknowledgement

The authors would like to express their sincere gratitude to the Faculty of Pharmacy at Agri Ibrahim Cecen University for its valuable support and contributions throughout this research. This work was conducted as part of the undergraduate thesis projects.

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Chapter 3

SOME AROMATIC COMPOUNDS AND PHARMACEUTICAL APPLICATIONS

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1. Introduction

Aromatic compounds are basic building blocks with wide applications in the chemical industry. The benzene-based nature of these compounds makes their use in a variety of industrial and pharmaceutical applications possible due to their high response to chemical reactions (Tanker & Tanker, 1990). Among the main areas where aromatic compounds are widely involved are the pharmaceutical industry, paint industry, food additives production, plastics and resin industry (Faydalıoğlu et. al., 2011).

Some of the compounds examined in this study are isolated from natural sources, while others are synthetically produced by petrochemical processes. For example, compounds such as benzaldehyde and cinnamaldehyde are of vegetable origin, while compounds such as toluene, aniline, and acetophenone are obtained by industrial synthesis (Pérez-Mayoral et. al., 2023; Renfew, 1991; White, 2023). The pharmacological effects of such compounds have also gained traction in the scientific literature in recent years. The antimicrobial and antioxidant effects of phenolic compounds such as thymol and carvacrol have been investigated in detail (Chroho et. al., 2024). Structures such as benzaldehyde and anthracene attract attention due to their anticarcinogenic potential. Several anticancer drugs (e.g., doxorubicin, mitoxantrone) are based on anthracene-like scaffolds. Anthracene itself is not commonly used therapeutically due to potential toxicity, but its derivatives are foundational in chemotherapy (Gewirtz, 1999).

Within the scope of this study, the chemical structures, methods of obtaining, usage areas and pharmaceutical effects of certain aromatic compounds are presented comprehensively in the light of the literature.

2. General Information

2.1. Benzaldehyde

Benzaldehyde is a colorless and volatile liquid in the class of aromatic aldehydes. This compound, whose chemical formula is C_6H_5CHO, is naturally found in almond, apricot, and cherry pits. Industrially, it is usually produced by oxidation of toluene or chlorination process. Its boiling point is about 179 °C, and it is known for its characteristic bitter almond smell (Catalano et. al.,2024).

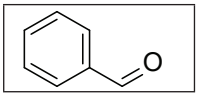

Figure 1: Benzaldehyde structure

Uses: Benzaldehyde is widely used in the food and cosmetics industries as a perfume and flavoring agent. It also plays an important role in the chemical industry as an intermediate for dyestuffs and pharmaceuticals. It is classified as a food additive (E1518) (Teaf et. al., 2015).

Pharmaceutical and Biological Effects: Recent studies have revealed that benzaldehyde may exhibit anti-carcinogenic properties. Chitosan-modified benzaldehyde forms biodegradable composites, and these structures have the potential for anti-tumor activity (Ding & Guo, 2022). It also requires controlled use, as it can cause irritation to the throat and respiratory tract if inhaled (Renfew, 1991).

2.2. Thymol and Carvacrol

Thymol and carvacrol are natural monoterpenes of a phenolic nature. These compounds are known for their particularly potent antimicrobial and antifungal effects (Rodriguez & Pérez, 2024). Chemically, thymol has the formula $C_{10}H_{14}O$ and is crystallizable. Carvacrol, on the other hand, has a similar structure, but is non-crystallizable and has a more volatile character (Tanker & Tanker, 1990; Mączka et. al., 2023).

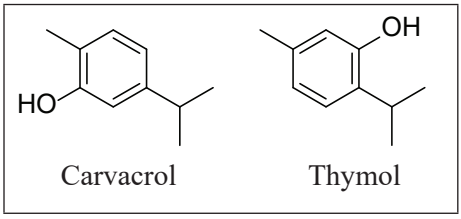

Figure 2: Carvacrol and Thymol structure

Uses: Thymol is used in mouthwashes and topical drug formulations for its antiseptic properties. It is also used as a flavoring and preservative in the perfumery, cosmetics, and food industries. Carvacrol, on the other hand, is especially valuable as a natural preservative to prevent spoilage in foods (Chroho et. al., 2024).

Pharmaceutical Effects: The antimicrobial, antioxidant and anti-inflammatory effects of thymol and carvacrol have been widely documented in the literature. Carvacrol has been reported to have an inhibitory effect in some studies, especially on lung cancer cells; however, this effect has not yet been confirmed by clinical trials. (Sampaio et. al., 2021; Gan et. al., 2025).

2.3. Cinnamaldehyde

Cinnamaldehyde ($C_6H_5CH=CHCHO$) is a natural aromatic aldehyde found in high proportion in nature, especially in cinnamon bark. This compound has a characteristic sweet, spicy aroma and is widely used as a flavoring and fragrance in food and cosmetic products (Cocchiara et. al., 2005).

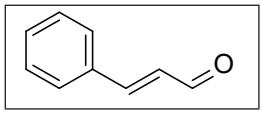

Figure 3: Cinnamaldehyde structure

Uses: Cinnamaldehyde is used as a sweetener and preservative in beverages, chewing gums, toothpastes, and other food products. In industry, it is used in the production of protective films thanks to its polymerizable structure that covers metal surfaces. Thanks to this property, cinnamaldehyde can protect steel surfaces against corrosive substances (Qu et. al., 2019).

Pharmaceutical Effects: In traditional medicine, it is used for digestive system disorders such as appetite suppression, gas and indigestion. In addition, some studies have shown that cinnamaldehyde has anti-inflammatory and antimicrobial properties (Haldar et. al., 2022).

2.4. Aniline

Aniline ($C_6H_5NH_2$) is a colorless liquid with a slightly oily structure, which is in the group of aromatic amines. It is obtained during the distillation of hard coal tar or by the reduction of nitrobenzene. When it comes into contact with light and air, it undergoes oxidation and turns brown (Anjalin et. al., 2020).

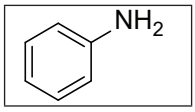

Figure 4: Aniline structure

Uses: Aniline is a key raw material, especially in the production of dyestuffs. Dyes such as aniline hydrochloride and aniline black are used

in the textile and leather industries. It is also involved in the pharmaceutical, resin, rubber and perfumery industries (Kirk, 1991).

Toxicological Properties : Aniline can inhibit oxygen transport by causing methemoglobinemia in the body. Therefore, care should be taken during its processing and use (Amini & Lowenkron, 2000).

2.5. Toluene

Toluene (C_7H_8) is in the class of aromatic hydrocarbons and is also known as methylbenzene. It is a colorless liquid with a characteristic odor. In industry, it is most often used as a solvent. The fact that it is less toxic than benzene has made toluene more preferable in industry (Rodriguez & Pérez, 2024).

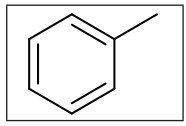

Figure 5: Toluene structure

Obtained: Today, toluene is obtained from pyrolysis gasoline by catalytic degradation and fractional distillation of kerosene. It is also collected as a by-product in the production of styrene.

Uses: As a solvent, it is common in paints, varnishes, and adhesives. It is a main ingredient in the production of plastics, ink formulations, and TNT (trinitrotoluene). It is also used in biochemistry laboratories to reveal hemoglobin by breaking down red blood cells (Renfew, 2016).

2.6. Acetophenone

Acetophenone ($C_6H_5COCH_3$) is one of the simplest aromatic ketones. It is a colorless and viscous liquid, with a pleasant odor. It is formed as a by-product during the oxidation of ethylbenzene. It is also obtained as an intermediate in the production of styrene and propylene oxide (Kirk, 1991).

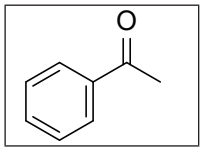

Figure 6:Acetophenone Structure

Uses: Acetophenone, which is used in the production of resins and inks, is also used as a flavoring agent in some chewing gums and food products. Thanks to its polymerization reactions with formaldehyde, it is valuable in the production of adhesives and coatings (PubChem, 2025).

Pharmacological Properties: In the 19th century, it was used as a hypnotic and anticonvulsant under the trade name "Hypnone". It has been accepted that it has a sedative effect at low doses. It is metabolized in the body to benzoic acid and hippuric acid (Kirk, 1991).

2.7. Benzoic Acid

Benzoic acid (C_6H_5COOH) is a white, crystalline solid in the class of aromatic carboxylic acids. It has low solubility in water. It is one of the most well-known preservative additives and is used in foods with the code E210 (PubChem, 2025).

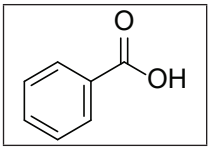

Figure 7: Benzoic Acid structure

Uses: Benzoic acid and its salts are used to prevent microbial spoilage in foods. It is especially preferred in acidic products such as fruit juices, pickles and carbonated drinks. It is also found in cosmetic products and antifreeze additives (Elvers, 1991).

Industrial Role: Most of the commercially produced benzoic acid is used as an intermediate in the production of phenol and caprolactam. In analytical chemistry, it is considered the reference standard (Elvers, 1991).

2.8. Phenol

Phenol (C_6H_5OH) is one of the simplest aromatic alcohols in which the hydroxyl group is directly attached to an aromatic ring. It exists in colorless or slightly pink crystalline form in pure form. It is partially soluble in water and shows weakly acidic properties. Although it is not an alcohol, it undergoes many chemical reactions due to the characteristic acidity of the phenolic hydroxyl group. Its purple coloration with FeCl3 solution is the identification reaction (Tanker & Tanker, 1990).

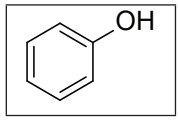

Figure 8: Phenol structure

Uses: Phenol has been used as a surgical disinfecting agent in the past with its antiseptic properties. Today, it is found in low concentrations in household cleaning products and mouthwashes. In addition, phenol is an important raw material in the production of plastics (especially phenol-formaldehyde resins), paints, explosives (picric acid), and pharmaceuticals (PubChem, 2025).

Natural and Synthetic Sources: Phenols are commonly found in nature in compounds such as thyme (thymol), cloves (eugenol), tyrosine, and serotonin. Synthetically, it is obtained by hydrolysis of chlorobenzene or oxidation of isopropylbenzene (cumene) (Elvers, 1991).

Pharmaceutical and Toxicological Effects: Phenol is highly toxic and can cause painless burns to the skin and mucous membranes. Therefore, it requires controlled use. In contrast, less toxic phenols (e.g., N-hexylresorcinol) are used in medicinal preparations, while derivatives such as butyl hydroxytoluene (BHT) are considered food antioxidants (Schmidt, 2023).

2.9. Anthracene

Anthracene ($C_{14}H_{10}$) is a polycyclic aromatic hydrocarbon (PAH) formed by the linear union of three benzene rings. It is in the form of colorless or slightly white crystals; however, it shows blue fluorescence under UV light. It is insoluble in water, but highly soluble in organic solvents (Somashekar & Chetana, 2016).

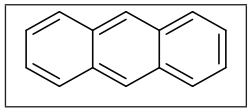

Figure 9: Anthracene structure

Uses: Anthracene is used as an intermediate in the production of dyes and pigments, especially in the synthesis of anthraquinone. Wood is also found in preservatives, insecticides and agricultural chemicals. It is used as an additive in the production of synthetic detergents and plastics (PubChem, 2025).

Pharmaceutical and Technological Applications: Anthracene derivatives (especially anthracyclines) play an important role in the development of chemotherapy drugs. These compounds, which act intercatively to DNA, provide an antitumor effect by stopping cell division. It is also involved in radiation detectors and dosimetric materials thanks to its scintillation properties (Renfew 2016; Shandilya et. al., 2020).

3. Conclusion

The chemical structures and functions of the aromatic compounds examined within the scope of this study reveal that they have versatile uses in various industries. Some compounds, such as benzaldehyde and thymol, are noted for their anticancer potential, while others find wide use as an antiseptic, solvent or preservative additive.

Considering the pharmaceutical and industrial potentials of aromatic compounds, it is of great importance to conduct more comprehensive research, discover new areas of use and evaluate them in biotechnological applications in the future. In particular, further studies on cancer treatment, antimicrobial agents and biologically active compounds will enable these compounds to be considered in a broader perspective in terms of health sciences.

Acknowledgement

This study was prepared from Serhat Bayram's Aromatic Compounds Lesson Research Study.

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Chapter 4

USE OF NATURAL PRODUCTS CONTAINING FURAN IN DRUG DESIGN

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1. Introduction

Furan is a heterocyclic organic compound formed by one oxygen atom and four carbon atoms in an aromatic ring (Figure 1) (Nivrutti 2024). The name Furan comes from the Latin word "furfur", which means "dandruff". In 1780, pyromusic acid (2-furoic acid), the first discovered furan compound, was found (Chandrashekarachar & Kesagudu, 2017). In 1832, Döbereiner discovered furfural, an important furonic compound, when he was reacting manganese oxide with sulfuric acid and sugar. In 1869, Limpricht was the first to propose that furan-derived compounds were derivatives of cyclic hydrocarbons as they are known today (Iroegbu et. al., 2020).

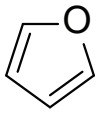


Figure 1: Furan ring

Furan is a country whose boiling point is close to room temperature, (31^0C) is a colorless, flammable and highly volatile liquid. It is soluble in organic solvents such as alcohol, ether, acetone, while it is slightly soluble in water. Its smell is quite strong and similar to ether chloroform (Manchare & Kanawade, 2023). Compounds containing furans; It is commonly found in food products, perfumes, synthetic drugs, natural herbal preparations, and environmental pollutants (Tian et. al., 2022). Furan; Of the foods, it is found in coffee, canned meat, bread, cooked chicken, sodium caseinate, nuts, canned fish protein and caramel. The primary source of furan formation in these foods is the thermal degradation of carbohydrates such as glucose, lactose, and fructose (Vranova & Ciesarova, 2009). Processes that cause furan formation include heat treatment of some foods containing vitamin C, amino acids, sugars, organic acids, carotene and PUFA (Alizadeh et. al., 2018).

Heterocyclic compounds are of critical importance in medicinal chemistry. The furan ring is one of these heterocyclic compounds. In drug discovery, furans, which can be obtained both synthetically and naturally, have potential in the synthesis of many drugs (Manchare & Kanawade, 2023). furanoflavonoids can be found in many different species, especially furanolactones, furanocoumarins, and various types of terpenoids (Banerjee et. al., 2015). These species can be found in the fruits of plants, their oils, and a variety of natural products such as seafood. The furan

ring can form the basal skeleton of numerous compounds with cardiovascular activities. These compounds are widely used due to their various effects such as antibacterial, antiviral, anti-inflammatory, antifungal, antitumor, antihyperglycemic, analgesic, anticonvulsant. Recent research has found that natural furans have positive biological activities such as antioxidant, antiproliferative, antiviral, and immune regulator (Alizadeh et. al., 2020). In animal studies, it has been shown that fura is absorbed quickly and intensively from the intestines and lungs, and due to its low polarity, it has been determined that it can enter various organs by passing through biological membranes (Vranova & Ciesarova, 2009). Furans can inactivate cytochrome P450 enzymes based on mechanism and cause potential drug-drug interactions when used in combination with other drugs. Despite their beneficial activities, a large number of furan-containing products have been found to have various toxic effects, especially liver damage, lung and kidney toxicity, and nervous system damage in rodents or humans. It has been categorized as a probable human carcinogen (class 2B) by the National Ministry of Toxicology and the International Agency for Toxicology (Tian et. al., 2022).

