ADVANCES IN BIOCHEMISTRY, PHARMACOLOGY, AND INDUSTRIAL CHEMISTRY: APPLICATIONS, EXTRACTION METHODS, AND EMERGING TRENDS

EDITOR

Assist. Prof. Dr. Nilgün ONURSAL

İKSAD

Publishing House

ADVANCES IN BIOCHEMISTRY, PHARMACOLOGY, AND INDUSTRIAL CHEMISTRY: APPLICATIONS, EXTRACTION METHODS, AND EMERGING TRENDS

EDITOR

Assist. Prof. Dr. Nilgün ONURSAL

AUTHORS

Assoc. Prof. Dr. Mustafa Oğuzhan KAYA

Assist. Prof. Dr. Zeynep ALKANALKAYA

Lect. Dr. Nurten YILMAZ

Dr. Nazangül ÜNAL

Lec. Mustafa ATALAN

Halil İbrahim TAŞ

Mehmet Tevfik ADICAN

Musa KARADAĞ

Serkan ÇELİK

Şeyhmus TÜMÜR

İKSAD Publishing House

Institution of Economic
Development and Social
Researches Publications®
(The Licence Number of Publicator: 2014/31220)
TURKEY TR: +90 342 606 06 75
USA: +1 631 685 0 853
E mail: iksadyayinevi@gmail.com
www.iksadyayinevi.com

ISBN: 978-625-378-100-2
Cover Design: İbrahim KAYA
December / 2024
Ankara / Turkey
Size = 16x24 cm

CONTENTS

PREFACE

This book is a comprehensive source that delves deeply into the latest developments and applications in the fields of biochemistry, pharmacology, and industrial chemistry. Each chapter allows for a thorough examination of scientific discoveries and innovations across a broad spectrum, guided by the most recent findings and methods in the relevant fields. One of the key topics of this book is *Polyphenol Oxidase (PPO), a fundamental component of biochemistry, and its significance in various industrial and pharmaceutical fields. Additionally, the **pharmacological effects of Allicin, with its potential health benefits, and the **industrial use and biological activities of salts, thickening agents, and pyrazole derivatives*, are major themes explored.

The book also presents a scientific perspective on the *geological and geomorphological features of Iğdır Province, including its underground water resources and the sustainable management of these resources. **Nuclear chemistry and its applications in medicine, particularly the effects of radioactive elements on biological systems, open new horizons in understanding, while **chemical risk factors in cosmetic laboratories* are also addressed as a significant topic.

Another notable focus of the book is the *bioactive potential of postbiotics* and their health benefits, shedding light on new research in this emerging field. Furthermore, cutting-edge studies in biotechnology and industrial chemistry are brought together in this work. This book caters not only to academic researchers but also to industry professionals, healthcare scientists, and chemical engineers.

We hope that this book provides readers with a broad perspective on biochemistry, pharmacology, environmental chemistry, and industrial chemistry, while pushing the boundaries of these disciplines. Through a growing scientific understanding and innovative applications, this work aims to contribute to the existing body of knowledge in these fields.

We hope you find value and insight in the rich content and information contained within this book.

Assist. Prof. Dr. Nilgün ONURSAL

Siirt University

CHAPTER 1

POLYPHENOL OXIDASE (PPO): BIOCHEMISTRY, EXTRACTION METHODS, APPLICATION AREAS AND INDUSTRIAL IMPORTANCE

Halil İbrahim TAŞ[1],

Assoc. Prof. Dr. Mustafa Oğuzhan KAYA*[1]

DOI: https://dx.doi.org/10.5281/zenodo.14563271

[1] Kocaeli Üniversitesi, Fen-Edebiyat Fakültesi, Kimya Bölümü Kocaeli, TÜRKİYE.
*Corresponding author: oguzhan.kaya@kocaeli.edu.tr Orcid ID:0000-0002-8592-1567
h_ibrahim39@hotmail.com Orcid ID: 0009-0006-1472-8264

INTRODUCTION

Polyphenol oxidase (PPO) is a copper-containing enzyme found in plants, fungi, animals, and some microorganisms. Known as a defense mechanism in plants, PPO also catalyzes the conversion of various phenolic compounds into quinones through oxidative reactions. The primary function of PPO is to hydroxylate monophenols into o-diphenols and subsequently oxidize o-diphenols to form reactive products called o-quinones. Through non-enzymatic reactions, o-quinones polymerize and transform into dark pigments such as melanin, resulting in undesirable darkening in fruits and vegetables (Yörük and Marshall, 2003; Vamos-Vigyazo, 1981).

The function of PPO in plants is to limit the effects of external factors by generating a protective response during environmental stress situations like injury and pathogen attacks. This reaction, known as enzymatic browning, can significantly reduce the quality of agricultural products. The browning triggered by PPO activity in products like apples, potatoes, and bananas creates a negative consumer perception and is considered a quality loss in the food industry (Nicolas et al., 1994; Whitaker, 1994). Thus, controlling PPO in food processing is essential to extending product shelf life and increasing consumer acceptance (Mathew and Parpia, 1971).

PPO is divided into subclasses like tyrosinase, catechol oxidase, and laccase. Tyrosinase catalyzes the hydroxylation of monophenols into o-diphenols and the subsequent oxidation of these o-diphenols, whereas catechol oxidase only oxidizes o-diphenols. Laccase, in turn, oxidizes phenols, resulting in the formation of radical intermediates and participating in the synthesis of biopolymers (Lerch, 1995; Sanchez-Ferrer et al., 1995). The substrate specificity of plant-derived PPO, along with its effectiveness in converting phenols at low concentrations, makes this enzyme ideal for biosensor design and eco-friendly biotechnological applications. Thanks to these properties, PPO has a wide range of applications in fields like biotechnology and healthcare (Whitaker, 1995; Solomon and Lowery, 1993).

2. PPO-Catalyzed Reactions and Mechanisms

PPO-catalyzed reactions occur in two stages: first, monophenols are hydroxylated into o-diphenols through tyrosinase activity; then, these o-diphenols are oxidized and transformed into o-quinones. These quinones are converted into melanin pigments through non-enzymatic polymerization reactions, forming dark-colored polymers (Nicolas et al., 1994). Two copper ions in the active site of PPO play a role in its catalytic effect. By interacting with oxygen molecules, PPO undergoes temporary structural changes in its active site, transforming the substrate into o-quinone. This process involves three main states of PPO: met form (Cu^{2+}), deoxy form (Cu^{+}), and ox form (Cu^{2+}). The enzyme initiates o-quinone formation by combining with oxygen and transitioning into the ox form (Lerch, 1995; Solomon and Lowery, 1993).

In the first stage, the ox form of PPO hydroxylates monophenols to produce o-diphenols. These o-diphenols are then oxidized into o-quinones, and these reactive quinones are transformed into melanin pigments through non-enzymatic reactions. This reaction cycle accelerates PPO's defense mechanism, creating resilience under oxidative stress conditions and against pathogen attack (Mathew and Parpia, 1971; Mayer and Harel, 1979).

3. Extraction and Purification Methods of PPO

The extraction and purification of PPO are essential for maintaining the biochemical properties of the enzyme and its efficient utilization in industrial applications. Given that PPO exhibits varying physical and chemical characteristics depending on its source, factors such as enzyme activity, purity, and cost are taken into consideration in the extraction process. The methods employed in PPO extraction vary according to the enzyme source and commonly include solvent precipitation, three-phase separation, temperature-induced phase separation, and chromatography (Batista et al., 2014; Panadare and Rathod, 2017).

3.1 Solvent Precipitation

Organic solvents are widely utilized for PPO extraction. Specifically, solvents like acetone and ethanol are used to precipitate proteins and separate PPO from impurities. Cooled organic solvents enable solvent precipitation at low temperatures, which aids in precipitating PPO without damaging the protein structure. Precipitates obtained using 50% acetone or 60% ethanol are often termed "acetone powder" and can be stored for extended periods, thus providing a stable form of PPO (Cheng et al., 2014; Bravo and Osorio, 2016).

3.2 Ammonium Sulfate Precipitation

A commonly used method to enhance PPO purity is ammonium sulfate precipitation. As a widely used salt in protein precipitation processes, ammonium sulfate maintains PPO stability in aqueous solutions. In this process, the enzyme is precipitated at low temperatures using 30-85%

ammonium sulfate. Many researchers prefer this method to purify PPO from impurities and achieve high yields (Nadar et al., 2017; Panadare and Rathod, 2017).

3.3 Temperature-Induced Phase Separation (TIPS)

The TIPS method is based on the principle that surfactants form a micellar phase in aqueous solutions as temperature increases. In this method, the enzyme dissolved at low temperatures precipitates by transitioning to the micellar phase when heated to 37°C. TIPS is widely used in PPO extraction as it effectively removes phenols. Non-ionic surfactants like Triton X-114 are employed, and the phases are easily separated by centrifugation (Onsa et al., 2000; Zaini et al., 2013).

3.4 Three-Phase Partitioning (TPP)

Three-phase partitioning (TPP) is an efficient and cost-effective method that removes enzyme impurities with solvents such as ammonium sulfate and t-butanol. TPP serves as both an extraction and purification method, enabling rapid and cost-effective PPO recovery. PPO is usually precipitated with ammonium sulfate and collected in the t-butanol phase via centrifugation (Niphadkar and Rathod, 2015; Alici and Arabaci, 2016; Kaya et al., 2024a).

3.5 Aqueous Two-Phase Extraction (ATPS)

Aqueous two-phase extraction (ATPS) purifies PPO using combinations of water-soluble polymers with salt or salt-alcohol. Polyethylene glycol (PEG) and phosphate salt combinations are typically preferred for PPO extraction. ATPS is a low-cost, scalable method regarded as environmentally friendly. This technique separates enzymes from impurities based on the physicochemical properties of different phases (Sojo et al., 1998; Vaidya et al., 2006).

3.6 Chromatographic Purification

Chromatographic techniques are among the most reliable methods for obtaining high-purity PPO. Methods such as gel filtration chromatography and ion exchange chromatography, which separate PPO by molecular weight, are frequently employed. For example, PPO can be purified to high levels of purity using Sephadex G-100 or DEAE-Sepharose columns. Affinity chromatography selectively purifies PPO by specific binding to its inhibitors or substrates (Whitaker, 1994; Espin et al., 1997; Kaya et al., 2024b).

Each of these methods aims to achieve the highest PPO purity based on its intended application. Optimization of PPO extraction and purification should be tailored to criteria such as enzyme yield, purity level, and stability.

4. Inhibition and Stabilization of PPO

Polyphenol oxidase (PPO) is one of the primary contributors to enzymatic browning, leading to quality deterioration, particularly in fruits and vegetables. In the food industry, inhibiting PPO activity is essential for preserving product appearance and extending shelf life. Stabilization of the enzyme is also necessary for its application in biotechnological and industrial contexts. Physical and chemical methods such as heat treatment, chemical inhibitors, ultraviolet (UV) light, and high-pressure processing are used for PPO inhibition, while methods like immobilization, low-temperature storage, and the use of preservative compounds are favored for enzyme stabilization (Nicolas et al., 1994; Tiwari and Cullen, 2013; Kaya et al., 2024a; Kaya et al., 2024b).

4.1 Physical Inhibition Methods

Heat treatment is one of the most commonly employed physical methods for PPO inhibition. PPO can generally be inhibited at temperatures ranging between 60-80°C; however, these temperatures can alter the taste and texture of certain foods (Chazarra et al., 1996; Nicolas et al., 1994). During heat treatment, PPO's structure deteriorates, resulting in deformations at the substrate binding site and subsequent loss of enzyme activity. Another physical method, high-pressure application, reduces PPO activity by disrupting its structure, breaking the hydrogen bonds within its protein structure (Barrett et al., 1991; Tiwari and Cullen, 2013).

Ultraviolet (UV) light also serves as a physical method to reduce PPO activity by breaking peptide bonds within the enzyme structure. This method is particularly effective for surface sterilization, although it is less effective than heat treatment or high pressure in PPO inhibition (Guray and Sanlı-Mohamed, 2013).

4.2 Chemical Inhibition Methods

Various chemical inhibitors are employed to control PPO activity. Common inhibitors include ascorbic acid, sodium metabisulfite, citric acid, and benzoic acid, which block PPO activity by different mechanisms. Ascorbic acid reduces quinones back to phenols, thus preventing enzymatic browning. Sodium metabisulfite also reduces quinones, halting the browning reaction; however, the health risks associated with this compound should be considered (Vamos-Vigyazo, 1981; Whitaker, 1994).

Organic acids such as citric acid inactivate PPO's active site by lowering the surrounding pH. Some phenolic compounds or metal ions can also temporarily inhibit PPO activity (Niphadkar and Rathod, 2015). The effectiveness of chemical inhibitors varies with conditions such as pH and temperature, so careful selection of inhibitors in food applications is essential (Mayer and Harel, 1979).

4.3 PPO Stabilization

In certain industrial applications, PPO stabilization ensures long-term enzyme use. Enzyme immobilization, a commonly used method for PPO stabilization, involves attaching the enzyme to a carrier matrix, which extends enzyme life and allows PPO to be reused in devices like biosensors (Espin et al., 1997).

Low-temperature storage is another frequently preferred PPO stabilization method. Freezing or storing PPO at low temperatures prevents enzyme degradation and preserves its activity; however, enzyme activity may decrease during re-thawing. Thus, adding stabilizing compounds, such as glycerol, can enhance enzyme stability (Tiwari and Cullen, 2013; Nadar et al., 2017).

Buffer solutions and preservative compounds also increase PPO's resistance to environmental changes. Stabilizing PPO is critical for its long-term use in biosensors, bioreactors, and wastewater treatment systems (Vaidya et al., 2006).

5. Industrial Applications and Usage Areas of PPO

Polyphenol oxidase (PPO) holds significant importance in the food industry, particularly in quality control and product processing. Enzymatic browning, catalyzed by PPO in food products, detracts from product quality and consumer acceptance. This section discusses the browning reactions induced by PPO in foods, inhibitors used to prevent these reactions, the positive roles of PPO in certain foods, and other industrial applications.

5.1 The Problem of Enzymatic Browning in Foods

Enzymatic browning in foods results from PPO oxidizing phenolic compounds, leading to undesirable color changes in fruits and vegetables. In products such as apples, bananas, and potatoes, PPO activity intensifies post-harvest or during processing-related injuries. This PPO-catalyzed reaction facilitates the oxidation of phenolic compounds into o-quinones, which subsequently polymerize to form brown or black pigments (Vamos-Vigyazo, 1981; Nicolas et al., 1994). The browning observed in fruits and vegetables decreases visual quality, affecting consumer appeal and the market value of the product (Mathew and Parpia, 1971).

5.2 Chemical Inhibitors Used to Prevent Enzymatic Browning

A range of chemical inhibitors is utilized to manage the browning reaction caused by PPO in foods. Ascorbic acid is a commonly used inhibitor that blocks PPO activity by reducing quinones and reversing them to phenols, preventing browning. Additional inhibitors, such as sodium metabisulfite and citric acid, reduce quinones or lower the pH to inhibit PPO activity (Vamos-Vigyazo, 1981; Whitaker, 1994). However, the health risks of certain chemical inhibitors should be carefully evaluated, and the use of compounds like sodium metabisulfite is regulated by legal standards (Chazarra et al., 1996).

5.3 Physical Methods to Prevent Enzymatic Browning

Physical methods for reducing PPO activity in foods include heat treatment, UV light, and high-pressure applications. Heat treatment is the most frequently used method in food processing to diminish PPO activity, typically at temperatures ranging from 60-80°C. However, it is important to note that high temperatures may affect the texture and nutritional value of foods (Nicolas et al., 1994). High-pressure applications reduce enzyme activity by altering PPO’s structure, helping to prevent browning while retaining the natural color, flavor, and nutritional value of foods (Barrett et al., 1991; Tiwari and Cullen, 2013).

5.4 Positive Effects of PPO: Color and Flavor Development in Fermented Products

In some instances, the oxidative effects of PPO in foods are considered beneficial. Particularly in the processing of black tea, cocoa, and coffee, PPO-catalyzed oxidation of phenolic compounds contributes to the distinctive color and aroma profiles of these products (Lourenco et al., 1992; Ullah, 1991). During the fermentation of tea, PPO oxidizes compounds such as catechins, which impart the characteristic color and flavor of black tea. Similarly, during cocoa fermentation, PPO oxidizes tannins and other polyphenols, leading to the flavor and color development specific to cocoa beans (Lee et al., 1991).

5.5 PPO in Food Processing: The Use of Biosensors

In the food industry, PPO-based biosensors play an important role in monitoring food quality and implementing strategies to prevent browning. Due to their sensitivity to phenolic compounds, PPO biosensors are particularly valuable in water quality control and the rapid detection of phenolic compounds, as they enable precise measurements even at low substrate concentrations. PPO-based biosensors are actively being developed for applications in detecting phenolic contents in foods and identifying browning reactions (Espin et al., 1997; Niphadkar and Rathod, 2015).

5.6 Studies Aimed at Extending Food Shelf Life

Research focused on controlling PPO-induced browning has led to the development of technologies that aim to extend the shelf life of fresh fruits and vegetables. The use of PPO inhibitors and enzyme stabilization techniques reduces browning reactions in foods, helping to maintain product freshness over extended periods. Furthermore, innovative packaging methods that limit PPO activity are crucial in enhancing the shelf life of food products (Vamos-Vigyazo, 1981; Whitaker, 1994).

6. Potential Health Effects of PPO and Future Research

Polyphenol oxidase (PPO) has the potential to generate free radicals and reactive oxygen species (ROS) during phenolic compound oxidation, thereby influencing oxidative stress in biological systems. Due to these properties, PPO may exert both positive and negative effects on health. In recent years, PPO's applications in health have expanded, especially in the areas of its anticancer, antibacterial, and antioxidant activities, fueling further research in this domain (Nicolas et al., 1994; Yörük and Marshall, 2003).

6.1 Anticancer Potential of PPO

Studies examining PPO as a cancer treatment agent suggest that this enzyme may exert direct or indirect effects against certain cancer types. Quinones produced during PPO's oxidative reactions may interact with cancer cells, potentially causing structural damage to cell membranes. This property highlights PPO's potential for selective toxicity toward cancer cells, positioning it as a promising biotechnological tool in cancer therapy (Sanchez-Ferrer et al., 1995; Vaidya et al., 2006).

PPO's catalytic properties also enable the synthesis of certain pharmaceutical compounds with anti-carcinogenic effects. By serving as a biocatalyst, PPO aids in the production of therapeutic agents through the modification of phenolic compounds, offering promising prospects for drug development in cancer treatment (Bull and Carter, 1973; Kahn and Pomerantz, 1980).

6.2 Antibacterial and Antifungal Effects of PPO

PPO's antibacterial effects are of particular relevance to oral health. Studies examining its inhibitory impact on bacteria responsible for dental caries, such as *Streptococcus*, indicate that PPO has the potential to prevent cavities. The enzyme's antibacterial effects are attributed to the cellular damage inflicted on bacteria by the free radicals generated in oxidative reactions (Felton et al., 1992; Hill, 1992).

In addition to its antibacterial properties, PPO has also been investigated for antifungal effects. Studies suggest that PPO could serve as a protective agent against fungal infections, particularly by inhibiting fungal growth in fruits and vegetables, thereby revealing its potential use as a natural preservative (Oba et al., 1992; Nozue et al., 1998).

6.3 Antioxidant Effects of PPO and Skin Health

The ability of PPO to oxidize phenolic compounds may also produce antioxidant effects, which has potential applications in skin health. By promoting melanin production, PPO is believed to offer natural protection against ultraviolet (UV) radiation. However, as this process may also increase free radical formation in the skin, controlled application is essential.

Consequently, PPO-based formulations with skin-protective properties are recommended for use in skincare products (Mathew and Parpia, 1971; Whitaker, 1994).

6.4 Future Research Directions and Potential Applications

PPO presents promising applications in biochemistry, biotechnology, and healthcare. Future research directions offer significant opportunities to explore innovative uses of PPO in the food, health, and environmental sectors:

- Development of Natural PPO Inhibitors in Foods: Discovering natural PPO inhibitors is increasingly important to prevent enzymatic browning in foods. Natural inhibitors derived from plant sources are viewed as an alternative to synthetic chemicals, enabling the control of PPO activity with fewer health risks (Lacki and Duvnjak, 1999).

- Development of PPO-Based Biocatalysts for Cancer Treatment: The creation of PPO-based biocatalysts with selective toxicity towards cancer cells could facilitate the use of this enzyme in oncology. Genetic engineering techniques, in particular, could regulate PPO structure and function to produce selective quinones for therapeutic purposes (Guray and Sanlı-Mohamed, 2013).

- Enhancing PPO in Biosensor Technologies: Developing PPO-based biosensors is crucial for environmental monitoring of phenolic compounds and food safety analyses. Due to their high sensitivity, PPO biosensors hold broad applications in environmental and biomedical analyses (Espin et al., 1997; Niphadkar and Rathod, 2015).

- Genetic Modification of PPO Properties: Genetic engineering techniques aimed at controlling PPO biosynthesis are important for reducing unwanted browning reactions in plants. Regulating PPO gene expression could improve agricultural product quality by reducing browning in crops (Ullah, 1991; Whitaker, 1994).

7. Conclusion

Polyphenol oxidase (PPO) plays an essential role in biological systems and industrial applications due to its biochemical structure and wide substrate specificity. The oxidative functions of PPO affect color, flavor, and defense mechanisms by oxidizing phenolic compounds within plant and animal cells (Nicolas et al., 1994; Yörük and Marshall, 2003). These properties hold value in various sectors, such as quality control, fermentation, and extending product shelf life in the food industry (Vamos-Vigyazo, 1981; Whitaker, 1994). Nevertheless, the undesirable enzymatic browning induced by PPO poses a challenge to consumer acceptance, lowers the commercial value of food products, and remains an issue that the industry must address (Mathew and Parpia, 1971).

Effective control measures for PPO provide solutions to maintain food visual quality by managing enzymatic browning. However, as some chemical inhibitors pose health risks, research into developing natural inhibitors is gaining significance (Chazarra et al., 1996; Whitaker, 1994). Additionally, physical methods such as high pressure, UV light, and heat treatment present promising alternatives for preserving food quality by limiting PPO activity (Barrett et al., 1991; Nicolas et al., 1994).

In the future, identifying new applications for PPO in biotechnology, food, and health sectors will allow for more efficient and reliable use of this enzyme. Particularly, exploring the anticancer, antibacterial, and antioxidant potentials of PPO offers substantial opportunities to develop innovative treatments in biomedicine (Guray and Sanlı-Mohamed, 2013; Sanchez-Ferrer et al., 1995). Modifying PPO functionality in plants through genetic engineering presents a promising approach for reducing browning reactions and extending the shelf life of agricultural products (Ullah, 1991; Whitaker, 1994).

PPO-based technologies in biosensor development also hold considerable value by enabling effective and sensitive analyses in fields such as environmental monitoring and food safety (Espin et al., 1997; Niphadkar and Rathod, 2015). Ultimately, PPO’s biochemical functions and wide application range foster the development of innovative solutions across food, health, and environmental sectors. Further in-depth research on PPO will enhance its effective and safe utilization, yielding sustainable benefits for both industrial and biological systems (Panadare and Rathod, 2017; Yörük and Marshall, 2003).

REFERENCES

Alici, E. H., & Arabaci, G. (2016). Three-phase partitioning as a rapid and efficient method for purification of polyphenol oxidase from Borage (Borago officinalis L.). Journal of Chromatography B, 1022, 177-182.

Barrett, D. M., Garcia, E. L., Russell, G. F., Ramirez, C. R., & Shirazi, A. (1991). Blanch time and cultivar effects on quality of frozen and stored cauliflower. Journal of Food Science, 56(4), 1014-1017.

Batista, K. A., Prudencio, S. H., & Fernandes, K. F. (2014). Changes in the activity of redox enzymes involved in browning during Solanum lycocarpum fruit development. Journal of the Science of Food and Agriculture, 94(8), 1555-1561.

Bravo, K., & Osorio, E. (2016). Characterization and purification of polyphenol oxidase from peach palm fruit (Bactris gasipaes). Journal of Agricultural and Food Chemistry, 64(7), 1424-1430.

Bull, C., & Carter, S. (1973). Studies on the bacterial tyrosinase. Journal of Biological Chemistry, 248(20), 6987-6993.

Chazarra, S., Garcia-Carmona, F., & Cabanes, J. (1996). Hysteresis and inactivation induced by SDS in mushroom polyphenol oxidase. Biochimica et Biophysica Acta (BBA) - Protein Structure and Molecular Enzymology, 1294(3), 316-324.

Cheng, W., Chen, G., Luo, Q., & Li, Y. (2014). Extraction of polyphenol oxidase from sweet potato by acetone precipitation combined with aqueous two-phase system. Food Chemistry, 145, 852-857.

Espin, J. C., Morales, M., & Garcia-Ruiz, P. A. (1997). Improvement of a continuous spectrophotometric method for polyphenol oxidase activity determination. Journal of Agricultural and Food Chemistry, 45(4), 1084-1089.

Guray, B. M., & Sanlı-Mohamed, G. (2013). Polyphenol oxidase activity in thermophilic bacteria and industrial applications. Process Biochemistry, 48(6), 931-937.

Kahn, V., & Pomerantz, S. H. (1980). The cross-linking of proteins and other polymers by tyrosinase. Archives of Biochemistry and Biophysics, 204(1), 149-159.

Kaya, M. O., Kerimak-Öner, M. N., Demirci, T., Musatat, A. B., Özdemir, O., Kaya, Y., & Arslan, M. (2024a). Rational Design, Synthesis, and Computational Investigation of Dihydropyridine [2, 3-d] Pyrimidines as Polyphenol Oxidase Inhibitors with Improved Potency. The Protein Journal, 43(4), 869-87.

Kaya, M. O., Demirci, T., Taş, H. İ., Karayağız, Ş., Musatat, A. B., Kaya, Y., Kerimak-Öner, M. N., Özdemir, O., & Arslan, M. (2024b). Synthesis and Evaluation of 1, 4-Dihydropyridine-Based Urea Derivatives as Polyphenol Oxidase Inhibitors. Türkiye Tarımsal Araştırmalar Dergisi, 11(2), 235-242.

Lacki, M. K., & Duvnjak, Z. (1999). Use of polyphenol oxidase for removal of phenols from synthetic wastewater in membrane reactors. Journal of Chemical Technology and Biotechnology, 74(5), 425-434.

Lerch, K. (1995). Tyrosinase: Mechanistic and structural studies. In Copper Proteins and Copper Enzymes (pp. 65-95). CRC Press.

Mathew, A. G., & Parpia, H. A. B. (1971). Food browning as a polyphenol reaction. Advances in Food Research, 19, 75-145.

Mayer, A. M., & Harel, E. (1979). Polyphenol oxidases in plants. Phytochemistry, 18(2), 193-215.

Nicolas, J. J., Richard-Forget, F. C., Goupy, P. M., Amiot, M. J., & Aubert, S. Y. (1994). Enzymatic browning reactions in apple and apple products. Critical Reviews in Food Science and Nutrition, 34(2), 109-157.

Niphadkar, P. S., & Rathod, V. K. (2015). Ultrasound assisted three-phase partitioning for extraction and purification of polyphenol oxidase from Solanum tuberosum (Potato). Food and Bioproducts Processing, 94, 463-470.

Panadare, D. C., & Rathod, V. K. (2017). Three-phase partitioning of polyphenol oxidase from Solanum tuberosum in batch and ultrasonic flow system. Journal of Food Process Engineering, 40(4), e12518.

Sanchez-Ferrer, A., Bru, R., & Garcia-Carmona, F. (1995). Novel procedure for extraction of a latent grape polyphenol oxidase using temperature-induced phase separation in Triton X-114. Plant Physiology, 91(4), 1481-1487.

Tiwari, B. K., & Cullen, P. J. (2013). Inactivation of polyphenol oxidase and peroxidase in apple juice using ultrasound. Innovative Food Science & Emerging Technologies, 19, 146-151.

Tsivinska, M., Synytsya, A., & Kaminskyy, D. (2015). Physicochemical properties and biological activities of polyphenol oxidase from mushroom Lactarius pergamenus. Journal of the Science of Food and Agriculture, 95(8), 1587-1593.

Ullah, A. (1991). The effect of pH on tyrosinase activity in sweet potatoes. Journal of Food Science, 56(3), 893-895.

Vamos-Vigyazo, L. (1981). Polyphenol oxidase and peroxidase in fruits and vegetables. Critical Reviews in Food Science and Nutrition, 15(1), 49-127.

Vaidya, B. K., Ingavale, S. S., & Rathod, V. K. (2006). Aqueous two-phase extraction of polyphenol oxidase from potato. Food Chemistry, 96(2), 177-183.

Whitaker, J. R. (1994). Principles of Enzymology for the Food Sciences. CRC Press.

Yörük, R., & Marshall, M. R. (2003). Physicochemical properties and function of plant polyphenol oxidase: A review. Journal of Food Biochemistry, 27(5), 361-422.

Zaini, R. G., Bakar, J., Rahman, R. A., & Karim, R. (2013). Optimization of polyphenol oxidase extraction from snake fruit (Salacca edulis Reinw) by response surface methodology. International Food Research Journal, 20(3), 1135-1142.

CHAPTER 2

POSTBIOTICS AND THEIR BIOACTIVE POTENTIAL: AN OVERVIEW

Lect. Dr. Nurten YILMAZ[*1,2],

Assoc. Prof. Dr. Mustafa Oğuzhan KAYA[3]

DOI: https://dx.doi.org/10.5281/zenodo.14563306

[1]Cukurova University, Vocational School of Karaisalı, Medicinal and Aromatic Plants Department, Adana, Turkey.
[2]Cukurova University, Biotechnology Research and Application Center, Adana, Turkey. Orcid ID: 0000-0003-3867-509X *Corresponding author: ntoy@cu.edu.tr
[3]Kocaeli University, Faculty of Arts and Science, Chemistry Department, Kocaeli, Turkey. oguzhan.kaya@kocaeli.edu.tr Orcid ID: 0000-0002-8592-1567

INTRODUCTION

Postbiotics, which are defined as preparations derived from non-living microorganisms and/or their constituents that confer a health benefit to the host, have received a great deal of attention in recent years. Traditionally, probiotics have been associated with living microbial cells, but new evidence suggests that non-living microbes, their structural components and metabolites also have significant health benefits. These non-viable forms, often referred to as postbiotics, include various preparations such as heat-killed probiotics, paraprobiotics, ghost probiotics and cell lysates. The International Scientific Association for Probiotic/Prebiotic Probiotics (ISAPP) has established a standardized definition of postbiotic, bringing clarity to this rapidly evolving field (Mishra et al., 2024; Soujanya et al., 2024).

The human GI tract, home to trillions of microbial cells known together as the GI microbiota (GM), plays an important role in maintaining overall health. This microbiota produces bioactive compounds, including specialised metabolites. These metabolites influence immune responses, metabolism and overall health. As a result, the microbiota has been likened to a 'metabolic organ' due to its extensive metabolic activities that are essential for the physiology of the host (Rajakovich and Balskus, 2019). The mutualistic relationship between the microbiota and the host ensures a stable environment for the microbes while providing benefits such as nutritional support, development of the immune system, resistance to pathogens, and integrity of the gut barrier (Rajakovich and Balskus, 2019). Dietary interventions such as fermented foods, fibre-rich vegetables, whole cereals, and prebiotics and probiotics are critical to maintaining this balance (Etxeberria, 2013; Shang et al., 2024).

Postbiotics represent a major step forward in the development of health-promoting biological products because they are safe, stable and effective without relying on live microbial cells. The term "postbiotic" is derived from the Greek words post (after) and bios (life). It emphasises the focus on non-viable microbial life forms and their bioactive compounds (Soujanya et al., 2024). They may contain intact inactivated cells, cellular debris or metabolic products such as proteins and peptides. Notably, postbiotics are not necessarily derived from probiotic strains, broadening their potential applications and enabling innovation (Bisht et al., 2024).

The ISAPP consensus emphasises that post-biotics must meet specific criteria, including a defined source of microbiota, known genomic sequences, reproducible technological processes, and evidence of documented health benefits. In contrast to previous definitions, the ISAPP framework emphasises the versatility of post-biotics for applications beyond the gut, e.g. on the skin or in the vagina, further extending their therapeutic and functional potential (Mishra et al., 2024; Vinderola et al., 2024).

As research continues to advance, postbiotics are increasingly recognised as an innovative solution that provides the health benefits of probiotics without the logistical challenges of maintaining the viability of live microorganisms. Their stability and convenience make them promising candidates for the next generation of dietary supplements and functional foods, with applications ranging from gut health to skin care (Liu et al., 2023; Arora et al., 2024).

Recent research highlights the growing importance of postbiotics in food technology and their potential applications in various sectors. Postbiotics, which include metabolites such as short chain fatty acids, peptides and bacterial lysates, are being used as natural preservatives due to their antimicrobial and antioxidant properties. For example, they are effective in the control of food-borne pathogens in fermented products, beverages and dairy products (Moradi et al., 2020a; İncili et al., 2023; Yılmaz et al., 2015-17; Yılmaz, 2022-24).

