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Address: Natoyolu Cad. Fahri Korutürk Mah. 157/B, 06480, Mamak, Ankara, Turkey.
Phone: +90 312 390 1 118
web: www.platanuskitap.com
e-mail: platanuskitap@gmail.com



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Contents

CHAPTER 1.....5

SALT STRESS IN WHEAT

Neslihan DORUK KAHRAMAN

Ali KAHRAMAN

CHAPTER 2.....25

UTILIZATION OF AROMATIC PLANTS IN FISH AND FISH PRODUCTS: AN OVERVIEW

Bilge BİLGİN FIÇICILAR

Ebru YILMAZ

CHAPTER 3.....41

APPLICATIONS OF ESSENTIAL OILS AND EXTRACTS OBTAINED FROM MEDICINAL AND AROMATIC PLANTS FOR ANESTHETIC PURPOSES IN THE AQUACULTURE

Ebru YILMAZ

Bilge BİLGİN FIÇICILAR

CHAPTER 4.....59

THE DEVELOPMENT OF THE TURKISH FISHERIES SECTOR IN THE LAST FIVE YEARS (2018-2022): A GENERAL EVALUATION

Adnan TOKAÇ

CHAPTER 5.....69

MARINE MACRO ALGAE DERIVED POLYSACCHARIDE: FUCOIDAN

Gözde YEŞİLTAŞ

Bengü ERGÜDEN

CHAPTER 6.....87

EFFECTS OF AGRICULTURAL NITROGEN POLLUTION on ECOSYSTEM, HUMAN HEALTH and BIODIVERSITY

Handan KARAOĞLU

Fatih SEYIS

CHAPTER 1

SALT STRESS IN WHEAT

Neslihan DORUK KAHRAMAN[1]
Ali KAHRAMAN[2]

[1]Res. Assist., Selcuk University, Faculty of Agriculture, ORCID: 0000-0002-3613-4399
[2]Prof. Dr., Selcuk University, Faculty of Agriculture, ORCID: 0000-0003-3203-4697

Introduction

Salinity affects soils in two ways. The first is that it contains dissolved salts at a level that restricts plants' water intake from the soil, and such soils are called saline soils. The second is the presence of sodium ions at a level that will disrupt the soil structure, and such soils are called sodic soils. Saline soils cause physiological drought. In other words, plants grown in salty soils fade because they cannot get enough water through the roots, even though there is enough water in the environment. In sodic soils, sodium ions bound to soil particles weaken the bond between soil particles, causing soil compaction and reduced water flow. Soils affected by salt are a global problem (Anonymous, 2022).

Soil salinity problem is a foremost limiting factor in arable agricultural lands. Salinity is defined as the accumulation of soluble salts, especially around semi-arid and arid climates, from the soil and the salt accumulation on the surface of soil and in areas close to the surface, as the soluble salts that are washed into the groundwater come to the surface from the soil through capillarity with high ground waters, and as a result of evaporation, the water separates from the soil. Primary Salinity occurs because of the decomposition of host rocks, salt storage oceans and climatic factors. Secondary Salinity occurs welded by intensive irrigation in agricultural areas and the rise of the groundwater level in varied salts to the soil surface, overgrazing, deterioration of the natural vegetation in the region and opening of agricultural land areas, and exposure to various chemicals that may cause soil salinity (Madhova et al., 2005).

Wheat (*Triticum aestivum* L.) is noted as the chiefly cereal species amongst all grains. It ranks first in the world among grains produced especially for human consumption. China is the biggest producer besides being a consumer of wheat. In China, the annual production of wheat has approximately 100 million tons value (Shi and Ling, 2018). While wheat is grown to a greater or lesser extent in more than 140 countries around the world, it is the main source of nutritional calories in more than 40 countries (Kamran et al., 2014). When we look at the history of wheat, as a result of the examination of wheat seeds unearthed in historical excavations, it can be seen that wheat dates back to B.C. It was revealed that it was cultivated around 7000 years ago. It is known that the breeding of wheat, called the Fertile Crescent, started in the region extending from Northern Syria to Southeastern Turkey, Northern Iraq, and Western Iran (Zohary and Hopf, 1994). Approximately 650 million wheat is produced every year in the world (FAO, 2021). *Triticum aestivum* L. (bread wheat), which can be grown as summer and winter cereals. Wheat, that is one of the basic crops by view of producing and breeding is strictly related to agriculture-based societies due to higher yield

values, processing, and nutritional properties (Jia et al., 2018). 95% of the wheat produced in the world consists of hexaploid bread wheat (2n = 6x = 42, BBAADD), followed by tetraploid durum wheat (2n = 4x = 28, BBAA), among other cultivated wheat species (Braun et al., 2010). Its productivity level remains lower even though it is grown in most of the arable land (38.8%) (FAO, 2016).

Salt stress affects about 20% of worldwide arable areas and it is constantly rising owing to changes in climate and anthropogenic actions (Arora, 2019). Drought stress in plants is considered one of the biggest threats to sustainable agriculture to meet the world's food needs (Lefevre et al., 2012). Stress signals stimulates the signaling process and control of transcription that activate stress response mechanisms that are functional in restoring the disturbed balance in the cell, repairing damage to the cell membrane, and protecting proteins. In this way, stress tolerance is achieved in plants (Mahajan and Tuteja, 2005; Shinozaki and Yamaguchi-Shinozaki, 2007).

Wheat (*Triticum aestivum*) is a plant that is moderately tolerant to salt. Since wheat is less tolerant to salinity during the germination and fertilization stages, the salinity level in the soil should not exceed EC 4-5 dS/m during these periods. When irrigation water salinity increases to 4.9 dS/m, there is a 10% decrease in yield potential, and when it increases to 8.7 dS/m, there is a 50% decrease (Ayers and Westcot, 1985). It is an inevitable fact that productivity will decrease further due to climate change, which causes various abiotic stress factors to increase. Different models of climate predict to production of wheat may decrease almost 6% ratio because of the disturbing environments (Asseng et al., 2015). Developing salt-tolerant plants has been the main goal for breeding of plants owing to maintain and increase in productivity of crops in arid and semi-arid lands. Additionally, many varieties with different salt tolerance have been used, the general development of breeding against salt stress by traditional methods has been slow and the desired success has generally not been achieved because the genetic feature of salt tolerance has not been well determined (Dodd and Pérez-Alfocea, 2012). It has been suggested that there may be a complex interaction between Si and IAA that mediates the mitigation of stress-induced harmful effects in plants, which has not yet been fully defined (Khan et al., 2021).

Wheat is considered a strategic product all over the world due to its strong adaptability, convenient production and being the raw material of bread. For this reason, breeding programs are carried out around the world to develop high-yield and high-quality varieties. Salinity is an important factor in ensuring sustainability in agricultural production. In this study, the salinity problem in

agricultural production was examined, the scientific data regarding salt stress in wheat were summarized and the results of the findings were presented.

Salt Stress in Wheat

Salinity is effective at all periods during plant growing period likewise germination stage, vegetative growing period, reproduction as well. Soil salinity causes toxicity of ion, osmotic based stress, mineral deficiency, oxidative based stress and makes it difficult to absorb water from the soil (Bano and Fatima, 2009). Almost all the world's water contains dissolved salts and trace elements. However, drainage water from agricultural lands, sewage and industrial waste resulting from human activities can also affect water quality. Some salts and some elements contained in irrigation water can affect both crop yield and soil structure, thus making the use of these waters in agricultural activities undesirable. Irrigation water salinity is the most important water quality criterion that negatively affects agricultural production and soil structure (Fipps, 2003).

Due to salinity, many functions in plants, especially photosynthesis, are disrupted, the amount of chlorophyll is reduced and damaged, and there are problems in the intake of potassium and some nutritional elements. Salinity exposes directly effects in plants with ion and osmotic types of stresses, it exhibits indirect effects by structural deteriorations (Botella et al., 2005; Hong et al., 2010).

As plants develop their own resistance mechanisms against abiotic stress, various interacting components that are involved in the perception of stress and the complex signal transmission network have been identified (Baxter et al., 2014; Colebrook et al., 2014). The salinity problem naturally occurs in arid and semi-arid regions where precipitation is low and evaporation is high, and in addition to these conditions, in areas opened to irrigation, it occurs when salts in the ground water rise to the upper layers due to excessive irrigation. In soils with salinity problems, sodium Cl^- and SO_4^{-2} salts are generally dominant, and the cause of salinity in nature is generally caused by Na (NaCl) salts (Shannon, 1985).

Plants respond very differently in salty environments depending on genotypic differences (Dajic, 2006). When plants are exposed to abiotic stress factors such as drought, salinity, high temperature or frost, heavy metals, radiation: while their growth and development are restricted, significant decreases in plant production occur (Vinocur and Altman, 2005). As a result, it inhibits the activity of some important enzymes, cell division and expansion (El-Hendawy et al., 2019).

The frequency and duration of stress conditions determine whether their effects on gene transcription remain temporal or can be transmitted to subsequent generations, known as epigenetic inheritance (González-Bosch, 2018).

With stress, changes usually occur in DNA or histone modifications and genes expression. While some of the modifications are observed only in the relevant individual, some of them can be transferred to subsequent generations as epigenetic marks. Epigenetic marks are maintained in the absence of stimuli, leading plants to “memorize” the stresses (He and Li, 2018).

The increase in endogenous production of the plant hormone "JA" is triggered by biotic and abiotic environmental signals to regulate plant growth, development, and defense. “JA” is involved in the regulation of plant developmental functions such as primary root growth, reproductive development, and leaf senescence (Huang et al., 2017). Map kinases function in the transmission pathway that produces osmolytes and antioxidants, which are activated by different stress types of likewise osmotic stress, frost, drought, wounding, salinity and pathogen infection, in the regulation of hormonal reactions, in cell cycle mechanisms and in responses to developmental processes. It is known that they take (Hirt, 1997; Nakagami et al., 2005; Jalmi and Sinha, 2015). Salt stress reduces germination by negatively affecting seed water uptake, the effects of enzymes involved in nucleic acid metabolism, protein metabolism and hormonal balance (Othman et al. 2006; Gomes-Filho et al., 2008).

Soils generally show minimum salinity at the time of planting, this is because planting is generally done after irrigation or after rainfall. As the growing season progresses, salinity increases and reaches its highest level at grain maturity (Munns and James, 2003). Salt stress during the development of a plant causes negative effects on metabolic processes such as oil metabolism, protein synthesis, photosynthesis, and stomatal closure in the plant (Parida and Das, 2005). Water contains many dissolved salts in different amounts (Fipps, 2003). The area covered by land on earth is 14 billion hectares, and crop production is currently carried out in 10% of this land area. 7% of the total land area in the world is affected by salt. These areas continue to increase due to unconscious irrigation and barrenness. It is reported that due to the increase in salinity, 30% of sustainable agricultural areas may be destroyed in the next 25 years and 50% in the middle of the 21st century (Bonilla et al., 2004; Ahmadi et al., 2009). Salt stress affects plants at many physiological and molecular levels. The most vital phase of the plant growth cycle is seed germination. In many studies on plants, it has been determined that salt stress negatively affects seed germination (Khodarahmpour et al., 2012).

In a study conducted on wheat seedlings with salt concentration (250 mM), they reported that salinity caused an increase in the accumulation of acrylonitrile styrene acrylate and glutathione compounds in seedling leaves and a decrease in water and ion toxicity in the plant (Li et al., 2013). Salts accumulate quickly in the plant and inhibit enzyme activity. In susceptible plants, it reduces the photosynthetic capacity of the plant and death occurs in old leaves. In phase 2, ions, especially Na+, accumulate in leaf blades based on transpiration flow rather than in the roots. Na+ accumulation, especially in old leaves, has a toxic effect. If the death rate of old leaves is higher than the rate of production of new leaves, the plant cannot meet the carbohydrate needs of young leaves and further reduces its growth rate (Munns and Tester, 2008). In a study, it was determined that application of 0.04 mM Cd to the environment where wheat seedlings were grown reduced the plants' nitrate uptake by 60 percent and potassium uptake by 56 percent compared to the control (Veselov et al., 2003). In another study, the effect of silicon (2 and 4 mM) on growth and physiological processes in wheat seedlings grown under NaCl (50 mM) salinity was examined. While salinity stress decreased root and shoot length, chlorophyll content, leaf tissue tolerance, total sugar, starch and potassium, sodium content was found to be higher in wheat seedlings grown on Hoagland nutrient medium. Addition of silicon to the nutrient medium ameliorated the negative effect of salt on growth by reducing sodium uptake into the shoot. It has also been found that silica increases the tolerance of leaf tissue to sodium (Trivedi et al., 2004).

As a result of a study using a total of 55 different durum wheat genotypes, they reported that winter varieties were more tolerant to salt stress than summer varieties (Turki et al., 2012). Osmolytes and antioxidants, which are the products of genes activated in case of stress, are the cell's response to stress. Proline, glycine, betaine, and sucrose can be counted among the osmolytes. Proline is functional in maintaining plasma membrane integrity and removing free radicals (Moustafa et al., 2014). In many studies, it has been reported that sensitive genotypes show higher increases in Na+/K+ ratios due to salt stress than salt-tolerant genotypes (Khan et al., 2002; Sairam et al., 2002).

In a study conducted to examine the effect of salinity on wheat yield and yield components in saline and non-saline soils, it was obtained that salt stress affects the plant straw weight, grain yield, plant and ear height, root and tillering number, ear weight, number of seeds and thousand grains. They observed that it reduces properties such as grain weight (Nia et al., 2012). Effect of silicon on wheat genotypes grown under different salinity stress was investigated. For this purpose, five wheat genotypes (Inqlab-91, Uqab 2002, SARC-1, SARC-3 and

SARC-5) were subjected to 0, 2 and 4 mM Si for forty days. It was grown in three salinity levels (0, 60 and 120 mM NaCl). As a result, it was determined that salinity stress significantly reduced root and shoot biomass to different degrees, and silicon (Si) application increased plant biomass and potassium concentration in shoots both in control and saline conditions (Tahir et al., 2010).

Salinity even changes ultra-structural components of the cells, damages the photo-synthesis mechanism, membrane core structure (Hasanüzzaman et al., 2014). One of the negative effects of salinity on the plant is the decrease in K+ components in the leaves in response to the increase in Na+ content (Shamsi and Kobraee, 2013). Two wheat genotypes (Aquab-2000 and SARC-3) were grown at 0 with 60 mM dose of NaCl concentrations, without and with by 2 mM concentration of Si. As a result, salinity stress reduced growth parameters, the Na ratio in the shoots increased and the K ratio decreased, however, the addition of Si It was determined that it significantly improved growth parameters in both genotypes (Tahir et al., 2011).

It has been stated that jasmonates are synthesized according to environmental stimuli. A previous report revealed that jasmonates act a key function in plant reproduction and growth, contribute to flower development, fruit ripening, growth inhibition, trichome formation, mediate stamen elongation and anther development by MYB24 and MYB21, and contribute to crop improvement through a signaling mechanism against several stress types (El-Esawi, 2016).

Plants absorb silicon from the soil through aquaporin channels in their roots, in the form of silicic acid [$Si(OH)_4$], an uncharged monomeric molecule, when pH is below 9. Silicon is generally bonded with oxides and silicates (Epstein, 1999; Erkan, 2014). Soils classified as saline with an EC value of 4 dS/m or more (Munns and Tester, 2008). Another mechanism that regulates the transcriptional and translational response during salt stress in the plant cell; Calcineurin B-like protein (CBL) is CBL-interacting protein kinase (Calcineurin B-like protein-interacting protein kinases/CIPK) complexes. It has been reported that overexpression of CBLs or CIPKs, which decode intracellular calcium signals, causes increased salt tolerance in various plant species through germination, seedling, and biomass production (Thoday Kennedy et al., 2015).

They reported that K and Ca uptake with salinity application was affected by salinity and high Na accumulation in plant tissues due to ion selectivity. K uptake and accumulation in plant tissue were strongly reduced due to high Na concentration (Ahmad et al., 2014).

By researching the data in the articles, they determined the effects of silicon on the negativities caused by heavy metals, minerals, and salinity stress on plants. Although it accumulates more in plants, Silicon is not listed as an essential nutrient, but it is considered a beneficial element for the growth of plants, especially in stressful environments, and research to date has reported that Silicon helps plants alleviate various biotic and abiotic stresses (Imtiaz et al., 2016).

In order to cope with the adversities caused by chloride, plants have developed various mechanisms to remove salt from the cells or to tolerate what is present in plant cells (Hasegawa et al., 2000).

In was emphasized that some of the plant growing regulators will increase the resistance of plants to salt. It is emphasized that plant growing regulators likewise abscisic acid, salicylic acid, jasmonic acid and polyamines may be applied to plants in this regard and it is suggested that their application will be beneficial (Yoon et al., 2009; Sripinyowanich et al., 2013).

They investigated the healing effect against the salinity effect by applying external proline to the leaves to the salt-tolerant ESW-9525 and partially tolerant "Khirman" wheat genotypes under controlled environmental conditions. They reported that it was confirmed that foliar applied proline promotes salt tolerance in wheat genotypes (Mahboob et al., 2016). The silicon effects by addition on wheats under salt stress were investigated. For this purpose, the effect of silicon addition (1 and 4 mM) on wheats grown as salinity stress (50, 150 mM NaCl) was examined. As a result, it was observed that plant biomass decreased in both salt concentrations, and many biochemical parameters related to salt tolerance improved with silicon addition (especially 1 mM) (Hajiboland et al., 2016).

In another study, significant decreases were observed in all yield components of plants exposed to salt stress comparing with control group plants (Qados, 2009). Since silicone alleviates negatively effects through stress and increases tolerance to stress, its application to plants has been adopted as an effective method (Zhang et al., 2020). According to the data obtained, it was revealed that root applied AsA increased the photosynthetic capacity of wheat plants against oxidative stress caused by salt stress and prevented the negative effects of salt stress on the growth of wheat by maintaining the ion balance (Athar et al., 2008). Under drought and salinity stress, the accumulation of organic and inorganic solvents that support low water potential without reducing the amount of available water is called osmotic adjustment (Serraj and Sinclair, 2002).

Saline soils have low fertility and high bioavailability of heavy metals (Rady et al., 2016). They reported that salt and drought stresses reduce growth of shoots,

photosynthetic pigments of the leaves, K+ content and trigger leaf oxidative stress, causing significant differences in the soluble proline, carbohydrates, total phenolic compounds, antioxidant activity, malondialdehyde and Na+ content (Fayez and Bazaid, 2014). In successful wheat cultivation, the germination phase of the seed and, also development of seedling known as maximum critic-sensitive periods for growing healthy plants (Almansouri et al., 2001).

In a study on the effect of silicon on wheat seedlings under salt stress, it was determined that 1 mM and 1.5 mM silicon added to 70 and 100 mM NaCl concentration in 10-day-old wheat seedlings grown in nutrient solution significantly increased wheat root and shoot weight and photosynthetic pigments in the leaves. (Sienkiewicz-Cholewa et al., 2018). It has been reported that H_2O_2 application reduces the pressure caused by salt stress, while increasing proline content, nitrogen assimilation, water retention capacity and the effectiveness of photosynthetic pigments (Ashfaque et al., 2014).

By applying different salt (0, -0.6 and -1.2 MPa NaCl) and ox-sin (0, 1 and 2 mg L^{-1} IAA) concentrations to three bread wheat genotypes, including Mahdavi, Pishtaz and Shiraz varieties; They examined the effects on germination percentage, radicle and hypocotyl length, seedling fresh weight, radicle fresh and dry weight, seedling dry weight, and hypocotyl fresh and dry weight. In their study, in which they stated that seed germination and the early period are the most sensitive periods in salt stress, they reported that the application of average dose (1 mg L^{-1}) of auxin could decrease the negative effectiveness by salt stress (Akbari et al., 2007).

They identified the salt effect as the main component of osmotic and ionic salt tension (Da Silva et al., 2008). They conducted a study to determine the effect of *Azospirillum brasilense* Sp248 and nitrogen fertilization on wheat irrigated with seawater. They reported that the research results clearly show that inoculation with *Azospirillum brasilense* Sp248 saves 20 units of nitrogen fertilization and reduces the chemical fertilizers needed, improves the nitrogen content, and provides economic savings by counteracting the effects of salinity (Alamri and Mostafa, 2009).

