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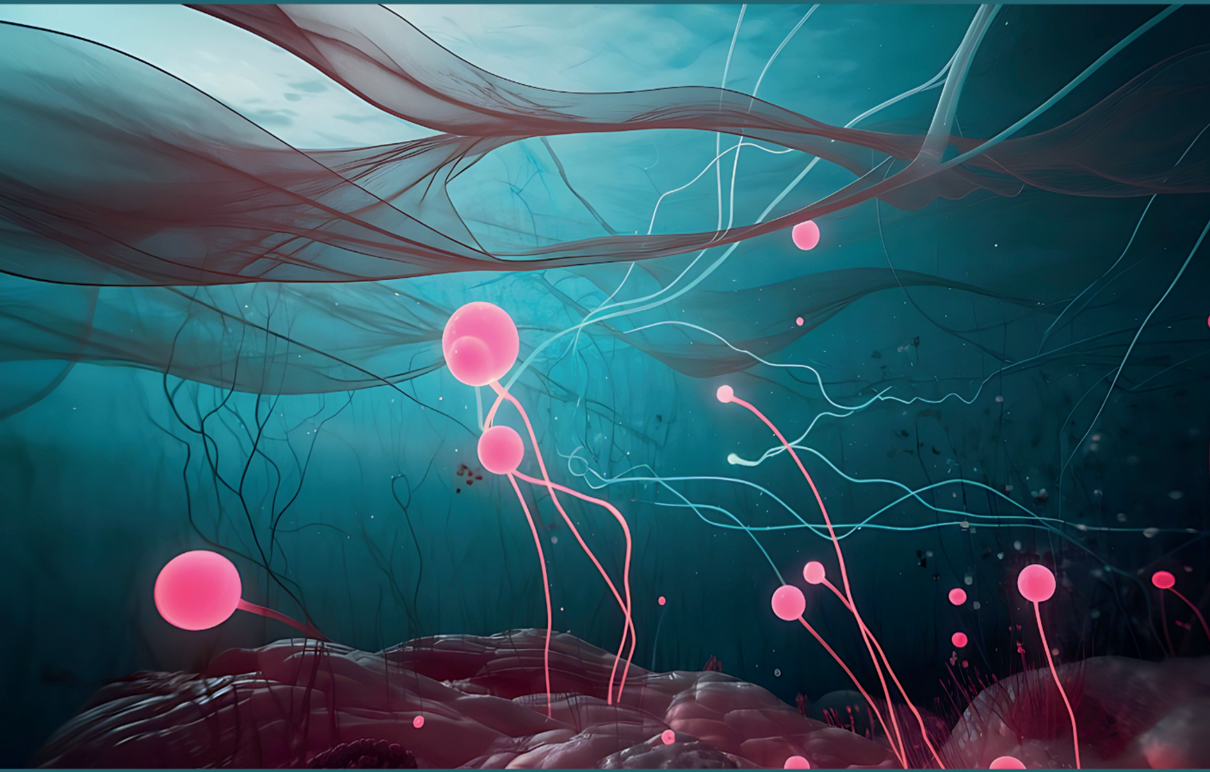
CURRENT APPROACHES IN AGRICULTURE, SCIENCE AND ENGINEERING



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Assist. Prof. Ahmet Haşim KESKİN, Ph.D.
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Chapter 1

RESPONSE TO OXIDATIVE STRESS: "ANTIOXIDANTS"

Ebru ÇÖTELİ[1] & Belgin ERDEM[2] & Sibel ÇELİK[3]

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Introduction

Metabolism has an innate oxidant-antioxidant balance. Disruption of this balance in metabolism is defined as oxidative stress (Zelzer et al., 2018). Substances that cause oxidative stress are divided into two classes: radicals and non-radicals. Radical ones are superoxide ($O^{\cdot}_2$), peroxyl ($L(R)OO^{\cdot}$), hydroperoxyl ($HOO^{\cdot}$), and hydroxyl ($^{\cdot}OH$) radicals. Those that are not radical: These are substances such as hypochlorite (^{-}OCl), singlet oxygen ($^{1}O_2$), hydrogen peroxide (H_2O_2), and ozone (O_3) (Abuja & Albertini, 2001).

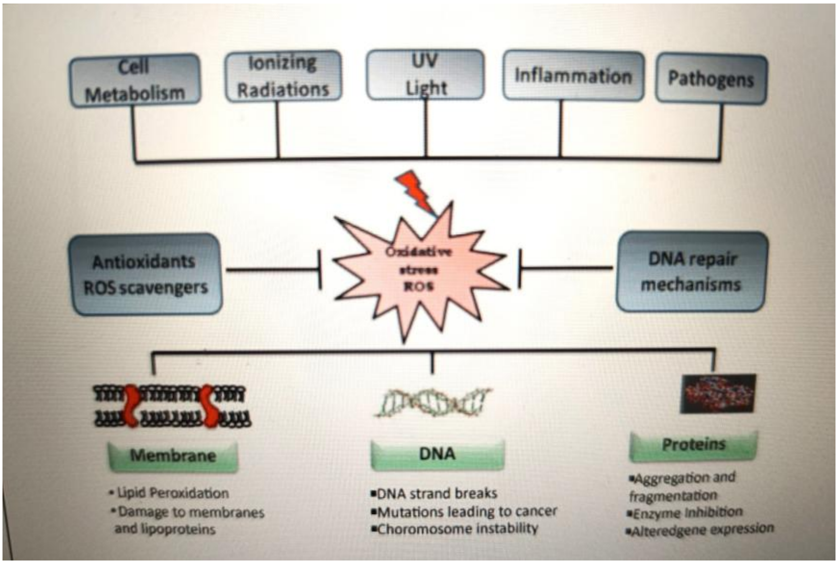

Figure 1. Sources of oxidative stress

Free Radicals and Their Occurrence

Free radicals are atoms or molecules containing one or more unpaired electrons. Due to unshared electrons, they are highly reactive, but their lifespan is very short. They may occur during the functioning of metabolism or due to external factors (Barber & Harris, 1994; Halliwell, 1994). Free radicals;

1. **1.** It is formed by homolytic cleavage of a covalently bonded molecule.

$$X : Y \rightarrow X^{\cdot} + Y^{\cdot}$$

2. **2.** If a molecule loses electrons, free radicals are formed. During electron loss, if there is an unshared electron in the outer orbital of the molecule, a radical occurs.

3. Free radicals are also formed through the transfer of electrons to a molecule. In this way, radicals are formed as an unshared electron is formed in the outer orbital of the molecule (Halliwell & Gutteridge, 1990).

Radicals consisting of oxygen are among the most important radicals found in biological systems. Oxygen, which is both necessary and toxic, has two unpaired electrons, and the fact that the unpaired electrons spin in the same direction in separate orbitals gives it the property of being a radical. By adding one electron to molecular oxygen, superoxide forms two electrons with the addition of hydrogen peroxide and hydroxy radicals via three-electron transfer (Fridovich, 2001; Nordberg & Arner, 2001).

$O_2 + e + H^+ \rightarrow HO_2^{\cdot}$ Hydroperoxyl radical

$HO_2^{\cdot} \rightarrow H^+ + O_2^{\cdot}$ Superoxide radical

$O_2^{\cdot} + 2H^+ + e \rightarrow H_2O_2$ Hydrogen peroxide

$H_2O_2 + e \rightarrow OH^- + {}^{\cdot}OH$ Hydroxyl radical

Mitochondria, in particular, play an important role in the production of ROS and RNS in the cell (Lambert & Brand, 2009; Valko et al., 2007). Reactive oxygen and nitrogen species are shown in Tables 1 and 2.

Table 1. Reactive oxygen species (ROS)

Radicals		**Nonradicals**	
Süperoxide	$O_2^{\cdot -}$	Hydrogen peroxide	H_2O_2
Hydroxyl	$OH^{\cdot}$	Hypochlorous acid	HOCl
Peroxyl	$ROO^{\cdot}$	Hypobromous acid	HOBr
Alkoxyl	$RO^{\cdot}$	Singlet oxygen	$^1O_2$
Hydroperoxyl	$HO_2^{\cdot}$	Ozone	O_3
Lipid peroxyl	$LOO^{\cdot}$		

Table 2. Reactive nitrogen species (RNS)

Radicals		**Nonradicals**	
Nitric oxide	$NO^{\cdot}$	Nitric acid	HNO_2
Nitrogen dioxide	$NO_2^{\cdot}$	Nitrosyl cation	NO^+
		Nitroxyl anion	NO^-
		Dinitrogen tetroxide	N_2O_4
		Dinitrogen trioxide	N_2O_3
		Peroxynitrite	$ONOO^-$
		Peroxynitric acid	ONOOH
		Nitronium cation	$NO_2^{\ +}$
		Nitrile chloride	NO_2Cl
		Alkyl peroxynitrite	ROONO

Free Radicals and the Diseases They Cause

Studies on free radicals show that these radicals are responsible for inflammatory diseases (Li et al., 2013), Alzheimer's (Pan et al., 2011), Diabetes Mellitus (Bashan et al., 2019), Parkinson's disease (Sevcsik et al., 2011), and cancer [prostate (Lim et al., 2005), colorectal (Jemal et al., 2011), breast (Brown et al., 2000)]. It has also been reported to cause diseases such as lung (Azad et al., 2008), hypertension (WHO, 2013), cardiovascular disease (Zhang et al., 2010), asthma (Fujisawa, 2005), rheumatoid arthritis (Vasanthi et al., 2009), aging (Krisko & Radman, 2019), and cataract (Costagliola et al., 1988; Costagliola et al., 1990). Diseases caused by free radicals are shown in Figure 2.

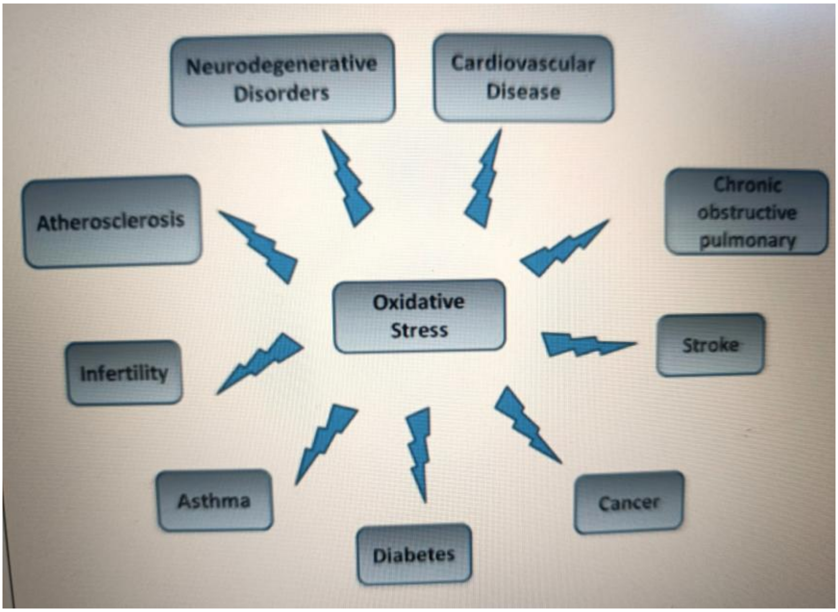

Figure 2. Diseases caused by oxidative stress (Forman et al., 2004; Packer et al., 2001).

Antioxidants

There is a balance between oxidant and antioxidant substances in metabolism. This balance is disrupted by the increase in the amount of free radicals. In this case, oxidative stress occurs (Amponsah-Offeh et al., 2023). These substances that minimize or clear the effects of these radicals are called antioxidants. Oxidant and antioxidant balance is shown in Figure 3.

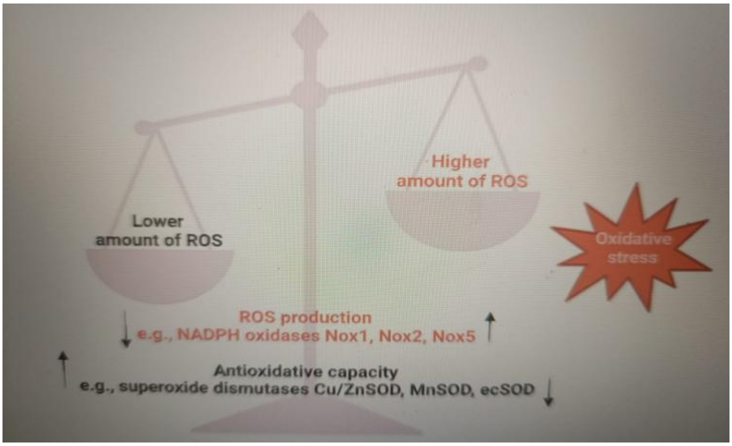

Figure 3. Oxidant and antioxidant balance in metabolism (Amponsah-Offeh et al., 2023)

Antioxidants fulfil their duties either by donating hydrogen ions to free oxygen radicals or by turning them into a weaker molecule. The membrane and liquid parts of the cell contain antioxidants (Young & Woodside, 2001). Antioxidants are classified as endogenous and exogenous antioxidants and food antioxidants:

Natural (Endogenous) Antioxidants

• Enzymes: SOD, CAT, GSH-Px, GSH-Rd, hydroperoxidase, etc.

• Non-enzyme antioxidants: such as α-tocopherol (E-vitamin), β-carotene (A-vitamin), ascorbic acid, melatonin, transferrin, ferritin, hemoglobin, albumin, bilirubin, and glutathione.

Exogenous Antioxidants (Drugs)

• Xanthine oxidase inhibitors

• NADPH oxidase inhibitors

• Recombinant superoxide dismutase

• Trolox-C.

Food Antioxidants

• Butyl Hydroxytoluene (BHT)

• Butyl Hydroxyanisole (BHA)

• Sodium Benzoate (Akkuş, 1995).

Superoxide Dismutase Enzyme (SOD)

SOD enzyme is the first defence against the toxic effects of free radicals in metabolism. is doing. This enzyme converts the superoxide radical into hydrogen peroxide and molecular oxygen. transforms (Fridovich, 1997).

$$2O_2^{\cdot -} + 2H^+ \xrightarrow{\textit{SOD}} H_2O_2 + O_2$$

Glutathione Peroxidase (GSH-Px)

Glutathione peroxidase enzyme, which is an intracellular enzyme containing selenocysteine in its active center, is a natural antioxidant found in metabolism. GSH-Px; Glutathione, which contains two thiol groups, oxidizes glutathione disulfide and reduces hydroperoxides and H_2O_2 (Açan & Tezcan, 1992).

GSH-Px

$$ROOH + 2GSH \rightarrow ROH + GSSG$$

GSH-Px

$$HOOH + 2GSH \rightarrow 2H_2O + GSSG$$

Glutathione Reductase (GSH-Rd)

Glutathione reductase enzyme contains selenium in its structure. GSSG (oxidized glutathione) protects the cell against peroxides by rapidly converting it into GSH (reduced glutathione) Glutathione, a substance found inside the cell that protects the cell's proteins against oxidative damage, is a molecule. Glutathione reductase enzyme plays a role in this reaction (Gözükara, 2001).

GSH-Rd

$$GSSG + NADPH + H^+ \rightarrow 2GSH + NADP^+$$

Vitamin E (Tocopherols)

It is a fat-soluble vitamin that inhibits or scavenges the production of free radicals. It is a powerful antioxidant due to its chain-breaking activity. It is available in eight different forms. Since this vitamin specifically scavenges peroxyl radicals very well, it protects the unsaturated fatty acids in the structure of membranes and lipoproteins against oxidative damage (Nordberg & Arner, 2001).

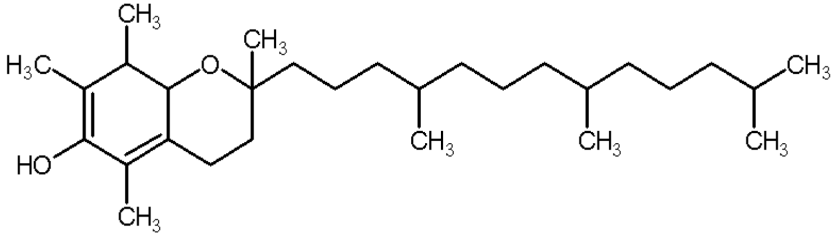

Figure 4. Structure of Vitamin E (α-Tocopherol)

Vitamin A (Carotenes)

It is a water-insoluble, fat-soluble vitamin. There are many unsaturated bonds in its structure. A clear representation of vitamin A is shown in Figure 5.

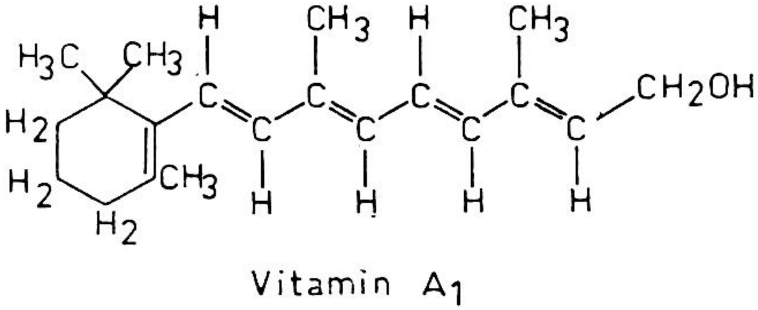

Figure 5. Structure of vitamin A

The most important vitamin A derivative is β-carotene. In particular, vitamin A is a vitamin required for antioxidant, cell membrane integrity, and synthesis of glycoproteins. This vitamin is especially effective in scavenging free radicals because it contains many long conjugated double bonds. In particular, β-carotene (CAR) reacts directly with the peroxyl radical (Nikolai et al., 2001).

$$\text{CAR-LOO}^{\cdot} \longrightarrow \text{LOO-CAR}^{\cdot}$$

Vitamin C (Ascorbic acid)

It is one of the water-soluble vitamins that are essential for the normal functioning of metabolism. (Lykkesfeldt, 2012). It has been reported that vitamin C, in particular, is important in the treatment of respiratory diseases, colds, and pneumonia (Kim et al., 2020). Vitamin C has many antioxidant functions, such as scavenging free radicals, preventing the production of reactive oxygen species, and coordinating antioxidant enzymes (Garcia-Diaz et al., 2014). The structure of vitamin C is shown in Figure 6.

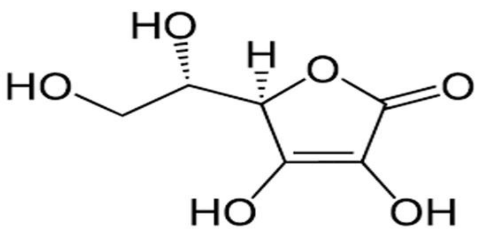

Figure 6. Structure of vitamin C ($C_6H_8O_6$)

Glutathione (GSH)

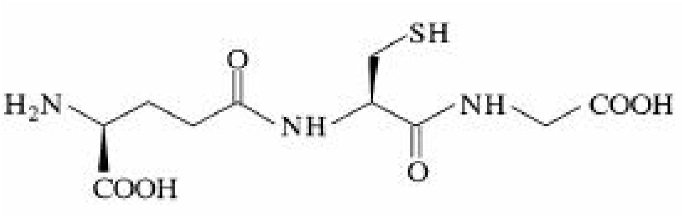

Figure 7. Structure of glutathione (GSH)

Glutathione (γ-glutamylcysteine glycine) is an important low molecular weight tripeptide containing a thiol group in the organism (Nelson & Cox, 2000; Shibata et al., 2003). The structure of the glutathione molecule is shown in Figure 7. The glutathione molecule is a tripeptide composed of three different amino acids: glutamate, cysteine, and glycine. In particular, this molecule shows properties such as antioxidant, immune system regulation, and detoxifying effect (Jamali & Majid, 2017). Glutathione has two different forms in metabolism: reduced (GSH) and oxidized (GSSG) (Mohan et al., 2020). Also, glutathione has anti-inflammatory effects (Hao et al., 2022) and positive effects on fatty liver disease. It has been reported that it may cause side effects (Honda et al., 2017).

CONCLUSION

In this study, free radicals formed during the normal process of metabolism, their types, and their effects on metabolism are emphasized. Additionally, their role in various chronic diseases caused by these radicals is explained. Particular attention has been drawn to "antioxidant substances" that will reduce or eliminate the effects of these radicals. The relationship between oxidant and antioxidant has been revealed.

REFERENCES

Abuja, P.M., & Albertini, R. (2001). Methods for monitoring oxidative stress, lipid peroxidation and oxidation resistance of lipoproteins. *Clinica Chimica Acta*, *306*, 1–17.

Açan, N.L., & Tezcan, E.F. (1992). Glutathione reductase. *Journal of Biochemistry*, *17*(2), 67–83.

Akkuş, İ. (1995). Free oxygen radicals and their physiopathological effects. Mimoza Publishing and Distribution, Konya, 1–15.

Amponsah-Offeh, M., Diaba-Nuhoho, P., Speier, S., & Morawietz, H. (2023). Oxidative stress, antioxidants and hypertension. *Antioxidants*, *12*, 281.