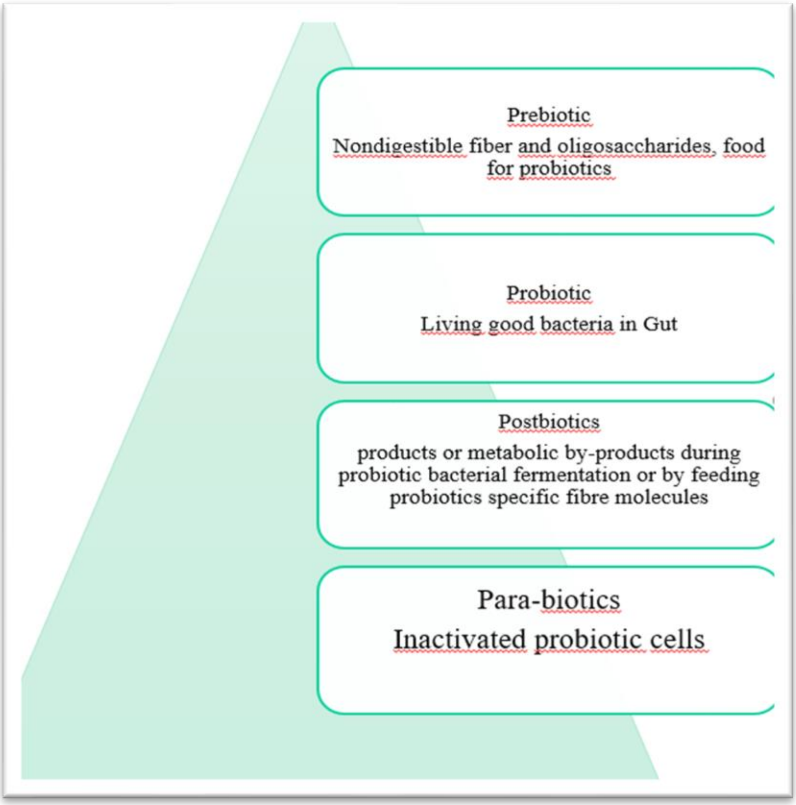
In food biotechnology applications, postbiotics are also being explored for their ability to enhance the functional properties of foods. This includes fortification with bioactive compounds to meet consumer demand for health-focused products such as probiotics, but without the constraints of live cell stability. For the development of functional foods and nutraceuticals tailored to gut health, metabolic support and immunity, this approach is particularly valuable (Sadeghi et al., 2022; Vlaicu et al., 2023)

In addition, their integration into packaging materials is an emerging area where postbiotics serve as biobased active packaging agents to reduce the risk of spoilage and contamination (Ritika and Rizwana, 2024).

In summary, postbiotics represent a disruptive innovation in health products, providing stable, bioactive microbial preparations with broad applicability. Their ability to improve health without the need for live organisms makes them a versatile alternative to traditional probiotics, supporting diverse health needs such as food tecnology, immune modulation, gut health and skin care. As research expands, postbiotics will play a central role in the development of functional foods and therapeutic interventions for a wide range of health concerns (Arora et al., 2024; Franco et al., 2024; Nataraj et al., 2020).

1.1. Definition and Distinction from Probiotics and Prebiotics

Postbiotics are "preparations of inanimate microorganisms and/or their constituents" distinct from probiotics and prebiotics, although they overlap functionally (Figure 1). Probiotics are made up of live microorganisms that, when administered in appropriate quantities, provide a health benefit to the host. In contrast, postbiotics do not require live microorganisms. Instead, they are by-products or metabolites of microbial activity or lysis. A mixture of probiotic and prebiotic that benefit host health by being utilized by microbes (Devlin et al., 2016). Postbiotics refer to the complex mixture of metabolites secreted by probiotics in cell-free supernatants. In contrast, parabiotics or paraprobiotics are inactivated probiotic microbial cells (either intact or disrupted, containing components such as peptidoglycan, teichoic acid and surface proteins) or crude cell extracts with a complex chemical composition Majhenic et al., 2017; Nataraj et al.,2020)



Figures 1: Probiotics, Prebiotics, postbiotics, parabiotics

Postbiotics was produced from Lactic acid bacteria specifically from probiotics with prebiotics. Postbiotics differ from prebiotics, which are non-digestible food components that selectively stimulate beneficial gut microbes. Prebiotics, such as fibre and oligosaccharides, act as 'food' for probiotics, promoting their growth and enhancing their beneficial effects on gut health such as Table 1. Postbiotics, on the other hand, are the final products of microbial metabolism. SCFAs, such as butyrate, acetate and propionate, are common postbiotics and play an important role in the maintenance of gut health by influencing immune modulation, digestion and gut barrier integrity (Peng et al., 2020; Peluzio et al., 2021).

Composition and safety profile are the key differences between postbiotics and probiotics. Probiotics require live microorganisms to be effective (El Far et al., 2023). Postbiotics avoid the potential risks associated with the administration of live microorganisms, such as the possibility of translocation, gene transfer or the development of antibiotic resistance. As a result, postbiotics have been seen as a safe and stable option, particularly in the clinical setting (Żółkiewicz et al., 2020). Postbiotics are easier to handle, with longer shelf life and less stringent temperature requirements, unlike probiotics, which require appropriate storage and transport conditions to maintain viability (Blazheva et al., 2022). This makes postbiotics more suitable for functional foods, food safety, supplements and therapeutics (Szydłowska and Sionek, 2022; Ozogul et al., 2015; Yılmaz, 2018).

Table 1. Definition and Distinction from Probiotics and Prebiotics

Term	**Example**	**Definition**	**Key Notes**	**Reference**
Probiotic	Bifidobacterium animalis subsp. lactis BB-12	Live microorganisms that confer a health benefit on the host in gut, ferment products	Must be genetically identified; viable dose must remain effective until shelf-life ends.	Jungersen et al., 2014
Prebiotic	Inulin, FOS, or GOS	A substrate selectively utilized by host microorganisms to provide a health benefit.	Not all fibers qualify; candidates include polyphenols, which are not fibers.	Kaewarsar et al., 2023
Para-biotics	*L. reuteri* DSM17938	Non-viable microbial cells (either intact or broken), or crude cell extracts	When properly administered, provide benefits to humans or animals.	Geraldo, e. al., 2019
Synbiotic	B. lactis BB-12 + Inulin	A mixture of Probiotic + Prebiotic that benefit host health by being utilized by microbes.	Two types: Complementary (separate probiotic and prebiotic and Synergistic microbe uses substrate	De Campos et al., 2022

			directly	
Postbiotic	Heat-killed Akkermansia muciniphila ATCC BAA-835	Inanimate microorganisms and/or their components that provide a health benefit.	Purified metabolites alone are not postbiotics	Keshavarz et al., 2021

In addition to their practical advantages, postbiotics have also been shown to have a number of health benefits. These include modulating immune responses, improving gut homeostasis, and exhibiting anti-inflammatory, antioxidant, and antimicrobial effects (Sharma and Shukla, 2016). Postbiotics also support gut barrier function, prevent colonization by pathogens, and can relieve symptoms associated with gastrointestinal disorders such as irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD). They offer an alternative to probiotics, especially for young children, older people and those with weakened immunity (Rafique et al., 2016).

Postbiotics are often classified according to their chemical composition and can be produced by various fermentation techniques or by bacterial lysis (Suárez et al., 2020). These include proteins (for example, lactopepin), organic acids (for example, propionic acid) (Toy et al., 2018), lipids (for example, butyrate), carbohydrates (for example, teichoic acids), and vitamins or co-factors (for example, B vitamins) (Moradi et al., 2020-2021). Such a classification is helpful in understanding the specific roles and applications of different postbiotics in health promotion. Furthermore, industrial-scale production methods of postbiotics are evolving, with the emergence of new technologies for improved yield, quality control, and bioavailability of these compounds (Balthazar et al., 2022).

1.2. Historical Development of Postbiotic Research

The concept of postbiotics is rooted in the long history of probiotic and prebiotic research, although it is relatively new in terms of formal research. The first studies on probiotics were carried out in the early twentieth century. In 1907, Elie Metchnikoff proposed that eating fermented foods containing beneficial bacteria would improve health and increase life expectancy (Anukam and Reid, 2007). However, the idea that non-living microbial components or by-products could also have therapeutic benefits came much later. The stage was set for the development of postbiotic research in the 1980s, when researchers began to identify certain microbial metabolites, such as short-chain fatty acids (SCFAs), as having significant health-promoting properties (Devlin et al., 016). In the late 1990s and early 2000s, the growth of interest in the gut microbiota and its role in human health was a catalyst for the investigation of postbiotics (Anukam and Reid, 2007). As researchers broadened their focus from live probiotics to the broader microbial ecosystem, they began to realise that it was not only the microorganisms themselves, but also their metabolic by-products, that could have a profound impact on health. These findings led to a better understanding of the physiological roles and mechanisms of action of postbiotics, and encouraged further exploration (Balthazar et al., 2022).

The 2010s marked a pivotal moment for the field with the introduction of a formal definition of postbiotics. In 2013, postbiotics were defined as 'inanimate microorganisms and/or their components that confer a health benefit to the host' by the ISAPP (ISAPP, 2021). This definition helped to distinguish postbiotics from probiotics and prebiotics, clarifying their role as metabolic products or by-products of probiotics rather than live microorganisms themselves. Research during this period also started exploring the therapeutic potential of postbiotics, focusing on their capacity for modulating the immune response, alleviating inflammation and supporting gut barrier integrity, particularly in vulnerable populations including infants, older people and those with compromised immune systems (Egan et al., 2016).

Since the 2010s, due to their safety profile, stability, and potential therapeutic applications, postbiotics have increasingly become a focus of academic and industrial research. Advances in the study of the microbiome, combined with improvements in metabolic analysis techniques such as metabolomics, have made it possible to more accurately identify and characterise postbiotics and their bioactive compounds (Balthazar et al., 2022). Recognised for their broad health benefits, including antimicrobial, immunomodulatory and anti-inflammatory effects, postbiotics have been incorporated into functional foods, nutraceuticals and clinical therapies, leading to a growing literature investigating their potential to treat gastrointestinal, metabolic and immunological disorders .Postbiotics research is now a dynamic and evolving field, with continuing studies investigating new postbiotic compounds and their applications in health and disease prevention. (Rafique et al., 20-23).

1.3. Composition and Classification of Postbiotics

Postbiotics are compounds produced during probiotic bacterial fermentation or by feeding probiotics specific fibre molecules, resulting in by-products commonly called postbiotics. Recently, the term postbiotics has been restricted to metabolites, cell-free supernatants (CFS) and soluble factors (products or metabolic by-products) secreted by live bacteria, sometimes not quite correctly called metabiotics (Rad et al., 2021).

These molecules have a specific chemical structure which may optimize host physiology and regulatory, metabolic and/or behavioural responses associated with host microbial activity and include short chain fatty acids (SCFAs), cell wall fragments, enzymes, exopolysaccharides and cell-free supernatants (Rad et al., 2022). Postbiotics can be produced by two main methods: natural fermentation or laboratory-based processes (Bomfim et al., 2020). Postbiotics have been shown to have a wide range of beneficial effects similar to those of probiotics, such as immune enhancement, anti-inflammatory properties, antimicrobial, antiviral, antioxidant, anti-obesity, anti-diabetic, anti-hypertensive, anti-proliferative, anti-mutagenic and anti-cancer activities (Rad et al., 2022). These effects have been demonstrated in both *in vitro* and *in vivo* studies, with no adverse effects such as inflammation reported (Moradi et al., 2020b). Postbiotics represent a safer alternative to live probiotics and are increasingly being considered for use in the food and pharmaceutical industries due to their established chemical structures, safe dosage and extended shelf life (Vinderola et al., 2024). However, the probiotic strain used and the nature of the postbiotic compounds themselves determine the specific beneficial effects of postbiotics (Nami et al., 2014). These postbiotics are found in fermented foods such as kefir, kimchi, sauerkraut, tempeh, yoghurt and certain pickles. They are also found in the human body. Some of the most important postbiotics are organic acids, SCFAs, tryptophan derivatives and bacteriocins. The benefits of postbiotics can be direct or indirect Direct benefits result from their effect on host cells, while indirect benefits promote growth in microbes that are beneficial to health, while inhibiting growth in those that are detrimental. They are also found in the human body. (Vinderola et al., 2023; Liu et al., 2023; Oleskin and Shenderov, 2020).

1.4. Postbiotics: Microbial metabolites and their effects

The human gut microbiome is a complex ecosystem consisting of more than 1,000 different species of microorganisms, including bacteria, fungi and viruses. These microorganisms play essential roles in human health, such as support of digestion, synthesis of vitamins, modulation of immune responses and influence on host behaviour (Anukam and Reid, 2007). Interactions between the microbiome and the host are dynamic and bi-directional. The microbiome produces a variety of metabolites and signalling molecules that influence immune maturation, metabolism and mucosal integrity, while microorganisms communicate with intestinal cells via the detection of hormones and peptides (Razzaq et al., 2019; Vernocchi et al., 2020). One of the most important types of microbial by-products are postbiotics, which are produced by metabolic processes in the gut. In Figure 2, postbiotics include metabolites, enzymes and structural molecules, each of which has a critical role in health promotion and disease prevention (Lagier et al., 2012; Rajakovich and Balskus, 2019).

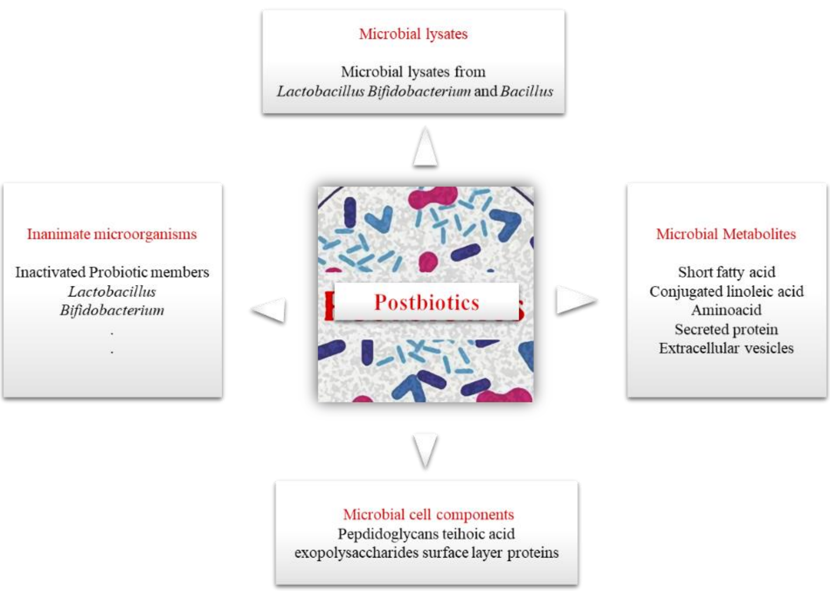


Figure 2: The microbiome produces a variety of metabolites are postbiotics.

Metabolites: Among the most important postbiotics are microbial metabolites, were listed in Table 2. These metabolites have a wide range of beneficial effects on the host. By nourishing intestinal epithelial cells, modulating the immune system and promoting mucosal integrity, SCFAs help maintain intestinal health. SCFAs have also been linked to preventing inflammatory diseases such as inflammatory bowel disease (IBD) and may play a role in treating conditions such as Metabolic Syndrome (MetS) and obesity. Other metabolites, such as tryptophan derivatives, also influence the immune response and gut-brain signalling, highlighting the importance of microbial metabolites in the regulation of host physiology (Lavelle and Sokol, 2020; Banfi et al., 2021).

Table 2: Postbiotics components and their effects on health

Component	Description	Health Effects	Examples	References
Short-Chain Fatty Acids (SCFAs)	Products of microbial fermentation of dietary fibers	- Support gut health, modulate immune system. -Prevent inflammatory diseases, improve metabolic syndrome	Acetate, Propionate, Butyrate	Abbasi et al., 2021 Rad et al., 2022 Moradi et al., 2020b
Bacteriocins	Antimicrobial peptides synthesized by bacterial ribosomes	- Inhibit the growth of pathogens. - Regulate gut microbiota, modulate immune response	Microcins produced by *Escherichia coli* Nissle	Abbasi et al., 2021; Veerappan et al., 2012
Active Peptides	Biologically active peptides produced by	- Modulate immune system, treat gluten sensitivity	DQ8-restricted gliadin peptide from *Lactococcus*	Fedorak, Demeria, 2012; Veerappa

	probiotics		*lactis*	n et al., 2012
Secreted Proteins	Proteins secreted by microorganisms	- Protects intestinal barrier, prevents damage from LPS and TNF-α - Prevents bacterial translocation and liver injury	Secreted protein from *Lactobacillus rhamnosus* GG (HM0539)	Nataraj et al., 2020
Extracellular Vesicles (EVs)	Membrane-bound vesicles secreted by bacterial cells	- Modulate immune system, reduce inflammation. - Improve lipid metabolism and protect against obesity and inflammatory diseases	EVs from *Akkermansia muciniphila*	Moradi et al., 2019; Toy 2018
Peptidoglycan (PG)	Major component of bacterial cell walls, particularly in Gram-positive bacteria	- Immune regulation and anti-cancer effects. - Alleviates obesity, reduces insulin resistance	*Lacticaseibacillus rhamnosus* CRL1505, *Bifidobacterium* spp.	Pyclik et al., 2020; Wang et al., 2024).
Teichoic Acid (TA)	A component of Gram-positive bacterial cell walls	- Immune stimulatory and anti-inflammatory effects	*Lactobacillus plantarum* (K8, K88, K5-5, K55-5)	Bhat et al., 2019
Exopolysacchari	Carbohydrate	- Anti-	*Bacillus*	Korotkyi

des (EPS)	s secreted by microorganisms.	inflammatory and immune-modulatory effects	*licheniformis* BioE-BL11, *Leuconostoc mesenteroides* BioE-LMD18 (Korean Kimchi)	et al., 2019; Aljumaah et al., 2020
Surface Layer Proteins (SLP)	Proteins located on the bacterial cell surface	- Antioxidant and immune-modulatory potential - Reduces inflammation and improves metabolic parameters	*Lentilactobacillus kefir* (DH5, LCM8, LCM9)	Mani-López et al., 2011; Rad et al., 2022
Microbial lysates	inactivated microorganisms by enzymatic digestion or physical fragmentation	lysed *Bacillus velezis* Kh2-2 improved immunity in immunosuppressed mice	*Bacillus velezis* Kh2-2 improved	Varian et al., 2017; Mi et al., 2022

Enzymes: Microbial enzymes, including proteases, lipases, glycosidases, and bacteriocins, play a vital role in the digestion and metabolism of nutrients in the animal gut. These enzymes, produced by the diverse gut microbiota, help break down complex macromolecules, facilitating nutrient absorption and enhancing the host's overall health. Bacteriocins, in particular, act as antimicrobial peptides, inhibiting the growth of pathogenic microorganisms while promoting the growth of beneficial bacteria. This dual role supports gut health by preventing pathogenic infections and maintaining a balanced microbiota. For instance, bacteriocins from *Escherichia coli* Nissle have been shown to inhibit enteric pathogens and improve gut healthymes produced by gut microorganisms, such as glutathione peroxidase in *Lactobacillus fermentum* strains, play an essential role in counteracting oxidative stress by neutralizing reactive oxygen species (ROS). These ROS can damage lipids, proteins, carbohydrates, and nucleic acids, impairing cellular function. Studies have shown that *Lactobacillus plantarum* postbiotics enhance antioxidant activity in serum and abomasum fluid, reducing lipid peroxidation. Similarly, lysates has shown potential in inhibiting colon cancer cell proliferatio (Liu et al., 2021; Liu and Kokare 2017; Mahakhan et al., 2023). Furthermore, microbial enzymes like cellulases, and hemicellulases break down complex carbohydrates such as starch, cellulose, and hemicellulose into simpler sugars that can be absorbed by the host, which is particularly crucial for herbivores consuming plant-based diets (Aspri et al., 2020). Microbial proteases also facilitate protein dehydrolyzing proteins into amino acids and smaller peptides, supporting growth, tissue repair, and metabolic functions. Together, these microbial enzymatic activities enhance lability of nutrients and provide protective effects against oxidative damage, thus improving the host's nutritional status and overall health (Razzaq et al., 2019).

Structural molecules: Integral to the composition of postbiotics are microbial cell components such as peptidoglycans (PGs), teichoic acids (TAs), exopolysaccharides (EPSs) and surface layer proteins (SLPs). These structural molecules play an important role in microbiome-host interactions and are commonly found in bacterial cell walls (Castro-López et al., 2021).

Peptidoglycan (PG): PG is the major component of the bacterial cell wall. It is particularly abundant in Gram-positive bacteria. It has been shown to have immunoregulatory effects and is able to modulate the immune response through the TLR4 signalling pathway. PG derived from *Lacticaseibacillus rhamnosus* and *Bifidobacterium* species has been shown to improve immune function and have anti-cancer properties. PG may also influence metabolic health by alleviating obesity insulin resistance and inflammation (Pyclik et al., 2020; Wang et al., 2024).

Exopolysaccharides (EPS): EPS are carbohydrates secreted by microorganisms that have been shown to have potential in the modulation of immune function and the reduction of inflammation. EPS derived *from Bacillus licheniformis* and Leuconostoc mesenteroides have been shown to have the ability to increase anti-inflammatory cytokines, such as IL-10, and decrease pro-inflammatory cytokines, such as IL-6 (Wang et al., 2024; Shah et al., 2024).

Surface layer proteins (SLP): SLPs play a critical role in promoting host health. These proteins have antioxidant properties and can modulate the immune system. SLP from Lentilactobacillus kefir have been shown to reduce inflammation and improve metabolic parameters such as insulin sensitivity and adipogenesis in animal models (Central, 2010; Gevers et al., 2014). But not all microbial components have a beneficial effect. For instance, lipoteichoic acid (LTA) from certain bacteria such as B. subtilis and S. aureus can cause undesirable physiological reactions such as fever and sleep disorders (Haberman et al., 2014).

Teichoic acids (TA): Accounting for 10-50% of the weight of the cell wall, TA is another major structural component of Gram-positive bacteria. TAs have been shown to have immunostimulatory and anti-inflammatory effects in humans. For example, TA derived from Lactobacillus plantarum has been shown to enhance the immune response and to reduce inflammation (Matsuzaki et al., 2022).

Bacteriocins: Bacteriocins are antimicrobial peptides produced by bacteria to inhibit the growth of pathogens. They have gained attention as potential microbiome editing tools due to their ability to selectively target pathogenic microorganisms while preserving beneficial bacteria. For example, microbicides produced by Escherichia coli Nissle may suppress the growth of pathogens such as Salmonella enterica and improve gut health during inflammatory bowel disease (Voloshyna et al., 2021) and food safety (Lahiri et al., 2021).

Extracellular vesicles (EVs): A variety of bioactive molecules, including proteins, lipids and RNA, are contained in extracellular vesicles released by bacteria. These vesicles have been shown to modulate the immune system and protect against inflammation. For example, EVs from Akkermansia muciniphila have been shown to reduce inflammation in the large intestine and liver, improve lipid metabolism and modulate the gut-adipose liver axis in obese mice (Xie, Li, Nie, 2024).

Inactivated microorganisms: Parabiotics, inactivation is the process by which a microbial strain is killed so that it cannot grow but retains functional cell structures and metabolites. However, some non-prebiotic strains, such as *Lactobacillus* and *Bifidobacterium*, also provide health benefits when taken in sufficient quantities (Ashrafian et al., 2020-21).

Microbial lysates: Microbial lysates are derived from inactivated microorganisms by enzymatic digestion or physical fragmentation, increasing bioavailability. For example, lysed *Lactobacillus reuteri* ATCC-PTA-6475 improved wound healing in mice through modulation of oxytocin secretion (Varian e.t al., 2017), and lysed *Bacillus velezis* Kh2-2 improved immunity in immunosuppressed mice (Mi et al., 2022).

1.5. Bioactive Properties of Postbiotics

Through the production of bioactive compounds such as organic acids, bacteriocins and other metabolites, postbiotics have significant antimicrobial properties (Table 3). Organic acids, including lactic acid and acetic acid, lower the pH of their environment, creating inhospitable conditions for many pathogens. These acids can disrupt microbial cell membranes. This leads to ion leakage and eventual cell death. Bacteriocins, such as nisin and pediocin, are ribosomally synthesised peptides produced by lactic acid bacteria (LAB). These molecules have been shown to inhibit the growth of microorganisms. In addition, postbiotic hydrogen peroxide and diacetyl inhibit spoilage organisms and pathogens (Moradi et al., 2020a, Toy et al. 2015-16).

Reuterin, a potent antimicrobial compound derived from Lactobacillus reuteri, has been shown to be effective against Gram-negative bacteria. This compound disrupts bacterial replication by interfering with DNA synthesis. In addition, exopolysaccharides (EPS) produced during fermentation contribute to the antimicrobial effect by interfering with biofilm formation. This reduces bacterial colonisation. The broad-spectrum activity of these compounds positions postbiotics as promising agents in food preservation and the treatment of infections caused by multidrug-resistant microorganisms (Jeon et al., 2022).

Table 3: Antimicrobial and Antioxidant Compounds in Postbiotics

Compound	Type	Source Organism	Mode of Action	References
Lactic Acid	Organic Acid	Lactobacillus spp., Bifidobacterium spp.	Lowers pH, destabilizes microbial membranes, and inhibits pathogen	Aljumaah et al., 2020; Chramostova et al., 2014

			growth.	
Acetic Acid	Organic Acid	Lactobacillus spp.	Acidifies environment, disrupts cellular metabolism in pathogens.	Toy et al., 2018
Bacteriocin	Protein/Peptid e	Lactococcus lactis, Lactobacillus plantarum	Forms pores in bacterial membranes, leading to leakage and cell death.	Voloshyna et al.,2021
Reuterin	Aldehyde Compound	Lactobacillus reuteri	Inhibits DNA synthesis, targets Gram-negative bacteria.	Jeon et al., 2022
Exopolysaccharid es	Polysaccharid es	Lactobacillus spp., Leuconostoc spp.	Reduces biofilm formation, protects against oxidative stress, and modulates immune response.	Jeong et al.,2 022
Hydrogen Peroxide	Reactive Oxygen Species	Lactobacillus spp.	Oxidizes microbial cell components, disrupting essential processes.	Kong et al., 2020
Diacetyl	Organic Compound	Lactobacillus spp., Leuconostoc	Disrupts bacterial metabolism, particularly in	Penna et al., 2023

		spp.	spoilage microorganisms.	
Short-Chain Fatty Acids (SCFAs)	Fatty Acids	Bifidobacterium spp., Lactobacillus spp.	Enhances antioxidant defenses by activating Nrf2 pathways, scavenges ROS.	Usta-Gorgun et al., 2020
Bioactive Peptides	Protein Fragments	Lactobacillus spp.	Inhibits lipid peroxidation, protects cellular membranes from oxidative damage.	Chai et al., 2020.
Glutathione	Antioxidant Peptide	Lactobacillus spp., Bifidobacterium spp.	Neutralizes reactive oxygen species, protects against oxidative stress in cells.	Yang et al., 2024

1.6. Anti-inflammatory and Immunomodulatory Effects

The anti-inflammatory effects of postbiotics are mediated through the modulation of the immune response of the host: Cytokine regulation: Postbiotics enhance secretion of anti-inflammatory cytokines (e.g. IL-10) while inhibiting inflammatory mediators such as TNF-α, IL-6 and IL-1β (Yeşilyurt et al., 2021). This balance is crucial for the management of chronic inflammatory conditions such as colitis and rheumatoid arthritis. Improvement of the intestinal barrier: Compounds such as SCFAs (butyrate, propionate) stimulate the growth of epithelial cells and the production of mucin, thus strengthening the intestinal barrier and reducing permeability (Direito et al., 2021). Toll-like receptor modulation: Postbiotics affect the

Toll-like receptor pathways, which promote immune tolerance and reduce systemic inflammation (Yeşilyurt et al., 2021). These effects are seen in conditions such as inflammatory bowel disease (IBD), asthma and allergic reactions. Significant reductions in colonic inflammation and oxidative stress have been demonstrated in animal models in a study of Lactobacillus paracasei postbiotics (Zhang et al., 2024).

Antioxidant, through their ability to neutralise free radicals and boost the body's antioxidant defences, postbiotics are effective in combating oxidative stress. Compounds such as glutathione, SCFAs and exopolysaccharides produced by LAB during fermentation play a central role in scavenging reactive oxygen species (ROS). This reduces oxidative damage to cells, which is a key factor in the ageing process and in many chronic diseases, such as diabetes, neurodegenerative disorders and cardiovascular disease (Lin et al., 2022).

Short-chain fatty acids such as butyrate and propionate activate the Nrf2 pathway, a key regulator of antioxidant defences. This leads to the upregulation of antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase. In addition, postbiotic bioactive peptides inhibit lipid peroxidation and protect cell membranes from oxidative damage (Karaca, et al., 2022).

LAB exopolysaccharides have been shown to reduce ROS generation in in vitro and in vivo models, supporting mitochondrial health and improving cellular function. The antioxidant activities of postbiotics are particularly beneficial in the management of metabolic disorders and the promotion of overall health. This provides additional justification for their inclusion in functional foods and dietary supplements (Shah et al., 2022).

1.7. Safety and Stability of Postbiotics

Postbiotics are believed to be a safer alternative to live probiotics because they are non-viable, eliminating the risks of uncontrolled growth, bacteraemia or transfer of antibiotic resistance genes (Abbasi et al., 2021). Toxicology safety evaluations of post-biotics often include in vitro cytotoxic assays, e.g. MTT or LDH assays, to evaluate potential cellular injury, and in vivo studies in animal models to observe systemic effects (Ansari et al., 2024). Non-genotoxicity, non-mutagenicity and absence of acute or chronic toxic effects are key safety parameters (Patnaik et al., 2021). For example, heat-inactivated *Lactobacillus rhamnosus* GG showed no adverse effects in high-dose studies, demonstrating its safety even in exaggerated consumption scenarios. Regulatory guidelines, e.g. EFSA and FDA, recommend a comprehensive safety profile, including allergenicity testing and dose-response studies, to establish acceptable daily intakes (Sanders et al., 2020). In addition, during production, it is necessary to control for potential endotoxin contamination from gram-negative bacterial lysates. In the case of Gram-positive postbiotics, the levels of lipoteichoic acid (LTA) are assessed to ensure that they do not induce inflammatory responses. Advances in bioengineering have enabled the development of purified postbiotic formulations with minimised risk of adverse reactions (Abbas et al., 2021).

Stability in a wide range of environmental and physiological conditions; Postbiotics are characterised by their exceptional stability compared to live probiotics. They remain bioactive even under extreme conditions such as heat treatment (70-90°C) or in an acidic environment (pH 2-4), which makes them suitable for incorporation into processed foods, beverages and pharmaceutical products (Balthazar et al., 2022). Studies on heat-killed Bifidobacterium breve showed retention of immunomodulatory properties after pasteurisation, while spray-dried Lactobacillus casei formulations retained antimicrobial activity over 12 months of ambient storage (Archer, 2008). Physiological stability is a further feature. Postbiotics retain their bioactive properties, such as short-chain fatty acid (SCFA) production, antioxidant enzyme activity and immune modulation, unlike live probiotics, which can lose viability during gastrointestinal transit. These properties are resistant to enzymatic degradation, bile salts and acidic gastric juices. Encapsulating technologies, such as alginate and chitosan, further enhance the delivery efficiency and stability of postbiotics in functional foods and dietary supplements (Devlin et al., 2016). The combination of safety and stability makes postbiotics particularly valuable for industrial applications, enabling them to meet the demands of global markets for bioactive ingredients that are effective, long-lasting and do not require refrigeration.

Conclusion

Postbiotics, derived from probiotic fermentation, are gaining attention for their health benefits, particularly in modulating the immune system, improving gut health and reducing inflammation. Unlike probiotics, postbiotics are nonviable, and growing but limited preclinical evidence supports their therapeutic effects. Further controlled clinical trials exploring mechanisms such as gut microbiome modulation, oxidative stress reduction and anti-inflammatory effects are needed to confirm their efficacy.

Postbiotics may also act in a synergistic manner with probiotics and prebiotics to improve gut health and immune function, offering the potential for personalised treatments based on microbiome profiles. However, challenges remain in terms of standardisation of production and assurance of consistent quality. As research continues, the role of postbiotics in healthcare and functional foods may expand as the full potential of postbiotics and their interactions with probiotics/prebiotics are understood.

REFERENCES

Abbasi, A., Aghebati-Maleki, A., Yousefi, M., & Aghebati-Maleki, L. (2021). Probiotic intervention as a potential therapeutic for managing gestational disorders and improving pregnancy outcomes. *Journal of Reproductive Immunology,* 143, 103244. https://doi.org/10.1016/j.jri.2020.103244.

Abbasi, A., Sheykhsaran, E., & Kafil, H. S. (2021). *Postbiotics: Science, technology and applications*. Bentham Science Publishers.

Aljumaah, M. R., Alkhulaifi, M. M., Abudabos, A. M., Alabdullatifb, A., El-Mubarak, A. H., Al Suliman, A. R., & Stanley, D. (2020). Organic acid blend supplementation increases butyrate and acetate production in *Salmonella enterica* serovar *Typhimurium* challenged broilers. *PLOS ONE, 15*, e0232831. https://doi.org/10.1371/journal.pone.0232831

Altveş, S., Yildiz, H. K., & Vural, H. C. (2020). Interaction of the microbiota with the human body in health and diseases. *Bioscience, Microbiota, Food Health, 39*, 23–32. https://doi.org/10.1016/j.foodres.2011.04.043

Ansari, F., Lee, C. C., Rashidimehr, A., Eskandari, S., Ashaolu, T. J., Mirzakhani, E., ... & Jafari, S. M. (2024). The role of probiotics in improving food safety; detoxification of heavy metals and chemicals. *Toxin Reviews, 43*(1), 63-91.