2. General Information

2.1. Sources of Natural Products Containing Furan Ring

2.1.1. Types of Terpenoids

It has been proven in studies that furanoditerpenoid, especially furanoditerpenoid, shows important biological activities. Major families containing furanoditerpenoids include Euphorbiaceae, Fabaceae, Lamiaceae, and various species of Asteraceae. These plants are used in traditional medicines, and furanoditerpenoids have been found to have anticancer, anti-inflammatory and antimicrobial bioactivities. Salvinorin A, derived from the furanoditerpenoid species Salvia divinorum, has been proven to induce psychoactive experiences in humans and has been used as an analgesic (Figure 2). Kahweol, another type of furanoditerpenoid, has been found to have inhibition, anti-inflammatory and antiangiogenic effects on osteoclast differentiation (Bao et. al., 2017). Terpenoid species are also quite commonly found in seafood. Heterocyclic structures are found in many seafood, especially sponges, corals and fungi. The tetrahydrofuran structure isolated from these substances has been found to show antitumor, antiprotozoal, antibacterial, antioxidant and cytotoxic activity against cancer cells (González-Andrés et. al., 2022).

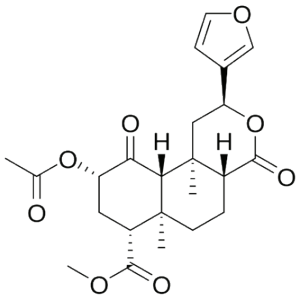


Figure 2: Salvinorin A structure

2.1.2. Furanoflavonoids

Pharmacological activities of furanoflavonoids include antifungal, antibacterial, antituberculosis, anti-inflammatory, and insecticidal effects (Maurya & Yadav, 2005). Derris indica (Lam.) plant has been used in folk medicine in the treatment of bronchitis, whooping cough, rheumatic joints and has been said to relieve indigestion in diabetic patients (Figure 3). In recent years, antidiabetic effects have been detected in the fruits and flowers of this plant. Moderate α-glucosidase inhibition and potent DPPH radical scavenging activity of plant-derived furanoflavonoids have been detected (Rao et. al., 2009).

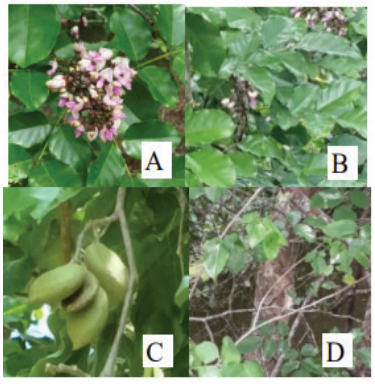


Figure 3: The flower (A), leaf (B), fruit (C), and branch (D) of the Derris indica plant (Vittaya et. al., 2023).

Furanoflavonoids also play a role in reducing the risk of cardiovascular diseases by lowering blood lipid levels.*Indigofera tinctoria* Strong antidyslipidemic efficacy of furanoflavones isolated from above-ground parts

was found in the experiments (Narender et. al., 2006). Karanja (*Pongamia pinnata*) is a tree used in the Indian traditional Ayurvedic system to treat various diseases. The seeds of this tree contain carangin, a furanoflavonoid with many medicinal properties **(**Figure 4**)**. Clovein has insecticidal, antihyperglycemic activity, anti-herpes and anti-HIV activities. Carangin in its raw form has been found to inhibit lipoxygenase-1. In addition, this compound is used in the treatment of psoriasis by scavenging nitric oxide and also acts against colitis (Rekha et. al., 2021).

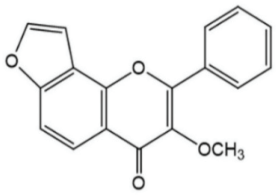


Figure 4: Karanjin structure

2.1.3. Furanolactones

Columbine is important in furanolactones, another furan ring-containing natural compound, due to its structural similarity to salvinorin A (Figure 5). This compound, which is isolated from the roots of Jateorhiza and Tinospora species, has been used in folk medicine due to its analgesic and antipyretic effects (Anil & Saylor, 2017). Diabetes is a major metabolic disease that arises due to either a complete lack of endogenous insulin or the body's reduced responsiveness to it at the peripheral level. Recognized as a chronic illness that necessitates continuous clinical management, diabetes mellitus (DM) is linked to high rates of illness and death across the globe, affecting populations in both industrialized and developing nations. In addition to its significant health consequences, DM imposes serious social and economic strains, severely impacting the well-being of millions. It continues to rank among the top causes of global mortality (Magliano, Boyko & Atlas, 2021).

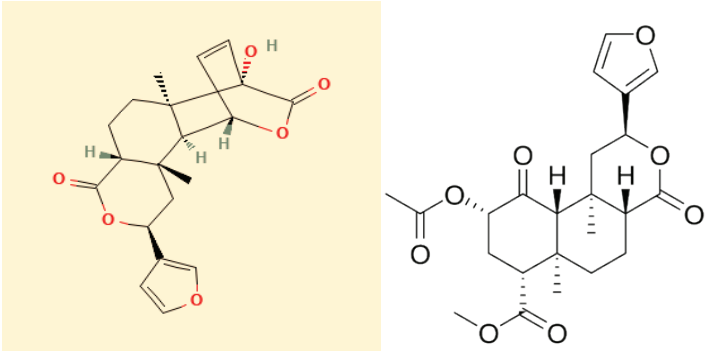


Figure 5: Columbine and salvinorin A structure

Artemisinin, a derivative of furanolactone, was isolated from *Artemisia annua* L. by a team from the Academy of Traditional Chinese Medicine and became the second natural compound used in the treatment of malaria after quinine (Figure 6). It was recognized as a first-line antimalarial drug, especially after the emergence of chloroquine resistance in the 1950s (Ma et. al., 2020). Artemisinin derivatives start to act quickly and have a short-term effect. The rapid onset of action allows them to be used especially in patients with severe malaria. The short duration of their effects slows down the development of resistance to artemisinin derivatives. The antimalarial effect of artemisinin is related to the endoperoxide bridge in its structure. This bridge breaks down on contact with heme (iron-containing compound), forming free radicals and damaging parasites. It does not harm healthy cells because these reactions occur in malaria parasites with high iron content. Parasites of the genus Plasmodium cause damage to the cell membrane, mitochondria, endoplasmic reticulum, and nutrient vacuole membrane (Meshnick, 2002).

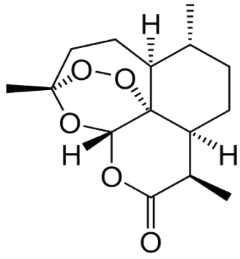


Figure 6: Structure of artemisinin (Dondorp et. al., 2010).

2.1.4. Furanocoumarins

Furanocoumarins are a class of organic compounds derived from the fusion of a furan ring and a coumarin compound (Dembitsky, 2024). Furanocoumarins are found in abundance in the Fabaceae and Rutaceae, especially in the Apiaceae family. It can be found in the leaves, fruits, roots and rhizomes of plants (Wink, 2015). Angelica archangelica fruit is one of the highest known sources of furanocoumarin. The furanocoumarins contained in the plant have a strong photosensitizing effect that can cause skin irritation, abnormal pigmentation, itching and erythema. Despite these effects, sufficient amounts of compounds are used in the treatment of skin lesions (vitiligo and psoriasis). Dihydroxide furanocorins, on the other hand, have spasmolytic and vasodilator effects. The most abundant furanocoumarin in the root and fruit of this plant is imperatorin (Figure 7). (Forycka & Buchwald, 2019). The compound, which has $C_{16}H_{14}O_4$ molecular formula, is synthesized in plants through shikimic acid, like other furanocoumarins (Kozioł & Skalicka-Woźniak, 2016). Imperatorin, which has a wide range of pharmacological activities, has anti-cancer, neuroprotection, anti-inflammatory, antihypertension and antibacterial effects (Deng et. al., 2020).

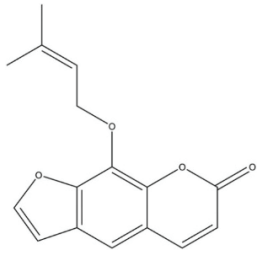


Figure 7: Structure of the imperator

2.1.5. Furan Fatty Acids

Fatty acids make up a large class of compounds that have many functions in cells. These hydrophobic compounds provide integrity for biological membranes, protect against toxins, and regulate the cellular response according to signals or stresses (Lemke et. al., 2014). Furan fatty acids are a class of heterocyclic fatty acids with a furan ring in the center of the molecule. Furan fatty acids with methyl or dimethyl substitutions in the furan ring are known as minor fatty acids in foods and are found in various places in the lipids of various fish, such as grass, wheat, potato, soybean oils (Alizadeh et. al., 2020). Furan fatty acids are photolaid, which

makes them very difficult to isolate. They are difficult to use as a standard during analysis. Known for their antioxidant properties, furan fatty acids are powerful radical scavengers that can protect polyunsaturated fatty acids (PUFAs) in biological systems from lipid peroxidation. (Mawlong et. al., 2016). Carlina oxide, which is obtained by steam distillation of the roots of the Carlina acaulis plant, which is very rich in furan fatty acids, has been used for a long time in Europe, especially due to its antimicrobial properties (Figure 8). It has been proven to be particularly effective against the MRSA strain and to show strong and selective activity against Trypanosoma brucei brucel, the parasite that causes African trypanosomiasis (sleeping sickness) (Smith, 2012). Carlina acaulis L., a member of the Asteraceae family, belongs to the dry and calcareous soils of the mountains of Southern and Central Europe. When this plant is used with sulfur, it is used in the treatment of skin exudates and various dermatological diseases, such as pustules, scars and skin cracks. It is also used in the treatment of ulcerations, skin infections, and swelling (Rosato et. al., 2021).

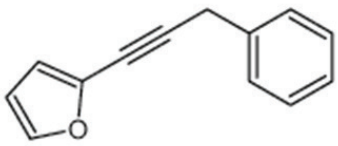


Figure 8: Carlina Oxide structure (Spinozzi et. al., 2023).

2.1.6. Benzofurans

Benzofuran is a heterocyclic compound formed by the fusion of benzene and the furan ring (Khanam, 2015). Natural products containing benzofuran ring are an important raw material of new drugs due to their various biological activities (Table 1). These activities include various effects such as anti-tumor, antibacterial, anti-oxidative, anti-inflammatory. Benzofuran compounds are found in the families *Rutaceae*, *Liliaceae*, and *Cyperaceae*, primarily *Asteraceae* (Miao et. al., 2019).

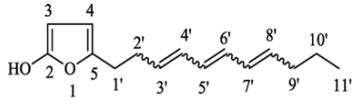
Table 1: Uses and sources of natural furan derivatives (Alizadeh et. al., 2020).

Furan derivatives	**Source**	**Effect**
Furano coumarins	Fruits (lemon peel, grapefruit), Vegetables (parsley, celery)	-Protection against lipid peroxidation -Inhibition of cyclooxygenase and lipoxygenase -Strengthening of enzymatic and non-enzymatic antioxidants
Benzofurans	Some trees (mulberry tree) and plants	-Suppression of $_{O2}$ production by neutrophils -Inhibits the production of nitric oxide (NO) -Alters MAPK pathways and PPAR-ɣ gene expression
Furan fatty acids	Fish, Herbs, Wheat, Potato, Soybean oils	-Hydroxyl radical scavengers -Antioxidant activity -Reduces mitochondrial dysfunction
Agarofurans	Some fruits and seeds	-Chelation of transition metal ions -Downregulation of NF-κB gene expression
The furanons	Some marine organisms, pineapple, mushrooms	-Inhibits the activation of NF-κB and MAPK pathways -Superoxide anion cleaners -Inhibits peroxidation

2.2. Pharmacological Activities of Natural Products Containing Furan Ring

2.2.1. Antibacterial activity

Infectious diseases have begun to seriously threaten human health in recent years. Since pathogenic bacteria are constantly developing resistance mechanisms, the discovery of new drugs has become a necessity. Furan ring-containing organic compounds are important candidates for new drugs (Venkateshwarlu et. al., 2013). Two new alkylated furan derivatives were found in the fungus strain Emericella sp. XL029 isolated from the leaves of the Panax notoginseng plant. The obtained furan derivatives showed moderate inhibitory activity against all agricultural pathogenic fungi and against 8 of the 13 bacterial species tested (Figure 9) (Wu et. al., 2018).



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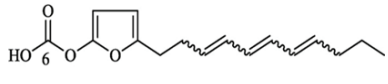

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Figure 9: Furan derivatives isolated from Emericella sp. XL029

Usnic acid can be counted among the organic furan compounds with antibacterial effects. Usnic acid is a lichen-derived secondary metabolite with broad biological effects. It is commonly found in Cladoniaceae, Usneaceae, Lecanoraceae, Ramalinaceae, and Parmeliaceae. Dibenzofuran contains the skeleton. In addition to its antibacterial effects, it exerts various activities such as anti-inflammatory, antiviral, anticancer and analgesic (Luzina and Salakhutdinov 2018). There are no synthetic derivatives of usnic acid, which is obtained completely naturally. It is effective against various strains of gram-positive bacteria. In particular, it inhibits the growth of streptococcus aureus, enterococci and mycobacteria (Cocchietto et. al., 2002). The mechanism of action of usnic acid on bacteria has been found to strongly inhibit the synthesis of RNA and DNA (Maciąg-Dorszyńska et. al., 2014).

2.2.2. Anti-inflammatory activity:

Inflammation is a biological response to infections, tissue damage and irritants, and it activates and eliminates inflammatory cells against these stimuli. Acute inflammation is the sudden onset of any infection or harmful stimulus. It causes pain, redness and swelling mediated by the production of pro-inflammatory markers such as leukotrienes, prostaglandins, histamine and thromboxanes, which elicit acute infection. An inflammatory condition that is not treated on an ongoing basis can lead to chronic diseases such as arthritis, cancer, cardiovascular diseases, and diabetes. The use of NSAIDs is needed to treat the inflammatory condition (Rekha et. al., 2021). Most of the NSAIDs on the market may cause serious side effects such as gastrintestinal bleeding and nephrotoxicity when used for a long time. For this reason, studies are being carried out for the discovery of new and more powerful anti-inflammatory drugs (Navidpour et. al., 2014). It has been found in experiments that furanocoumarins obtained from the stem shell of Moraceae, one of the natural products containing furan rings, have an anti-inflammatory effect. In the experiment, the effect of carrageenan-induced foot edema, which is a type of inflammation in chicks, was determined. Inhibiting effect of furanocoumarins obtained from Kaffir lemon on Inducible Nitric Oxide Synthase and COX-2 production has been found (Alizadeh et. al., 2020). The green-lipped mussel, Perna canaliculus, occurs off the coast of New Zealand and is one of the main food sources of the indigenous Maori culture in coastal areas. Compared to the inland Maori people, the incidence of arthritis is very low in coastal areas who consume this food. After it was predicted that this food could be made an anti-inflammatory drug in the future, researches were carried out. Perna canaliculus underwent various processes to obtain a lipid-rich extract. The resulting extract was found to contain five major classes of lipids, including sterol esters, triglycerides, free fatty acids, sterols, and

polar lipids. Studies have found that the anti-inflammatory effect of mussels is due to the furan fatty acids it contains (Wakimoto et. al., 2011).