Azad, N., Rojanasakul, Y., & Vallyathan, V. (2008). Inflammation and lung cancer: Roles of reactive oxygen/ nitrogen species. *Journal Toxicol. Environ. Health*, *11*, 1–15.

Barber, D.A., & Harris, S.R. (1994). Oxygen free radicals and antioxidants: Arewiev. *Am. Pharmavy*, *34*(9), 26–35.

Bashan, N., Kovsan, J., Kachko, I., Ovadia, H., & Rudich, A. (2009). Positive and negative regulation of insulin signaling by reactive oxygen and nitrogen species. *Physiol. Rev.*, *89*, 27–71.

Brown, N.S., Jones, A., Fujiyama, C., Harris, A.L., & Bicknell, R. (2000). Thymidine phosphorylase induces carcinoma cell oxidative stress and promotes secretion of angiogenic factors. *Cancer Res*., *60*, 6298–6302.

Costagliola, C., Iuliano, G., Menzione, M., Nesti, A., Simonelli, F., & Rinaldi, E. (1988). Systemic human diseases as oxidative risk factors in cataractogenesis I. Diabetes. *Ophthalmic Res*., *20*, 308–316.

Costagliola, C., Iuliano, G., Menzione, M., Simonelli, F., Tortori, A., Masturzi, B., di Benedetto, A., & Rinaldi, E. (1990). Systemic human diseases as oxidative risk factors in cataractogenesis. II. Chronic renal failure. *Exp. Eye Res*., *51*, 631–635.

Forman, H.J., Fukuto, J.M., & Torres, M. (2004). Redox signaling: thiol chemistry defines which reactive oxygen and nitrogen species can act as second messengers. *Am J Physiol Cell Physiol*, *287*(2), C246–C256.

Fridovich, I. (1997). Superoxide anion radical, superoxide dismutases and related matters. *J. Biological Chemistry*, *272*(30), 18515–18517.

Fridovich, I. (2001). Oxidative stres. Encyclopedia of Life Sciences. Nature Publishing Group. pp. 1–5.

Fujisawa, T. (2005). Role of oxygen radicals on bronchial asthma. *Curr. Drug Targets Inflamm. Allergy*, *4*, 505–509.

Garcia-Diaz, D.F., Lopez-Legarrea, P., Quintero, P., & Martinez, J.A. (2014). Vitamin C in the treatment and/or prevention of obesity. *Journal of nutritional science and vitaminology*, *60*(6), 367–379.

Gözükara, E. (2001). Biochemistry, 2:710.

Halliwell, B. (1994). Free radicals, antioxidants, and human disease: curiosity, cause, or consequence? *The Lancet*, *344*, 721–724.

Halliwell, B., & Gutteridge, J.M.C. (1990). Role of free radicals and catalytic metal ions in human disease: An overview. *Methods Enzymol*, *49*(3), 577–587.

Hao, W.T., Huang, L., Pan, W., & Ren, Y.L. (2022). Antioxidant glutathione inhibits inflammation in synovial fibroblasts via PTEN/PI3K/AKT pathway: An in vitro study. *Arch Rheumatol*, *37*(2), 212–222.

Honda, Y., Kessoku, T., Sumida, Y., Kobayashi, T., Kato, T., Ogawa, Y., Tomeno, W., Imajo, K., Fujita, K., Yoneda, M., Kataoka, K., Taguri, M., Yamanaka, T., Seko, Y., Tanaka, S., Saito, S., Ono, M., Oeda, S., Eguchi, Y., Aoi, W., Sato, K., Itoh, Y., & Nakajima, A. (2017). Efficacy of glutathione for the treatment of nonalcoholic fatty liver disease: an open-label, single-arm, multicenter, pilot study. *BMC Gastroenterol*, *17*(1), 96.

Jamali, M., & Majid, A. (2017). Intravenous glutathione for fair skin; to give or not to give? *J Pak Med Assoc.*, *67*(7), 1127.

Jemal, A., Bray, F., Center, M.M., Ferlay, J., Ward, E., & Forman, D. (2011). Global cancer statistics. *CA Cancer J. Clin.*, *61*, 69–90.

Kim, T.K., Lim, H.R., & Byun, J.S. (2020). Vitamin C supplementation reduces the odds of developing a common cold in Republic of Korea Army recruits: randomised controlled trial. *BMJ Mil Health*, *168*(2), 117–123.

Krisko, A., & Radman, M. (2019). Protein damage, ageing and age-related diseases. *Open Biol.*, *9*, 180–249.

Lambert, A.J., & Brand, M.D. (2009). Reactive oxygen species production by mitochondria. *Methods Mol. Biol.*, *554*, 165–181.

Li, X., Fang, P., Mai, J., Choi, E.T., Wang, H., & Yang, X.F. (2013). Targeting mitochondrial reactive oxygen species as novel therapy for inflammatory diseases and cancers. *J. Hematol. Oncol.*, *6*, 1–19.

Lim, S.D., Sun, C., Lambeth, J.D., Marshall, F., Amin, M., Chung, L., Petros, J.A., & Arnold, R.S. (2005). Increased Nox1 and hydrogen peroxide in prostate cancer. *Prostate*, *62*, 200–207.

Lykkesfeldt, J. (2012). Ascorbate and dehydroascorbic acid as biomarkers of oxidative stress: validity of clinical data depends on vacutainer system used. *Nutrition research*, *32*(1), 66–69.

Mohan, S., Mohan, L., Sangal, R., & Singh, N. (2020). Glutathione for skin lightening for dermatologists and cosmetologists. *Int J Res Dermatol.*, *6*(2), 284–287.

Nelson, D.L., & Cox, M.M. (2000). Lehninger, Principles of Biochemistry 3rd Ed. Worth Publishing: New York, ISNB 1-57259, 153–156.

Nikolai, E.P., Tatyana, V.L., Tatyana, A.K., & Lowell, P.K. (2001). Carotenoids as scavengers of free radicals in a Fenton reaction: Antioxidants or prooxidants? *Free Rad. Bio. And Med*., *31*(3), 398–404.

Nordberg, J., & Arner, E.S.J., (2001). Reactive oxygen species, antioxidants and the mammalian thioredoxin system. *Free Radical Biology and Medicine*, *31*(11), 1287–1317.

Packer, L., Weber, S.U., & Rimbach, G. (2001). Molecular aspects of alphatocotrienol antioxidant action and cell signalling. *J Nutr*., *131*, 369S–73S.

Pan, X.D., Zhu, Y.G., Lin, N., Zhang, J., Ye, Q.Y., Huang, H.P., & Chen, X.C. (2011). Microglial phagocytosis induced by fibrillar β-amyloid is attenuated by oligomeric β-amyloid: Implications for Alzheimer's disease. *Mol. Neurodegener*, *6*, 1–17.

Sevcsik, E., Trexler, A.J., Dunn, J.M., & Rhoades, E. (2011). Allostery in a disordered protein: Oxidative modifications to a-synuclein act distally to regulate membrane binding. *J. Am. Chem. Soc*., *133*, 7152–7158.

Shibata, H., Sasaki, N., Hondjoh, T., Ohishi, I., Takiquchi, M., Ishioka, K., Ahmed, M., Soliman, M., Kimura, K., & Saito, M. (2003). Feline leptin: immunogenic and biological activities of the recombinant protein and its measurement by ELISA. *J. Vet Med Sci*, *65*, 1207–1211.

Valko M, Leibfritz D, Moncol J, Cronin, M.T.D., Mazur, M., & Telser, J. (2007). Free radicals and antioxidants in normal physiological functions and human disease. *Int J Biochem Cell Biol*., *39*, 44–84.

Vasanthi, P., Nalini, G., & Rajasekhar, G. (2009). Status of oxidative stress in rheumatoid arthritis. *Int. J. Rheum. Dis*., *12*, 29–33.

WHO (2013). A global brief on hypertension. In World Health Day 2013; WHO: Geneva, Switzerland.

Young, I.S., & Woodside, J.V. (2001). Antioxidants in health and disease. *J Clin Pathol*., *54*, 176–186.

Zelzer, S., Wonisch, W., Rinnerhofer, S., Niedrist, T., Tatzbe, F., Cvirn, G., Wultsch, G., & Mangge, H. (2018). The workload of heavy workers is associated with increased low-grade inflammation, emotional and oxidative stress. *Free Radical Biology and Medicine*, *124*, 577.

Zhang, N., Bradley, T.A., & Zhang, C. (2010). Inflammation and reactive oxygen species in cardiovascular disease. *World J. Cardiol*., *2*, 408–410.

Chapter 2

TODAY IN TERMS OF FOOD SAFETY; PRIORITIES IN AGRICULTURAL EXTENSION

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1-INTRODUCTION

Associating the beginning of civilisation with writing is widely used in terms of documentation. In every field, the first written source related to it is presented as scientific data. With its versatile interaction in social life, it constantly designs different writing-based opportunities. The creation of records is the basis of many vital processes. Food is included in life as a requirement of living things every day and continuously. The primary priority of health life depends on safe food. The awareness of the producer, the consumer who wants to reach healthy food is required. Economic concepts have spread to every aspect of life with diversifying needs. Food safety and reliability can be improved by raising awareness. Educating the producer for the protection of the consumer is seen as the most effective way of agricultural extension in general.

Extension and trainings have an effective function in reflecting innovations to our lives. Today, as a social and technical innovation process, extension enters our lives through a non-linear process. Advertisements for marketing and our interest in products have become a part of our lives. Learning groups and networks provide people with opportunities to increase their interest and knowledge, empowerment, create spaces for communication, exchange of information, negotiation, experimentation and powerful tools for the development of skills and competences.

The advertising sector is constantly generating data to direct our consumption. With product placements, it is aimed to initiate the formation of virtual needs in our psychology. Visual data trigger the dimension of interest. The theme of the visual that attracts attention on the billboard aims to introduce you to the product.

The history of agricultural extension works dates back to ancient times. Agricultural extension has been a very important force and element of social innovation in the development of agriculture for centuries. Although today's extension models are products of the last two centuries, the history of extension spans almost four thousand years due to its evolution. Today, people and organisations responsible for carrying out agricultural extension activities help rural people to adapt to changing socio-economic conditions and to adopt modern agricultural technologies (Cinemre and Demiryürek, 2005).

Food safety has emerged as an important conceptual framework especially in recent years. There are very important studies on this subject in recent years (Giray and Soysal, 2007; Koç and Uzmay, 2015). Food safety has taken its place in social life with its indispensable function in terms of all actors in the market, national security and community welfare issues. Its importance is becoming more and more important day by

2- SAFE FOOD

Sustainability and competitiveness in agricultural production should be managed together in an ecological and economic framework. The transition to more sustainable forms of agriculture with quality, healthy and safe products concern all segments of society. It is a social policy objective to transfer social awareness and learning and the innovations it foresees into co-production. The use of systems that enable and incentivise technology-mediated adaptation, budget allocation and widespread, effective use requires the participation of a wide range of public-led stakeholders. Likewise, clustering and participatory approaches should be developed with farm and area-specific management solution approaches such as cooperatives, unions, non-governmental organisations.

In the 2019-2023 Strategic Action Plan of the Ministry of Agriculture and Forestry; 'to increase welfare in rural areas; to ensure stable food supply by increasing productivity and quality in agricultural production; to ensure food and feed safety from production to consumption; to take necessary measures for plant, animal health and welfare; to protect fisheries and aquaculture resources, to ensure sustainable operation; to ensure sustainable management of soil and water resources; to effectively combat climate change, desertification and erosion and to protect biodiversity and ensure sustainable management' (Anonymous, 2024a).

Today, the development of basic life skills in societies starts with family-based individual education. New extension, education-training and development approaches based on systems thinking and social learning perspectives based on a wide range of theoretical views on learning and change have emerged. In agricultural extension, it has contributed to the creation of new business lines, especially in the field of crop and animal production. Education is the most important investment in the future of societies. Agricultural trainings contribute to raising awareness of the people in the region where they are carried out and making their investments with a focus on food safety

3-AGRICULTURAL EXTENSION

Publication in the context of food safety in the public sector; the purpose, scope and definitions are to protect and ensure food and feed safety, public health, plant and animal health, animal breeding and welfare, considering consumer interests and environmental protection. Scope of the relevant Law; all stages of production, processing and distribution of food, substances and materials in contact with food and feed, control of plant protection product and veterinary medical product residues and other residues and contaminants, epidemic or contagious animal diseases, control of harmful organisms in plants and plant products, It covers the welfare of farm and experimental animals and domestic and ornamental animals, zootechnical issues, veterinary health and plant protection products, veterinary and phytosanitary services, entry and exit procedures of live animals and products into and out of the country and official controls and sanctions related to these issues (Anonymous, 2010).

These developments, which imply a balance between environmental, social and economic sustainability, are taking their place in our lives in system approaches such as agricultural information and knowledge systems (AKIS) and recently agricultural innovation system (AIS) approach. Record keeping and traceability must be more accessible in the future. In the dissemination of innovations, it is useful to focus on the co-design of transfer of technology and design. In this regard, the creation of organised initiatives should be developed to manage the articulation, conflict and unpredictability of multiple dimensions of innovation.

Agricultural education and extension is recognised as important for the transition to more sustainable forms of agriculture, including economic, social, environmental factors and trade-offs. Education and extension approach and modes therefore need to be transformed to promote learning and double-loop learning through their relationship with research, thus making it easier for farmers to deal with relevant issues. In a rapidly changing world, the pluralist school of agricultural extension has given prominence to concepts such as diversity, sustainability and marginality, urban farming, poverty, equity, distribution, changes in rural areas. In emerging models of innovation and entrepreneurship, new roles, capacities and methods should be developed for extension. Similarly, today, the word extension is generally used to mean: ‘a system of education for the planned transmission of information to help people form sound opinions and make sound decisions. In other words, extension is a conscious form of social interaction and communication process. Extension is the conscious communication of information, technology and innovations to help people form healthy opinions and make the right decisions (Demiryürek, 2010; Ban and Hawkins, 1996; Leeuwis and Van den Ban, 2004). From this point, we can generally say that the concept of extension is an informal, out-of-school form of adult education and expresses the function of communication and interaction between two parties. However, the important point here is that the person with the problem eventually solves the problem himself/herself, while the extension agent helps to solve the problem by providing information support, eliminating uncertainties and offering alternatives. As explained in the 'self-help' principle of extension, the extension agent does not solve people's problems directly but tries to enable people to stand on their own feet by providing them with problem-solving skills (Demiryürek, 2010).

4-RURAL COMMUNICATION AND BIG DATA PROCESSING

In Turkey, agricultural advisory services are defined as services carried out by non-governmental organisations, chambers of agriculture, companies and independent agricultural advisors for a fee in order to meet the needs of agricultural enterprises on agricultural information, techniques and methods in a timely and adequate manner (Anonymous, 2024c).

In agriculture, industry and other sectors, big data, i.e. numerical and textual data, are produced in large quantities. In parallel, it has reached great potential in utilising ICTs for communication, information sharing and information preservation and thus fostering social interaction and multi-actor innovation. However, there is also abuse of ICTs and Big Data. There are significant barriers that need to be overcome in order to fully utilise data from the right perspective. These obstacles can be grouped as technical, organisational and psychological. The most real and accurate common sense information sharing should be foreseen in mass media. In order to transform producer-originated information into consumer preference, social media tools, mainly advertising, are also widely used.

Farmers may not be able to access information due to lack of reliable and fast internet connection, personal and cultural reservations, limited availability of appropriate information. In order to reduce problems in agricultural production and food safety, it is necessary to provide easily accessible and user-friendly internet infrastructure. In our country, there are negativities in internet accessibility that can be evaluated as economic difficulties and technical weaknesses (Anonymous, 2024d).

Using social media and different communication tools, lectures should be organised for producers and good examples in the field of application should be shown. Professional agricultural education and extension teams should be formed for this purpose.

Agricultural extension is closely related to production in rural areas. Nowadays, agricultural production is carried out at a considerable level in areas that are urbanised as metropolises. A multilateral and wide-ranging food design, which is monitored and managed by the public with a scientific mind, should be developed for sustainability.

5-CONCLUSION AND SOLUTION SUGGESTIONS

The concept of food security can be considered as the most risk-free way of organising the danger of hunger. Food security refers to access to healthy food. Increasing economic opportunities make safe food more attractive. In production prioritising food security, the fact that the cost is above the market price is less taken into consideration. The use of pesticides increases yield and quality. Although it increases visual appeal, it is seen that it brings very serious risks in terms of health.

In toxicological studies conducted to date, it has been determined that pesticides cause poisoning in humans by entering through the skin, mouth and respiratory tract. Again, poisoning can be seen as acute or chronic poisoning depending on the dose as a result of accidental or direct ingestion of pesticides during application. Apart from the harmful effects of pesticides on humans, pesticides also affect parasiticides and predators, which are the most important factors that suppress pests in nature. These beneficial insects are more sensitive to pesticides and are highly affected by pesticides. The populations of natural enemies, which keep the pest populations in balance, are affected by the continuous use of pesticides and the pests on which the natural enemy pressure is removed become a problem. As a result of the pollution in the soil caused using pesticides, microorganisms in the soil are also affected by pesticides. In addition, honeybees, wildlife and domestic animals are also heavily affected using pesticides (Altıkat et al., 2009; Yıldırım, 2008). In many similar studies, the multifaceted interaction of food and production is revealed through multidisciplinary studies.

Innovation studies are increasingly focussed on facilitation and the processes of human interaction that facilitation and learning engender. There is a need for teams specialised in each area of the various foods and able to objectively update accurate information. However, traditional extension advisors should be encouraged to take on new roles. In this context, support should be provided to increase the basic competences of extension strategies and methods, developers. More research is needed to improve the effectiveness of extension in the area of food safety in relation to education and training as well as institutional clustering and governance structures (including financing mechanisms). Recommendations that are broadly applicable, fair and focused on the solution process should be operationalised. A transformative, constructive and participatory structure should be created by operating the instructive model where knowledge is transferred. Young farmers and especially women farmers should be prioritised with positive discrimination in the provision of support and grants.

Acting at the centre of sustainability, the role of agricultural extension and education should be planned to encourage learning about current innovations and our understanding of transformation and transformation that will emerge accordingly.

There should be efforts to share a diversity of theoretical perspectives, case studies and practical examples that will make a constructive contribution to the debate on food production and food safety in the context of sustainability-oriented systems.

Food advertisements and various publications in various communication channels, especially in social media, create a level of knowledge in consumers. It is important for both producers and consumers to reach the right information in today's world. Agricultural extension and training activities to be carried out on agriculture and food should teach accurately and effectively. In this way, consumers will be provided with proper nutrition and access to healthy food.

RESOURCES

Anonymous, (2010) Resmî Gazete. Veteriner Hizmetleri, Bitki Sağlığı, Gıda ve Yem Kanunu Kanun Numarası: 5996 Kabul Tarihi: 11/6/2010 Yayımlandığı Resmî Gazete: Tarih: 13/6/2010 Sayı: 27610 Yayımlandığı Düstur: Tertip:5 Cilt:49 [Erişim.10.12.2024] www. mevzuat.gov.tr.

Anonymous, (2021). Ticaret Bakanlığı. Yeşil Mutabakat Eylem Planı. [Erişim Tarihi:12.12.2024] https://ticaret.gov.tr/data/60f1200013b876eb28421b23/MUTABAKAT%20YE%C5%9E%C4%B0L.pdf

Anonymous, (2024a). Tarım ve Orman Bakanlığı [Erişim Tarihi:01.12.2024] https://www.tarimorman.gov.tr/SGB/Duyuru/100/Bakanligimiz-2019-2023-Stratejik-Plani-_guncellenmis-Versiyon_-_2022_-Yayimlanmistir

Anonymous, (2024b). Tarım ve Orman Bakanlığı [Erişim Tarihi:01.12.2024] https://www.tarimorman.gov.tr/EYDB/Belgeler/TDYH/yonetmelik.pdf

Anonymous, (2024c) Tarım ve Orman Bakanlığı. Tarımsal Yayım ve Danışmanlık Hizmetleri Uygulama Esasları. [Erişim:10.12.2024] https://www.tarimorman.gov.tr/Konular/Egitim-Ve-Yayim/Tarimsal-Danismanlik

Anonymous, (2024d). İstanbul Planlama Ajansı. [Erişim Tarihi:12.12.2024] https://ipa.istanbul/yayinlarimiz/genel/hanehalki-bilisim-teknolojileri-kullanim-arastirmasi-2024/

Akdoğan, A., Divrikli, Ü., ve Elçi, L. (2012). Pestisitlerin önemi ve ekosisteme etkileri. Akademik Gıda, 10(1), 125-132.

Altıkat, A., Turan, T., Torun, F. E., & Bingül, Z. (2009). Türkiye'de Pestisit Kullanımı ve Çevreye Olan Etkileri. Atatürk Üniversitesi Ziraat Fakültesi Dergisi, 40(2), 87-92.

Ban, A. V. D., and Hawkins, H. S. (1996). Agricultural extension (pp. ix+-294).