Anukam, K. C., and Reid, G. (2007). Probiotics: 100 years (1907–2007) after Elie Metchnikoff's observation. *Communicating current research and educational topics and trends in applied microbiology*,1, 466-474.

Archer, D. B. (2008). *Food biotechnology* (Vol. 111). Springer Science & Business Media.

Arora, R., Kaur, R., Babbar, R., Dhingra, S., Dhingra, A. K., & Grewal, A. S. (2024). Evolving advances in the cosmetic use of probiotics and postbiotics: health, regulatory and marketing aspects. Current *Pharmaceutical Biotechnology*, 25(11), 1349-1361.

Ashrafian, F., Keshavarz Azizi Raftar, S., Lari, A., Shahryari, A., Abdollahiyan, S., Moradi, H. R., Masoumi, M., Davari, M., Khatami, S., Omrani, M. D., et al. (2021). Extracellular vesicles and pasteurized cells derived from *Akkermansia muciniphila* protect against high-fat induced obesity in mice. *Microbial Cell Factories, 20*(1), 219. https://doi.org/10.1186/s12934-021-01709-w

Ashrafian, F., Shahriary, A., Behrouzi, A., Moradi, H. R., Raftar, S. K. A., Lari, A., Hadifar, S., Yaghoubfar, R., Badi, S. A., Khatami, S., et al. (2019). *Akkermansia muciniphila*-derived extracellular vesicles as a mucosal delivery vector for amelioration of obesity in mice. *Frontiers in Microbiology, 10*, 2155. https://doi.org/10.3389/fmicb.2019.02155

Aspri, M., Papademas, P., & Tsaltas, D. (2020). Review on non-dairy probiotics andtheir use in non-dairy based products. *Fermentation*, 6(1), 30.

Balthazar, C. F., Guimarães, J. F., Coutinho, N. M., Pimentel, T. C., Ranadheera, C. S., Santillo, A., ... & Sant'Ana, A. S. (2022). The future of functional food: Emerging technologies application on prebiotics, probiotics and postbiotics. *Comprehensive Reviews in Food Science and Food Safety*, 21(3), 2560-2586.

Banfi, D., Moro, E., Bosi, A., Bistoletti, M., Cerantola, S., Crema, F., ... & Baj A. (2021). Impact of microbial metabolites on microbiota–gut–brain axis in inflammatory bowel disease. *International journal of molecular sciences,* 22(4), 1623.

Bhat, M. I., Sowmya, K., Kapila, S., & Kapila, R. (2019). Potential probiotic *Lactobacillus rhamnosus* (MTCC-5897) inhibits *Escherichia coli* impaired intestinal barrier function by modulating the host tight junction gene response. *Probiotics and Antimicrobial Proteins*, 1-12. https://doi.org/10.1007/s12602-019-09608-8

Bisht, V., Das, B., Hussain, A., Kumar, V., & Navani, N. K. (2024). Understanding of probiotic origin antimicrobial peptides: a sustainable approach ensuring food safety. *NPJ Science of Foo*d, 8(1), 67.

Blazheva, D., Mihaylova, D., Averina, O. V., Slavchev, A., Brazkova, M., Poluektova, E. U., ... & Krastanov, A. (2022). Antioxidant potential of probiotics and postbiotics: A biotechnological approach to improving their stability. *Russian Journal of Genetics, 58*(9), 1036-1050.

Bomfim, V. B., Neto, J. H. P. L., Leite, K. S., de Andrade Vieira, É., Iacomini, M., Silva, C. M., dos Santos, K. M. O., & Cardarelli, H. R. (2020). Partial characterization and antioxidant activity of exopolysaccharides produced by *Lactobacillus plantarum* CNPC003. *LWT, 109,* 349. https://doi.org/10.1016/j.lwt.2020.109349.

Castro-López, C., Garcia, H. S., Martinez-Avila, G. C. G., González-Córdova, A. F., Vallejo-Cordoba, B., & Hernández-Mendoza, A. (2021).

Genomics-based approaches to identify and predict the health-promoting and safety activities of promising probiotic strains–A probiogenomics review. *Trends in Food Science & Technology*, 108, 148-163.

Chai, K. F., Voo, A. Y. H., & Chen, W. N. (2020). Bioactive peptides from food fermentation: A comprehensive review of their sources, bioactivities, applications, and future development. *Comprehensive Reviews in Food Science and Food Safety, 19*(6), 3825-3885.

Chramostova, J., Mošnová, R., Lisova, I., Pešek, E., Drbohlav, J., & Nemeckova, I. (2014). Influence of cultivation conditions on the growth of *Lactobacillus acidophilus*, *Bifidobacterium sp.*, and *Streptococcus thermophilus*, and on the production of organic acids in fermented milks. *Czech Journal of Food Sciences, 32*(5).

Darbandi, A., Asadi, A., Mahdizade Ari, M., Ohadi, E., Talebi, M., Halaj Zadeh, M., ... & Kakanj, M. (2022). Bacteriocins: properties and potential use as antimicrobials. *Journal of Clinical Laboratory Analysis,* 36(1), e24093.

De Campos, T. A. F., de Marins, A. R., da Silva, N. M., Matiucci, M. A., Dos Santos, I. C., Alcalde, C. R., ... & Feihrmann, A. C. (2022). Effect of the addition of the probiotic Bifidobacterium animalis subsp. Lactis (BB-12) in free and microencapsulated form and the prebiotic inulin to synbiotic dry coppa. *Food Research International,* 158, 111544.

Devlin, A. S., Marcobal, A., Dodd, D., Nayfach, S., Plummer, N., Meyer, T., et al. (2016). Modulation of a circulating uremic solute via rational genetic manipulation of the gut microbiota. *Cell Host & Microbe, 20*(6), 709-715. https://doi.org/10.1016/j.chom.2016.10.021

Direito, R., Rocha, J., Sepodes, B., & Eduardo-Figueira, M. (2021). Phenolic compounds impact on rheumatoid arthritis, inflammatory bowel disease and microbiota modulation. *Pharmaceutics, 13*(2), 145.

Egan, K., Field, D., Rea, M. C., Ross, R. P., Hill, C., & Cotter, P. D. (2016). Bacteriocins: Novel solutions to age old spore-related problems? *Frontiers in Microbiology, 7*(APR). https://doi.org/10.3389/fmicb.2016.00461.

El Far, M. S., Zakaria, A. S., Kassem, M. A., Wedn, A., Guimei, M., & Edward, E. A., (2023). Promising biotherapeutic prospects of different probiotics and their derived postbiotic metabolites: in-vitro and histopathological investigation, *BMC Microbiology,* 23(1):122.

Etxeberria, U., Fernández-Quintela, A., Milagro, F. I., Aguirre, L., Martínez, J. A., & Portillo, M. P., (2013). Impact of polyphenols and polyphenol-rich dietary sources on gut microbiota composition, *Journal of Agricultural and Food Chemistry*, 61(40):9517–9533. https://doi.org/10.1021/jf402506c.

Fedorak, R., & Demeria, D. (2012). Probiotic bacteria in the prevention and the treatment of inflammatory bowel disease, *Clinics in North America*, 41:821–842.

Franco, W. (2024). Postbiotics and parabiotics derived from bacteria and yeast: current trends and future perspectives, CyTA-Journal of Food, 22(1):2425838.

Garai-Ibabe, G., Dueñas, M. T., Irastorza, A., Sierra-Filardi, E., Werning, M. L., López, P., Corbí, A. L., & Fernández de Palencia, P., (2010). Naturally occurring 2-substituted (1,3)-β-D-glucan producing *Lactobacillus suebicus* and *Pediococcus parvulus* strains with potential utility in the production of functional foods, *Bioresource Technology,* 101(23):9254–9263, https://doi.org/10.1016/j.biortech.2010.07.05.

Gevers, D., Kugathasan, S., Denson, L. A., Vázquez-Baeza, Y., Van Treuren, W., Ren, B., Schwager, E., Knights, D., Song, S. J., Yassour, M., et al. (2014).The treatment-naive microbiome in new-onset Crohn's disease, *Cell Host & Microbe*, 15:382–392.

Glorieux, G., & Tattersall, J. (2015). Uraemic toxins and new methods to control their accumulation: Game changers for the concept of dialysis adequacy, *Clinical Kidney Journal*, 8(4):353–362, https://doi.org/10.1093/ckj/sfv034.

Haberman, Y., Tickle, T. L., Dexheimer, P. J., Kim, M. O., Tang, D., Karns, R., Baldassano, R. N., Noe, J. D., Rosh, J., Markowitz, J., et al. (2014). Pediatric Crohn disease patients exhibit specific ileal transcriptome and microbiome signature, *Journal of Clinical Investigation*, 124:3617–3633.

Hill, C., Guarner, F., Reid, G., Gibson, G. R., Merenstein, D. J., Pot, B., Morelli, L., Canani, R. B., Flint, H. J., Salminen, S., et al. (2014). The International Scientific Association for Probiotics and Prebiotics Consensus Statement on the Scope and Appropriate Use of the Term Probiotic, *Nature Reviews Gastroenterology & Hepatology*, 11:506–514.

İncili, G. K., Akgöl, M., Karatepe, P., Tekin, A., Kanmaz, H., Kaya, B., & Hayaloğlu, A. A. (2023). Whole-cell postbiotics: An innovative approach for extending the shelf life and controlling major foodborne pathogens in chicken breast fillets, *Food and Bioprocess Technolo*gy, 16(7):1502-1524.

Jaworska, K., Bielinska, K., Gawrys-Kopczyńska, M., & Ufnal, M. (2019). TMA (trimethylamine), but not its oxide TMAO (trimethylamine-oxide), exerts hemodynamic effects - implications for interpretation of cardiovascular actions of gut microbiome, *Cardiovascular Research*, 115(14):1948–1949, https://doi.org/10.1093/cvr/cvz231.

Jeong, Y. R., Kim, Y. E., & Lee, S. H. (2022). Review on the structural features and biological activities of reuterin, *Yakhak Hoeji*, 66(4):169–174.

Jungersen, M., Wind, A., Johansen, E., Christensen, J. E., Stuer-Lauridsen, B., & Eskesen, D. (2014). The Science behind the Probiotic Strain Bifidobacterium animalis subsp. lactis BB-12®. Microorganisms, 2(2), 92-110.

Kaewarsar, E., Chaiyasut, C., Lailerd, N., Makhamrueang, N., Peerajan, S., & Sirilun, S. (2023). Optimization of mixed inulin, fructooligosaccharides, and galactooligosaccharides as prebiotics for stimulation of probiotics growth and function. *Foods*, 12(8), 1591.

Karaca, B., Yılmaz, M., & Gürsoy, U. K. (2022). Targeting Nrf2 with probiotics and postbiotics in the treatment of periodontitis, *Biomolecules*, 12(5):729.

Keshavarz Azizi Raftar, S., Abdollahiyan, S., Azimirad, M., Yadegar, A., Vaziri, F., Moshiri, A., ... & Zali, M. R. (2021). The anti-fibrotic effects of heat-killed *Akkermansia muciniphila* MucT on liver fibrosis markers and activation of hepatic stellate cells. *Probiotics and Antimicrobial Proteins*, 13, 776-787.

Kong, Y., Olejar, K. J., On, S. L., & Chelikani, V., The potential of Lactobacillus spp. for modulating oxidative stress in the gastrointestinal tract, *Antioxidants*, 9(7):610, (2020).

Korotkyi, O., Dvorshchenko, K., Vovk, A., Dranitsina, A., Tymoshenko, M., Kot, L., & Ostapchenko, L. (2019). Effect of probiotic composition on oxidative/antioxidant balance in blood of rats under experimental osteoarthritis. *Ukr. Biochem. J*, *91*, 49-58. https://doi.org/10.15407/ubj91.06.049.

Lagier, J. C., Million, M., Hugon, P., Armougom, F., & Raoult, D., Human gut microbiota: repertoire and variations, Frontiers in Cellular and Infection *Microbiology*, 2:136, (2012).

Lahiri, D., Nag, M., Dutta, B., Sarkar, T., Pati, S., Basu, D., ... & Ray, R. R. (2022). Bacteriocin: A natural approach for food safety and food security. *Frontiers in Bioengineering and Biotechnology*, 10, 1005918.

Lavelle, A., & Sokol, H. (2020). Gut microbiota-derived metabolites as key actors in inflammatory bowel disease, *Nature Reviews Gastroenterology & Hepatology*, 17:223–237.

Lin, W. Y., Lin, J. H., Kuo, Y. W., Chiang, P. F. R., & Ho, H. H. (2022). Probiotics and their metabolites reduce oxidative stress in middle-aged mice, *Current Microbiology*, 79(4):104.

Liu, C., Ma, N., Feng, Y., Zhou, M., Li, H., Zhang, X., & Ma, X. (2023). From probiotics to postbiotics: Concepts and applications, *Animal Research and One Health*, 1(1):92-114.

Liu, X., & Kokare, C., (2017). *Chapter 11* – Microbial enzymes of use in industry, in G. Brahmachari (Ed.), *Biotechnology of Microbial Enzymes*, pp. 267–298, Academic Press.

Mahakhan, P., Apiso, P., Srisunthorn, K., Vichitphan, K., Vichitphan, S., Punyauppapath, S., & Sawaengkaew, J. (2023). Alkaline protease production from Bacillus gibsonii 6BS15-4 using dairy effluent and its characterization as a laundry detergent additive, *Journal of Microbiology and Biotechnology*, 33(2):195–202, https://doi.org/10.4014/jmb.2210.1000763.

Majhenic, A.C.; Lorbeg, P.M.; Treven, P. Enumeration and identification of mixed probiotic and lactic acid bacteria starter cultures. *In Probiotic Dairy Products*, 2nd ed.; Tamime, A.Y., Thomas, L.V., Eds.; John Wiley & Sons Ltd.: New York, NY, USA, 2017; pp. 207–251.

Mani-López, E., García, H., & López-Malo, A. (2012). Oscillrganic acids as antimicrobials to control *Salmonella* in meat and poultry products. *Food Research International, 45,* 713-721. https://doi.org/10.1016/j.foodres.2011.04.043

Matsuzaki, C., Shiraishi, T., Chiou, T. Y., Nakashima, Y., Higashimura, Y., Yokota, S. I., Yamamoto, K., & Takahashi, T. (2022). Role of lipoteichoic acid from the genus Apilactobacillus in inducing a strong IgA response, *Applied and Environmental Microbiology*, 88(8):e0019022, https://doi.org/10.1128/aem.00190-22.

Mishra, N., Ashique, S., Farid, A., & Garg, A. (2024). Synbiotics in Metabolic Disorders: Mechanisms, Therapeutic Potential, and Future Perspectives, CRC Press.

Moradi, M., Kousheh, S. A., Almasi, H., Alizadeh, A., Guimarães, J. T., Yılmaz, N., & Lotfi, A.(2020).Postbiotics produced by lactic acid bacteria: The next frontier in food safety, *Comprehensive Reviews in Food Science and Food Safety*, 19(6):3390-3415,

Moradi, M., Molaei, R., & Guimarães, Peng, M., Tabashsum, Z., Anderson, M., Truong, A., Houser, A. K., Padilla, J., ... & Biswas, D. (2020). Effectiveness of probiotics, prebiotics, and prebiotic-like components in common functional foods. *Comprehensive Reviews in Food Science and Food Safety*, *19*(4), 1908-1933.

Nataraj, B. H., Ali, S. A., Behare, P. V., & Yadav, H. (2020). Postbiotics-parabiotics: The new horizons in microbial biotherapy and functional foods. *Microbial cell factories*, 19, 1-22.

Ozogul, F., Tabanelli, G., Toy, N., & Gardini, F. (2015). Impact of cell-free supernatant of lactic acid bacteria on putrescine and other polyamine formation by foodborne pathogens in ornithine decarboxylase broth. *Journal of agricultural and food chemistry*, 63(24), 5828-5835.

Özogul, F., Toy, N., Özogul, Y., & Hamed, I. (2017). Function of cell-free supernatants of *Leuconostoc, Lactococcus, Streptococcus, Pediococcus* strains on histamine formation by foodborne pathogens in histidine decarboxylase broth. *Journal of Food Processing and Preservation,* 41(5), e13208.

Peluzio, M. D. C. G., Martinez, J. A., & Milagro, F. I. (2021). Postbiotics: Metabolites and mechanisms involved in microbiota-host interactions. *Trends in Food Science & Technology*, 108, 11-26.

Peng, M., Tabashsum, Z., Anderson, M., Truong, A., Houser, A. K., Padilla, J., ... & Biswas, D. (2020). Effectiveness of probiotics, prebiotics, and prebiotic-like components in common functional foods. *Comprehensive reviews in food science and food safety*, 19(4), 1908-1933.

Petrov, S. (2023). At the boundaries of food and medicine: The role of the regulation on the transformation of the probiotic applications in Europe and the United States from 2000 until present time.

Pyclik, M., Srutkova, D., Schwarzer, M., & Gorska, S. (2020). Bifidobacteria cell wall-derived exo-polysaccharides, lipoteichoic acids, peptidoglycans, polar lipids and proteins–their chemical structure and biological attributes. *International Journal of Biological Macromolecules, 147*, 333-349.

Rad, A. H., Abbasi, A., Kafil, H. S., & Ganbarov, K. (2020). Potential pharmaceutical and food applications of postbiotics: A review. *Current PharmaceuticalBiotechnology*. https://doi.org/10.2174/1389201021666200516154833

Rad, A. H., Aghebati Maleki, L., Samadi Kafil, H., Abbasi, A. (2020). Postbiotics: A novel strategy in food allergy treatment, Critical Reviews in Food Science and Nutrition, 1-8.

Rad, A. H., Aghebati Maleki, L., Samadi Kafil, H., Fathi Zavoshti, H., & Abbasi, A. (2021). Postbiotics as promising tools for cancer adjuvant therapy. *Advanced Pharmaceutical Bulletin, 11*. https://doi.org/10.34172/apb.2021.007

Rad, A. H., Hosseini, S., and Pourjafar, H. (2022). Postbiotics as dynamic biological molecules for antimicrobial activity: A mini-review. Biointerface Res. Appl. Chem, 12(5), 6543-6556.

Rad, A.H., Aghebati-Maleki, L., Kafil, H.S., & Abbasi, A. (2020). Molecular mechanisms of postbiotics in colorectal cancer prevention and treatment. *Critical Reviews in Food Science and Nutrition*, 1-17. https://doi.org/10.1080/10408398.2020.1765310.

Razzaq, A., Shamsi, S., Ali, A., Ali, Q., Sajjad, M., Malik, A., & Ashraf, M. (2019). Microbial proteases applications. *Frontiers in Bioengineering and Biotechnology, 7*, 110. https://doi.org/10.3389/fbioe.2019.0011065.

Riaz Rajoka, M. S., Mehwish, H. M., Zhang, H., Ashraf, M., Fang, H., Zeng, X., Wu, Y., Khurshid, M., Zhao, L., & He, Z. (2020). Antibacterial and antioxidant activity of exopolysaccharide mediated silver nanoparticle synthesized by *Lactobacillus brevis* isolated from Chinese koumiss. *Colloids and Surfaces B: Biointerfaces, 186*, 110734.

Ritika, & Rizwana. (2024). Edible Packaging: Extension of Shelf Life and Improvement of Food Quality. *Food Coatings and Preservation Technologies*, 167-210.

Sadeghi, A., Ebrahimi, M., Shahryari, S., Kharazmi, M. S., & Jafari, S. M. (2022). Food applications of probiotic yeasts; focusing on their techno-functional, postbiotic and protective capabilities. *Trends in Food Science & Technology, 128*, 278-295.

Sanders, M. E., Akkermans, L. M., Haller, D., Hammerman, C., Heimbach, J. T., Hörmannsperger, G., & Huys, G. (2010). Safety assessment of probiotics for human use. *Gut Microbes, 1*(3), 164-185.

Shah, I. A., Kavitake, D., Tiwari, S., Devi, P. B., Reddy, G. B., Jaiswal, K. K., ... & Shetty, P. H. (2024). Chemical modification of bacterial exopolysaccharides: Antioxidant properties and health potentials. *Current Research in Food Science*, 100824.

Shang, Z., Pai, L., & Patil, S. (2024). Unveiling the dynamics of gut microbial interactions: a review of dietary impact and precision nutrition in gastrointestinal health. *Frontiers in Nutrition, 11*, 1395664.

Silva, L. F., Sunakozawa, T. N., Monteiro, D. A., Casella, T., Conti, A. C., Todorov, S. D., & Barretto Penna, A. L. (2023). Potential of cheese-associated lactic acid bacteria to metabolize citrate and produce organic acids and acetoin. *Metabolites*, *13*(11), 1134.

Soujanya, K., Supraja, T., Manasa, C., & Das, D. (2024). Pre and Probiotics to Postbiotics: A Changing Paradigm. *Journal of Advances in Microbiology*, *24*(11), 19-33.

Suárez, N., Ferrara, F., Rial, A., Dee, V., and Chabalgoity, J. A. (2020). Bacterial lysates as immunotherapies for respiratory infections: Methods of preparation. Frontiers in bioengineering and biotechnology,8, 545.

Szydłowska, A., & Sionek, B. (2022). Probiotics and postbiotics as the functional food components affecting the immune response. *Microorganisms, 11*(1), 104.

Toy, N. (2018). Farklı gıdalardan tanımlanan laktik asit bakterilerinin organik asit üretimi, antimikrobiyal aktivitesi ve antibiyotik direnç özelliklerinin araştırılması (Doctoral dissertation, Doktora Tezi. Çukurova Üniversitesi, Fen Bilimleri Enstitüsü).

Toy, N., Özogul, F., & Özogul, Y. (2015). The influence of the cell free solution of lactic acid bacteria on tyramine production by food borne-pathogens in tyrosine decarboxylase broth. Food Chemistry, 173, 45-53.

Usta-Gorgun, B., & Yilmaz-Ersan, L. (2020). Short-chain fatty acids production by *Bifidobacterium* species in the presence of salep. *Electronic Journal of Biotechnology, 47*, 29-35.

Veerappan, G. R., Betteridge, J., & Young, P. E. (2012). Probiotics for the treatment of inflammatory bowel disease. *Current Gastroenterology Reports, 14,* 324–333.

Vinderola, G., Cotter, P. D., Freitas, M., Gueimonde, M., Holscher, H. D., Ruas-Madiedo, P., ... & Cifelli, C. J. (2023). Fermented foods: A perspective on their role in delivering biotics. *Frontiers in Microbiology, 14*, 1196239.

Vinderola, G., Sanders, M. E., Cunningham, M., & Hill, C. (2024). Frequently asked questions about the ISAPP postbiotic definition. *Frontiers in Microbiology, 14*, 1324565.

Vlaicu, P. A., Untea, A. E., Varzaru, I., Saracila, M., & Oancea, A. G. (2023). Designing nutrition for health—Incorporating dietary by-products into poultry feeds to create functional foods with insights into health benefits, risks, bioactive compounds, food component functionality and safety regulations. *Foods, 12*(21), 4001.

Voloshyna, I. M., Soloshenko, K. I., Krasinko, V. O., Lych, I. V., & Shkotova, L. V. (2021). Bacteriocins *Lactobacillus*—an alternative to antimicrobial drugs. *Biopolymers & Cell, 37*(2), 85.

Wang, J., Wu, T., Fang, X., Min, W., & Yang, Z. (2018). Characterization and immunomodulatory activity of an exopolysaccharide produced by *Lacbacillus plantarum* JLK0142 isolated from fermented dairy tofu. *International Journal of Biological Macromolecules, 115*, 985–993. https://doi.org/10.1016/j.ijbiomac.2018.04.099.

Wang, P., Wang, S., Wang, D., Li, Y., Yip, R. C. S., & Chen, H. (2024). Postbiotics—peptidoglycan, lipoteichoic acid, exopolysaccharides, surface layer protein and pili proteins—Structure, activity in wounds and their delivery systems. *International Journal of Biological Macromolecules, 133*, 195.

Wegh, C. A., Geerlings, S. Y., Knol, J., Roeselers, G., & Belzer, C. (2019). Postbiotics and their potential applications in early life nutrition and beyond. *International Journal of Molecular Sciences, 20*(19), 4673. https://doi.org/10.3390/ijms20194673.

Xie, J., Li, Q., & Nie, S. (2024). Bacterial extracellular vesicles: An emerging postbiotic. *Trends in Food Science & Technology*, 143, 104275.

Yang, W. (2024). Evaluation of the antioxidant activity and identification of potential antioxidant peptides in commercially available probiotic Cheddar cheese. *LWT, 205*, 116486.

Yeşilyurt, N., Yılmaz, B., Ağagündüz, D., & Capasso, R. (2021). Involvement of probiotics and postbiotics in the immune system modulation. *Biologics, 1*(2), 89-110.

Yilmaz, N., Özogul, F., Moradi, M., Fadiloglu, E. E., Šimat, V., & Rocha, J. M. (2022). Reduction of biogenic amines formation by foodborne pathogens using postbiotics in lysine-decarboxylase broth. *Journal of biotechnology*, 358, 118-127.

Zhang, J., Duan, X., Chen, X., Qian, S., Ma, J., Jiang, Z., & Hou, J. (2024). *Lactobacillus rhamnosus* 1.0320 postbiotics ameliorate dextran sodium sulfate-induced colonic inflammation and oxidative stress by regulating the intestinal barrier and gut microbiota. *Journal of Agricultural and Food Chemistry.*

Żółkiewicz, J., Marzec, A., Ruszczyński, M., & Feleszko, W. (2020). Postbiotics—a step beyond pre-and probiotics. *Nutrients, 12*(8).

CHAPTER 3

ALLICIN AND PHARMACOLOGICAL EFFECTS

Lecturer Mustafa ATALAN[1]

DOI: https://dx.doi.org/10.5281/zenodo.14563318

[1] Uşak Üniversitesi, Eşme Meslek Yüksekokulu, Eczane Hizmetleri Bölümü, Uşak, Türkiye. mustafa.atalan@usak.edu.tr. Orcid ID: 0000-0001-8543-6951

1.INTRODUCTION

Garlic (Allium sativum L.) produces allicin, a protective compound with a variety of biological properties. The garlic (Allium sativum L. Family: Amaryllidaceae) plant has been used for medicinal purposes since ancient times. Sanskrit manuscripts dating back approximately 5,000 years emphasize its medicinal benefits, and it appears to have been used in traditional Chinese medicine for at least 3,000 years (Savairam et al., 2023). The predominant and most physiologically active organosulfur compound in garlic is allicin (diallylthiosulfinate), a thioester of sulfenic acid that was first isolated and discovered in 1944 (Figure 1). Fresh garlic clove contains 4-5 mg of allicin.

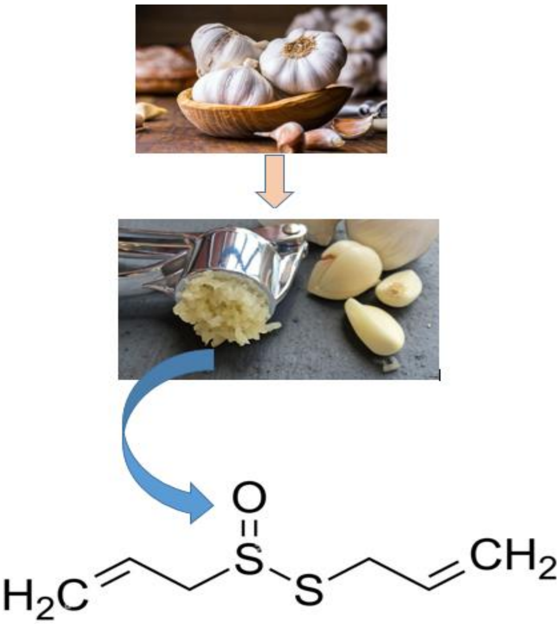


Figure 1. Chemical Structure of Allicin

When a garlic clove is damaged, alliin (S-allyl cysteine sulfoxide) is converted into allicin, pyruvate and ammonia by the enzyme alliin alkyl-sulfonate-lyase (alliinase) (Miron et al., 2008) (Figure 2).

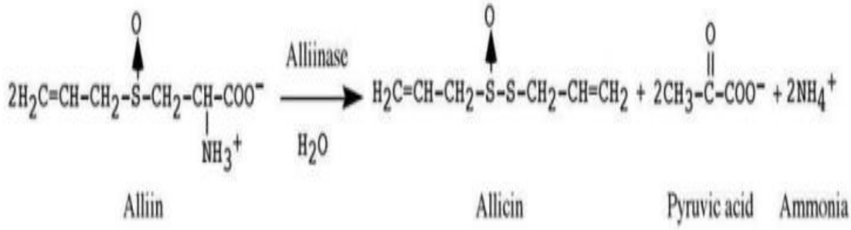


Figure 2. Synthesis of allicin from alliin with allynase enzyme

Allicin is poorly soluble in water and has a distinctive odor reminiscent of freshly crushed garlic (Marchese et al., 2016). Allicin has high permeability due to its low molecular weight and favorable lipophilic properties. This makes it easier for allicin to cross the blood-brain barrier and phospholipid bilayers (Liu et al., 2015). The biological half-life of allicin at 4°C is estimated to be around one year. However, it is important to note that this half-life can vary based on the solvent used, such as vegetable oil (Rahman, 2007). Allium vegetables, such as garlic (Allium sativum) and onion (Allium cepa), contain organosulfur compounds that have demonstrated several preventive benefits across various disease states (Roseblade et al., 2017). Garlic is rich in enzymes, vitamins, proteins, and volatile oils, including alliin, allicin, diallyl disulfide (DADS), diallyl trisulfide (DATS), and various organosulfur compounds (Okada et al., 2005). These compounds exhibit numerous significant pharmacological effects. Allicin, recognized for its antioxidant properties, also provides neuroprotection, anti-Alzheimer, anti-inflammatory, anticancer, cardioprotective, and antidiabetic effects. The antioxidant capability of allicin arises from its direct interaction with free radicals or reactive oxygen species (ROS). Allicin serves as a substrate for glutathione synthesis. It is well-established that allicin combines with glutathione or L-cysteine to produce S-allylmercaptocysteine (Sánchez-Gloria et al., 2021). Another recent study has also proven that garlic extract (GE) can stop lipid peroxidation and scavenge some radicals (Sánchez-Gloria et al., 2021). In addition to all these properties, allicin has also been shown to scavenge hydroxyl radicals and stop hydroxyl radical-induced lipid peroxidation of liver homogenates (Okada et al., 2005). Previous studies have demonstrated that Allicin exhibits an anti-cancer effect on various tumor types, including gastric carcinoma, breast cancer, glioblastoma, and HCC, by inhibiting cell division and inducing cell death (Zou et al., 2016). Allicin, known for its oxidizing properties, is a highly unstable compound; it degrades and decomposes into secondary organosulfur compounds due to factors such as pH, solvent, and temperature. The allylthio group is the most effective component of allicin's anticancer properties. However, this unstable group cannot deliver the desired effects of allicin in combating cancer due to its inherent instability. The instability of the allistio group also restricts the use of allicin as a medicinal drug. While allicin is a potent therapeutic compound found in garlic, it is rapidly transformed into other organosulfur compounds due to its instability, preventing allicin from delivering the anticipated effects.To address this issue, researchers have attempted to create garlic powder or preparations containing allicin with high levels of allicin. They assert that by administering the precursor and enzyme separately, these two components interact and become active in the stomach. The Central Food Technological Research Institute (CFTRI) produces garlic powder capsules that contain 50 mg of enzyme for this purpose (Panda, 2003, page 686). Replacing saturated alkanes and/or benzyl groups with the allylthio group has been demonstrated to eliminate this instability, enhance potency, and prolong the chemical's half-life by preventing thiosulfinate degradation under biological conditions and during storage (Roseblade et al., 2017).