It was determined that salicylic acid applied during salt stress caused the amount of auxin and cytokinin in wheat to remain unchanged and increased cell division and productivity in the root apical meristem (Shakirova et al., 2003). In a study they conducted on bread wheat, they examined the effect of two several salt concentrations (9 and 15 dSm^{-1} NaCl) on coleoptile and root development.

According to the results, they determined that salt stress reduced coleoptile and root development (Moud and Maghsoudi, 2008).

In a study conducted under laboratory conditions, two types of winter wheat were used. Polyethylene glycol (PEG) was applied to wheat seeds in pre-treatment. It was observed that there were differences in germination rates among varieties throughout the application.

In order to plants to survive in extreme environment stress statues, plant cells have widespread and effective mechanisms to repair and detect DNA damage to maintain their genome stability and to eliminate genetic alterations (Roy, 2014). According to the results obtained, it was reported that the pigment content in the wheat plant increased with the addition of K, the amount of lipid peroxidation was suppressed, and the damage caused by salt stress in antioxidant enzymes was reduced by the addition of K (Ahanger and Agarwal, 2017). Application of Si to wheat plants exposed to polyethylene glycol stress increased the endogenous ABA level, while causing a decrease in JA and IAA levels (Xu et al., 2017). In a study conducted to examine the effects of wheat on yield, physiological characteristics and growth development under salt stress were investigated. At the end of the study, it was observed that all plants irrigated with the highest salt concentration (50 mM NaCl) died (Akhtar et al., 2015).

Salicylic acid has important roles in growth and development, flowering, stomatal regulation, photosynthesis, respiration, osmolyte regulation (glucose, fructose, sorbitol and proline), senescence and ion uptake in plants under salt stress (Vicente and Plasencia, 2011). ABA synthesis increases in roots exposed to stress. It moves to the stem parts of the plant and stimulates the closure of stomata to prevent evaporation (Nakashima et al., 2014).

About 6.5% of total land over the world and about 19.5% ratio of the irrigated lands are affected by salt (FAO, 2018). Environmental stress, covering salinity stress, can provoke approximately 50% ratio of losing (Acquaah, 2007). Salt stress appears as one of the most important abiotic types of stress factors that limit production of crop, especially in the semi-arid and arid zones (Nawaz et al., 2010). They predicted that 50% of arable land will be affected by salinity by 2050 (Bouthour et al., 2015). Based on this, because of this study, literature information on the subject has been conveyed, and it can be said that there is a need to conduct research on salinity, which is an important stress factor, especially by view of physiological reactions.

Conclusions

Wheat (*Triticum* sp.) uses several mechanisms to adaptation salinity conditions. In epigenetic processes, heritable DNA methylation and histone modifications may be an option to keep stress memory longer (Chinnusamy and Zhu, 2009). DNA methylation by methyltransferase under stress conditions depends on mechanisms such as RNA interference and can rapidly and reversibly alter the plant DNA genome. This type of modification allows DNA to adapt to a mixed environment. After the plant is stressed, somatic cells remember the stress experience by epigenetic mechanisms (Peng and Zhang, 2009).

Biotic (symbionts, parasites, pathogens, herbivores) and abiotic (salinity, drought, temperature, humidity, light, nutrients, wind, ionizing radiation, and pollutants) stress factors threaten agricultural sustainability in many regions of the world, causing significant crop losses (Mickelbart et al., 2015). Salt stress causes water and ion toxicity, nutrient element irregularities, oxidative stress, changes in metabolic processes, membrane damage, decrease and irregularities in cell division, and deterioration of the genetic structure in plants.

Plants that are growing in salt stress need to extra energy sources to maintain tolerance and a better growth. It is emphasized that plant species need to establish a balance among supply of energy for salt stress (Bandehagh and Taylor, 2020). The emergence of soil salinity, which causes critical economic losses, is a result of improper water management, high evaporation, and seawater application (Tuteja, 2007).

For a sustainable agriculture, adaptation and application studies are carried out to identify species and genotypes which are resistant/tolerant to drought stress or to enhance and improve their resistance, and they remain popular (Hamrouni et al., 2001; Al-Barrak, 2006; Bettaieb et al., 2009; Bybordi, 2010).

Soil salinity can occur from natural causes or incorrect irrigation methods, reducing soil quality to an extent that compromises the entirety of the self-regulating capacity in soils.

Salinity is one of the biggest sources of damage worldwide in semi-arid and arid regions, which greatly reduces the production of agriculture under non-irrigated and irrigated regions over the world. Instead of temporary and expensive solutions, it is necessary to determine plant genotypes that can produce economic products by showing normal development and growth in areas where salinity is a problem, and that have high tolerance against salt welded stresses, in addition to breeding of new plant varieties.

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CHAPTER 2

UTILIZATION OF AROMATIC PLANTS IN FISH AND FISH PRODUCTS: AN OVERVIEW

Bilge BİLGİN FIÇICILAR[1]
Ebru YILMAZ[2]

[1]Dr., Ordu University, Fatsa Marine Sciences Faculty, Fisheries Technology Engineering, Ordu, Türkiye, Orcid: 0000-0002-7217-5905
[2]Dr., Ordu University, Fatsa Marine Sciences Faculty, Fisheries Technology Engineering, Ordu, Türkiye, Orcid:0000-0002-4090-558X

Fish is a valuable dietary supply of vital components, such as high-quality proteins, lipid-soluble vitamins (A and D), and minerals, that are important for human health. Fish is rich in n-3 polyunsaturated fatty acids (PUFAs), specifically eicosapentaenoic (EPA, C20:5) and docosahexaenoic acids (DHA, C22:6), that have crucial roles in various metabolic and physiological processes (Khalili Tilami & Sampels, 2018; Kulawik, Özogul, Glew, & Özogul, 2013). A wide range of research has resulted in several scientific data regarding their functional significance in cardiovascular disease, brain health, immune system, allergy, pregnancy, and infancy. However, preserving fish is essential to extend its shelf life, minimize food waste, and guarantee food safety, given its high susceptibility to spoilage. The quick degradation of fish is mainly caused by its biological composition, which includes a high level of moisture and the presence of enzymes and microorganisms that contribute to processes like lipid and protein oxidation and microbial decay (Konfo et al., 2023).

A variety of preservation technologies have been utilized to extend the shelf life of fish and fish products. These technologies involve traditional methods like drying, smoking, and salting, as well as contemporary techniques like refrigeration, freezing, vacuum packaging, smart packaging, ultrasound, pulsed electric field, fluorescence spectroscopy, hyperspectral imaging technique, high-pressure processing, and modified atmosphere packaging. These techniques are used to process economically viable fish products while minimizing damage to their quality, to meet consumer demands.

In the last decade, there has been a growing interest in using natural antioxidants and natural extracts to enhance the preservation of fish. This interest is motivated by consumer demand for products with fewer artificial additives and a general shift towards more natural and sustainable methods of preserving food. This chapter will discuss the mechanism and uses of these natural preservatives in order to preserve the quality and prolong the shelf life of fish and fish products.

Fish spoilage

Upon being captured, fresh fish can quickly decade as transitioning into a state commonly referred to as rigor mortis immediately after death. This condition results in the fish becoming rigid due to muscle stiffening, which occurs a few hours post-mortem. While handling and storing fish after death, factors such as temperature, oxygen levels, proteases (either from the fish itself or from microorganisms), and moisture can cause undesirable changes in the fish's color, odor, texture, and flavor (Sriket, 2014). The deterioration of fish is mainly caused by three processes: enzymatic autolysis, which refers to the self-digestion of the

fish's tissues by its own enzymes; oxidation, which results in the degradation of fats within the fish, leading to unpleasant flavors and odors; and the proliferation of microorganisms, which can both spoil the fish and pose health hazards to consumers (Lone Gram & Dalgaard, 2002; "Spoilage of Fish and Other Seafoods," 2016).

Autolysis, a natural process where a fish's enzymes break down its proteins, occurs right after rigor mortis ends. This marks the beginning of degradation, quickly setting in post-harvest, driven by enzymatic actions that cause both chemical and biological transformations, leading to the breakdown of essential molecules (Ghaly, 2010). This activity not only impacts the texture, contributing to spoilage but also sets the stage for bacterial growth. However, it does not directly result in the off-flavors and odors often associated with spoiled fish. These particular sensory changes are mainly linked to enzymes present in the fish's gastrointestinal tract and muscles, which induce alterations in the fish's sensory qualities during processing and storage (Hansen, Gill, Røntved, & Huss, 1996).

Changes that occur in chilled or frozen fish after death are caused by a chain of enzyme activities that affect the structure and quality of the tissue. Glycolytic enzymes catalyze the conversion of glycogen into lactic acid, resulting in a decline in pH levels of fish following death. Autolytic enzymes responsible for the breakdown of nucleotides, specifically ATO, ADP, AMP, and IMP, lead to the constant accumulation of hypoxanthine, a substance linked to a loss in freshness. Proteolytic enzymes, such as cathepsins, chymotrypsin, trypsin, and carboxy-peptidases, specifically target proteins and peptides in the fish muscle, resulting in tissue softening that can lead to belly bursting. Calpain, another proteolytic enzyme, selectively targets myofibrillar proteins, and softens the fish flesh. Collagenolytic enzymes breakdown connective tissue, resulting in a decrease in the firmness and texture of the fish's flesh, hence altering its overall texture and firmness. Trimethylamine oxide (TMAO) demethylase converts TMAO into formaldehyde, which can act as a preservative but may become undesirable at elevated levels. The combined enzymatic activity accelerate the decomposition of fish after death, ultimately affecting its quality and shelf life (Tavares et al., 2021). Fish use Trimethylamine Oxide (TMAO) as an osmoregulatory agent to prevent dehydration in marine habitats and tissue water saturation in freshwater conditions. Bacteria, including *Shewanella putrifaciens*, *Aeromonas* spp., psychrotolerant *Enterobacteriaceae, P. phosphoreum*, and *Vibrio* spp., are capable of deriving energy by converting TMAO to TMA,

resulting in the production of off-flavors similar to ammonia (Gram and Dalgaard, 2002).

The composition of the microflora present on freshly caught fish is reflective of the microbial populations inhabiting the aquatic environment from which the fish are sourced. Such microflora often comprise bacterial genera including Pseudomonas, Alcaligenes, Vibrio, Serratia, and Micrococcus(L. Gram & Huss, 2000). The proliferation and metabolic activities of these microorganisms are principal contributors to the spoilage of fish, leading to the formation of compounds such as amines and biogenic amines including putrescine, histamine, and cadaverine along with organic acids, sulfides, alcohols, aldehydes, and ketones. These compounds are responsible for the development of undesirable off-flavors that render the fish unacceptable for consumption, as indicated by the research *of* (Abuhlega & Ali, 2022; Bilgin & Gençcelep, 2015; Saha Turna, Chung, & McIntyre, 2024)

In the context of unpreserved fish, spoilage is typically caused by Gram-negative fermentative bacteria such as members of the *Vibrionaceae* family, while spoilage of refrigerated or chilled fish is predominantly caused by psychrotolerant Gram-negative bacteria, including *Pseudomonas* spp. and *Shewanella* spp (L. Gram & Huss, 2000; Rathod, Nirmal, Pagarkar, Özogul, & Rocha, 2022). Microbial contamination, encompassing pathogenic bacteria, viruses, and parasites, originates from aquatic environments and is associated with direct contact with these environments, ingestion of contaminated sediments or feed, as well as post-harvest contamination (Lone Gram & Huss, 1996). It is crucial to distinguish between non-spoiling and spoiling bacteria in fish storage, as the majority of bacteria present do not contribute to spoilage. However, only a small percentage of the microbial population in fish is actually responsible for spoilage, known as specific spoilage organisms. These organisms can overpower other bacteria and produce metabolites by breaking down non-protein nitrogen in fish muscle. These metabolites result in undesirable and objectionable off-flavors in the fish, adversely affecting its sensory qualities and making it unacceptable to consumers (Lone Gram & Dalgaard, 2002; Lone Gram & Huss, 1996).

The fish flesh contains a non-protein-nitrogen (NPN) component, including amino acids and nucleotides that act as a nutritional supply for microorganisms. The degradation of amino acids that contain sulfur, such as cysteine and methionine, is especially significant during the spoiling process since it results in the formation of unpleasant-smelling chemicals such as hydrogen sulfide and methyl mercaptan (Lone Gram & Dalgaard, 2002).

Seafood, rich in lipids and particularly abundant in fats that include long-chain polyunsaturated fatty acids (PUFAs), is susceptible to lipid oxidation, which plays a crucial role in generating off-flavors and odors that negatively affects the sensory quality of the product. This oxidation not only affects the taste and smell but also the nutritional profile of seafood by reducing the levels of fat-soluble vitamins and essential nutrients. The lipid oxidation process is characterized by a free radical mechanism that unfolds in three phases: the initiation phase, during which free radicals are generated; the propagation phase, in which these radicals undergo reactions with oxygen; and the termination phase, which concludes the reaction with the creation of stable, non-reactive end products. Furthermore, fish muscles include iron-bound proteins such hemoglobin, ferritin, myoglobin, hemosiderin, and transferrin along with other metals. These proteins and metals can be released during storage and have a significant impact on beginning and/or promoting lipid oxidation (Alishahi & Aïder, 2012). The lipid oxidation biochemical pathway culminates in the synthesis of reactive aldehyde compounds, notably malonaldehyde (MDA) and 4-hydroxynonenal (HNE), which serve as indicative biomarkers for spoilage and the degradation of seafood products.

The incorporation of natural plant-based substances, such as essential oils, plant extracts, hydrocolloids, and phenolic compounds, has gained popularity in the realm of seafood preservation due to their potent antimicrobial and antioxidative properties, offering significant promise for applications within the food industry. These botanical extracts and essential oils, sourced from various parts of plants including petals, leaves, fruits, peels, stems, roots, and xylems, owe their antioxidative capabilities to their rich content of volatile organic compounds, terpenes, and phenolics.

Natural additives

Plant-derived products

Natural compounds derived from plants, including essential oils, plant extracts, hydrocolloids, and phenolic compounds, have been used for preserving seafood lately. These substances are highly valued for their potent antimicrobial and antioxidant properties, showcasing significant promise for application across the seafood industry. The antioxidant effects of essential oils and plant extracts are based on the presence of volatile organic compounds, terpenes, and phenolics. These chemicals are obtained from many sections of plants, including petals, leaves, fruits, peels, stems, roots, and xylems. The food industry has recognized the dual benefits of using derivatives from aromatic plants, both as natural flavor

enhancers and as preservatives, which effectively prolong the shelf life of their products. Integrating aromatic plant derivatives into seafood is expected to enhance the nutraceutical benefits of these foods, as a result of the inherent health-promoting features of these plant derivatives.

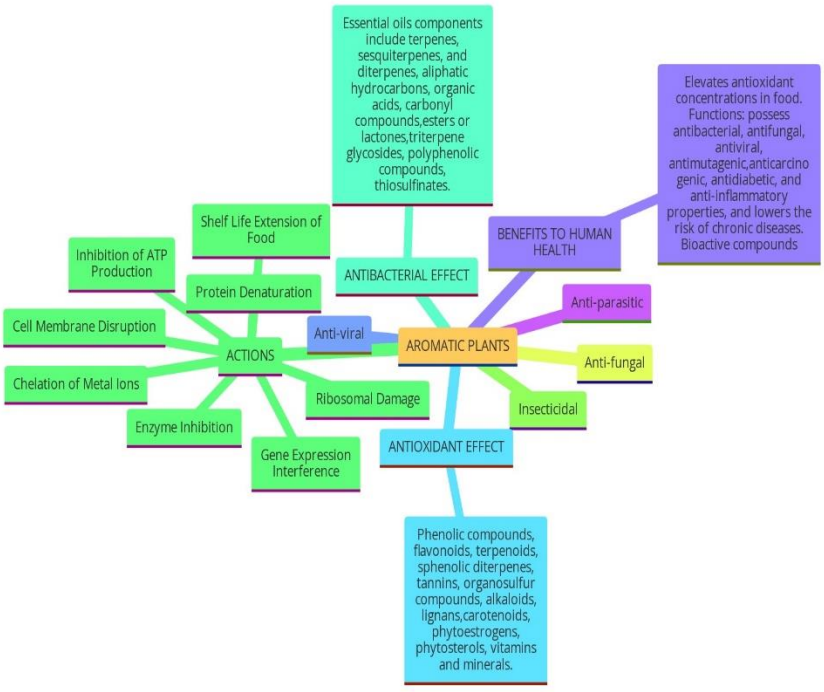


Figure 1- Aromatic plants and their effects on food systems

Numerous studies have explored the preservation benefits of plant extracts and essential oils as natural antioxidants and antimicrobials to enhance the quality and extend the shelf life of seafood by inhibiting or delaying oxidative processes and bacterial spoilage (Attouchi & Sadok, 2012; Balikçi, Özogul, Durmus, Uçsr, & Gokdogsn Tekin, 2022; Bilgin & Gençcelep, 2015; Chaula et al., 2019; Doğruyol, Ulusoy, Mol, & Ucok Alakavuk, 2021; Eskandari, Hosseini, Gholamzadeh, Mousavi Khaneghah, & Hosseini, 2015; Fellenberg, Carlos, Peña, Ibáñez, & Vargas-Bello-Pérez, 2020; Gai, Ortoffi, Giancotti, Medana, & Peiretti, 2015). Plants such as tea, laurel, rosemary, turmeric, thyme, oregano, fennel, mint, sage, garlic, cumin and clove, have been extensively studied for their application in the seafood industry. A comprehensive review of their effectiveness as natural preservatives to prolong the shelf life and enhance the quality of seafood products is detailed in Table 1.