Cinemre, H. A., & Demiryürek, K. (2005). Tarımsal Yayım ve Haberleşme. Ondokuz Mayıs Üniversitesi Ziraat Fakültesi Ders Kitabı, (17), 5.

Demiryürek, K., (2010). Tarımsal Yayım ve Danışmanlık Kavramları ve Felsefesi. [Erişim: 07.12.2024]www.academia.edu/48317093/Tarımsal_Yayım_ve_Danısmanlık_Kavramları_ve_Felsefesi

Koç, G., ve Uzmay, A. (2015). Gıda Güvencesi ve Gıda Güvenliği: Kavramsal Çerçeve, Gelişmeler ve Türkiye. Tarım Ekonomisi Dergisi, 21(1 ve 2), 39-48.

Leeuwis, C., and Van den Ban, A. (2004). Communication for Rural İnnovation: Rethinking Agricultural Extension Blackwell Science. Experimental Agriculture, 41(2), 269-269.

Yıldırım, E. (2008). Tarımsal zararlılarla mücadele yöntemleri ve kullanılan ilaçlar. Atatürk Üniversitesi Ziraat Fak. Yayınları, Yayın, (219).

Chapter 3

RESEARCH AND DEVELOPMENT (R&D) ACTIVITIES IN THE AGRICULTURAL SECTOR

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1- INTRODUCTION

Agriculture is one of the most important production activities carried out by human beings. We can define agriculture as a set of activities carried out for food production under the main title of plant and animal production. Agriculture maintains its importance today as in the past. The worldwide pandemic process and the subsequent Russia-Ukraine war have shown us how strategically important agriculture is. In our world, depending on the increasing population, the most important agenda item will be the feeding/non-feeding of humanity with the available resources. The deterioration of the world's natural balance has intensely affected agriculture and the environment.

Due to the increase in the world population, increasing demand for more crop yields, the need for efficient use of limited natural resources, and the increasing use of information and communication technology, interest in technological innovations in agriculture has started to increase.

Agriculture is being transformed by Research and Development (R&D) and innovation. We can even state that this transformation is faster today than in the past. Among the factors that increase productivity in agriculture is the use of technology. Therefore, the development of technology and methods is the most important agenda item for scientists. Studies on R&D and innovation are of great importance. Studies on R&D and innovation are becoming increasingly important in science, agriculture, health, education, industry, tourism, business and many other fields. It makes a difference in issues such as providing competitive advantage for businesses, understanding customers' expectations for consumption and predicting market positions.

R&D activities are of great importance in the agricultural sector as in other sectors. R&D involves the development of new technologies, improvement of existing methods, and efforts to obtain solutions. R&D and innovation studies carried out in the field of agriculture is an approach that aims to increase productivity, economic and environmental sustainability and quality products by using new and advanced technological methods and approaches in the agricultural sector. R&D and innovation studies aim to produce agricultural products that are more effective, efficient and environmentally sensitive than conventional agricultural practices.

2- MATERIAL AND METHOD

In order to review the literature on R&D and innovation studies and to determine the effects of technology use on the agricultural sector, the main material of the study was carried out through articles, reviews, reports and studies conducted by relevant institutions and organizations within the scope of scientific studies on the field.

3- FINDINGS AND DISCUSSION

Economist Romer (1990) stated that "*economic growth in the long run can be achieved through technological innovations, technological innovations will emerge as a result of R&D activities, and there will be a strong correlation between R&D, innovation and economic development*". In Romer's model, the most important engine of economic growth is R&D activities.

In a study conducted in the US, the relationship between R&D expenditures financed by the public and private sectors and economic growth was analyzed and it was determined that a 10% increase in R&D expenditures would lead to a 7% increase in real incomes (Griliches, 1998). When the impact of R&D expenditures on the economy in 21 OECD countries between 1965 and 1990 was analysed, it was determined that there was a very strong positive relationship between R&D expenditures and growth and that a 1% increase in R&D expenditures would increase real domestic income by 0.08% (Freire-Serén, 1999). In a study on the effect of R&D expenditures on economic growth in Turkey between 1990 and 2005, it was determined that there is a positive relationship between R&D expenditures and economic growth in the long run (Altın and Kaya, 2009).

In the agricultural sector, different approaches and programs are carried out in major countries with regard to R&D and innovation activities. In the European Union, the innovation and technology transfer network (EIP-AGRI) infrastructure program was established to support agricultural innovation and to promote and share innovations with farmers and stakeholders. EIP-AGRI supports R&D in areas such as sustainable agricultural practices, soil management, water use and agricultural data analytics. Research in the field of biotechnology includes studies on plant breeding and genetic engineering, and regulations and studies are carried out in the field of GMO (Genetically Modified Organisms). Organic agriculture research focuses on the sustainability and quality of organic farming methods and organic products. Smart agriculture technologies such as sensor technologies, remote monitoring and data analytics are being developed and used in Europe.

The United States is engaged in R&D and innovation efforts that are shaping the future of agriculture. Biotechnology and genetic engineering are the main areas where the United States focuses its R&D and innovation efforts. It is a pioneer in the field of agricultural biotechnology and studies are carried out to produce productive and disease-resistant plants through plant breeding studies. Biological control methods and new plant protection products are being developed for disease and pest control. Water management and drought studies are being carried out in different regions for the efficient use of water resources and to combat drought, as water is the most important strategic resource in the future. In the field of smart agriculture, scientific studies are carried out in the field of robotic technologies such as automatic harvesting machines, drone use, other agricultural robot technologies, analysis of agricultural data and the use of big data in order to increase disease-crop prediction and productivity.

R&D and innovation efforts in agriculture in China emphasize genetic and plant breeding to develop high-yielding rice and wheat varieties. Efforts are also being made in smart agricultural technologies, data analytics and environmentally friendly agricultural practices.

India carries out genetic and plant breeding studies to increase productivity in important strategic products such as rice and wheat due to population density and to meet consumption needs. It carries out R&D projects to popularize organic agriculture practices.

In Brazil, R&D studies are carried out on biofuel production and the development of biofuel plants for alternative energy sources. Sustainable forestry and soil management research is carried out in Brazil, where a significant amount of the world's forest wealth is located.

In Turkey, R&D projects are being developed to ensure the efficient use of water resources, promote organic agriculture and popularize environmentally friendly production methods. Studies are also being carried out in the field of data analytics and smart agricultural technologies.

The ratio of gross domestic R&D expenditure to gross domestic product (GDP) in Turkey increased from 0.80% in 2009 to 1.06% in 2019. Gross domestic R&D expenditure amounted to 45 billion 954 million TL in 2019. When we examine the education level of R&D personnel according to 2019 data, we see that 32.8% of them have a doctorate or higher, 24.6% have a master's degree, 32.5% have a bachelor's degree, 5.1% have a vocational college and 5% have high school and below (Anonymous, 2023a).

R&D and innovation in agriculture are studies carried out to increase productivity, environmental sustainability, ensure food security and make the agricultural sector more efficient. In today's world of rapid technological developments, the agricultural sector also has its share of this rapid development. Precision Agriculture was one of the concepts put forward to use technology in agricultural production. Today, the trend is the concept of Smart Farming. The rapid change in information technologies has inevitably started to affect the agricultural sector. If we determine the framework of the concept of precision agriculture and smart farming, precision agriculture is an agricultural system that increases productivity by mapping agricultural areas in detail with satellite images and sensors and by using water, fertilizer and other resources optimally (Morgan and Ess, 2003; Srinivasan, 2006). Smart agriculture is an agricultural system that enables more efficient and sustainable agriculture by monitoring soil moisture, weather conditions, plant growth and diseases in the agricultural field using technologies such as sensor technologies, remote monitoring, data analytics and artificial intelligence (Pivoto et al., 2017). In the smart agriculture approach, studies on artificial intelligence, deep learning, machine learning and data processing come to the fore. Smart agriculture is a management concept for the use of advanced technologies such as big data, cloud and Internet of Things (IoT) to monitor and analyze operations in the agricultural sector. In fact, precision agriculture and smart agriculture are not separate concepts, and today smart agriculture is used more inclusively instead of precision agriculture (Anonymous, 2023b).

Innovations used in agriculture can be summarized as geolocation systems, yield imaging and mapping technologies, soil sampling and mapping of soil properties, remote sensing technologies, technologies for determining field and crop conditions, data processing and decision-making technologies, variable-level application of precision agriculture technologies, automatic steering, hydroponic and aeroponic systems, agricultural robots, biotechnology and pesticide management, agricultural data analytics, water management and recycling and energy efficiency studies (Keskin et al., 2018).

4- CONCLUSIONS AND RECOMMENDATIONS

Productivity gains will be achieved through innovation. By using sensors, remote monitoring systems and data analytics for yield, soil moisture, plant growth, diseases and pests will be monitored more closely, reducing the unnecessary use of agricultural inputs.

In order to ensure food security, innovation efforts will enable the development of more efficient production methods and plant species, while increasing food production and meeting the food needs of the growing world population. Thanks to genetic engineering and plant breeding studies, the nutritional value of plants will be increased, and better-quality products will be obtained. Developing plants that are resistant to the risks posed by climate change and other natural events will reduce the risks of agriculture.

Innovation in agriculture supports the sustainable use of natural resources. Precision farming methods will optimize the use of water and fertilizers, reducing their environmental impact. Innovation can increase farmers' incomes by providing better crop yields. Agricultural technologies and innovation will support economic growth by creating new jobs.

Energy efficiency can be improved by using renewable energy sources and energy-efficient mechanization technologies. Innovation can improve the skills of farmers and technical staff by encouraging the learning of new methods and the sharing of this knowledge.

Innovation in agriculture will make traditional agriculture more efficient, sustainable and effective by combining it with modern technology. It will shape a brighter future for the agricultural sector, benefiting both producers and consumers.

5-RESOURCES

Altın, O. ve Kaya, A. A., (2009). Türkiye'de Ar-Ge Harcamaları ve Ekonomik Büyüme Arasındaki Nedensellik İlişkisinin Analizi. Ege Akademik Bakış: 9 (1) 2009: 251-259.

Anonymous, (2023a). www.tuik.gov.tr. [Erişim Tarihi: 11.07.2023]

Anonymous, (2023b). https://www.techtarget.com/iotagenda/definition/smart-farming. [Erişim Tarihi: 13.07.2023]

Freire-Serén, M. Jesús (1999). Aggregate R&D Expenditure and Endogenous Economic Growth, UFAE and IAE Working Papers, No. WP 436.99.

Griliches, Z. (1998). Introduction to "R&D and Productivity: The Econometric Evidence. NBER Chapters, in: R&D and Productivity: The Econometric Evidence, pages 1-14 National Bureau of Economic Research, Inc.

Keskin, M., Şekerli, Y. E., Say, S. M., ve Arslan, A. (2018). Hassas Tarım Teknolojileri ile Sağlanabilecek Faydalar. Tarım Türk Dergisi, 30, 14-17.

Morgan, M. and D. Ess. (2003). The Precision-Farming Guide for Agriculturists, 2d Edition. Moline, IL: John Deere Publishing.

Pivoto, D., Waquil, PD, Talamini, E., Finocchio, CPS, Dalla Corte, VF ve de Vargas Mores, G. (2017). Scientific development of smart farming technologies and their application in Brazil. Information Processing in Agriculture 5:21-32.

Romer, P. M. (1990). Endogenous technological change. Journal of political Economy, 98(5, Part 2), S71-S102.

Srinivasan, A. (2006). Handbook of Precision Agriculture. Food Products Press, New York

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Chapter 4

THE ROLE OF COPPER IN HUMAN HEALTH AND DISEASE AND SOME APPLICATIONS OF COPPER COMPLEXES

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1. INTRODUCTION

Copper stands out as a trace metal with a very important and versatile role in biological systems. In essence, it carries out transport and storage tasks inside the body by binding to ceruloplasmin, albumin, and other proteins. Furthermore, by forming complexes with biomolecules (particularly proteins and nucleic acids), externally applied copper compounds have an impact on biochemical processes (Iakovidis et al., 2011). The effect of copper on human health has been investigated in detail from molecular physiology and medical-chemical perspectives (Daniel et al., 2004). These studies reveal the important role of copper's transport, metabolism and homeostasis at the cellular level in human diseases (Balamurugan & Schaffner, 2006). The close relationship of copper with iron metabolism and the synergistic effects of these two elements have also been frequently emphasized in studies. Current research focuses on mechanisms related to copper homeostasis and iron metabolism, especially in order to better understand the effect of copper on physiological and pathological processes (Arredondo & Núñez, 2005). New methods for the detection and treatment of disorders linked to copper may be made possible by a deeper comprehension of these processes.

Studies on various biochemical processes that could contribute to the biomedical applications of copper complexes are scarce, despite the fact that the homeostasis of inorganic uncomplexed copper in humans has been mainly established. The increasing interest in copper complexes stems from the potential applications of such compounds in health and medicine. These complexes are notable as antimicrobial, antiviral, anti-inflammatory, antitumor, enzyme inhibitor and chemical nuclease. They are effective in fighting infections, reducing inflammation, suppressing cancer cells and inhibiting enzyme activity. Copper complexes may be effective in combating bacteria and viruses, can be used to reduce inflammatory processes, may show tumor growth inhibitory or lethal effects in cancer treatment, may regulate biochemical processes by targeting the activity of specific enzymes, and may have the potential to modify or damage genetic material by targeting DNA (Jiang et al., 2022). These versatile biological activities of copper complexes carry the potential to offer innovative solutions in drug development and therapeutic applications. Therefore, research on the biochemical effects of copper complexes is of great importance in the fields of medicinal chemistry and biotechnology. In this study, the available data in the literature were examined by taking into account the different physiological activities of copper and especially the biochemical effects and potential applications of copper complexes were emphasized.

An important element in human health: Copper

Organic copper found in foods is metabolized by the liver and transported and stored safely. However, inorganic copper in drinking water or copper supplements largely bypasses the liver and passes directly into the free copper pool in the bloodstream. This poses a potential risk of toxicity because inorganic copper can cross the blood-brain barrier. The stomach and small intestine absorb around half of the average person's daily dietary copper intake, which is about 25 μmol or 1.5 mg. Portal blood that has been linked to albumin carries the absorbed copper to the liver. The liver transports copper to peripheral tissues via ceruloplasmin and albumin. Approximately 10% of the total body copper (approximately 1200 μmol or 80 mg) is stored in the liver. Bile transports excess copper into the gut, where it is expelled as feces. The total of unabsorbed dietary copper and copper expelled back into the gut is known as fecal copper excretion (Iakovidis et al., 2011).

Copper homeostasis is maintained by the balance of absorption efficiency in the intestine and excretion via bile. Absorption efficiency is increased at low copper intake, while this efficiency is decreased at high intake. However, copper balance is mainly regulated by the endogenous excretion mechanisms of the liver.

Copper is a key component of a number of metalloenzymes that are vital in many biological processes, such as hemoglobin synthesis, drug and xenobiotic metabolism, carbohydrate metabolism, catecholamine production, connective tissue protein cross-linking (e.g., collagen and elastin), and antioxidant defense mechanisms. Enzymes that require copper, including cytochrome c oxidase, superoxide dismutase, ferrooxidases, monoamine oxidase, and dopamine β-monooxygenase, are involved in the reduction of reactive oxygen species (ROS) or molecular oxygen. These copper-dependent enzymes contribute to the reduction of ROS and molecular oxygen (Borkow & Gabbay, 2004).

Copper deficiency is rare but is associated with symptoms such as normocytic and leukopenia, hypochromic anemia, and osteoporosis. Although this situation is not common in the general population, ensuring adequate copper intake is important for maintaining optimal health and metabolic processes.

2. COPPER'S FUNCTİON İN HUMAN HEALTH AND HOW IT AFFECTS DİSORDERS

2.1. Copper-Related Disorders and Oxidative Stress

Copper plays a crucial role in maintaining health through its involvement in various enzymatic processes, but an imbalance in copper levels can lead to significant health issues. Anemia, immunosuppression, liver and kidney damage, and developmental toxicity can all result from excessive copper exposure, even if copper homeostasis systems assist avoid toxicity. The main cause of these consequences is oxidative damage to macromolecules and cell membranes. Copper's ability to generate reactive oxygen species (ROS) contributes to oxidative stress, which is associated with a range of health problems. It is believed that copper induces tissue damage by generating free radicals in a manner similar to the Fenton reaction. Studies using the electron spin resonance (ESR) spin-trapping technique have shown evidence of copper-mediated hydroxyl radical formation in living organisms. Interestingly, copper deficiency can also impair the oxidative defense system, leading to elevated ROS levels and oxidative damage to biomolecules such as lipids, DNA, and proteins, as seen in human cell culture models and clinically evident copper deficiency (Bonham et al., 2002; Gaetke, 2003). While excessive copper can damage DNA and interfere with its repair, it can also bind to cysteine thiols, causing oxidation and cross-linking of proteins. This disruption in protein structure and function can interfere with cellular processes. Thus, copper has a "double-edged sword" effect, where both its excess and deficiency can be harmful. Maintaining copper homeostasis is essential to prevent oxidative stress and safeguard overall health (“Spotlight,” 2010).

2.1.1. Wilson's Disease (WD)

Wilson's disease (WD) is an autosomal recessive disorder of copper metabolism caused by a genetic mutation in the ATP7B gene (Bull et al., 1993). The ATP7B gene is responsible for encoding a copper transport protein found in the trans-Golgi network. This protein plays a vital role in directing copper to the secretory pathway, facilitating its binding to ceruloplasmin and enabling its excretion into bile (Gitlin, 2003). The pathophysiology of Wilson's disease is characterized by excessive copper accumulation and the resulting oxidative damage, activation of cell death pathways, and eventual copper leakage into the plasma pool. As a result, copper accumulation occurs in extrahepatic tissues. Hepatic copper overload is characterized histopathologically by swollen hepatocytes, inflammation, and cytoskeletal changes in individuals with WD, and this process eventually leads to cirrhosis (Müller et al., 2004). Wilson's disease may present with severe neurological symptoms. However, if diagnosed in a timely manner, treatment is possible. Treatment options include chelating agents, low-copper diets, and high-zinc (Zn) supplements (Brewer & Askari, 2005).

2.1.2. Menkes Disease (MD).

The X-linked recessive condition known as Menkes disease (MD) is brought on by mutations in the ATP7A gene, which transports copper (Tang et al., 2008). This gene functions as a pump that transports copper into and out of cells, specifically providing transport to the trans-Golgi network for enzymes that require copper. In Menkes disease, copper trafficking within the cell is impaired, but copper uptake in peripheral tissues is normal. The real source of the problem is severely impaired copper absorption in the gastrointestinal tract. This leads to a deficiency of developmentally important copper enzymes, and as a result, replaceable copper deficiency develops (DiDonato & Sarkar, 1997). The clinical manifestations of MD include a disease process that begins in infancy and ends in progressive neurological disorders and death. Copper deficiency, especially in the fetal brain, leads to severe brain damage. Preventing copper absorption from the intestines has a devastating effect on brain development, so early diagnosis and treatment are of great importance. In peripheral tissues, copper can accumulate in the form of metallothionein, but the disruption of intracellular copper traffic prevents the normal use of copper in the body (Tapiero et al., 2003).

2.1.3. Alzheimer’s Disease (AD).

Alzheimer's disease (AD) is a degenerative neurological disorder marked by progressive cognitive decline and loss of functional abilities. In patients with AD, increased cerebrospinal fluid copper levels have been observed with normal plasma copper levels. In addition, some studies have reported increased free copper plasma levels in patients with AD. In a rabbit model, studies found that trace amounts of copper (0.12 ppm) added to drinking water worsened AD brain pathology and cognitive function loss (Brewer, 2009; Squitti et al., 2021). These conclusions are corroborated by population-based research that suggests diets high in saturated and trans fats and high copper intake may be linked to faster cognitive deterioration. Copper's involvement in AD may be linked to its interactions with β-amyloid peptide and amyloid precursor protein, specifically in amyloid plaques and neurofibrillary tangles. Through cellular oxidative stress, this interaction might play a role in the disease's etiology. By preventing amyloidogenic peptide from aggregating and lowering β-amyloid peptide oxidation, copper ions can lower reactive oxygen species (ROS) generation. The precise molecular process, however, is unknown from research on copper metabolism in prion disorders and Alzheimer's disease (Haeffner et al., 2005). It has been commonly recognized that Alzheimer's disease is caused by aberrant brain copper distribution, copper buildup in amyloid plaques, and copper deficiency in surrounding cells, even though recent research have demonstrated that copper prevents the creation and accumulation of β-amyloid plaques in vitro.

To precisely grasp copper's role in AD, more research is necessary (Hureau & Faller, 2009).

2.1.4. Cancer

Increased levels of ceruloplasmin and copper have been observed in various tissues in association with cancer. Ceruloplasmin is a protein that carries approximately 90% of serum copper and has been associated with cancer progression. However, the evaluation of copper deficiency as an anticancer strategy is an interesting area of research, although clinical studies have generally not been encouraging. Copper's precise function in the development of cancer is unknown, however it is most likely related to oxidative stress and the generation of reactive oxygen species (ROS) (Goodman et al., 2004; Gupte & Mumper, 2009).