2.2.3. Antioxidant activity

Furan fatty acids can have antioxidant and radical scavenging effects and are considered to be important bioactive compounds that can protect sensitive polyunsaturated fatty acids (PUFA) from oxidation (Buscato et. al., 2020). In general, it is a common opinion that plants containing PUFA show antioxidant activity. The idea that furan fatty acids exhibit antioxidant activity comes from the fact that they protect PUFAs from oxidation. The antioxidant activity of naturally occurring furan acids on the oxidation of linoleic acid has been observed. Lipoxygenase 1 oxidizes linoleic acid to produce peroxy radicals. Furan fatty acids react with the peroxy radical and thus act as a natural radical scavenger (Mawlong et. al., 2016).

2.2.4. Anticancer activity

Cancer is a disease characterized by the uncontrolled growth and spread of normal cells and causes a significant number of deaths in the world. Among the causes of cancer are errors in genetic material, enzymes and proteins involved in the control of cell growth and proliferation. Problems in cancer treatment include the high resistance of cancer cells and damage to normal cells when targeting cancer cells. Natural products containing furanocoumarins and derived furan ring are being seriously researched to develop safer and more effective anticancer drug structures. 8-hydroxypsoralene, a furanocoumarin derivative isolated from the fruits of Wample (Clausena lansium) shells, was determined to show antiproliferative activity against various cells (Figure 10). The anticancer activity of this compound is associated with mitosis cell disruption at the telophase stage and reduces the amount of cellular protein, mitotic index, and colony formation during cell proliferation (Bhattarai et. al., 2021).

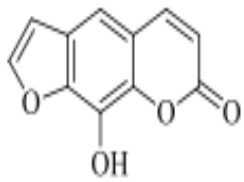

Figure 10: Structure of 8-hydroxypsoralen (Bhattarai et. al., 2021).

Xanthotoxin, one of the other types of furano coumarins and bergapten (Figure 11) showed cytotoxic activity against malignant cancers MPR2, MDR1, and BCRP Xanthotoxin appeared to inhibit the growth of neuroblastoma and metastatic colon cancer cells through intrinsic and extrinsic apoptotic induction (Bhattarai et. al., 2021).

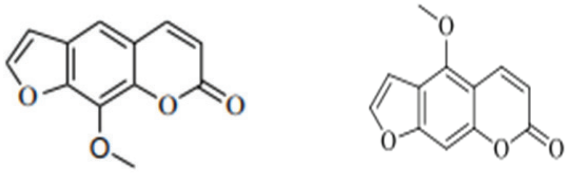

Figure 11: Structure of Xanthotoxin and Bergapten

2.2.5. Antifungal activity

Fungal infection has become a serious threat to humanity, causing high morbidity and mortality worldwide every year. Fungal infection can occur frequently, especially in patients with weak immune systems. Therefore, it is necessary to discover new antifungal active substances with low toxicity and high bioavailability. In recent years, heterocyclic compounds have come to the fore with their antifungal activities (Tighadouini et. al., 2020). Sesamin is a very important furan derivative against fungal infections such as candida, which occur in diabetes, cancer, AIDS, organ transplantation and immunosuppressed conditions (Figure 12). This drug can be targeted against the enzyme exo-1,3-β-glucanase in candida species, disrupting their structure. This enzyme is very important in the remodeling of the cell wall in candida species. Helping to maintain the shape and integrity of the cell, exo-1,3-β-glucanase is also involved in the regeneration of the cell wall (Wadhwa et. al., 2023).

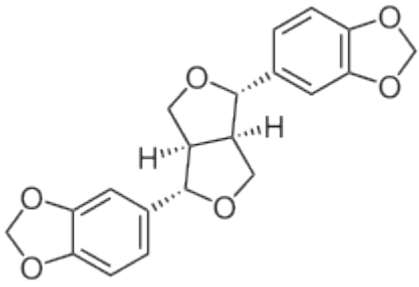

Figure 12: Structure of Sesamin

2.2.6. Vasodilator activity

Khellin is a furanocoumarin-derived compound derived from the Ammi visnaga plant (Figure 13). It is traditionally used for medicinal purposes due to its antispasmodic and vasodilator effects. It helps to get more oxygen to the heart muscle by widening the coronary arteries. Its advantage over other agents includes its effect on dilating the coronary vessels without lowering blood pressure or affecting the heart muscle. The number of anginal attacks decreased and cardiovascular tolerance increased in patients treated with Khellin. Drug-induced dependence has not developed (Anrep et. al., 1949).

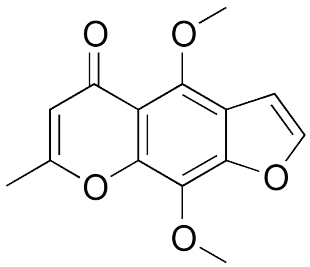

Figure 13: Khellin's structure

2.2.7. Antiparasitic activity

*Trichomonas vaginalis*is an anaerobic, flagellated protozoan parasite that affects the urogenital tract in humans and causes trichomoniasis, the most common non-viral sexually transmitted infection in the world. It is estimated that there are 276 million cases of this disease per year. *Trichomonas vaginalis, premature birth,* It can increase the risk of pelvic inflammatory disease and HIV acquisition and transmission. For a long time, in most countries *T. vaginalis*It is limited to 5-nitroimidazoles in its treatment and the drugs approved by the US Food and Drug Administration are used as metronidazole and tinidazole, but the development of resistance to these drugs over time has made the discovery of new drugs mandatory. The antimalarial, antitumor, antifungal and antibacterial activities of N-acylhydrazone derivatives are known. Considering the antibacterial, antiviral, anti-inflammatory, antifungal, antitumor, etc. activities of furan derivatives, furanyl N-acylhydrazone (Figure 14). compound was designed by molecular hybridization technique. In silico and biochemical analyses have shown that these compounds can target the parasite's energy metabolism and antioxidant defense system. At the same time, it has been determined that the nitro groups of these compounds can act by disrupting the redox balance of the parasite (Alves et. al., 2020).

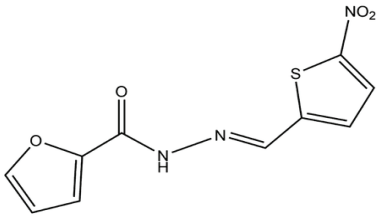

Figure 14: Furanyl N-acylhydrazone structure

2.2.8. Neuroprotective activity

The most common neurodegenerative diseases known in the world include Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. The term neurodegenerative disease is collectively used for non-communicable neurological disorders. These individuals have difficulty in using their physical movement, critical thinking, cognitive function, mental orientation, speech, memory, and motor skills. The main problem in the treatment of these diseases is that the drugs given for the underlying conditions are temporary and not a permanent treatment. Bioactive compounds in the class of flavonoids have neuroprotective effects through various mechanisms such as modulation of NF-kB pathway, inhibition of oxidative stress, modulation of PI3K/Akt. Karangin has been proven to be effective in diseases such as Alzheimer's and Parkinson's through modulation of molecular targets such as adenosine A2A receptor, α-synuclein, catechol-O-methyltransferase, monoamine oxidase B, angiotensin-converting enzyme, β-zone APP cutting enzyme, glycogen synthase kinase-3, TNF-α converting enzyme and acetylcholinesterase, which play instrumental in the progression of these diseases. In addition, this compound has the ability to cross the blood-brain barrier thanks to its furan ring, has an antioxidant and anti-inflammatory effect. The oral bioavailability of carangin is good, but alternative routes of administration (such as intranasal) may increase the plasma level and efficacy. In addition, its interaction with the gut microbiota may enhance its effect on the brain (Gnanaraj et. al., 2024). Eudesmin (Figure 15), another furan-derived compound, shows a neuroprotective effect by suppressing A β aggregation and preserving synaptic function. Eudesmin isolated from the Araucaria araucana tree native to Chile It also has properties such as anti-inflammatory, cytotoxic, antifungal, antibacterial, immunostimulant and nitric oxide (NO) inhibitor (Castillo et. al., 2023).

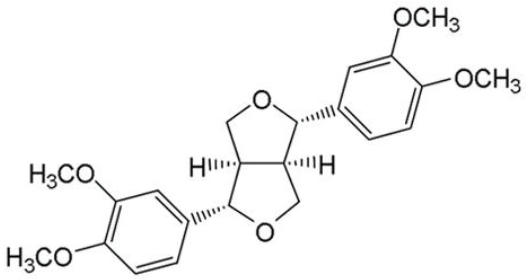

Figure 15: Eudesmin structure (Jiang et. al., 2015).

2.2.9. Antihyperglycemic activity

Diabetes mellitus is one of the risk factors for the development of coronary artery disease, myocardial infarction, hypertension and dyslipidemia. Clinically, patients with diabetes are characterized by an increase in blood glucose level, followed by mild hyperlipidemia. The fastest growing threat to public health is non-insulin-dependent diabetes melittus, which accounts for about 85% of all cases. There is an increase in this disease with the consumption of calorie-rich foods. Although existing drugs are used in the treatment of diabetes, interest in natural remedies has increased due to their potential for side effects (Reddy et. al., 2009). The number of natural resources used to reduce the intensity of diabetes is also very limited. Osthol, one of the furanocoumarins with antidiabetic effects, relieves hyperglycemia in mice. Retinoid X receptor of psoralen (Figure 16) derivatives obtained from Radix Angelicae dahuricae -αIt has been found to affect the transcriptional regulation of enzymes, and this effect is being used in various diseases, especially diabetes and obesity. Another furanocoumarin is *Byakangelicin* It is being investigated that it may be an aldose reductase inhibitor for the treatment of diabetic cataracts (Shalaby et. al., 2014).

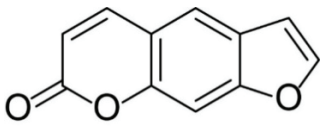

Figure 16: Structure of Psoralen (Ren et. al., 2020)

3. Conclusion

Heterocyclic compounds are critical in the discovery of new drugs. Their wide range of biological activities is that they are obtained both synthetically and naturally, and due to their wide biological activity and low polarity, they can pass through biological membranes and enter various organs over other compounds. Furans; They are found in nature as furanoflavonoids, furanocoumarins, furanolactones, furanoterpenoids, benzofurans, and furan fatty acids. Isolation of furans from other compounds is usually done using extraction and chromatographic methods. With the development of resistance of bacteria to the antibiotics used today, new drugs need to be found. For this reason, the antibacterial properties of furans are very important. The anticancer activity of furans has also been found in experiments. It has been determined that it suppresses the proliferation of tumor cells, triggers apoptosis and antioxidant activities. In long-term use of anti-inflammatory drugs on the market, it may cause side effects such as gastrointestinal bleeding and nephrotoxicity. The anti-inflammatory effects of furanocoumarins can be used to invent new drugs. However, more research is required on the toxicity profiles, metabolic stability, and pharmacokinetic and pharmacodynamic properties of these bioactive compounds. Its effects on the human body should be comprehensively studied through clinical studies.

After all; Natural products containing furans have been identified as having versatile and promising potential in drug design. More scientific data need to be obtained on the pharmacological efficacy and safety of these compounds.

Acknowledgement

This study was prepared by my student Mustafa KARAKALE from Agri İbrahim Cecen University Faculty of Pharmacy research project thesis.

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Chapter 5

TYPE 3 DIABETES

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1. Introduction

Dementia refers to a collection of disorders characterized by a progressive decline in cognitive functions, including memory, executive capabilities, and the ability to carry out everyday activities independently. This condition typically deteriorates over time. While it predominantly affects elderly individuals, it is not an inevitable outcome of the aging process itself. Factors that elevate the risk of developing dementia encompass advanced chronological age (with a higher incidence observed in those 65 years and older), systemic hypertension, elevated blood glucose levels (diabetes mellitus), excess body weight or obesity, cigarette smoking, excessive alcohol consumption, physical inactivity, social isolation, and clinical depression. It is essential to distinguish dementia from other forms of cerebral injury or disease that directly or indirectly damage the brain. The boundaries between different types of dementia can be indistinct, and mixed forms frequently co-occur. Alzheimer's disease (AD) is recognized as the most prevalent form, potentially accounting for 60-70% of all dementia cases globally (WHO).

2. General Information

2.1. Alzheimer's Disease

Alzheimer's disease (AD) stands as a significant worldwide health challenge, representing a progressive neurodegenerative disorder with a multifaceted etiology. It is estimated to be responsible for 60-70% of all dementia diagnoses. Clinically, AD is marked by an insidious onset of cognitive and behavioral impairments. Pathologically, it is defined by the extracellular deposition of amyloid-beta (Aβ) plaques and the intracellular aggregation of hyperphosphorylated tau protein, forming neurofibrillary tangles (NFTs). These characteristic neuropathological hallmarks are typically detectable approximately a decade before the manifestation of overt clinical symptoms, serving as crucial diagnostic biomarkers for AD. Concurrent with these cerebral lesions are profound synaptic dysfunction, widespread neurodegeneration, and neuronal dysregulation. Advanced age is consistently acknowledged as the most critical independent risk factor for the development of sporadic AD (SAD) (Michailidis et. al., 2022).

AD is inherently a multifactorial disorder, arising from a complex interplay of genetic predispositions, environmental factors, and lifestyle choices. The economic and societal burden imposed by AD on healthcare systems is substantial and is projected to escalate considerably in the coming decades. Despite extensive scientific inquiry and numerous clinical trials, the precise mechanisms driving AD pathogenesis remain

largely unelucidated, thereby impeding the development of effective disease-modifying therapies to date (González et. al., 2022).

The clinical spectrum of AD includes, but is not restricted to, profound memory deficits, alterations in personality, symptoms of depression and anxiety, and various other neuropsychiatric disturbances. Early and accurate diagnosis is of paramount importance for implementing interventions aimed at potentially slowing disease progression and managing its symptomatology. Contemporary research emphasizes that integrating information from diverse biomarkers significantly enhances the diagnostic power for cognitive disorders. Specifically, multimodal biomarkers such as Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), and cerebrospinal fluid (CSF) analyses provide complementary insights into AD pathophysiology. Recent advancements in artificial intelligence (AI) demonstrate substantial promise in improving the diagnostic and prognostic precision for cognitive disorders like AD by expertly extracting and synthesizing intricate information derived from brain-based biomarkers. These AI-driven methodologies leverage sophisticated feature selection and classification techniques applied to neuroimaging and other biomarker datasets to achieve superior accuracy rates (Tahernia et. al., 2023).

Two primary classifications of AD have been identified (Michailidis et. al., 2022):

1. Early-onset familial AD (FAD): This subtype constitutes a minor proportion of cases and is etiologically linked to specific genetic mutations, notably those in the amyloid precursor protein (APP) gene or the presenilin 1 and 2 (PSEN1/2) genes.