Table 1- Studies about plants extract and plant essential oils and their effect in seafood products

Aromatic Plant	**Effect**	**Product**	**Citation**
Tea polyphenols (0.2% w/v)	Inhibited microbiological growth, hindered chemical deterioration, extended shelf life by 6–8 days	Ungutted crucian carp	(Li et al., 2012)
Laurel essential oil (4% v/w)	Extended shelf life; reduced biochemical parameters and bacterial growth; slower rate of free fatty acids and peroxide development	Rainbow trout fillets	(Ozogul et al., 2017)
Rosemary essential oil (0.85% v/w)	Extended shelf life, most significant improvement in microbiological, chemical, and sensory attributes, with lower counts of total mesophilic aerobic bacteria, coliform bacteria, *Staphylococcus–Micrococcus* spp., and yeasts and moulds	Fish patty (Bonito Fish)	(Guran, oksuztepe, coban, & ıncılı, 2015)
Turmeric and shallot extracts (1.5% v/v)	Individual and combined treatments of turmeric and shallot extracts at 1.5% v/v concentration effectively enhanced the shelf life and quality of rainbow trout under refrigerated storage	Vacuum packaged rainbow trout	(Pezeshk, Rezaei, & Hosseini, 2011)
Pulicaria inuloides essential oil (0.3% w/w, 0.2% w/w)	Efficient control of *L. monocytogenes*, *E. coli*, and *S. aureus*; reduced the inoculated pathogens by 2 log CFU/g up to the end of storage period	Fish fillet	(Nabil Qaid M. Al-Hajj & Waleed Aboshora, 2017)
Basil, rosemary, Laurel, Oregano, Fennel extracts (1% v/v)	Maintained mesophilic aerobic bacteria count below 5 log CFU/g; TVB-N, TBARS, and pH values remained within acceptability limits	Salmon slices	(Doğruyol et al., 2021)
Mentha spicata mint ethanol extract (1% v/v)	Reduced putrescine, cadaverine, spermidine, histamine, and tyramine by 27–66% in 21 days.	Sardine fillets	Houchier et al., 2015
Rosemary oil (3% v/w)	Reduced putrescine, cadaverine, histamine, and tyramine by 86–94% in 9 days. Improved oxidative stability of the lipids and the fatty acid profile.	Rainbow trout	(Peiretti, Gai, Ortoffi, Aigotti, & Medana, 2012)

Aromatic Plant	Effect	Product	Citation
Mentha piperita essential oil (0.25%, 0.50% v/w)	Reduction in the formation of peroxides and TBARS, indicating decreased lipid oxidation	Chilled tambatinga	(Pretto et al., 2024)
Oregano essential oil (0.1% v/v)	Extended shelf life to 8 days; effective in inhibiting microbial growth, delaying lipid oxidation, and retarding the increase of TVB-N, putrescine, hypoxanthine, and K-value.	Grass carp fillets	(Huang, Liu, Jia, Zhang, & Luo, 2018)
Rosemary essential oil (1% v/w)	Extended shelf life to 12 days; reduced total bacterial count, psychrophilic bacteria, total mold, and yeast. Reduced counts of *Staphylococcus aureus*, *Escherichia coli*, and *Bacillus cereus*.	Carp fish flesh fingers	(Abdeldaiem, Ali, & Ramadan, 2017)
Chitosan nanoparticles loaded with fennel essential oils (1% v/v)	Significant reduction in peroxide value, total volatile nitrogen, and thiobarbituric acid value, lower counts of mesophilic, psychotropic, *Pseudomonas*, and lactic acid bacteria compared with control	Huso huso fish fillets	(Maghami, Motalebi, & Anvar, 2019)
Garlic essential oil (2% w/v)	Improved sensory quality; significant reduction in pH increase, significant reduction in TMA-N; Reduced TBA; reduction in *Staphylococcus* and *Pseudomonas* counts	Nile tilapia fillets	(Hussein, Eissa, Foda, Hussein, & El-Sheikh, 2023)
Thyme extract (0.5% w/v)	Extended shelf life by 9 days longer than control; strong antimicrobial and antioxidant activity	Nile tilapia fillets	(Khalafalla, Ali, & Hassan, 2015)
Tea polyphenols (2% w/v)	Effective in inhibiting bacterial growth; Delayed lipid oxidation; lower TVB-N and TBARS; stabilized freshness and physical qualities (color and texture)	Refrigerated sea bass fillets	(Wang et al., 2021)
Thyme powder (1% w/w)	Extended shelf life by approximately 5 days; lower values of TVB-N, TMA-N, and TBA	Ice-Stored gilthead sea bream fillets	(Attouchi & Sadok, 2012)

Aromatic Plant	Effect	Product	Citation
Bayberry leaf extract (0.2% w/v)	Reduced bacterial growth; significantly reduced TVB-N, K-value, and TBARS compared to the control group	Large yellow croaker	(Su et al., 2014)
Cumin extract (1% v/v)	Retarded lipid oxidation and microbial spoilage; shelf life extension up to 6–9 days; higher-quality product based on sensory analysis	Refrigerated silver carp	(Eskandari et al., 2015)
Red grape pomace extracts (1%, %3 v/v)	Delayed lipid oxidation and cadaverine formation for 6 days under refrigeration	minced rainbow trout patties	(gai et al., 2015)
Oregano extract (470 mg/L)	Utilizing extracts in marinades enhanced the oxidative stability and color of fillets.	Rainbow trout fillets	(Fellenberg et al., 2020)
Thyme extract (0.05% w/v)	The extract suppressed microbial deterioration and effectively controlled the biochemical parameters, hence extending the product's shelf-life.	Atlantic mackerel minced balls	(Balikçi et al., 2022)
Laurel essential oil (2% w/v)	Laurel essential oil improved the sensory attributes of fish, slowed down microbial decay, and prolonged shelf life.	Rainbow trout fillets	(Aksoy, 2019)
Clove extract (2% w/v)	Substantially decreased lipid oxidation by 56%; enhanced preservation of omega-3 fatty acids; reduced levels of secondary lipid oxidation byproducts.	Sun- dried sardines	(Chaula et al., 2019)
Basil essential Oil (1% w/v)	Extended shelf life by 5 days (based on TVB-N) and 3 days (based on thiobarbituric acid-reactive substances); Effective in inhibiting TVB-N formation and lipid oxidation	Atlantic mackerel fillets	(Karoui & Hassoun, 2017)

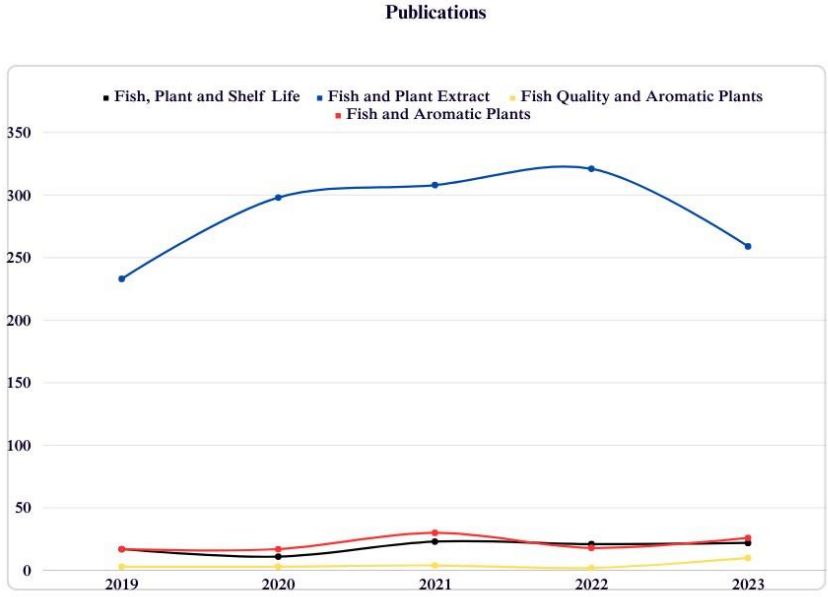


Figure 2- The number of articles indexed in Scopus using the search terms presented in the chart

The Figure 2 presents a comparison of the number of publications from 2019 to 2023 across four different keywords: Fish, Plant and Shelf Life; Fish and Plant Extract; Fish Quality and Aromatic Plants; and Fish and Aromatic Plants. The data is sourced from Scopus and visualized with distinct colored lines for each topic. Between 2019 and 2022, the number of publications on Fish, Plant, and Shelf Life remained stable, averaging around 300 publications, suggesting a continuous interest in research in this field. Publications on extracts from fish and plants consistently appear, though less frequently, indicating a specialized or underexplored scientific field.

In conclusion, the food sector currently has an increasing tendency towards the utilization of natural additives to decrease dependence on synthetic preservatives. However, a complete transition has not yet occurred, and there is insufficient documentation regarding the specific amounts and allowed usage of both natural and synthetic preservatives in the official compendium that regulates the use of additives in different food items. Hence, it is essential to not only

identify and assess novel natural additives, but also extensively analyze their safety profiles and mechanisms of action, while establishing strict regulatory criteria for their application.

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CHAPTER 3

APPLICATIONS OF ESSENTIAL OILS AND EXTRACTS OBTAINED FROM MEDICINAL AND AROMATIC PLANTS FOR ANESTHETIC PURPOSES IN THE AQUACULTURE

Ebru YILMAZ[1]
Bilge BİLGİN FIÇICILAR[2]

[1]Dr., Ordu University, Fatsa Marine Sciences Faculty, Fisheries Technology Engineering, Ordu, Türkiye, Orcid:0000-0002-4090-558X
[2]Dr., Ordu University, Fatsa Marine Sciences Faculty, Fisheries Technology Engineering, Ordu, Türkiye, Orcid: 0000-0002-7217-5905

INTRODUCTION

The use of plants for therapeutic purposes is almost as old as human history. The first written records on medicinal plants are seen in the works and tablets of Mesopotamia (circa 5000 BC), Sumerians (circa 4000 BC), and the Chinese (circa 3700 BC) (Demirezer, 2010; Arslan et al., 2015). It has been revealed that out of the existing 422,000 plant species worldwide, approximately 12.5%, which is 52,885 species, can be used for medicinal purposes. The countries that collect and cultivate medicinal plants the most are China and India, and a large part of these plants are obtained by wild collection (TAGEM, 2021).

According to a World Health Organization report, out of approximately 70,000 plants used for medicinal purposes around the world, about 21,000 are used in the pharmaceutical industry (Kaya, 2010). The global trade of medicinal and aromatic plants has been increasing since 2001 according to the current data. The export value, which was 18.3 billion US Dollars in 2001, reached 70.7 billion US Dollars in 2019.

Medicinal and aromatic plants have been used for human, animal, and even plant health through trial-and-error methods, and sometimes via professional medicine since the existence of humanity. Today, methods that some groups call alternative medicine have been scientifically proven by experts in pharmacy, medicine, and molecular biology, and have begun to re-enter people's lives with approval from authorities (Taşcı et al., 2015). Especially since the 1990s, the increasing demand for natural products has led to the rapid development of the herbal medicine and cosmetic industry (TAGEM, 2021).

Compared to Europe, Turkey is particularly rich in terms of seed plants. Of the 11,707 taxon plants that grow naturally in our country, about 3,035 are endemic to Turkey (Güner et al., 2012). In our country, only about 1,000 of the most naturally growing species are used for medicinal purposes (Kaya, 2010).

Due to its geographical location, climate and plant diversity, agricultural potential, and large land area, Turkey is one of the leading countries in the trade of medicinal and aromatic plants. Turkey's importance in this field arises from the fact that our country's flora contains many of the plant species that provide herbal products used as inputs in the established herbal medicine, plant chemicals, food and additives, cosmetics, and perfumery industries in developed countries. Therefore, these plants are mostly collected from the wild and marketed. Medicinal and aromatic plants are predominantly gathered from the Aegean, Marmara, Mediterranean, Eastern Black Sea, and Southeastern Anatolia Regions (Bayram et al., 2010). The term phytotherapy, which means treatment

with medicinal plants, was first used by the French physician Henri Leclerc (1870-1955) (Faydaoğlu and Sürücüoğlu, 2011)

General Uses of Medicinal and Aromatic Plants

Throughout history, medicinal and aromatic plants have been used for both medical and food purposes, and their importance has gradually increased. Today, these plants are widely used in both alternative and modern medicine. Around 80% of the global population primarily relies on herbal plants for managing their health conditions. In developed countries, the active ingredient of 25% of the drugs used is of plant origin (Farnsworth et al., 1985; Gül and Çelik, 2016) (Figure 1).



Figure 1. Medicinal and aromatic plants (URL, 1)

In addition to therapeutic use, medicinal aromatic plants are utilized in the production of a wide range of products such as cosmetic products, essential oils, herbal health products, coloring dyes, plant protection products, and intermediates that can be obtained from these products (Lubbe and Verpoorte, 2011).

It is estimated that 50% of the medicinal and aromatic plants traded worldwide are used in the food industry, 25% in cosmetics, and 25% in the pharmaceutical industry. Although the global trade in herbal drugs is estimated to be at levels of 10-13 billion dollars, unfortunately, despite its rich flora, Turkey only has a share of approximately 50-60 million dollars. This is also because we export medicinal and aromatic plants raw mostly without processing (Bahtiyarca Bağdat, 2006).

Medicinal and aromatic plants contain natural compounds that can help in the treatment of various diseases and the protection of health. The general areas of

the usage of these plants are as follows (Faydaoğlu and Sürücüoğlu, 2011; Göktaş and Gıdık, 2019);

- For medical purposes (in the field of treatment),
- Food, spices, and soft drinks,
- Perfumery and cosmetics industry,
- As a biofuel,
- As an anaesthetic.

Essential Oils in Anaesthetic Applications in Fish

Anaesthesia is a biological state induced by chemical or non-chemical methods and is defined by partial or complete loss of sensation, responsiveness, and voluntary neuromotor control. Anaesthetics are physical or chemical substances that first produce a sedative effect and then trigger loss of balance, loss of mobility, loss of consciousness, and finally loss of reflex response in an organism as a result of higher concentrations or prolonged exposure (Summerfelt and Smith, 1990). Anaesthetic substances cause sedation, a decrease in movements, and a decrease in metabolic activities depending on the concentration (Karataş, 2005). Substances used as anesthetics should allow the organism to enter anesthesia as quickly as possible, exit from anesthesia shortly, have no harmful effects during and after anesthesia, be easy to use and obtain, and be economical (Brown, 2011).

In the aquaculture sector, anaesthetics or sedatives can be used at various stages of production for many aquatic products from fish to crustaceans (Otay et al., 2014). There are several reasons for using anaesthesia in fish and other aquatic animals (Brønstad, 2022). Under current intensive aquaculture conditions, fish are subjected to various practices such as weighing, measuring, sorting by size, milking, transportation, vaccination, surgical operations, and tagging (Mylonas et al., 2005; Weber et al., 2009). Research has shown that fish, fish larvae, and other aquatic invertebrates experience pain, distress, and discomfort, and respond to stressful and harmful stimuli in a manner like other phylogenetically advanced animals (Sneddon et al., 2003; Barr et al., 2008; Crook et al., 2013; Eckroth et al., 2014; Wu and Li, 2015; Lopez-Luna et al., 2017). In practices performed on fish, numerous chemical anesthetics such as MS-222 (tricaine), quinaldine, benzocaine, and phenoxyethanol are used (Coyle et al., 2004) (Figure 2).

However, many studies have reported that these types of chemical anesthetics have toxic effects on fish, including symptoms such as death, respiratory problems, coughing behaviors, and startle responses (Karataş, 2005).



Figure 2. Fish anaesthesia (URL, 2)

When selecting an anesthetic for a specific purpose, it is necessary to consider features such as ease of use for the operator, safety for fish, humans, and the environment, the degree of effectiveness, solubility in water or a solvent, economic aspects, and commercial availability (Akbulut et al., 2012). Essential oils, being complex compounds obtained from various parts of plants (such as root, stem, and leaves) through distillation or pressing and containing different components, can vary in terms of their biological effects (Toroğlu and Çenet, 2006). These oils possess effects such as analgesic, antibacterial, antifungal, antiviral, antioxidant, sedative, and anesthetic (Maksimović et al., 2005). Recently, it has been observed that products derived from medicinal and aromatic plants have found their place as an option in aquaculture and fish anesthesiology. However, since herbal products are complex mixtures containing different components, their anesthetic effects can vary (Hoseini et al., 2018). Considering the studies on aquaculture, clove (*Eugenia caryophyllata*) oil is mostly used as anaesthetic (Akbulut et al, 2012), the anaesthetic effects of alternative plant oils such as peppermint (*Mentha piperita*), basil (*Ocimum basilicum*), thyme (*Thymus vulgaris*), lavender (*Lavandula angustifolia*), rosemary (*Rosmarinus officinalis*) and eucalyptus (*Eucalyptus globulus*) have also been investigated. The anaesthetic effect of clove oil is mainly due to eugenol phenols, eugenol acetate and cariophylene-5 (Briozzo et al., 1989; Keene et al., 1998; Karataş, 2005). In recent studies, the use of clove oil for fish anaesthesia has gained popularity among other anaesthetics and has become more preferred (Akbulut et al., 2012). Clove oil, which has become increasingly popular in this way, is a natural, inexpensive, easily available, odorous, herbal anaesthetic that is safe for human and environmental health, almost completely excreted from the fish body through

urine within 24 hours, and has a low toxicity risk (Fischer et al., 1990; Woody et al., 2002; Fernandes et al., 2017) (Figure 3).



Figure 3. Clove (Eugenia caryophyllata) oil (URL, 3)

Studies conducted with clove oil were aimed at calming fish for a short period of time for purposes such as weighing, labelling, vaccination or milking and were tested in many fish species. As examples of these studies; 40 and 50 mg l^{-1} in rainbow trout (*Oncorhynchus mykiss*) (Metin et al., 2015), 200-800 mg l^{-1} in carp (*Cyprinus carpio*) (Otay et al, 2014), 25 mg l^{-1} in sea bass (*Dicentrarchus labrax*) (Mylonas et al., 2005), 40-55 µl l^{-1} in sea bream (*Sparus aurata*) (Mylonas et al., 2005), 0.22-0.90 g l^{-1} in roe sturgeon (*Acipenser gueldenstaedtii*) (Akbulut et al, 2011a), 160 mg l^{-1} in juvenile yellowmouth (*Argyrosomus regius*) (Cárdenas et al., 2016), 75-150 mg l^{-1} in goldfish (*Carassius auratus*) (Perdikaris et al., 2010), 80-100 mg l^{-1} in Nile tilapia (*Oreochromis niloticus*) (Simoes et al, 2011), 0.5-3 ml l^{-1} in angelfish (*Pterophyllum scalare*) (Hekimoğlu and Ergün, 2012) and 125 µl l^{-1} in oilfish (*Pseudophoxinus anatolicus*) (Erbatur et al., 2018). Among the main components of peppermint (*Mentha spicata)* oil, which is another of the anaesthetic substances used, are carvone, limonene, carveols, carvyl acetates, menthol, borneol, linalool, menthone, jasmone and perilalcohol (Akgül, 1993). Carvone, which is a component that gives smell and flavour to mint plant, has a sedative and anaesthetic effect on the central nervous system (Roohi and Imanpoor, 2015) (Figure 4). In previous studies, peppermint oil was used in carp (*Cyprinus carpio)* 3, 5 and 7 ml l^{-1} (Roohi and Imanpoor, 2015), juvenile nil tilapia (*Oreochromis niloticus*) 40-160 µl l^{-1} (De Oliveira Hashimoto et al, 2016), in Persian sturgeon (*Acipencer persicus*) 300-1000 mg l^{-1} (Mazandarani and Hoseini, 2018), and in rainbow trout (*Oncorhynchus mykiss*) at concentrations of 200 ml-1 (Metin et al., 2015).



Figure 4. Peppermint (Mentha spicata) oil (URL, 4)

Basil (*Ocimum basilicum*) oil contains linalool, linalyl acetate, cineole, myrcene, a-terpineol and geranyl as main constituents (Brada et al., 2011) (Figure 5). Among the Lamiaceae species, basil is the plant with the highest amount of cisoric acid (Lee, 2010; Telci et al., 2015). It was reported that clove basil (*Ocimum gratissimum*) essential oil showed anaesthetic effect in silver catfish (*Rhamdia quelen*) at concentrations of 30-300 µl l-1 (De Lima Silva et al., 2012), *Brycon cephalus* at concentrations of 20-80 µl l-1 (Ribeiro et al., 2016), and local basil *(Ocimum americanum*) essential oil showed anaesthetic effect in Brycon cephalus at concentrations of 200-500 mg l-1 (De Lima Silva et al., 2015).



Figure 5. Basil (Ocimum basilicum) oil (URL, 5)

Thyme (*Origanum vulgare*) contains carvacrol and thymol as the main components and p-cymene and γ-terpinene compounds are also found at high rates (Daouk et al., 1995; Sokovic et al., 2002; Esen et al., 2007; Uçar et al., 2015). Studies have reported that oregano oil at concentrations of 50-75 µl l-1 (Bodur et al., 2018) has an anaesthetic effect in the juvenile yellow mouth (*Argyrosomus regius*) and sea bass (*Dicentrarchus labrax*) fish (Figure 6).



Figure 6. Thyme (Origanum vulgare) oil (URL, 6)

The two most important components of lavender (*Lavandula angustifolia*) oil are linalyl acetate and linalool. The narcotic effect of linalyl acetate and the sedative effect of linalool are very strong (Kara, 2011) (Figure 7). Lavender oil was reported to have a sedative effect on rainbow trout (*Oncorhynchus mykiss*) (Metin et al., 2015) and carp (*Cyprinus carpio*) fish (Balkaya, 2019) at a concentration of 200 mg l-1.



Figure 7. Lavender (Lavandula angustifolia) oil (URL, 7)

Rosemary oil (*Rosmarinus officinalis*) consists of cineole, α-pinene, camphor, camphene, ß-pinene, myrcene, borneol, bornylacetate, terpineol, linalool, terpineol, limonene and caryophyllene (Simon et al., 1984; Bayrak, 2006; Uçar et al., 2015). Ghazilou and Chenary (2011) determined that rosemary oil at concentrations of 0.25-1 ml l-1 showed anaesthetic effect in carp fish (*Cyprinus carpio*) (Figure 8).



Figure 8. Rosemary (Rosmarinus officinalis) oil (URL, 8)

Eucalyptus (*Eucalyptus globulus*) oil is rich in cineole, has antiseptic properties and is widely used in aromatherapy (Yaylı, 2013; URL, 9) (Figure 9). It has been reported that the optimal dose for anaesthesia is 300 µl l-1 in juvenile yellow mouth (*Argyrosomus regius*) and 200-300 µl l-1 in sea bass (*Dicentrarchus labrax*) (Bodur et al., 2018; Metin et al., 2018).