Additionally, recent research has demonstrated that copper proteins are linked to metabolic alterations in cancer cells. Copper is also essential for angiogenesis, or the creation of new blood vessels, where it plays a crucial role, especially by promoting the migration and proliferation of human endothelial cells. These findings reveal an important aspect of understanding the potential role of copper in the development and progression of cancer. However, more research is needed to fully understand the effects of copper on cancer (Tisato et al., 2010).

3. LİGAND-BASED COPPER COORDİNATİON COMPOUNDS WİTH DİFFERENT DONOR ATOMS

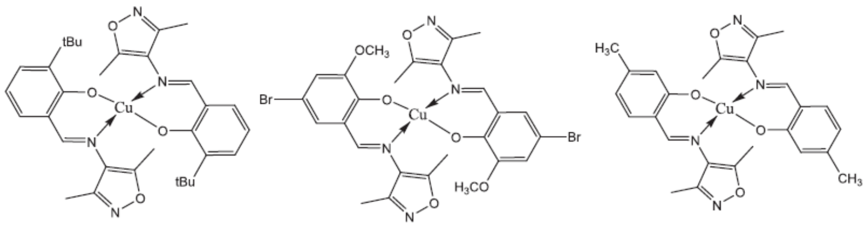
3.1. N- and O-Donor Ligands

Ligands containing N&O donor sites have a significant effect on the chemical behavior and structural properties of transition metal complexes. Such ligands have bidentate or polydentate binding modes, being able to bind to the metal center via both nitrogen (N) and oxygen (O) atoms.

In a study, copper(II) complexes containing N,O-donor isoxazole Schiff base ligands (Figure 1) were synthesized and characterized by various methods. The analyses showed that the complexes have a square planar structure. The interactions of these complexes with DNA were examined by UV-vis absorption and fluorescence quenching titration measurements and it was determined that they bind with CT-DNA in an intercalative binding mode. The binding affinity order was found to be C1 > C3 > C2.

DNA cleavege activities of the complexes were tested on supercoiled plasmid DNA (pBR 322) in the presence of H_2O_2 (oxidative cleavege) and UV light (photolytic cleavege). The results showed that all complexes exhibited significant

DNA cleavege activities. In addition, it was determined that the antimicrobial activity of Cu(II) complexes was higher compared to free Schiff bases. This increase was attributed to the coordination effect of the copper ion (Pradeep Kumar et al., 2023).



C1 C2 C3

Figure 1 isoxazole Schiff bases and their binary Cu(II) complexes

Two aspirin anions (A) and the phenanthroline derivative N-(1,10-phenanthroline-5-yl)-nonanamide (L) were produced as ligands for a copper(II) complex called CuLA (Figure 2). CuLA demonstrated exceptional DNA cleavage and cytotoxicity. Significant cell arrest in the G1 phase and a comparatively low amount of cellular ROS were noted in SKOV-3 cells treated with the combination.

The redox activity of the copper(II) center was only marginally impacted by the addition of aspirin to the copper complex as compared to the analog of CuLA, while the complex's mitochondrial accumulation was greatly boosted. Significant impairment of mitochondrial activities resulted, and more significantly, aspirin showed anti-inflammatory potential by inhibiting COX-2 to the complex in LPS-stimulated macrophages. Given the detrimental consequences of conventional platinum-based chemotherapeutics and the beneficial role of inflammatory cytokines in the tumor microenvironment, copper complexes with various cellular targets and anti-inflammatory properties may signal a new direction in the development of anticancer medications (Shi et al., 2019).

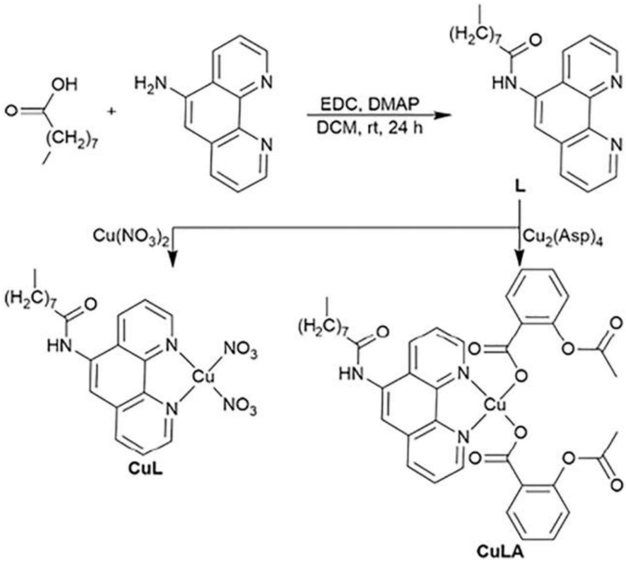


Figure 2 Copper complexes with ligand L via a synthetic pathway. Aspirin is referred to as Asp.

3.2. N- and S-Donor Ligands

In recent years, N, S donor ligand transition metal complexes have become an important area of research due to their encouraging results in antibacterial and antifungal activities. Among these complexes, thiosemicarbazones stand out as strong sulfur donor ligands, especially for transition metal ions.

The biological activity of thiosemicarbazones and their derivatives generally increases as a result of complexation with metal ions. This increase results from the interaction of the ligands with the transition metal, resulting in a more effective structure that benefits from the properties of both the ligand and the metal (Byrnes et al., 1990; Chandra & Sharma, 2009; Mishra & Soni, 2008; Singh et al., 2006).

Pyrazole-based metal complexes are among the compounds that attract attention as anticancer agents due to their N, S donor properties. These complexes show biological activity by providing strong coordination to metal ions through the nitrogen atom of the pyrazole ring and the attached sulfur groups (Ansari et al., 2017; Tigreros & Portilla, 2020).

Metal complexes of ligands obtained by the interaction of carvone with thiosemicarbazones (Figure 3) were synthesized and the free radical scavenging activity of these compounds was investigated. The investigated compounds exhibited quite strong antioxidant activity and this showed that the test compound ligand IPMCHTSC and IMCHPhTSC and their complexes have strong antioxidant properties.

Tests conducted under laboratory conditions revealed that the synthesized compounds have great potential as synthetic antioxidants. The results indicate that these compounds can be used as dietary antioxidants and may have positive effects on health due to their free radical damage preventing properties. These findings emphasize the potential of metal complexes and organic ligands to increase antioxidant activities (Choudhary et al., 2011).

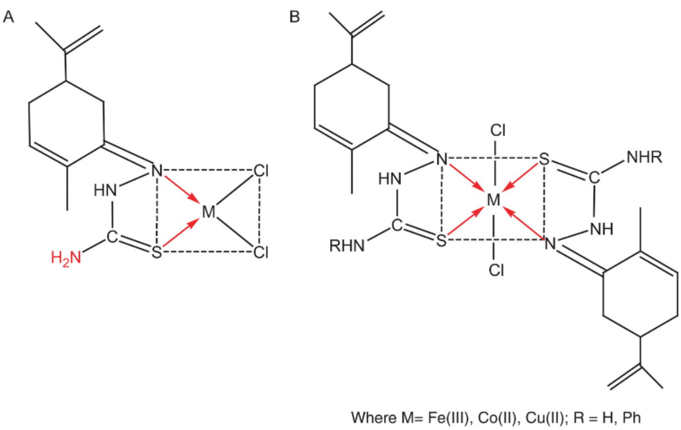


Figure 3 Structural formula for the carvone thiosemicarbazone complexes

The coordination of the copper center to free ligands was crucial in enhancing inhibition, according to the MTT assay analysis of a group of N, S donor pyrazole-based ligands and their Cu(II) complexes (Figure 4). These complexes may be good candidates for additional testing for anticancer applications. Compared to other synthetic compounds, the complex [Cu(EtNCSPz)$_2$] exhibited superior activity in the in vitro MTT experiment. Docking experiments found that when the copper core was coordinated with ligands, the complexes interacted better than when the ligands were unbound. Additionally, the CDK2 protein-bound complex [Cu(PhNCSPzMe$_3$)$_2$] (18) and the EGFR-bound ligand Na[PhNCSPzPh$_2$] (10) had the greatest binding energies of all the compounds that were examined, with a binding energy of -9.81 kcal/mol and -8.85 kcal/mol, respectively. On the other hand, QSAR studies showed that the dipole moment value was directly related to the IC50 values obtained and had a strong effect on the anticancer cytotoxicity response (Ghorbanpour et al., 2022).

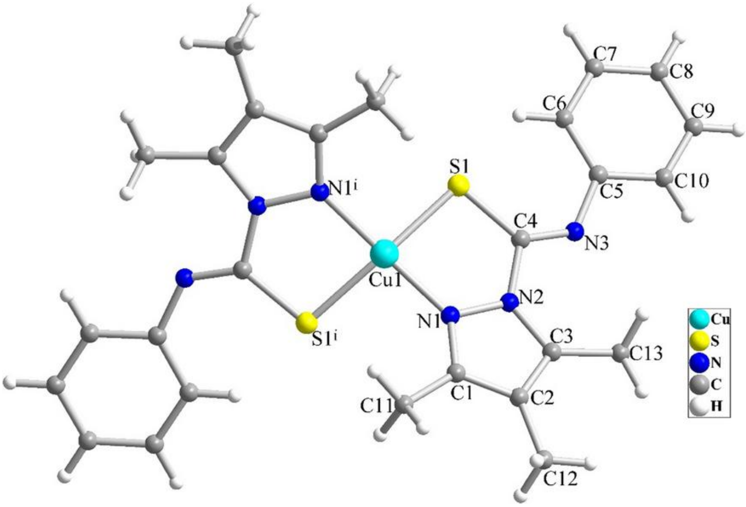


Figure 4 As anticancer drugs, copper (II) complexes with ligands based on N, S donor pyrazoles

Cu-ATSM 14 (Figure 5) is a biologically active copper coordination compound based on thiosemicarbazide and has been used as a PET hypoxia imaging agent in head and neck cancers by labeling with radioactive isotopes such as 64Cu, 62Cu, 60Cu. Clinical studies have shown that Cu-ATSM provides better results compared to the widely used 18-fluorodeoxyglucose (FDG). The accumulation of the drug in hypoxic regions has been associated with Cu(II)/Cu(I) redox transitions.

The hypoxia-specific working mechanism of Cu-ATSM includes the following: Entry into the cell via passive diffusion begins with the passive entry of Cu-ATSM labeled with radioactive isotope into the cells. In the intracellular environment, Cu(II) compound is reduced to Cu(I). In normoxic conditions, Cu(I) is rapidly oxidized to Cu(II) by intracellular oxygen and leaves the cell. Under hypoxic conditions, Cu(I) becomes stable and dissociates into the ligand-metal ion. This process leads to the accumulation of the radionuclide in hypoxic tumor regions. It binds to intracellular chaperone proteins, providing hypoxia-specific targeting.

This mechanism ensures that Cu-ATSM accumulates only in hypoxic tumor cells, while preventing damage to healthy cells. This selectivity makes Cu-ATSM a promising agent for both hypoxia imaging and potential cancer therapy.

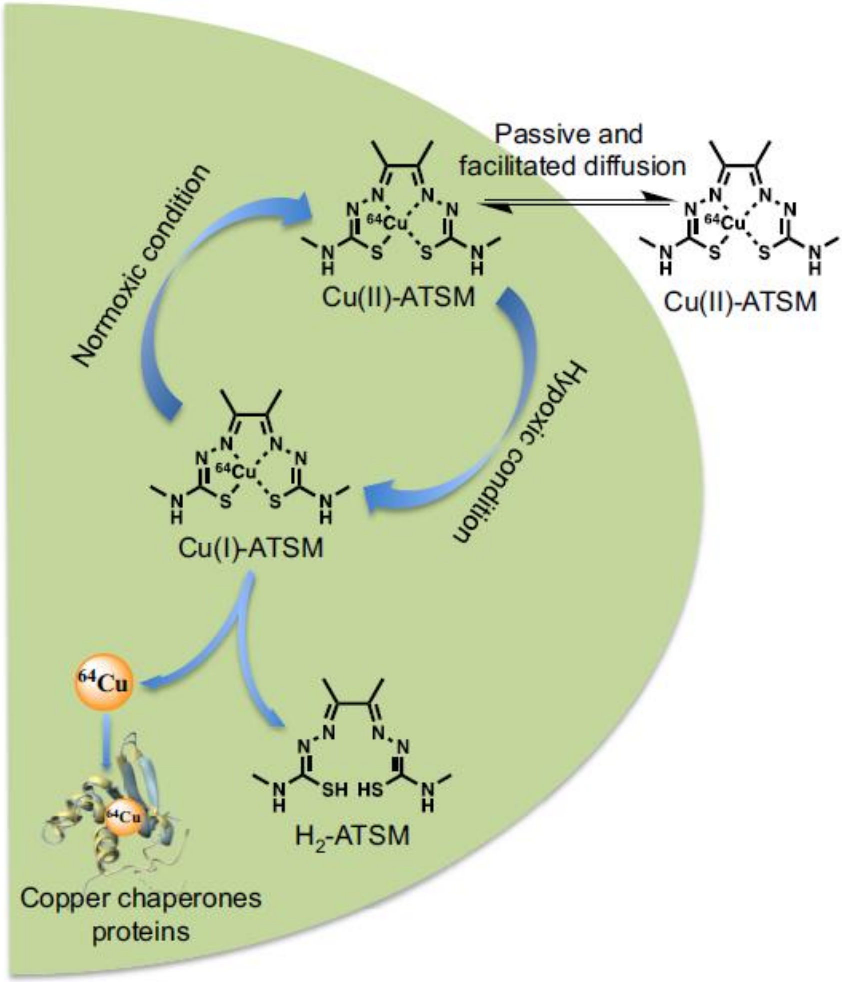


Figure 5 The cellular 64Cu-ATSM uptake and retention mechanism can be summarized as follows: Under hypoxic conditions, Cu(II)-ATSM (oxidation state of copper-64 +II) is reduced to Cu(I)-ATSM (oxidation state of copper-64 +I) via intracellular reduction processes. This reduction leads to the destabilization of the complex and releases free copper-64. The released copper-64 is captured by intracellular copper chaperone proteins and accumulates there. This process is an important mechanism for effective imaging and targeting of hypoxic regions.

3.3. N/N Donor Ligands

N-donor ligands are ligands that contain one or more nitrogen atoms in their structure and coordinate to a metal ion through these nitrogen atoms. The nitrogen atom carries a free electron pair (lone pair) to form a bond with the metal ion. This feature allows N-donor ligands to form stable complexes with transition metals and other metal ions. N-donor ligands have a wide range of uses in coordination chemistry due to their strong binding ability to metals and their flexibility.

The newly synthesized copper(II) heteroleptic mononuclear complexes have been extensively studied in terms of both their structural and biological properties, and very promising results have been obtained. These copper(II) complexes containing N/N donor ligands have been successfully synthesized and structurally characterized. Such complexes are known to exhibit high stability and biological activity in coordination chemistry.

Their interactions with DNA were studied by UV-vis absorption, fluorescence and CD (circular dichroism) titrations, and it was determined that the complexes exhibited intercalative binding to DNA (Figure 6). Intercalative binding means that the complex inserts between DNA base pairs and creates changes in the structure of DNA, and this mechanism is generally of critical importance for the effectiveness of anticancer agents. Protein interaction studies were performed using BSA (bovine serum albumin). These studies showed that the complexes interacted with the protein via a static quenching mechanism. Static quenching revealed that the complexes formed a stable complex with BSA and could play an important role in drug transport processes in biological systems. In vitro cytotoxicity studies of the complexes on HepG-2 (hepatocellular carcinoma) cell line showed that they had effective cytotoxic activity and provided satisfactory IC_{50} values. These results indicate that the complexes have a high potential to inhibit the growth of cancer cells and are promising in terms of anticancer drug development processes. In conclusion, the interaction with DNA, protein binding and cytotoxicity properties of these complexes have made them valuable candidates for anticancer drug development processes. In addition, they offer potential application areas for advanced biological studies such as genomic effects and topoisomerase activities. The use of such complexes in areas such as cancer therapy and biomolecule interactions can provide significant contributions to future drug development processes. However, the examination of additional parameters such as biological safety, specific targeting capabilities and pharmacokinetic properties of these complexes is of critical importance for transition to clinical applications (Tummalapalli et al., 2017).

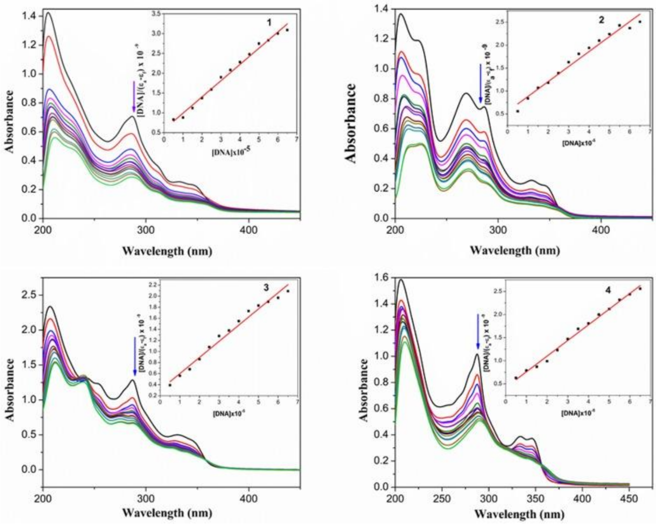


Figure 6 Spectra of electronic absorption showing the titration of complexes 1–4 against DNA. The arrows show that as the concentration of DNA increases (0–26 μM), the absorbance decreases. The inset graph's intercept can be used to compute the intrinsic binding constant.

Using bioactive chromone pharmacophore and N,N-donor auxiliary ligands, three new copper(II) therapeutic complexes were created for application as anticancer chemotherapeutic drugs. The interactions of these complexes with ct-DNA and tRNA (Table 1), as well as the structure-activity connections between them, were investigated using UV-vis, fluorescence, EPR, and circular dichroism techniques. Research showed that the complexes have a greater affinity for binding tRNA than ct-DNA. Additionally, it was shown that the biological activity was greatly impacted by structural alterations of the N,N-donor ligands utilized in the complexes, such as 1,10-phenanthroline, 2,2′-bipyridine, and 1R,2R-DACH.

The single-strand cleavage activity of the complexes with pBR322 DNA was examined and it was determined that all complexes exhibited effective cleavage ability via oxidative mechanisms. This mechanism includes reactive oxygen species (ROS), singlet oxygen ($^1O_2$), superoxide anion ($O_2^{\cdot -}$) and peroxide-assisted cleavage reactions. Similarly, the cleavage activity of the complexes on tRNA was also effectively performed depending on time and concentration.

The in vitro cytotoxic activities of the complexes were evaluated in four different human cancer cell lines using the SRB assay. The results showed that the GI_{50} value of the synthesized complexes was <10 μg mL^{-1} (<20 μM) in most cell lines. Growth curve data revealed that especially complex 1 showed high activity against MIA-Pa-Ca-2 (pancreatic cancer), HeLa (cervical cancer) and MCF-7 (breast cancer) cell lines and had a stronger cytotoxic effect compared to the standard drug adriamycin (ADR). Complexes 2 and 3 were found to be effective on a wide spectrum of cancer cells.

Particularly, complex 1 showed great promise for chemotherapeutic interventions in pancreatic cancers, while other complexes exhibited an active profile against most of the cancer cell lines tested. These results suggest that the synthesized copper(II) complexes are strong candidates for future investigations as antitumor chemotherapeutic agents (Arjmand et al., 2018).

Table 1 The binding constant values for interaction of complexes **1–3** with ct-DNA/tRNA

			Emission spectroscopy	
Complexes		**Absorption spectroscopy K_b (×10^4 M^{-1})**	**K (×10^4 M^{-1})**	**K_{sv} (×10^4 M^{-1})**
1	ct-DNA	5.81(±0.2)	4.77(±0.31)	6.12(±0.05)
	tRNA	9.4(±0.11)	8.4(±0.1)	9.4(±0.4)
2	ct-DNA	2.5(±0.4)	1.8(±0.08)	3.8(±0.13)
	tRNA	4.7(±0.2)	5.6(±0.05)	7.2(±0.1)
3	ct-DNA	3.05(±0.1)	3.89(±0.4)	4.68(±0.02)
	tRNA	2(±0.12)	6.8(±0.21)	8.8(±0.5)

3.4. S Donor Ligands

S donor ligands are ligands that contain sulfur atoms and can bind to metal ions through these atoms. These ligands generally have an important place in coordination chemistry due to their high coordination abilities and chemical diversity. S/S donor ligands can bind to transition metals and heavy metal ions with high affinity thanks to the strong donor properties of sulfur atoms. S/S donor ligands offer innovative solutions in various areas by modulating both the chemical and biological properties of the complexes they form with metals.