2. Late-onset sporadic AD (SAD): Comprising approximately 97% of all AD diagnoses, SAD is associated with a multitude of predisposing factors, including genetic polymorphisms of the Apolipoprotein E (APOE) gene, as well as prevalent comorbidities such as hyperlipidemia, systemic hypertension, Type II Diabetes (T2D), and coronary artery disease (CAD).

2.2. Type 2 Diabetes

Type 2 Diabetes (T2D), a pervasive chronic metabolic disorder, is experiencing a remarkable global surge in prevalence. A growing body of scientific evidence increasingly implicates T2D in the development and progression of neurodegenerative conditions, particularly AD. T2D is fundamentally characterized by dysregulated blood glucose levels, which originate from a generalized impairment in either insulin secretion, in-

sulin action, or both. A crucial pathogenic factor in T2D is the compromised responsiveness of insulin-sensitive tissues, such as the liver, adipose tissue, and skeletal muscle, to insulin's effects (insulin resistance). This insulin resistance invariably leads to hyperglycemia, a state defined by pathologically elevated concentrations of glucose in the bloodstream (González et. al., 2022).

T2DM has been consistently linked to an augmented susceptibility to cognitive impairment, encompassing both mild cognitive impairment (MCI) and overt dementia (Janoutová et. al., 2022). Empirical evidence indicates that T2D can elevate the risk of dementia and AD by 45% or more (González et. al., 2022). This robust correlative relationship supports the intriguing hypothesis that T2DM may play a causative role in the development of AD pathology (Janoutová et. al., 2022). Indeed, accumulating findings in recent years increasingly propose that AD could represent a cerebrum-specific variant of diabetes mellitus, termed "Type 3 Diabetes." Consequently, the imperative to incorporate insulin resistance into the established understanding of β-amyloid and tau protein's roles in peripheral nervous system and organ dysfunction is now recognized (González et. al., 2022).

2.3. Type 3 Diabetes

A notable convergence of pathophysiological mechanisms characterizes both T2DM and AD. These include chronic systemic inflammation, elevated oxidative stress, mitochondrial compromise, dysregulated insulin signaling, the accumulation of advanced glycation end products (AGEs), and the features associated with metabolic syndrome. The heightened susceptibility of the brain's neurovascular unit (NVU), neuroglia, and neurons to the deleterious effects of T2DM is attributed to a combination of age-related factors (e.g., chronic age-dependent disorders) and distinct metabolic perturbations (e.g., hyperglycemia, AGEs and their receptor interactions, hyperinsulinemia-induced insulin resistance, oxidative stress, inflammation, and remodeling of vascular and microvascular NVU/neuroglial components) (Janoutová et. al., 2022).

Despite its relatively modest mass, the human brain consumes approximately 20% of the body's total glucose, underscoring its immense metabolic demand, particularly for supporting synaptic activity. Within the cerebral context, an estimated 95% of glucose is utilized for the generation of adenosine triphosphate (ATP). Consequently, any disturbance in glucose metabolism can adversely affect cellular regulatory processes, and a reduction in ATP levels may precipitate impairments in synaptic function (Michailidis et. al., 2022).

Although a significant portion of cerebral glucose metabolism operates independently of direct insulin regulation, insulin receptors are widely distributed across various brain regions crucial for processes such as memory consolidation, cognition, and the regulation of energy homeostasis. Insulin resistance has been demonstrably shown to substantially increase the propensity for developing SAD, while the pre-existing diagnosis of T2DM further escalates the risk of AD (Michailidis et. al., 2022).

Prolonged exposure to states of hyperglycemia has been definitively linked to a decline in cognitive function and other aspects of mental well-being. Hyperglycemia exhibits a strong correlation with the emergence of cognitive impairment and dementia, suggesting a potential etiological link. Glucotoxicity can induce structural damage and functional derangement within cerebral cells and neurons, potentially leading to cerebral microhemorrhages and an enhanced accumulation of amyloid-beta. These are considered plausible underlying mechanisms in diabetes-associated dementia (Janoutová et. al., 2022).

Epigenetic modifications, such as glycosylations, have been implicated in disrupting proper protein folding and triggering endoplasmic reticulum (ER) stress. Specifically, glycosylations influence post-translational modifications of the Tau protein, thereby facilitating its self-assembly from an alpha-helical conformation into a beta-sheet structure. The latter conformation is inherently prone to aggregate formation. In the context of AD, observations include an increase in phosphorylation, concomitant with reductions in ubiquitination and methylation. Particularly, diminished lysine methylation has been noted in AD patients. This phenomenon is explained by reduced glucose uptake stemming from the downregulation of GLUT receptors. Decreased glucose uptake is directly correlated with tau hyperphosphorylation, which subsequently contributes to neurodegeneration and neuroinflammation (Michailidis et. al., 2022).

AD and T2D are globally recognized health challenges. Recent years have seen a burgeoning interest in their intricate interrelationship. Both conditions share fundamental pathophysiological mechanisms, including cerebral atrophy, reduced cerebral glucose metabolism, and central nervous system insulin resistance. A deeper understanding of these shared mechanisms is critically important for developing novel, targeted strategies for the prevention and effective treatment of both debilitating diseases (Janoutová et. al., 2022; Michailidis et. al., 2022).

The precise concentration of insulin within the brain is carefully maintained through the selective transport of peripheral pancreatic insulin across the blood-brain barrier. The primary roles of insulin in the brain

involve the regulation of nutrient intake, body weight, feeding behaviors, and overall energy homeostasis. Furthermore, it exerts influence over neurotransmitter systems and receptor densities, and modulates memory processes such as long-term potentiation and long-term depression (Michailidis et. al., 2022).

Insulin resistance represents a pivotal pathological feature observed in both peripheral tissues and within the central nervous system. Peripheral insulin resistance culminates in hyperinsulinemia, which, in turn, exacerbates the risk of T2D. Research indicates that insulin resistance may contribute to β-amyloid accumulation by leading to diminished levels of insulin-like growth factor 1 (IGF-1) and impaired insulin uptake into the brain. This could establish a detrimental feedback loop where elevated β-amyloid levels counteract insulin and IGF-1 receptor binding, prompting the release of pro-inflammatory mediators and the initiation of further insulin resistance (Michailidis et. al., 2022).

Central nervous system insulin resistance can induce a range of behavioral alterations, including increased anxiety, hyperphagia, and phenotypes resembling depression. Disruptions in insulin signaling pathways are well-established correlates of cognitive impairment. The coining of Alzheimer's disease as "Type 3 Diabetes" underscores the critical significance of dysregulated insulin signaling and glucose metabolic disturbances within the brain (Tahernia et. al., 2023; González et. al., 2022).

A multitude of shared pathophysiological mechanisms clarify the complex association between Type 2 Diabetes and Alzheimer's disease. These include the intricate interplay of β-Amyloid and Tau Protein pathologies, Endoplasmic Reticulum (ER) Stress, Neuroinflammation, Oxidative Stress and Mitochondrial Dysfunction, Advanced Glycation End Products (AGEs), Metabolic Syndrome, Amylin (Islet Amyloid Polypeptide - IAPP), Tau Post-Translational Modifications, and Microglial Activation.

2.3.1. β-Amyloid and Tau Protein

The defining pathological hallmarks of Alzheimer's disease involve the anomalous hyperphosphorylation of intracellular tau proteins and the extracellular deposition of β-amyloid plaques (Tahernia et. al., 2023). Through their aggregation, β-amyloids possess the capacity to form neurotoxic soluble oligomeric species. The insulin-degrading enzyme (IDE) assumes a crucial role in the nexus between insulin resistance and Alzheimer's disease, given its enzymatic ability to cleave both β-amyloid and insulin. In states of insulin resistance, the preferential degradation of insulin by IDE may compromise β-amyloid clearance, thereby fostering its detrimental accumulation. Tau protein, essential for microtubule stability,

undergoes hyperphosphorylation, which subsequently leads to the formation of neurofibrillary tangles—a core contributor to the pathophysiology of Alzheimer's disease. Dysregulation within insulin and IGF signaling pathways can instigate the hyperphosphorylation of the tau protein (Michailidis et. al., 2022).

2.3.2. Endoplasmic Reticulum Stress

The Endoplasmic Reticulum (ER) is an indispensable intracellular organelle critical for protein synthesis, proper folding, and quality control. ER stress is characterized by the accumulation of misfolded proteins, reflecting an imbalance between the protein folding capacity and the demands of protein synthesis. ER stress, triggered by factors such as chronological aging and genetic mutations, has been implicated in the pathogenesis of neurodegenerative disorders, including T2D and Alzheimer's disease. Robust scientific evidence indicates that ER stress activates intricate signaling pathways that modulate tau phosphorylation, influence the amyloid cascade, and contribute to synaptic dysfunction (González et. al., 2022).

2.3.3. Neuroinflammation

Neuroinflammation is a prominent feature observed during the early phases of Alzheimer's disease. It is characterized by an elevated concentration of inflammatory cytokines and the localized aggregation of microglial cells around amyloid plaques. Neuroinflammation exacerbates AD pathology by promoting oxidative damage, inducing tau protein hyperphosphorylation, contributing to β-amyloid accumulation, and impairing the integrity of the cholinergic system. Furthermore, inflammation originating from peripheral insulin resistance and obesity can traverse the blood-brain barrier (BBB), subsequently leading to neuroinflammation and insulin resistance within the cerebral parenchyma (Michailidis et. al., 2022).

2.3.4. Oxidative Stress and Mitochondrial Dysfunction

Insulin resistance possesses the potential to amplify oxidative stress, thereby contributing significantly to neurodegeneration in Alzheimer's disease. The brain exhibits particular susceptibility to oxidative stress-induced damage due to its relatively low endogenous antioxidant capacity and high concentrations of pro-oxidant metal ions. Mitochondrial dysfunction and the excessive generation of reactive oxygen species (ROS) play a vital role in the pathology of T2D and are intricately linked to both neuronal degeneration and diminished ATP production observed in Alzheimer's disease (Michailidis et. al., 2022).

2.3.5. Advanced Glycosylation End Products

Advanced Glycation End Products (AGEs) represent a diverse class of protein- or lipid-derived adducts formed non-enzymatically via the Maillard reaction. AGEs are hypothesized to play a significant role in the progression of Alzheimer's disease, contributing to neurotoxic effects by promoting the aggregation of amyloid oligomers and facilitating tau protein glycation. In the context of hyperglycemia, AGEs serve as a critical molecular bridge connecting insulin resistance and neurodegeneration (Michailidis et. al., 2022).

2.3.6. Metabolic Syndrome

The core defining features of metabolic syndrome, specifically visceral adiposity, a range of metabolic dysregulations, and insulin resistance, have been consistently correlated with both cognitive impairment and cerebral atrophy. In patients diagnosed with T2DM, a discernible reduction in cerebral glucose metabolism has been empirically documented in specific brain regions, including the frontal, temporal, and parietal cortical areas (Michailidis et. al., 2022).

2.3.7. Amylin

Amylin (Islet Amyloid Polypeptide - IAPP) is a peptide hormone co-secreted with insulin from the β-cells of the pancreas. Elevated amylin levels are characteristic of individuals with obesity or insulin resistance, and both amylin accumulation and its corresponding receptors have been observed within the cerebral tissue of Alzheimer's patients. It is hypothesized that amylin can be internalized by neurons, subsequently inducing intracellular oxidative stress and inflammatory responses, thereby reinforcing the pathological interplay between Alzheimer's disease and T2D (Michailidis et. al., 2022).

2.3.8. Tau Post-Translocation Modifications

Tau protein serves as a crucial microtubule-associated protein, providing structural stability to microtubules. In the progression of Alzheimer's disease, significant alterations manifest in the post-translational modifications of tau protein, encompassing phosphorylation, methylation, ubiquitination, and glycosylation/cleavage. Notably, the hyperphosphorylation of tau is a key event leading to the formation of neurofibrillary tangles, a hallmark pathological feature common to numerous neurodegenerative disorders (González et. al., 2022).

2.3.9. Microglial Activation

Microglial activation assumes a central role within neuroinflammatory mechanisms. Extracellular ATP, released from damaged cells, acts as a potent stimulus for microglial activation, triggering the subsequent release of pro-inflammatory cytokines. While microglia contribute beneficially to tissue repair and maintenance of homeostasis, their sustained or excessive activation can lead to the release of neurotoxic factors that exacerbate inflammatory processes, thereby accelerating neurodegeneration (González et. al., 2022).

3. Conclusion

The compelling interrelationship between T2D and AD underscores the existence of common molecular and cellular targets for therapeutic intervention in both diseases. Ongoing investigations are exploring the potential beneficial effects of incretin receptor agonists, such as Semaglutide, and various oral antidiabetic agents, including Metformin, on the pathological trajectory of Alzheimer's disease. Of particular interest is the intranasal administration of insulin, which demonstrates promise in enhancing brain insulin signaling, potentially leading to improvements in cognitive performance and metabolic integrity. Furthermore, the application of 18F-Fluorodeoxyglucose Positron Emission Tomography (F18-FDG-PET) as a potential biomarker for assessing cerebral glucose metabolism holds substantial diagnostic and prognostic value (González et. al., 2022).

In summation, the intricate and multifaceted connection between AD and T2D robustly supports the presence of shared pathogenic mechanisms. A more comprehensive elucidation of these common pathways is indispensable for the development of novel and targeted strategies aimed at the prevention and efficacious treatment of both debilitating conditions. Research in this dynamically evolving field offers considerable promise for future therapeutic advancements by illuminating the critical crosstalk between neurodegeneration and metabolic dysregulation.

Acknowledgement

The authors would like to express their sincere gratitude to the Faculty of Pharmacy at Agri Ibrahim Cecen University for their valuable support and contributions throughout this research.

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Chapter 6

EMULGEL TECHNOLOGY FOR TOPICAL APPLICATION OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

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1. Introduction

Non-steroidal anti-inflammatory drugs, or NSAIDs, are the most commonly prescribed family of drugs because of their shown ability to reduce pain and inflammation (Khan et. al., 2022). However, severe side effects include gastrointestinal bleeding or ulceration, hypertension, cardiovascular events, and acute renal failure, which can result from high systemic drug concentrations following oral NSAID therapy (Mwangi et. al., 2021). Local application techniques are therefore becoming increasingly significant.

Since the skin is an organ that is easily accessible, dermal delivery of drugs has long been considered as a possible drug delivery technique. Among the many benefits of this administration method are the avoidance of first-pass effects and gastrointestinal irritation. In this regard, topical gel formulations provide a practical and efficient drug delivery method. However, the challenges associated with delivering hydrophobic drugs are among these systems' most significant drawbacks. At this stage, hydrophobic drug transport through the skin is significantly aided by emulgel systems, which combine emulsion and gel systems.

Oil-in-water (O/W) or water-in-oil (W/O) combined with a gelling ingredient is the emulgel formulation. Recent years have seen the development of novel formulations for topical drug administration that have demonstrated their potential to transport hydrophobic medications. Additionally, it is anticipated that emulgel will play a significant role in loading hydrophobic drugs into gel formulations (Sabalingam & Siriwardhene, 2022).