PHARMACOKINETICS OF ALLICIN

The isolation, determination, and standardization of allicin is further complicated by its high volatility, reactivity, and instability. Temperature, extraction solvent, concentration and storage conditions can all have a significant effect on the half-life of allicin. In conclusion, allicin stability appears to be higher in an acidified paste than in other garlic processing media (unsalted garlic paste, chopped fried garlic and fried sliced garlic) (Prati et al., 2014). Allicin is an unstable compound that quickly decomposes into various organosulfur compounds that are water- and oil-soluble (Gao et al., 2013). Additionally, allicin is highly reactive and capable of forming covalent bonds through redox biotransformations. In thiosulfinates, the electron-withdrawing effect of the oxygen atom creates an electrophilic sulfur nucleus that easily combines with thiol groups (Leontiev et al., 2018). The primary antibacterial effect of allicin is due to its interaction with protein thiol groups, including the thiol groups of different enzymes (Mathialagan et al., 2017). The bioavailability of allicin is a critical issue, as it is produced from alliin and alliinase after absorption, which is often hindered by gastrointestinal conditions that block these enzymes (Lawson and Hunsaker, 2018). On the other hand, the enzyme pure allinase is inert below pH 3.5 or when heated; it is most active at pH 7.0 and 35 °C (Gebreyohannes and Gebreyohannes, 2013). Therefore, many garlic supplement brands have adopted an enteric-coated formulation to protect the alliinase enzyme and prevent gastric upset. Allicin can momentarily raise the pH of a high-protein meal to 4.4 or higher, thereby preserving the enzymatic activity of alliinase (Lawson and Hunsaker, 2018). In a 2013 study, researchers tested the breath of volunteers who ate 38 grams of raw garlic for allyl methyl sulfide, allyl methyl disulfide, diallyl sulfide, diallyl disulfide, diallyl trisulfide, dimethyl sulfide, and acetone. The highest levels of diallyl sulfide, diallyl methyl disulfide, diallyl trisulfide, diallyl disulfide, and dimethyl sulfide were reached within two to three hours (Gao et al., 2013). In a study conducted by Lawson and Hunsaker in 2018; After consuming 23 different garlic products for 32 hours in healthy individuals (6 women and 7 men), the area under the curve (AUC) of the primary respiratory allicin metabolite (allyl methyl sulfide) was measured. It was stated that the bioavailability or bioequivalence levels of allicin varied between 36% and 104% for enteric tablets, 80-111% for non-enteric tablets, 26-109% for garlic powder capsules, 16% for boiled garlic, 30% for roasted garlic, 19% for pickles and 66% for foods containing acidic chopped garlic (Lawson and Hunsaker, 2018). Garlic has an antibacterial effect due to Allicin. One milligram of this substance corresponds to 15 Oxford Units of Penicillin (Panda, 2003, page 686).

ANTIOXIDANT EFFECT OF ALLICIN

In the mid-20th century, allicin was first identified as an antibacterial agent. As research progressed, it was discovered that it also had antifungal, antioxidant, antihypertensive, anti-inflammatory, and anticancer properties (Marchese et al., 2016). Allicin has been found to have a potent antioxidant activity that may guard against oxidative stress and associated illnesses (Hosseini and Hosseinzade, 2015). Through its reaction with thiol-containing enzymes, allicin functions as a potent antioxidant. Allicin's antioxidant qualities are due to its ability to inhibit hydroxyl and superoxide radicals. Another significant role of allicin is to inhibit the generation of nitric oxide (NO) (Rahman, 2007). Reactive oxygen species (ROS) are very unstable molecules that, when they multiply, lead to tissue damage and oxidative stress (Kelsey et al., 2010). Furthermore, it was shown that allicin inhibits xanthine oxidase, an enzyme that generates superoxide, most likely through interactions with the thiol groups of the enzyme. This inhibitory impact aids in further reducing oxidative stress by lowering ROS production.

Additionally, allicin may function as a precursor to specific biological agents or regulate the sulfhydryl group of thiol proteins, which would ultimately lessen oxidative stress in cells (Xiao and Parkin., 2002). By lowering the synthesis of conjugated diene hydroperoxides, which are compounds derived from reactive oxygen species (ROS) and possess antioxidant qualities, allicin was discovered to be a potent inhibitor of lipid peroxidation. Allicin's ability to shield lipids and cellular components from oxidative damage is further supported by this process (Okada et al.,2005). It has also been investigated how allicin affects several cellular processes and oxidative stress-related activities. For instance, allicin has been demonstrated to lessen arsenic trioxide-induced liver damage by upregulating the expression of Nrf2, heme oxygenase 1, and Krüppel-like factor 9 (KLF9) protein while downregulating NF-κB levels. These alterations imply that allicin may lessen oxidative stress and apoptosis, which in turn may lessen oxidative stress-induced cellular damage (Yang et al., 2017). Allicin efficiently lowers intracellular ROS levels in the heart and lessens oxidative stress in diseases such as ventricular hypertrophy, per in vivo research employing animal models. Allicin can also considerably lower intracellular ROS levels in cardiac myocytes, according to in vitro studies, suggesting that it has the ability to scavenge ROS and shield cells from oxidative injury (Liu et al., 2010). Studies have shown that the ability of the hydroxyl radical to scavenge free radicals can increase in direct proportion to the allicin concentration (Li et al., 2017).

CONCLUSION

An important bioactive substance found particularly in garlic (Allium sativum) is allicin. This sulfur-containing chemical molecule is well known for both its wide range of pharmacological effects and its distinctive odor. The ability of allicin to neutralize reactive oxygen species (ROS) forms the basis of its antioxidant effects, which are crucial in reducing oxidative stress. According to studies, allicin protects against oxidative damage, increases the amount of antioxidant enzymes in cells, and inhibits lipid peroxidation. These findings point to a potential treatment for some chronic diseases, including cancer, neurological diseases, and cardiovascular diseases.

Allicin's anti-inflammatory and immunomodulatory properties, together with its antioxidant activities, offer a complete defense. However, allicin's limitations in terms of bioavailability and chemical instability should be taken into account when used in clinical settings. Future research should focus on creating dosage schedules and formulations that will increase allicin's bioavailability. In this context, a deeper understanding of allicin's molecular actions will allow us to fully exploit the therapeutic potential of this beneficial compound.

These findings highlight the pharmacological importance of allicin and lend credibility to the many health-related uses of its antioxidant properties. Allicin from garlic has the potential to be an important natural and medicinal compound in future studies and clinical applications.

REFERENCES

Gao, C., Jiang, X., Wang, H., Zhao, Z., & Wang, W. (2013). Drug metabolism and pharmacokinetics of organosulfur compounds from garlic. *J Drug Metab Toxicol*, *4*(5), 1-10.

Gebreyohannes, G., & Gebreyohannes, M. (2013). Medicinal values of garlic: A review. *International Journal of Medicine and Medical Sciences*, *5*(9), 401-408.

Hosseini, A. and Hosseinzadeh, H. (2015). A review of the effects of Allium sativum (Garlic) in metabolic syndrome. Journal of endocrinological research, 38, 1147-1157.

Kelsey, N. A., Wilkins, H. M., & Linseman, D. A. (2010). Nutraceutical antioxidants as novel neuroprotective agents. *Molecules*, *15*(11), 7792-7814.

Lawson, L. D., & Hunsaker, S. M. (2018). Allicin bioavailability and bioequivalence from garlic supplements and garlic foods. *Nutrients*, *10*(7), 812.

Leontiev, R., Hohaus, N., Jacob, C., Gruhlke, M. C., & Slusarenko, A. J. (2018). A comparison of the antibacterial and antifungal activities of thiosulfinate analogues of allicin. *Scientific reports*, *8*(1), 6763.

Li, F., Li, Q., Wu, S., & Tan, Z. (2017). Salting-out extraction of allicin from garlic (Allium sativum L.) based on ethanol/ammonium sulfate in laboratory and pilot scale. *Food Chemistry*, *217*, 91-97.

Liu, C., Cao, F., Tang, Q. Z., Yan, L., Dong, Y. G., Zhu, L. H., ... & Li, H. (2010). Allicin protects against cardiac hypertrophy and fibrosis via attenuating reactive oxygen species-dependent signaling pathways. *The Journal of nutritional biochemistry*, *21*(12), 1238-1250.

Liu, S. G., Ren, P. Y., Wang, G. Y., Yao, S. X., & He, X. J. (2015). Allicin protects spinal cord neurons from glutamate-induced oxidative stress through regulating the heat shock protein 70/inducible nitric oxide synthase pathway. *Food & function*, *6*(1), 320-329.

Marchese, A., Barbieri, R., Sanches-Silva, A., Daglia, M., Nabavi, S. F., Jafari, N. J., ... & Nabavi, S. M. (2016). Antifungal and antibacterial activities of allicin: A review. *Trends in Food Science & Technology*, *52*, 49-56.

Mathialagan, R., Mansor, N., Al-Khateeb, B., Mohamad, M. H., & Shamsuddin, M. R. (2017). Evaluation of allicin as soil urease inhibitor. *Procedia engineering*, *184*, 449-459.

Miron, T., Wilchek, M., Sharp, A., Nakagawa, Y., Naoi, M., Nozawa, Y., & Akao, Y. (2008). Allicin inhibits cell growth and induces apoptosis through the mitochondrial pathway in HL60 and U937 cells. *The Journal of Nutritional Biochemistry*, *19*(8), 524-535.

Okada, Y., Tanaka, K., Fujita, I., Sato, E., & Okajima, H. (2005). Antiodidant activity of thiosulfinates derived from garlic. *Redox Report*, *10*(2), 96-102.

Panda, H. (2003). Herbal Foods and Its Medicinal Values. National Institute of Industrial Research (NIIR), page 686, Delhi, India.

Prati, P., Henrique, C. M., Souza, A. S. D., Silva, V. S. N. D., & Pacheco, M. T. B. (2014). Evaluation of allicin stability in processed garlic of different cultivars. *Food Science and Technology*, *34*, 623-628.

Rahman, M. S. (2007). Allicin and other functional active components in garlic: Health benefits and bioavailability. *International Journal of Food Properties*, *10*(2), 245-268.

Roseblade, A., Ung, A., & Bebawy, M. (2017). Synthesis and in vitro biological evaluation of thiosulfinate derivatives for the treatment of human multidrug-resistant breast cancer. *Acta Pharmacologica Sinica*, *38*(10), 1353-1368.

Sánchez-Gloria, J. L., Martínez-Olivares, C. E., Rojas-Morales, P., Hernández-Pando, R., Carbó, R., Rubio-Gayosso, I., ... & Osorio-Alonso, H. (2021). Anti-inflammatory effect of allicin associated with fibrosis in pulmonary arterial hypertension. *International Journal of Molecular Sciences*, *22*(16), 8600.

Savairam, V. D., Patil, N. A., Borate, S. R., Ghaisas, M. M., & Shete, R. V. (2023). Allicin: A review of its important pharmacological activities. *Pharmacological Research-Modern Chinese Medicine*, 100283.

Xiao, H., & Parkin, K. L. (2002). Antioxidant functions of selected allium thiosulfinates and S-alk (en) yl-L-cysteine sulfoxides. *Journal of Agricultural and Food Chemistry*, *50*(9), 2488-2493.

Yang, D., Lv, Z., Zhang, H., Liu, B., Jiang, H., Tan, X., ... & Zhang, Z. (2017). Activation of the Nrf2 signaling pathway involving KLF9 plays a critical role in allicin resisting against arsenic trioxide-induced hepatotoxicity in rats. *Biological trace element research*, *176*, 192-200.

Zou, X., Liang, J., Sun, J., Hu, X., Lei, L., Wu, D., & Liu, L. (2016). Allicin sensitizes hepatocellular cancer cells to anti-tumor activity of 5-fluorouracil through ROS-mediated mitochondrial pathway. *Journal of Pharmacological Sciences*, *131*(4), 233-240.

CHAPTER 4

GEOLOGICAL, GEOMORPHOLOGICAL FEATURES AND UNDERGROUND WATER RESOURCES OF IĞDIR PROVINCE

Musa KARADAĞ[12,*]
Şeyhmus TÜMÜR[3]

DOI: https://dx.doi.org/10.5281/zenodo.14563326

[1] [1]Department of Chemical and Chemical Processing Technologies, Vocational School of Technical Sciences, Igdir University, Igdir, Türkiye
[2]Research Application Laboratory and Research Center (ALUM), Iğdır University, Iğdır, Türkiye. Orcid: 0000-0003-2498-3403, Mail: musa.karadag@igdir.edu.tr; dengemusa@hotmail.com
[3] Dicle University, Faculty of Engineering, Department of Civil Engineering, Department of Building, Diyarbakır,
Türkiye. Orcid: 0000-0001-7589-8941, **mail**: stumur@dicle.edu.tr
Corresponding author: musa.karadag@igdir.edu.tr; dengemusa@hotmail.com

INTRODUCTION

Iğdır province is located in the Eastern Anatolia Region, in one of the unique regions in terms of geology and ministry of Turkey. Having international championships such as Armenia, Nakhchivan Autonomous Republic and Iran in the north increases the reconstruction of the province. This region, which also hosts Mount Ararat, the highest mountain in Turkey, draws attention with its wide alluvial plains and rich hydrogeological features. In particular, Iğdır Plain is shaped by alluviums carried by the Aras River and has a vital development in terms of contracted production and usable water resources. The climatic characteristics of the region play a role in the formation and renewal of breeding waters. Although it is located in the Eastern Anatolia Region, where the continental climate is dominant, Iğdır province shows a milder climate with microclimate effects (Karaoğlu, M ., & Çelim, Ş. 2018; Tırınk, S. 2021; and Karaoğlu, M., & Yalçın, AM 2018). Limited annual rainfall and increased evaporation in summer months lead to effective sustainability of water. Underground water resources have an indispensable system in meeting these structural, agricultural and drinking water needs.

The geological structure of Iğdır has a dynamic structure where different rock types coexist. Alluvial units, volcanic rocks and sedimentary formations play an important role in the presence and transmission of secreted water traces. The expendability and storage capacities of these units allow the evaluation of both the quantity and quality of the water used. Especially the alluvial structures located in the Iğdır Plain enable the continuation and sustainability of the main aquifer system in the region (Karaoğlu, M. 2011; and Karataş, A. 2022). This can be produced, the potential water potential of Iğdır province, its hydrogeological structure and water management issues can be addressed. The evaluations made on the usability and quantity in the region aim to provide a basis for the protection of sustainable water use and storage. In addition, the effects on agricultural and industrial economic water resources and the measures that can be taken to minimize these effects will be addressed. In this context, the study aims to make a significant contribution to the effective management and protection of water resources of Iğdır province.

1. GEOGRAPHICAL AND CLIMATIC CHARACTERISTICS OF IĞDIR PROVINCE

Iğdır province is located in the Eastern Anatolia Region, which is the most populated region in Turkey. It is neighboring Armenia, Nakhchivan Autonomous Republic, local Ağrı and Kars provinces to the north. The most striking feature of Iğdır is that it hosts Mount Ararat, the highest mountain in Turkey. In addition, Iğdır Plain, which is a large and fertile plain, is located in the city center and its surroundings. This plain is covered with alluviums carried by the Aras River and is of great importance in terms of agriculture. Climate conditions show Iğdır or microclimate characteristics. Although the continental climate is generally effective in the Eastern Anatolia Region, a milder climate rule is applied in Iğdır Plain. Summers are hot and dry, winters are cold and snowy. The average temperature in summer can exceed 30°C and the highest temperatures can reach 40°C. In winter, the temperature drops below 0°C and the lowest temperatures can drop to -20°C. The amount of precipitation is below the storage in Turkey, and the annual average is around 250-300 mm. Precipitation is usually concentrated in the spring and autumn months. Iğdır's flat and climatic characteristics offer a suitable environment for its management. The Aras River and its tributaries have the main elements of water availability in the region and are of vital importance for management irrigation. There were fertile lands thanks to the production of cotton, wheat, barley, sugar beet and fruit and vegetable (Karaoğlu, M ., & Erdel, E. 2022; Aydın, T., & Çelik, MA 2019; Biçer, A. 2021). In addition, the presence of Mount Ararat negatively affects Iğdır in terms of tourism; It offers potential for activities such as mountaineering, nature walks and winter sports. With these air conditioning and climatic characteristics, Iğdır province is significantly shaped in terms of economy and social aspects.

2. GEOLOGICAL AND GEOMORPHOLOGICAL FEATURES OF IĞDIR PROVINCE

Iğdır province is located in the Eastern Anatolia Region of Turkey and has its own unique geological and geomorphological features. In this section, the geological structure, underground resources, tectonic and seismic features and geomorphological elements of Iğdır province are discussed. The geological and geomorphological structure determines the regional division and hydrogeological features. These features play an important role in groundwater formation and emergence. The geological structure of Iğdır province is formed by the combination of rocks from various periods (Aydın, T ., & Çelik, MA 2019; and Avci, V., et al., 2022) Iğdır province contains various rock types from different geological periods. The regular geological units in the region are as follows:

2.1. Alluviums

The alluviums carried by the Aras River and its branches cover large areas in the Iğdır Plain. There are various debris such as alluviums, sand, silt, clay and gravel. These units have high permeability and water storage units. These alluviums have high permeability and water storage storage properties, which makes them important aquifers for underground water resources. Alluviums are sedimentary materials carried and deposited by water currents. Rivers, streams and rivers deposit materials such as gravel, sand, clay and silt as alluvium. Alluviums play an important role in the formation of fertile agricultural lands and are important water sources in terms of hydrogeology. In this section, the definition, formations, types and general characteristics of alluviums can be selected. Alluviums are formed as a result of the transportation and accumulation activities of water, they are generally sedimentary rocks formed from sediments (Singh, A ., et al., 2020; Maghami, S., et al.2021). The routine features of alluviums are as follows: Alluviums consist of materials with various grain sizes such as gravel, sand, silt and clay. Alluviums generally have a layered structure and layers with different sizes can be separated. Alluviums, especially sandy and gravelly layers, are compatible with high water permeability. Alluviums are folded materials carried and deposited by water currents and have great value in terms of geological features and human activities. Alluviums, which form highly productive agricultural lands and water resources, are also valuable as construction materials. The study of alluviums provides critical information in terms of natural sustainable marketing and marketing planning. Alluviums have various physical and chemical structures and have many economic and powerful uses. Here are some important features and areas of use: Alluviums are rich in minerals and form extremely fertile soils for agriculture (Azarafza, M ., et al., 2018; Jafari, M. K., et al.,2002). Alluviums play an important role in the storage and storage of groundwater; Highly permeable layers ensure the efficient operation of water wells. Sand and gravel obtained from alluviums are used in the construction sector for concrete and mortar use.

2.2. Volcanic Rocks

As a result of the volcanic condition of Mount Ararat and its disorder, there are volcanic rocks such as basalt, andesite and tuff. These rocks have the opportunity to store water with their cracks and formations . Iğdır's growing Mount Ararat is covered with rocks such as basalt, andesite and tuff, which are observed as a result of volcanic eruptions. Volcanic rocks can store and transmit water thanks to their cracks and formations. Volcanic rocks store and transmit water in their cracks and cracks. These aquifers are important in terms of water supply, especially in mountainous areas. Volcanic rocks are rocks formed as a result of magma emerging from the surface of the earth and cooling on the surface (Barr, S. M ., & Charusiri, P. 2011; Irvine, TN, & Baragar, WRAF 1971). These rocks gain different physical and chemical properties during the solidification of magma. Volcanic rocks cover a large part of the Earth's surface and provide important information about geology. In this section, the definition, formation, types and general characteristics of volcanic rocks can be selected. Volcanic rocks are formed by the emergence of volcanic results of magma under the Earth's crust and cooling and solidifying there. These rocks usually have a fine-grained or glassy structure due to rapid cooling. Routine characteristics of volcanic rocks are as follows: Rapid cooling of magma at the surface causes the fine-grained or glassy textures to be erased (McPhie, J. 1993; Wood, W. W ., & Fernandez, L. A. 1988). Some volcanic rocks may have a porphyritic texture in which large crystals are dispersed in a fine-grained matrix. Volcanic rocks may have different mineral compositions depending on the chemical composition of the magma.

Volcanic rocks are rocks that are formed as a result of the rapid cooling of displaced magma and have various physical and chemical artifacts. These rocks provide important information about geological features and have various industrial uses. The study of volcanic rocks provides important contributions to research in the field of earth sciences and helps to effectively evaluate their natural use.

2.3. Sedimentary Rocks

The region contains sedimentary rocks such as limestone, sandstone, marl and shale from the Paleozoic, Mesozoic and Tertiary periods. Some sedimentary rocks such as limestone are stored in groundwater formed by karst structures and play an important role when monitored. Sedimentary rocks are one of the most common rock types in the world and cover a large part of the earth's surface. These rocks are formed by the disintegration and petrification of sediments formed as a result of various results. Sedimentary rocks provide important information about geological history and provide underground possibilities (e.g. fossil fuels and their production), potentially having great opportunities. In this section, the definition of sedimentary rocks, their formations, types and general characteristics can be selected. Sedimentary rocks are rocks composed of physical and chemical parts, fragments, pieces, accumulation and petrification parts (Krynine, PD 1948; Boggs Jr, S. 2009; Tucker, ME 2003; and Narr, W ., & Suppe, J. 1991). These rocks are usually folded and fossils can be found in them. The routine features of sedimentary rocks are as follows: Sedimentary rocks consist of layers formed by the results of accumulation. These layers are revealed by the breaking and loosening of folds. Sedimentary rocks combine the accumulations of organisms that lived in the past. These fossils provide valuable information for the science of paleontology. Sedimentary rocks show great diversity in terms of physical and chemical properties depending on the formations. Weathering is the disintegration of rocks with their physical and chemical parts and its continuation. International disintegration occurs by the mechanical disintegration of rocks, while chemical disintegration occurs by the dissolution or transformation of the fracture of minerals. Erosion is the process of breaking away from the ground by external factors such as gravity, water, wind or glacier movements. Erosion causes groups of torsion (Kraus, MJ 1999; Chang, C ., et al., 2006; and McLennan, SM, & Taylor, SR 1991). Transportation is the process of breaking away from each other by elements such as water, wind or glaciers in another region. The transportation process occurs at different speeds according to the size and distribution of the folds.

Sedimentary rocks are rocks that provide important information about geological history and contain economically valuable resources. These rocks, which are formed as a result of differences, provide research areas for geologists and have a high probability of natural deterioration. The study of sedimentary rocks contributes to the identification of groundwater, fossil fuels and mineral deposits and their sustainable growth.

2.4. Metamorphic Rocks

Metamorphic rocks are found in deeper and older geological structures of the region. These rocks are generally impermeable to water, but fracture systems allow water movement. Metamorphic rocks are formed as a result of high temperature, pressure and chemical properties of pre-existing rocks, and physical and mineralogical changes stopping. These rocks recrystallize and gain new properties with the changes that occur deep in the earth's crust. Metamorphic rocks provide important information about geological information and have various industrial uses. In this section, the definition, formations, types and general properties of metamorphic rocks can be selected. Metamorphic rocks are formed by the end of the original rocks (protolith) being played with the products called mineralogical, chemical and altered metamorphism (Touret, JLR 2001; Ferry, JM 2000; and Schreyer, W. 1995) . Different properties of these rocks: During metamorphic processes, original minerals can transform into new minerals. The structure of rocks can be rearranged due to metamorphic features, which can cause the growth of foliated (leafy) or non-foliated (non-leafy) textures. Metamorphic rocks are generally formed under high pressure and temperature conditions, which increases their value. The geological and geomorphological features of Iğdır province are the basic elements that shape the natural structure and economic activities of the region. The complex geological structure of the region, rich underground resources and active tectonic activity make Iğdır geologically interesting (Smithson, SB 1971; Elliott, D. 1973; and Liou, J. G ., et al., 1998). These features are of great importance in terms of the determination of the natural sustainable management of Iğdır and regional development.

Metamorphic rocks are rocks that are formed under high pressure and temperature conditions deep in the earth's crust and are subject to various physical and chemical changes. These rocks provide important information about geological features and have various industrial uses. The study of metamorphic rocks provides important contributions to research in the field of earth sciences and helps to effectively evaluate natural resources.

3. GROUNDWATER POTENTIAL

Groundwater resources are vital natural resources that meet many regional water needs. Iğdır province allows Turkey to gain a place and host various production water reserves. In this section, the potential potential, geological and hydrogeological features, water quality and sustainable management systems of Iğdır province will be detailed. The geological structure of Iğdır province is an important factor that can directly provide employment potential (Karaaslan, Y. 2024). The main geological units in the region consist of sedimentary rocks, volcanic rocks and alluviums. Sedimentary rocks have suitable ownership and permeability properties for water flow and permits. In Iğdır province, especially Oligocene and Miocene sedimentary units form important water aquifers. Volcanic rocks in the region play a limited role in production activities due to their impermeable properties. However, they can accumulate water locally in cracks and fractures (Öztürk, M ., et al., 2016; Karahan, G., 2020; and Oklu, H., et al., 2024). Alluviums cover large areas in the Iğdır Plain and form important production water aquifers. These units with high permeability are critical in terms of water temperature and transmission.

3.1. Iğdır Province Groundwater Potential

The production water potential in Iğdır province varies depending on the hydrogeological structure of the region, climatic conditions and human climate. The main production water reservoirs are as follows: **Iğdır Plain Aquifer:** Iğdır Plain has extensive alluvial values and has a high production potential. The alluviums extending throughout the plain allow for easy cleaning and transmission of water. This aquifer is an important source for management irrigation and drinking water supply. **Mountainous Area Aquifers:** Fractures and cracked zones located in the mountains contain a certain limited amount of production water. These aquifers are generally used to meet local water needs.

Production water quality in Iğdır province varies according to the purpose of use of water. In general, water found in alluvial aquifers is suitable for management and drinking water intended use (Utlu, M ., & Ghasemlounia, R. 2021; Şahin, G., et al., 2024). However, negative effects of human events on water quality can be seen.

a) **Chemical Composition** : The chemical composition of groundwater is generally rich in bicarbonate, calcium, magnesium and sodium ions. Regular monitoring and evaluation should be carried out for the protection of water.
b) **Pollutants:** Agricultural activities, fertilizer and pesticide use may adversely affect the characteristics of the breeding water. In addition, industrial activities and uncontrolled waste disposal may also pose a threat to water security. Preparation of control parts of industrial and structural components is important for their preservation. For this purpose, appropriate waste

management and environmental protection measures must be taken.

Iğdır province is a rich region in terms of production water potential. Alluvial aquifers provide important resources for management and supply of drinking water. However, sustainable sustainable management and protection of water is vital to meet regional water needs (Aşkan, E ., et al., 2021; Öztürk, M., et al., 2016). This section addresses the production potential of Iğdır province and the management of this gain, providing important information on the sustainable use of water in the region.

4. AQUIFERS AND WATER-BEARING LAYERS

The underground water resources in Iğdır are stored in aquifers consisting of alluvial and volcanic rocks. These aquifers are fed by the alluviums of the Aras River and volcanic rocks in the foothills. Aquifers and water-bearing layers are geological formations with critical depressions in the behavior and transmission of distribution (Wang, Y ., et al., 2022) . In this section, the definition of aquifers, their types, the characteristics of water-bearing layers and their movements, hydrogeological developments can be selected. In addition, the role of aquifers in water management and their effects on water quality will also be discussed. Aquifers are systems where water is stored and transmitted, protected or transmitted.

4.1. Free Aquifers

Unconfined aquifers are aquifers where the water is exposed to atmospheric pressure at the water level and where water can move. Such aquifers generally vary depending on the direct characteristics of the surface water and factors such as the water table, precipitation and evaporation. Unconfined aquifers are storage units of water that are exposed to atmospheric pressure from the sun and have direct relations with the surface water. In this section, the definition, formation, hydrogeological properties, water carrying capacities, renewal and expansion options of unconfined aquifers are presented (Lin, J ., et al., 2013; Al-Sudani, HIZ 2019). In addition, the role of unconfined aquifers in water management and their effects on water quality will also be discussed. Unconfined aquifers are storage water reservoirs that are not limited by permeable layers above the water table. The water in these aquifers is directly exposed to atmospheric pressure and the water table is located close to the ground. Unconfined aquifers are usually formed by folded layers (sand, gravel) or fractured rocks.

These structures allow water to move. Unconfined aquifers receive water directly from precipitation, surface water, and rivers. This water infiltrates the aquifer and stops, allowing the aquifer to renew. The flow in the aquifer is moving, depending on the presence of the water table and the hydraulic gradient. The movement of water is directed by the power of the program and the topographic slope. The hydrogeological characteristics of unconfined aquifers have critical servers in terms of water flow and transmission. The protection rate of unconfined aquifers, the storage data of water are determined, while the movement distribution and directional effects of the spent water. High security and permeability allow water to move more easily and quickly within the aquifer. Hydraulic conductivity is the rate at which water moves in unit intervals of an aquifer under a unit hydraulic gradient. Hydraulic high conductivity in unconfined aquifers allows water to be transmitted quickly and effectively. Hydraulic conductivity is the rate at which water moves in unit intervals of an aquifer under a unit hydraulic gradient. Hydraulic high conductivity in unconfined aquifers allows water to be transmitted quickly and effectively. The water table represents the upper limit of the water contained in unconfined aquifers. The level of the water table varies depending on factors such as precipitation, evaporation, vegetation and human activities. The water carrying capacity of unconfined aquifers depends on the size of the aquifer, its visibility rate and hydraulic conductivity. This capacity determines the ability of the aquifer to store and transmit water (Burazer, M ., et al., 2010; and Kirsch, R. 2009). Regeneration capacity refers to the amount of water the aquifer receives from precipitation and surface spring water. The regeneration capacity in unconfined aquifers generally varies depending on the type and climate conditions directly with surface water. The discharge capacity is the water of the aquifer subjected to discharge through natural sources, rivers or man-made wells. This capacity is of great importance in terms of sustainable water use of the aquifer. Regeneration is depleted by precipitation, surface water and water leaking into the aquifer from rivers to agriculture. The regeneration rate varies depending on factors such as precipitation and topography. Discharge is the natural or artificial release of water from an aquifer. While natural discharge occurs through springs and rivers, artificial discharge continues through wells and water abstraction structures. Unconfined aquifers are critical resources in terms of water management and should be carefully managed for sustainable water use. Protecting the regeneration ensures sustainable protection of unconfined aquifers. It is important to prevent pollution of water in these areas and to ensure that water reaches the aquifer by natural separation. Water withdrawal from unconfined aquifers should be managed in accordance with the transport of the aquifer. Excessive water withdrawal can cause lowering of the water table and long-term damage to the aquifer (Albouy, Y ., et al., 2001; Khalilidermani, M., et al., 2021). Protection of unconfined aquifers is achieved by preventing the protection of water from agricultural, industrial and industrial wastes. Pollution control increases the usability of water for drinking and irrigation purposes.

Free aquifers are important geological units with high production water storage and transmission capacity, hydrogeological features and water carrying capacity. Sustainable management of these aquifers is of great importance for long-term availability of water resources. Backup and storage of renewal and versions contribute to the protection of the role of free flows in water management and their protection.

4.2. Confined Aquifers

Confined aquifers are layers containing water trapped between impermeable or semi-impermeable layers. The water in these aquifers is under a higher pressure according to the layer characteristics and the water level may rise due to natural pressure when a water well is opened. Confined (confined) aquifers are a special type of reproductive water reservoirs and, unlike unconfined aquifers, their water is compressed by the impermeable layers on it and carried under high pressure (Carr, MH 1979; Tawfiq, LN M ., et al., 2018). In this section, the basic features such as geological formation, hydrogeological properties, water carrying capacity, renewal and discharge of the resulting aquifers will be selected. In addition, the effects of these aquifers on water management and problems will be discussed. Confined aquifers are water reservoirs that are compressed by impermeable layers on it and are under pressure of these layers. In such aquifers, water moves with the pressure created by the upper layers and, unlike free aquifers, there is no direct interaction of water with the surface.

In confined aquifers, the aquifer is composed of two impermeable layers (usually clay, salt rocks or hard rocks). These layers prevent the movement of the water temperature and keep the water in the upper part of the aquifer under high pressure. The characteristic of these aquifers is that the water is stored under the water. The water can be found at a level higher than the level at which the information stored in the impermeable layers can move.

The pressure of the water in the aquifer can be at the water level of the yield. In confined aquifers, the pressure of the upper impermeable layer regulates the movement of the water so that the water level is stopped according to the equilibrium (Wang, J. A ., & Park, HD 2003; Nordbotten, J. M., & Celia, MA 2006). The water in the aquifer content is usually excessively mobile and is usually found at a lower level in the lower part of the aquifer where the water is in the water.

The hydrogeological features of pressurized aquifers, water currents and perspectives are quite different. These features are as follows: The permeability and protection features of pressurized aquifers determine the scope and direction of water movement. High permeability and protection rates in these aquifers allow water to move quickly. Hydraulic conductivity refers to the extreme movement of water in the aquifer. In pressurized aquifers, the movement of water under high pressure is an important factor in the hydraulic conductivity properties of the aquifer. Extreme movement of water in such aquifers is generally faster. Pressurized aquifers generally have a large water carrying capacity. This water capacity varies depending on the self-protection, permeability and totality of the aquifer. The portability of water in these aquifers, especially in large agricultural water basins, forms an important water source. The renewal and discharge of pressurized aquifers differ according to the characteristic features of these aquifers. Pressurized aquifers are renewed by processing the leaking water on the surface. However, unlike unconfined aquifers, this regeneration process is usually slower and more promising. Regeneration areas are usually located at the boundaries of the aquifer, and the protection of these buildings is important. The discharge of water from pressurized aquifers usually occurs through wells or natural springs. The discharge of water in pressurized aquifers can cause the information of the upper layers to spread directly to the outside of the sun. This death process can lead to the decrease of the water level of the aquifer and change the hydrogeological balance (Zhang, Y. Q ., et al., 2017; Wu, YX, et al., 20165). The system of water level and pressure plays a critical role in the water management of existing aquifers. Monitoring these parts is important for the sustainable use of water. Excessive water withdrawal can lead to the decrease of the water level of the initial aquifers and the change of the temperature of the water in these aquifers. It is important to limit the framework and increase sustainable use. The protection of water in pressurized aquifers requires special measures against pollution risks.

Pesticides, industrial wastes and other products used in agriculture can threaten the water protection of existing aquifers. The lowering of the water table or the loss of pressure in the aquifer can reduce the water pollution. Uncontrolled discharge of the aquifer and insufficient regeneration capacity can open the way for periods . Confined aquifers represent an important resource as production water reserves and have different dynamics in terms of water carrying capacity, hydrogeological features and water flow. The management of these aquifers has a critical learner for sustainable water use and marketing. In this section, basic information about the formation, characteristics and management of aquifers was presented. The effective emergence of these aquifers is important for the efficient reproduction.