Disulfiram, originally developed for alcoholism treatment, has demonstrated significant anticancer potential in recent studies, particularly against hematological malignancies and solid tumors. However, its clinical use in cancer therapy has been limited due to instability in gastric conditions and rapid degradation in the bloodstream. This study addresses these challenges by encapsulating disulfiram in folate-receptor-targeted PLGA nanoparticles (NPs), allowing for targeted delivery, controlled release, and enhanced stability.

Physicochemical properties, such as size and morphology, were optimized to exploit the enhanced permeability and retention (EPR) effect, enabling NPs (10–220 nm) to penetrate leaky tumor vasculature while avoiding rapid renal clearance or elimination by the immune system. Folate-conjugated NPs (DS-PPF-NPs) exhibited higher drug content, improved encapsulation efficiency, and a sustained release profile, with an initial burst followed by prolonged release over 96 hours.

Targeted delivery of DS-PPF-NPs was particularly effective against folate receptor-positive breast cancer cells (MCF7), demonstrating superior cellular uptake via folate receptor-mediated endocytosis. Folate conjugation further enhanced the affinity and cytotoxicity of the NPs, leading to increased ROS production and apoptosis induction in MCF7 cells compared to free disulfiram or non-targeted NPs (DS-P-NPs).

MTT assays confirmed that disulfiram-loaded NPs were significantly more cytotoxic to breast cancer cell lines (MCF7 and 4T1) than free disulfiram, likely due to higher cellular internalization and the ability to bypass drug resistance mechanisms such as P-glycoprotein pumps. In vivo studies revealed notable tumor growth inhibition, attributed to the improved stability and accumulation of encapsulated disulfiram at the tumor site.

Overall, encapsulating disulfiram in folate-receptor-targeted PLGA-PEG NPs (Figure 7) provides a promising strategy for enhancing its therapeutic efficacy, offering a cost-effective and clinically translatable approach to cancer treatment (Fasehee et al., 2016).

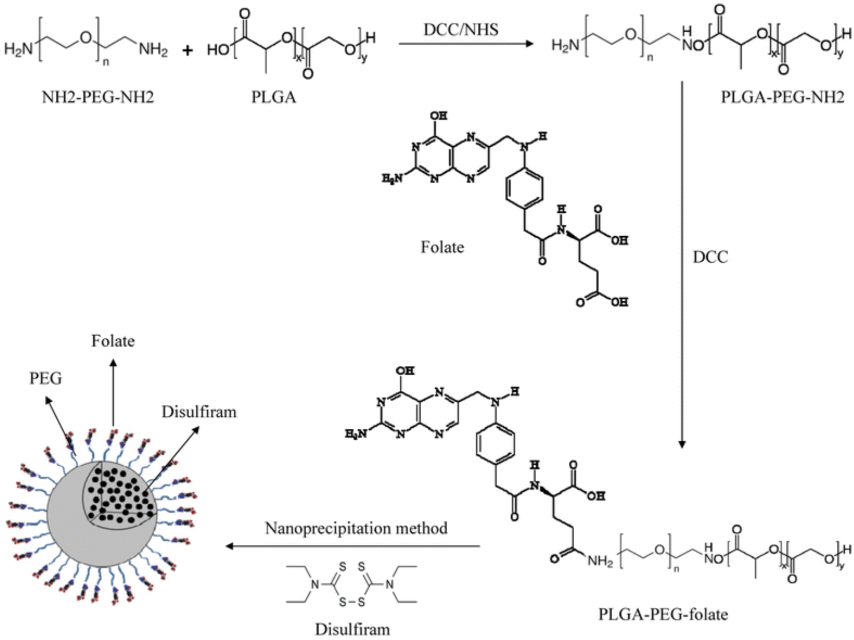


Figure 7 A representation of PLGA-PEG-folate synthesis and NPs preparation procedure

The study by Yang et al. investigates the anti-tumor effects of DSF-Cu (Disulfiram-Copper), a drug traditionally used for alcoholism treatment, on nasopharyngeal cancer cells (CNE-2Z) and normal epithelial cells (NP69-SV40T) (Figure 8). The findings show that DSF-Cu selectively induced apoptosis in CNE-2Z cells without affecting NP69-SV40T cells, causing significant G2/M phase arrest by disrupting α-tubulin and microtubule structures, which inhibited cancer cell proliferation. Additionally, DSF-Cu generated excessive ROS, triggering the NF-κB signaling pathway, leading to inflammation and apoptosis. The study also observed changes in cell membrane ultrastructure, including shrinkage and surface smoothing, in CNE-2Z cells. Furthermore, DSF-Cu increased cell stiffness and adhesion, suggesting a disruption of the cytoskeleton. The treatment also upregulated E-cadherin expression, promoting stronger cell adhesion and reducing migration, which could inhibit tumor progression. Overall, DSF-Cu shows promise as a treatment for nasopharyngeal carcinoma due to its ability to alter cancer cell mechanics and induce cell death (Yang et al., 2017).

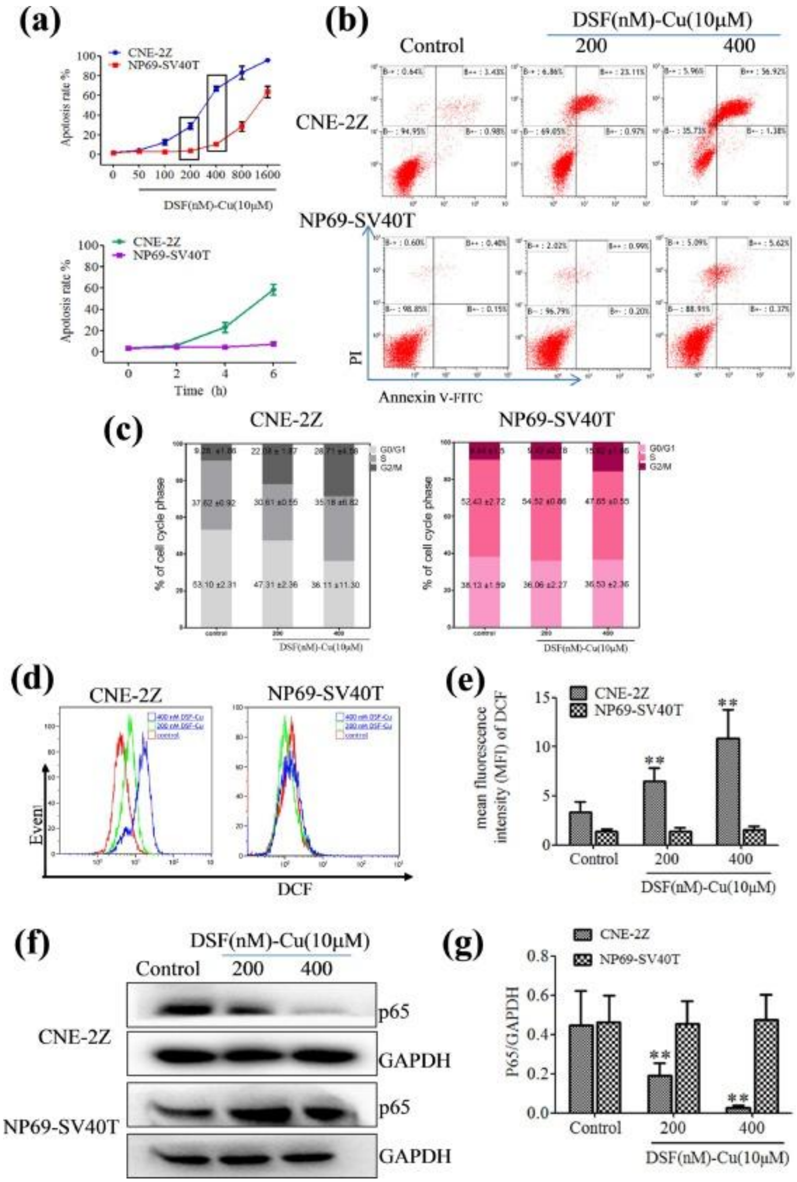


Figure 8 In human nasopharyngeal cancer CNE-2Z cells, DSF-Cu caused cytotoxicity. (a) Time-dependent and dose-dependent curves for CNE-2Z and NP69-SV40T cells treated with DSF-Cu 400 nM and different concentrations of DSF chelated with 10 μM CuCl2 for 6 hours, respectively (b) Illustrations of DSF-Cu-induced apoptosis in NP69-SV40T and CNE-2Z cells (c) A statistical examination of the G2/M cell cycle arrest caused by DSF-Cu in NP69-SV40T and CNE-2Z cells (d) and statistical analysis (e) **P < 0.01 in relation to control. The statistical analysis (g) and the Western blot analysis (f) show that DSF-Cu inhibits the NF-κB signaling-related protein p65 in CNE-2Z and NP69-SV40T cells

3.5. N-, O-, and S-Donor Ligands

O-, N-, and S-tridentate ligands are molecules that bind three donor atoms (usually oxygen, nitrogen, and sulfur) to a metal atom. Such ligands form strong and stable complexes with the metal and are often found in important compounds in coordination chemistry. Tridentate ligands increase stability by binding to the metal atoms at three sites, because this bonding style provides a stronger and more symmetrical interaction with the metal center. These tridentate ligands form 5- or 6-membered ring structures by binding to the metal at three different sites. The stability of such structures is due to the way the ligand bonds to the metal. The coordination environment of the metal is usually stronger and more stable, because these structures have a property called the "chelating effect." The chelating effect allows the ligand to form a stronger and tighter bond around the metal atom. O-, N-, and S-tridentate ligands bind to the metal center, changing the chemical and physical properties of the complex. These complexes are widely used in catalysts, biological systems, medical applications and analytical chemistry.

Recent studies suggest new perspectives for thiosemicarbazones (TSCs) as anticancer agents, particularly their metal complexes. While TSCs with 2-pyridyl groups have been widely studied, salicylaldehyde derivatives also show promising potential. Copper(II) complexes of these derivatives (1-6) (Figure 9) exhibit remarkable anticancer activity, being much more effective than cisplatin against various cancer cell lines, including pancreatic and colon cancers. Complex 1 is notably more effective than cisplatin, showing potent activity in resistant spheroid models, which are more representative of real tumors. The study highlights the importance of subtle structural variations in the ligands, with copper(II) complexes formed from 3-methoxy 2-hydroxyphenyl thiosemicarbazones being more active than others. The complexes primarily localize in mitochondria and target Protein Disulfide Isomerase (PDI), a copper-binding protein involved in cancer cell survival. Unlike other metal-based TSC complexes, these copper complexes do not induce significant oxidative stress but inhibit PDI with much higher potency than Bacitracin, a standard inhibitor. PDI is found in multiple cellular locations, including the surface, mitochondria, nucleus, and cytosol. The compounds may inhibit mitochondrial PDI, leading to cancer cell death without oxidative stress. Further studies are needed to clarify the exact mechanism of action. Preliminary in vivo results are encouraging, and despite challenges with solubility, these metal-based TSC complexes show great promise as cancer therapies (Carcelli et al., 2020).

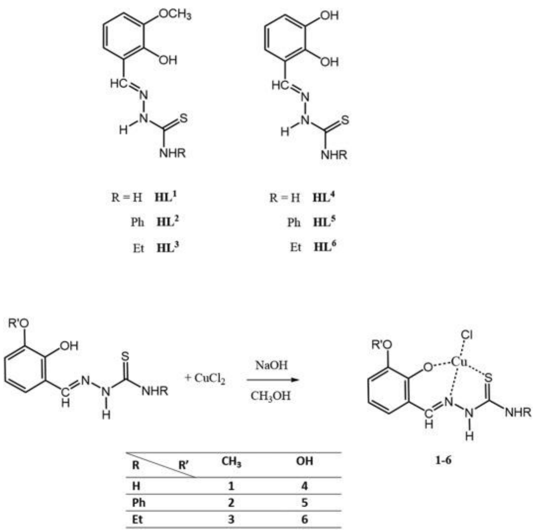
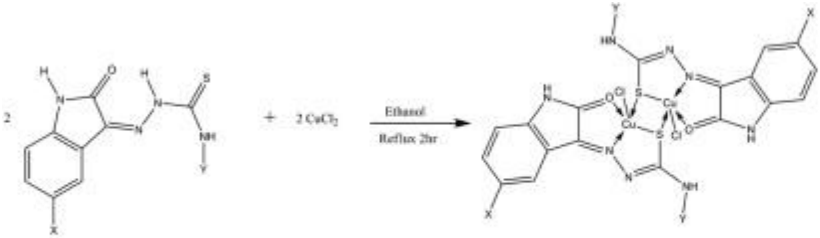


Figure 9 The ligands HL^1-HL^6 and the corresponding copper(II) complexes 1–6.

Qasem Ali et al. have produced and studied six Cu(II) complexes (Figure 10) with tridentate ligands using a variety of spectroscopic techniques. Single-crystal X-ray crystallography was used to determine the crystal structures of CuL2 and CuL3, which showed 5-coordinate complexes with deformed square-pyramidal geometry. Viscosity measurements, UV spectra, and fluorescence spectra were used to examine the complexes' binding interactions with CT-DNA. The results showed an intercalative binding mode. The range of the binding constants (Kb) was 1.6×10^5 to 14.6×10^5 M^{-1}. The complexes' ability to cause plasmid DNA breakage in a concentration-dependent manner was demonstrated by gel electrophoresis tests.

While CuL3–CuL6 showed both oxidative and hydrolytic DNA cleavage capabilities, CuL1 and CuL2 only showed oxidative DNA cleavage. Dose-dependent cytotoxicity with low IC_{50} values ranging from 0.08 to 8.6 μM was found in in vitro anti-proliferative experiments against the human colon cancer cell line (HCT 116). Complexes exhibited higher anti-proliferative effects than the conventional medication 5-fluorouracil (IC_{50} = 7.3 μM) (Ali et al., 2014).



Compound	X	Y
CuL1	H	Phenyl
CuL2	CH_3	Phenyl
CuL3	F	Phenyl
CuL4	NO_2	CH_3
CuL5	CH_3	CH_3
CuL6	CH_3	CH_2CH_3

Figure 10 Synthetic route and structures for the compounds **CuL1**–**CuL6**.

4. CONCLUSİON

Copper is an essential trace element with a multifaceted role in human health, impacting various biochemical processes and physiological functions. Its importance spans from enzymatic activity to cellular metabolism and oxidative stress regulation. Both deficiency and excess of copper can lead to significant health issues, emphasizing the need for a balanced homeostasis. The biomedical potential of copper complexes has emerged as a promising field of research, showcasing antimicrobial, anti-inflammatory, and antitumor activities. These complexes' ability to interact with DNA, modulate oxidative mechanisms, and target specific cellular pathways highlights their therapeutic versatility. Additionally, copper's role in diseases like Wilson's disease, Menkes disease, Alzheimer's, and cancer underscores its dual nature as both a vital nutrient and a potential contributor to pathological states. The development of innovative copper-based compounds, particularly through the strategic design of ligands with tailored donor properties (N, O, S), opens new horizons in medicinal chemistry. These advances present significant opportunities for creating effective and targeted therapeutic agents, particularly in cancer and neurodegenerative disease treatments. In conclusion, copper's dual role in health and disease necessitates careful modulation to harness its therapeutic potential. Continued interdisciplinary research into copper's biochemical roles and the development of advanced coordination compounds holds great promise for future medical breakthroughs.

References

Ali, A. Q., Teoh, S. G., Eltayeb, N. E., Khadeer Ahamed, M. B., & Abdul Majid, A. M. S. (2014). Synthesis of copper(II) complexes of isatin thiosemicarbazone derivatives: In vitro anti-cancer, DNA binding, and cleavage activities. *Polyhedron*, *74*, 6–15. https://doi.org/10.1016/j.poly.2014.02.025

Ansari, A., Ali, A., Asif, M., & Shamsuzzaman, S. (2017). Review: biologically active pyrazole derivatives. *New Journal of Chemistry*, *41*(1), 16–41. https://doi.org/10.1039/C6NJ03181A

Arjmand, F., Afsan, Z., & Roisnel, T. (2018). Design, synthesis and characterization of novel chromone based-copper(<scp>ii</scp>) antitumor agents with *N* , *N* -donor ligands: comparative DNA/RNA binding profile and cytotoxicity. *RSC Advances*, *8*(65), 37375–37390. https://doi.org/10.1039/C8RA06722H

Arredondo, M., & Núñez, M. T. (2005). Iron and copper metabolism. *Molecular Aspects of Medicine*, *26*(4–5), 313–327. https://doi.org/10.1016/j.mam.2005.07.010

Balamurugan, K., & Schaffner, W. (2006). Copper homeostasis in eukaryotes: Teetering on a tightrope. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research*, *1763*(7), 737–746. https://doi.org/10.1016/j.bbamcr.2006.05.001

Bonham, M., O'Connor, J. M., Hannigan, B. M., & Strain, J. J. (2002). The immune system as a physiological indicator of marginal copper status? *British Journal of Nutrition*, *87*(5), 393–403. https://doi.org/10.1079/BJN2002558

Borkow, G., & Gabbay, J. (2004). Putting copper into action: copper-impregnated products with potent biocidal activities. *The FASEB Journal*, *18*(14), 1728–1730. https://doi.org/10.1096/fj.04-2029fje

Brewer, G. J. (2009). The Risks of Copper Toxicity Contributing to Cognitive Decline in the Aging Population and to Alzheimer's Disease. *Journal of the American College of Nutrition*, *28*(3), 238–242. https://doi.org/10.1080/07315724.2009.10719777

Brewer, G. J., & Askari, F. K. (2005). Wilson's disease: clinical management and therapy. *Journal of Hepatology*, *42*(1), S13–S21. https://doi.org/10.1016/j.jhep.2004.11.013

Bull, P. C., Thomas, G. R., Rommens, J. M., Forbes, J. R., & Cox, D. W. (1993). The Wilson disease gene is a putative copper transporting P–type ATPase similar to the Menkes gene. *Nature Genetics*, *5*(4), 327–337. https://doi.org/10.1038/ng1293-327

Byrnes, R. W., Mohan, M., Antholine, W. E., Xu, R. X., & Petering, D. H. (1990). Oxidative stress induced by a copper-thiosemicarbazone complex. *Biochemistry*, *29*(30), 7046–7053. https://doi.org/10.1021/bi00482a014

Carcelli, M., Tegoni, M., Bartoli, J., Marzano, C., Pelosi, G., Salvalaio, M., Rogolino, D., & Gandin, V. (2020). In vitro and in vivo anticancer activity of tridentate thiosemicarbazone copper complexes: Unravelling an unexplored pharmacological target. *European Journal of Medicinal Chemistry*, *194*, 112266. https://doi.org/10.1016/j.ejmech.2020.112266

Chandra, S., & Sharma, A. K. (2009). Antifungal and Spectral Studies of Cr(III) and Mn(II) Complexes Derived from <math> <mn mathvariant="bold">3</mn> <mo>,</mo> <msup> <mn mathvariant="bold">3</mn> <mo>′</mo> </msup> </math> -Thiodipropionic Acid Derivative. *Research Letters in Inorganic Chemistry*, *2009*, 1–4. https://doi.org/10.1155/2009/945670

Choudhary, A., Sharma, R., Nagar, M., & Mohsin, M. (2011). Transition metal complexes with N, S donor ligands as synthetic antioxidants: Synthesis, characterization and antioxidant activity. *Journal of Enzyme Inhibition and Medicinal Chemistry*, *26*(3), 394–403. https://doi.org/10.3109/14756366.2010.518966

Daniel, K. G., Gupta, P., Harbach, R. H., Guida, W. C., & Dou, Q. P. (2004). Organic copper complexes as a new class of proteasome inhibitors and apoptosis inducers in human cancer cells. *Biochemical Pharmacology*, *67*(6), 1139–1151. https://doi.org/10.1016/j.bcp.2003.10.031

DiDonato, M., & Sarkar, B. (1997). Copper transport and its alterations in Menkes and Wilson diseases. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, *1360*(1), 3–16. https://doi.org/10.1016/S0925-4439(96)00064-6

Fasehee, H., Dinarvand, R., Ghavamzadeh, A., Esfandyari-Manesh, M., Moradian, H., Faghihi, S., & Ghaffari, S. H. (2016). Delivery of disulfiram into breast cancer cells using folate-receptor-targeted PLGA-PEG nanoparticles: in vitro and in vivo investigations. *Journal of Nanobiotechnology*, *14*(1), 32. https://doi.org/10.1186/s12951-016-0183-z

Gaetke, L. (2003). Copper toxicity, oxidative stress, and antioxidant nutrients. *Toxicology*, *189*(1–2), 147–163. https://doi.org/10.1016/S0300-483X(03)00159-8

Ghorbanpour, M., Soltani, B., Mota, A., Jahanbin Sardroodi, J., Mehdizadeh Aghdam, E., Shayanfar, A., Molavi, O., Mohammad-Rezaei, R., Ebadi-Nahari, M., & Ziegler, C. J. (2022). Copper (II) complexes with N, S donor pyrazole-based ligands as anticancer agents. *BioMetals*, *35*(5), 1095–1111. https://doi.org/10.1007/s10534-022-00426-0

Gitlin, J. D. (2003). Wilson disease. *Gastroenterology*, *125*(6), 1868–1877. https://doi.org/10.1053/j.gastro.2003.05.010