The objective of this research is to examine the possible application of emulgels as a topical dose form to lessen the systemic side effects of NSAIDs. The structure, carrier characteristics, formulation, and benefits of emulgel systems in terms of their efficacy against NSAIDs were disclosed for this purpose. Current research on NSAID-containing emulgel formulations was reviewed in the literature.

2. General Information

2.1. General Use and Side Effects of NSAIDS

Globally, pain is regarded as a serious public health issue. Acute pain that is not adequately managed can result in major health issues and a higher risk of chronic pain. In the pharmacological treatment of pain, there are essentially two primary methods: the use of opiate/opioid-derived analgesics and NSAIDs, which work by inhibiting cyclooxygenase (COX) isoenzymes (Brune & Patrignani, 2015).

NSAIDs make up 5% of all prescription medications, making them one of the most widely used over-the-counter drugs globally (Bindu et. al., 2020). NSAIDs not only reduce inflammation but also have analgesic and antipyretic properties. These medications work by blocking COX enzymes, which control the rate at which other prostanoids like prostaglandins and thromboxanes are synthesized (Wongrakpanich et. al., 2018). Both COX-1 and COX-2 enzymes are inhibited by traditional NSAIDs, which are linked to major gastrointestinal adverse effects like an increased risk of bleeding and ulcers (Arfeen et. al., 2024). By binding to a polar arginine molecule present in both forms of COX, NSAIDs sterically hinder enzyme activity. By lowering the amount of prostaglandins generated, this inhibition lessens fever and pain (Haley & von Recum, 2019). Homeostasis in the kidneys, gastrointestinal system, and other organs is maintained in part by COX-1. Because they decrease the COX-1 enzyme, the majority of NSAIDs have serious gastrointestinal adverse effects (Khalil et. al., 2024).

The creation of selective COX-2 inhibitors, or "coxibs," which are intended to inhibit COX-2 while sparing COX-1 at therapeutic levels, resulted from efforts to prevent the gastrointestinal adverse effects linked to COX-1 inhibition (Brune & Patrignani, 2015). Nevertheless, a number of reports of COX-2 inhibitors' adverse effects on the cardiovascular system started to surface, and later placebo-controlled research also revealed that these inhibitors were linked to a higher risk of atherothrombotic vascular events (Bindu et. al., 2020).

2.2. Topical Use of NSAIDS

Topical drug administration is the process of applying a formulation containing a drug to the skin in order to treat a skin problem (Patel et. al., 2021). Topical drug delivery is used as ophthalmic, rectal, vaginal and topical routes via the skin for localized effect in the body (Jain et. al., 2019). Topically applied analgesics have a far better side effect profile since they lessen local pain with less systemic effects (Leppert et. al., 2018). Hepatotoxicity, hypertension, cardiovascular events, and bleeding or ulcers in the gastrointestinal tract are among the adverse consequences of oral NSAID medication. Using topical formulations that can minimize systemic concentrations of analgesics while providing effective concentrations at the site of inflammation can help lower the risk of adverse effects (Barkin, 2015). Topical analgesics are given directly to the area that is causing pain or discomfort. Targeted external drug administration may have less systemic effects than oral counterparts and more pharmacological effects on surface structures including ligaments, saccules, and joints (Stanos, 2020).

In the literature, several benefits of topical NSAID formulations are regularly emphasized (Benbow & Campbell, 2019; Md et. al., 2020). These advantages include preventing variability in the gastrointestinal system and bypassing first-pass metabolism, thus avoiding some limitations encountered in systemic drug distribution. The ability to apply the drug directly to the desired area allows for local concentration of the pharmacological effect. In addition, topical application is generally better tolerated by patients, which can positively affect treatment compliance. It is also an important advantage that it offers an alternative route of administration in cases where oral formulations cannot be used or are not tolerated. The ease of application of topical forms can increase cost-effectiveness compared to other routes in some cases. In addition, potential drug-drug interactions can be reduced thanks to limited passage into the systemic circulation. Another notable aspect of these formulations is that the targeted therapeutic effect can be achieved in a shorter period of time without the need for dose adjustment (McPherson, 2013).

2.3. Emulgel Technology

Gels are dosage forms made by encasing water or hydroalcoholic liquids in networks of colloidal organic or inorganic substances (Vanpariya et. al., 2021). Gel formulations typically offer faster release of drugs than conventional ointments and creams (Jain et. al., 2019). The usage of gel formulations is severely limited by their insufficiency in delivering hydrophobic medications, despite their benefits in terms of patient compliance and simplicity of application (Panchal & Rathi, 2018). Because they are not soluble in the aqueous phase, active components with hydrophobic structures do not release drugs in gels appropriately, making them unsuitable for inclusion in gel formulations. Drug delivery methods based on emulsion-gel are employed to lessen these drawbacks (Sabalingam & Siriwardhene, 2022).

Emulsions are created by mixing two or more often incompatible liquids. The use of emulsifiers helps stabilize emulsions and allows the oil and water phase to mix (Patel et. al., 2021).

Emulgel is the term for any water-oil or oil-water emulsion that has been gelled using a gelling agent. For drugs that are hydrophobic or have low water solubility, the emulsified gel offers a reliable and practical delivery system (Singh & Singh, 2022). Emulgel serves as a dual control release mechanism since it possesses both emulsion and gel characteristics. While water-in-oil emulsions are more frequently employed for moisturizing and dry skin therapy, oil-in-water emulsions are best suited for water-washable medication bases and general cosmetic applications

(Alexander et. al., 2013). Thixotropic, non-greasy, simple to apply and remove, emollient, non-staining, long shelf life, biologically friendly, transparent, and aesthetically pleasing are just a few of the benefits of emulgels for dermatological usage (Khullar et. al., 2012). Other benefits include avoiding the first-pass metabolic process, improving patient compliance, and being easy to use and comfortable. On the other hand, drawbacks include the potential for allergic reactions, skin irritation that can lead to contact dermatitis, and the formation of bubbles during the emulgel formulation process (Alburyhi et. al., 2025).

Based on their structural characteristics, emulgel systems can be categorized into three main groups: macroemulsion gels, nanoemulsion gels, and microemulsion gels. Systems with emulsion droplet diameters more than 400 nm, an opaque appearance, and easy microscopic observation are known as macroemulsion gels. The interfacial film created by surfactants and co-surfactants stabilizes nanoemulsion gels, which are thermodynamically stable dispersions with droplet sizes smaller than 100 nm. They are uniformly dispersed in the water and oil phases and appear transparent or translucent. Since phase coalescence is not seen, microemulsion gels are systems with droplet sizes ranging from 10 to 100 nm, a clear appearance, and a high degree of thermodynamic stability (Mutta, 2021).

2.3.1. Preparation of Emulgel

The process of producing emulgel involves two consecutive steps: The process begins with the preparation of an emulsion, followed by the gelation of the emulsified droplets. While hydrophobic emulsifiers stabilize water-in-oil emulgels, hydrophilic emulsifiers typically stabilize oil-in-water emulgels (Oppong et. al., 2024). When preparing an emulsion, the hydrophilic components are added to the aqueous phase, and the hydrophobic components are added to the oil phase. To assure gelation, a gelling agent is used to prepare the gel phase after the emulsion is ready. Lastly, the gel and emulsion are combined to create a fully homogenous composition (Milutinov et. al., 2023).

2.3.2. Emulgel Components

Emulgels are complicated semisolid dosage forms that combine the qualities of gels and emulsions. To ensure stability, effectiveness, and patient compliance, their formulation calls for a number of useful excipients. The hydrophilic matrix of the emulsion is formed by the aqueous phase, which typically consists of alcohols or water. The oil phase, on the other hand, is made up of lipophilic materials like mineral oils or other paraffin combinations. In topical emulsions, these oils offer beneficial occlusive and sensory qualities in addition to acting as drug carriers. Emulsifying

agents are essential for facilitating the emulsification process during production and, particularly, for preserving the emulsion's long-term stability. Gelling agents are also included to improve the dosage form's overall consistency and often serve as thickening agents. Permeation enhancers are an additional component. These are specific compounds that interact with the skin's natural components to temporarily and reversibly increase skin permeability (Jain et. al., 2019; Joshi et. al., 2022; Panchal & Rathi, 2018).

To prevent skin irritation, emulgels' pH value should be near to the skin's natural pH; typically, this is set at 5.4 or 5.5. Particularly when gelling chemicals like Carbopol are employed to breakdown the polymer chain and create a gel structure, substances like triethanolamine are essential for adjusting pH (Milutinov et. al., 2023)

Table 1: Examples of Excipients Generally Used in Emulgel Formulations

Emulgel Components	Example
Aqueous phase	Water, alcohol
Oil phase	Castor oil, cottonseed oil, jojoba oil, thyme oil, olive oil, fish liver oil, corn oil, wheat germ oil, rosehip oil, liquid paraffin, isopropyl myristate, etc.
Emulsifying agents	PEG 40 stearate, Span 20, Tween 80, Span 60, Tween 20 etc.
Gelling agents	Carbopol 934, Karbopol 940, HPMC, NaCMC etc.
Permeability enhancers	Sodium lauryl sulfate, palmitate, oleic acid, lecithin, etc.
pH-modifying agent	Triethanolamine

Source: Ahmed et. al., 2022; Alexander et. al., 2013; Milutinov et. al., 2023

2.4. Emulgel formulations in NSAIDs

Emulgels containing NSAIDs had a superior anti-inflammatory and analgesic response as compared to traditional gel formulations. The drug's release profile and bioavailability have been enhanced by the formulation's incorporation of penetration enhancers. NSAIDs used topically have demonstrated an enhanced drug release profile and a considerable decrease in systemic adverse effects (Sabalingam & Siriwardhene, 2022). Emulgel formulations have been developed for many NSAIDs. Examples of these drugs include Naproxen (Khan et. al., 2022), Diclofenac (Yahaya et. al., 2023), Ibuprofen (Bolla et. al., 2020), Piroxicam (Saxena et. al., 2013), Indomethacin (Kondawar & Wadkar, n.d.), Ketoprofen (Ambala & Vemula, 2015), Dexibuprofen (Burki et. al., 2020), Lornoxicam (Mahaparale and Gaware 2017).

Khan et. al. developed an emulgel formulation containing Naproxen, an NSAID, and Eugenol, an aromatic hydroxy phenolic compound. Its goal is to eliminate negative reactions and enhance analgesic and anti-inflammatory effects. The emulsion phase was prepared using Tween 80 (10%), sepineo-P600 (6%), olive oil (6%), ethanol (4%), liquid paraffin (6%), propylene glycol (8%). Gel phase is composed of 2% Carbopol 934. In vivo experiments on carrageenan-induced paw edema were used to assess the effectiveness of the described emulgel. The conventional marketed product (Voltral®) and the emulgel formulation had pain reaction times of 10.36 ± 0.47 and 11.16 ± 0.17, respectively. These results were not statistically significant ($p > 0.05$). Additionally, it was determined that the analgesic and anti-inflammatory properties of naproxen and eugenol work in concert when applied transdermally as naproxen-eugenol emulgel (Khan et. al., 2022).

Yahaya et. al. developed diclofenac emulgel formulation and investigated the suitability of sesame oil as an oily phase. Various emulgel formulations were made with varying amounts of gelling agents (xanthan gum or gelatin), surfactants (Tween-80 and/or cremophor EL-30), and oil (sesame oil and/or Labrafac CC). In comparison to commercially available diclofenac emulgel, the created emulgel had comparable anti-inflammatory action. Additionally, it demonstrated a 50% greater anti-inflammatory effect than aqueous diclofenac dispersion. Additionally, it was determined that sesame oil has the potential to be a lipophilic ingredient in emulgel formulations for the topical administration of hydrophobic drugs (Yahaya et. al. 2023).

In another study, an emulgel formulation of etoricoxib, which is also an NSAID and used in the treatment of joint pain, inflammation, and arthritis, was prepared. Different concentrations of Carbopol 934 (1%, 1.5%, 2%) and Carbopol 940 (1%, 1.5%, 2%) were used for the gel phase. The emulsion was prepared using olive oil, Span 20, Tween 20, and ethanol. At the end of the study, the effect of using different gelling agents on the release rate was emphasized. It was also concluded that etoricoxib emulgel was successfully formulated and topically compatible(Negi & Kumar, 2019).

Another NSAID Dexibuprofen containing emulgel formulation was prepared by combining it with Capsaicin. Capsaicin is the main carotenoid found in Capsicum genus with analgesic, antioxidant and anti-inflammatory effects. Different formulations were developed using varying ratios of Carbopol 940, liquid paraffin, ethanol, tween 80, span 80, propylene glycol. It was determined that the optimized emulgel successfully prevented carrageenan-induced paw edema in rats. Comparing it to the

commercially available diclofenac sodium emulgel (Dicloran®), it was also found to exhibit greater analgesic activity. As an alternative to the conventional topical dosage form, the study's findings demonstrated the promising synergistic potential of dexibuprofen-capsaicin emulgel (Burki et. al., 2020).

Lornoxicam is another NSAID for which emulgel formulation has been developed. Triethanolamine (5%) was used as a solvent in the formulation of Lornoxicam emulgel, while carbopol 934 and carbopol 940 were used as gelling agents. Cetosterol alcohol, liquid paraffin, and glycerine monostearate were also used as other excipients. Results of in vitro drug release indicated that emulgel based on carbopol 940 offered superior release. Additionally, it was discovered that the gelling agent concentration significantly impacted the drug release from emulgel (Mahaparale & Gaware, 2017).

3. Conclusion

The development of NSAID emulgel formulations has been the subject of numerous studies. There are extremely few unfavorable side effects and numerous benefits to these compositions. The created emulgels have demonstrated favorable outcomes in terms of homogeneity, viscosity, drug penetration rate into the skin, drug release profile, and therapeutic outcomes. The effectiveness of various emulsifiers, gelling agents, and auxiliary ingredients utilized in the emulgel formulation has also been noted. Future research will focus on developing and studying emulgel formulations of various medications, including NSAIDs.

Acknowledgement

The authors would like to express their sincere gratitude to the Faculty of Pharmacy at Agri Ibrahim Cecen University for their valuable support and contributions throughout this research.

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Chapter 7

THE ROLE OF FORESTS IN SOIL ECOLOGY AND CLIMATE CHANGE

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1. Introduction

Forest ecosystems are not only home to a large part of the living diversity on earth; at the same time, they are natural systems that play fundamental roles on a global scale, especially in the fight against climate change and the protection of ecological balance (FAO, 2022; UNEP, 2023; Bonan, 2008). Forests, which cover approximately 31% of the world's land area (FAO, 2022), are home to the majority of biodiversity; It ensures the continuity of vital processes such as carbon cycle, regulation of water regime, soil formation and nutrient cycling (Pan et. al., 2011). Forest soils, in particular, are at the center of physical and biological interactions that ensure the continuity of ecosystem services. Forests perform these functions largely through soil structure, microbial biodiversity, and the accumulation of organic matter. Therefore, forest soils are of strategic importance not only for agricultural production but also for the stabilization of the climate system (Lal, 2005; Smith et. al., 2020; Ghasemi et. al., 2023).