4.3. Semi-Confined (Semi-confined) Aquifers

Semi-incipient aquifers are a transitional type between unconfined and current aquifers, and are aquifers that are under pressure under the influence of upper and lower impermeable layers. Semi-incipient (or semi-confined) aquifers are growth water reservoirs that contain the characteristics of both unconfined and initial aquifers. In such aquifers, water is partially confined by impermeable layers and may have some pressure on it. The hydrogeological characteristics of semi-incipient aquifers are important in terms of water movement and transportability. In this section, detailed information about the definition, formation, hydrogeological characteristics, carrying capacity and reaction management of semi-incipient aquifers will be presented. Semi-incipient aquifers are aquifers that have impermeable or low-permeable layers on them, but are not completely spherical (Maples, S. R ., et al., 2019; Bakker, M. 2006; and Unland, N. P., et al., 2015). Semi-published aquifers have impermeable layers on them that limit the movement of water. However, these layers completely prevent the movement of water, ensuring its proper functioning. The temperature of the water is usually higher compared to unconfined aquifers, but not as pronounced as in aquifers. In intermittent aquifers, the movement of water is resistant to both hydrostatic equilibrium and the effects of impermeable layers. The vulnerability of water may be restricted by the semi-permeable properties of the upper impermeable layers, but water movement is still possible. The water carrying capacity of these aquifers is generally lower than in unconfined aquifers, but higher than in the initial aquifers. The characteristics of these aquifers may vary according to environmental conditions. The portability of water depends on the permeability of the aquifer and the speed of water transfer between the layers.

The hydrogeological characteristics of intermittent aquifers are important factors that affect both the movement of water and the renewal processes of the aquifer. Intermittent aquifers generally have moderate permeability and character. In such aquifers, the rate and direction of water displacement vary according to the permeability and properties of the aquifer layers. The disbursement rates of semi-published aquifers are generally lower than those of unconfined aquifers. The hydraulic conductivity of the semi-published aquifers is affected by the hydrostatic pressure of the aquifer and the transportability of water. In these aquifers, the movement of water is generally forward, but the rate of overflow varies depending on the water carrying and resistance layers of the aquifer. The regeneration process of semi-published aquifers is different from that of unconfined aquifers. These aquifers are usually partially modified. Water can be accessed from the surface water source or from the tributary aquifers, but the regeneration process may be slow due to the restrictive effect of the impermeable layers above the aquifer. The water carrying capacity of semi-published aquifers varies depending on the aquifer interval, permeability and protection. These aquifers usually feed large amounts of water resources, but they can accommodate small and medium-sized production water basins. The regeneration and discharge of semi-published aquifers vary according to the characteristics of the aquifer. These processes are of great importance in terms of production water management. The regeneration process of semi-permeable aquifers occurs when water seeps from the surface and enters agriculture. However, this process may be slower compared to completely unconfined aquifers (Batlle-Aguilar, J ., et al., 2017; and Odling, NE, et al., 2015). In semi-permeable aquifers, the regeneration time of water depends on the permeability of the aquifer and the water flow rate. Regeneration areas are usually located in the upper part of the aquifer. The depletion process of semi-permeable aquifers may cause a decrease in water yield. This process may occur due to excessive water withdrawal or naturally. Depletion may lead to a cooling of the aquifer capacity, so water management methods must be carefully planned. Water management of semi-permeable aquifers aims to conserve water and ensure sustainable use. Water withdrawal from semi-permeable aquifers must be done carefully. Otherwise, the water level of the aquifer may decrease and symptoms may appear. The regulation of water exchange is important for the long-term preservation of the aquifer. Semiannual aquifers may be more sensitive to pollution. Therefore, flashover effects should be considered to protect the protective water. Chemicals used in agriculture, industrial wastes and other pollutants can deteriorate the water quality of these aquifers. Preserving the water level of semiannual aquifers and preventing their prohibition is of critical importance for environmental health. In addition, the overexploitation of these aquifers can have disastrous consequences. Semiannual (semi-limited) aquifers are a special source of produced water that contains the characteristics of both unconfined aquifers and initial aquifers. The hydrogeological characteristics of these aquifers, their water carrying capacity, regeneration and expansion are of great importance in terms of water management (Orecchia, C ., et al., 2022; Dwivedi, SN, et al.,2015) . The efficient presentation of semiannual aquifers plays a critical role for the sustainable use of water and the maintenance of growth protection.

Aquifers and water-bearing layers play a critical role in the behavior and transmission of distribution. The characteristics of these geological units have a direct effect on the movement of water and moisture. Sustainable water management and protection of aquifers are of great importance for the long-term availability of water (Jeng, D. S. , Li, L., & Barry, D. A. 2002). This chapter provides basic information about aquifers and water-bearing layers, thus increasing the magnification for the management and protection of this wildlife.

5. ARAS RIVER AND UNDERGROUND WATERS

The Aras River and its breeding waters form an important water source, especially in Iğdır and the surrounding areas. The Aras River serves as a natural border between Armenia, Azerbaijan, Turkey and Iran, and the water resources in this region also show that a large amount is formed (Nasehi, F ., & Fataei, E. 2012). Below you can find academic information about the relationships between the Aras River and aggressive waters and the suspicious hydrogeological features of these waters.

5.1. General Characteristics of the Aras River

The Aras River is a 1,072 km long stream that passes through the borders of four countries. It takes its source from the mountains of Armenia and enters Iğdır, Turkey, where it merges with the water resources that grow there. Then it passes through Azerbaijan and flows into the Caspian Sea near the Iranian border. (Saber, R ., et al., 2021). One of the elements that play an important role in the feeding of the Aras River is long-term mountainous rainfall and melting snow, but the level of this water source changes depending on seasonal changes and local climatic conditions. The asset waters of the stream can also be available in the same way that currencies are available.

5.2. Aras River and Groundwater Relationship

The beds of the Aras River are directly located with reproductive water sources. The waters of the river interact with the economic aquifers and these activities can lead to increased growth or melting. Especially the river bed in the region where the Aras River is located is an important source for the feeding of agricultural aquifers. Aquifers are generally renewed by the waters feeding the Aras River (Yanık, B. 1997). Groundwater aquifers are fed by the ground percolation of waters descending from the mountains. In the agricultural lands around the Aras River, agricultural waters can be supplied in the areas where water percolates. In addition, the impermeable layers in the upper part of the aquifers can prevent the storage of water in the ground or lead to water leakage.

The water level of the Aras River interacts with changes in the growth water level. An increase in the groundwater level can cause the river's water level to increase, because production water can directly seep into the rivers. Water leaking into the water resources obtained from the Aras River can help replenish the aquifers. This ensures that the growth is constantly fresh. However, in case of excessive water withdrawal, the level of production water can decrease, which can change the river's recharge. Agricultural activities and industrial wastes can pollute the Aras River's release waters (Ataei Giklou, I. , et al., 2020) . Pollution of the river and its aquifers can pose a threat to both ecosystems and human health in the region. Therefore, the protection of the Aras River's water region is of critical importance in terms of water resources for its protection. The passage of the Aras River has water resources located in the provinces of Iğdır, Ağrı, Erzurum and Kars. Economic waters in this region play a vital role, especially in terms of water supply used in agriculture. Fertile agricultural areas such as the Iğdır plain are fed by agricultural water resources. The alluvial grounds around the Aras River provide a suitable environment for breeding water reservoirs . Groundwater is used for management irrigation and supply of drinking water in Iğdır. (Dehghani, A ., et al., 2022) . Especially in the summer months, when agricultural practices are intensive, the demand for underground water increases.

5.3. Groundwater Quality

Groundwater quality has a critical structure in terms of sustainability of water access, protection of healthy ecosystems and supply of drinking water for people. Although groundwater is exposed to less dirt compared to surface water, it can lose its power against heating with excessive heating. This can be caused by agriculture, agricultural activities, industrial attacks, domestic waste and natural minerals. Therefore, the release of protection water is a great necessity to determine whether the water is suitable for its intended use (Uzundumlu, A ., et al., 2020; Karaoğlu, M., et al., 2018). One of the different features of groundwater is its chemical composition. Groundwater contains various chemical information by interacting with the surrounding rocks, minerals and organic substances. While these examples can be harmful, some increase the productive feature of water. For example, high amounts of dissolved iron or manganese can reveal the color of the water and create a bad taste. On the other hand, excessive nitrate and ammonium can indicate that plants are decomposing, that the water is dirty and agricultural policies can be shown. Therefore, it is very important to indicate the chemical parameters in the formation of protective water.

In addition to the physical and biological freedom of groundwater, microbiological diversity also poses a major threat. Groundwater can be contaminated with bacteria, viruses and other pathogens. In particular, the close structure of the water system, the ground leakage of wastewater, is suitable for the reproduction of microorganisms, and this poses health risks (Altın, Ö ., et al., 2023). Such pollution can lead to serious problems in industrial waters used for drinking water supply. Microbiological analyzes are one of the most basic tools in maintaining sustainability and constitute an important parameter in determining the drinkability of water. In addition, in order for the protection water to be renewable and protected, water resources should be expanded, water treatment technologies and sustainable water management policies and strategies should be developed (Kaysim, A. 2018).

6. GEOTHERMAL POTENTIAL

Geothermal energy is an environmentally friendly and sustainable energy alternative as an energy source obtained from temperature differences in the earth's crust. This energy coming from the depths of the earth manifests itself in the form of natural hot water sources, steam and hot rocks at nearby points on the ground. Geothermal potential determines whether the underground temperatures in a region and the geological structure of the earth's crust are suitable for energy production. The evaluation of this potential creates important opportunities not only in terms of energy production, but also in many products such as regional development, agriculture, health and tourism (Koc, A ., et al., 2019; Genç, MS, et al., 2021). The use of geothermal energy, especially electricity production, heating and cooling systems are widely used. Geothermal energy sources offer a great advantage in terms of continuous and continuous energy production compared to other alternative energy sources. Therefore, geothermal potential plays an important role for current energy changes, especially in regions where energy demand increases. However, it is of great importance that the technologies used during geothermal energy production are environmentally friendly and stored in a sustainable manner.

Geothermal potential depends on the geological structure of a region and the thermal properties of the earth's crust. In order to evaluate this potential, it is necessary to first determine the underground hot water reserves, their temperature levels and the depths of these reservoirs. Especially volcanic regions, areas with intense hot water flows and tectonically active regions are areas with high geothermal potential. Geothermal reservoirs are generally located in areas close to magma chambers and the geothermal energy potential is learned by drilling in these regions (Şahin, G ., et al., 2024; Ekinci, N., et al., 2016). In addition to the temperature of use of geothermal energy, the usable temperature ranges of hot water are also an important factor. In addition to determining the geothermal energy potential, infrastructure infrastructure and infrastructure infrastructure are also required for the effective use of this energy. The installation of geothermal power plants provides great economic benefits with its high replacement capacity and long-term low operating costs. Therefore, the development of geothermal potential and its use for regional energy production constitutes an important strategy for local development and increasing energy independence. In addition, geothermal energy resources provide the possibilities of touristic places such as hot springs and thermal treatment centers, which are also used in the tourism sector . In this context, the evaluation of geothermal potential is critical not only in terms of energy production, but also in terms of economic development, environmentally friendly practices and social benefits.

7. CONCLUSION

As a result, Iğdır province constitutes an important region in terms of water resources of Turkey with its geological structure and hydrogeological features. Different geological units such as alluvial structures, volcanic and sedimentary rocks, evaluation of growth potential and sustainable management perspective provide basic elements (Kabakus, N ., & Aslan, MT 2023). Especially alluvial areas such as Iğdır Plain play a critical role in meeting the agreement and usage water needs in the region thanks to their high permeability and water storage capacity. However, the sustainability of this standard depends on effective management and preservation of density. Production water resources in Iğdır province are affected by human activities as well as natural factors. Agricultural irrigation, fertilizer and pesticide use and industrial wastes, production water is directly reliable. This physical, regular, controlled collection of environments in the form of water and the development of sustainable use policies are of great importance. Especially the effects of transfer and industrial systems on water should be planned. The interaction between the Aras River and the water resources of the power plants has an important place in understanding the hydrogeological dynamics of the region. Water transport and leaks in the river provide renewal of both the water level of the river and the producible water resources (Tunçel, E ., et al., 2024; Turkes, M. 2020). A comprehensive evaluation of the relationships on the ecosystem in this connection has a critical structure in terms of the effectiveness of water management.

As a result, the sustainable use and protection of the marketing of Iğdır province has a structure that can be recorded not only in terms of meeting regional water needs, but also for maintaining the balance of economic development and activity (Akbulut, N. E .,. and 2022). Going forward, the water structure should be adopted with an integrated approach for a more effective management and its usability ensures that it is preserved both beautifully and qualitatively.

REFERENCES

Akbulut, N. E ., Bayarı, S., Akbulut, A., Özyurt, NN, & Sahin, Y. (2022). Rivers of Turkey. In Rivers of Europe (pp. 853-882) . Elsevier.

Albouy, Y ., Andrieux, P., Rakotondrasoa, G., Ritz, M., Descloitres, M., Join, J. L., & Rasolomanana, E. (2001). Mapping coastal aquifers by joint inversion of DC and TEM soundings-three case histories. Groundwater, 39(1), 87-97.

Al-Sudani, HIZ (2019). Groundwater system of Dibdibba sandstone aquifer in south of Iraq. Applied Water Science, 9(4), 72.

Altın, Ö. Ü. A. Y. , & Tanık, Z. (2023). Sustainability Strategies of Greenhouse Sector in Iğdır Province and Green Economy Model Proposal: Geothermal Greenhouse. Astana Publications.

Aşkan, E. , Topcu, Y., & Şahin, AN (2021). Determining consumption preferences of consumers considering quality attributes of drinking water: case of Iğdır. Italian Journal of Food Science, 33(2), 156-165.

Ataei Giklou, I ., Alijanpour, A., & Banj Shafiei, A. (2020). Investigation some of structural characteristics in Aras riparian forest stands. Forest Research and Development, 6(2), 277-293.

Avci, V. , Sunkar, M., & Toprak, A. (2022). Morphometric Analysis of Mount Ararat (Eastern Anatolia, Türkiye). Journal of Advanced Research in Natural and Applied Sciences, 8(3), 505-526.

Aydin, T ., & Çelik, MA (2019). Altitudinal Zone Land Use Changes in Iğdir Plain Using Overlay Analysis Combined with Remote Sensing Methods. J Remote Sens GIS, 8(263), 2.

Aydin, T ., & Çelik, MA (2019). Altitudinal Zone Land Use Changes in Iğdir Plain Using Overlay Analysis Combined with Remote Sensing Methods. J Remote Sens GIS, 8(263), 2.

Azarafza, M ., Ghazifard, A., & Asghari-Kaljahi, E. (2018). Effect of clay minerals on geotechnical properties of fine-grained alluviums of South Pars Special Zone (Assalouyeh). In Proceedings of the 36th National and the 3rd International Geosciences Congress of Iran.

Bakker, M. (2006). Analytical solutions for interface flow in combined confined and semi-confined, coastal aquifers. Advances in water resources, 29(3), 417-425.

Barr, S. M ., & Charusiri, P. (2011). Volcanic rocks.

Batlle-Aguilar, J ., Banks, E. W., Batelaan, O., Kipfer, R., Brennwald, MS, & Cook, P. G. (2017). Groundwater residence time and aquifer recharge in multilayered, semi-confined and faulted aquifer systems using environmental tracers. Journal of Hydrology, 546, 150-165.

Biçer, A. (2021). Analysis of Climatic Parameters with Meteorological Data of East Anatolia Region of Turkey. Bartın University International Journal of Natural and Applied Sciences, 4(1), 110-124.

Boggs Jr., S. (2009). Petrology of sedimentary rocks. Cambridge university press.

Burazer, M ., Žitko, V., Radaković, D., & Parezanović, M. (2010). Using geophysical methods to define the attitude and extension of water-bearing strata in the Miocene sediments of the Pannonian Basin. Journal of Applied Geophysics, 72(4), 242-253.

Carr, M. H. (1979). Formation of Martian flood features by release of water from confined aquifers. Journal of Geophysical Research: Solid Earth, 84(B6), 2995-3007.

Chang, C ., Zoback, M. D., & Khaksar, A. (2006). Empirical relations between rock strength and physical properties in sedimentary rocks. Journal of Petroleum Science and Engineering, 51(3-4), 223-237.

Dehghani, A ., Roohi Aminjan, A., & Dehghani, A. (2022). Trophic transfer, bioaccumulation, and health risk assessment of heavy metals in Aras River: case study—Amphipoda-zander–human. Environmental Science and Pollution Research, 29(20), 30764-30773.

Dwivedi, S. N ., Shukla, R. R., Singh, R., Adhikari, S. K., Nambi, K. A., Purty, S. S., & Roy, G. K. (2015). Determining the recharging capacity of an injection well in a semi-confined alluvial aquifer. Current Science, 1177-1181.

Ekinci, N. , Kavaz, E., & Cinan, E. (2016). Measurements of indoor 222Rn in Igdir, Turkey with CR-39 detectors. Asian J Chem, 28(4), 921-926.

Elliott, D. (1973). Diffusion flow laws in metamorphic rocks. Geological Society of America Bulletin, 84(8), 2645-2664.

Ferry, J. M. (2000). Patterns of mineral occurrence in metamorphic rocks. American Mineralogist, 85(11-12), 1573-1588.

Genç, M. S. , & Karipoğlu, F. (2021, May). Wind-solar site selection using a GIS-MCDM-based approach with an application in Kayseri province/Turkey. In 7th Iran Wind Energy Conference (IWEC2021) (pp. 1-4). IEEE.

Irvine, T. N. , & Baragar, WRAF (1971). A guide to the chemical classification of the common volcanic rocks. Canadian journal of soil sciences, 8(5), 523-548.

Jafari, M. K ., Bakhshayesh, M. K., Sohrabi, A., & Razmkhah, A. (2002). Seismic Geotechnical Properties of South Tehran Alluviums.

Jeng, D. S ., Li, L., & Barry, D. A. (2002). Analytical solution for tidal propagation in a coupled semi-confined/phreatic coastal aquifer. Advances in Water Resources, 25(5), 577-584.

Kabakus, N. , & Aslan, M. T. (2023). How increased electric vehicle ownership has changed air quality ?

Karaaslan, Y. (2024). Examining Crop Yield Losses in Iğdır Plain Irrigation Systems in Türkiye Amidst Water Constraints. Sustainability, 16(14), 5859.

Karahan, G ., Kapdan, E., Bingoldag, N., Taskin, H., Bassari, A., & Atayoglu, AT (2020). Environmental health risk assessment due to radionuclides and metal (loid) s for Igdir province in Anatolia, near the Metsamor nuclear power plant. International Journal of Radiation Research, 18(4), 863-874.

Karaoğlu, M. (2011). Agricultural meteorological aspects of Iğdır climate study. Journal of the Institute of Science and Technology, 1(1), 97-104.

Karaoğlu, M. , & Çelim, Ş. (2018). Geology and Soil Properties of Eastern Anatolia Region and Iğdır. Journal of Agriculture, 1(1), 14-26.

Karaoğlu, M ., & Erdel, E. (2022). A Study of Soil and Land Features with Geographic Information Systems (GIS) Analysis: Iğdır, Turkey. Turkish Journal of Agricultural Research, 9(2), 198-208.

Karaoğlu, M ., & Yalçın, AM (2018). Soil Salinity and Iğdir Plain Example. Journal of Agriculture, 1(1), 27-41.

Karaoğlu, M ., & Yalçın, AM (2018). Soil Salinity and Iğdir Plain Example. Journal of Agriculture, 1(1), 27-41.

Karataş, A. (2022). The Use of Geographic Information in Spatial Organization in the Early Iron Age: The Example of the Middle Aras Basin. Amisos, 1(The Special Issue (The Middle Aras Basin)), 37-55.

Kaysim, A. (2018). Evaluation of support policies in terms of livestock enterprises: The example of Iğdır province (Master's thesis, Institute of Science).

Khalilidermani, M ., Knez, D., & Zamani, M. A. M. (2021). Empirical Correlations between the Hydraulic Properties Obtained from the Geoelectrical Methods and Water Well Data of Arak Aquifer. Energies, 14(17), 5415.

Kirsch, R. (2009). Aquifer structures–pore aquifers. In Groundwater Geophysics: A Tool for Hydrogeology (pp. 391-446) . Berlin, Heidelberg: Springer Berlin Heidelberg.

Koc, A. , Turk, S., & Şahin, G. (2019). Multi-criteria of wind-solar site selection problem using a GIS-AHP-based approach with an application in Igdir Province/Turkey. Environmental Science and Pollution Research, 26, 32298-32310.

Kraus, M. J. (1999). Paleosols in clastic sedimentary rocks: their geologic applications. Earth-Science Reviews, 47(1-2), 41-70.

Krynine, P. D. (1948). The megascopic study and field classification of sedimentary rocks. The Journal of Geology, 56(2), 130-165.

Lin, J ., Lin, T., Ji, Y., Chen, Z., Zhao, Y., & Li, H. (2013). Non-invasive characterization of water-bearing strata using a combination of geophysical techniques. Journal of Applied Geophysics, 91, 49-65.

Liou, J. G ., Zhang, R. Y., Ernst, W. G., Rumble, DIII, & Maruyama, S. (1998). High-pressure minerals from deeply subducted metamorphic rocks. Reviews in Mineralogy, 37, 33-96.

Maghami, S ., Sohrabi-Bidar, A., Bignardi, S., Zarean, A., & Kamalian, M. (2021). Extracting the shear wave velocity structure of deep alluviums of "Qom" Basin (Iran) employing HVSR inversion of microtremor recordings. Journal of Applied Geophysics, 185, 104246.

Maples, S. R ., Fogg, G. E., & Maxwell, R. M. (2019). Modeling managed aquifer recharge processes in a highly heterogeneous, semi-confined aquifer system. Hydrogeology Journal, 27(8), 2869-2888.

McLennan, S. M ., & Taylor, S. R. (1991). Sedimentary rocks and crustal evolution: tectonic setting and secular trends. The Journal of geology, 99(1), 1-21.

McPhie, J. (1993). Volcanic textures: a guide to the interpretation of textures in volcanic rocks.

Narr, W. , & Suppe, J. (1991). Joint spacing in sedimentary rocks. Journal of Structural Geology, 13(9), 1037-1048.

Nasehi, F. , & Fataei, E. (2012). Measurement of residue levels of agro-chemicals in water and sediment of Aras River. Journal of Food, Agriculture & Environment, 10(1), 933-936.

Nordbotten, J. M ., & Celia, M. A. (2006). Similarity solutions for fluid injection into confined aquifers. Journal of Fluid Mechanics, 561, 307-327.

Odling, N. E ., Serrano, R. P., Hussein, M. E. A., Riva, M., & Guadagnini, A. (2015). Detecting the vulnerability of groundwater in semi-confined aquifers using barometric response functions. Journal of Hydrology, 520, 143-156.

Oklu, H. , Gürbüz, R., & Alptekin, H. (2024). Management of Johnsongrass (Sorghum halepense (L.) Pers.) in Alfalfa Cultivation Areas of Iğdır Province. Journal of Agriculture, 7(1), 45-62.

Orecchia, C ., Giambastiani, B. M., Greggio, N., Campo, B., & Dinelli, E. (2022). Geochemical characterization of groundwater in the confined and unconfined aquifers of the Northern Italy. Applied Sciences, 12(15), 7944.

Öztürk, M. , Altay, V., Altundağ, E., & Gücel, S. (2016). Halophytic plant diversity of unique habitats in Turkey: Salt mine caves of Çankırı and Iğdır. In Halophytes for food security in dry lands (pp. 291-315) . Academic Press.

Öztürk, M. , Altay, V., Altundağ, E., & Gücel, S. (2016). Halophytic plant diversity of unique habitats in Turkey: Salt mine caves of Çankırı and Iğdır. In Halophytes for food security in dry lands (pp. 291-315) . Academic Press.

Saber, R ., Isik, V., & Caglayan, A. (2021). Structural styles of the Aras fault zone with implications for a transpressive fault system in NW Iran. Journal of Asian Earth Sciences, 207, 104655.

Schreyer, W. (1995). Ultradeep metamorphic rocks: The retrospective viewpoint. Journal of Geophysical Research: Solid Earth, 100(B5), 8353-8366.

Singh, A ., Patel, A. K., Deka, J. P., & Kumar, M. (2020). Natural recharge transcends anthropogenic forcing that influences arsenic vulnerability of the quaternary alluviums of the Mid-Gangetic Plain. NPJ Clean Water, 3(1), 27.

Smithson, S. B. (1971). Densities of metamorphic rocks. Geophysics, 36(4), 690-694.

Şahin, G. , Koç, A., Doğan, S. Ş., & van Sark, W. (2024). Assessment of Wind Energy Potential and Optimal Site Selection for Wind Energy Plant Installations in Igdir/Turkey. Sustainability, 16(20), 8775.

Şahin, G. , Koç, A., Doğan, S. Ş., & van Sark, W. (2024). Assessment of Wind Energy Potential and Optimal Site Selection for Wind Energy Plant Installations in Igdir/Turkey. Sustainability, 16(20), 8775.

Tawfiq, L.N. M. , & Jabber, A.K. (2018, May). Steady State Radial Flow in Anisotropic and Homogenous in Confined Aquifers. In Journal of Physics: Conference Series (Vol. 1003, No. 1, p. 012056) . IOP Publishing.

Tırınk, S. (2021). Environmental effects and diffuse pollutant load calculation of animal wastes in Iğdır province and its districts. Black Sea Journal of Engineering and Science, 4(2), 43-50.

Touret, J. L. R. (2001). Fluids in metamorphic rocks. Lithos, 55(1-4), 1-25.

Tucker, M. E. (2003). Sedimentary rocks in the field. John Wiley & Sons.

Tunçel, E. , Gutiérrez, F., Gökkaya, E., Seyitoğlu, G., & Çiçek, İ. (2024). Tectonic geomorphology and deep-seated gravitational slope deformations (DSGSDs) in the Acıgöl Graben, Turkey. Geomorphology, 464, 109374.

Turkes, M. (2020). Climate and drought in Turkey. Water resources of Turkey, 85-125.

Unland, N. P ., Cartwright, I., Daly, E., Gilfedder, B. S., & Atkinson, A. P. (2015). Dynamic river–groundwater exchange in the presence of a saline, semi-confined aquifer. Hydrological Processes, 29(23), 4817-4829.

Utlu, M. , & Ghasemlounia, R. (2021). Flood prioritization watersheds of The Aras River, based on geomorphometric properties: Case study Iğdır Province. Journal of Geomorphological Research, (6), 21-40.

Uzundumlu, A. , Aşkan, E., & Çelik, Z. (2020). Determination of the place of municipal tap water as drinking water in consumer preferences: The example of Iğdır province. Journal of the Institute of Science and Technology, 10(2), 1350-1360.

Wang, J. A ., & Park, H. D. (2003). Coal mining above a confined aquifer. International Journal of Rock Mechanics and Mining Sciences, 40(4), 537-551.

Wang, Y ., Pu, Z., Ge, Q., & Liu, J. (2022). Study on the water-richness law and zoning assessment of mine water-bearing aquifers based on sedimentary characteristics. Scientific Reports, 12(1), 14107.

Wood, W. W ., & Fernandez, L. A. (1988). Volcanic rocks.

Wu , Y. Environmental protection using dewatering technology in a deep concentrated aquifer beneath a shallow aquifer. Engineering Geology, 196, 59-70.

Yanık, B. (1997). Transboundary and border water resources in Turkey.

Zhang, Y. Q ., Li, M. G., Wang, J. H., Chen, J. J., & Zhu, Y. F. (2017). Field tests of pumping-recharge technology for deep confined aquifers and its application to a deep excavation. Engineering Geology, 228, 249-259.

CHAPTER 5

COSMETICS LABORATORIES IN CHEMISTRY AND CHEMICAL RISK FACTORS

Musa KARADAĞ[1,2,*]
Mehmet Tevfik ADICAN[3]
Serkan ÇELİK[4]

DOI: https://dx.doi.org/10.5281/zenodo.14563338

[1] Department of Chemical and Chemical Processing Technologies, Vocational School of Technical Sciences, Igdir University, Igdir, Türkiye. [2]Research Application Laboratory and Research Center (ALUM), Iğdır University, Iğdır, Türkiye. **Orcid**: 0000-0003-2498-3403, **Mail**: musa.karadag@igdir.edu.tr; dengemusa@hotmail.com
[3]Mardin Artuklu Üniversitesi, Meslek Yüksekokulu, Elektrik Ve Enerji Bölümü, Elektrik Programı, Mardin, Türkiye. **Orcid**: 0000-0001-7733-9676, **Mail**: mtadican@artuklu.edu.
[4]Mardin National Education, Mardin, Türkiye. **Orcid**: 0009-0009-8950-3504, **Mail** : matserkancelik@gmail.com
Corresponding author: musa.karadag@igdir.edu.tr; dengemusa@hotmail.com

INTRODUCTION

A) CHEMICAL IDENTIFICATION OF RISK FACTORS.

Chemistry and cosmetics in the laboratory of scientific research and product development are critical environments where they are conducted. In this lab, various chemical substances, when attempting to potential risks and hazards that are moved in this list should also be considered. Chemical risks to laboratory personnel and comprehensive system stands out as a threat, and this risk is vital to sustaining a proper way.

Includes articles on a wide variety of chemical risks; toxic substances, flammable and explosive substances, corrosive substances, allergens as many different chemicals, may be present in the laboratory environment. This item accidents during operations with only threatening the safety of people remains at the same time, laboratory equipment packages and damages. Hence, the dimensions of the chemical risk assessment and management, essential to maintaining a safe work environment involved inis warm. Chemistry and cosmetics in laboratories and an understanding of the risks of these chemicals to identify risks and appropriate control measures requires a systematic approach. Safety data sheets (MSDS), is an important part of this process, and provides the necessary information for the safe use of chemical classification. In addition, the classification and the determination of appropriate security measures according to the class of chemical risks, the risk management module is the provision gerekemek(Dovjak et al., 2019; Aziz et al., 2022; Zhao et al., 2014; and Kaserzon et al., 2017)

In this section, chemical and cosmetics in the laboratories of chemical risk factors will be the focus of the spread. Chemical classification of risks in this risk assessment and the role of safety data sheets will be discussed in detail. In our laboratory, these risks employees recognize, understand, and provide the necessary information for safe working methods to adopt. In this way, it is aimed to minimize risks and maintain a safe laboratory environment chemical.

B) CLASSIFICATION OF CHEMICAL RISKS

Chemical substances, by their nature, different hazards and risks. These hazards and risks, physical and chemical properties of chemical groups, exposure routes, and are classified according to their effects on human health.

A correct classification of chemical risks, by these methods is an essential step for you to work in a safe way. In this section, the general views and the properties of each class of chemical groups can be selected. Classification of chemical risks in laboratories and industrial spans the details of the dangers of chemical substances examined for the distribution and storage is a basic step(Lundgren, A.., 1992; Rank, J., 2005; Felter, S., et al. 2021).

These products, chemical properties, physical and chemical properties, exposure routes, and is resistant to impacts on human health. Chemical substances, their nature different hazards, carries, and this risk should be classified in a systematic way to effective risk management.

1. Toxic Substances

Toxic substances are chemical substances that can cause harmful effects to human health. These substances can cause various acute or chronic health problems can be divided into different sections. Toxic accurate classification and the classification of the groups, in a safe manner is critical for these items to work with. This section of toxicology, definition, classification, effects, and management are discussed. Toxic substances, certain chemicals at exposure levels that are said to cause harmful effects in living organisms(Woodwell, G. M., 1967; Oblokulov, S. S., 2023; Shannon, M., 2000; and Gagliano-Candela, R., & Aventaggiato, L. 2001) Toksisit, A refers to the degree of insanity, and this effect, dosage, duration of exposure, and the maddening physical-chemical properties vary depending on. Toxic substances are generally direct contact, inhalation, ingestion or through the skin may be accessed. Toxic substances usually are classified according to the degree of harmfulness and the corruption of the domain. These impressions, the chemical classifications and properly maintained for safe operation is required.

1.1. Acute Toxins

Changing as acute, short-term exposure are the result of the things that quickly emerged. high doses can cause serious health problems with exposure in a short period of time. (Schle E., et al.,1992; Gable, R. S. 2004; Petejova, N., et al. 2019). For instance, essential oils are compounds mostly acute toxins, toxicity caused by the inhibition of these compounds takes place through physiological and nutrition, we can say that..

Examples: Cyanide, carbon monoxide, sarin gas.

Effects: acute poisoning usually results in a sudden and violent way, for example, the BAS transition, in general, breathing air, and can cause death.

1.2. Chronic Toxins

Chronic diseases, long-term exposure are the things that show results. These substances, however, low-dose continuous exposure creates adverse effects on health(Moradi, H., et al.2013; Gillery, P., & Jaisson, P. 2014; Lauriola, M., et al 2023; and Lu, P. H., et al. 2021). If we are going to do sampling, sometimes drugs and other xenobiotics may cause liver damage in susceptible individuals.

Examples: Lead, asbestos, benzene.

Effects: Chronic disease is usually long-term and occur in cancer, organ injury and repair defects can cause.