Goodman, V. L., Brewer, G. J., & Merajver, S. D. (2004). Copper deficiency as an anti-cancer strategy. *Endocrine-Related Cancer*, *11*(2), 255–263. https://doi.org/10.1677/erc.0.0110255

Gupte, A., & Mumper, R. J. (2009). Elevated copper and oxidative stress in cancer cells as a target for cancer treatment. *Cancer Treatment Reviews*, *35*(1), 32–46. https://doi.org/10.1016/j.ctrv.2008.07.004

Haeffner, F., Smith, D. G., Barnham, K. J., & Bush, A. I. (2005). Model studies of cholesterol and ascorbate oxidation by copper complexes: Relevance to Alzheimer's disease β-amyloid metallochemistry. *Journal of Inorganic Biochemistry*, *99*(12), 2403–2422. https://doi.org/10.1016/j.jinorgbio.2005.09.011

Hureau, C., & Faller, P. (2009). Aβ-mediated ROS production by Cu ions: Structural insights, mechanisms and relevance to Alzheimer's disease. *Biochimie*, *91*(10), 1212–1217. https://doi.org/10.1016/j.biochi.2009.03.013

Iakovidis, I., Delimaris, I., & Piperakis, S. M. (2011). Copper and Its Complexes in Medicine: A Biochemical Approach. *Molecular Biology International*, *2011*, 1–13. https://doi.org/10.4061/2011/594529

Jiang, Y., Huo, Z., Qi, X., Zuo, T., & Wu, Z. (2022). Copper-Induced Tumor Cell Death Mechanisms and Antitumor Theragnostic Applications of Copper Complexes. *Nanomedicine*, *17*(5), 303–324. https://doi.org/10.2217/nnm-2021-0374

Mishra, A. P., & Soni, M. (2008). Synthesis, Structural, and Biological Studies of Some Schiff Bases and Their Metal Complexes. *Metal-Based Drugs*, *2008*, 1–7. https://doi.org/10.1155/2008/875410

Müller, T., Langner, C., Fuchsbichler, A., Heinz-Erian, P., Ellemunter, H., Schlenck, B., Bavdekar, A. R., Pradhan, A. M., Pandit, A., Müller-Höcker, J., Melter, M., Kobayashi, K., Nagasaka, H., Kikuta, H., Müller, W., Tanner, S. M., Sternlieb, I., Zatloukal, K., & Denk, H. (2004). Immunohistochemical analysis of Mallory bodies in Wilsonian and non-Wilsonian hepatic copper toxicosis. *Hepatology*, *39*(4), 963–969. https://doi.org/10.1002/hep.20108

Pradeep Kumar, M., Ayodhya, D., & Shivaraj. (2023). Novel copper (II) binary complexes with N,O-donor isoxazole Schiff base ligands: Synthesis, characterization, DPPH scavenging, antimicrobial, and DNA binding and cleavage studies. *Results in Chemistry*, *5*, 100845. https://doi.org/10.1016/j.rechem.2023.100845

Shi, X., Fang, H., Guo, Y., Yuan, H., Guo, Z., & Wang, X. (2019). Anticancer copper complex with nucleus, mitochondrion and cyclooxygenase-2 as multiple targets. *Journal of Inorganic Biochemistry*, *190*, 38–44. https://doi.org/10.1016/j.jinorgbio.2018.10.003

Singh, K., Singh, D. P., Singh Barwa, M., Tyagi, P., & Mirza, Y. (2006). Some bivalent metal complexes of Schiff bases containing N and S donor atoms. *Journal of Enzyme Inhibition and Medicinal Chemistry*, *21*(6), 749–755. https://doi.org/10.1080/14756360600838648

Spotlight. (2010). *Chemical Research in Toxicology*, *23*(10), 1517–1518. https://doi.org/10.1021/tx100295m

Squitti, R., Ventriglia, M., Simonelli, I., Bonvicini, C., Costa, A., Perini, G., Binetti, G., Benussi, L., Ghidoni, R., Koch, G., Borroni, B., Albanese, A., Sensi, S. L., & Rongioletti, M. (2021). Copper Imbalance in Alzheimer's Disease: Meta-Analysis of Serum, Plasma, and Brain Specimens, and Replication Study Evaluating ATP7B Gene Variants. *Biomolecules*, *11*(7), 960. https://doi.org/10.3390/biom11070960

Tang, J., Donsante, A., Desai, V., Patronas, N., & Kaler, S. G. (2008). Clinical outcomes in Menkes disease patients with a copper-responsive ATP7A mutation, G727R. *Molecular Genetics and Metabolism*, *95*(3), 174–181. https://doi.org/10.1016/j.ymgme.2008.06.015

Tapiero, H., Townsend, D. M., & Tew, K. D. (2003). Trace elements in human physiology and pathology. Copper. *Biomedicine & Pharmacotherapy*, *57*(9), 386–398. https://doi.org/10.1016/S0753-3322(03)00012-X

Tigreros, A., & Portilla, J. (2020). Recent progress in chemosensors based on pyrazole derivatives. *RSC Advances*, *10*(33), 19693–19712. https://doi.org/10.1039/D0RA02394A

Tisato, F., Marzano, C., Porchia, M., Pellei, M., & Santini, C. (2010). Copper in diseases and treatments, and copper-based anticancer strategies. *Medicinal Research Reviews*, *30*(4), 708–749. https://doi.org/10.1002/med.20174

Tummalapalli, K., C.S, V., Munusami, P., Pathak, M., & M.M., B. (2017). Evaluation of DNA/Protein interactions and cytotoxic studies of copper(II) complexes incorporated with N, N donor ligands and terpyridine ligand. *International Journal of Biological Macromolecules*, *95*, 1254–1266. https://doi.org/10.1016/j.ijbiomac.2016.11.022

Yang, Y., Li, M., Sun, X., Zhou, C., Wang, Y., Wang, L., Chen, L., Liang, Z., Zhu, L., & Yang, H. (2017). The selective cytotoxicity of DSF-Cu attributes to the biomechanical properties and cytoskeleton rearrangements in the normal and cancerous nasopharyngeal epithelial cells. *The International Journal of Biochemistry & Cell Biology*, *84*, 96–108. https://doi.org/10.1016/j.biocel.2017.01.007

Chapter 5

BIOLOGICAL IMPORTANCE AND SPECTROSCOPIC PROPERTIES OF COPPER: SYNTHESIS OF [CuL_2] COMPLEX OF (Z)-4-methyl-N'-(phenyl(pyridin-2-yl)methylene)benzenesulfonohydrazide AND INVESTIGATION OF ITS SPECTROSCOPIC PROPERTIES

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1. INTRODUCTION

Copper plays important roles in vital biochemical processes in organisms (Festa & Thiele, 2011; Peña et al., 2019; Tisato et al., 2010). Its function as a catalytic cofactor in redox and metabolic reactions and its being a basic component in the structure of many enzymes show that it is indispensable for biochemical mechanisms (Ruiz-Azuara & E. Bravo-Gomez, 2010). In recent years, copper complexes have come to the forefront in cancer treatment research. These molecules attract great attention due to their biological activity and effects on cellular processes (Mariani et al., 2021; McGivern et al., 2018; Mo et al., 2018).

The variable coordination structures and catalytic properties of copper complexes make them an important component in the active sites of enzymes. These properties mediate many biochemical reactions at the cellular level. Studies show that cancer cells have a higher affinity for copper ions compared to other metals and absorb these ions more easily. The uptake of copper ions into the cell may contribute to processes that promote blood vessel formation and metastasis (Gou et al., 2021; Iovan et al., 2017; YANG et al., 2015).

The therapeutic effects of copper complexes are based on various mechanisms. It can induce tumor cell death by increasing reactive oxygen species (ROS), disrupt protein homeostasis by inhibiting proteasome, and prevent vessel formation that provides nutrition to cancer cells with its anti-angiogenesis effect. In addition, copper complexes trigger tumor cell death by covalently binding to the DNA of cancer cells. This mechanism offers a broader antitumor spectrum of action compared to cisplatin, while reducing the risk of toxicity and resistance (YANG et al., 2015).

Copper complexes have lower toxicity, fewer side effects, and a lower risk of developing cellular resistance than traditional chemotherapeutic agents, making them a promising option in cancer treatment. In addition, the ability to increase the specificity of these complexes to biological targets through structural modifications shows the potential to optimize their therapeutic efficacy. Therefore, the investigation of the biochemical role of copper and the therapeutic potential of copper complexes continues to open new doors in the field of cancer biology and treatment (Chaston et al., 2004; Kaczmarek et al., 2018; Wu et al., 2023).

Copper indeed exists in two common oxidation states: Cu(I) (cuprous) and Cu(II) (cupric). Here’s a detailed breakdown of their characteristics based on your description:

Cu(I) (Copper Ions in the +1 Oxidation State):

Electronic Configuration of Cu(I) is [Ar] $3d^{10}$. This full 3d orbital results in no unpaired electrons, making Cu(I) diamagnetic. Diamagnetic because of the absence of unpaired electrons. Typically larger than Cu(II) due to its lower charge, but specific data is required for comparison.

Cu(II) (Copper Ions in the +2 Oxidation State):

Electronic Configuration of Cu(II) is [Ar] $3d^9$. The 3d orbital has one unpaired electron. Paramagnetic due to the presence of the single unpaired electron. Approximately 0.73 Å, smaller than Cu(I) because of its higher positive charge, which pulls electrons closer to the nucleus.

Significance of Magnetic Properties:

- Diamagnetism in Cu(I) arises from paired electrons in its orbitals, leading to no net magnetic moment.
- Paramagnetism in Cu(II) stems from the unpaired electron in the 3d orbital, which aligns with external magnetic fields and exhibits weak attraction.

These properties play critical roles in the chemistry of copper compounds, influencing their reactivity, bonding, and interaction with ligands in coordination complexes.

The crystal field effect causes the d-orbitals of the Cu^{2+} ion (d^9) to divide into t_{2g} and e_g levels in an octahedral crystal field. The electronic configuration of Cu^{2+} in an octahedral crystal field is $t_{2g}^6e_g^3$, which corresponds to the ^2E_g term as the ground state. The e_g orbitals are partially filled, making this configuration prone to distortions caused by the Jahn-Teller effect. The excited state configuration is $t_{2g}^5e_g^4$, corresponding to the $^2T_{2g}$ term. The only expected electronic transition is $^2E_g \rightarrow ^2T_{2g}$, with an energy difference of 10Dq, representing the crystal field splitting energy in an ideal octahedral field.
Due to the partially filled eg orbitals in the d^9 configuration, Cu^{2+} often exhibits Jahn-Teller distortion. This distortion lowers the symmetry from octahedral to tetragonal, resulting in:

- **Elongation**: Compared to equatorial bonds, axial bonds are longer.
- **Compression**: Compared to equatorial bonds, axial bonds are shorter.

The tetragonal distortion causes further splitting of the eg and t_2 levels. This alters the energy levels, broadens spectral lines, and may allow additional electronic transitions depending on the degree of distortion.

In the ground state ^2E_g , due to the Jahn-Teller effect, a splitting is observed, leading to a reduction in symmetry for the Cu^{2+} ion. In tetragonal symmetry, this splitting results in the ^2E_g ground state dividing into $^2B_{1g}(d_{x^2-y^2})$ and $^2A_{1g}(d_{z^2})$states. Similarly, the excited $^2T_{2g}$ term splits into $^2B_{2g}(d_{xy})$ and $^2E_g(d_{xz}, d_{yz})$ levels.

The ^2E_g ground state further splits into $^2A_{1g}(d_{x^2-y^2})$ and $^2A_{2g}(d_{z^2})$ in a rhombic (D_{2h}) field, whereas the $^2T_{2g}$ term breaks into $^2B_{1g}(d_{xy})$, $^2B_{2g}(d_{xz})$, and $^2B_{3g}(d_{yz})$.

In an elongated tetragonal field, the energy level diagram for d-orbitals displays the splitting caused by axial elongation (Chemistry, 2023), with the $d_{x^2-y^2}$ having the highest energy, followed by d_{z^2}, d_{xy}, and d_{xz}/d_{yz} orbitals. This is illustrated schematically in Figure 1.

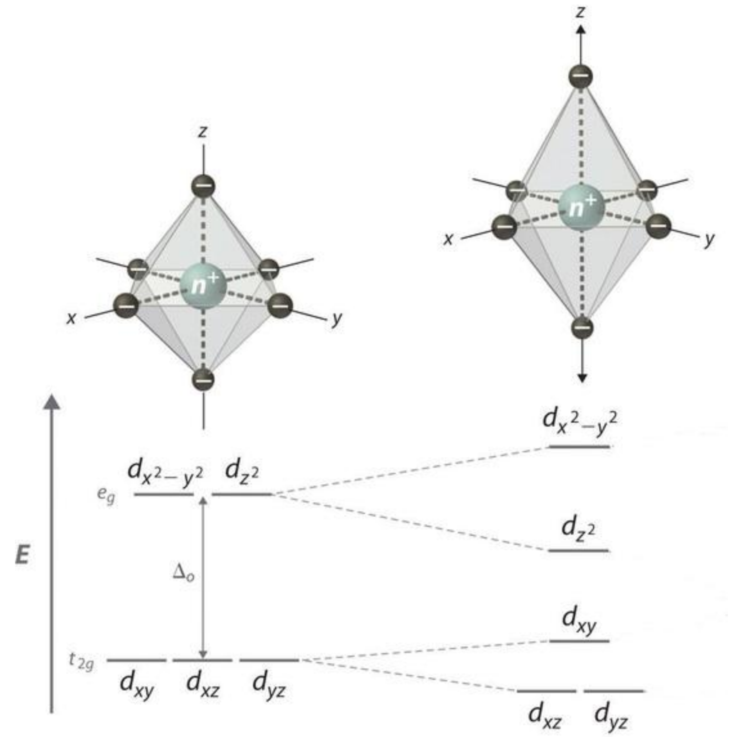


Figure 1 Illustration of tetragonal distortion (elongation) for an octahedral complex.

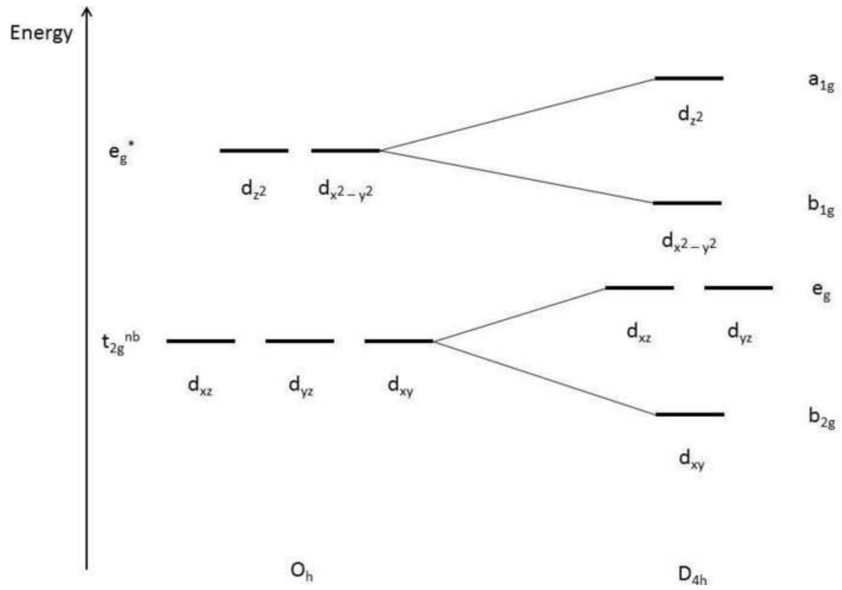


Figure 2 Illustration of tetragonal distortion (compression) for an octahedral complex.

A contraction in the equatorial xy-plane or a tetragonal elongation along the z-axis are the usual characteristics of the Jahn-Teller distortion (Figure 2) (Chemistry, 2023) seen in Cu^{2+} complexes. In extreme cases, this distortion can lead to a square planar geometry, reducing the symmetry to D_{4h}.

For Cu^{2+} in octahedral coordination with rhombic symmetry, the ground state $^2A_{1g}(d_{x^2-y^2})$ transitions to the following excited states:

1. $^2A_{1g}(d_{x^2-y^2}) \rightarrow {}^2A_{2g}(d_{z^2})$
2. $^2A_{1g}(d_{x^2-y^2}) \rightarrow {}^2B_{1g}(d_{xy})$
3. $^2A_{1g}(d_{x^2-y^2}) \rightarrow {}^2B_{2g}(d_{xz})$
4. $^2A_{1g}(d_{x^2-y^2}) \rightarrow {}^2B_{3g}(d_{yz})$

These transitions correspond to the energy differences arising from the splitting of the d-orbitals in the rhombic field, as depicted in Figure 6.

In the rhombic field, the most intense optical absorption band is typically the $^2A_{1g}(d_{x^2-y^2}) \rightarrow {}^2B_{1g}(d_{xy})$ transition. The energy of this transition is directly related to 10Dq, which depends on the nature of the ligands and the surrounding crystal field environment (Li et al., 2012).

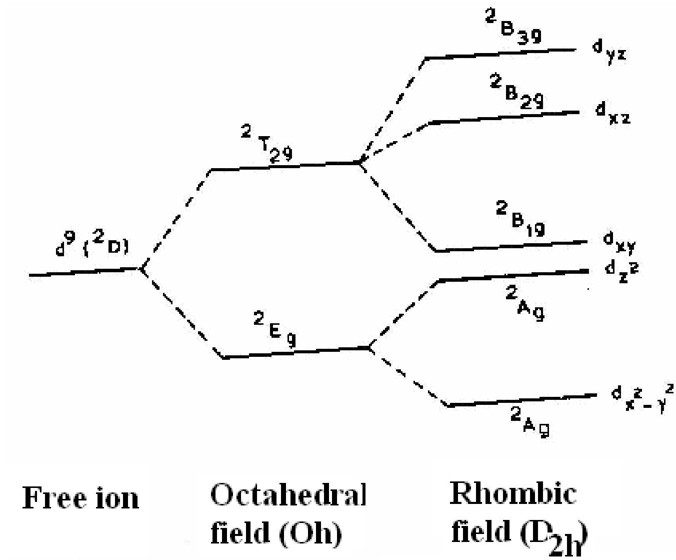


Figure 3 Energy level diagram of d-orbitals in rhombic distortion.

In this work, $[CuL_2]$ complex of (Z)-4-methyl-N'-(phenyl(pyridin-2-yl)methylene)benzenesulfonohydrazide has been synthesized. The structure of the synthesized complex was investigated by elemental analysis, IR and UV-vis spectroscopy methods.

2. EXPERİMENTAL

2.1. Materials

Sigma/Aldrich provided all of the materials used in this experiment, which were utilized exactly as supplied. All of the compounds that were utilized without additional purification were of reagent grade and were acquired from commercial vendors.

2.2. Physical measurements

Elemental analysis was performed using the Thermo Flash 2000 Elemental Analyzer. A Thermo Evolution UV-Visible Spectrophotometer running at room temperature in DMSO solution between 200 and 1100 nm was used to record the electronic absorption spectra of the title compounds. The Thermo Scientific Nicolet iS10 FT-IR spectrophotometer was utilized to record the infrared spectrum utilizing ATR.

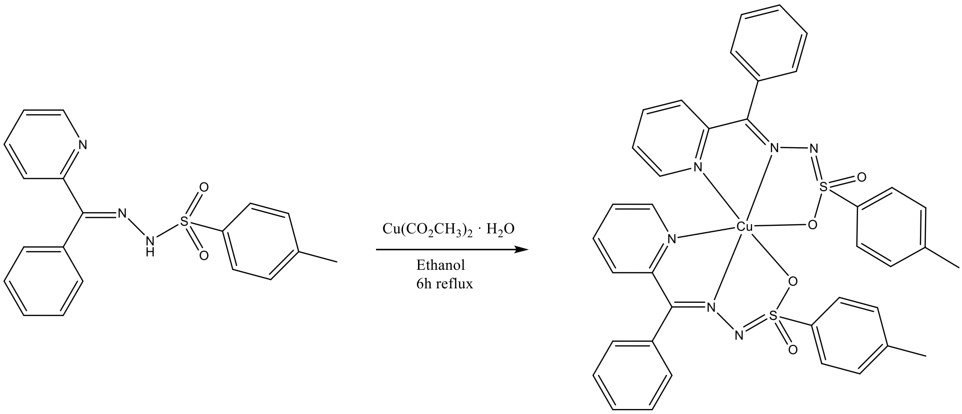
2.3. Synthesis of compounds

2.3.1. Synthesis of HL

The synthesis of the HL ligand ((Z)-4-methyl-N'-(phenyl(pyridin-2-yl)methylene)benzenesulfonohydrazide) was carried out according to literature work (Çınarlı et al., 2019).