Today, global warming and climate change are one of the major environmental problems that threaten these ecosystem services. Global temperature increase affects forest dynamics, altering soil carbon solubility, microbial activity, and water holding capacity (Davidson & Janssens, 2006; Schuur et. al., 2015). Rising temperatures, an increase in the frequency of extreme weather events, and seasonal imbalances increase the rate of carbon dissolution in forest soils, triggering greenhouse gas emissions (Gatica et. al., 2020; Cadisch et. al., 1996; Beillouin et. al.,2021; Canadell & Raupach, 2008). Healthy forest soils can contribute to slowing down this change by absorbing carbon from the atmosphere. This two-way relationship reveals that forests are both victims and solution partners of climate change (Bai, 2022).

Scientific research conducted in recent years has shown that the carbon storage capacity of forest soils is not limited to organic matter and living vegetation on the surface; it also revealed that deep earth horizons also contain significant amounts of carbon (Dhaliwal et. al., 2019). In addition, the sensitivity of microbial and enzymatic activity in forest soils to climate change can cause the carbon stored in the soil to be released rapidly into the atmosphere, further increasing global warming (Brown et. al., 2023). Changes in the physical, chemical, and biological properties of soils, especially in combination with anthropogenic impacts and climatic stressors, seriously threaten the carbon storage capacity and overall functionality of forest ecosystems (Montgomery, 2021; Smith et. al., 2022).

In this study, the functions of forests in soil ecology, their carbon storage capacities and their interaction with climate change will be exami-

ned in the light of current scientific data. In addition, sustainable forest management strategies and adaptation approaches will be evaluated, emphasizing the importance of protecting forests in the face of current ecological threats.

2. General Information

2.1. Ecological Functions of Forest Soils

Forest soils provide a basic biophysical infrastructure for forest ecosystems to maintain their functional integrity and multifaceted ecological services. These soil systems are not only an environment in which organic and inorganic components are passively accumulated; it is also central to critical biogeochemical functions such as microbial metabolism, carbon and nitrogen cycles, humification processes, and water-holding capacity (Condron et. al., 2010; Wang et. al., 2024; Lal, 2005). These processes, which take place in forest soils, are of vital importance both in terms of protecting soil health and maintaining ecosystem services that ensure the sustainability of forest ecosystems. In particular, the activity of microbial communities plays a decisive role in carbon sequestration and the efficiency of nutrient recycling mechanisms (van der Heijden et. al., 2008). In this context, forest soils are an indispensable natural resource in the fight against climate change and increasing ecosystem resilience.

The breakdown of woody and fibrous plant residues by soil microorganisms and the action of enzymes involved in this process contribute to long-term carbon storage by transforming organic matter into stable compounds in the soil (Schimel et. al., 2019). At the same time, aggregate stability and porosity of forest soils directly affect both the healthy development of plant roots and the movement and retention of groundwater. These properties increase the resilience of forest soil to external stresses and strengthen the ecosystem's capacity to adapt to changing environmental conditions (Six et. al., 2004; Lehmann & Kleber, 2015). Thus, both the habitats of soil creatures are protected and basic ecosystem functions such as the carbon and nutrient cycle can be maintained.

Thus, forest soils function not only as a ground for plant roots, but also as a dynamic biological-environmental transition area that manages the chemical cycles of forest ecosystems, supports their productivity, and ensures the continuity of climate regulatory processes. Therefore, monitoring and protecting soil quality should be considered as one of the key building blocks of climate change-resilient forestry practices (Dhaliwal et. al., 2019; Brown et. al., 2021).

2.1.1. Carbon Sequestration and Soil Organic Matter

Soil functions as one of the largest and most critical carbon stores in forest ecosystems. It consists of a complex combination of soil organic matter, plant remains, microorganisms and humus structures, which play a vital role in the global carbon cycle by enabling long-term storage of carbon. This process is considered an important mechanism in mitigating the effects of climate change by contributing to balancing carbon dioxide levels in the atmosphere (Lal, 2020).

Carbon sequestration is the ability of life and ecosystems to store carbon from the atmosphere through natural means. Forests, peat bogs, and coastal wetlands are among the ecosystems with high carbon storage capacity. Carbon can accumulate in plant tissues, such as long-lived tree bark or extensive root systems.

A significant part of the carbon taken from the atmosphere as a result of photosynthesis; It accumulates in the soil through leaf fall, root release and other organic waste. Microbial decomposition and humification processes in the soil, on the other hand, contribute to the long-term storage of carbon by ensuring its sequestration (Smith et. al., 2022).

Healthy soil carbon stocks are important for global climate regulatory mechanisms. Deforestation and soil erosion cause these carbon reserves to be released back into the atmosphere as carbon dioxide, accelerating climate change (Montgomery, 2021). Therefore, the conservation of soil carbon is of strategic importance in the fight against climate change.

Healthy and balanced soil carbon stocks are of critical importance in terms of global climate regulatory mechanisms. Forest soils contribute to the balancing of carbon dioxide levels in the atmosphere by storing a large amount of organic carbon. However, human-induced activities such as deforestation and soil erosion lead to the breakdown of these valuable carbon reserves and their release back into the atmosphere as carbon dioxide. This process triggers positive feedback mechanisms that lead to the acceleration of global climate change (Montgomery, 2021; Ding et. al., 2019). The loss of soil carbon is not only limited to negative impacts on the climate, but also leads to deterioration of soil health, disruption of nutrient cycling and weakening of the functional integrity of forest ecosystems. Therefore, protecting and increasing soil carbon stocks should be considered as a strategic priority in the fight against climate change; Sustainable forestry practices and soil management policies should be strengthened in line with this goal. Effective management of soil carbon is a fundamental requirement not only for the reduction of carbon emissions, but also for the continuity of biodiversity and ecosystem services (Lal, 2004).

2.1.2. Soil Biodiversity and Microbial Activity

Forest soils stand out as complex habitats where high microbial diversity and activity are observed. Soil microorganisms play critical roles in organic matter mineralization, maintenance of nutrient cycles, and soil structure (van der Heijden et. al., 2015). Symbiotic organisms such as mycorrhizal fungi establish mutually beneficial relationships with tree roots, increasing the water and mineral uptake of plants, while at the same time making significant contributions to the stabilization of soil structure.

Mutual biotic and abiotic interactions between forest vegetation and soil are decisive for the sustainability of the carbon cycle. Plant species' defoliation, root secretions, and dead root biomass constitute key inputs for soil organic matter, and these processes promote the replenishment of soil carbon sinks (Prescott, 2010; Cotrufo et. al., 2013). Hard-to-decompose organic materials of coniferous species with a high lignin content; On the other hand, the components of broadleaf species, which are more easily broken down and support microbial activity, create diversity in soil carbon dynamics (Cornwell et. al., 2008). These species differences have a direct impact on soil carbon stability, microbial biodiversity, and enzymatic activities (Berg & McClaugherty, 2014).

Temperature increases and drought events due to climate change can restructure the carbon cycle by altering forest composition. In particular, the proliferation of water-stress-resistant species can limit microbial metabolism and lower carbon mineralization rates by reducing soil moisture content (De Vries et. al., 2018). This could lead to both a decrease in soil carbon sink capacity and a weakening of the role of forests in climate regulation.

The diversity and functional capacity of soil microorganisms are among the main indicators of soil health. Climate change can accelerate organic matter decomposition by affecting microbial activity, especially through rising soil temperatures and disturbances in moisture balance. This process results in a decrease in the carbon sequestration capacity of the soil and therefore negatively affects ecosystem functions (Smith et. al., 2022).

2.1.3. Soil Physical and Chemical Properties

Physical and chemical properties such as soil texture, water holding capacity, pH, and the presence of nutrients are critical in the functionality of forest soils. These properties promote root development, facilitate the water uptake of plants, and provide a favorable environment for microbial life; hence, they are key determinants of the sustainability of forest ecosystems (Wang et. al., 2017).

Processes such as soil deterioration, intense erosion and acidification impair soil health, negatively affecting plant growth and carbon sequestration. Therefore, monitoring and improving physical and chemical parameters in soil management is critical for increasing the resilience and resilience of forest ecosystems (Lal, 2004; Montgomery, 2021).

2.1.4. Role in the Water Cycle and Erosion Control

Forest soils play a vital role in regulating the hydrological cycle, thanks to their capacity to absorb and store water. The porosity of the soil increases the rate of infiltration by reducing the surface runoff of rainwater; this mechanism ensures that the risk of flooding is minimized (Calder, 1999; Nepstad et. al., 1994). The positive effect of roots on soil structure is an important biological mechanism in the prevention of erosion (Pimentel & Kounang, 1998).

In the case of deforestation, the bare surface of the soil leads to increased surface runoff of water and the transport of soil (Montgomery, 2021; Lal, 2020). This, in turn, both reduces soil fertility and causes pollution of water resources (Busari et. al., 2015; Blanco-Canqui & Lal, 2008). Soil erosion seriously threatens soil health, especially in sloping and at-risk areas (Montgomery, 2021; Morgan, 2005; Pimentel et. al., 1998).

2.2. Sustainable Forest Management and Adaptation Strategies

In the face of the accelerating effects of climate change, the sustainability of forest ecosystems is possible not only with the protection of tree cover, but also with ecological integrity approaches that focus on soil health. Soil; it is the source of key biotic and abiotic interaction networks, such as carbon sequestration, water infiltration and retention capacity, nutrient cycling, and microbial functionality (Brussaard et. al., 2007; Lal, 2004). Soil organic matter and biodiversity are critical to the sustainability of the climate regulation capacity of forests (van der Heijden et. al., 2008). Rising temperatures, droughts, and extreme weather events weaken soil structural stability and biotic interactions, reducing the resilience capacity of forest ecosystems (Schimel et. al., 2019; Crowther et. al., 2016). For this reason, sustainable forest management approaches should prioritize the protection of soil functions and the strengthening of adaptive capacity. Monitoring and supporting the structural and functional integrity of soil biota to secure long-term carbon sinks offers an effective nature-based solution approach to climate change (Smith et. al., 2020; Wang et. al., 2024).

2.2.1. Species Selection and Genetic Diversity Based on Soil Health

In forest species selection, it is important to choose tree species that

are compatible with soil conditions and support rhizosphere activities and soil health, increasing ecosystem resilience. Plant-soil feedbacks play important regulatory roles in organic matter accumulation and nutrient cycling processes by modulating the soil microorganism composition of certain tree species (Bever, Schultz, & Miller, 2019). For example, ectomycorrhizal tree species increase carbon sequestration capacity by optimizing the circulation of essential nutrients such as nitrogen and phosphorus in the soil, optimizing organic matter decomposition and carbon storage (van der Heijden et. al., 2015).

In addition, genetic diversity contributes to the functional stability of forest soils by giving them the ability to adapt to different environmental stressors. The presence of various genotypes diversifies soil nutrient cycling through root secretions, defoliation, and microbial interactions in response to microhabitat differences (Kuyper et. al., 2024; Jump & Peñuelas, 2005). Therefore, the conservation and promotion of not only native species but also genetic variation in sustainable forestry practices is of strategic importance for the functional continuity of forest soils in the face of climate change.

2.2.2. Soil-Oriented Adaptive Forestry and Management Policies

Adaptive forestry principles prioritize soil health and mandate the development of management plans that are flexible and based on up-to-date scientific data. Parameters such as soil structure, water holding capacity, organic carbon content, and microbial activity should be regularly monitored, and management strategies should be dynamically revised in response to the increasing impacts of climate change (Puettmann et. al., 2009; Nave et. al., 2019).

Erosion control, ensuring the continuity of soil cover, and supporting the cycle of organic matter are critical to prevent soil degradation (Montgomery, 2021; Lal, 2020). In addition, fire management practices should be structured to protect soil carbon stocks. Because the increasing fire intensity in recent years has significantly increased soil organic carbon losses (Bowman et. al., 2009; Doerr & Santin, 2016).

Sustainable forest management policies proposed by the Food and Agriculture Organization of the United Nations (FAO, 2018); It focuses on soil conservation, carbon sequestration, and the continuity of ecosystem services. These policies should be adapted and implemented through the integration of early warning systems, climate change projections, and local ecological conditions (Roshani et. al., 2022). Thus, the negative effects of climate change on forest soils can be minimized and the functional integrity of ecosystems can be preserved.

2.2.3. Ecosystem-Based Forest Restoration and Soil Rehabilitation Physical and Chemical Properties

Restoration work increases soil structure and carbon stability by supporting natural ecosystem progress. Methods that promote the activities of soil microorganisms and saprophytic fungi lead to improvement in soil biochemistry (van der Heijden et. al., 2008). In addition, multispecies and native species-based afforestation strategies that protect soil health ensure the sustainability of biodiversity and soil functions (Chazdon, 2014).

Improving soil health in forest restoration practices is a key priority for the long-term recovery of ecosystem functions. Effectively controlling soil erosion, increasing organic carbon stocks, and promoting microbial diversity are among the critical goals of restoration processes (Rey Benayas et. al., 2009; Crouzeilles et. al., 2017). Promoting natural ecosystem progression enhances the success of restoration in terms of improving soil structure and increasing carbon stability (Galliart et. al., 2019). Promoting the activities of the soil microbiome and saprophytic fungi creates positive changes in soil biochemistry by optimizing organic matter decomposition (van der Heijden et. al., 2008; Waring et. al., 2021). In addition, afforestation strategies that use native species and promote biodiversity contribute to the sustainability of soil functions (Chazdon, 2014). Recent studies show that restoration strengthens ecosystem resilience by increasing soil carbon sequestration in the fight against climate change (Perring et. al., 2015; Nave et. al., 2019). Therefore, multidisciplinary approaches and practices in accordance with local ecosystem characteristics are critical for the protection of forest soil health and the continuity of ecosystem services.

2.2.4. Local Communities Involvement and Traditional Land Knowledge

The knowledge of local and indigenous communities about the soil is considered a critical resource in sustainable forestry and soil management. Traditional soil management practices can be complemented by modern scientific approaches to soil conservation and fertility (Berkes et. al., 2000).

Participatory and community-based management approaches increase the social acceptance and implementation success of land management strategies, and support sustainability by strengthening the livelihoods of local communities (Agrawal et. al., 2008; Larson et. al., 2010). In addition, the contribution of local knowledge to climate change adaptation is becoming increasingly important for the protection of soil health and the continuity of ecosystem services (Reyes-García et. al., 2021).

Therefore, sustainable forest management based on soil health plays a critical role in terms of both ecological resilience and socio-economic development (Jandl et. al., 2007). Current research shows that the participation of local communities increases success in ecosystem management and points to the need for policies to support this integration (Karp et. al., 2023).

3. Conclusion

Forest soils are vital for the sustainability of ecosystem functions. These soils are at the center of many critical ecological functions, such as carbon sequestration, nutrient cycling, water holding capacity, and biodiversity (Lal, 2020). With the rapid progression of climate change, the dynamics of carbon stocks and microbial activity in forest soils have become more complex, and soil health has been adversely affected by increasing temperature and irregular rainfall regimes (Crowther et. al., 2016; Manzoni et. al., 2022).