1.3. Neurotoxins

Neurotoxins are chemicals that have harmful effects on the nervous system. This network is the nervous system (neurons) communication between disrupts the release of neurotransmitters, purchase, or directly interfere with the function or functions allows you to deploy and nerve transmission. Neurotoxins, naturally occurring biological agents (e.g., snake venom, some plant-derived alkaloids) or synthetic chemicals (for example, some insect stings, heavy metals) may be. Harmful effects on the nervous system neurotoxins are showing. These substances can cause nerve damage in the central and peripheral nerves(Ong, A. a., & Sherris, D. A. 2019; goonetillek, A., & Harris, J. B. 2004; and barber, C. M., et al., 2004). Neurotoxins central nervous system (brain and spinal cord) and peripheral nervous system effects would have. Neurotoxins, which affect the central nervous system, disruptions in cognitive functions, neurodegenerative diseases, and can cause a decline in motor skills. If you are neurotoxins that act upon the peripheral nervous system Nov weakness, paralysis, and sensory disturbances may cause.

Examples: Mercury, lead, and some pesticides.

Effects: Neurological events between Nov weakness, loss of coordination, memory loss, and seizures in the lobby.

1.4. Are hepatotoksin

Hepatotoksin, or biological agents are chemical substances that damage the liver. These toxins, the liver cells (hepatocytes) of the liver is toxic and disrupts the normal functions direct or indirect. Are hepatotoksin, drugs, industrial chemicals, natural toxins (for example, some fungi and plant toxins) and can come from various sources such as environmental pollutants. Hepatotoksin, are substances that cause harmful effects on the heart. Since the liver is the body appear to function in detoxification, toxic effects on this organ, causing serious health problemsur(Wu, J., et al.1999; Quan, N. V., et al., 2020;and msagat, T. A., et al. 20006). Drug use among hepatotoksin routes of exposure to chemical substances, working with environmental exposure and consumption of contaminated water or food facility. The risk of hepatotoxicity, genetic factors, alcohol consumption, nutritional status, and may vary depending on individual factors such as other health conditions.

Hepatotoksin recognition and Prevention of exposure to these toxins, the liver is critical to the maintenance of Health. Safe to prevent liver damage, drug use, and reducing exposure to chemical substances, such as regular medical checks and measures should be taken.

Examples: Alcohol, aflatoxins, some systems (eg. acetaminophen).

Effects: enzyme rise in the hearts of Hepatotoxicity, jaundice and it may lead to heart surgery.

1.5. Are nefrotoksin

Nefrotoksin the term refers to chemical substances that creates harmful effects on the kidneys. These substances can disrupt the normal function of the kidneys and can cause kidney problems and can lead to serious structural damage. Nefrotoksin through different mechanisms can cause damage to the kidneys and may come from various sources. Nefrotoksin and substances that can have a damaging effect on the kidneys. These organs filter waste products from the kidneys to remove toxic substances may cause damage(Uber, A. M., & Sutherland, S. M. 2020; Kovacic, P.,2002; and Jones, D. P., & Chesney, R. W., 2009).

Examples: cadmium, some antibiotics (eg. gentamicin), some improvement solutions.

Effects: Nephrotoxicity vaccine, electrolyte imbalance and may result in a decrease of consumption.

Toxic effects, duration of exposure, the dose and varies depending on the characteristics of the person. Generally the effects of toxic products are examined under four main headings: **Acute Effects**: Fast and occur as a result of short term exposure. Examples of a bass bag, stomach and respiratory devices, devices. **Chronic Effects**: Long - term exposure affects resulting from it. permanent and progressive health problems. **Dose-related Effects**: Exposure, depending on the dose, the rate of chemical maddening effects. Higher doses will generally have a more severe impact. **Exposure of the way**: Chemical entering the rave route (inhalation, ingestion, skin contact), and determines the effects of the components.

Drugs that are used when working with toxic substances, and harmful effects of these products are less generalizes to download. These measures are used in accordance with regulations the Occupational Safety and health: **Risk Assessment**: Toxic hazards identification and classification of risks, to minimize exposure is required. **Exposure Controls**: Good ventilation, personal protective equipment, to ensure proper use and storage conditions. **Training and awareness-raising**: Chemical substances with the employees, depending on the hazards and safe work methods in the training of these categories is required. **Emergency Changes**: Chemical analysis and determination of exposure to substances in the case of emergency to arise, it is important that the staff be maintained by the application. Toxic substances, chemical and cosmetics that need to be made complete in the laboratories frequent and chemicals. In this way, accurate classification and effective management, in terms of job safety and employee health is critical. By working with these types of patients received appropriate toxic substances and provides a safe working environment helps to minimize pests.

2. Flammable and explosive substances

Flammable and explosive substances, heat, spark or flame combustion or explosion when exposed to precipitating factors such as the reactions of chemical substances. These substances, industrial, military, and everyday life in several areas, and are substances that need to be addressed carefully in terms of security(Wang, W. B., et al., 2015; Baranov, A. M., & Osipova, T. V. 2022; and Worsfold, P. M., et al., 2012). Flammable and explosive substances, under certain conditions, are chemical substances that have the potential of combustion or explosion. Such items, improper shipping, storage, or the use thereof in the case of a serious explosion and there is a risk of explosion. Appropriate precautions to minimise the risks of working with these materials chemistry and cosmetics in the laboratory is vital to be taken. This section of flammable and explosive distributions definition, classification, effects and the safe management will be discussed. Flammable and explosive substances, under certain conditions, flammable, or explosive chemicals. Such substances, explosion and increases the risk of explosion and therefore require special attention(Ren, C., et al., 2012; Schubert, H., et al.,2008; Wichman, I. S. (2003).

- **Flammable substances:** these substances, flammable reaches a point when they may burn easily. Gasoline, alcohol and flammable substances are examples of substances such as acetylene.

- **Explosive substances:** these substances, pressure, may explode due to temperature or other external factors. Takes place between TNT and ammonium nitrate explosive substances.

2.1. Definition and classification of flammable substances

Flammable substances, or burning when in contact with a source of ignition when it reaches a certain temperature are chemical substances that are running. Combustion is a chemical reaction that reacts with oxygen and expose to light and heat. Flammable substances, usually light point and flammability classes are classified according to(Mullerova J. 2018; Wichman, I. S., 2003; McManus, 2018 and N. Janssens, M. L. 2005). When working with flammable and Explosive Substances, and minimize the dangers to ensure safety, always have the most current security protocols and regulations must be complied with. To have a detailed knowledge about the properties and behavior of these substances, it is critical to manage risks and prevent accidents.

Flash point: boiling point is the lowest temperature that is required for mingling with the air to burn it. With a low flash point materials are more flammable.

The Flammability Classes:

Class I: flash point 38°below the liquids (eg. gasoline, ethanol).

Class II: flash point 38°C and 60°C between fluids (eg. diesel fuel).

Class III: flash point 60°C. at temperatures above liquids (eg. engine oil).

Risk of fire: flammable substances improperly stored or when it is processed there is a risk of explosion.

Health effects: respiratory tract vapors of burning materialscontinue le why the deaths may be. When working with flammable and explosive substances, in order to take a variety of security measures to minimize risks. These measures are used in accordance with occupational safety regulations. Flammable materials well ventilated areas and away from heat source, must be stored in suitable containers.

2.2. Definition and classification of explosive materials

Explosive substances, quickly gas, by means of heat and pressure deficit are the materials in a chemical reaction. This reaction is usually shock, starts with a trigger, such as shock or heat. Explosions can cause severe damage and injury. Triggered by the shock wave from the exploding at high speed and substances. (Berman, S. B., et al., 2024; Suceska, M. 2012; and Lee, P. R. 1998). Safe storage of explosive substances, transportation and security protocols and specific arrangements are available for use. These protocols aim to minimize the potential dangers of explosive substances. Explosive substances, in appropriate circumstances and at a certain distance should be kept. Storage areas should be well ventilated and precautions should be taken against the risk of fire.

Explosive products are classified according to the explosion characteristics and user characteristics.

High explosives: explosives with impact or Shock (eg. TNT, RDX, nitroglycerin).

Low Explosives: items that are generally used as the propellant and the combustion process is slower (eg. powder, nitrocellulose).

Risk of explosion: explosive substances, under certain conditions, shock waves, with high heat and pressure carries a risk of explosion.

Injury and Damage: Explosion, serious injury and property damage.

Flammable and explosive substances, inappropriate, serious hazards will occur. Of these pests, the effects of exposure varies, depending on the type and conditions. Explosive substances, specially designed, minimized the risk of explosion should be stored in the storage areas.

Flammable and explosive substances if executed with appropriate personal protective equipment (e.g., flammable extinguishers, protective clothing) in the lobby. The staff that run with these substances, should be trained in the proper usage and installation of the emergency. Types of extinguishers to be used in case of a flare up and use with combustible material must have knowledge about. Explosive modules explosion risk in case of an emergency evacuation and must be resolved. Flammable and component materials, chemical and cosmetics and chemicals commonly used in laboratories that need to be made in full(Ren, C., et al.,2012; Wichman, I. S., 2003; Wang, W. B.,2015). In this way, accurate classification and effective management, in terms of job safety and employee health is critical. Working with flammable and explosive substances received by the appropriate measures in these categories provides a safe working environment and helps to minimize pests.

3. Corrosive Substances

Through the chemical reaction of surfaces in contact with corrosive substances are substances that are damaging. These substances may cause severe burns and tissue damage of the skin and mucous membranes. Sulfuric acid and sodium hydroxide, commonly can be given as examples of corrosive substances. Corrosive substances are substances which cause serious damaging effects on surfaces that are in contact with the chemical chemical(Grundlingh, J., et al., 2017 ;Alves, L. M., et al. 2019; Hall, A. H., et al. 2019; Gumaste, V. V., & Dave, P. B. 1992; and Hartnett, K. M., et al., 2011). These substances, metals, and other materials may be damaged tissues, and the storage of severe burns, injuries, and property damage may result. Used with corrosive materials chemistry and cosmetics in the laboratory is of great importance to take appropriate security measures. In this section, corrosive classification definition, classification, effects and the safe management will be discussed in detail.

3.1.Definition and classification of corrosive substances

Chemically corrosive substances or metals when in contact with living tissue with the stored chemicals. The contact surfaces of these substances can lead to skin damage and usually acidic or alkaline storage. Corrosive substances, and pH values are usually classified according to their chemical structure(Alves, L. M., et al., 2019; Sharma, M., et al. 2021; Gerner, I., et al. 2000)

Acids: pH value below 7, which are substances. For example, sulfuric acid, hydrochloric acid.

Bases: pH value of 7 substances. For example, sodium hydroxide, hydroxide of energy.

Other corrosive substances: This category because the corrosive effects of other substances that have specific chemical properties enters. For example, hydrogen peroxide, ammonia.

Corrosive effects, and the duration of exposure varies, depending on the contact surface. These effects can lead to serious damage both living tissue on both metals.

3.2. Effects On Living Tissue

Corrosive substances, usually acidic or alkaline properties, are chemical compounds which can cause damage to the tissue in contact with living tissue. These substances in the tissues by initiating chemical reactions disrupts the cellular structure, cell death and can cause corrosive effects on organic surfaces may show. Corrosive substances are generally corrosive, flammable, or toxic properties and skin, eye, respiratory tract and digestive system damage(Cadwell, L. M. 2018; Ionescu, F., et al.,2019; and Eliaz, N. 2019)

Skin and eye Contact : Corrosive substances in direct contact with severe burns to skin and eyes, irritation and it can cause permanent damage.

The way Exposure : Corrosive vapours or gases in the respiratory tract to work with serious deterioration of the respiratory tract and can cause severe burns.

System sindir Exposure : Corrosive format if swallowed, may cause burns and severe damage to the internal organs in the digestive process.

3.3. The Effects On Metals

Corrosive substances in contact with metals, by initiating chemical reactions on the metal surface and corrosive substances are weakening the structural integrity of these metals. Oxides are generally acidic or basic metal surfaces can have properties and corrosive substances, salts, or other changes to form reaction products. Metal is exposed to these substances, the etching on the metal surface, cracking, and melting may lead to adverse effects such as corrosion. Interaction with corrosive substances, metal stresses, mechanical durability and can shorten their lifespan. (Vernon, W. H. J., 1949; Ilincev, G. 2002; Zarasvand, K. A., & Rai, V. R. 2014; and Umoren, S. A., & Solomon, M. M. 2017)

Corrosion: corrosive substances, and erodes the metal when in contact with metals chemical results are extinguished.

Surface Damage: roughness and uniformity of these substances can lead to deterioration of resistance on metal surfaces.

Corrosive things, trying various security measures in order to minimize risks should be taken. These measures are useful in accordance with the regulations for Occupational Safety. Goods corrosive, durable and leak-proof containers should be stored in(Al-Mashhadani, H. A., et al., 2021; and Ramasamy, K., & Gumaste, V. V. 2003).. These containers must be constructed in accordance with the chemical features. Corrosive material, well-ventilated areas, away from sources of heat and light must be stored in. Corrosive substances employees with personal protective equipment (PPE), protective gloves, goggles, face shield, and appropriate personal protective laboratory coats, such as moisturizers. The employment of personnel with these substances, the correct handling, storage and installation should be trained in emergency. Quick and effective first aid in case of contact with corrosive substances apply. In case of skin or eye contact should be washed with plenty of water. In case of the dissolution of corrosive suitable cleaning kits cleaning the affected area should be used and must be cleaned up immediately.

Corrosive materials, chemical and cosmetics are dangerous chemicals that should be maintained in the laboratory. This group is appropriate precautions to be taken correctly understanding and classification results, in terms of Occupational Safety and employee health is critical. Corrosive substances received by working with appropriate drugs, provides a safe working environment and helps to minimize such pests.

4. Allergens and irritants

Allergens are substances that can create an over reaction by the connection system. Due to contact with irritants are substances which cause deformation. Latex and formaldehyde, and ammonia is one of the common examples of some cosmetic irritants warning policies. Chemical risks, can be caused by a variety of sources. These resources, raw materials, products, and final products can be categorized as Dec(Nosbaum, A., et al., 2009; and Pedersen, L. K., et al.,2004).

The chemistry and uses of cosmetics raw materials, can accommodate various chemical risks. For example, while parabens are used as preservatives, harmful and allergenic substances may show some effects. There is a risk that occur during chemical production in Dec products. In these cases, as the result of the completion of the reaction or its deterioration may occur. Final cosmetic products, various cheating needs to go through before it reaches the chemical analysis. This analysis is essential to ensure the processes and functioning of the product. However, the final product is still at a low level , although the chemicals can be found(Tortolero, S. r., et al., 2002;and lepoittevi, J. P., & Lafforgue, C. 2020).

Safety data sheets (MSDS), chemical critical to ensure safe storage of vendors. MSDS 's physical and chemical properties of the chemical, health effects, first aid measures, fire-fighting precautions what to do in case of accidental exposure, and includes the features. This information and the distribution of chemical risks in the process of division is used as the basic source.

Chemical risk factors in a correct manner, the opening of a safe working environment in the laboratory of chemistry and Cosmetics has constantly monitoring critical. In this section, the selected processes and resources, and management of chemical risks will help the circulation. How to assess and control these risks in the future on the platform developments and strategies that will be taken will be discussed.

C) MANAGEMENT OF CHEMICAL RISK FACTORS

The management of chemical risks, the risk assessment process begins with. This process will identify the potential hazards of chemicals, exposure and analysis of the process is done in order to evaluate the degree of risk. The process of risk assessment consists of the following steps(Walters, D. 2006; Whaley, P., et al., 2016; Papazoglou, I. A., et al. 2003; and Aziz, H., et al., 2022).

a.Description: physical and chemical investigation of the chemical pollution. Toxicity data (LD50, LC50, etc.). Chemical carcinogen, mutagen or teratogen is to determine whether or not.

b. Exposure assessment: exposure routes (inhalation, skin contact, ingestion) determination. Evaluation of the properties and duration of exposure. In the normal course of exposure and estimation.

c. Risk Characterization: the merging of Hazard and exposure information. Risk level (low, medium, high) determination. The simplification of the determination of risk and management plans should be provided.

Safety precautions for the management of chemical risks in a series and good laboratory practices (GLP - good laboratory practice) should be adopted: a minimum of exposure to chemical substances to download the appropriate personal protective equipment(PPE; goggles, gloves, lab coat, mask) use should be provided. personal protective equipment(PPE)'seducation n, I, use, and maintenance. about properly should be informed(Barsouk, A., et al., 2021; Gwinn, M. R. et al. 2017; and Aqlan, F., & Ali, E. M. 2014).

D) RESULTS

Effective management of chemical risks, and the protection of the health of employees is critical to the operation of laboratory safety. Chemical risk assessment, security measures, emergency plans and training for the disclosure of this fundamental process elements. Risk management is a continuous process chemical process and the purchase of electricity in the full-information technologies and New needs updating. Management of Risk Factors in cosmetics chemistry and chemical laboratory, in terms of Occupational Safety and health is vital. In this section, Selected Topics, a correct classification of chemical risks, and applications includes Basic Rules for classification and management(Lim, D. s., et al., 2018; Pistollato, F., et al. 2021; and from alnuqay, M. A. 2024).. The management of chemical risks in a laboratory environment for the exchange of employees in addition to providing analysis and equipment - borne hazards contributes to reduce the.

Chemical risk factors, management, and in the process the risk assessment process begins with hazard identification, exposure assessment and risk characterization steps are tracked. Of these steps in a laboratory environment and to determine the risks of rules for the planning of measures to be taken against these risks is critical. Also, safety data sheets (MSDS) and chemical systems design, technological and provides the information necessary for the safe use of parts separation.

The adoption of safe working practices in a laboratory environment, the chemical can be done to minimize risks. Personal protective equipment the use of laboratory layout and cleanliness, correct specifications and labeling of chemicals such as good laboratory practices, which are the basic elements of this process. Also the addition of emergency plans and interventions, chemical accidents and exposure, must be prepared to respond quickly and effectively. These plans for emergencies such as chemical spills and explosions specified formations and emergency systemsdown a regular control. The management of chemical risks, training, and is of considerable importance. Laboratory employees regularly training, raise awareness of Chemical Safety and secure working environment contributes to maintaining and constantly updated with new information(kanayam H., et al. 2012;Lehman, A. J., et al. 1955). This training programs, working with chemicals, personal protective equipment use, emergency response applicationshould cover topics such as S.

As a result, effective management of chemical risk factors, chemical and cosmetics laboratories in a safe environment for the execution of critical monitoring feature. Backup and strategies discussed in this section, chemical risk assessment, and offers a basic guide to minimize cell. Future research and technological development, the exchange of chemical risk management needs to be updated on a continuous basis. In this way, the health and health of employees in the laboratory environment can be protected at the same time, technical and equipment sourceof the risks can be minimized Li(Kaushik, M., et al.,2023; Harvey, P. W., & Everett, D. J. 2006).

REFERENCES

Al-Mashhadani, H. A., Alshujery, M. K., Khazaal, F. A., Salman, A. M., Kadhi, M. M., Abbas, Z. M., ... & Dreamland, H. F. (2021, March). Anti-corrosive inhibitor for carbon steel in saline and acidic substance such as Green media. S Journal of Physics: Conference Series (Vol. 1818, No. 1, p. 012128). IOP Publishing.

Kaushik, M., Farooq, U., Ali, M. S., Ansari, M. J., Iqbal, Z., & Mirza, M. A. (2023). Regulatory status and safety concern of chemicals used in cosmetics and personal care products. Dermato, 3(2), 131-157.

Pistollato F., Madia, F. Corvi, R., Munn, S., Grignard, E., Pai, A., ... & Zuang, V. (2021). Current EU regulatory requirements for the assessment of chemicals and cosmetic products: challenges and opportunities for introducing a new approach methodologies. Archives of toxicology, 95, 1867-1897.

Harvey, P. W., & Everett, D. J. (2006). Regulation of endocrine-disrupting chemicals: an overview and critical deficiencies in Toxicology and risk assessment for human health. Best Practice & Research Clinical Endocrinology & Metabolism, 20(1), 145-165.

From Alnuqay, A. M. (2024). The dark side of beauty: an in-depth analysis of the toxicological impact and health hazards of synthetic cosmetics and personal care products. Frontiers in public health, 12, 1439027.

Lim, D. S., Roh, T. H., Kim, M. K., Kwon, Y. C., Choi, M. S., Kwack, S. J., & Lee, B. M. (2018). Non-cancer cells, and dermal sensitization risk assessment of heavy metals in cosmetics. Journal of toxicology and Environmental Health, Part B, 81(11), 432-452.

Kanayam H., Sato, K., Mori, T., Hirai, T., Umemur, T., Tamura, T., ... & Kusaka, Y. (2012). Work-related medical doctors in allergy: atopy, exposure to domestic animals, eczema induced by the surgical profession as potential risk factors of common chemicals and membership. International Archives of Occupational and environmental health, 85, 455-466.

Lehman, A. J., Patterson, W. I., Davidow, B., Hagan, E. C., Woodard, G., Laug, E. P., ... & Vos, J. B. (1955). The procedures for the appraisal of the toxicity of chemicals, foods, drugs and cosmetics. Food, Drug, Cosmetic Law Journal, 10(10), 679-748.

Barsouk, A., Thandra, K. C., In Saginal, K., Rawla, P., & Barsouk, A. (2021). Chemical risk factors of primary liver cancer: an update. Hepatic Medicine: evidence and research, 179-188.

Gwinn, M. R., Axelrad, D. A., Bahadori, T., Bussard, D. Cascio, W. E., Deener, K., ... & Burke, T. A. (2017). Chemical Safety Assessment: traditional vs. Public Health perspectives. American Journal of Public Health, 107(7), 1032-1039.

Aqlan, F., & Ali, E. M. (2014). Integrating lean principles and fuzzy bow-tie analysis for risk assessment in chemical industry. Journal of loss prevention in the process industries, 29, 39-48.

Alves, L. M., Cotta, R. A., Ciarelli, M. P., Salles, E. O., Coco, K. F., & Samatelo, J. L. (2019). Electrochemical corrosion of the corrosive substances and types of noise using Signal Processing and Identification through machine learning. *Journal of control, automation and electrical systems,30*, 16-26.

Alves, L. M., Cotta, R. A., Ciarelli, M. P., Salles, E. O., Coco, K. F., & Samatelo, J. L. (2019). Electrochemical corrosion of the corrosive substances and types of noise using Signal Processing and Identification through machine learning. Journal of control, automation and electrical systems, 30, 16-26.

Aziz, H., Aaleagha M. M. Azadbakht, B., & Samadyar, H. (2022). Identification and assessment of health, safety and Environmental Risk Factors and FMEA using Delphi methods of chemical industry (a case study). Anthropogenic Pollution, 6(2).

Aziz, H., Aaleagha M. M. Azadbakht, B., & Samadyar, H. (2022). Identification and assessment of health, safety and Environmental Risk Factors and FMEA using Delphi methods of chemical industry (a case study). Anthropogenic Pollution, 6(2).

Baranov, A. M., & Osipova, T. V. (2022). Latest progress in Sensors for pre-explosive Detection of flammable gases: a review. Sensors & Materials, 34.

Barber, C. M., Isbister, G. K., & Hodgson, W. C. (2013). Alpha-neurotoxins. Toxicon, 66, 47-58.

Berman, S. B., Hafizah, M. A. E., Ruyat, Y., & Rosyida, E. D. I. (2024). Use of explosives: Classification and regulation. The Indonesian Journal of interdisciplinary research in science and Technology, 2(5), 545-556.

Cadwell, L. M. (2018). Macroscopic observations of the effects of corrosive substances pre-bone and soft tissue when subjected to heating (master's thesis, Boston University).

Dovjak, M., Kukec, A., Dovjak, M., & Kukec, A. (2019). Identification of Health Risk Factors and their parameters. Creating healthy and sustainable buildings: an assessment of health risk factors, 83-120.

Eliaz, N. (2019). Corrosion of metallic biomaterials: a review. Materials, 12(3), 407.

Felter, S. P., Bhat, V. S., Botham, P. A. Bussard, D. A., Casey, W., Hayes, A. W., ... & Played Across Europe, E. V. (2021). Assessing chemical carcinogenicity: hazard identification, classification and risk assessment. Toxicology insight from the forum state-of-the-science workshop. Critical reviews in Toxicology, 51(8), 653-694.

Gable, R. S. (2004). Acute toxic effects of club drugs. Journal of psychoactive drugs, 36(3), 303-313.

Gagliano-Candela, R., & Aventaggiato, L. (2001). Entomological specimens for the detection of toxic substances. International Journal of Legal Medicine, 114, 197-203.

Gerner, I., Out Zina, S., Graetschel, G., & Schle, E. (2000). The introduction of a decision support system for Development into alternative methods of local irritancy/corrosivity testing strategies. A decision support system for the fundamental rules of creation. Alternatives to laboratory animals, 28(5), 665-698.

Gillery P., & Jaisson, P. (2014). Post-translational modification derived products (PTMDPs): chronic diseases of toxins?. Clinical Chemistry and Laboratory Medicine 52(1), 33-38.

A Goonetillek., & Harris, J. B. (2004). Clostridium neurotoxins. Journal of Neurology, Neurosurgery & Psychiatry, 75(suppl 3), iii35-iii39.

Grundlingh J., Payne, J., & Hassan, T. (2017). Attacks with corrosive substances are increasing in the UK. Bmj, 358.

Gumaste, V. V., & Dave, P. B. (1992). Ingestion of corrosive substances by adults. In the American Journal of Gastroenterology (Springer Nature), 87(1).

Hall, A. H., Jacquemin, D., Henny, D., Mathieu, L. Josset, P., & Meyer, B. (2019). Ingestion of corrosive substances: a review. Critical reviews in toxicology, 49(8), 637-669.

Hartnett, K. M., Fulginiti, L. C., & Di Modica, F. (2011). The effects of corrosive substances on human bone, teeth, hair, nails, and soft tissue. Journal of Forensic Sciences, 56(4), 954-959.

Ilincev, G. (2002). The research results of the corrosion effects on heavy metals in liquid Pb, bi, and Pb–Bi corrosion of structural materials with and without Front program that called. Nuclear engineering and design, 217(1-2), 167-177.

Ionescu, F., Reclar, And L. Ardelean, L. C., & Blatter, A. (2019). Comparative analysis intended to come into direct or prolonged contact with the corrosion resistance of titanium alloys of live tissues. Materials, 12(17), 2841.

Janssens, M. L. (2005). Material flammability. S Handbook of environmental degradation of Materials (pp. 207-225). William Andrew Publishing.

Jones, D. P., & Chesney, R. W. (2009). Nephrotoxins. In Pediatric Nephrology.

Kaserzon, S. L., Heffernan, L. A., Thompson, K., Mueller, J. F., & Ramos, M. J. G. (2017). Rapid screening and identification of chemical hazards in surface and drinking water using high-resolution mass spectrometry and a case-control filter. Chemosphere, 182, 656-664.

Kovacic P., Buckshot, A., & Wu-Weis, M. (2002). Nephrotoxins: widespread role of oxidative stress and electron transfer. Current medicinal chemistry, 9(8), 823-847.

Lauriola, M., Farre, R., Evenepoel, P., Overbeek, P. A., & Meijers, B. (2023). Food-derived uremic toxins in chronic kidney disease. Many toxins, 15(2), 116.

Lee, P. R. (1998). Explosives explosives fundamentals and development of technology. Explosive effects and applications (pp. 23-45). New York, NY: Springer New York.

Lepoittevi, J. P., & Lafforgue, C. (2020). The molecular aspects of irritant contact dermatitis and allergic to bee stings. Contact dermatitis, 1-18.

Lu, P. H., Yu, M. C., Wei, M. J., & Kuo, K. L. (2021). The therapeutic strategies for control of uremic toxins in chronic kidney disease. Many toxins, 13(8), 573.

Lundgren, A. (1992). Environmental hazard classification of chemicals. Toxicology letters, 64, 535-545.

McManus, N. (2018). Atmospheric Ignitable and explosive Hazards. Safety and health in confined spaces (pp. 111-160). CRC Press.

Moradi, H., Sica, D. A., & Kalantar-Zadeh, K. (2013). Cardiovascular burden associated with uremic toxins in patients with chronic kidney disease. The American Journal of Nephrology, 38(2), 136-148.

Msagat, T. A., Siame, B. A., & Shushu, D. D. (2006). Evaluation of methods for the isolation, detection and quantification of cyanobacterial hepatotoxins. Aquatic Toxicology, 78(4), 382-397.

Mullerova, J. (2018). Divission Of Flammable Substances And Materials Based On Their Composition And Classification, Properties And Characteristics. International multidisciplinary Scientific Geoconference: SGEM, 18(5.2), 189-196.

Nosbaum, A., Vocanson, M., Rozieres A, Hennino, A., & Nicolas, J. F. (2009). Irritant contact dermatitis and allergic to bee stings. European Journal of Dermatology, 19(4), 325-332.

Oblokulov, S. S. (2023). The Identification Of The Main Aspekts Of Toxic Substances. Journal Of Applied Medical Sciences, 6(4), 26-31.

Ong, A. A., & Sherris, D. A. (2019). Neurotoxins. Facial Plastic Surgery, 35(03), 230-238.

Papazoglou, I. A., Bellamy, L. J., Hale, A. R., Aneziris, O. N., Ale, B. J. M., Post, J. G., & Oh, J. I. H. (2003). I-Risk: Risk Management methodology for an integrated development of technical and chemical installations. Journal of loss prevention in the process industries, 16(6), 575-591.

Pedersen, L. K., Johansen, J. D., Held, E., & Agner, T. (2004). Augmentation of exposure by a combination of skin response to allergens and irritants–a review. Contact dermatitis, 50(5), 265-273.

Petejova, N., Martinek, A., Zadrazil, J., & Teplan, V. (2019). Toxic Acute kidney injury. Renal failure, 41(1), 576-594.

Quan, N. V., Dang Xuan, T., & Teschke, R. (2020). Potential hepatotoxins found in herbal medicinal products: a systematic review. International Journal of Molecular Sciences, 21(14), 5011.

Ramasamy, K., & Gumaste, V. V. (2003). Corrosive ingestion in adults. In the journal clinical gastroenterology, 37(2), 119-124.

Rank, J. (2005). Classification and risk assessment of chemicals: the case of DEHP in the light of REACH. The Journal of Transdisciplinary Environmental Studies, 4(3), 1-15.

Ren, C., Yuan, X., Wang, J., Zhang, X., & Li, J. (2012). Study pre-road transportation of flammable and explosive hazardous materials emergency response rank mode. Procedia Engineering, 45, 830-835.

Ren, C., Yuan, X., Wang, J., Zhang, X., & Li, J. (2012). Study pre-road transportation of flammable and explosive hazardous materials emergency response rank mode. Procedia Engineering, 45, 830-835.

Schle E., Mischke, U., Roll, R., & Kaiser, D. (1992). A national validation study of the acute-toxic-class method—an alternative to the LD 50 test. Archives of toxicology, 66, 455-470.

Schubert, H., & Kuznetsov, A. (Eds.). (2008). Detection of liquid explosives and flammable agents in connection with terrorism. Springer Science & Business Media.

Shannon, M. (2000). Ingestion of toxic substances by children. New England Journal of Medicine, 342(3), 186-191.

Sharma, M., Jindal, H., Kumar, D., Kumar, S., & Kumar, R. (2021). Overview Pre-Corrosion, Classification And Control Measure: A Study In. Journal On Future Engineering & Technology, 17(2).

Suceska, M. (2012). Test methods for explosives. Springer Science & Business Media.

Tortolero, S. R., Bartholomew, L. K., Tyrrell, S., Abramson, S. L., Sockrider, M. M., Markham, C. M., ... & Parcel, G. S. (2002). Environmental allergens and irritants in schools: a focus front asthma. Journal of school health, 72(1), 33-38.

Uber, A. M., & Sutherland, S. M. (2020). Nephrotoxins, and nephrotoxic acute kidney injury. Pediatric Nephrology, 35(10), 1825-1833.

Umoren, S. A.., & Solomon, M. M. (2017). Synergistic corrosion inhibition effect of mixtures of metal cations and organic compounds: a review. Journal of Environmental Chemical Engineering, 5(1), 246-273.

Vernon, W. H. J. (1949). The corrosion of metals. The Royal Society of Arts Journal, 97(4798), 578-610.

Walters, D. (2006). The efficacy of strategies for small enterprises in chemical risk management in Europe: evidence for success?. Health and safety policy and Practice, 4(1), 81-116.

Wang, W. B., Jiang, H. L., & Zhang, Y. P. (2015). Analysis of risks of radio frequency flammable and explosive environments. Advanced Materials Research, 1092, 717-721.

Wang, W. B., Jiang, H. L., & Zhang, Y. P. (2015). Analysis of risks of radio frequency flammable and explosive environments. Advanced Materials Research, 1092, 717-721.

Whaley, P., Halsall, C., Agerstrand, M., AIAS If E., Benford, D., Bilot, G., ... & Taylor, D. (2016). Implementing systematic review techniques in chemical risk assessment: challenges, opportunities and recommendations. Environment International, 92, 556-564.

Wichman, I. S. (2003). Material flammability, combustion, toxicity and fire hazard of transportation. Progress in energy and combustion science, 29(3), 247-299.

Wichman, I. S. (2003). Material flammability, combustion, toxicity and fire hazard of transportation. Progress in energy and combustion science, 29(3), 247-299.