Figure 9. Eucalyptus (Eucalyptus globulus) oil (URL, 10)

Conclusions

Natural fish stocks are decreasing due to many factors such as overfishing, non-compliance with fishing bans, pollution of water resources and global warming. The need for animal protein is increasing day by day in parallel with the population growth rate worldwide. This increasing demand has prompted entrepreneurs to increase fish farming in sea and inland waters. The aquaculture sector has been developing increasingly all over the world in recent years. Fish breeders also use anaesthetic substances in many applications such as milking, vaccination, and measurement in their farms so that their fish are not damaged by stress. In the selection of anaesthetic substances, since they offer fish for human consumption, they mostly prefer organic or vegetable origin, non-toxic or residue-free substances. When we look at the studies on anaesthetic substances in aquaculture in recent years, it is seen that these studies are mostly focused on medicinal and aromatic plant oils. In the history of the world, it is possible to come across old information that medicinal and aromatic plants have been used continuously since the existence of humanity. Our country, which has rich vegetation and different climate types, is very rich in medicinal and aromatic plants.

In recent years, the importance of natural herbal resources and medicinal plants carrying these substances has increased due to reasons such as more side effects of synthetic origin substances and the resistance of organisms to synthetic drugs used as antimicrobials (Faydaoğlu and Sürücüoğlu, 2013). In the aquaculture sector, anaesthetics, camoterapotics, immunostimulants or growth-enhancing feed additives are widely used. The chemical content of these products may cause residues and threaten health. However, such problems can be prevented by using herbal products instead of chemical products (Çelik, 2020). To adequately utilize the sustainable production and market potential of medicinal and aromatic plants, these products must be of the desired quantity and quality. The development of improved varieties for quality and standard products that meet the demands of consumers and industrialists, determination of suitable ecological conditions, timely harvesting of natural plants without harming nature, post-harvest processes, and processing technology will increase production and market opportunities in medicinal and aromatic plants (Bayram et al., 2010). In order to know the value of the medicinal and aromatic plant diversity of our country and to make its diversity sustainable, it is possible to increase the cultivation areas and farmer support. Farmer training about these plants is very important in terms of recognizing their biological properties and understanding their importance. The sale of these plants is also significant in foreign exports and

provides foreign currency inflow to our country. It may be possible for more entrepreneurs to be interested in medicinal and aromatic plant cultivation in the coming years through advertising, promotion, and subsidies.

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CHAPTER 4

THE DEVELOPMENT OF THE TURKISH FISHERIES SECTOR IN THE LAST FIVE YEARS (2018-2022): A GENERAL EVALUATION

Adnan TOKAÇ[1]

[1]Prof. Dr., Ege Üniversitesi Su Ürünleri Fakültesi, ORCID: 0000-0002-2968-7315

INTRODUCTION

The Turkish fisheries sector has experienced significant developments over the past five years. This evaluation will be based on various data sources, including sectoral trends, statistics, and information obtained from different references. The general assessment to be conducted within this scope will proceed sequentially through the main headings provided below.

1. **Production and Foreign Trade:** Türkiye holds a significant position as a producer and exporter in the fisheries and aquaculture sector. According to the data from the Turkish Statistical Institute (TURKSTAT), Turkey's aquaculture production has shown a steady increase over the past five years. During the same period, the export of aquaculture and animal products has also risen (TURKSTAT, 2023a; TURKSTAT, 2023b)

2. **Investments and Technology:** In recent years, the fisheries and aquaculture sector in Turkey has grown by focusing on technological innovations and modern production methods. Specifically, increased investments in fishing vessels, aquaculture farming and seafood processing facilities have been observed. This has enhanced the sector's efficiency and increased its competitiveness both domestically and internationally

3. **Sustainability and Controls:** In recent years, the importance of sustainability and environmental factors in the Turkish aquaculture sector has been steadily increasing. There has been a tightening of controls on fishing activities and aquaculture farms, and sustainability standards have been raised. This represents a positive step towards the sector's long-term growth and environmental protection**.**

4. **Domestic Market and Consumption Habits:** In Turkey, consumption habits regarding seafood products have been changing. With economic growth, increasing income levels, and rising health awareness, people have been inclining towards consuming more fish and seafood. This trend has contributed to the expansion of the domestic market and supported growth in the sector (FAO, 2022).

5. **International Competition and Trade Agreements:** The fisheries and aquaculture sector of Turkey competes in international markets. Trade agreements with the European Union and other countries have facilitated the increase in Turkish seafood exports and aided the sector in complying with international standards. (TİM. (2023).

FISHERIES AND AQUACULTURE PRODUCTION AND FOREIGN TRADE

The production quantities of Turkish fisheries and aquaculture over the past five years covering 2018-2022 are provided in Table 1. Based on the data in Table 1, we can evaluate several key points regarding how fisheries and aquaculture production in Turkey has changed through fishing and farming as follows.

Table 1. Fisheries and aquaculture production quantity (tons) in Türkiye for the last five years (2018-2022)

Years	Fisheries	Aquaculture	Total
2018	*314.318*	314.537	628.631
2019	*463.168*	373.356	836.524
2020	*364.400*	421.411	785.811
2021	328.165	471.686	799.851
2022	335.003	514.805	849.808

Source: TURKSTAT, 2023b

Firstly, the total fisheries and aquaculture production varies each year. There is a significant increase observed from 2018 to 2019 in this variation amount, followed by a decreasing trend from 2019 to 2020 and subsequently until 2021. However, there is a renewed increase observed from 2021 to 2022. This variability indicates that the sector experiences fluctuations depending on various factors (economic, environmental, market demand, etc.)

Moreover, there are significant differences between fisheries and aquaculture production. Particularly, the quantity of products obtained through fishing is higher than aquaculture in 2018 and 2019. However, starting from 2020, the quantity of products obtained through aquaculture has increased and surpassed the quantity obtained through fishing since 2021. This indicates that initially, aquaculture is gaining increasing importance in aquaculture production, but in fact, it does not necessarily point to a healthy developmental plan, raising questions about the sustainability of aquaculture in the future. Overall, there is an increasing trend in aquaculture-based aquaculture production from 2018 to 2022. Especially, there is a continuous increase in the quantity of products obtained through aquaculture from 2018 to 2022. This indicates the rapid development of aquaculture in Turkey and its becoming a significant production method.

Economic factors, the status of natural resources, technological advancements, market demand, and similar factors can influence the production quantity in the fisheries and aquaculture sector. Therefore, considering these factors is crucial for maintaining stable growth in the sector. Consequently, the aquaculture sector in Turkey exhibits a dynamic structure, and the production quantity through both fishing and aquaculture varies over time. The reasons and effects of these changes are important considerations for stakeholders in the sector.

As evident from the values in Table 2, Turkey's seafood exports have generally followed an increasing trend over the past five years from 2018 to 2023. Over the five-year period from 2018 to 2022, both the quantity and value of exports have consistently risen. This indicates that Turkey has experienced steady growth in seafood exports

Tablo 2. Son beş yıllık (2018-2022) Türkiye su ürünleri dış ticareti

	İhracat		İthalat	
Yıllar	Miktar (ton)	Değer ($)	Miktar (ton)	Değer ($)
2018	177.500	951.793.070	98.315	188.965.220
2019	200.226	1.025.617.723	90.684	189.438.745
2020	192.462	1.020.673.539	80.525	127.415.564
2021	238.732	1.376.291.922	104.708	217.179.174
2022	251.416	1.651.496.218	115.189	312.980.444

Kaynak: TÜİK, 2023a

On the other hand, the quantity and value of seafood imports to Türkiye have shown variability over the years. However, there does not appear to be a consistent upward trend from 2018 to 2022. Particularly in 2020, a decrease in both quantity and value was observed. Türkiye's seafood trade balance is generally positive, meaning that exports exceed imports. This indicates that Türkiye generally has a trade surplus in seafood and meets domestic demand with foreign demand. Especially in 2021 and 2022, significant increases in export value were observed. This demonstrates that Türkiye conducts its exports with more valuable products and enhances its competitiveness in the international market. The import value showed a significant increase especially in 2021, but experienced a decrease in 2022. The reasons behind these fluctuations may vary, including factors such as exchange rates, supply-demand balance, and economic conditions.

In conclusion, Türkiye's seafood foreign trade has generally grown and fluctuated over the past five years. While the increasing trend in exports sends a

positive signal, fluctuations in imports and changes in the trade balance should be closely monitored.

INVESTMENTS AND TECHNOLOGİES IN THE FISHERIES SECTOR

The investments and technological developments in the Turkish fisheries sector over the past five years have greatly contributed to the overall development of the industry. The investments and technological innovations that have occurred in the sector during this period can be examined in detail with data obtained from various sources.

First and foremost, it is observed that investments in aquaculture have been increasing steadily in recent years, particularly in fish farming. The modernization and automation of technological systems used on farms have led to increased productivity. Furthermore, advancements in sensor technologies for water quality control and improvements in water treatment systems have constituted significant parts of investments in fish farming. Similar technological advancements have also been observed in seafood processing facilities. Automation investments in processing facilities have made production processes more efficient, leading to the successful achievement of goals such as improving product quality and reducing waste. Additionally, technological innovations in packaging and storage processes have supported advancements in the sector.

Moreover, investments and technological developments in fishing vessels and fishing methods in Turkey over the past five years indicate a significant transformation in the seafood sector. Substantial investments have been made in the modernization of fishing vessels in Turkey in recent years. Strengthening and modernizing the technological equipment on fishing vessels have greatly contributed to increasing fishing efficiency. Investments in areas such as the development of navigation systems on vessels, underwater mapping technologies, and modernization of fishing equipment have ensured the adaptation of the fishing industry to international standards.

In addition to investments and technological advancements, sustainability and monitoring have been significant focal points in the Turkish fishing sector over the past five years. Various monitoring mechanisms and surveillance systems have been developed to ensure the protection of seas and the sustainable management of fish stocks. This represents an important step for the long-term growth of the sector and the preservation of marine resources.

SUSTAINABILITY AND CONTROLS

In Türkiye, significant developments have occurred in the supervision and sustainability of the fishing sector over the past five years. During this period, efforts to enhance the sustainability of fishing activities and environmental protection measures have been actively supported by various institutions, primarily the Ministry of Agriculture and Forestry (Ministry of Agriculture and Forestry, 2023). Primarily, strengthening inspection mechanisms aimed to minimize the environmental impacts of fishing activities and promote sustainable fishing practices. In this context, increasing the number of inspection teams and conducting inspections more rigorously have been ensured. Particularly, monitoring the production processes in aquaculture facilities and verifying the compliance of these facilities with the prescribed standards have been crucial steps toward sustainability in the sector. Furthermore, inspections have been intensified regarding the management of inputs and wastes in aquaculture facilities. Issues such as the control of chemical usage, monitoring of water quality, and waste management have been focal points of inspections. Thus, the aim has been to reduce environmental impacts and preserve water resources.

Another notable development during this period has been the elevation of sustainability standards in the sector. The Ministry of Agriculture and Forestry has undertaken various efforts to implement international sustainability standards in Türkiye. Adapting these standards to local conditions and implementing them in collaboration with stakeholders in the sector has made fishing activities more sustainable.

In 2022, the 199,702 inspections carried out by the Coast Guard Command played a critical role in preventing illegal fishing and ensuring the conservation and sustainable use of aquatic resources. As a result of these inspections, 480 tons of illegally caught seafood were confiscated, and a total of 8,021 individuals and businesses engaged in illegal fishing activities and sales were fined a total of 37,120,000 Turkish Lira. Additionally, 169 vessels that violated the rules at sea and acted contrary to sustainable fishing principles were seized (BSGM, 2022). These measures represent significant steps taken to promote the conservation of aquatic resources and encourage sustainable fishing practices that can be passed on to future generations.

DOMESTIC MARKET AND CONSUMPTION HABITS

In the past five years, the fisheries sector in Türkiye has experienced significant developments in terms of domestic market and consumer habits. The

changes observed in the sector during this period have been shaped by various factors.

Firstly, economic growth and increasing income levels have led to significant changes in consumption habits in Turkey. With people developing a greater health consciousness, there has been an increase in the consumption of fish and seafood. This trend has contributed positively to the growth of the domestic market demand for seafood products (Turkish Statistical Institute [TURKSTAT], 2023).

Moreover, changes in health and nutrition trends in recent years have led consumers to make preferences towards healthier and balanced diets. Fish and seafood are preferred as part of healthy eating programs due to their richness in protein, omega-3 fatty acids, and other essential nutrients. This has further increased the demand for seafood products in the domestic market and supported the growth of the sector (FAO, 2022).

However, with the expansion of the domestic market, issues of reliability and quality in the supply chain have also gained importance. Consumers have become more sensitive to the safety and quality of products. Therefore, it is crucial for businesses in the seafood sector to adhere to hygiene standards and ensure the traceability of products.

To gain a more detailed understanding of these changes in the domestic market and consumption habits in Türkiye, it is necessary to examine data obtained from various sources. These data can be sourced from institutions such as the Turkish Statistical Institute (TURKSTAT), the Food and Agriculture Organization (FAO), as well as academic research studies.

INTERNATIONAL COMPETITION AND TRADE AGREEMENTS

In the last five years, the Turkish aquaculture sector has experienced significant developments in the context of international competition and trade agreements. The changes observed in the sector during this period have been shaped by trends in the international trade environment and changes in Turkey's trade policies.

Firstly, Türkiye's aquaculture sector has shown significant progress in terms of competitiveness in international markets. Investments and technological advancements in recent years have contributed to the diversification and increase in Turkish a fisheries exports. Additionally, various incentive and support policies aimed at enhancing the sector's international competitiveness have been effective (TIM, 2023). Furthermore, Turkey's fisheries sector has been

strengthened through international trade agreements. Trade agreements signed by Turkey with the European Union (EU) and other countries have facilitated the increase in aquaculture exports and bolstered the sector's position in international markets. These trade agreements have opened up new markets for Turkish aquaculture exporters and reduced trade barriers.

However, along with the increase in international competition, some challenges have emerged in the sector. Particularly, pressures related to compliance with quality standards and competitive pricing should be considered. Additionally, uncertainties in the international trade environment and changes in trade policies also pose challenges for the sector. Evaluating Türkiye's fisheries sector in the context of international competition and trade agreements is important for understanding the direction of the sector's future development.

CONCLUSION AND EVALUATION

Over the past five years, the Turkish aquaculture sector has experienced significant developments across various facets, showcasing its dynamic nature and adaptability to changing trends. In terms of production and foreign trade, the sector has demonstrated consistent growth, with both aquaculture and fisheries contributing to increased output and exports. However, fluctuations in import quantities and values have been observed, highlighting the need for careful monitoring and management.

Investments and technological advancements have played a crucial role in enhancing the sector's productivity and competitiveness. Particularly, investments in aquaculture facilities and processing plants have led to efficiency gains, while advancements in technology have improved production processes and product quality. Sustainability and regulatory efforts have also been notable, with strengthened enforcement measures aimed at minimizing environmental impacts and promoting sustainable fishing practices. Additionally, efforts to elevate sustainability standards have been made through collaborations with international organizations, contributing to the sector's long-term viability. Changes in domestic consumption patterns, driven by economic growth and heightened health awareness, have spurred increased demand for fish and seafood products in the domestic market. However, ensuring product safety, quality, and traceability remains paramount to meeting consumer expectations.

On the international front, the Turkish aquaculture sector has made significant strides in competitiveness, facilitated by investments, technological advancements, and trade agreements. Nevertheless, challenges such as compliance with quality standards and competitive pricing persist, necessitating

ongoing efforts to address them. In conclusion, the Turkish aquaculture sector has undergone remarkable progress over the past five years, positioning itself as a key player in the global market. Continued attention to sustainability, technological innovation, international competitiveness, and domestic demand will be critical to sustaining this growth trajectory and ensuring the sector's long-term prosperity.

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CHAPTER 5

MARINE MACRO ALGAE DERIVED POLYSACCHARIDE: FUCOIDAN

Gözde YEŞİLTAŞ[1]
Bengü ERGÜDEN[2]

[1]Gebze Technical University, Department of Bioengineering
ORCID-0000-0003-4099-2959
[2]Assoc. Prof. , Gebze Technical University, Department of Bioengineering
ORCID-0000-0002-8621-3474

Since ancient times, marine creatures have been used as a source of bioactive substances and essential medicinal ingredients. Marine flora and fauna, such as algae, bacteria, sponges, fungi, corals, diatoms, etc., constitute more than 90% of the total aquatic biomass. These creatures are taxonomically very different from each other and have a rich pharmacological spectrum. Especially in recent years, research on the biological activities of algae has made significant progress, especially on their composition and applications in human nutrition and animal feed. Algae have many uses: they are used as feed, pharmaceuticals, energy sources, fertilizers, in cosmetics and various other industrial applications. Their bioactive properties are largely due to the presence of phenols, vitamins, minerals, sterols, polysaccharides and many other biologically active compounds in their structure. These compounds have shown to possess antimicrobial, antioxidant, anti-cancer, anti-inflammatory, and anti-diabetic activities.

Fucoidan, a sulfated polysaccharide found in the cell wall structure of marine algae, was first isolated by Kylin in 1912 (Kylin, 1912). It consists of polysaccharides containing sulfated L-fucose groups as a structural skeleton. The main source of fucoidan is brown marine algae (Phaeophyceae), and it is found in high concentrations in the cell walls of these marine creatures. It is especially abundant in brown seaweed collected from deep, cold sea waters. It has also been isolated from some marine invertebrates and sea urchins (Cardoso et al., 2016).

The structure of fucoidan differs in different algal species, but even within the same species polysaccharide backbone present in the fucoidan structure may have different structures. Thus the term "fucoidan" refers to a large group of sulfated polysaccharides containing fucose (Tocaciu et al., 2018). Fucose is the main active group of the molecule, and is one of the sugar structures function in cell-to-cell communication (Obluchinskaya et al., 2021). In addition to fucose, fucoidan may contain other monosaccharides such as glucose, galactose, mannose, and xylose. These sugar molecules can form different 3D structures by bonding to each other from different positions in different species. Figure 1 shows a general view of fucoidan, and two examples isolated from the algae A. nodosum and F. vesiculosus. They have a backbone containing sulfate groups attached to

the fucose main structures at 2- and 4-positions. Fucoidan obtained from F. evanescens also has a similar backbone formed by sulfate attached to fucose structures in the 2- and 4-position. Acetate groups of the structure can be found at the C-4 and C-3 positions of the fucose units (acetate groups are not shown in the Figure) (Cardoso et al., 2016; Obluchinskaya et al., 2021).

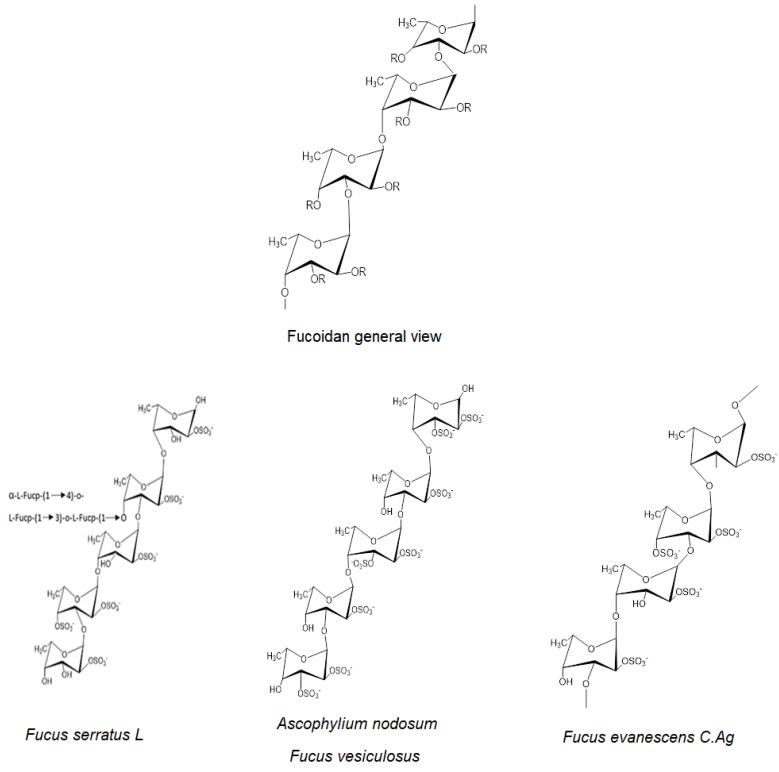


Figure 1. General representation of the structure of Fucoidan and examples from some species

Figure 2 shows fucoidan molecules isolated from Chorda phylum and Laminaria saccharina species. These compounds have a poly-α-(1→3) fucopyranoside backbone with sulfate bonded at C-4 and some C-2 positions, and in some structures the fucose groups may be acetylated at C-2. Fucoidans obtained from Cladosiphon okamuranus have an α-(→3)-linked-1-fucopyranose structure with sulfate groups at C-4. Some of the

fucose groups in the side chains may be O-acetylated (not shown) (Wu et al., 2016).