Soil ecosystems are both sensitive and resilient to climate change, especially in terms of organic matter content and diversity of microorganism communities. Maintaining soil health is essential for long-term storage of soil carbon; however, anthropogenic interventions, deforestation, and soil degradation negatively affect these cycles, increasing carbon emissions (Wang et. al., 2017). Furthermore, soil erosion and structural degradation reduce water-holding capacity and limit the development of plant roots, weakening the resilience of the forest ecosystem (Powlson et. al., 2021). As a result, for the protection and improvement of forest soils:

3.1. Species Selection and Genetic Diversity Based on Soil Health

Carbon storage capacity and biodiversity of forest soils should be monitored regularly as critical indicators for monitoring climate change impacts (Lal, 2020). Evaluation of basic parameters such as soil structure, pH value, moisture content, and microbial activity with modern laboratory techniques is important in the sustainable management of soil health (Lal, 2020; Schimel et. al., 2019). Practices that support soil health; Methods such as organic matter fortification, balanced nutrient management, and erosion control should be integrated into forestry practices to ensure the continuity of ecosystem functions (Rillig et. al., 2021; Tian et. al., 2022). Furthermore, monitoring impacts on the soil microbiome and faunal diversity is critical to optimizing the carbon cycle (Fierer et. al., 2022). These approaches contribute to both improving soil health and increasing the resilience of forest ecosystems in the fight against climate change.

3.2. Conservation of Biodiversity and Microbial Communities

Conservation of soil microorganisms and symbiotic relationships is vital for forest ecosystems to maintain their critical role in carbon cycling and nutrient mineralization. Management strategies that support the functions of mycorrhizal fungi, nitrogen-fixing bacteria, and other beneficial microorganisms should be developed (van der Heijden et. al., 2020; Tedersoo et. al., 2021). These strategies directly contribute to improving soil health and increasing carbon sequestration. In addition, adaptive measures should be put in place to mitigate the negative effects of climate change on microbial communities (Naylor & Coleman-Derr, 2021). Thus, sustainable forest management will support both ecosystem functionality and the fight against climate change.

3.3. Prevention of Erosion and Soil Degradation

Prevention of soil erosion, especially in sloping forest areas, is a critical element for ecosystem health and sustainable forestry. Strengthening of root systems, widespread use of cover crops, and effective land use planning significantly reduce soil loss (Montgomery, 2021; Zhang et. al., 2022). In addition, these measures support the conservation of soil structure, increasing water holding capacity and ensuring the continuity of biodiversity (Lal, 2020; Pimentel & Burgess, 2021). Integrated approaches to erosion control play a fundamental role in mitigating the negative effects of climate change and increase the resilience and adaptability capacity of forest ecosystems.

3.4. Soil Management for Climate Adaptation

Increasing the moisture-holding capacity of forest soils is critical to adapt to changing climatic conditions. Effective retention of water in the soil strengthens ecosystem resilience to climatic extremes such as drought and extreme rainfall (Smith et. al., 2022). Increasing the organic matter content improves soil structure, favoring the storage of water and promoting the activities of microorganisms (Brown et. al., 2021). In addition, sustainable soil management practices contribute to balancing the water cycle, reducing the negative effects of climate change. In this context, improving soil health should be adopted as the main strategy to increase the adaptation and resilience of forest ecosystems. In short, sustainable forest management based on soil health plays a critical role in both ecological resilience and socio-economic development (Jones et. al., 2020).

3.5. Soil-Based Training and Participation in Sustainable Forest Management

Increasing the awareness of forest managers and local communities on soil health is critical for sustainable forest management (Berkes et. al., 2000). Participatory management models and the integration of local information systems strengthen the conservation of soil ecosystems and increase social acceptance (Silva et. al., 2022). These approaches allow for the development of effective strategies for monitoring and improving soil health.

As a result, the continuity of ecosystem services provided by forests against climate change largely depends on the protection of soil health. The development and implementation of soil management strategies in the light of scientific data plays a fundamental role in ensuring the long-term resilience of forest ecosystems (Liu et. al., 2021).

Acknowledgement

The abstract of this study was presented at the 2nd National Forestry Symposium (May 14–16, 2025).

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Chapter 8

THE CLINICAL ROLE OF NOVEL BIOMARKERS IN PARACETAMOL TOXICITY

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1. Introduction

Paracetamol, also known as acetaminophen, is a widely used drug molecule worldwide with analgesic (pain-relieving) and antipyretic (fever-reducing) effects (Brodie and Axelrod 1947; Bertolini et al. 2006; Warwick 2008). It is a medication used for the treatment of bodily pains, especially headaches, toothaches, muscle pains, and symptoms of illnesses such as the common cold, and it is available over-the-counter (Bertolini et al. 2006). Due to its effectiveness at low doses and its broad therapeutic effects, its use is common and considered safe (Neuberger et al. 1980).

Paracetamol is metabolized in the liver and eliminated from the body. Normally, acetaminophen is inactivated through sulfation and glucuronidation pathways (Forrest 1982). However, at high doses or with continuous use, it can be metabolized by the liver's microsomal enzymes into a toxic intermediate called N-acetyl-p-benzoquinone imine (NAPQI). NAPQI induces oxidative stress in the liver, damaging cell membranes, which can ultimately lead to liver injury and hepatotoxicity. While high-dose acute exposure to NAPQI may result in liver failure and death, chronic low-dose use may also lead to hepatotoxic effects. (Chun et al. 2009; McGill et al. 2013; Tong et al. 2015).

In cases of acute paracetamol toxicity, the Rumack-Matthew nomogram is used for diagnosis; however, this nomogram is not effective for repeated doses or chronic use (Vale and Proudfoot 1995; Dart et al. 2006). Acetylcysteine is used as an antidote in the treatment of paracetamol toxicity. Administration within 8–10 hours after overdose can minimize or completely prevent liver damage and toxic effects (Dear and Bateman 2020).

In this chapter; the areas of use of paracetamol, biochemical and pharmacological properties, toxic effects, treatment approaches, differences between acute and chronic toxicity, and current approaches based on artificial intelligence, nanotechnology and omics technologies in the evaluation of paracetamol toxicity will be discussed in detail.

2. General Information

2.1. History of Paracetamol

Paracetamol, a para-aminophenol derivative, also known as acetaminophen or APAP (an abbreviation used among American pharmacists, derived from its alternative chemical name N-acetyl-para-aminophenol), was first synthesized in 1873 by Harmon Northrop Morse by reducing p-nitrophenol with acetic acid (Brodie and Axelrod 1947; Bertolini et al. 2006). In 1948, Brodie and Axelrod demonstrated that paracetamol had

fewer toxic effects compared to the compound acetanilide of that time (Brodie and Axelrod 1947; Brodie et al. 1948). As a result of the studies conducted, paracetamol was introduced into clinical use nearly 20 years later, in 1955, under the brand name 'Tylenol'. It was later marketed in the UK under the name 'Panadol' and for pediatric use as 'Panadol Elixir'. It has long been used as an analgesic and antipyretic, and has been reported in studies to be quite safe in terms of side effects (Brodie et al. 1947; Bertolini et al. 2006; Dear and Bateman 2020).

The United States Food and Drug Administration (FDA) has approved paracetamol as a safe over-the-counter medication, but also emphasizes that overdose can lead to liver failure. In 2011, the FDA introduced a regulation limiting the amount of paracetamol to 325 mg in prescription combinations to prevent high-dose usage that could result in severe liver damage (FDA 2011).

2.2. Paracetamol Metabolism

Paracetamol is primarily metabolized in the liver, and the predominant pathways in this process are glucuronidation (50% to 70%) and sulfation (25% to 35%). Metabolites that undergo sulfation by the enzymes SULT1E1, SULT1A1 and SULT1A3, and glucuronidation by the enzymes UGT1A1 and UGT1A6 are eliminated from the body via the urine. Only 2-5% of the drug is excreted unchanged from the body (Zhao & Pickering 2011; McGill et al 2013). Other enzymes that play a smaller role in metabolism are cytochrome p450 enzymes. These enzymes, particularly CYP2E1, catalyze the oxidation process, leading to the formation of the toxic metabolite NAPQI. (McGill et. al., 2013). Under normal conditions, NAPQI is conjugated with glutathione to provide detoxification, but when high doses of paracetamol are used, NAPQI is released as a result of depletion of glutathione stores, damaging the cells in the liver and causing toxic effects. In addition, a small portion of paracetamol undergoes deacetylation to form the p-aminophenol compound, which is then converted into the N-arachidonoylphenolamine (AM404) compound, which is associated with the analgesic effect, by the fatty acid amide hydrolase (FAAH) enzyme in the brain (Graham et. al., 2013). Phase I and Phase II metabolic reactions play a role in this process. In Phase I, the drug undergoes oxidation by cytochrome P450 enzymes, increasing its polarity, and in Phase II, it is made water-soluble by sulfation and glucuronidation and excreted from the body in the urine (Zhao & Pickering, 2011).

2.3. Paracetamol Toxicity

Paracetamol (acetaminophen) is a widely used and considered safe drug. However, it can cause serious toxic effects in case of misuse, abuse

or overdose. The most striking aspect is that it presents an insidious clinical course, often asymptomatic in the early stages, but capable of leading to severe organ failure over time and requiring intensive treatment to manage these serious outcomes. (Fisher & Curry, 2019).

The toxicity caused by paracetamol is also directly related to the metabolism of the drug. Under normal conditions, it is detoxified by sulfation and glucuronidation in the liver, converted into harmless metabolites and excreted from the body through the kidneys. However, as a result of high-dose exposure, a toxic intermediate, NAPQI, is formed by cytochrome P450 (CYP2E1) enzymes. While NAPQI is normally neutralized by binding with glutathione, in the event of overdose, NAPQI, which is released as a result of depletion of glutathione stores, binds to intracellular proteins and causes various serious consequences such as cell death, mitochondrial dysfunction and oxidative damage (Isbister & Chiew, 2021). When taken in high doses, paracetamol can cause serious toxic effects and damage to the liver, kidneys, central nervous system, cardiovascular system and gastrointestinal system. Paracetamol poisoning can develop acutely or chronically and in both cases can have serious clinical consequences (Fisher and Curry 2019; Chidiac et al. 2023).

2.4. Toxicity Management and Treatment

The treatment of paracetamol toxicity varies depending on the time of ingestion and the patient's clinical condition. Gastrointestinal decontamination may be considered in patients presenting within the first few hours. If the patient is conscious, the use of activated charcoal is recommended; however, gastric lavage and whole bowel irrigation are generally not effective (Janssen & Singh-Saluja, 2015; Agrawal & Khazaeni, 2023).

The most effective treatment for paracetamol toxicity is the administration of N-acetylcysteine (NAC). NAC prevents liver damage caused by the toxic metabolite NAPQI, replenishes glutathione, and acts as an antioxidant. If administered within 8 hours of ingestion, NAC can be completely protective against liver toxicity. However, NAC is still recommended even for patients presenting after 24 hours. NAC treatment is indicated for patients with evidence of liver injury based on the Rumack-Matthew nomogram, those with unknown ingestion time but serum levels above 10 mcg/mL, and those with toxic serum acetaminophen levels (Fukumoto, 2010; Agrawal & Khazaeni, 2023). NAC can be administered both orally and intravenously (IV). The IV route is often preferred due to its shorter hospital stay and better tolerability, as the oral form has an unpleasant taste and odor. Oral NAC is administered over 72 hours in 18 doses, whereas IV treatment follows a 20-hour protocol. IV NAC

is especially preferred in cases of fulminant hepatic failure and during pregnancy. In patients with fulminant liver failure, NAC treatment may be required for more than 72 hours until liver transplantation or clinical recovery occurs (Agrawal & Khazaeni, 2023).

In severe cases, hemodialysis may be effective for rapidly removing paracetamol and its toxic metabolites, particularly in patients with renal failure. Additionally, it is not necessary to adjust NAC dosing or repeat paracetamol level measurements in patients with alcoholism or chronic disease (Agrawal & Khazaeni, 2023).

2.5. Traditional Liver Enzymes and Their Limitations

Laboratory tests play a crucial role in the diagnosis of liver diseases and the differentiation of their underlying causes. Currently, liver tests are generally divided into three main categories:

Tests indicating liver function, including serum bilirubin, serum proteins, and coagulation parameters (e.g., prothrombin time, INR).

Tests indicating liver injury, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), γ-glutamyl transferase (GGT), lactate dehydrogenase (LDH), and occasionally glutamate dehydrogenase (GLDH).

Viral hepatitis serologies.

A fourth category is alpha-fetoprotein (AFP), which serves as a biomarker of hepatocyte proliferation.

Although ALT and AST are among the most commonly used parameters in both clinical diagnostics and research involving liver injury, there remains considerable uncertainty regarding their proper application and interpretation. Furthermore, recent data have highlighted the limitations of serum aminotransferases in both early detection of liver injury and the prediction of patient prognosis.

In recent years, a number of newly developed biomarkers have shown potential to either replace or at least complement serum aminotransferases for certain applications. Some studies suggest that one or more of these novel biomarkers may soon supplement or even replace existing biomarkers in clinical practice. Therefore, it is essential to understand how aminotransferases function, why their use is limited, and what roles the emerging biomarkers might play in the future for the diagnosis and monitoring of liver injury (McGill, 2016).

2.6. Novel Biomarkers

Paracetamol (acetaminophen) overdose is one of the most common reasons for hospital admission, and the decision to initiate treatment largely depends on the ingested dose and the timed plasma paracetamol concentration. However, patients often present to the hospital either before liver injury (acute liver injury, ALI) has occurred or at a stage too early for existing tests (e.g., alanine aminotransferase, ALT) to detect any damage. As a result, this early clinical uncertainty limits the ability to assess hepatocellular injury and complicates personalized treatment decisions. Therefore, novel biomarkers capable of identifying paracetamol-induced ALI at the earliest possible stage are needed. Such biomarkers could support more accurate treatment in high-risk patients while enabling safe and timely discharge in low-risk individuals.

MicroRNAs are short, non-coding RNAs involved in the regulation of gene expression. Among them, certain microRNAs including miR-122 possess ideal features for use as biomarkers, such as high stability, tissue specificity, and detectability across multiple species. Recent studies have shown that miR-122 is highly liver-specific and becomes detectable in serum following liver injury. Moreover, microRNAs play critical roles in numerous cellular processes such as cell proliferation, metabolism, and differentiation, providing an additional layer of post-transcriptional gene regulation. Studies have demonstrated that miR-122 levels increase reliably following liver injury induced by hepatotoxicants. For example, after treatment with the reference hepatotoxin carbon tetrachloride in rats, serum miR-122 levels were reported to increase by 6000-fold. These features—high sensitivity, specificity, practicality, and translatability—make miR-122 an attractive candidate for evaluating liver injury in toxicology studies (Sharapova et al., 2016).