2.3.2. Synthesis of [CuL_2]

A heated solution of HL (0.301 g, 1 mmol) in ethanol (20 mL) was mixed with a solution of $Cu(CO_2CH_3)_2 \cdot H_2O$ (0.099 g, 0.05 mmol) in ethanol (10 mL). For five to six hours, the reaction mixture was refluxed. The dark brown precipitate was filtered and allowed to air dry. Scheme 1 displays the chemical structure of [CuL_2].



Scheme 1 Chemical structures of [CuL_2]

3. RESULTS

3.1. Elemental Analysis of [CuL_2]

The theoretical and experimental elemental analysis results of the complex [CuL_2] are given in Table 1. When the elemental analysis results of the complex are examined, it is seen that the experimental and theoretical results are in harmony.

Table 1 Theoretical and experimental elemental analysis results of the complex [CuL_2]

[CuL_2]	%C	%H	%N	%S
Theoretical	59,71	4,22	10,99	8,39
Experimental	60,64	4,17	10,35	7,88

3.2. IR studies of [CuL_2]

The distinctive absorption bands at 3066, 1578, 1532, 1347, and 1166 cm^{-1} in the compounds' infrared spectra are caused by n $(N\text{-}H)_{(hydrazinic)}$, $\nu(C{=}N)_{azo}$, $\nu(C{=}N)_{pyr}$, $\nu_{as}(SO_2)$, and $\nu_s(SO_2)$, respectively (Çınarlı et al., 2019).

The absence of the ν(N−H) band at 3066 cm^{-1} in the complex's IR spectrum indicates the deprotonation of the hydrazinic N−H group during coordination (Ali et al., 2008).

The shifts in the $\nu(C{=}N)_{azo.}$, $\nu(C{=}N)_{pyr.}$ (from 1532 cm^{-1}) bands in the IR spectrum of the complex suggest involvement of both the azo (C=N) and pyridyl (C=N) groups in coordination with the metal ion (Emam et al., 2017).

The $\nu_{as}(SO_2)$ and $\nu_s(SO_2)$ bands, initially at 1347 and 1166 cm^{-1} shift to 1310 and 1146 cm^{-1} respectively, in the spectrum of the complex. This downward shift indicates that the SO_2 oxygen atoms are directly coordinating to the metal ion (Çınarlı et al., 2025).

New bands were observed at 557 cm^{-1} and 446 cm^{-1}, which were ascribed to ν(M−O) and ν(M−N), respectively, provides strong evidence for the formation of metal-oxygen and metal-nitrogen bonds, confirming the ligand's coordination behavior (Özdemir et al., 2013). These spectral observations collectively demonstrate the ligand's multidentate coordination through the deprotonated hydrazinic N−H, $\nu(C{=}N)_{azo.}$, $\nu(C{=}N)_{pyr.}$, and SO_2 groups, leading to a robust complexation with the metal ion.

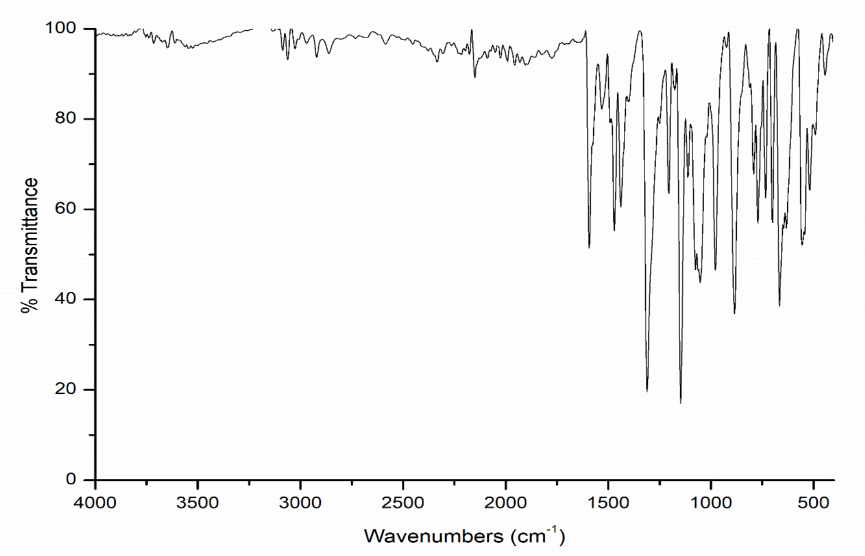


Figure 4 IR spectrum of [CuL_2]

3.3. UV-Vis. studies of [CuL_2]

The anticipated spin-allowed d-d transitions in Cu(II) complexes with square planar geometry (D_{4h} symmetry) or elongated tetragonal distortion are $^2A_{1g}$⟵$^2B_{1g}$, $^2B_{2g}$⟵$^2B_{1g}$, and ^2E_g⟵^2B1_g. These transitions are predicted to occur in the ranges 850–550 nm, 645–555 nm, and 580–500 nm. However, in practice, these transitions often appear as a single broad band rather than distinct peaks. This broadening and overlap arise due to the following factors:

- **Small Energy Splittings**: The energy differences between the d-orbital levels in Cu(II) complexes are typically small, resulting in closely spaced absorption bands that blend together.
- **Vibronic Coupling**: Interactions between electronic transitions and vibrational modes can cause additional broadening of the absorption bands.
- **Tetragonal Distortion**: While the distortion splits the degenerate e_g and t_{2g} levels of an ideal octahedral field, the resultant splitting energy is still not large enough to fully separate the transitions.
- **Spin-Orbit Coupling**: Cu(II) has a single unpaired electron (d^9 configuration), and spin-orbit coupling may further mix states, complicating the spectral profile.

The broad absorption band observed in the range 660–700 nm is attributed to an envelope of this transitions. The inability to resolve these bands individually is due to their overlapping nature, influenced by the factors mentioned above.

The ligand–metal charge transfer (LMCT) transition is the primary cause of the strong bands seen at 358 nm in the Cu(II) complex (Santiago et al., 2020). The intraligand π–π * transitions, which experienced slight changes in comparison to the free ligand, are represented by the remaining bands of the complexes at about 280 nm. It is believed that the n→π* transition occurs beneath the charge transfer transition. In the UV spectra of the complex, two bands were observed at 520 and 852 nm. These bands are thought to be ^2E_g⟵^2B1_g and $^2A_{1g}$⟵$^2B_{1g}$ transitions (Figure 4 and Figure 5) (Mangalam & Prathapachandra Kurup, 2011).

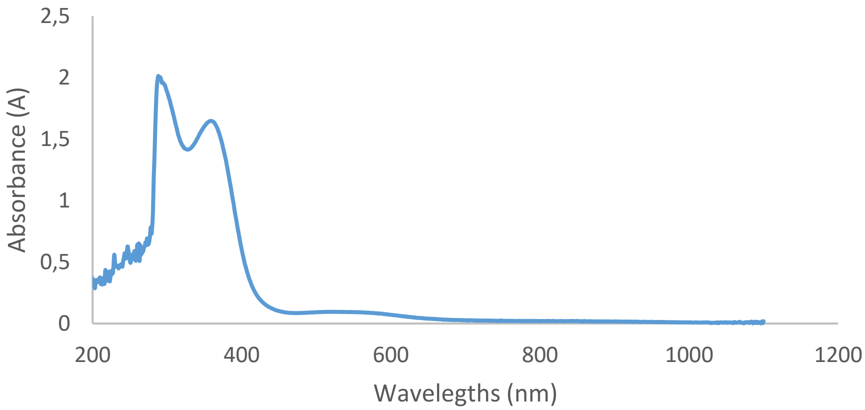


Figure 4 UV spectrum of $[CuL_2]$ complex in DMSO 10^{-4} M

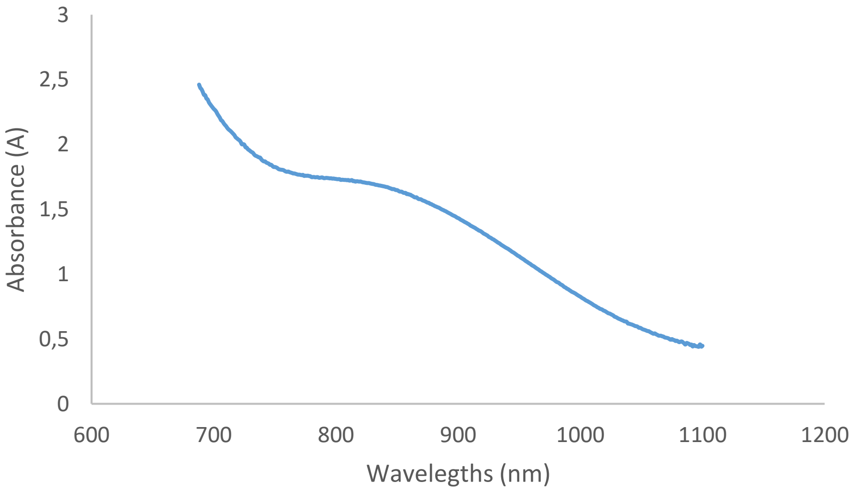


Figure 5 UV spectrum of $[CuL_2]$ complex in DMSO 10^{-2} M

CONCLUSIONS

The distinct properties of copper complexes, including their ability to generate reactive oxygen species (ROS), disrupt protein homeostasis, and inhibit angiogenesis, demonstrate their promising role in cancer treatment. Furthermore, the structural versatility and lower toxicity of copper-based compounds compared to traditional chemotherapeutic agents make them an attractive area of research.

In summary, this study's results add to the expanding corpus of information about copper complexes and their uses in medicinal chemistry. Further investigations into their mechanistic pathways and biological activities are necessary to fully harness their therapeutic potential in oncology and beyond.

This study highlights the synthesis, characterization, and analysis of the [CuL2] complex. The experimental results, including elemental analysis, IR spectroscopy, and UV-Vis spectroscopy, confirm the successful synthesis of the complex and its robust coordination behavior. The observed shifts in vibrational frequencies and absorption bands provide evidence of effective metal-ligand interactions.

References

Ali, M. A., Mirza, A. H., Hamid, M. H. S. A., Bernhardt, P. V., Atchade, O., Song, X., Eng, G., & May, L. (2008). Synthesis, spectroscopic and structural characterization of diphenyltin(IV) complexes of acetone Schiff bases of S-alkyldithiocarbazates. *Polyhedron*, *27*(3), 977–984. https://doi.org/10.1016/j.poly.2007.11.030

Chaston, T. B., Watts, R. N., Yuan, J., & Richardson, D. R. (2004). Potent Antitumor Activity of Novel Iron Chelators Derived from Di-2-Pyridylketone Isonicotinoyl Hydrazone Involves Fenton-Derived Free Radical Generation. *Clinical Cancer Research, 10*(21), 7365–7374. https://doi.org/10.1158/1078-0432.CCR-04-0865

Chemistry, L. (2023). *https://chem.libretexts.org/Bookshelves/Inorganic_Chemistry/Supplemental_Modules_and_Websites_(Inorganic_Chemistry)/Coordination_Chemistry/Structure_and_Nomenclature_of_Coordination_Compounds/Coordination_Numbers_and_Geometry/Jahn-Teller_Distortions?readerView*.

Çınarlı, M., Ataol, Ç. Y., Zeyrek, C. T., Öğütcü, H., Açık, L., & Batı, H. (2025). Design, synthesis, characterization, theoretical calculations, molecular docking studies, and biological evaluation of new Fe(II) and Cu(II) complexes of 2-acetylpyridine derivative sulfonyl hydrazone Schiff base. *Journal of Molecular Structure*, *1321*, 140112. https://doi.org/10.1016/j.molstruc.2024.140112

Çınarlı, M., Çınarlı, E., Ataol, Ç. Y., İdil, Ö., & Kariptaş, E. (2019). Synthesis, structural characterization, Hirshfeld surface analysis, antimicrobial activity, and DNA cleavage studies of (Z)-4-methyl-N’-(phenyl(pyridin-2-yl)methylene)benzenesulfonohydrazide and its Co(II), Ni(II) and Zn(II) complexes. *Journal of Molecular Structure*, *1196*, 760–770. https://doi.org/10.1016/j.molstruc.2019.07.008

Emam, S. M., AbouEl-Enein, S. A. E., & El-Seady, S. M. (2017). Coordination Behavior of N-Donor Schiff Base Derived from 2-Benzoylpyridine Toward Mn(<scp>II</scp>), Co(<scp>II</scp>), Ni(<scp>II</scp>), Cu(<scp>II</scp>), Zn(<scp>II</scp>), Pd(<scp>II</scp>), and Cr(<scp>III</scp>) Metal Ions: Synthesis, Spectroscopic and Thermal Studies, and Biological Activity. *Journal of the Chinese Chemical Society*, *64*(3), 261–281. https://doi.org/10.1002/jccs.201600752

Festa, R. A., & Thiele, D. J. (2011). Copper: An essential metal in biology. *Current Biology*, *21*(21), R877–R883. https://doi.org/10.1016/j.cub.2011.09.040

Gou, Y., Chen, M., Li, S., Deng, J., Li, J., Fang, G., Yang, F., & Huang, G. (2021). Dithiocarbazate-Copper Complexes for Bioimaging and Treatment of Pancreatic Cancer. *Journal of Medicinal Chemistry*, *64*(9), 5485–5499. https://doi.org/10.1021/acs.jmedchem.0c01936

Iovan, D. A., Wrobel, A. T., McClelland, A. A., Scharf, A. B., Edouard, G. A., & Betley, T. A. (2017). Reactivity of a stable copper–dioxygen complex. *Chemical Communications*, *53*(74), 10306–10309. https://doi.org/10.1039/C7CC05014C

Kaczmarek, M. T., Zabiszak, M., Nowak, M., & Jastrzab, R. (2018). Lanthanides: Schiff base complexes, applications in cancer diagnosis, therapy, and antibacterial activity. *Coordination Chemistry Reviews*, *370*, 42–54. https://doi.org/10.1016/j.ccr.2018.05.012

Li, L., Shi, X., M., C., & L., G. (2012). Atomic and Molecular Low-n Rydberg States in Near Critical Point Fluids. In *Advanced Aspects of Spectroscopy*. InTech. https://doi.org/10.5772/50128

Mangalam, N. A., & Prathapachandra Kurup, M. R. (2011). Versatile binding properties of a di-2-pyridyl ketone nicotinoylhydrazone ligand: Crystal structure of a Cu(II) complex. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, *78*(3), 926–934. https://doi.org/10.1016/j.saa.2010.11.032

Mariani, D., Ghasemishahrestani, Z., Freitas, W., Pezzuto, P., Costa-da-Silva, A. C., Tanuri, A., Kanashiro, M. M., Fernandes, C., Horn, A., & Pereira, M. D. (2021). Antitumoral synergism between a copper(II) complex and cisplatin improves in vitro and in vivo anticancer activity against melanoma, lung and breast cancer cells. *Biochimica et Biophysica Acta (BBA) - General Subjects*, *1865*(10), 129963. https://doi.org/10.1016/j.bbagen.2021.129963

McGivern, T. J. P., Afsharpour, S., & Marmion, C. J. (2018). Copper complexes as artificial DNA metallonucleases: From Sigman's reagent to next generation anti-cancer agent? *Inorganica Chimica Acta*, *472*, 12–39. https://doi.org/10.1016/j.ica.2017.08.043

Mo, Q., Deng, J., Liu, Y., Huang, G., Li, Z., Yu, P., Gou, Y., & Yang, F. (2018). Mixed-ligand Cu(II) hydrazone complexes designed to enhance anticancer activity. *European Journal of Medicinal Chemistry*, *156*, 368–380. https://doi.org/10.1016/j.ejmech.2018.07.022

Özdemir, Ü. Ö., Akkaya, N., & Özbek, N. (2013). New nickel(II), palladium(II), platinum(II) complexes with aromatic methanesulfonylhydrazone based ligands. Synthesis, spectroscopic characterization and in vitro antibacterial evaluation. *Inorganica Chimica Acta*, *400*, 13–19. https://doi.org/10.1016/j.ica.2013.01.031

Peña, Q., Lorenzo, J., Sciortino, G., Rodríguez-Calado, S., Maréchal, J.-D., Bayón, P., Simaan, A. J., Iranzo, O., Capdevila, M., & Palacios, Ò. (2019). Studying the reactivity of "old" Cu(II) complexes for "novel" anticancer purposes. *Journal of Inorganic Biochemistry*, *195*, 51–60. https://doi.org/10.1016/j.jinorgbio.2019.03.011

Ruiz-Azuara, L., & E. Bravo-Gomez, M. (2010). Copper Compounds in Cancer Chemotherapy. *Current Medicinal Chemistry*, *17*(31), 3606–3615. https://doi.org/10.2174/092986710793213751

Santiago, P. H. O., Santiago, M. B., Martins, C. H. G., & Gatto, C. C. (2020). Copper(II) and zinc(II) complexes with Hydrazone: Synthesis, crystal structure, Hirshfeld surface and antibacterial activity. *Inorganica Chimica Acta*, *508*, 119632. https://doi.org/10.1016/j.ica.2020.119632

Tisato, F., Marzano, C., Porchia, M., Pellei, M., & Santini, C. (2010). Copper in diseases and treatments, and copper-based anticancer strategies. *Medicinal Research Reviews*, *30*(4), 708–749. https://doi.org/10.1002/med.20174

Wu, Y., Hou, L., Lan, J., Yang, F., Huang, G., Liu, W., & Gou, Y. (2023). Mixed-ligand copper(II) hydrazone complexes: Synthesis, structure, and anti-lung cancer properties. *Journal of Molecular Structure*, *1279*, 134986. https://doi.org/10.1016/j.molstruc.2023.134986

YANG, Y., HUANG, T., ZHOU, S., FU, Y., LIU, Y., YUAN, Y., ZHANG, Q., LI, S., & LI, C. (2015). Antitumor activity of a 2-pyridinecarboxaldehyde 2-pyridinecarboxylic acid hydrazone copper complex and the related mechanism. *Oncology Reports*, *34*(3), 1311–1318. https://doi.org/10.3892/or.2015.4087

Chapter 6

ANTENNA STRUCTURES FOR AEROSPACE APPLICATIONS

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Introduction

Aerospace is a term that encompasses aviation and space technologies. This field includes both intra-atmospheric flights (aviation) and space activities (space technologies). In general, it deals with aircraft, spacecraft, satellite systems, rockets and their design, production, testing and operation. It takes its place in the industrial sector with aviation, space technologies, defense and security, aviation systems and engineering applications [1].

Aerospace is generally understood to refer to the academic and professional field of aerospace engineering, which focuses on the design, analysis, and development of systems used in both aviation and space technologies. Aerospace engineering covers various fields such as aviation, space, defense, satellite technology development. It covers all military and commercial studies [2].

Antenna structures, commonly known as antennas, are devices designed for transmitting and receiving electromagnetic waves [3]. They play a crucial role in various communication systems, including radar, television broadcasting, GPS (Global Positioning System), and other wireless technologies. Antennas function as transmitters by converting electrical energy into electromagnetic energy, and they also receive electromagnetic waves, converting those signals back into electrical energy. Different applications are preferred for different antenna structures. There are antenna structures such as dipole, monopole, horn, Vivaldi, microstrip, fractal, Yagi-Uda, parapobile and etc. These structures are designed and produced for various tasks. Antennas are frequently used in mobile phones, radar systems, air defense, GPS, satellite-based navigation systems, military applications, defense and scientific research [4].

Antenna structures are designed according to operating frequencies. The operating frequency varies depending on the environment in which communication will be established. The operating environment of the antenna is one of the important factors affecting its efficiency. The higher the antenna efficiency, the more positively it is processed.

In aerospace technologies, antennas perform many critical functions such as communication, data transfer, navigation, radar and scientific observations. Especially in mobile platforms such as spacecraft and aircraft, antenna design and placement are of great importance [1], [5], [6].

The communication between the ground and space and between the antennas is very important. The smooth communication with the aircraft depends on this communication. Highly directional antennas are generally preferred, especially for the vehicles on the ground and in the atmosphere [7], [8].

Antennas, which are one of the most important elements of communication, play an active role in effective communication between the ground command center and vehicles in the aviation industry. In addition, in radar structures frequently used in aviation, the dynamic structures of antennas bring various advantages. These advantages can be listed as accurate direction determination, proper target detection, and accurate speed measurement. Positioning antennas and antenna structures are effective for precise communication between satellites and receiver integrated circuits. When examined with the requirements of the modern world, they are highly used/researched and developed elements in precise measurement and high-quality communication [9], [10].

In aerospace applications, it is necessary to give importance to the performance outputs of antennas. With these performances, the most suitable solution can be produced in antenna structures. An antenna that is resistant to environmental parameters will not be affected by the effects coming from the environment and will ensure that communication progresses smoothly. The weight effect of antennas is important under necessary conditions. Here, especially when the most optimum amount of the total weight of aircraft vehicles is considered, an antenna design with appropriate weight will ensure the effective continuity of the current technology. The gain value, which is one of the most important parameters of antennas, is calculated in direct proportion to efficiency and directionality, and the sensitivity of communication will be increased with high gain. It is very important for the bandwidth of the antenna to be narrow or wide according to the application to be designed. Because some applications require narrow bandwidth while others require wide bandwidth. Due to this feature, the functionality of the antenna will change and the design will adapt to the application correctly. [11].