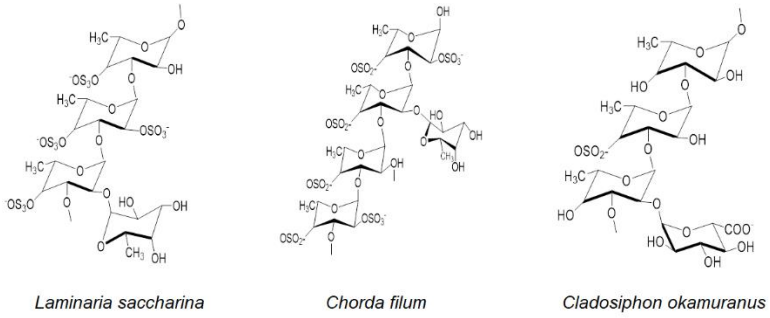


Figure 2. Fucoidans isolated from brown algea *Laminariales* and *Chordariales*

Isolation of fucoidan from brown algae species involves many stages. After cleaning the algae, it must be dried and ground. Alternatively, another method is to cut fresh macroalgae into pieces and place them in a dark, moist place to collect the resulting filtrate. Lipids, phenols, and proteins are then extracted using various solvents (e.g., ethanol, acetone, their mixture, or a mixture of chloroform, methanol, and water). As an alternative to traditional solvent extraction (with water, weak acid or ethanol), other procedures such as ultrasound-assisted extraction, microwave-assisted extraction, or enzyme-assisted extraction can also be used for fucoidan extraction (Hsu and Hwang, 2019). Extraction with ethylenediaminetetraacetic acid (EDTA) is another method used to obtain fucoidan. The prominent benefit of this process is that it allows simultaneous pigment removal with EDTA and high efficiency fucoidan extraction. The next step is purification, which is usually carried out using chromatographic methods or membranes, regardless of the previous protocol used to extract a particular polysaccharide (Hsu and Hwang, 2019; Myers et al., 2016).

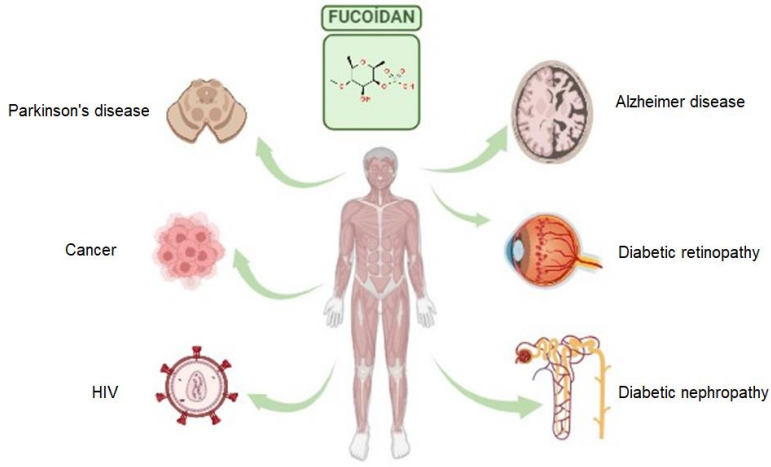


Figure 3. Biological activity of fucoidan and its effects on human health (Designed using the BioRender program)

Due to its wide range of biological activities, fucoidan is gaining popularity in medicine and pharmacy. Fucoidan is a non-toxic, biocompatible and biodegradable chemical authorized by the US Food and Drug Administration (FDA) as a food additive in the Generally Recognized as Safe (GRAS) category. The bioactivity of fucoidan is affected by various parameters, such as the presence of sulfate groups on it and the molecular weight of the polysaccharide. Some fucoidans have antioxidant (Lim et al., 2014), anticoagulant (Colliec et al., 1991), antibacterial (Marudhupandi and Kumar, 2013), antifungal (Phull et al., 2017), antileishmanial (Phull et al., 2017), anti-inflammatory (Apostolova) properties, 2020) and immunomodulatory (Peng et al., 2019) properties. Fucoidan, with high antioxidant capacity, is a promising therapeutic candidate for the treatment of various diseases. It was shown to reduce neuronal cell death and thus has been proposed as a strong pharmacological candidate in the treatment of neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease. Fucoidan inhibits cellular growth and the initiation of apoptosis, leading to the death of cancer cells. Fucoidan also helps maintain healthy kidney and eye function by regulating diabetic nephropathy and retinopathy. Moreover, fucoidan

possess antiviral properties and is a promising phytoactive pharmacophore for HIV treatment (Huang and Yang, 2016).

It is also suggested that fucoidan has a positive effect in the treatment of cancer patients by increasing the effectiveness of chemotherapy and reducing its negative effects (Hwang et al., 2016). Despite various publications on the versatile biological activity of fucoidan and numerous scientific findings regarding its use in drug delivery, no fucoidan-based medical product has been approved by the FDA. Therefore, it is only available as a regenerative, anti-cancer and anti-inflammatory factor in cosmetics, functional foods and dietary supplements for people with weakened immune systems, musculoskeletal, cardiovascular or intestinal diseases (Tsai et al., 2017). However, clinical studies have been conducted on fucoidan as a synergistic anticancer drug. Coadministration of fucoidan with anticancer drug has been shown to help reduce side effects and improve therapeutic outcomes of conventional anticancer therapy, while having no effect on plasma concentrations of the drug. In phase III-IV clinical studies, the effect of oligo fucoidan was investigated in lung cancer patients treated with platinum-based chemotherapy. Fucoidan has also been tested in patients with metastatic colorectal cancer given irinotecan, 5-fluorouracil, folinic acid, or bevacizumab (Huang et al., 2016). Fucoidan has also been shown to help reduce the negative effects of anti-cancer chemotherapy.

Pharmaceutical Properties of Fucoidan

Fucoidan is hygroscopic, light brown or yellow powder. It is insoluble in organic solvents, but soluble in water. Fucoidan solutions are not very viscous and the viscosity of aqueous fucoidan depends on many factors such as concentration, temperature, pH, molecular weight, degree of branching of the molecule and number of sulfate groups attached. As an example, basic properties of the fucoidan aqueous solution obtained from Laminaria japonica are given in Table 1 (Zha et al., 2012). The molecular weight of fucoidan tested was 10.5 kDa. It was determined that both fucose and sulfate groups had a composition of more than 27%. As the polysaccharide concentration increases, the pH of the solutions decreases,

but its viscosity increases without any signs of gelation (Pawar et al., 2019).

Table 1. Effect of fucoidan aqueous solution concentration on physical properties

Fucoidan Concentration (%w/w)	Colour	pH	Viscosity
1	Yellowish	5.23	-
2	Partly yellow	5.05	3.5
3	Yellow	4.96	4.2
5	Dark yellow	4.72	7.2
10	Brownish	4.61	18.8
20	Brown	4.47	100.8
30	Dark brown	4.45	507.0

Reference: Zha vd., 2012

Jae-Geun et al. determined that aqueous solutions of fucoidan isolated from Undaria pinnatifida, Laminaria religiosa, Sargassum fulvellum, and Hizikia fusiforme had low viscosity and pseudoplastic behavior (Jae-Geun et al., 1995; Jae-Geun, 1997). The presence of ions and extra-linked functional groups can affect the viscosity of fucoidan. When the fucoidan solutions obtained from Ascophyllum nodosum, Fucus vesiculosus and Saccharina longicruris were compared, it was seen that the fucoidan isolated from Fucus vesiculosus had the maximum viscosity. The viscosity of Cladosiphom okamuranus fucoidan solutions increases linearly with increasing polymer concentration (up to 2%) as well as with the addition of sugar, sodium chloride and calcium chloride (Obluchinskaya et al., 2021; Wang et al., 2019; Chen et al., 2018). Fucoidan molecules have been shown to be stable in both acidic and alkaline environments: they have been reported to remain stable in the pH range of 5.8 - 9.5. Fucoidan, unlike other polysaccharides, does not gel. However, when fucoidan is mixed with polymers with opposite net charges, gels can form due to electrostatic interactions. Fucoidan appears to be a valuable adjuvant in pharmaceutical technology due to its properties such as interacting with cytokines macrophages and growth factors. These properties allow the protection of the drug substance as well as increasing drug activity (Obluchinskaya et al., 2021; Cai et al., 2018).

Toxicity of Fucoidan

Fucoidan is a chemical that is non-toxic, biocompatible and biodegradable. Consequently, it can be used in pharmacy and biomedicine. Fucoidans from Fucus vesiculosus and Undaria pinnatifida have been certified as Generally Recognized as Safe (GRAS) food additives by the Food and Drug Administration (FDA) in the United States at doses up to 250 mg/day. Fucus vesiculosus preparations are registered in various countries of Europe. In one study, no changes were seen in rats given fucoidan from Laminaria japonica at 4000 mg/kg body weight for 7 days. When fucoidan was fed orally at a dose of 300 mg/kg body weight to animals, no significant side effects were observed, but when the dose was as high as 900 mg/kg b.w., blood clotting time increased significantly. 2000 mg/kg b.w. fucoidan from Laminaria japonica, did not cause changes in hematological parameters body weight, or food and water consumption, after 28 days of oral treatment (Fernando et al., 2019). Only two biochemical markers differed: Creatinine and triglyceride levels were substantially lower in rats given 0.9 percent saline solution. No difference was detected between the fucoidan-administered rats and control group in histological examinations of organs such as brain, heart, kidney and liver.

However, 600 mg/kg body weight of fucoidan obtained from Cladosiphon okamuranus, did not cause significant changes. At higher doses of 1200 mg/kg body weight per day, anticoagulant activity of fucoidan was seen. 1000 mg/kg b.w. of fucoidan isolated from Undaria pinnatifida, did not affect nutrition, body weight, hematological and biochemical parameters of rats, and no change in organs was observed examined microscopically. When the dose was at 2000 mg/kg body weight, hemoglobin concentration, high-density lipoprotein (HDL), and alanine transaminase levels changed significantly (Obluchinskaya et al., 2021; Fernando et al., 2019). Differences between studies point out that the toxicity of fucoidans is related to the fucoidan’s molecular weight, as well as the species from which they are obtained.

Subcutaneous application of fucoidan has also been tested for safety (Fernando et al., 2019). Subcutaneous and oral administration of fucoidan (molecular weight 10-300 kDa) obtained from Fucus vesiculosus and

Laminaria japonica (molecular weight 10-300 kDa) in dogs with hemophilia A had no adverse effects. Additionally, as a result, their hemostasis improved. A study conducted on horses reached similar conclusions regarding the safety of fucoidan. It was observed that the solution containing 2500 mg fucoidan injected intraperitoneally during abdominal surgery was not affected by laboratory test findings. The majority of measurements did not differ between the control and test groups, and neutrophils, leukocytes, antithrombin III, prothrombin and hematocrit values were found to be within normal limits (Obluchinskaya et al., 2021; Zayed and Ulber, 2019).

In addition, the genotoxicity of fucoidan was examined by both in vitro and in vivo methods. Fucoidan from Undaria pinnatifida (regardless of molecular weight) had no deleterious effects in bacterial reverse mutation and chromosome aberration tests at concentrations of 5000 g/plate and 5000 g/mL, respectively. Moreover, in an ICR mouse micronucleus experiment, fucoidan administration at doses up to 2000 mg/kg body weight showed no signs of genotoxicity (Obluchinskaya et al., 2021; Fernando et al., 2019; Zayed and Ulber, 2019).

The safety of taking fucoidan orally has also been studied in humans. Fucoidan isolated from Cladosiphon okamuranus was given to 20 healthy adult volunteers at a dose of 4.05 g of for two weeks. Low-density lipoprotein cholesterol and total cholesterol levels were found to be very low in the blood samples of these volunteers. As a result, the amount of chloride ions in the water increased significantly. However, the criteria defining the liver and kidneys remain the same. Similarly, administration of 300 mg of fucoidan isolated from Fucus vesiculosus or 100 mg and 1000 mg of fucoidan derived from Laminaria japonica, Macrocystis pyrifera and Fucus vesiculosus to individuals with osteoarthritis had no effect on blood test results or the changes were clinically insignificant.

Pharmaceutical Use of Fucoidan

Fucoidan can be delivered by forming various dosage forms (Figure 4), such as nanoparticles, microparticles, films and hydrogels. The ionic structure of fucoidan explains its widespread use in pharmaceutical technologies. Polysaccharide with a negative charge can form compounds with oppositely charged molecules. The most commonly used method of producing particles from fucoidan is polyelectrolyte complexation. Self-assembly, ionic cross-linking, coacervation and spray drying are some of the other ways. Various drugs (ciprofloxacin, doxorubicin, rifabutin, gentamicin, and isoniazid), growth factors (basic fibroblast growth factor) and proteins (β-lactoglobulin, bovine serum albumin) are carried by fucoidan-based particles (Lu et al., 2017). Fucoidan is important for its use not only as a drug release adjuvant but also as an independent molecule with therapeutic properties (Obluchinskaya et al., 2021; Cumashi et al., 2007).

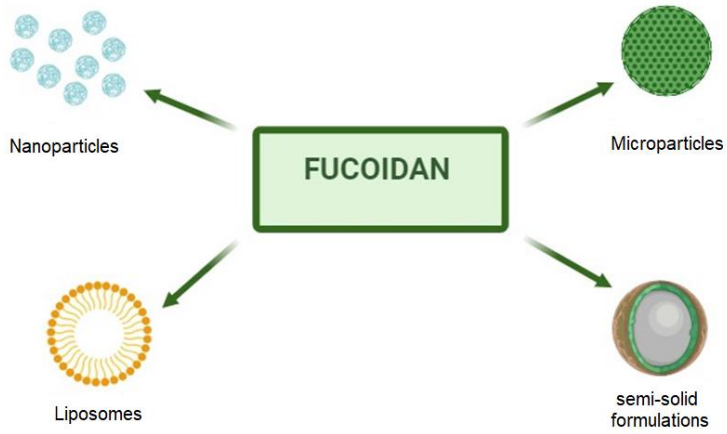


Figure 4. Use of fucoidan in different dosage structures (Designed using the BioRender program)

The main production technique of fucoidan nanoparticles is polyelectrolyte self-assembly, which allows the binding of a polyanionic molecule to a polycationic molecule. The polycationic molecule used in

most applications has been chitosan. Considering the documented bioactivity of both polymers, this combination was not only effective in drug delivery but also therapeutically useful (Venkatesan et al., 2022; Shannon and Abu-Ghannam, 2016).

Various preparation methods have been proposed for the synthesis of fucoidan nanoparticles. Different parameters need to be evaluated for each method. The most common method for synthesis has been polyelectrolyte cross-linking. In this method, various criteria such as initial polymer concentration, polycation type, pH of the solution, weight fraction of the polymer mixture, presence of cross-linker, and reaction time are important parameters. The structure of the proposed drug also affects the drug loading in fucoidan nanoparticles. To achieve high capture efficiency, positively charged drugs should be allowed to bind to negatively charged groups present on the surface of fucoidan. Positively charged pharmaceuticals act as cross-linking agents, resulting in fucoidan drug-loaded nanoparticles that improve drug delivery and control (Rajeshkumar et al., 2021).

During the production of fucoidan nanoparticles, uncharged drugs are kept sealed. The drug is dissolved in a solution of either fucoidan or a positively charged cross-linking agent. To modulate the drug release profile, various cross-linkers such as glutaraldehyde, and tripolyphosphate have been used to cross-link the produced chitosan/fucoidan nanoparticles. Some hydrophobic drugs are dissolved in the anti-solvent of the fucoidan solution and retained there during particle nanoprecipitation. At the tumor location, the majority of fucoidan nanoparticles exhibit sustained drug release that is pH dependent. Drugs encapsulated in nanoparticles are later released, allowing better targeting and accumulation in cancer cells (Obluchinskaya et al., 2021; Oliveira et al., 2020; Tran et al., 2020). Additionally, compared with natural fucoidan, fucoidan nanoparticles formed via encapsulation in liposomes showed better efficacy against osteosarcoma cells. The effect has been demonstrated in vivo in a xenograft model of osteosarcoma. Nanofucoidan increased permeability across the Caco-2 cell line (Tran et al., 2020; AlNadhari et al., 2021).

By Pinheiro and coworkers, hollow chitosan/fucoidan nanoparticles were formed using the layer-by-layer self-assembly method on polystyrene nanoparticles, and then treated with THF (tetrahydrofuran) for 12 hours. It has been determined that these nanoparticles have antioxidant and antibacterial properties (Pinheiro et al., 2015). The hollow nanoparticles are loaded with Poly-L-lysine, which has a 45 percent capture efficiency and a pH-dependent release pattern that can be further slowed by a cross-linker. These findings suggest that chitosan/fucoidan nanoparticles are capable of encapsulation of various bioactive substances (Hsu et al., 2017).

In another study, gemcitabine-loaded fucoidan/chitosan nanoparticles were evaluated in a human breast cancer cell line. Gemcitabine could be encapsulated with an efficiency of 35-42 %, 84 % drug released was reached in the first four hours. Compared to free gemcitabine, these particles had a 25% higher cytotoxic effect without increasing endothelial cell toxicity. Fucoidan/chitosan nanoparticles were also developed to prevent the degradation of proteins under gastric conditions. To treat inflammatory bowel disease, the particles were loaded with soluble eggshell membrane protein. Based on the principle of targeting fucose receptors by fucoidan, this protected the protein from degradation and enabled its transport to intestinal cells. Moreover, the particles worked together with the immunomodulatory function of fucoidan, enhancing the anti-inflammatory effect of SEP (Obluchinskaya et al., 2021; Zhang et al., 2015).

The cationic polymer polyethyleneimine has also been used to make fucoidan nanoparticles. The electrostatic interaction between the polymer aqueous solution at pH 7 resulted in the formation of empty nanoparticles. A similar process was used to make doxorubicin-loaded particle, which showed a higher cytotoxic effect against breast cancer cells (2.64-fold). The increased effect may also be attributed to the immune-modulating activities of fucoidan, as seen by the increase in plasma IL-6 levels and reversal of tumor-associated macrophage polymerization. The particles also altered the pharmacokinetics of doxorubicin, causing biphasic release with two drug peaks at 1 and 6 hours. This resulted in increased drug

accumulation in tumor cells (Obluchinskaya et al., 2021; Atashrazm et al., 2016).

In a recent study by Chu et al., tumor-targeting nanoparticles were created by combining PEG-gelatin, hyaluronic acid and fucoidan (Chu et al., 2019). Particles containing both epigallocatechin gallate and curcumin have been used to synergistically destroy prostate cancer cells. In the acidic environment of the tumor, the elaborated system exhibited pH-dependent release, optimizing its distribution in vivo. Due to the inclusion of hyaluronic acid and fucoidan, the particles were able to actively bind to CD44 and p-selectin receptors (Tocaciu et al., 2018).

The synthesis of hydrophobically modified fucoidan derivatives (e.g., acetylated fucoidan) capable of self-assembly into nanoparticles is another way to create fucoidan nanoparticles. Acetylated fucoidan nanoparticles were produced and loaded with doxorubicin for cancer immunochemotherapy. The drug's first-order release kinetics and loading efficiency were found to be 71%. It has been shown that particles can increase cell immunological responses while also reducing drug efflux across MDR cancer cell membranes (Obluchinskaya et al., 2021; Etman et al., 2021).