Recently, other sensitive biomarkers such as high mobility group box-1 (HMGB1), keratin-18 (K18, both cleaved and full-length forms), and glutamate dehydrogenase (GLDH) have been identified in acetaminophen-induced acute liver injury. While cleaved K18 indicates apoptosis, full-length K18 reflects necrosis; HMGB1 is associated with cell death and immune activation. GLDH, found in hepatic mitochondria, serves as a marker for mitochondrial damage. These blood-based biomarkers have been applied in patients with acetaminophen-induced liver toxicity in the United States and the United Kingdom, and some have demonstrated superior predictive accuracy compared to conventional tests. Studies in patients with acetaminophen-induced liver injury have reported that biomarkers such as miR-122, HMGB1, and necrotic K18 can detect liver injury early and reliably. Moreover, these biomarkers have been shown to

provide faster and more accurate results than traditional methods. Nevertheless, human studies evaluating the clinical value of these biomarkers in detecting acetaminophen-induced liver injury earlier than existing methods remain limited. Therefore, further research is needed to better understand their clinical utility and impact on patient management (Antoine et al., 2013).

3. Conclusion

Paracetamol, a widely used and considered safe analgesic and antipyretic drug worldwide, can cause severe liver damage when taken in high doses or used for a prolonged period. Traditional diagnostic methods are often insufficient for early detection of acute toxicity. This limitation may lead to delays in treatment and adversely affect patient prognosis.

In recent years, novel biomarkers such as miR-122, HMGB1, and K18 have shown promising results in the early and sensitive detection of liver injury. These biomarkers offer advantages over existing tests due to their specificity, early detectability, and ability to reflect the underlying mechanisms of cellular damage. However, further studies are needed before these biomarkers can be routinely applied in clinical practice. Advanced research in this area may enable earlier diagnosis of paracetamol-induced liver injury and support personalized treatment approaches.

Acknowledgement

The authors thank the Faculty of Pharmacy at Agri Ibrahim Cecen University for their support. This work is based on undergraduate theses, with the biomarker section added independently by the authors.

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Chapter 9

APPLICATIONS OF ARTIFICIAL INTELLIGENCE IN TOXICOLOGY

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1. Introduction

Artificial Intelligence (AI) is a technology that enables computers and machines to learn like humans, make autonomous decisions, distinguish objects, and solve problems. In other words, it is a type of programming designed to perform human-like mental functions (Yılmaz & Ölçer 2021). AI is actively used in many fields such as engineering, finance, education, security, marketing and sales, and healthcare (Akkoyun, 2022). Machine learning, a subset of artificial intelligence, enables systems to learn from data and make inferences based on this learned data (Das et. al., 2015). Machine learning systems, which can predict with stored data, offer information different from what is already known and improve their capabilities autonomously, are categorized into three types: supervised learning, unsupervised learning, and reinforcement learning.

Toxicology is the branch of science that studies the harmful effects of substances, chemicals, and certain conditions on humans, animals, and the environment; it investigates the mechanisms and processes causing these harmful effects and works on their prevention and mitigation. Artificial intelligence and machine learning applications have begun to be implemented in various fields of toxicology, including cardiovascular toxicology, neurotoxicity, nanotoxicology, toxicokinetics, dermal toxicity, and carcinogenesis. This section aims to evaluate how artificial intelligence and machine learning techniques are used in toxicological research and the current scientific developments in this emerging field (Lin & Chou 2022; Pérez Santín et. al., 2021).

2. General Information

2.1. Toxicology

Toxicology is a scientific discipline that studies the harmful effects of chemical substances or environmental factors on humans, animals, and living organisms in general. This field attempts to understand the toxic effects and their underlying mechanisms and develops various methods for prevention and remediation of these harmful effects. Furthermore, toxicology plays a critical role in chemical safety, risk analysis, and environmental protection.

Toxicology encompasses many subfields including chemical toxicology, organ system toxicology, environmental toxicology, toxicokinetics, occupational toxicology, food toxicology, and clinical toxicology (Lin & Chou 2022).

This science, which has a long history, developed when humans accidentally discovered the harmful effects of substances in their environment.

Records dating back to around 1500 BC show that substances from plants like hemlock, opium, certain metals, and poisons used on arrows were applied against enemies or for internal executions. Basic concepts of toxicology began to take shape during the Renaissance and Enlightenment periods.

Traditionally known as the "science of poisons," this discipline is concerned with the physical and chemical properties of toxic substances, their behavioral and physiological effects on living systems, qualitative and quantitative analytical methods, and developing treatments for poisonings (Langman & Kapur 2006).

Toxicology is closely related to many sciences including biology, chemistry, pharmacology, genetics, anatomy, psychology, mathematics, and statistics. It functions to understand mechanisms causing toxic effects, predict these effects beforehand, and develop treatment strategies.

Its main goal is to protect humans and their environments from hazards. Therefore, toxicological data is critical for risk assessment studies that help prevent adverse health effects in humans. Using these data, safe exposure limits are established, and preventive measures are taken against harmful events (Lee, 2018).

2.2. Artificial Intelligence (AI)

Artificial intelligence (AI) is a technology that aims to enable computers and machines to imitate human intelligence and perform tasks requiring cognitive functions. In recent years, AI has rapidly developed, creating significant changes in human life and gaining an important position (Ciallella & Zhu 2019; Zhang & Lu 2021). AI has been developing for more than 70 years. The first artificial neural network was proposed in 1943, and the term "artificial intelligence" was officially introduced in 1956. In the 1980s, AI accelerated significantly with the recognition and acceptance of backpropagation algorithms. In the 21st century, new application areas emerged with the contribution of the internet (Ciallella & Zhu 2019). In addition to Alan Turing, who laid the theoretical foundation by proposing a mathematical computer model, neurologists McCulloch and Pitts developed the first neural network model in 1943. Psychologist Rosenblatt's "Perceptron" model in 1957 is also among the important milestones in AI (Jiang et. al., 2022).

AI currently holds critical importance in healthcare. Computer-assisted diagnosis programs were first used by physicians in the 1950s, and today AI is actively used in clinical decisions, disease diagnosis, treatment, and drug discovery. AI and automation systems also play a major role in processing and analyzing medical data (Secinaro et. al., 2021).

2.3. Machine Learning (ML)

Machine learning (ML), a subset of artificial intelligence, encompasses many disciplines such as statistics, probability theory, and algorithms. The algorithms in this field enable making predictions or decisions without explicit programming by learning from data. Its foundations date back to the 17th century, drawing on Bayes and Laplace's least squares and Markov chain derivatives. The term machine learning was first introduced by Arthur Samuel and has since made significant advancements, playing an important role in biometric recognition, medical diagnosis, natural language processing, and many other fields (Jiao et. al., 2020).

Machine learning generally consists of three phases: model building, performance evaluation, and deployment. The first phase starts with defining a user-specified problem, preparing data, and selecting an appropriate model. In the second phase, tests are applied to determine the best-performing model. Finally, the model is deployed and solutions are generated using real data. Machine learning learns abstract patterns like humans, analyzes these patterns, and develops more complex analytical models in large computing systems based on the data obtained (Kühl et. al., 2019).

The main goal of machine learning is to develop computer programs that can solve problems without explicit programming. Generally, machine learning is divided into three main types: supervised, unsupervised, and reinforcement learning (Lin & Chou 2022).

Types of Machine Learning

Supervised Learning: Uses labeled data to create predictive models and learns to make correct predictions for unknown inputs. In toxicology, it is used to classify chemicals as toxic or non-toxic using toxicological data. Accurate training requires toxicological data. Supervised learning uses classification for qualitative outcomes and regression for quantitative predictions (Sinha et. al., 2020).

Unsupervised Learning: Unlike supervised learning, it uses unlabeled data. It often employs clustering algorithms that group data based on similarities. Semi-supervised and reinforcement learning methods also fall under this category. Semi-supervised learning adapts model behavior based on environmental changes (Jiao et. al., 2020).

Reinforcement Learning: This method improves a system's actions through reward and punishment mechanisms. For example, a robot is rewarded when it successfully carries a load and penalized when it fails. Over time, this technique improves the robot's behavior (Akkoyun, 2022).

2.4. Machine Learning Algorithms Used in Toxicology

Support Vector Machines (SVM)

Developed by Vapnik and his team, SVM is one of the most widely used ML algorithms. It processes chemical data by transforming original input descriptors into a higher-dimensional space using a kernel function to perform classification. The SVM model determines a hyperplane that maximizes the distance between chemical classes using the kernel function and other parameters. This feature allows SVM to be extensively used in chemical toxicity prediction and has facilitated the development of 304 different models so far (Guo et. al., 2023).

Decision Trees (DT)

Decision trees are models used for classification and regression, shaping processes in tree-like structures. Each node represents a feature, and each branch corresponds to possible values of that feature. DT algorithms provide intuitive models that simplify the interpretation of chemical toxicity predictions. However, because the cutoff points in these algorithms ignore the values of chemical features, chemicals with different properties at similar points can be assigned to the same class. This can negatively affect model performance, and few toxicological prediction models have been developed using DT (Guo et. al., 2023).

Random Forests

Widely used in various applications, this model is an ensemble learning method that combines multiple decision trees for classification. It creates parallel decision trees on different data subsets and typically produces results using majority voting or averaging. This approach minimizes overfitting and increases prediction accuracy. It employs bagging and random feature selection techniques to construct decision trees. Random forests can handle both classification and regression problems and perform well with categorical and continuous data (Sarker, 2021).

Artificial Neural Networks (ANN) and Deep Learning (DL)

Neural networks mimic the functioning of the human brain and aim to recognize significant relationships within data. Artificial neural networks (ANN) model artificial or biological neurons and consist of three layers (input, hidden, and output), where neurons are connected by weights. These weights are adjusted to minimize errors between predicted and actual outputs.

Deep neural networks (DNN) are extensions of ANN with many hidden layers, enabling them to recognize much more complex data. DNNs

offer better opportunities for modeling complex relationships between chemical structures and toxic effects, where traditional machine learning models struggle. In toxicity prediction, deep learning methods such as Multilayer Perceptron (MLP) and Convolutional Neural Networks (CNN) rank among the most used algorithms, with 78 and 9 models respectively (Guo et. al., 2023; Nasnodkar et. al., 2023; Mahesh, 2020).

2.5. Data Sources and Digital Infrastructures

Bioactivity databases that provide information on the biological activities of chemicals are frequently utilized in *in silico* toxicological analyses (Prachayasittikul et. al., 2015). For instance, the ChemNavigator database is commonly used before conducting docking studies and quantitative structure-activity relationship (QSAR) analyses (Macalino et. al., 2015; Prachayasittikul et. al.,, 2015). ZINC, another valuable resource, is particularly suitable for docking studies due to its extensive library of drug-like three-dimensional compounds (Macalino et. al., 2015).

ChEMBL includes bioactivity data, ADMET properties (absorption, distribution, metabolism, elimination, and toxicity), and binding affinity information (Gaulton et. al.,, 2017). PubChem, a publicly accessible database, is also a key resource for *in silico* design and toxicological research (Kim et. al.,, 2019). Additionally, BindingDB provides extensive data on protein-ligand interactions and binding affinities, supporting biological and toxicological analyses (Gilson et. al., 2015).

Target databases play a critical role in identifying drug-target interactions and understanding the roles of these targets in disease mechanisms. The Therapeutic Target Database (TTD), for example, offers comprehensive data on drug-interacting therapeutic targets (Yang et. al., 2016). Meanwhile, the Protein Data Bank (PDB) serves as a global repository of three-dimensional structural data for biological macromolecules (Berman et. al., 2000).

2.6. Artificial Intelligence-Based Modeling Techniques

2.6.1. Computer-Aided Drug Design (CADD)

Every year, a vast number of chemicals are discovered and stored in digital databases, necessitating effective processing of this information. The effects of drugs on humans are based on the interaction between the drug molecule (ligand) and the target biomacromolecule. The nature of these interactions is determined by the atomic structure of the ligand and the dynamics of these atomic bonds.

Computational chemistry, which enables in-depth analysis of molecular interactions, can predict the pharmaceutical properties and pharmaco-

logical effects of drugs. Driven by these analyses, it has become possible to design new drugs in silico. The drug development process involves multiple stages including target identification, validation, lead identification, and optimization. At all these stages, models supported by experimental studies are developed through analysis of the required biological and chemical data (Macalino et. al., 2015; Prachayasittikul et. al., 2015; BioinfoRange, 2020).

2.6.2. Structure-Based Drug Design (SBDD)

This approach is based on designing new molecules that can bind to the target site by using the three-dimensional structural information of the target protein or enzyme. At the core of this process lies data on protein-ligand interactions. In this process, structure-based virtual screening (SBVS), molecular docking, and molecular dynamics (MD) simulations are the most commonly employed methods (Batool, Ahmad, & Choi, 2019; Macalino et. al., 2015).

SBDD comprises two main approaches:

De novo design: New structures are created by selecting and assembling small molecular fragments that fit into the binding site.

Virtual screening: Existing compound databases are screened to identify molecules with high potential to bind to the target (Zhong et. al., 2018; BioinfoRange, 2020).

2.6.3. Ligand-Based Drug Design (LBDD)

When three-dimensional structural data of the target protein is unavailable, information obtained from previously known active ligands is used to predict new potential compounds. The fundamental assumption here is that structurally similar molecules exhibit similar biological activities (Macalino et. al., 2015).

Quantitative Structure-Activity Relationships (QSAR):

QSAR attempts to mathematically analyze the relationship between the biological activities and structural properties of compounds. The accuracy of the model depends directly on the quality of data, the selection of molecular descriptors, and the model's validity. 3D QSAR methods like CoMFA represent advanced examples of this approach. More advanced models such as 4D, 5D, and 6D QSAR have been developed, which account for factors like ligand conformation, receptor flexibility, and solvation effects, respectively (Taft et. al., 2008; BioinfoRange, 2020).

Pharmacophore-Based Modeling:

This method identifies common features shared by compounds exhibiting similar biological activities. It helps in identifying active molecules without requiring information about the binding site. Software such as Discovery Studio, PHASE, and LigandScout are frequently used to automatically generate pharmacophore models. To improve model sensitivity, pharmacophore validation and refinement are essential. (Singh et. al., 2021; Shim & MacKerell, 2011, Macalino et. al., 2015).

2.6.5. Prediction of ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) Properties

Identifying the pharmacokinetic and toxicological properties of drug candidates early in the drug development process is crucial. Therefore, virtual screening methods are used to filter out unsuitable compounds before experimental testing.

Classic rules such as Lipinski's Rule of Five are commonly applied. Tools like ChemBioServer and FAF-Drugs2 analyze and filter compounds based on toxicity, physicochemical properties, and reactivity. Additionally, tools like SMARTCyp and MetaSite enable prediction of metabolic pathways and toxic effects of compounds (Macalino et. al., 2015; Prachayasittikul et. al., 2015).

3. Conclusion

Studies show that artificial intelligence and machine learning systems provide faster, more accurate, and cost-effective toxicity predictions compared to traditional methods. These technologies enable large-scale data analysis, enhancing decision-making in toxicological assessments. However, their reliable use requires high-quality, standardized datasets and transparent, interpretable models. The development of hybrid systems and interdisciplinary collaboration is also essential. In conclusion, AI and ML technologies have the potential to transform risk assessment in toxicology and play a critical role in improving human health and environmental safety.

Acknowledgement

The authors would like to express their sincere gratitude to the Faculty of Pharmacy at Agri Ibrahim Cecen University for their valuable support and contributions throughout this research. This work was conducted as part of undergraduate thesis projects.

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