Wichman, I. S. (2003). Material flammability, combustion, toxicity and fire hazard of transportation. Progress in energy and combustion science, 29(3), 247-299.

Woodwell, G. M. (1967). Ecological toxic substances and cycles. Scientific American, 216(3), 24-31.

Worsfold, P. M., Amyotte, P. R., Khan, F. I., Dastidar, A. G., & Eckhoff, R. K. (2012). Nontraditional explosibility of dusts review. Industrial & Engineering Chemistry Research, 51(22), 7651-7655.

Wu, J., Danielsson, A., & Zern, M. A. (1999). Toxicity of hepatotoxins: new insights into mechanisms and therapy. Expert opinion in the pre-investigational drugs, 8(5), 585-607.

Zarasvand, K. A., & Rai, V. R. (2014). Microorganisms: induction and inhibition of corrosion in metals. International Biodeterioration & Biodegradation, 87, 66-74.

Zhao, L., Xu, Y., Hou, H., Shangguan, Y., & Li, F. (2014). Source identification and health risk assessment of metals in urban soils around the Tanggu chemical industrial district, Tianjin, China. Science of the Total environment, 468, 654-662.

CHAPTER 6

NUCLEAR CHEMISTRY AND ITS APPLICATIONS IN MEDICINE

Lecturer Mustafa ATALAN[1]

DOI: https://dx.doi.org/10.5281/zenodo.14563361

[1] Uşak Üniversitesi, Eşme Meslek Yüksekokulu, Eczane Hizmetleri Bölümü, Uşak, Türkiye. mustafa.atalan@usak.edu.tr. Orcid ID: 0000-0001-8543-6951

1.INTRODUCTION

While in chemical reactions, changes occur only in the electrons located orbitals of an atom, in nuclear reactions, changes occur not only in the electrons of the atom but also in its nuclear structure. As a result of these reactions occurring at the nuclear level, the nature of an atom changes.

Nuclear chemistry is a branch of chemistry that deals with reactions in the nucleus. Nuclear chemistry, which is younger than other branches of chemistry, emerged with the discovery of X-rays in 1895 by Wilhelm Conrad Röntgen, a German physicist. While working with cathode rays, Röntgen observed that some substances outside the cathode ray tube emitted radiation and realized that this light, which he called X-ray, was caused by the ray emitted by the cathode ray tube [1]. Following Röntgen's studies, Antoine Becquerel investigated the hypothesis of whether naturally fluorescent substances emit X-rays independently of the effects of external stimuli, and as a result of this research, he concluded that these substances emit X-rays. To verify this hypothesis, Becquerel held the photographic plate in a dark environment without light for a few days and observed that the uranium-containing material emitted a continuous beam, which he called "Becquerel ray", even in the dark. Marie Curie observed the same radiation in thorium that Becquerel observed and concluded that this radiation was a feature related to the structure of the atom. Marie Curie first used the term "radioactivity" to describe the emissions observed in uranium and thorium. Marie Curie and Pierre Curie discovered two new radioactive elements (polonium and radium), after uranium and thorium. Marie Curie, Pierre Curie and Henri Becquirel received the Nobel Prize for their work in the field of radioactivity (1903) [2]. After all these studies, Ernest Rutherford discovered the two types of radiation (alpha (α) and beta (β) radiations) emitted by radioactive substances, and claimed that the new element formed as a result of radioactive decay would lose its properties and turn into another atom.

The nucleus of an atom contains particles called protons and neutrons, and there is a very strong attraction force between these particles. In stable nuclei, the neutron/proton (n/p) ratio is equal to 1, if this value exceeds 1.5, the stability of the atom is disrupted and the atom is exposed to various reactions at the nucleus to become stable again. If the n/p ratio is different from 1, the number of particles with the same charge will increase and these particles will apply a repulsive force to each other [3]. Nuclear reactions can occur spontaneously or can be carried out by humans. While nuclear reactions in unstable nuclei occur naturally, nuclear reactions in stable nuclei are performed artifactually by human. Of the nearly 300 isotopes of 92 elements existing today, about 60 are unstable. All nuclei with atomic numbers greater than 83 are unstable [3]. The energies of these reactions, known as “radioactive emissions,” are quite high. Elements that undergo nuclear reactions are called "radioactive elements".

With the addition of new radioactive elements to scientific studies and the addition of new features to the known properties of these elements, the interest in radioactive elements has also increased and as a result, the areas of use of these elements have expanded day by day. Radioactive emission, also known as radiation, is used in many areas such as medicine, pharmaceuticals, paint-textiles, defense and food to change the physical, chemical or biological properties of substances and to reduce their harmful effects on the environment. The expansion of the use of radiation has led to the emergence of a new branch of science called "nuclear chemistry". Also, the use of nuclear chemistry in medicine and pharmacy has led to the emergence of the branch of "nuclear medicine" in medicine. In this section, the use of radioactive nuclei in nuclear medicine will be focused.

1.1. TYPES OF RADIOACTIVE RADIATION

An atom is a structure consisting of a nucleus at its center and orbitals with certain energy levels around which electrons are located. The nuclei of atoms contain protons and neutrons, all of these particles are called "nucleons". The number of electrons in the orbitals of the nucleus is equal to the number of protons [4]. The ratio of neutron and proton numbers in the nucleus of a non-radioactive element is equal to 1 (Figure 1). The region where stable nuclei are located on the graph of the number of protons versus the number of neutrons is called the "stability zone". Nuclei outside this area due to their composition undergo radioactive decay.

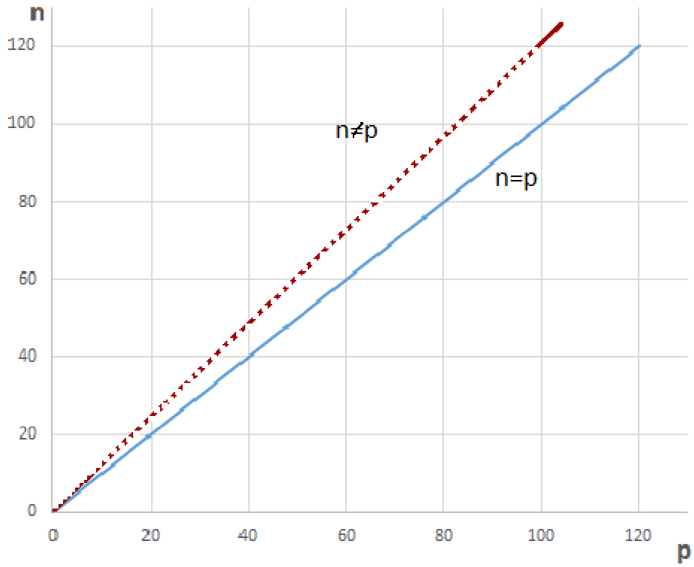


Figure 1. Stability zone of atoms

Radioactive elements produce radioactive radiation such as α, β, γ radiation thanks to the electrons, protons and neutrons in their structures. The weakest of these radioactive radiations, α-ray, can be blocked by paper, while the stronger β-ray can pass through paper but not aluminum. The stronger of the two, γ-rays, can pass through both paper and aluminum, but not lead or concrete. Since these radiations have high energy, they have the ability to ionize atoms of substances. This is a very risky situation, especially for the DNA in the living cell.

DNA is a macromolecule that is likely to be damaged by ionization, and DNA damage causes biological damage, especially cancer, in living creatures. The extent of this damage depends on the dose of exposed radiation. Since radiation emitted in the form of particles and waves cannot be directly detected by human senses, it is necessary to be well protected from radiation. Special devices such as a Geiger device must be used to detect radiation [5].

1.1.1. ALPHA (A) RADIATION

An alpha particle is a bir ${}^{4}_{2}He$ nucleus formed by radioactive decay. In this decay, both the number of protons and neutrons decrease. Thus, another nucleus that is smaller, more stable and has different properties is formed. If an atom is bombarded with alpha particles, the number of both protons and neutrons increases by two units [6-7].

$$^{239}_{94}\text{Pu} \rightarrow {}^{4}_{2}\alpha + {}^{235}_{92}\text{U}$$

$$^{230}_{90}\text{Th} \rightarrow {}^{4}_{2}\alpha + {}^{226}_{88}\text{Ra}$$

Although α radiation, which Rutherford described as the radioactive radiation with the lowest impact, loses its energy rapidly, it has a high potential to damage human cells. Despite this, alpha particles are used in many fields, especially in medicine. Some of these;

- Cancer treatment: Cancerous tissues are destroyed by administering very low concentrations of radium-226. Alpha particles destroy cancer cells and usually do not harm healthy cells around the cancer cell. For this purpose, cobalt-60 and radium-223 are also used.
- Cardiac Pacemaker: For this purpose, radioactive elements with a long half-life are preferred. The element with a long half-life serves as a long-lasting battery here. Plutonium-238 (half-life 88 years) was generally preferred in pacemakers, but its toxicity and disposal problems prevented its usage. Plutonium-238 is also used in spacecraft due to its long life.

In addition, Americium-241 is used in smoke detectors, and strontium-90 is used as a fuel source in remote sensing stations. Polonium-210 is used as a static eliminator in paper plants [5].

1.1.2. BETA (β *or* β^-) RADIATION

It is observed in nuclei of unstable elements with high neutron/proton ratio. In this radiation, when a neutron converts to a proton, an electron (e^-) and an anti-electron neutrino (n_e) are ejected.

$$n \rightarrow \rho + e^- + n_e$$

After beta radiation, the mass of the atom does not change but the atomic number increases by 1. [7-8].

$$^{186}_{73}Ta \rightarrow ^{186}_{74}W + ^{0}_{-1}e$$

$$^{27}_{12}Mg \rightarrow ^{27}_{13}Al + ^{0}_{-1}e$$

Beta irradiation is used for the prevention of restenosis after coronary artery stenting, in ophthalmology for the treatment of pterygium (Sr-90) and treatment of age-related macular degeneration, to control wound healing after glaucoma drainage surgery, and for the treatment of choroidal melanoma (Ru-106) [5].

1.1.3. GAMMA RADIATION (ɣ):

Gamma rays are high energy photons. They have very short wavelengths, so their energies are quite high. The energy of the nucleus changes with gamma radiation. Gamma radiation usually occurs after alpha or beta decay because the nucleus may remain excited due to a previous radioactive decay. After a gamma ray, there is no change in either the atomic number or the mass number of the nucleus [3].

A nucleus exposed to a particle bombardment can also emit gamma radiation.

$$^{40}_{18}Ar \rightarrow \gamma + ^{40}_{18}Ar$$

$$^{59}_{27}Co + ^{1}_{0}n \rightarrow ^{60}_{27}Co + \gamma$$

Gamma radiation easily passes through living material. Three different measurement units are used to measure gamma radiation: Giga Becquerel (GBq), gray (Gy) and Roentgen (R). Gamma radiation has a wide range of applications. Gamma radiation is used in the sterilization of medical devices, the reduction of bacteria that cause spoilage in food samples, skin cancers, lymphomas and inflammatory skin disorders, and the preparation of disposable medical materials [5].

***1.1.4.* POSITRON (β^+) RADIATION**

Every substance has a mirror image called antimatter. They have the same properties as matter in every way except for charge. The first discovered antiparticle was the positron and discovered by Carl Anderson in 1932. The positron is the antiparticle of the electron and is therefore considered a (+) charged electron. The positron is the same as the electron in every respect except its charge. When a particle and an antiparticle meet, they destroy each other. During this destruction process, photons, bosons or gluons, which are uncharged force carriers, are formed. For this reason, we do not encounter positrons in nature.

The positron particle is the opposite of the beta particle in terms of charge. In positron radiation, unlike beta radiation, a proton turns into a neutron. In this radiation, there is no change in atomic mass, but the atomic number decreases by 1. After positron bombardment, the mass of the atom does not change, but the atomic number increases by 1. [7, 9].

$$\mathrm{p} \rightarrow \mathrm{n} + \beta^{+} + n_e$$

$$^{38}_{19}K \rightarrow {}^{38}_{18}Ar + {}^{0}_{1}e$$

$$^{15}_{7}N + {}^{0}_{1}e \rightarrow {}^{15}_{8}O$$

1.1.5. NEUTRON (n) RADIATION

It is the radiation of neutron particles ($^{1}_{0}n$). In neutron radiation, the atomic mass decreases by 1, while the atomic number remains constant. When bombarded with neutron particles, the atomic number does not change, but the atomic mass increases by 1. [3].

$$^{59}_{27}Co + {}^{1}_{0}n \rightarrow {}^{60}_{27}Co + \gamma$$

$$^{238}_{92}U + {}^{1}_{0}n \rightarrow {}^{239}_{92}U$$

1.1.6. PROTON (p) RADIATION:

It is the ejection of a proton or a $^{1}_{1}H$ from the atomic nucleus. This reaction is not common. In this decay, the atomic and mass numbers decrease by one and the type of element changes. In proton bombardment, atomic and mass numbers increase by one [3].

$$^{12}_{6}C + ^{1}_{1}P \rightarrow ^{13}_{7}N + \text{energy}$$

$$^{45}_{21}Sc + ^{1}_{0}n \rightarrow ^{45}_{20}Ca + ^{1}_{1}H$$

1.2. DIAGNOSTIC USAGE OF RADIOACTIVE ELEMENTS

Nowadays, with the rapid advancement of technology, there has been an increase in the number and type of technological devices. Although these devices have provided indispensable conveniences in our lives, their unconscious and incorrect use causes various health problems. For example; many devices such as cell phones, computers, wireless modems cause serious health problems, especially in children, due to the radiation they emit. Parallel to today's developing technology, there have been changes in the types and natures of diseases. This situation has caused existing diagnostic and treatment methods to often be inadequate. Although radiation is one of the main causes of many health problems today, the use of radiation in the right disease and in the right dose is an indispensable factor in the diagnosis and treatment of many diseases, especially cancer.

There are 1800 radioisotopes discovered today, and approximately 200 of them are used in medicine for diagnostic and therapeutic purposes. In order for a radioisotope to be used in medicine, it must have sufficient energy, a short (desirable) half-life, be easily available and cheap, have high purity and low toxicity, and be able to bind to the target organ or tissue [10]. Radioisotopes are used not only in the diagnosis and treatment of cancer but also in the diagnosis and treatment of a wide variety of diseases such as cardiovascular diseases, neurological disorders, monitoring of bone metabolism and blood circulation. (Table1) [11]. Radioisotopes used for therapeutic purposes in medicine are called "*radiopharmaceuticals*". Radiopharmaceuticals are quite different from other drugs. These are drugs that are highly effective at very low doses and have no pharmacological effects [12-13]. Radiopharmaceuticals diagnose and treat diseases by binding to DNA protein receptors or interacting with biological molecules. Approximately 95% of the radiopharmaceuticals used in nuclear medicine are used for diagnostic purposes and the rest are used for treatment purposes. These drugs are implemented directly to the patient by experts in the correct dose, therefore these drugs must be sterile and pyrogen-free.

Radiopharmaceuticals are applied intravenously, intradermally, intrathecally, subcutaneously, orally, and by inhalation. Radiopharmaceuticals applied orally may be in the form of solutions, colloids or capsules. [14-16]. Radiopharmaceuticals must go through all the processes in the drug development process (phase studies and quality control studies).

Table 1. Radioactive elements widely used in medicine for diagnostic and therapeutic purposes.

Isotope	Half-Life	Radiation	Application	Reference
Tc-99	6.02 h	Gamma	PET imaging is used to image the brain, lungs, heart, kidneys and liver.	[17]
I-131	8 d	Beta	It is used in the treatment of hyperthyroidism and thyroid cancer.	[18]
Lu-177	6.71 d	Beta	It is mostly used in the treatment of neuroendocrine tumors.	[19]
Y-90	2.67 d	Beta	It is used as a therapeutic approach in liver cancers.	[20]
R-186	3.72 d	Beta	It is used in radiosynovectomy treatment.	[21]
Er-169	9.04 d	Beta	It is frequently used in radiosynovectomy treatment. It is also considered suitable for tumors that β− emissions cannot treat.	[22]
Xe-133	5.2 d	Gamma	Used to view air movement in the lungs.	[23]
I-124	4.2 d	Pozitron	It is widely used in thyroid dosimetry and tumor targeting.	[24]
Re-186	3.8 d	Beta	It is used as palliative treatment for metastatic bone pain.	[25]
Cu-64	12.7 h	Beta	Hypoxia is used in tumor diagnosis.	[26]

2. DISCUSSION AND CONCLUSION

The use of radiation, which is the main cause of many diseases based on gene damage, especially anomalies and cancer, in many areas such as medicine, agriculture, industry, and energy has provided great benefits to society. The determining factor here is the dose of radiation exposed. Today, early diagnosis is very important for many types of cancer such as breast cancer. This is a factor that makes the patient's treatment more effective and the increases the patient's survival probability. Radiopharmaceuticals and radiation are indispensable factors in the diagnosis and treatment of many diseases such as cancer. Nuclear medicine uses very small amounts of radioactive elements and radiopharmaceuticals. Today, it does not seem possible to avoid radiation completely. Radiation is not a substance that can be seen with the eye or perceived by any of our other senses. Therefore, since we cannot determine the dose of radiation we are exposed to, we need to avoid substances that can emit radioactive radiation (such as mobile phones and Wi-Fi) as much as possible and at the same time, we need to consume active ingredients such as antioxidants (vitamins A, C and E) that form a natural shield against these substances.

REFERENCES

[1] Anderson, C. J., Ling, X., Schlyer, D. J., & Cutler, C. S. (2019). A short history of nuclear medicine. *Radiopharmaceutical chemistry*, 11-26.

[2] Sekiya, M.and Yamasaki, M. (2015). Antoine Henri Becquerel (1852–1908): a scientist who endeavored to discover natural radioactivity. *Radiological physics and technology*, *8*, 1-3.

[3] Ebbing, D., & Gammon, S. D. (2007). *General chemistry*. Cengage Learning. Houghton Mıfflın Company, New York, ABD.

[4] Aslan, N. (2022). Nükleer Kimya. Iksad Publishing House, Ankara.

[5] Karmaker, N., Maraz, K. M., Islam, F., Haque, M. M., Razzak, M., Mollah, M. Z. I., ... & Khan, R. A. (2021). Fundamental characteristics and application of radiation. *GSC Advanced Research and Reviews*, *7*(1), 064-072.

[6] Loveland, W. D., Morrissey, D. J., & Seaborg, G. T. (2017). *Modern nuclear chemistry*. John Wiley & Sons.

[7] Choppin, G., Liljenzin, J. O., & Rydberg, J. (2002). *Radiochemistry and nuclear chemistry*. Butterworth-Heinemann

[8] Nagy, S. (2010). Kinetics of radioactive decay & growth. *Budapest, Hungary: ELTE, KI*.

[9] Green, J., & Lee, J. C. (2013). *Positronium chemistry*. Elsevier.

[10] Motahari, S. M., & Alemzada, F. (2024). Radiopharmaceuticals: Production, Physics, and Clinical Applications in Nuclear Medicine: A Short Review. *Afghanistan Journal of Basic Medical Science*, *2*(2), 43-52.

[11] Talip, Z., Favaretto, C., Geistlich, S., & Meulen, N. P. V. D. (2020). A step-by-step guide for the novel radiometal production for medical applications: case studies with 68Ga, 44Sc, 177Lu and 161Tb. *Molecules*, *25*(4), 966.

[12] Aşikoglu M., Radyofarmasotikler, In: Gursoy AZ.(eds). Farmasotik Teknoloji - Temel Konular ve Dozaj Şekilleri- *Controlled Release Systems Association Publication*, Istanbul. (2004); 399-407

[13] Saha, G. B. (1998). Radiopharmaceuticals and methods of radiolabeling. *Fundamentals of nuclear pharmacy*, 80-111.

[14] Yildiz, D. Tıpta kullanılan indiyum-111 radyoizotopunun üretimindeki farklı reaksiyonların tesir kesiti değerlerinn hesaplanması (Master's thesis, Institute of Science).

[15] Boyd, C. M., & Dalrymple, G. V. (1974). Basic science principles of nuclear medicine.

[16] Pharmacopoeia, B. (2001). Radiopharmaceutical Preparations, Volume Ü. *Her Majesty's Stationary Office, London*, 2577-2637.

[17] Jensen, M. (2024). Nuclear isomers in medicine. *The European Physical Journal Special Topics*, 1-5.

[18] Bhatia, N., Dhingra, V. K., Mittal, P., & Saini, S. (2023). Radiation Safety and External Radiation Exposure Rate of Patients Receiving I-131 Therapy for Hyperthyroidism and Remnant Ablation as Outpatient: An Institutional Experience. *World Journal of Nuclear Medicine*, *22*(03), 203-207.

[19] Sulieman, A., Mayhoub, F. H., Salah, H., Al-Mohammed, H. I., Alkhorayef, M., Moftah, B., ... & Bradley, D. A. (2020). Occupational and ambient radiation exposures from Lu-177 DOTATATE during targeted therapy. *Applied Radiation and Isotopes*, *164*, 109240.

[20] Tafti, B. A., & Padia, S. A. (2019, May). Dosimetry of Y-90 microspheres utilizing Tc-99m SPECT and Y-90 PET. In *Seminars in nuclear medicine* (Vol. 49, No. 3, pp. 211-217). WB Saunders.

[21] Turkmen, C. (2009). Safety of radiosynovectomy in hemophilic synovitis: it is time to re-evaluate. *J Coagul Disord*, *1*(1), 29-36.

[22] Formento-Cavaier, R., Köster, U., Crepieux, B., Gadelshin, V. M., Haddad, F., Stora, T., & Wendt, K. (2020). Very high specific activity erbium 169Er production for potential receptor-targeted radiotherapy. *Nuclear Instruments and Methods in Physics Research Section B: Beam Interactions with Materials and Atoms*, *463*, 468-471.

[23] National Academies of Sciences, Engineering, and Medicine. (NASEM), (2016). Medical Isotope Production and Utilization. In *Molybdenum-99 for Medical Imaging*. National Academies Press (US).

[24] Qaim, S. M., & Spahn, I. (2018). Development of novel radionuclides for medical applications. *Journal of labelled compounds and radiopharmaceuticals*, *61*(3), 126-140.

[25] Kucuk, N. O., Ibis, E., Aras, G., Soylu, A., Baltaci, S., Beduk, Y., ... & Canakci, N. (2001). *Palliative effect of Re-186 HEDP in different cancer patients with bone metastases* (No. IAEA-TECDOC--1228).

[26] Kim, J. Y., Park, H., Lee, J. C., Kim, K. M., Lee, K. C., Ha, H. J., ... & Cheon, G. J. (2009). A simple Cu-64 production and its application of Cu-64 ATSM. *A(pplied Radiation and Isotopes*, *67*(7-8), 1190-1194.

CHAPTER 7

THICKENING AGENTS

Dr. Nazangül ÜNAL[1]

DOI: https://dx.doi.org/10.5281/zenodo.14563367

[1] Uşak University, Eşme Vocational School, Department of Pharmacy Services, Uşak, Türkiye. nazangul.unal@usak.edu.tr. Orcid ID: 0000-0001-9481-1354

INTRODUCTION

Nowadays, with the increase in urbanization rates, people have started to prefer processed foods rather than natural foods. Due to this increasing demand for processed foods, the food industry has continued to increase the variety and content of their products day by day in order to survive among their competitors. The food industry has added many substances such as colorants, preservatives, thickening agents (TAs), acidity regulators, etc. to their products to extend their shelf life and make them more attractive and tasteful. Food additives added to foods directly affect food quality. This section of the book will focus on two thickening agents (xanthan and carrageenan) that are commonly used in the food industry and directly affect the quality of foods.

Hydrocolloids are substances that increase the texture, taste and rheological properties of food products and extend their shelf life, and forming viscous dispersions/gels when dispersed in water. Since TAs are hydrocolloid substances, they increase product quality by performing all the functions of hydrocolloids (forming viscous mixtures, extending the shelf life of food, etc.). TAs do this by controlling moisture. TAs have found use in many industries; in the food industry (soups, ice creams, sauces, jams, cakes, candies, etc.), in cosmetics (toothpaste), in textiles (textile colorants) (Cong et al., 2022; Himashree et al., 2022; Saha and Bhattacharya, 2010). Commonly used TAs in the food industry are starch, xanthan, guar gum, sodium alginate, carrageenan, locust bean gum, gelatin, agar and carboxymethyl cellulose (CMC) (Saha and Bhattacharya, 2010).

TAs show different rheological properties in the product depending on the chemical structure of them. These properties vary depending on factors such as temperature, concentration of the active compound, solubility, ionic strength, pH, and the presence of lyophilic substances (Himashree et al., 2022; Saha and Bhattacharya, 2010). TAs are classified in various ways according to their chemical properties, sources, thickening mechanisms, and degradability (Cong et al., 2022; Himashree et al., 2022). The main sources of TAs include microorganisms, land and sea plants, and animal sources. Pectin and cellulose are obtained from plants; gelatin and chitosan are obtained from animal sources; xanthan is obtained from fermentation products; carrageenan, agar, and alginate are obtained from seaweeds and guar gum and locust bean gum are obtained from seeds (Himashree et al., 2022). According to their sources; also, they can be divided into three groups as synthetic, semi-synthetic and natural. These substances can also be classified as gum based, plant based, microbe based and protein based. Protein based thickeners are whey protein and soy protein, plant based thickeners are moringa seeds, tomato pomace, corn starch, rice flour, tapioca starch, etc., gum based thickeners are guar and xanthan gums, and microbe based thickeners are salecan, micro algae, bacterial cellulose. Protein-based thickeners have important functions such as forming viscous liquids or gels with hydration, emulsification, stabilization, thickening. Polysaccharides obtained from plant extracts are a source of additives for various industries, particularly the food industry. These act as food thickeners. Gum-based thickeners are high molecular weight hydrophilic biopolymers. When two or more gums are added to a food at the same time, they can create a synergistic effect and improve the quality of the food. TAs obtained from microbial sources are derived from sources such as microalgae, bacteria and fungi. They increase both the quality and rheological properties of the product by acting as texturizers, stabilizers or emulsifiers. They are used in products such as bread, ice cream, ketchup, and sauce (Himashree et al., 2022).

Carrageenan

Carrageenans are sulphated polysaccharides of D-galactose and 3,6-anhydro-D-galactose. It is a thickener obtained from the cell walls of Rhodophyceae class red seaweeds and is frequently used in the food industry (Cong et al., 2022; Hotchkiss et al., 2016; Unal, 2010; Zia et al., 2017). The red seaweed species that are sources of carrageenan eucheuma, cripus, chondrus, solieria, sarconema, agardhiella, gigarti-nastellate, iridaea, hypnea and agardhiella (Li et al., 2014; Zia et al, 2017). Carrageenan has been accepted as a food additive in the European Union and is designated E 407 (Necas and Bartosikova, 2013; Unal, 2010).

Carrageenans are used in many industries; in food industry they are used as gelling, thickening and protein suspending agent, stabilizer, and emulsifier, in cosmetic products such as toothpaste, creams, shampoo, in pharmaceutical industry they are used as excipient in pills and tablets (Li et al., 2014; Zia et al., 2017). Carrageenan is resistant to enzymatic degradation. They have widely used in the pharmaceutical industry due to their biological activities (anticoagulant, antiviral, antitumor, immune-modulatory, anti-hyperlipidemic, etc.) (Li et al., 2014; Zia et al., 2017). Carrageenans have anticoagulant effects due to the sulfate groups they contain and have negative effects on the immune system and human intestinal epithelial cells (Zia et al., 2017). Because of the gastrointestinal side effects, the use of low molecular weight carrageenan in medicines is limited (Unal, 2010). Another reason that limits the use of carrageenan in the pharmaceutical industry is their high viscosity. Carrageenan has been used as a gelling/viscosity increasing agent for controlled drug release and long-term retention due to its negative charge and gelling properties (Li et al., 2014).

Six types of carrageenans (iota (i), kappa (κ), lambda (λ), Mu (μ), Nu (v), and theta (θ)) are present but three of them ((iota (i), kappa (κ), lambda (λ)) are commercially used (Cong et al., 2022; Li et al., 2014; Unal, 2010). Carrageenans are anionic polimers because of their half ester sulphate moieties and differ from each other depending on the their sulphate substituent position and presence of the 3,6-anhydro bridge. Number of sulphate groups are one for κ-carrageenan, two for i– carrageenan, and three for λ–carrageenan (Li et al., 2014; Unal, 2010; Zia et al., 2017). Kappa (κ)-carrageenan, which is the most used carrageenan among carrageenans, is made up of 4-linked 6-anhydro-α-galactopyranose and 3-linked β-D-galactose 4-sulfate that alternate and have one negative charge per repeating unit of the disaccharide. There are two sulfate groups per disaccharide repeating unit in iota (i)-carrageenan. κ and ι-carrageenans show gel-forming properties in the presence of cations such as K^+ and Ca^{2+}. Unlike κ and ι-carrageenan, lambda (λ)-carrageenan does not exhibit any 3, 6-anhydride bridge. λ-carrageenan exhibits the strongest antioxidant activity and the ability to scavenge free radicals. Carrageenans are soluble in hot water, only the lambda form is soluble in cold water without forming gels, and lambda carrageenan cannot form gels because it does not have 3,6 anhydrous bridges. Carrageenans are insoluble in fats, oils, and organic solvents. Carrageenan is used in dairy products, puddings, meat products, jellies, pet foods, supplemental drinks and baby foods (Hotchkiss et al., 2016; Li et al., 2014; Zia et al., 2017). The average molecular weight range of carrageenans used in foods is ≈ 400-600 kDa. Carrageenan is used in foods at very low doses (0.1-2%). The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has stated that “carrageenan is not a concern when used in infant formula or formula for special medical purposes at concentrations up to 1000 mg/L.” Furthermore, the US Food and Drug Administration maintains that the level at which carrageenan is used in foods to achieve functionality is safe and there is no need for any restrictions (Hotchkiss et al., 2016).

Xanthan

Xanthan gum (XG, $C_{35}H_{49}O_{29}$), also known as corn sugar gum, is a high molecular weight anionic polysaccharide, which is an extracellular polymer obtained from a pathogenic bacterium called Xanthomonas Campestris (a gram-negative bacterium) (Bhat et al., 2022; Farpour et al., 2021; Furtado et al., 2022; Hassabo et al., 2023; Petri, 2015). It was discovered in the 1950s by Allene Rosalind Jeanes in the United States Department of Agriculture, USA (Petri, 2015).

XG is a pentasaccharide biopolymer consisting of two glucose, two mannose and one glucuronic acid units (Bhat et al., 2022; Farpour et al., 2021; Unal, 2010). It is an anionic polysaccharide due to the acetic acid and pyruvic acid present in its structure (Bhat et al., 2022; Furtado et al., 2022; Hassabo et al., 2023). The molecular weight of it varies between $2x10^6$ -$20x10^6$ Da depending on the content of glucose, mannose, glucuronic acid, acetate, pyruvate and galactose in the molecule (Bhat et al., 2022; Unal, 2010). This value varies depending on pH, temperature and shaking.

XG can be dissolved in cold and hot water, is almost odorless, tasteless, has a white or pale yellow powder appearance, can form transparent viscous solutions when dissolved in water, is compatible with most metallic salts, and has thermal stability. It is also stable in acidic and basic solutions, non-toxic, biodegradable and biocompatible (Bhat et al., 2022; Farpour et al., 2021; Furtado et al., 2022; Hassabo et al., 2023). In addition to all these properties, being a pseudoplastic substance, being resistant to amylase, being inexpensive to produce and having unique rheological properties have made it an indispensable substance in many branches of industry (cosmetics, textiles, petroleum, etc.), especially in the food and pharmaceutical industries (Bhat et al., 2022; Farpour et al., 2021; Furtado et al., 2022; Hassabo et al., 2023; Petri, 2015; Unal, 2010). XG has the ability to be mixed with hot and cold liquids over a wide pH range (pH 1.5-11.0) (Farpour et al., 2021; Furtado et al., 2022). It can produce sufficiently viscous liquids even at very low concentrations (<1%) (Farpour et al., 2021). The content of XG in food products varies between 0.05% and 0.7% by weight (Bhat et al., 2022; Petri, 2015). XG is commonly used in fruit juices, powdered drinks, chocolates, jellies, margarine, yogurt, confectionery, sauces, frozen meals, etc. (Bhat et al., 2022; Farpour et al., 2021; Hassabo et al., 2023). It is used as a gelling agent in varying amounts into the food products (0.05-0.03% in bakery products, 0.1-0.5% in salad dressings and 0.1-0.3% in ready-made foods) to increase their water-binding properties (Bhat et al., 2022).

Due to its physicochemical properties and acid resistance, XG is used as an excipient in drugs together with other thickening agents and is used in drug delivery applications as supporting hydrogels. High molecular weight XG acts as a carrier for drugs and proteins (Bhat et al., 2022; Petri, 2015). It is used as a thickening, suspending and stabilizing agent in liquid oral pharmaceutical formulations just like in foods, allowing the liquid to maintain its homogeneity. (Bhat et al., 2022). Since XG is resistant to many enzymes found in the gastrointestinal system, liquids prepared with it remain intact until they reach the colon, which may cause XG to interact with some drugs (Farpour et al., 2021). XG is also used in biomedical applications due to its biocompatibility and biodegradability in living organisms. It is also used in packaging materials because of its stability in both hot and cold water and its physicochemical and pseudoplastic properties. It has been also used in personal care products such as toothpaste, shampoo, cream and lotion to provide the desired viscosity, stability and suspension of insoluble solid particles (Bhat et al., 2022). Its chemical properties have caused it to keep the skin moisturized for longer and to have anti-aging activity, which has made it attractive for the cosmetics industry. It does not accumulate in the body, so its use is safe (Furtado et al., 2022).