Chen and others synthesized nanoparticles from arginine-modified chitosan and thiolated fucoidan and examined their ability to transport both hydrophilic and hydrophobic drugs upon oral administration (Chen, et al., 2018). The particles were able to transport both FITC-dextran and curcumin across Caco-2 cells and exhibited pH-responsive structure, disassembly, and drug release. Fucoidan reduced P-glycoprotein efflux of drugs, while chitosan increased tight junction opening (Chiang et al., 2021).

Conclusion

Fucoidan is an important component in various medical formulations. It can be used as a medicinal ingredient or excipient, allowing the creation of a pharmacological form with the desired properties. However, the use of fucoidan in the pharmaceutical industry brings with it some difficulties. The diversity of properties of fucoidan is due to differences in algal growth conditions, pollution of the marine environment and the wide variety of

species that produce it. As a result, appropriate extraction and purification processes are needed to produce the raw material with the specified qualities. Sugar composition and sulfate content, as well as differential molecular weight (10-2000 kDa), affect the properties of fucoidan. Another disadvantage is the lack of gelling ability, which is an important feature in drug dosage form design. This limitation can be solved by mixing fucoidan with another substance. Fucoidan can be combined with polymers (derivatives of chitosan) or other compounds with a positive charge (polyallamine hydrochloride, polyethyleneimine, protamine, poly(lactide-co-glycolide), hexadecylamine poly(isobutylcyanoacrylate) and poly-l-orithin) (Obluchinskaya et al., 2021; Cai et al., 2018; AlNadhari et al., 2021). The wide range of biological activity of this polysaccharide contributes to the application of engineered drug carriers such as liposomes, microparticles, nanoparticles or semisolids. The use of fucoidan not only preserves the loaded active ingredient but can also increase its potency and increase the effectiveness of the treatment.

The use of fucoidan in the biomedicine and pharmaceutical industry and its potential in wide range of applications will likely continue to increase due to these properties. Fucoidan is a potential biopolymer that can be used to treat cancer in various ways. The polymer has excellent drug delivery properties and active targeting capabilities, as well as natural anticancer qualities. Fucoidan has recently been investigated in the context of cancer treatment with promising results in terms of efficacy and safety.

However, because fucoidan is a natural polymer, it requires extensive processing before it can be used medically, and the structure of the extracted polymer is highly dependent on the source. These mentioned factors can greatly hinder its use. Consequently, further research is needed to reveal robust structural activity linkages that will pave the way for the production of a polymer with the expected activity and possibly safety.

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CHAPTER 6

EFFECTS OF AGRICULTURAL NITROGEN POLLUTION on ECOSYSTEM, HUMAN HEALTH and BIODIVERSITY

Handan KARAOĞLU [1]
Fatih SEYIS [2]

[1]Assoc. Prof. Dr., Recep Tayyip Erdoğan University, Faculty of Agriculture, Department of Field Crops, Orcid: 0000-0001-6838-1856
[2]Prof. Dr. Recep Tayyip Erdoğan University, Faculty of Agriculture, Department of Field Crops, Orcid: 0000-0003-1028-162X

1. INTRODUCTION

The rapidly increasing human population on a global scale from past to present has dramatically increased the need for food and agricultural production, and in this context, the green revolution has come to the agenda and efforts have been made to meet the increasing food demand through the adoption of production systems in which various fertilizers are applied for various plants and the use of more efficient resources (Polat, 2018). In addition to fertilization and irrigation activities, approaches such as the application of advanced agricultural technologies, more effective utilization of agricultural land, and genetic improvements are thought to increase the yield of agricultural products and improve the possibilities of meeting the increasing food demand (Blanco, 2011).

The green revolution was also the period in which significant increases in the use of artificial fertilizers began in order to achieve higher yields per unit of agricultural area (Pingali, 2012). From this process to the present day, the use of artificial fertilizers has continued to increase dramatically. When FAO data are examined, it is determined that the total amount of fertilizer used in the world in 1961 was approximately 32 million tons and the share of nitrogen fertilizers in this amount was 38%, while the total amount of fertilizer used in the world in 1998 reached approximately 113 million tons and the share of nitrogen fertilizers in total fertilizer reached 72%. In 2019, it was determined that the total amount of fertilizer consumed in the world continued to increase and reached approximately 181 million tons and the share of nitrogen fertilizers increased to 87%. It has been observed that nitrogen fertilizers have almost never lost their title as the most intensively applied fertilizers worldwide since the green revolution (FAOSTAT, 2023). In addition to all these, various studies have shown that the size of land used for the production of plant and animal foods on the globe, which has a constant physical capacity, started to increase rapidly in the 1700s and reached its highest level in 2000. After the millennium, it was determined that a downward trend in the available agricultural land began and is still continuing (Ritchie, 2022). Therefore, while the world population and food demand continue to increase in parallel, the fact that agricultural land has started to decrease has further increased the pressure to provide products with the highest possible yield per unit area or living thing, making the use of fertilizers almost indispensable (Xiang et al., 2020). However, the intensive use of chemical fertilizers, especially nitrogen fertilizers, for more efficient agricultural production has brought many problems.

The main problems arising from intensive artificial fertilizer applications can be summarized as follows: damage or destruction of natural habitats, air,

water and soil pollution, soil acidification and crusting, decline in soil fertility, crop yield and quality, increase in the cost of agricultural production, significant losses in ecosystem diversity and biodiversity, disruptions in the functioning of ecosystems, eutrophication, global warming, damage to the ozone layer, failure to ensure food security, unhealthy food content, declines in drinking water quality and related health problems in animals and humans (Cüre, 2022). All these problems have led scientists to develop fertilizers that can both guarantee food supply security and are environmentally friendly, do not reduce the efficiency of nutrient uptake, and remain unwashed in the soil long enough for plants to benefit more effectively. In this context, organic farming practices, organic fertilizers, bio-fertilizers, slow-release or nano-fertilizers, or integrated nutrient management that combines the advantages of different fertilizers instead of artificial fertilizers, are recommended to producers today as an alternative to conventional agriculture carried out with intensive chemical use. It is also suggested that conservation tillage, cover cropping and crop rotation practices can be adapted to provide balanced nutrients to plants (Aykas et al., 2010).

In this review, it is aimed to contribute to raising awareness on the common responsibilities that all segments of society, including decision-makers, should assume in order to compensate for all these damaged components by addressing the health and environmental problems, ecosystem and biodiversity impacts caused by nitrogen fertilizers applied in excessive amounts without considering the consequences. It is thought that ensuring the continuity of implementation of sensitive solutions to compensate for the damage caused will be a challenging process, but it is also the only option that can provide a healthy, quality and sustainable life for current and future generations.

2. BASIC INFORMATION ABOUT FERTILIZERS

Fertilizers are substances of natural or artificial origin that are applied to the soil or plant organs to provide plants with the nutrients necessary for their development. They are applied to restore nutrients to the soil that have been depleted by crop harvesting, thereby improving soil properties and increasing yields at the next harvest. They are invaluable elements of sustainable modern agriculture, because the supply of quality, healthy and sufficient food to the growing world population is only possible with the right fertilization support (Sharma and Chetani, 2017; Usman et al., 2015). There are three main nutrients that plant cells need to maintain their normal physiological functions (Omidire et al., 2015) In addition to these macronutrients (N, P, K, etc.) and micronutrients (Zn, Mn, Fe, etc.), fertilizers can also contain various other elements and impurities (Sharma and Chetani, 2017).

Fertilizers can be classified in various ways according to the number (mono-nutrient, multi- nutrient,) and type (inorganic, organic, bio, macro, micro) of nutrients they contain, their physical structure (solid, liquid) and the way they are applied (foliar fertilizer, slow-release fertilizer) (Neue, 1993). Briefly defined, organic fertilizers are animal and plant wastes from agriculture such as blood meal, bone meal, plant stems. They are cost-effective and easily available from local products (Aksoy, 2001). Bio-fertilizers (microbial fertilizers): products that contain living microorganisms such as fungi or bacteria to promote plant growth and yield. They are markedly environmentally friendly, cost-effective and small in volume (Aboudrare, 2009). Inorganic fertilizers are chemical or artificial fertilizers. There is ample evidence that when properly selected and applied, they can significantly enhance soil properties and fertility and significantly increase crop yields (Gezgin, 2015; Scherer et al., 2005; Ojeniyi, 2000). Although they have advantages over organic fertilizers, such as higher nutrient content and solubility, hence rapid availability, sufficiency in smaller quantities, and being more acceptable than organic fertilizers, they are costly. They also cause significant damage to ecosystems, biodiversity and human, animal and environmental health if they are not properly selected, applied at the right time, in the right form and at the right dose (Mahajan Gupta and Sharma, 2008, Hijbeek et al., 2018). Each type of fertilizer is different in nature and function. They also have different advantages and disadvantages. Therefore, proper fertilizer management is an absolute necessity for both productivity and a healthy and safe environment. Therefore, a fertilization strategy that blends the use of chemical, organic and biofertilizers in a balanced way can be developed, implemented and evaluated (Trenkel, 1997).

Fertilizers generally contain the following nutrients in varying proportions:

2.1. Essential Macronutrients

Nitrogen (N): It is the main component of substances such as chlorophyll, amino acids and nucleic acids, which are crucial for plant cells and their functioning. It is therefore essential for photosynthesis and leaf growth.

Promotes the growth of leaves. Nitrogen deficiency results in poor growth and slow development, while nitrogen overuse delays ripening and reduces leaf quality

Phosphorus (P): Since it contains high-energy bonds in the ATP molecule, it is involved in many vital plant processes such as energy production and transfer, root, flower, seed and fruit development. In connection with these, it directly affects crop yield.

Potassium (K): Acts as an activator of enzymes used in photosynthesis and respiration. It promotes vigorous plant growth, movement of water within the plant, flowering and fruiting processes, and fruit flavoring (Mani, 2002).

2.2. Secondary Macronutrients

Calcium (Ca): It is present in the natural structure of the soil as compounds such as lime and gypsum and is involved in regulating the availability of nutrients in the soil and their transport to the plant. In this way, it affects plant growth. It also plays a role in the activation of some plant enzymes and photosynthesis. It also participates in plant structure.

Magnesium (Mg): It is one of the components of the chlorophyll molecule. Accordingly, it is involved in photosynthesis and plant nutrition. It is involved in numerous enzymatic reactions both as a carrier and as an effective activator.

Sulfur (S): A structural component of some amino acids and vitamins. It is also essential for the growth and functioning of chloroplasts. It is involved in the iron-sulfur complexes of the electron transport system of photosynthesis. It is important in the fixation of nitrogen (N_2) by legumes and in the conversion of nitrate (NO_3) first to amino acids and then to proteins (Mani, 2002).

2.3. Micronutrient Elements

Copper (Cu): Important for photosynthesis and the production of lignin, a cell wall component that increases durability. It is also important for grain production.

Iron (Fe): In plants, it is both essential for photosynthesis and acts as an enzyme cofactor.

Manganese (Mn): Very important for the construction of chloroplasts and therefore for photosynthesis.

Molybdenum (Mo): It is a cofactor for enzymes involved in amino acid production and plays a role in nitrogen metabolism.

Zinc (Zn): Activator for many enzymes. It is involved in the production of mRNA from the DNA template by transcription and accordingly has important functions in protein metabolism.

Boron (B): It is involved in many important functions in plants such as flowering, pollen germination, fruiting, cell division. It also protects plants against pathogen entry and infections.

Silicon (Si): Strengthens the cell wall and therefore plant structures. It makes plants healthier and more productive.

Cobalt (Co): It is especially necessary for *Rhizobium* bacteria, which establish a symbiotic relationship with legumes and provide them with carbohydrate needs, while converting the nitrogen of the air into a nutrient form that the legume can use by fixation, to fulfill this fixation function.

Vanadium (V): Used by some nitrogen-fixing microorganisms such as *Azotobacter*. It is used instead of the more common molybdenum or iron (Mani, 2002).

3. REASONS FOR THE USE OF ARTIFICIAL NITROGENOUS FERTILIZERS in TODAY'S AGRICULTURAL PRODUCTION SYSTEMS

Fertilizers are essential components of efficient agricultural production and have been the basis of world food production since the green revolution (Cui et al., 2018; FAI, 2020). While they cause significant decreases in product yield and quality when they are not applied adequately, it has been observed that they increase yields by 50%-100% in different crop production systems with the right application strategies (Gezgin, 2015; Cüre, 2022).

To guarantee food supply against growing demand, the world's agricultural systems aim to achieve the highest possible yield per unit area. To achieve this goal, they adopt a production style that uses not only artificial fertilizers but also various agrochemicals such as pesticides and herbicides. In other words, they try to eliminate any disruptions that could reduce crop yields. However, in the hope of higher yields, agrochemicals are applied in higher than recommended doses, in other words, in excess of the need.

is very common today (Shukla et al, 2022; Wang and Lu, 2020; Taban and Namlı, 2019), increasing input costs and decreasing production profit, environmental pollution (soil, water, air pollution), food pollution, decreasing food and drinking water quality, increasing greenhouse gas emissions, deterioration of soil structure, deficiencies in micronutrient content, damage and inability of beneficial soil organisms to function and thus decrease in soil fertility, biodiversity losses, certain health problems in humans and animals, even plants and beneficial microorganisms. Because in most agro-ecosystems around the world, about 20-70% of the intensively applied nitrogen fertilizers are transformed into different forms of pollutants and emitted into the environment (Qiao et al., 2015; Kopittke et al., 2019). The main reason for this is that excessive nitrogen fertilizer application reduces the efficiency of nutrient assimilation (Lubkowski, 2016), and some of this emission occurs through evaporation of nitrogenous compounds in the form of greenhouse gases, some through reaction with organic compounds in the soil, and the rest through leaching from the soil

and penetration into surface and groundwater (Körschens et al., 2013). Despite all these problems, it is impossible to achieve and sustain a healthy, qualified and sufficient food supply for the world's human and animal population without fertilizers (Yaylı and Kılıç, 2021). What is important here is to achieve quality, sufficient and sustainable food supply with a functional and rich biodiversity in a healthy and safe ecosystem without exploiting natural resources with the right fertilization approach.

As mentioned above, it is obvious that the misuse/excessive use of chemical fertilizers, which is far from scientific foundations, has a strong impact not only on human beings but also on all living and non-living components of the earth. In order to prevent these damages, which are very difficult to compensate, from becoming even more malignant or at least to start taking small steps towards improvement, it is very important that all segments of society develop a sensitive and conscious approach to the correct use of artificial fertilizers and other agricultural chemicals and ensure the continuity of this attitude together. Instead of these harmful artificial fertilizers, the use of new technologies such as organic fertilizers, controlled-release fertilizers, bio-fertilizers, which have more positive effects on both plant growth and soil health, can be expanded, or integrated fertilization programs that combine the unique advantages of all these fertilizer types can be carried out.

Impacts of Nitrogenous Chemical Fertilizers on Natural Resources

3.1. Water and Drinking Water Pollution

It is known that water, the most important natural resource after air, is the most important equation variable for the sustainability of life. From a biological point of view, it i s vital for the existence of all living things, from bacteria to the most advanced organisms, for all biochemical transformations that take place in their bodies and for their development. Moreover, all living organisms

More than 70% is composed of water. Therefore, a deterioration in water quality poses a serious threat to the ecosystem and biosphere's ability to interact in a balanced and healthy manner and to the health of living organisms (Bibi et al., 2016). And unfortunately, many countries around the world have sufficient freshwater but face the risk of this precious resource becoming unsafe to use as a result of mistakes in agricultural and industrial activities (Pawari and Gawande 2015).

It is an accepted fact that nitrogen fertilizers have been increasingly applied in agricultural areas around the world since the green revolution and that nitrogen

fertilizers are the most widely applied of all fertilizer types (FAOSTAT, 2023). In addition, it has been determined that 20-70% of the nitrogenous compounds contained in fertilizers are lost before they can be used due to rainfall, runoff from the soil surface, agricultural drainage and erosion (Kopittke et al., 2019) if they are applied at values exceeding the actual need (Shukla et al., 2022; Wang and Lu, 2020; Taban and Namlı, 2019), as many producers do. It has been observed that even if nitrogen fertilizers are applied under the most favorable conditions, plants can only utilize about 50% of it, 2-20% of the remaining part evaporates as greenhouse gases, 15-25% interacts with existing organic compounds in the soil, and 2-10% leaches into surface waters and groundwater resources, where they turn into important pollutants (Sönmez and Demir, 2011; Körschens et al., 2013).

Nitrogen compounds [nitrate (NO_3), nitrite (NO_2) and ammonium (NH_4)] are the main pollutants of the aquatic environment. Therefore, nitrogen pollution in surface, groundwater and drinking water is mostly caused by the unconscious use of nitrogen fertilizers [Varol and Davraz, 2015; Yue et al., 2018]. These polluting compounds in water can be caused by intensive fertilization in crop production as well as poor waste management of farm manure, which is released as a by-product in animal production (Yaylı and Kılıç, 2021).

Nitrogenous compounds that seep deep from the soil surface and enter groundwater sources are of serious concern. This is because research results have shown that nitrate pollution in groundwater sources is often not localized but spreads over very large areas, and it has been shown that nitrate pollution in groundwater, which is often used as a source of drinking water in the world, is often at high levels that far exceed the self-cleaning capacity of these environments (Fenton et al., 2009). This situation has striking consequences (İkincikarakaya et al., 2013).

The upper permissible limit of nitrate concentration in drinking water is set by the World Health Organization (WHO, 2017), the Turkish Ministry of Agriculture and Forestry (MoAF, 2020) and the EU Drinking Water Directive (EU, 2008) at 50 mg/l nitrate (NO3), equivalent to 11.3 mg/l nitrogen (N) (Ward et al., 2018). However, Canadian water quality guidelines set the upper limit for long-term exposure at 13 mg/l nitrate (equivalent to a nitrogen concentration of 2.9 mg/l) (CCME, 2013). Other studies have recognized two different maximum acceptable concentrations for surface and groundwater bodies, 25 and 50 mg/l nitrate (equivalent to 5.65 and 11.3 mg/l nitrogen), respectively (PellicerMartínez and Martínez-Paz 2016).

Despite all these limitations and action plans, nitrate levels in drinking water have been reported to be higher than the upper permissible limit in many different countries around the world (Liu et al., 2009; Mohsenipour et al., 2014; Kuştul et al., 2020). Therefore, due to the known harmful effects on the environment and human health, it is of great importance to determine the level of nitrate and similar nitrogen compounds in water, to control them periodically and to try to keep them within the limits in accordance with the standards in order to provide healthy drinking water [Kuştul et al., 2020]. For this, the right fertilization approach in plant production and the right waste management in animal production are very important (Yaylı and Kılıç, 2021).

3.1.1. Effects of Water Pollution From Agriculture on Human Health

One of the most important indicators of water pollution is nitrate, a key component of nitrogen fertilizers (Yue et al., 2018). Nitrate is the most common form of dissolved nitrogen found in surface and groundwater. A wide range of health problems have been found to occur when nitrate concentration exceeds 50 mg/L in drinking water or when high nitrate accumulation occurs in the body.

For humans and animals, rather than the nitrate compound itself in the body, the conditions in the digestive tract and the reduction of this compound to nitrite with the help of intestinal flora show toxic effects (Ağaoğlu et al., 2007). The resulting nitrite compound causes a condition known as "Methemoglobinemia" (blue baby disease) in humans, especially in infants, which is known as a decrease or disappearance of the blood's ability to carry oxygen. This condition, which is more common when well water with a nitrate concentration above 45mg/L is consumed as drinking water, is formed due to the transformation of hemoglobin into methemoglobin, which cannot bind to oxygen, as the charge of iron in hemoglobin increases from +2 to +3. The harmful effects vary from difficulty breathing, bruising, loss of consciousness, unconsciousness, fainting and death (Rodríguez-Maroto et al., 2009). It is a combination of congenital heart defects leading to cyanosis (bluish purple skin) (Ahada and Suthar 2018). In infants, the reduction of nitrate compounds ingested through contaminated water to nitrite in the digestive tract has been found to cause methemoglobinemia and stomach cancers, as well as abnormal pain, birth defects in the central nervous system and diabetes (Vasanthavigar et al., 2010).

In adults, continuous consumption of drinking water containing high levels of nitrate for 6 months can lead to death, while long-term consumption of nitrate-contaminated drinking water is known to cause cancer (Moon et al., 2006). It has been determined that high nitrate levels in drinking water can cause nervous

system diseases and heart rhythm disturbances in humans (Gunatilake and Gunatilake, 2004). It has also been found to increase the risk of cancer in the digestive system and cause problems in the urinary tract (Wasik et al., 2001).

High levels of nitrate in pregnant women through drinking water have been found to cause miscarriages (Rodríguez-Maroto et al., 2009), low birth weights and stillbirths (Atasoy et al., 2011).

On the other hand, increased nitrate concentrations in drinking water have been shown to cause significant health problems such as high blood pressure (Malberg et a l ., 1978), goiter (Seffner, 1995), thyroid dysfunction (Van Maanen et al., 1994), cancers, and increased digestive system disorders (Rodríguez-Maroto et al., 2009). In fact, it was found that long- term consumption of drinking water with nitrate contamination between 11-16 mg/L can cause hyperthyroidism, and long-term consumption of drinking water with nitrate contamination between 19-26 mg/L can cause spontaneous abortions in women (Rodríguez- Maroto et al., 2009).

(Burkholder et al., 2007). It is also known to trigger immune system damage and the emergence of various hereditary diseases (Weyer et al., 2002). Nitrate, which enters the human body through water and food containing high levels of nitrate, is first reduced to nitrite, and then nitrite is converted into nitrosamine compounds as a result of interactions with secondary amines. Nitrosamines are known to be toxic, teratogenic, embryopathic, mutagenic and carcinogenic compounds (Ekici et al., 2008). Nitrosamines have been found to cause cancers in the stomach, intestines, liver and kidneys, non-Hodgkin's lymphoma (Özdemir et al., 2007), as well as high blood pressure and birth defects (Sönmez, 1992).

In addition, carcinogenic substances such as nitrate and related nitrosamines can accumulate in the structures of plants grown in soils and water where high levels of nitrogen fertilizers are used, so the consumption of these foods can be harmful and pose serious threats to human health. (Taşkaya, 2004; Ebenstein, 2008).

In addition, the leaching of these nutrient compounds from the soil into aquatic ecosystems, especially as a result of the overuse of nitrate and phosphate fertilizers, leads to eutrophication, where algae multiply excessively and completely cover the environment. When exposed to the toxins of some of these algae, people may also face problems such as skin rashes and stomach pain (Garnier et al., 2010; Farm Sanctuary, 2014). Another negative effect of eutrophication in aquatic ecosystems can be defined as the stagnation of water by preventing its normal flow due to increased plant density. In this stagnant aquatic

environment, infectious pathogens m a y increase rapidly. Contact with water harboring these pathogens can cause diseases caused by these pathogens in humans. Thus, nitrogen fertilizer pollution in water can cause many unexpected health problems. (Ebenstein, 2008).

Consuming the products of livestock that drink contaminated water or are exposed to contaminated water, or consuming the livestock themselves as food, also causes harmful chemicals in contaminated water to accumulate in the body. These toxic compounds cause health problems such as weakened immune system, inflammation, infertility and similar reproductive disorders, respiratory and gastrointestinal system diseases, cancer, and even death in humans (Juneja and Chauhdary, 2013).

3.1.2. Effects of Agricultural Water Pollution on Animal Health

Since water is an essential compound for the life of all living things or the habitat of many living things, water pollution has a direct impact on the health of both flora and fauna. Water pollution causes the death of fish, water birds, molluscs, seaweeds and many other marine or freshwater creatures that can be consumed as human food, and when it does not cause death, it accumulates in their bodies and when these creatures are consumed by humans as food, these harmful chemicals in their bodies enter the human body. In humans, these pollutants accumulated in adipose tissue or other tissues can suppress the immune system and exhibit toxic, allergic and inflammatory properties. These harmful chemicals, which can even accumulate in the eggshells of waterfowl, can reduce waterfowl populations (Owa, 2013).

An important harmful effect of intensive use of nitrogen fertilizers is eutrophication. Eutrophication can be defined as the growth of aquatic plants and algae at a density that covers the entire water body when nutrients in the form of nitrogen compounds increase in water. Due to the resulting decrease in oxygen, aquatic species such as fish can die, and the bad odor and increased water pollution caused by their decay can harm recreational activities. It can also lead to the proliferation of unwanted species. In another aspect, eutrophication causes the water to become cloudy, damaging the ability of aquatic organisms to find food and feed. It also clogs the gills of fish. Some algae that proliferate due to eutrophication produce toxins that can cause illness or death in dolphins, turtles, fish, seabirds and shellfish. In addition, nitrogen compounds that enter the bodies of ruminants through consumption of nitrogen-contaminated water have been shown to cause health problems such as stomach cancer, goiter, birth defects and heart disease. Therefore, the pollution caused by artificial nitrogen fertilizers

causes serious damage to biodiversity (Garnier et al., 2010; Farm Sanctuary, 2014).

3.1.3. Air Pollution

Air is a natural resource of primary importance for the survival of living organisms on earth. For this reason, pollutants that change the natural composition of the air cause very important health problems in living organisms. Intensive agricultural production is one of the major contributors to the release of harmful nitrogen oxides (NO, N_2 O, NO_2) and other greenhouse gases (NH_3 , CO_2 , CH_4 , etc.) that cause global warming.

is recognized as an important source of global warming. Among agricultural factors, the largest source of these global warming emissions has been identified as excessive application of nitrogen fertilizers (Wang et al., 2017). Greenhouse gases such as N_2 O (di nitrogen monoxide or nitrous oxide), other nitrogen oxides and NH_3 (ammonia) are released into the air by bacteria from over-fertilized soils. Among these gases, N_2 O is a major pollutant with a greenhouse effect 310 times stronger than carbon dioxide (Rütting et al., 2018). In addition, alkaline N_2 O and ammonia (NH3) react with acidic gases (such as SO_2) in the atmosphere and turn into acids such as nitric acid and acetic acid, triggering the formation of acid rain (Sharma and Chetani, 2017). Again, these greenhouse gases (N_2 O and NH_3) react with acidic gases in the air and promote the abundant formation of the pollutant P.M2.5, a harmful particle (Huang et al, 2016). In addition, these greenhouse gases, especially N_2 O, a type of reactive nitrogen, have the ability to increase global warming by damaging the system that reduces carbon dioxide and thus global warming (Gu et al., 2018). Another harmful feature of reactive nitrogen such as N_2 O is that it damages the ozone layer, preventing it from trapping ultraviolet radiation (Cooper et al., 2017). Methane emission from paddy fields is also an important agricultural problem whose concentration is intensified by ammonium-containing fertilizers. Methane, an important greenhouse gas, has the potential to amplify the greenhouse effects of carbon dioxide and nitrous oxide that can promote global warming (Chen, 2006). In addition, greenhouse gases such as CO_2 , CH_4 , CH , N_2 O have also been found to be released during the production of nitrogen fertilizers and contribute to the existing harmful effects (Cooper et al., 2017).

3.1.3.1. Effects of Air Pollution on Human Health

To briefly summarize the causes of air pollution originating from intensive agriculture: as mentioned above, it can be said that excessive use of nitrogen fertilizers and errors in the storage and management of farm manure, which is a

by-product of animal production, cause the emission of nitrogen oxides (NO, N_2 O, NO_2) together with other greenhouse gases, leading to air pollution, greenhouse effect, ozone depletion, acid rain and high amounts of particulate matter (PM2.5) accumulation in the air we breathe.

Exposure to PM2.5 particles, which are formed due to the presence of NH_3 and N_2 O in the atmosphere, has been associated with health problems such as premature deaths, asthma and similar respiratory diseases, and methemoglobinemia in infants in India (Bishnoi, 2018; Huang et al., 2016). Similarly, it ranks first in the world in terms of nitrogen fertilizer use.

In China, agricultural PM2.5 pollution is the 4th leading cause of death (Lim et al., 2012). Exposure to this particulate matter (PM2.5) has been found to have negative effects on human health such as respiratory problems, cardiovascular problems, and various lung diseases (Gao et al., 2018). In another long-term study conducted in Sao Paulo, Brazil between 1996 and 2010, it was found that the morbidity (morbidity rate) of respiratory diseases increased by 2.43% due to the increase in $N2O$ concentration (Bravo et al., 2016).

Long-term exposure to air pollution is commonly associated with the development of respiratory diseases such as heart disease, lung cancer and emphysema, and can also damage the nervous system, kidneys, liver and other organs. These negative consequences are predicted to increase due to the overuse of agrochemicals.

It has also been found that the destruction of the ozone layer due to greenhouse gas emissions leads to an increase in skin diseases and cancers when humans and animals are exposed to ultraviolet radiation that cannot be trapped by ozone (Cooper et al., 2017). In addition, acid rain, which occurs when alkaline greenhouse gases react with acidic gases in the atmosphere, has been observed to damage vegetation, aquatic ecosystems and buildings (Sharma and Chetani, 2017).

3.1.4. Soil Pollution

Soil is the natural environment where not only soil organisms but also plants settle, feed and live. In the ecosystem, it is the system where both nutrients are decomposed and the nutrient and water cycle takes place. Since it undertakes many different functions, whether it is healthy and efficient directly affects the yield in agricultural production. In order to maximize the yield in agricultural production and feed the growing population, the application of chemical fertilizers by farmers has become necessary in today's agriculture. However, for

efficient production, fertilization must be carried out at the right time, with the right fertilizer, at the right dose and with the right method. In order to choose the right fertilizer, soil and leaf analyses are required to determine the missing nutrients. Indiscriminate and excessive application of fertilizers to agricultural areas without soil analysis can lead to undesirable situations such as soil compaction, acidification, deterioration of its structure, imbalance of the nutrients it contains and crop quality. Consequently, all this leads to a decrease in both soil and plant fertility and product quality (Zaman et al., 2022). The application of fertilizers to agricultural fields in larger quantities than recommended in the belief that it will provide higher yields has become quite common in today's agricultural world (e.g., Taban and Namlı 2019). However, contrary to expectations, the benefit from intensive fertilization increases up to a certain level, after which intensive fertilization starts to harm rather than benefit (Şahin, 2016). Moreover, it harms not only agricultural production but also human and environmental health.

Excessive application of nitrogenous synthetic fertilizers also leads to acidification of soil pH and formation of soil crust, reducing organic matter and humus content. Nitrate (NO_3), which cannot be utilized by plants and mixes into the soil, kills beneficial microorganisms that perform biological nitrogen fixation, leading to deterioration of soil structure, loss of the fertile top layer by erosion, increased salinity and reduced yields (Smith and Siciliano, 2015; Arora, 2016). It also reduces nutrient utilization efficiency. It has been found that intensive nitrogen fertilizer applications in China and India (about 4 times higher than the world average) have reduced nitrogen use efficiency (the ratio of harvested product for nitrogen input) in agricultural production to half of the world average (Adhya et al., 2010; Cui et al., 2018).

All these negative changes can lead to an increase in harmful organisms in the soil. Soil acidity increases the concentration of toxic ions in the soil, reduces phosphate uptake by plants and inhibits their growth (Cooke, 1982). With the decrease in organic matter and humus in the soil, the nutrient storage capacity of the soil decreases. The intensive application of nitrogen fertilizers to agricultural fields destroys the balance between the three macronutrients (N, P and K), resulting in deficiencies in plant micronutrients. In addition, it damages the fertile top soil layer, reducing both soil and crop yields. Sandy soils are more prone to soil acidification than clay soils. Clay soils can buffer the effects of intensive synthetic fertilization. (Kaplan and Sonmez, 2007). In addition, repeated or intensive application of nitrogenous synthetic fertilizers increases the amount of nitrate in the soil and then in vegetables such as lettuce and spinach or plants such

as fruits and grains to levels that threaten human health (Atılgan et al., 2007; Sattar et al., 2014).

3.1.4.1. Effects of Soil/Food Pollution on Human Health

Today, quality and safe food is of great importance in maintaining human health. If the food content does not meet health standards, the associated risks can lead to many digestive disorders and diseases such as cancer. In this context, food-related health violations are very dangerous. This is because poor quality food has claimed the lives of around 420,000 people worldwide, and unhygienic food products have claimed the lives of around 600 million people.

The intensive and unbalanced use of nitrogen-based synthetic fertilizers to ensure high yields in agricultural production increases the levels of nitrate in fruits and vegetables such as watermelon, strawberries, cabbage, spinach, beetroot and so on. In addition, the nitrate content in meat and meat products also increases as a result of the treatment of these foods with nitrate compounds that give them color, taste and long-term storage properties (Abdumuminova et. al., 2021).

Excess nitrate intake through contaminated drinking water, vegetables and fruits has been found to cause significant health problems, especially in children and the elderly. Nitrate compounds taken into the body are absorbed in the stomach and most of them are excreted in the urine within 8 hours. However, high intake can cause poisoning. Symptoms of nitrate poisoning include a markedly enlarged stomach and liver 1-6 hours after ingestion, yellowing of the whites of the eyes, weakness and digestive difficulties. In addition, certain effects such as severe headache, dizziness, darkening of the eyes, drowsiness, inability to move properly may also occur.

Research has shown that nitrate in food and water is harmful to humans, causing various cancers and methemoglobinemia. It has also been found that nitrate has a vasodilating effect and causes a drop in arterial blood pressure, sinus arrhythmia, chest pain and shortness of breath. However, it has also been shown to have certain benefits for the body and standards have been set for the permissible daily intake of nitrate in food (Abdumuminova et. al., 2021).

The most well-known benefit of nitrate and nitrite, which are converted into nitric oxide when taken into the body, has been found to have positive effects on the cardiovascular system. Recently, recipes containing nitrate have been developed to protect against infectious diseases and to protect the heart and blood vessels. Animal studies have shown that nitrite and nitrate in the body lower

blood pressure through their antioxidant effects. Blood The conversion of nitrate to nitrite and nitric oxide has been shown to be the reason for this decrease in pressure. In this context, it can be said that the benefits and harms of external nitrate intake into the body should be well examined. Nevertheless, it is useful to limit the amount of nitrate that the elderly and infants take into their bodies through food or water.

According to the World Health Organization, the permissible amount of nitrate in foods is 3.7 mg per 1 kg per day for adults and 222 mg for an adult weighing 60 kg on average. It has been determined that daily nitrate consumption exceeding these values is harmful to human health (Abdumuminova, et. al., 2021).

3.1.5. Harmful Effects of Nitrogenous Chemical Fertilizers on Plants

It was determined that the amount of salt in the soil increased in case of intensive use of nitrogen chemical fertilizers. It was observed that the tips of the plant structures were damaged and turned brown and the lower leaves of the plants turned yellow due to the increased amount of salt. It was observed that the intense fertilizer and the salinity caused by it damaged the roots, loosening the roots and decreasing the ability to absorb water. As a result, it was determined that the tendency of the plants to wither and lie down increased. All these negativities result in decreases in crop yield and quality (Bhattacharyya et. al., 2016).

Another damage caused by the intensive use of fertilizers on plants was found to reduce the colonization of mycorrhizal fungi in the roots. When these conditions occur, *Rhizobium* bacteria responsible for fixation, which convert nitrogen in the air into nitrogen that the plant can use as nutrients, are unable to fulfill their duties (Wauters et al., 2010).

In addition, it has been determined that mycorrhizal fungi provide benefits to plants with which they establish symbiotic relationships, such as promoting plant growth by increasing the absorption ability of the root and converting certain minerals into a form that the plant can use, and making plants more resistant to soil-borne infections and some other diseases by strengthening the roots (Özgönen, 2014). The negative effects of fertilizers on the symbiotic relationship established with mycorrhizal fungi deprive plants of all these advantageous interactions and negatively affect their development and yield.

3.2. Effects of Animal and Plant Production Wastes on Environment and Human Health

According to Ministries of Agriculture and Environmental Protection Agencies, agricultural waste is not only agricultural chemicals such as farmyard manure, artificial fertilizers and pesticides, but also any waste material, organic or inorganic, solid or liquid, resulting from the cultivation, care, breeding, harvesting, processing and marketing of plants and animals. In this context: farm manure, urine, artificial fertilizers, litter/bedding material, dirty water from washing animal shelters, slaughterhouse wastewater, waste milk, waste feed, animal carcasses, animal viscera, blood, horns, bones, fur, placenta, birth fluids and tissues, fetal membranes, fetuses excreted from the body of the mother animal as a result of abortion, shells of nuts (walnuts, almonds, etc.), grain shells, sugar, etc.), grain husks, sugarcane bagasse, waste wood, used paper and plastic packaging, obsolete machinery and equipment parts (Ashworth and Azedero 2009). All of these wastes pose serious risks to the health and environment of people living near agricultural holdings or farm workers.

Research on agricultural workers has shown that in most parts of the world, women are usually employed as farm workers and are often responsible for the cleanup and disposal of livestock waste. It has also been found that women are much more involved in agriculture than men, both as business owners and as workers, and are therefore more vulnerable to the harmful effects of agricultural waste (United States Department of Agriculture USDA, 2013). The average daily manure production of a dairy cow is 43 kg, fattening cattle 29 kg, sheep

2.40 kg, goat 2.05 kg, meat chicken 0.19 kg and egg chicken 0.13 kg (Yağlı and Koç, 2019). Based on this, it can be said that especially dairy cows produce 20 times more waste than humans and these wastes are accumulated in random open-top storages. As the amount of manure increases or the warehouses fill up due to rainfall, its content seeps into nearby lands or aquatic ecosystems, causing an unaesthetic appearance and serious pollution. As a result of this situation, which is defined as non-point source pollution, it has been observed that in addition to nitrogenous compounds, drug-resistant bacteria and some other microorganisms are also spread to the environment (National Resources Defense Council (NRDC), 2013). In addition, it has been observed that employees of animal production facilities or people living in the vicinity inhale the unbearable odor and many harmful gases such as ammonia, hydrogen sulfide, carbon dioxide, etc. released during manure decomposition. Hydrogen sulphide, which is known to be the most harmful of the gases released, has been found to cause significant health problems such as shortness of breath, cough, asthma,

bronchitis, sore throat, runny nose, burning eyes, headache, fatigue, nausea, diarrhea, tension, and depression.

It has also been reported that nitrate compounds leaching into groundwater are associated with blue baby syndrome, which causes death in infants, and spontaneous abortions in women (NRDC, 2013). In another study, it was found that long-term consumption of drinking water with nitrate contamination between 11-16 mg/L can lead to hyperthyroidism, while nitrate contamination of 19-26 mg/L can induce spontaneous abortions in women (Burkholder et al., 2007).

The U.S. Department of Environment, Food and Rural Affairs (2012) stated that pregnant women and their unborn babies should avoid contact with farm animal waste, including birth and postpartum fluids and fetus excreted from the mother animal's body after abortion, as exposure to these wastes can threaten the health of pregnant women and their unborn babies, and pregnant women may experience a zoonotic infection with fever and flu-like symptoms. They also noted that slaughterhouse waste, such as bones and viscera, and similar animal wastes pose major problems for environmental health and aesthetics, in addition to their harmful effects on human health.

It has been found that if all the manure in a manure tank that breaks down for any reason reaches a nearby aquatic ecosystem, it can cause mass mortality of aquatic organisms such as fish that live there. However, two key nutrients in animal feces, phosphorus and nitrogen, have been found to often cause eutrophication when they leach into water bodies. That is, the introduction of high amounts of phosphate and nitrate into aquatic habitats has been shown to trigger the overgrowth of algae, leading to oxygen depletion and the death of other organisms sharing the same environment (Farm Sanctuary, 2014).