In 1969, the FDA approved XG as a non-toxic and safe polymer, allowing it to be used as a food additive in many food products without specific amount restrictions (Bhat et al., 2022; Farpour et al., 2021; Petri, 2015). In 1980, XG was added to the European Economic Community list as a food emulsifier/stabilizer with the code E415 (Unal, 2010).

CONCLUSIONS

In this section of the book, thickening agents (especially carrageenan and xanthan), which are very important for the food and pharmaceutical industries, are discussed in detail. These macromolecules, which are used for many purposes such as thickening, gelling, emulsifying agents etc., are used in many products such as puddings, confectionery, sauces, soups, powdered fruit drinks, various medicines, toothpastes, shampoos due to their physicochemical properties. As the number of studies on TAs increases, their usage areas will increase accordingly. Some of the substances used as thickeners have been accepted as safe by the FDA, but some studies show that overdose of these substances may cause digestive system diseases. Therefore, the effects of these substances on health should be investigated in more detail and the maximum dose that is safe for health should be determined and this dose should be stated on the label. This is very important for both clinical and food chemistry. Since these substances are considered safe in foods and the amount of use of many of them in food is not limited, studies on this subject are quite limited. In addition, the fact that these substances are macromolecules and form highly viscous liquids has made their analysis very difficult in terms of analytical chemistry. Methods that allow quantitative analysis of TAs should be developed and diversified. This is very important for quality control and routine analysis of many products, especially foods and drugs.

REFERENCES

Bhat, I. M., Wani, S. M., Mir, S. A., & Masoodi, F. A. (2022). Advances in xanthan gum production, modifications and its applications. *Biocatalysis and Agricultural Biotechnology*, *42*, 102328.

Cong, L., Zou, B., Palacios, A., Navarro, M. E., Qiao, G., & Ding, Y. (2022). Thickening and gelling agents for formulation of thermal energy storage materials–A critical review. *Renewable and Sustainable Energy Reviews*, *155*, 111906.

Farpour, S., Farpour, H., & Salarinejad, A. (2021). A narrative review on Xanthan Gum characteristics: A thickening agent used for dysphagia. *Journal of Rehabilitation Sciences & Research*, *8*(2), 97-99.

Furtado, I. F., Sydney, E. B., Rodrigues, S. A., & Sydney, A. C. (2022). Xanthan gum: Applications, challenges, and advantages of this asset of biotechnological origin. *Biotechnology Research and Innovation Journal*, *6*(1), 2-8.

Hassabo, A. G., Mohamed, N. A., El-Salam, A., Neaama, A., Gouda, N. Z., & Othman, H. (2023). Application of modified xanthan as thickener in the printing of natural and synthetic fabrics. *Journal of Textiles, Coloration and Polymer Science*, *20*(1), 41-56.

Himashree, P., Sengar, A. S., & Sunil, C. K. (2022). Food thickening agents: Sources, chemistry, properties and applications-A review. *International Journal of Gastronomy and Food Science*, *27*, 100468.

Hotchkiss, S., Brooks, M., Campbell, R., Philp, K., & Trius, A. (2016). The use of carrageenan in food. *Carrageenans: sources and extraction methods, molecular structure, bioactive properties and health effects*, 229-243.

Li, L., Ni, R., Shao, Y., & Mao, S. (2014). Carrageenan and its applications in drug delivery. *Carbohydrate polymers*, *103*, 1-11.

Necas, J., & Bartosikova, L. (2013). Carrageenan: a review. *Veterinarni medicina*, *58*(4), 187-205.

Petri, D. F. (2015). Xanthan gum: A versatile biopolymer for biomedical and technological applications. *Journal of Applied Polymer Science*, *132*(23).

Saha, D., & Bhattacharya, S. (2010). Hydrocolloids as thickening and gelling agents in food: a critical review. *Journal of food science and technology*, *47*, 587-597.

Ünal, N. (2010). *Polyion-sensitive optodes and their analytical applications* (Master's thesis, Fen Bilimleri Enstitüsü).

Zia, K. M., Tabasum, S., Nasif, M., Sultan, N., Aslam, N., Noreen, A., & Zuber, M. (2017). A review on synthesis, properties and applications of natural polymer-based carrageenan blends and composites. *International journal of biological macromolecules*, *96*, 282-301.

CHAPTER 8

PROPERTIES AND VARIOUS APPLICATIONS OF PYRAZOLE DERIVATIVES

Assist. Prof. Dr. Zeynep ALKAN ALKAYA[1]

DOI: https://dx.doi.org/10.5281/zenodo.14563371

[1] Usak Unıversıty, Banaz Vocational School, Chemical Technology And Laboratory Technology, Usak, Turkiye, zeynep.alkan@usak.edu.tr, Orcid ID: 0000-0003-0934-4195

INTRODUCTION

Heterocyclic compounds form a vital and distinctive category within organic chemistry. Comprising over half of all identified organic substances, these compounds exhibit a broad spectrum of, chemical, biological and physical characteristics, making them indispensable for various applications due to their versatile reactivity and stability (Li et al., 2014; Ebenezer et al., 2022). They are used as organocatalysts, protecting groups, intermediates, and chiral auxiliaries in syntheses. Among heterocyclic compounds, five-membered rings containing nitrogen atoms constitute an important group that stands out with its wide range of biological activities (Alam et al., 2016; Gregory et al., 1990; Ferreira, et al., 2010).

Pyrazoles are considered one of the most important heterocyclic compounds, with the formula $(CH)_3N_2H$. They consist of a five-membered ring containing two connected nitrogen atoms and three carbon atoms (Figure 1). Pyrazoles are among the most extensively studied compound groups within the azole family. Interest in pyrazole chemistry has significantly increased over the past decade, which can be attributed to the discovery of the impressive properties exhibited by many pyrazole derivatives. Pyrazole was first described by Ludwig Knorr in 1883 (Knorr, 1883), and Edward Buchner successfully synthesized it for the first time in 1889. (Hassani et al., 2023). The pyrazole core serves as a building block in many organic ligands and plays a significant role in organic synthesis, functioning as both a directing and transforming group (Karrouchi et al., 2018; Meng et al., 2019). Additionally, pyrazole derivatives possess a wide range of pharmaceutical applications. These compounds are classified as protein glycation inhibitors and exhibit various biological activities, including antioxidant, antidiabetic, antiviral properties, anti-inflammatory, antidepressant, antibacterial antifungal, anticancer and antitubercular (Fustero et al., 2011; Ansari et al., 2017; Karrouchi et al., 2018; Bennani et al., 2020).

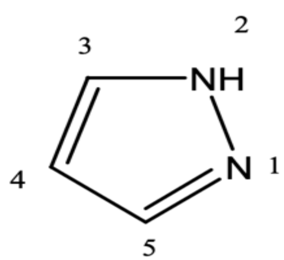


Figure 1: Pyrazole

1. Structural Features of Pyrazoles

The wide range of biological and synthetic applications offered by pyrazoles has made them significant targets for research groups in organic and medicinal chemistry. Notably, certain pyrazole derivatives have been utilized in the formation of metal complexes due to the presence of a pyridine-like N-atom in the corresponding ligand. Although nucleophilic substitution reactions on pyrazoles are rare, appropriately functionalized pyrazoles can enhance their reactivity towards both electrophiles and nucleophiles. Reactivity can be controlled by introducing electron-donating or electron-withdrawing groups. Therefore, the physicochemical properties of pyrazoles primarily depend on the nature of the nitrogen atoms and the electronic effects of substituent groups on the ring (Khan et al., 2016; Naim et al., 2016; Castillo et al., 2018).

The nitrogen atom (N1) exhibits "pyrrole-like" characteristics due to the conjugation of its lone pair of electrons with the aromatic system. In contrast, the nitrogen atom (N2) demonstrates "pyridine-like" behavior because its lone pair of electrons does not participate in resonance interactions. Due to this difference between the nitrogen atoms, pyrazoles react with both acids and bases (Figure 2) (Faria et al., 2017). Over the years, a wide range of studies, synthesis methods, and synthetic analogs have been reported (Trofimenko 1972; Fustero et al., 2011; Kumari et al., 2014).

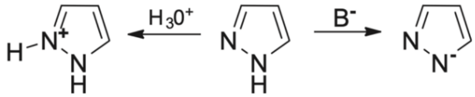
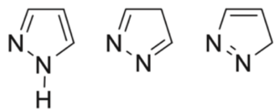


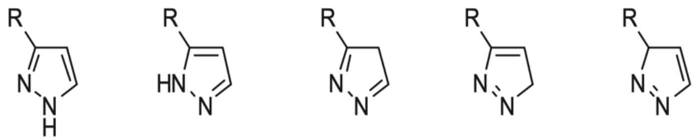
Figure 2: Cations and Anions Derived from Pyrazole

Another important structural feature of pyrazole is prototropic tautomerism. In unsubstituted pyrazoles, three tautomers are possible (Figure 3), while monosubstituted pyrazoles can exhibit five tautomers (Figure 4). The most interesting structures are 1a, 2a, and 2b, as they preserve aromaticity (Gilchrist 1992; Faisal et al., 2019; Kumar et al., 2020).



(1a) (1b) (1c)

Figure 3: Tautomers in Unsubstituted Pyrazoles



(2a) (2b) (2c) (2d) (2e)

Figure 4: Tautomers in Substituted Pyrazoles

The first natural pyrazole, 1-pyrazolyl-alanine, was isolated from watermelon seeds in 1959 (Behr et al., 1967). Pyrazole derivatives have a long history of use in the agricultural chemicals and pharmaceutical industries as herbicides and active pharmaceutical compounds. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used in the treatment of rheumatic diseases such as rheumatoid arthritis and pain management. NSAIDs exhibit anti-inflammatory effects through their inhibitory action on cyclooxygenase (COX), an enzyme essential for the biosynthesis of prostaglandins from arachidonic acid. Cyclooxygenase exists in two isoforms, COX-1 and COX-2 (Magda et al., 2012). Recent studies have shown that pyrazole-based COX-2 inhibitors have achieved significant success, underlining the critical role of these heterocyclic structures in medicinal chemistry. The widespread presence of pyrazole nuclei in biologically active compounds has increased the need for effective strategies for the synthesis of these heterocyclic structures (Perez et al., 2009; Chauhan et al., 2011; Tigeros et al., 2020).

Pyrazoles substituted in various ways with aromatic and heteroaromatic groups exhibit a wide range of biological activities. Since the first syntheses defined by Knorr, methods for accessing the pyrazole core have significantly advanced and diversified. Additionally, several different methods are used to obtain substituted pyrazoles. Some of the most commonly used methods include (Faisal et al., 2019; Karrouchi et al., 2018):

-**Cyclocondensation of hydrazine and similar derivatives with carbonyl systems:** This method is a commonly used reaction mechanism for the direct synthesis of the pyrazole ring.

-**Dipolar cycloaddition reaction:** This technique involves the attachment of reactive dipolar species to form the pyrazole ring.

-**Multicomponent reactions:** This method involves the combination of different starting materials in a single reaction to form the desired pyrazole derivatives. It is often preferred due to its efficiency. These methods are fundamental approaches used to enhance the structural diversity of the pyrazole core and to obtain biologically active molecules.

2. Various Applications of Pyrazoles

Pyrazoles are a class of biologically active compounds that play a significant role in various pharmaceutical and medical applications. These compounds have a broad research area due to their different biological activities. Some of the most well-known biological activities of pyrazoles include antimicrobial, antifungal, anti-inflammatory, anticancer, anticonvulsant, antiviral, neuroprotective effects, and angiotensin-converting enzyme (ACE) inhibition (Abrigach et al., 2016; Faria et al., 2017). These biological activities expand the pharmaceutical applications of pyrazole derivatives and offer new therapeutic options. Therefore, the biological efficacy of pyrazole compounds plays a crucial role in shaping drug development and therapeutic strategies.

2.1. Antibacterial Application of Pyrazoles

Antibacterial is a term used to describe substances that are effective against bacteria, either by killing them or inhibiting their growth. These substances can damage bacterial cell walls, interfere with protein synthesis, or disrupt other essential functions necessary for bacterial survival, thus treating infections. Devasahayam Dabholkar et al. (Dabholkar et al., 2009) synthesized a range of compounds, including isoxazole and pyrazole derivatives, as part of their research. The newly synthesized compounds were investigated for antibacterial activity. All the synthesized compounds showed good activity against S. aureus and C. Diphtheriae bacteria when compared with other derivatives.

Saleh et al. (Saleh et al. 2021), synthesized N-(Trifluoromethyl) phenyl-substituted pyrazole derivatives (Figure 5) and discussed their effectiveness as antimicrobial agents. Many of these new compounds have been observed to be effective in inhibiting the growth of Gram-positive bacteria resistant to antibiotics.

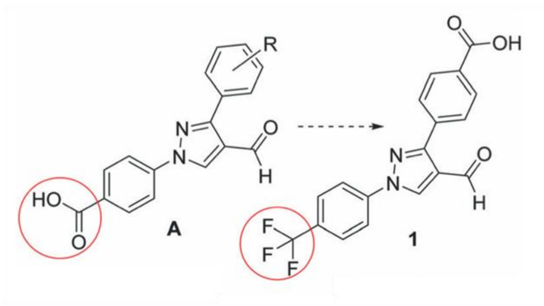


Figure 5: The compound designed and synthesized by Saleh et al.

Tanimate et al. (2004) synthesized a novel 5-vinylpyrazole derivative compounds (Figure 6) and evaluated their antibacterial and DNA gyrase inhibitory activities. The investigated compound showed promising antibacterial activity against bacterial strains such as *Enterococcus faecalis* and *Staphylococcus aureus*.

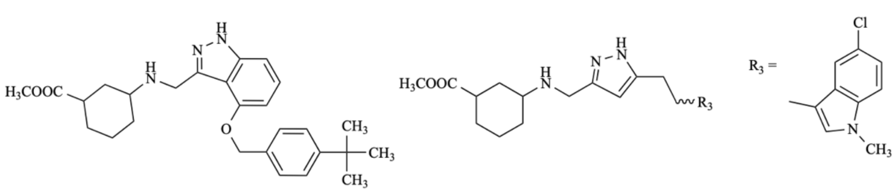


Figure 6: Compounds Synthesized by Tanitame et al.

Gomez et al. (2007) synthesized various pyrazole derivative compounds and evaluated their antimicrobial activities in vitro. The compounds with the strongest antibacterial properties are shown in Figure 7.

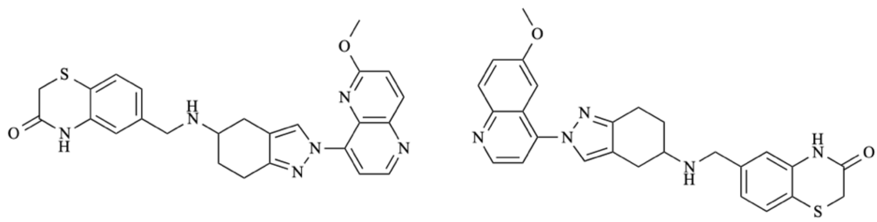


Figure 7: Compounds Synthesized by Gomez et al.

Liu et al. (2018), obtained derivatives of a new coumarin-pyrazole carboxamide compound and evaluated their in vitro antibacterial activities. against *Listeria monocytogenes*, *Staphylococcus aureus*, *Salmonella*, and *Escherichia coli* bacterial strains. Some of the evaluated compounds (Figure 8) exhibited remarkable antibacterial activity, particularly against the *Salmonella* strain.

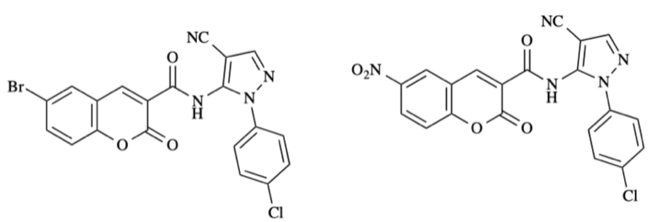


Figure 8: Some Compounds Synthesized by Liu et al.

2.2. Anticancer Application of Pyrazoles

Anticancer agents are substances that inhibit the growth of cancer cells, stop their proliferation, or induce cell death. These types of drugs play a crucial role in cancer treatment and are commonly used through methods such as chemotherapy, biological therapy, or immunotherapy (Nussbaumer et al., 2011). R. Kalirajan et al. (2010) synthesized a new pyrazole derivative (Figure 9) and demonstrated its anticancer activity in their study. This research highlights that the pyrazole core can serve as an important building block in the development of potential anticancer agents.

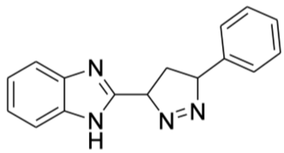


Figure 9: Compound Synthesized by R. Kalirajan et al.

Zheng et al. (2009) synthesized various pyrazole derivatives (Figure 10) and investigated their effects on the growth of lung cancer cells. The results were positive, demonstrating that pyrazole derivatives could be considered as potential anticancer agents.

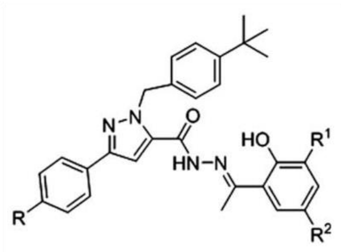


Figure 10: The compound synthesized by Zheng et al.

Lian et al. (2009) synthesized pyrazole derivative compound (Figure 11) and investigated the effects of all the compounds on the growth of lung cancer cells. The study concluded that all the compounds inhibited the growth of the cancer cells.

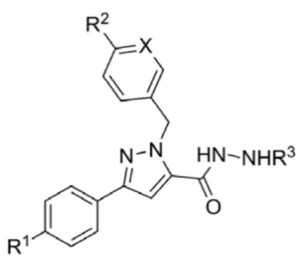


Figure 11: The compound synthesized by Lian et al.

2.3. Antifungal Application of Pyrazoles

Antifungal refers to substances or drugs used to treat or prevent fungal infections. Antifungal agents can inhibit the growth of fungal cells or kill them (Houst et al., 2020). Karthikeyan et al. (2007) synthesized various pyrazole and pyrazoline compounds (Figure 12). All the compounds were tested for their antibacterial and antifungal activities, and the compounds exhibited very good activity.

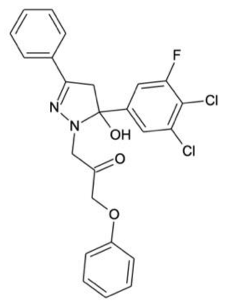


Figure 12: One of the compounds synthesized by Karthikeyan et al.

Vijesh et al. (2011) synthesized two new pyrazole compounds combined with imidazole (Figure 13). These compounds were tested in vitro for their antimicrobial effects against various bacterial and fungal species. The compounds exhibited very good activity.

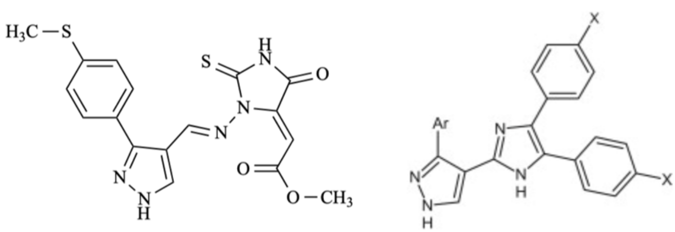


Figure 13: Compound synthesized by Vijesh et al.

Nagamullu et al. (2016) synthesized various pyrazole derivatives. One of these compounds (Figure 14) showed particularly good activity against three different fungal species.

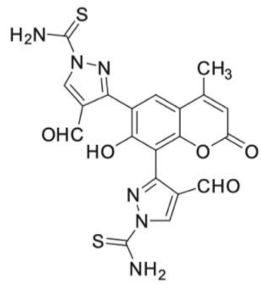


Figure 14: The compound synthesized by Nagamullu et al.

2.4. Analgesic and Anti-inflammatory Application of Pyrazoles

Analgesic refers to substances or drugs that relieve or reduce pain. Analgesics typically work by suppressing nerve endings that transmit pain signals to the brain or by inhibiting the production of chemical substances that cause pain (Duthie et al., 1987). The term anti-inflammatory refers to substances that reduce or prevent inflammation in the body. Sivakumar et al. (2010) synthesized various pyrazole derivative compounds (Figure 15). These compounds were then evaluated for their analgesic (pain-relieving) and anti-inflammatory (inflammation-reducing) activities, and their positive effects were reported in their study.

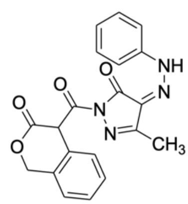


Figure 15: One of the compounds synthesized by Sivakumar et al.

Dias et al. (2011) synthesized the compound (4-methylthiophen-3 yl) (1H-pyrazol-1-yl) methanone (Figure 16) and noted in their study that this compound exhibited good analgesic (pain-relieving) activity.

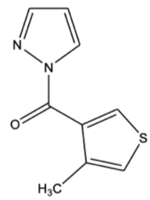


Figure 16: The compound synthesized by Dias et al.

2.5. Anticonvulsant Application of Pyrazoles

Anticonvulsant refers to drugs and substances used to control or prevent seizures, convulsions, and tremors that occur in neurological disorders like epilepsy. Anticonvulsants help regulate the abnormal electrical activity of nerve cells in the brain (Stefan et al., 2007). Singh et al. (2010) synthesized a pyrazole derivative compound in their study (Figure 17), evaluated it for anticonvulsant activity and reported positive results.

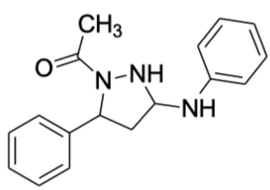


Figure 17: One of the compounds synthesized by Singh et al.

REFERENCES

Abrigach, F., Touzani, R. (2016). Pyrazole derivatives with NCN junction and their biological activity: A review. *Med. chem*, *6*, 292-298.

Alam, R., Wahi, D., Singh, R., Sinha, D., Tandon, V., Grover, A., Rahisuddin. (2016). Design, synthesis, cytotoxicity, HuTopoIIα inhibitory activity and molecular docking studies of pyrazole derivatives as potential anticancer agents. *Bioorg. Chem*., 69, 77–9.

Hassani, I.A.E., Rouzi, K., Assila, H., Karrouchi, K., Ansar, M.H. (2023). Recent advances in the synthesis of pyrazole derivatives: a review. *Reactions*, *4*(3), 478-504.

Ansari, A.; Ali, A.; Asif, M.; Shamsuzzaman, S. (2017). Review: Biologically active pyrazole derivatives. *New J. Chem*., 41, 16–41

Behr L.C., Fusco R., Jarboe C.H. (1967). The chemistry of heterocyclic compounds pyrazoles, pyrazolines, pyrazolidines, indazoles and condensed rings. *New York: Interscience Publisher.*

Bennani, F.E.; Doudach, L.; Cherrah, Y.; Ramli, Y.; Karrouchi, K.; Ansar, M.; Faouzi, M.E.A. (2020). Overview of recent developments of pyrazole derivatives as an anticancer agent in different cell line. *Bioorganic Chem*., 97, 103470.

Castillo, J.C., Portilla, J. (2018). Recent advances in the synthesis of new pyrazole derivatives. *Targets Heterocycl. Syst,,* 22, 194-223

Chauhan, A., Sharma, P.K., Kaushik, N. (2011). Pyrazole: a versatile moiety. Int. J. *ChemTech Res,* 3(1), 11-17.

Dabholkar, V.V., Ansari, F.Y. (2009). Synthesis and characterization of selected fused isoxazole and pyrazole derivatives and their antimicrobial activity. *Journal of the Serbian Chemical Society*, 74(11), 1219-1228.

Devasahayam, G., Scheld, W. M., Hoffman, P. S. (2010). Newer antibacterial drugs for a new century. *Expert opinion on investigational drugs*, *19*(2), 215-234.

Dias, L.R.S., Salvador, R.R.S. (2012). Pyrazole carbohydrazide derivatives of pharmaceutical interest. *Pharmaceuticals*, *5*(3), 317-324.

Duthie, D. J. R., Nimmo, W. S. (1987). Adverse effects of opioid analgesic drugs. *BJA: British Journal of Anaesthesia*, *59*(1), 61-77.

Ebenezer, O., Shapi, M., Tuszynski, J.A. (2022). A review of the recent development in the synthesis and biological evaluations of pyrazole derivatives. *Biomedicines*, 10(5), 1124.

Faisal, M., Saeed, A., Hussain, S., Dar, P., Larik, F.A. (2019). Recent developments in synthetic chemistry and biological activities of pyrazole derivatives. *Journal of Chemical Sciences*, *131*, 1-30.

Faria, J.V., Vegi, P.F., Miguita, A.G.C., Santos, M.S., Boechat, N., Bernardino, A.M.R. (2017). Recently reported biological activities of pyrazole compounds. *Bioorganic & medicinal chemistry*, 25(21), 5891-5903.

Ferreira, S.B., Sodero, A.C., Cardoso, M.F., Lima, E.S., Kaiser, C.R., Silva Jr, F.P., Ferreira, V.F. (2010). Synthesis, biological activity, and molecular modeling studies of 1 h-1, 2, 3-triazole derivatives of carbohydrates as α-glucosidases inhibitors. *Journal of medicinal chemistry*, *53*(6), 2364-2375.

Fustero, S., Sánchez-Roselló, M., Barrio, P., Simon-Fuentes, A. (2011). From 2000 to mid-2010: A fruitful decade for the synthesis of pyrazoles. Chemical reviews, 111(11), 6984-7034.

Gilchrist T.L. (1992). Heterocyclic chemistry. New York: Longman Scientific.

Gomez, L., Hack, M.D., Wu, J., Wiener, J.J., Venkatesan, H., Santillán Jr, A., ... Jones, T.K. (2007). Novel pyrazole derivatives as potent inhibitors of type II topoisomerases. Part 1: synthesis and preliminary SAR analysis. *Bioorganic & medicinal chemistry letters*, *17*(10), 2723-2727.

Gregory, W.A., Brittelli, D.R., Wang, C.L.J., Kezar III, H.S., Carlson, R.K., Park, C.H., ... Rajagopalan, P. (1990). Antibacterials. Synthesis and structure-activity studies of 3-aryl-2-oxooxazolidines. 2. The "A" group. *Journal of medicinal chemistry*, *33*(9), 2569-2578.

Houšť, J., Spížek, J., Havlíček, V. (2020). Antifungal drugs. *Metabolites*, *10*(3), 106.

Jamwal, A., Javed, A., Bhardwaj, V. (2013). A review on Pyrazole derivatives of pharmacological potential. *J. Pharm. BioSci*, *3*, 114-123.

Kalirajan, R., Rathore, L., Jubie, S., Gowramma, B., Gomathy, S., Sankar, S., Elango, K. (2010). Microwave assisted synthesis and biological evaluation of pyrazole derivatives of benzimidazoles. *Indian J Pharm Edu Res*, 44(4), 358-62.

Karrouchi, K., Mortada, S., Issaoui, N., El-guourrami, O., Arshad, S., Bouatia, M., Sagaama, A., Benzeid, H., Karbane, M.E., Faouzi, M.E.A. (2022). Synthesis, crystal structure, spectroscopic, antidiabetic, antioxidant and computational investigations of Ethyl 5-hydroxy-1-isonicotinoyl-3-methyl-4, 5-dihydro-1H-pyrazole-5-carboxylate. *Journal of Molecular Structure*, *1251*, 131977.

Karrouchi, K., Radi, S., Ramli, Y., Taoufik, J., Mabkhot, Y. N., Al-Aizari, F. A., Ansar, M. H. (2018). Synthesis and pharmacological activities of pyrazole derivatives: A review. *Molecules*, 23(1), 134.

Karthikeyan, M.S., Holla, B.S., Kumari, N.S. (2007). Synthesis and antimicrobial studies on novel chloro-fluorine containing hydroxy pyrazolines. *European journal of medicinal chemistry*, 42(1), 30-36.

Khan, M.F., Alam, M.M., Verma, G., Akhtar, W., Akhter, M., Shaquiquzzaman, M. (2016). The therapeutic voyage of pyrazole and its analogs: a review. *European journal of medicinal chemistry*, *120*, 170-201.

Kumar, H., Bansal, K.K., Goyal, A. (2020). Synthetic methods and antimicrobial perspective of pyrazole derivatives: An insight. *Anti-Infective Agents*, *18*(3), 207-223.

Kumari, S., Paliwal, S., Chauhan, R. (2014). Synthesis of pyrazole derivatives possessing anticancer activity: Current status. synthetic communications, 44(11), 1521-1578.

Li, M., Zhao, B. X. (2014). Progress of the synthesis of condensed pyrazole derivatives (from 2010 to mid-2013). *European Journal of Medicinal Chemistry*, *85*, 311-340.

Lian, S., Su, H., Zhao, B. X., Liu, W. Y., Zheng, L. W., Miao, J. Y. (2009). Synthesis and discovery of pyrazole-5-carbohydrazide N-glycosides as inducer of autophagy in A549 lung cancer cells. *Bioorganic & medicinal chemistry,* 17(20), 7085-7092.

Liu, H., Ren, Z. L., Wang, W., Gong, J. X., Chu, M. J., Ma, Q. W., ... Lv, X. H. (2018). Novel coumarin-pyrazole carboxamide derivatives as potential topoisomerase II inhibitors: Design, synthesis and antibacterial activity. *European journal of medicinal chemistry*, *157*, 81-87.

Magda, A. A., Abdel-Aziz, N. I., Alaa, A. M., El-Azab, A. S., ElTahir, K. E. (2012). Synthesis, biological evaluation and molecular modeling study of pyrazole and pyrazoline derivatives as selective COX-2 inhibitors and anti-inflammatory agents. Part 2. *Bioorganic & medicinal chemistry*, *20*(10), 3306-3316.

Meng, Y., Zhang, T., Gong, X., Zhang, M., Zhu, C. (2019). Visible-light promoted one-pot synthesis of pyrazoles from alkynes and hydrazines. *Tetrahedron Lett*., 60, 171–174.

Naim, M. J., Alam, O., Nawaz, F., Alam, M. J., Alam, P. (2016). Current status of pyrazole and its biological activities. *Journal of Pharmacy and Bioallied Sciences*, *8*(1), 2-17.

Nagamallu, R., Srinivasan, B., Ningappa, M.B., Kariyappa, A. K. (2016). Synthesis of novel coumarin appended bis (formylpyrazole) derivatives: Studies on their antimicrobial and antioxidant activities. *Bioorganic & medicinal chemistry letters*, *26*(2), 690-694.

Nussbaumer, S., Bonnabry, P., Veuthey, J. L., Fleury-Souverain, S. (2011). Analysis of anticancer drugs: a review. *Talanta*, *85*(5), 2265-2289.

Perez, J., Riera, L. (2009). Pyrazole complexes and supramolecular chemistry. *European Journal of Inorganic Chemistry*, *2009*(33), 4913-4925.

Saleh, I., Kc, H. R., Roy, S., Abugazleh, M. K., Ali, H., Gilmore, D., & Alam, M. A. (2021). Design, synthesis, and antibacterial activity of N-(trifluoromethyl) phenyl substituted pyrazole derivatives. RSC *Medicinal Chemistry*, 12(10), 1690-1697.

Singh, A., & Rana, A. C. (2010). Synthesis and anticonvulsant activity of 1-[(4, 5-dihydro-5-phenyl-3-(phenylamino) pyrazol-1-yl)] ethanone derivatives. *J. Chem. Pharm. Res*, *2*, 505-511.

Stefan, H.T.J.F., Feuerstein, T.J. (2007). Novel anticonvulsant drugs. *Pharmacology & therapeutics*, *113*(1), 165-183.

Tanitame, A., Oyamada, Y., Ofuji, K., Suzuki, K., Ito, H., Kawasaki, M., Yamagishi, J. I. (2004). Potent DNA gyrase inhibitors; novel 5-vinylpyrazole analogues with Gram-positive antibacterial activity. *Bioorganic & Medicinal chemistry letters*, *14*(11), 2863-2866.

Tigreros, A., Portilla, J. (2020). Recent progress in chemosensors based on pyrazole derivatives. *RSC advances*, *10*(33), 19693-19712.

Trofimenko, S. (1972). Coordination chemistry of pyrazole-derived ligands. Chemical reviews, 72(5), 497-509.

Vijesh, A. A., Isloor, A. M., Telkar, S., Peethambar, S. K., Rai, S., Isloor, N. (2011). Synthesis, characterization and antimicrobial studies of some new pyrazole incorporated imidazole derivatives. *European Journal of Medicinal Chemistry*, *46*(8), 3531-3536.

Yerragunta, V., Suman, D., Swamy, K., Anusha, V., Patil, P., Naresh, M. (2014). Pyrazole and its biological activity. *PharmaTutor*, *2*(1), 40-48.

Zheng, L.W., Wu, L.L., Zhao, B.X., Dong, W.L., Miao, J.Y. (2009). Synthesis of novel substituted pyrazole-5-carbohydrazide hydrazone derivatives and discovery of a potent apoptosis inducer in A549 lung cancer cells. *Bioorganic & medicinal chemistry.* 17(5), 1957-1962.

İKSAD
Publishing House

ISBN: 978-625-378-100-2