Vegetable wastes generated from harvesting and product processing during crop production are also included in the scope of agricultural wastes. Crop wastes such as cereal husks, legume husks, sugarcane bagasse, vegetable and fruit peels, root and tuber shells are usually burned in bulk for disposal. As a result of this process, toxic substances such as nitrogen oxides, carbon monoxide, volatile organic compounds, which create particle pollution in the environment and threaten human health, are released into the air (USEPA, 2014). Another study on the harms of burning agricultural waste showed that 40% of carbon dioxide, 32% of carbon monoxide, 20% of particulate matter and 50% of polycyclic aromatic hydrocarbons released into the environment worldwide are released by burning plant waste such as grass, leaves, stems, straw, bark and wood. This waste incineration process is considered to be one of the most important sources

of dioxins due to the agrochemicals absorbed by the plant waste to be incinerated. The most intensive week for the incineration of plant waste in Taiwan It has been reported that dioxin concentration in the atmosphere is up to 17 times higher than in weeks without incineration. Similarly, in China, dioxin emissions in provinces with more intensive agricultural production were found to be higher than in other provinces (Environmental Cooperation Commission, 2014) (CEC, 2014).

The most important reasons why dioxins pose a problem for health and the environment are that they remain unchanged in the soil for a very long time, they are stored in the fat tissues of animals and humans, they can travel very long distances in the atmosphere, and they can be found in places very different from the areas where they are produced. Women exposed to dioxins may experience reproductive system problems such as prolonged menstruation, early menopause and, if pregnant, neurological problems in the fetus. In addition, regardless of gender, fluctuations in thyroid hormone levels and cancer can also be seen due to dioxin exposure, as well as acne-like rashes called chloracne in areas such as armpits, cheeks and behind the ears (CEC, 2014).

Market areas also generate large amounts of agricultural waste from fruits, vegetables, cereals and pulses. These wastes can reach 10 metric tons per day and create environmental pollution as they are left in the market area (Arati, 2006).

When these high amounts of plant and animal wastes originating from agricultural processes are recycled with the right methods, it is thought that useful products that can be used for different purposes such as biogas, animal feed, compost, bio-fertilizer can be obtained and can provide significant additional income to farmers. In addition, since agricultural wastes will be greatly reduced by recycling, natural resources in the environment will also be protected. For example, it has been determined that renewable energy resources obtained from recycling rice waste can be used to fuel various agricultural machinery, and in this way, farmers can reduce input costs by producing their own fuel (Gagelonia, 2013; Essiet, 2014). Similarly, briquettes produced by recycling vegetable wastes such as saw dust, cotton stalks, peanut shells and rice husks were found to be cheaper, have lower ash content and higher combustion potential than coal (Sabiti, 2011).

Since recycling of agricultural wastes is not yet widespread and directives on the management of these wastes are not complied with, these wastes have the potential to create serious environmental and health problems as mentioned above. The wastes generated during the production, processing and marketing of

agricultural products have the potential to cause serious environmental and health problems.

The damage caused by agricultural wastes is both inconvenient and regrettable in many respects. Therefore, it has become imperative for sustainable production, the environment and human health to pay utmost attention to the management of agricultural wastes. Sustainability is the state in which humans and nature can exist in productive harmony. It is the creation and continuity of conditions in which all the needs of present and future generations can be met. It is possible in the presence of healthy and functional ecosystems and this is the process that can offer humanity a quality life. For this reason, it is an indispensable equation variable for the future of humanity that agriculture, the most widespread and oldest human activity on earth, is carried out in a nature-friendly, scientific manner without exploiting resources.

3.2. Impacts of Agriculture and Nitrogenous Fertilizers on Biodiversity

In order to meet their basic needs such as nutrition and shelter, human beings have radically altered about half of both terrestrial and wetland areas of the globe (Ceballos et al., 2015; Polat, 2018). In other words, natural ecosystems have been transformed by humans on a global scale and to the extent of exploitation, and predictions from various studies have shown that this exploitation will continue to increase in the future (Sage, 2020). Due to these transformations, which have occurred faster than the ability of wild populations to develop adaptations, the extinction of many species has reached the highest extinction level in the last 65 million years. As these rapid ecosystem transformations are predicted to continue in the future, the trend of declining biodiversity is expected to continue (Ceballos et al., 2020). Declining biodiversity means that ecosystem diversity is impoverished and the functioning of existing ecosystems is severely impaired. Therefore, it is becoming increasingly difficult to sustain vital needs such as clean air, clean water, stable climate, fertile soil and sufficient food (Newbold et al., 2015).

Agriculture, the oldest and most widespread activity of humankind, is the most important cause of biodiversity loss, which is one of the global and major problems of today's world. Agricultural factors that harm biodiversity are the expansion of agricultural areas from the past to the present and the pollution caused by the intensive use of agricultural chemicals such as fertilizers. The expansion of agricultural areas triggers the loss of natural habitats, while agricultural pollution renders existing habitats uninhabitable. The consequences of both situations are quite striking (Cordier et al., 2021). The human-induced

loss of natural habitats is one of the main causes of the endangered species on the IUCN (International Union for the Conservation of Nature) Red List (IUCN, 2015).

It has been identified as the primary threat for 85% of all species in danger of extinction. The most important trigger of natural habitat loss is agriculture, as mentioned above.

Today, anthropogenic factors, especially agriculture, threaten many species from many different groups (Díaz et al., 2020). However, amphibians have been identified as the most endangered vertebrate taxon globally (IUCN, 2023; Harfoot et al., 2021). When the 2023 data of the IUCN organization are examined, it is seen that the worldwide decline rate of amphibians is 41%, and the most important threat, which ranks first among the main factors threatening amphibians, is agriculture. Fish follow amphibians with a 34% decline rate, while agriculture ranks third among the factors threatening fish. According to IUCN data, the worldwide decline rate of mammals is 26% and agriculture ranks third among the main threat factors of these creatures. While the rate of decline of reptiles is 21%, agriculture ranks first among the threats of reptiles, just like amphibians. The global decline rate of birds is the lowest among other vertebrate taxa, at 12%, and agriculture ranks third among threats to birds. Invertebrates are also highly vulnerable to agriculture. For example, the global decline rate of crustaceans is

40%, agriculture ranks first among the current threat factors. In addition, agricultural production is highly detrimental not only to animal biodiversity but also to the biodiversity of plants not involved in agricultural production. For example, the Cycadales, a group of decorative, palm-like trees, have a very serious decline rate of 70% worldwide and agriculture ranks second among the threats to these trees. In the case of conifers (Coniferae), agriculture is the second most important threat and their decline rate is 34% worldwide. As can be seen from the data, agriculture always ranks in the top three among the 12 main biodiversity threats identified by IUCN for all the aforementioned living groups, changing the lives of all living things. In addition, when the threat of 'pollution' among the 12 main threats is analyzed, it is seen that among the sub-headings of this threat, agricultural pollution is always much more prominent and intensely effective than other pollution threats. These data are a striking indication of how agriculture, or more precisely, the mistakes made in agricultural practices, are seriously damaging biodiversity worldwide. For a sustainable and healthy life, finding urgent solutions to harmful practices in agricultural production and ensuring the continuity of these solutions are essential for a livable world to exist.

If we talk about the interactions of nitrogen fertilizer pollution, which is the main subject of the present review, with the above-mentioned living groups, the following can be said:

It has been explained in previous sections that nitrogen fertilizers are applied in many countries at levels far in excess of current needs in the hope that they will increase crop yields (e.g., Taban and Namlı, 2019), and that they are therefore washed out of the soil and into aquatic ecosystems, where they are important sources of nitrogen pollution. To recall briefly:

Approximately 20-70% of intensively applied nitrogen fertilizers are emitted into the environment in most agroecosystems in the form of different forms of pollutants (Qiao et al., 2015; Kopittke et al., 2019). The main reason for this is that excessive nitrogen fertilizer application reduces nutrient assimilation efficiency (Lubkowski, 2016), and some of this diffusion occurs through the volatilization of nitrogenous compounds in the form of greenhouse gases, some through reaction with organic compounds in the soil, and the rest through leaching from the soil and penetration into surface and groundwater (Körschens et al., 2013).

Since agricultural systems can create significant wildlife reservoirs, much attention should be paid to the proper use of chemicals (e.g., herbicides, pesticides, and fertilizers), especially those applied to increase crop yields (Wang, 2020). The main agricultural factor that threatens various vertebrate and invertebrate species is the pollution caused by nitrogen fertilizers and similar agricultural chemicals. Several studies have shown that nitrogenous compounds negatively affect growth and reproductive activities in molluscs (Simplicio et al., 2017), crustaceans (Soucek and Dickinson, 2016), insects (Camargo et al., 2005), fish (Simplicio et al., 2017) and amphibians (Trudeau et al., 2020). As mentioned above, amphibians are the vertebrate class most vulnerable to agricultural impacts (IUCN 2023; Harfoot et al., 2021). The global decline in amphibians has been linked to the use of agrochemicals (e.g., Polo- Cavia et al., 2016). In agricultural areas with intensive chemical fertilization, impoverishment of amphibian biodiversity has been observed (e.g., Schiesari and Corrêa 2016).

Their basic anatomical features, such as their high skin permeability (Freitas et.al., 2019) and the fact that they have an aquatic larval stage in which they cannot avoid harmful water conditions (Daam et al., 2020), lead to increased sensitivity to biological or chemical pollutants in amphibians (Slaby et al., 2019), making them vulnerable to environmental degradation (Bovo et al., 2018). Therefore, amphibians have been recognized as ideal biological indicators of

aquatic and agroecosystems (Slaby et al., 2019). The sensitivity of amphibian communities as indicator species to degraded environmental health may be higher than the most advanced man-made monitoring devices or chemical analyses (Şişman et al., 2021). In addition, many

Given that the breeding season of amphibian species coincides with agricultural activities, exposure to agricultural pollution will be of high ecological importance to amphibians throughout their life cycle (Goessens et al., 2022).

For the reasons mentioned above, the mechanism of action of nitrogen fertilizers on amphibians, which are considered as indicators of agricultural pollution, will be discussed in more detail in this section.

Agricultural nitrogen pollution in aquatic ecosystems damages both aquatic larval and terrestrial adult stages of amphibians. However, since amphibian larvae, unlike terrestrial adults, cannot escape from the water bodies they inhabit due to their anatomy, the damage to larvae is much more pronounced than to adults (Daam et al., 2020). Many studies have reported that pollution b y nitrogenous compounds directly negatively affects tadpole growth and development (Ilha and Schiesari, 2014), activity levels (Egea-Serrano et al., 2011) and survival (Ilha and Schiesari, 2014). A documented detrimental secondary effect of these compounds is that they significantly impair tadpoles' defense behavior from predators (Sievers et al., 2018), which may indirectly trigger a reduction in tadpole survival (Ilha and Schiesari, 2014).

In addition, nitrate and nitrite compounds are thought to suppress the immune system of amphibians (Camargo and Alonso, 2006), promote the formation of secondary compounds that cause mutations and cancers (Nugent et al, 2001), and act as endocrine disruptors affecting the thyroid function and hormonal balance of amphibians (Guillette and Edwards, 2005). On top of that, nitrite compounds oxidize hemoglobin to methaemoglobin, a form that cannot carry oxygen (Huey and Beitinger, 1980) and can negatively affect osmoregulation, neurotransmission, muscle contraction and the function of the heart and mitochondria (Camargo and Alonso, 2006). Ammonium ion can reduce sodium concentrations in the body to lethal levels (Russo, 1985).

In addition to direct mortality, these physiological changes can indirectly reduce population survival by causing sublethal effects on individual growth, development and behavior (Marco and Ortiz-Santaliestra, 2009). Slower growth makes tadpoles more susceptible to habitat desiccation and predation, as they remain in the aquatic environment for longer periods of time and are of a size that can be captured by predators with limited mouth openings (Wilbur, 1997).

However, sometimes in some drying wetlands, tadpoles respond to the drying of their environment by accelerating the metamorphosis process to avoid death in a "stress response" (Ruso et al., 2021). But this acceleration,

This may have negative consequences on the functioning of the immune system of tadpoles (Gervasi and Foufopoulos, 2008) and their size at the end of metamorphosis (Gomez-Mestre et al., 2013). Smaller individuals have reduced mobility and therefore increased risk of predation (Beck and Congdon 2000). Therefore, tadpole growth and development is crucial for the survival of the individual as an adult and its reproductive ability (Todd et al., 2011). Slower growth can also reduce future reproductive success because slow-growing tadpoles tend to become smaller-sized adults at the end of metamorphosis, and smaller-sized adults have lower fecundity and mating success (Berven, 1990). Likewise, fluctuations in behavioral traits such as activity levels are important because activity enables foraging and predator avoidance (Werner and Anholt, 1993) and affects tadpoles' competitive abilities (Dayton and Fitzgerald, 2001). Recurrent adversities such as failure to complete metamorphosis and reproductive failure can also lead to localized declines or extinctions in amphibian populations if conditions are severe enough (Donald et al., 2011).

In conclusion, in the light of all this information, it can be concluded that nitrogen pollution from agricultural sources is a factor that causes serious damage to world biodiversity, animal, human and environmental health, sustainable production and life in many different aspects. In this context, it is of utmost importance to determine the necessary protective measures urgently and to ensure the continuity of their implementation.

4. CONCLUSIONS and RECOMMENDATIONS

The rapid increase in the world population and the parallel increase in the demand for food has confronted producers with the necessity of obtaining the highest possible yield from the unit area. This has triggered various fertilization systems and pesticide applications, and efforts have been made to increase the efficiency of agricultural production as much as possible. On the other hand, agricultural lands have been gradually expanded to support production, leaving less and less space for natural habitats and habitat diversity. At the same time, new agricultural technologies have been developed to ensure even higher yields, a n d chemical fertilizers have gradually replaced natural fertilizers. In fact, these chemical fertilizers, with their easy use and concentrated content, have been applied uncontrollably to agricultural areas around the world in higher quantities than necessary. Among artificial fertilizers, the excessive use of nitrogen-based

fertilizers compared to other types of fertilizers has gradually reduced the efficiency of nitrogen uptake by disrupting the nutrient balance. These fertilizers

As a result, some of the nitrogen fertilizers applied evaporate as greenhouse gases and pollute the air, some of them bind to other compounds in the soil and pollute the soil and the plants growing there, and some of them are washed out of the soil and pollute the water. As a result of these anthropogenic changes, which occur at a much higher rate than the rate at which nature renews itself, human beings have begun to face many ecological, medical and economic problems.

The destruction of natural habitats, air, water, soil pollution and eutrophication have caused significant damage to biodiversity. Damage to biodiversity and ecosystem diversity has led to significant problems in ecosystem functioning; stable climate, clean environment (air, water, soil) and sustainable production have become increasingly unattainable. Soil acidification, crusting and salinization have damaged nitrogen fixation bacteria, leading to a decline in soil fertility, structure, agricultural production efficiency and crop quality. It has also led to the loss of the fertile top layer of soil through erosion. The accumulation of fertilizer components as pollutants, especially in soil and water, has led to unhealthy food content and declines in drinking water quality. This is because the same pollutants accumulate in the plants and animals that obtain their food and water from these sources. At the last link in the chain are humans who feed on plants and animals containing these unhealthy components. Therefore, excessive fertilizer applications cause significant health problems in humans and animals, and even in plants and beneficial microorganisms. In addition, fertilizers have caused an increase in the cost of agricultural production and significant economic losses, both because they are applied in excessive doses and washed out of the soil before they can be used by the plant, and because they reduce the efficiency of nitrogen uptake and reduce its conversion into crops. Nitrogen oxides and many other greenhouse gases released from agricultural ecosystems have triggered global warming, ozone depletion and the formation and increase of harmful particles such as P.M2.5 particles in the air, causing many health problems, especially cancers and respiratory diseases. Water and soil pollution caused by faulty fertilization has also been shown to trigger similar health problems.

Despite all the problems it causes, it is not possible to achieve and sustain a healthy, qualified and sufficient food supply for the world's human and animal population without fertilizers. What is important here is to ensure quality, sufficient and sustainable food supply in a healthy, safe and rich biodiversity

ecosystem without exploiting natural resources with the right fertilization approach.

In order to achieve this, today, nature-friendly organic agriculture is an alternative to traditional or conventional agriculture, which is based on the intensive application of chemicals.

practices, environmentally friendly organic fertilizers, bio-fertilizers, slow-release fertilizers or nano-fertilizers, or new environmentally friendly technologies can be promoted instead of artificial fertilizers. In addition, proper storage and waste management of farm manure and other wastes from animal production, which is another means of food supply, can be ensured. Producers can be included in training programs organized by official extension agencies on proper fertilizer use, proper waste management, obtaining useful products (e.g. biogas, renewable energy, animal feed, bio-fertilizer) through recycling of agricultural wastes and thus producing additional inputs. After the program, serious controls can be carried out to check how much the information provided is incorporated into agricultural production and necessary corrections can be made. Although regulations setting the upper limits for nitrate compounds in water and food have been published and certain action plans have been implemented, large-scale research can be carried out on the reasons for the persistence of water pollution. Stricter controls on the sale and use of fertilizers can be introduced to ensure that they are used at the correct dosage. Informative meetings and trainings on the damages caused by excessive fertilizer use can be organized under the management of official agricultural extension agencies. Various incentive systems can be established to increase the participation of producers. Most importantly, preliminary studies can be carried out on how to replace the traditional incomplete knowledge on which most producers base their agricultural activities with scientific knowledge in the most effective way. Correcting the traditional agricultural attitudes that farmers are familiar with and rely on, especially their misinformation about the correct dosage of fertilizers, will be a difficult process that will require persistent approaches and intensive efforts, but there must be a way to achieve this for the sustainability of a livable world. It should not be forgotten that ensuring the continuity of solution-oriented practices across all stakeholders is at least as important as replacing traditional agricultural attitudes with scientific attitudes.

Now, if we open a new parenthesis on fertilizer applications, which are the main source of all problems:

Fertilizer application is very important and necessary for today's agricultural production system, as it restores nutrients that are missing from the soil, enriches the soil and promotes the growth and yield of crops. However, in order to reduce the different types of hazards caused by overuse of fertilizers, producers should use fertilizers in sensible and sustainable ways, firstly by conducting soil and leaf analyses and then applying the right fertilizers selected according to the needs at the right time with the right dose and method. Therefore, in order to ensure both improved and sustainable agricultural production and to protect the environment and eliminate the threat of pollution from chemical fertilizers, environmentally friendly organic fertilizers, controlled-release fertilizers, bio-fertilizers, fertilizers with improved nutrient utilization efficiency, especially for nitrogen, and different Nano-fertilizers with a more effective role in increasing production. Even integrated use of these different types of nutrient providers should be adopted in order to benefit from their different advantages at the same time. In this way, it is thought that both production cost and pollution hazard can be minimized.

The following are some examples of fertilizers that can be used instead of or integrated with artificial fertilizers:

a) **Bio-fertilizers:** This type of fertilizer contains live micro-organisms. Such substances are known to help expand the root system and promote better seed germination. In general, a healthy plant usually has a healthy rhizosphere, which should be dominated by beneficial microbes. Biofertilizers differ from chemical and organic fertilizers in that they do not provide any nutrients directly to the crops and are special cultures of bacteria and fungi. Biofertilizer production technology is relatively simple and the cost of installation is very low compared to chemical fertilizer plants (Trenkel, 1997).

b) **Nano-fertilizers:** "Nano fertilizers are synthesized or modified form of conventional fertilizers, bulk fertilizers or fertilizers derived from different vegetative or reproductive parts of the plant by different chemical, physical, mechanical or biological methods with the help of nanotechnology used to improve soil fertility, productivity and quality of agricultural products. Nanoparticles can be made entirely from bulk materials. For example, the plant produced from nano-TiO2-treated seed recorded greater dry weight, higher photosynthetic rate and chlorophyll-a formation compared to the control

c) **Slow Release Fertilizers:** Involve a slower release of nutrients than common fertilizers. However, the rate, pattern and duration of release are not well controlled. In controlled-release fertilizers, however, the rate, pattern and duration of release are well known. The different types of slow or controlled-release fertilizers are:

I. Organic-N Low Solubility Compounds such as urea-formaldehyde (UF) and Isobutyleden-diurea (IBDU).

II. For example, fertilizers coated with organic polymer coatings, which are thermoplastics or resins, and fertilizers coated with inorganic materials such as sulfur or mineral- based coatings.

III. Inorganic Low Solubility Compounds: Fertilizers such as metal ammonium phosphates and partially acidified phosphate rock (PAPR) (Singh et al., 2017).

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