Antenna technology is an indispensable innovation for very specific tasks in aviation and space applications. Antenna structures are among the reliable equipment that meets the needs of radar, positioning, detection, and communication. By increasing the operational efficiency of this technology, aerospace applications can also become more advanced. [12]. This section examines some antenna structures designed for aerospace applications. Some of the antenna structures' features, challenges, and contributions to the aerospace industry are highlighted.

Antenna Applications for Aerospace

As mentioned above, antenna structures are frequently used and researched in aerospace applications. Below are basic sample antenna structures for application areas.

Radar Antennas

Radar technology plays a crucial role in air traffic control, collision avoidance, and weather monitoring, ensuring safety and efficiency in our skies. For advanced applications, essential features such as a wide frequency range, rapid direction-changing capability, and high sensitivity are vital. These attributes guarantee optimal performance, especially in dynamic and complex operational environments. Notably, the wideband application range is invaluable for radar systems, enabling precise detection and tracking of targets across diverse distances and speeds. Also, by resonating across multiple frequencies, it increases the resolution value. Thus, harmonics are reduced. One of the important factors in increasing the resolution value is wideband technology. In addition, the security and accuracy of the system are also improved [13].

Continuing with an example, AESA (Active Electronically Scanned Array) radar antennas serve as a very important advance in military technology, prominently featured in modern aircraft like the F-35 fighter jet. These antennas, with their scanning speed and adaptability, enable the simultaneous tracking of multiple targets. They eliminate the need for mechanical movement through electronic beam steering. Thus, response times and reliability are significantly increased [14], [15].

Radar antennas used in meteorology are of active importance in the fight against weather conditions. For example, in the development of severe weather opposition such as storms, it is a radar technology used to obtain real-time information about storm movement and strength. They are very important because they play an active role in ensuring the health and continuity of humanity and existing structures [16], [17].

Satellite Communication Antennas

Antenna structures used in satellite communications are used in numerous applications, including effective communication between the Earth and satellites in orbit, weather forecasting, navigation, and global communications. For this purpose, they are designed using certain features such as wide coverage, high gain, and low signal-to-noise ratio. These features are critical to ensure that signals can be transmitted and received over large distances with minimal interference and maximum clarity [18], [19]. By focusing on these features, a real and healthy communication system can be made even under difficult conditions. Moving forward by prioritizing accuracy and sensitivity in design will contribute to the development of performance and the quality of communication.

Antennas used in satellite communication must be meticulously designed for demanding applications and analyzed according to the demands. Ka-band antennas and reflective antennas are structures that can be given as examples for these types of applications. They have critical processing capabilities in communication with high data rates [20], [21]. Ka-band antennas are particularly prized for their compact design and ability to operate at higher frequencies, which allows for precise detection and seamless communication. Reflective antennas, such as parabolic reflectors, are favoured for their gain and directional characteristics, ensuring accurate target identification and dependable performance in both civilian and military radar systems. [22].

GNSS and GPS Antennas

Antenna structures designed for GNSS and GPS applications must have high accuracy and reliability. Thus, it will be able to perform precise positioning [23]. Antennas engineered for these functions are integrated seamlessly into various systems, leveraging their compact size, low power consumption, and multi-band capabilities to their fullest potential. These attributes are particularly advantageous across a range of platforms, from agile drones to large-scale aerospace systems, where efficiency and space optimization are critical [22], [24].

Patch antennas are essential in drones and commercial aircraft, thanks to their compact size and lightweight design, which are suitable for space-restricted applications [25]. These antennas not only ensure reliable performance for communication and navigation systems, but also optimize efficiency while maintaining a minimal footprint. Their easy integration into the aircraft or drone structure makes them a good choice for the latest aviation technologies. The antenna also improves performance and increases overall functionality with its existing structure [26].

Remote Sensing Antennas

Remote sensing antenna structures are antennas that contribute significantly to the observation of the Earth’s surface. Their roles are critical in vital applications such as environmental monitoring, disaster management, and climate research. To achieve this goal, they must have high values, wide viewing angles, and all-weather performance [27], [28].

High-resolution antennas and analyses are delivered accurately and effectively. Additionally, multispectral imaging antennas capture data across a range of wavelengths, providing useful insights into atmospheric conditions and surface transformations [29]. This information is crucial for sectors like agriculture, forestry, and urban planning, where understanding changes directly impacts outcomes.

In addition, all-weather antennas must provide reliable performance under all environmental conditions, ensuring uninterrupted monitoring regardless of challenges such as cloud cover or precipitation. By investing in advanced antenna technology, antenna structures that both protect nature and operate smoothly with sustainability should be designed [9].

Synthetic Aperture Radar (SAR) antennas are tools for satellites aimed at capturing high-resolution images of the Earth's surface. These advanced antennas play a crucial role in Earth observation missions, such as the European Space Agency's Sentinel-1 satellite [30], [31]. By emitting microwave signals that are reflected off the Earth’s surface, SAR antennas can collect detailed images regardless of weather conditions or the presence of sunlight. This ability to produce precise images from orbit makes SAR antennas sought after for monitoring environmental changes, mapping terrain, effectively managing disasters, and improving military surveillance capabilities. Potential designs should be developed with SAR technology. [32].

As another example, LIDAR-enabled antennas are revolutionizing the way we explore and understand our planet [33]. By measuring distances with great precision using laser pulses, they create usable structure profiles for a multitude of applications. With their ability to provide high-resolution topographic mapping, vegetation analysis, and infrastructure monitoring, LIDAR systems are dynamic structures both in airborne and satellite platforms [34].

Aircraft Communication Antennas

Aircraft communication antennas are used to provide seamless communication between aircraft and ground control towers and between vehicles in the airspace. They are vital for safe and efficient operations. Antenna structures that provide fast connectivity, minimal interference, and reliability are indispensable for these applications [35]. These essential features ensure uninterrupted and high-quality communication, even in difficult conditions or during high-speed manoeuvres. The ability to maintain stable and effective communication links is essential for air traffic control, safety measures and operational success, making advanced antenna systems not only valuable but also indispensable for modern aviation [36], [37]. Below are examples of antennas that are highly favored for these critical applications.

For example, VHF/UHF antennas are widely used for voice and data transmission on commercial aircraft. They also provide clear and reliable communication between aircraft and air traffic control towers [38]. These antennas operate within the very high frequency (VHF) and ultra high frequency (UHF) bands, facilitating efficient line-of-sight communication that is crucial for both short-range and long-range air travel [39]. Their ability to support both voice and data transmission ensures that critical information can be exchanged in real time, which enhances flight safety and operational efficiency [40].

Also, SATCOM antennas are essential components of both modern commercial and military aircraft, enabling satellite-based communication [41]. These antennas provide global connectivity, even in remote areas or over oceans where traditional ground-based communication systems are unavailable.

UAV (Unmanned Aerial Vehicles) Antennas

Antennas are vital components for the effective control and data transmission of unmanned aerial vehicles (UAVs) [42]. With the demands of UAV operations, such as remote piloting and the need for real-time data Exchange, it's essential that these antennas are lightweight, compact, and energy-efficient. Their small size and minimal power consumption not only make them ideal for UAV integration, but they also enable significant reductions in weight and enhancements in battery life [43].

Directional antennas are designed to provide line-of-sight (LOS) communication, ensuring a direct, unobstructed path between the transmitting and receiving antennas [44]. This type of antenna is ideal for applications where precise and reliable communication over long distances is required, such as in point-to-point communication systems, satellite communication, and certain radar applications.

5G and LTE antennas represent the next generation of communication technology that provides ultra-fast data transfer and expanded coverage [45]. These modern antennas are optimized for high bandwidth and long-range communication, enabling a range of applications from mobile data services to IoT (Internet of Things) devices. 5G antennas, in particular, are designed to handle massive data traffic, offering speeds up to 100 times faster than previous generations [46]. LTE antennas, used in 4G networks, support high-speed internet and voice communication with low latency, ensuring fast, seamless connectivity for users in both urban and remote areas [47]. Both types of antennas are crucial to the continued evolution of mobile networks, facilitating faster and more reliable communications for a wide range of applications.

Conclusion

When aerospace and antenna applications are examined, it is seen that it is an indispensable equipment of the industry. When the antenna structures given above are examined, it is presented with various examples for both aviation and space applications. While antenna structures appear as an important part of every communication, their value for these applications is also obvious. It is a book section designed on special antenna structures used especially in radar systems, remote sensing systems, UAVs, satellite communication systems, GNSS/GPS systems and aircraft communication systems.

It is clearly presented in the section how effective antenna structures are in navigation and remote sensing with high resolution. It is also presented that the resolution value can be increased and location accuracy can be improved with wide-band applications.

With the help of patch antennas used for effective communication between vehicles, both communication quality is increased and dynamic communication structures are achieved.

Directional antennas contribute to the development of 5G communication technology. With this development, the diameter of IoT applications is increased. In addition, antenna structures are served as a sector open to development with the design width of the applications.

In light of all this data, the indispensable effect of antenna structures is presented in the aerospace field. The added value that will be added to the sector by improving the parameter values of antennas is expressed in the section.

References

[1] J. Sobieszczanski-Sobieski and R. T. Haftka, “Multidisciplinary aerospace design optimization: Survey of recent developments,” *Struct. Optim.*, vol. 14, no. 1, pp. 1–23, 1997.

[2] R. Blockley and W. Shyy, *Encyclopedia of aerospace engineering*. American Institute of Aeronautics and Astronautics, Inc., 2010.

[3] C. A. Balanis, “Anten teorisi : Analiz ve Tasarım,” 3rd ed., Nobel Akademik Yayıncılık, 2013, p. 843.

[4] H. J. Visser, *Antenna theory and applications*. John Wiley & Sons, 2012.

[5] W. H. Kummer and E. S. Gillespie, “Antenna Measurements—1978,” *Proc. IEEE*, vol. 66, no. 4, pp. 483–507, 1978.

[6] K. Krishnakumar, “Intelligent systems for aerospace engineering - An overview,” *Natl. Aeronatics Sp. Adm. Ames Reseach Cent. - Rep.*, no. May, pp. 1–15, 2003.

[7] N. Kravchenko and M. Kliuev, “Novel method of multi-axis EDM machining of thin-walled Al-Mn parabolic reflector for aerospace applications,” *Procedia CIRP*, vol. 113, pp. 64–69, 2022.

[8] M. S. Gatti, “A phased array antenna for deep space communications,” in *2008 IEEE Aerospace Conference*, 2008, pp. 1–8.

[9] V. Akan and E. Yazgan, “Antennas for space applications: A review,” *Adv. Radio Freq. Antennas Mod. Commun. Med. Syst.*, pp. 139–171, 2020.

[10] W. Gregorwich and R. B. Ward, “An autonomous antenna for aerospace applications,” in *1993 IEEE Aerospace Applications Conference Digest*, 1993, pp. 99–108.

[11] D. N. Mavris and O. J. Pinon, “An overview of design challenges and methods in aerospace engineering,” in *Complex Systems Design & Management: Proceedings of the Second International Conference on Complex Systems Design & Management CSDM 2011*, 2012, pp. 1–25.

[12] K. Cohen, “Grand challenges in intelligent aerospace systems,” *Front. Aerosp. Eng.*, vol. 2, no. September, pp. 1–4, 2023.

[13] G. Beziuk, T. C. Baum, K. Ghorbani, and K. J. Nicholson, “Structurally integrated radar in an aerospace composite laminate,” *IEEE Trans. Components, Packag. Manuf. Technol.*, vol. 11, no. 11, pp. 1835–1843, 2021.

[14] G. Sabino, “AESA applications by new technologies evolution,” in *2019 IEEE International Symposium on Phased Array System & Technology (PAST)*, 2019, pp. 1–4.

[15] M. Zeeshan, M. S. Arif, M. Umair, and S. M. T. Javed, “Survey of Systems Engineering Approaches for Design and Development of AESA Radar for

Fighter Aircraft," in *2019 16th International Bhurban Conference on Applied Sciences and Technology (IBCAST)*, 2019, pp. 956–962.

[16] S. Fukao, K. Hamazu, and R. J. Doviak, "Radar for meteorological and atmospheric observations," 2014.

[17] P. L. Smith, K. R. Hardy, and K. M. Glover, "Applications of radar to meteorological operations and research," *Proc. IEEE*, vol. 62, no. 6, pp. 724–745, 1974.

[18] J. Sosa-Pedroza, F. Martínez-Zúniga, and M. Enciso-Aguilar, "Planar antennas for satellite communications," *Satell. Commun. N. Diodato (Ed.), InTech*, pp. 367–394, 2010.

[19] M. A. S. Natera *et al.*, "New antenna array architectures for satellite communications," in *Advances in Satellite Communications*, IntechOpen, 2011.

[20] H. Bayer, A. Krauss, T. Zaiczek, R. Stephan, O. Enge-Rosenblatt, and M. A. Hein, "Ka-band user terminal antennas for satellite communications [antenna applications corner]," *IEEE Antennas Propag. Mag.*, vol. 58, no. 1, pp. 76–88, 2016.

[21] Y. Rahmat-Samii and R. Haupt, "Reflector antenna developments: a perspective on the past, present and future," *IEEE Antennas Propag. Mag.*, vol. 57, no. 2, pp. 85–95, 2015.

[22] W. A. Imbriale and L. Boccia, "Space Antenna Handbook," 2012.

[23] A. Kumar, S. Kumar, P. Lal, P. Saikia, P. K. Srivastava, and G. P. Petropoulos, "Introduction to GPS/GNSS technology," in *GPS and GNSS Technology in Geosciences*, Elsevier, 2021, pp. 3–20.

[24] E. KONAKYERI, S. Paker, and O. PALAMUTCUOGULLARI, "GPS Helix Antenna Design," *Istanbul Univ.-Journal Electr. Electron. Eng.*, vol. 9, no. 2, pp. 935–941, 2009.

[25] M. Singh and H. Singh, "A triband microstrip patch antenna in Ku and J band for satellite and aerospace applications," *Aerosp. Syst.*, vol. 5, no. 4, pp. 663–670, 2022.

[26] D. R. Minervino, A. G. D'Assunção, A. F. dos Santos, J. B. D. Dantas, and P. H. da Fonseca Silva, "Arrays of rectangular patch microstrip antennas for aerospace applications," in *2013 SBMO/IEEE MTT-S International Microwave & Optoelectronics Conference (IMOC)*, 2013, pp. 1–4.

[27] P. Gamba *et al.*, "Wireless passive sensors for remote sensing of temperature on aerospace platforms," *IEEE Sens. J.*, vol. 14, no. 11, pp. 3883–3892, 2014.

[28] H. J. Kramer and A. P. Cracknell, "An overview of small satellites in remote sensing," *Int. J. Remote Sens.*, vol. 29, no. 15, pp. 4285–4337, 2008.

[29] M. Soleh, A. S. Nasution, A. Hidayat, H. Gunawan, and A. Widipaminto, "Analysis of antenna specification for very high resolution satellite data

acquisition through direct receiving system (DRS)," *Int. J. Remote Sens. Earth Sci.*, vol. 15, no. 2, pp. 113–130, 2019.

[30] S. Dobricic *et al.*, "Europe's Earth Observation, Satellite Navigation and Communications Missions and Services for the benefit of the Arctic," 2021.

[31] R. Torres *et al.*, "GMES Sentinel-1 mission," *Remote Sens. Environ.*, vol. 120, pp. 9–24, 2012.

[32] K. N. Urata, J. T. Sri Sumantyo, C. E. Santosa, and T. Viscor, "Development of an L-band SAR microsatellite antenna for earth observation," *Aerospace*, vol. 5, no. 4, p. 128, 2018.

[33] T. Fahey, M. Islam, A. Gardi, and R. Sabatini, "Laser beam atmospheric propagation modelling for aerospace LIDAR applications," *Atmosphere (Basel).*, vol. 12, no. 7, p. 918, 2021.

[34] S. S. Panda, M. N. Rao, P. S. Thenkabail, D. Misra, and J. P. Fitzgerald, "Remote Sensing Systems—Platforms and Sensors: Aerial, Satellite, UAV, Optical, Radar, and LiDAR," in *Remote Sensing Handbook, Volume I*, CRC Press, 2016, pp. 3–86.

[35] M. Tooley and D. Wyatt, *Aircraft communications and navigation systems*. Routledge, 2017.

[36] D. G. Koshy and S. N. Rao, "A study of various aircraft communication technologies," in *2017 2nd International Conference on Communication and Electronics Systems (ICCES)*, 2017, pp. 521–524.

[37] J. Liu, I. Demirkiran, T. Yang, and A. Helfrick, "Communication schemes for aerospace wireless sensors," in *2008 IEEE/AIAA 27th Digital Avionics Systems Conference*, 2008, pp. 5-D.

[38] R. A. Burberry, *VHF and UHF antennas*, no. 35. IET, 1992.

[39] X. Zhang, F. Sun, G. Zhang, and L. Hou, "Compact UHF/VHF monopole antennas for CubeSats applications," *IEEE Access*, vol. 8, pp. 133360–133366, 2020.

[40] F. Paonessa *et al.*, "VHF/UHF antenna pattern measurement with unmanned aerial vehicles," in *2016 IEEE Metrology for Aerospace (MetroAeroSpace)*, 2016, pp. 87–91.

[41] A. I. Zaghloul, R. K. Gupta, E. C. Kohls, L. Q. Sun, and R. M. Allnutt, "Low cost flat antennas for commercial and military SATCOM terminals," *2001 MILCOM Proc. Commun. Network-Centric Oper. Creat. Inf. Force (Cat. No. 01CH37277)*, vol. 2, pp. 795–799, 2001.

[42] A. H. Kelechi *et al.*, "The Recent Advancement in Unmanned Aerial Vehicle Tracking Antenna: A Review," *Sensors*, vol. 21, no. 16. 2021.

[43] G. Virone *et al.*, "Antenna Pattern Verification System Based on a Micro Unmanned Aerial Vehicle (UAV)," *IEEE Antennas Wirel. Propag. Lett.*, vol. 13, pp. 169–172, 2014.

[44] F. Bohagen, P. Orten, and G. Bien, "Optimal design of uniform rectangular antenna arrays for strong line-of-sight MIMO channels," *Eurasip J. Wirel. Commun. Netw.*, vol. 2007, 2007.

[45] K. Ramahatla, M. Mosalaosi, A. Yahya, and B. Basutli, "Multiband Reconfigurable Antennas for 5G Wireless and CubeSat Applications: A Review," *IEEE Access*, vol. 10, pp. 40910–40931, 2022.

[46] L. H. Wang, F. R. Hsiao, Y. X. Zhang, and T. W. Chiu, "AI-based antenna technology for 5G software-defined radio platform," *ISAP 2018 - 2018 Int. Symp. Antennas Propag.*, no. 69, pp. 1–2, 2019.

[47] M. Zhai, P. Li, X. Feng, Q.-M. Cai, X. Cao, and Y. Zhu, "An Wideband Orthogonal Dipole Antenna for LTE Base Station Applications," in *2022 International Applied Computational Electromagnetics Society Symposium (ACES-China)*, 2022, pp. 1–2.

Chapter 7

A NORMALIZATION APPROACH TO DETECT CANCER TISSUE WITH ELECTROMAGNETISM

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Introduction

Cancer is one of the diseases that people suffer the most in the world. After the diagnosis is made, the treatment process begins. However, before starting the treatment, detailed information about the tissue is needed. This information is obtained by reporting the tissue after it is removed by surgical intervention. This is done by the science of pathology. Pathology examines the causes of diseases, the way they affect tissues and organs, especially the morphological (formal, visual) features of diseased tissues and organs [1]. Tissues removed from organs are converted into pathological tissue samples and these samples are examined by pathologists. Pathologists, who examine tissue samples, prepare reports that are important for the patient and doctor in terms of investigating and treating the disease. When pathologists prepare the reports, they use light microscopy. They take each sample under a microscope and examine it with the naked eye. Pathological tissue samples are prepared by pathologists. Nowadays, it can take months to reach these reports depending on the number of patients and samples [2]. Access to these reports is crucial, especially for patients in need of urgent treatment. Therefore, it is important to shorten the time to reach the report [3].

A glass slide is used in pathological tissue samples for examining in the light microscopy. Normally, the thicknesses of these samples are between 3-5 μm. But, here the thickness of tissue samples is prepared by 10 μm, taking into account the effect of skin depth. The skin effect changes inversely with frequency. Therefore, the thicker the tissue sample, the higher the stability of the study [4]–[6]. The standard dimension of used glass slide is 26x76x1 mm^3.

Horn antenna structures use for several purposes in the literature [7]–[9]. Especially, having high gain values of them becomes the reason for preference in medical areas. Adequate directivity is an another advantage of them [10]. In this work, horn antenna structures are selected because of high gain and directivity values. In order to show the differences between normal and tumorous tissue, it is expected that all electromagnetic energy transmitted and reflected from the antenna fall on the tissue. The directivity value is an important parameter that expresses this [11]. By using two identical E-plane pyramidal horn antennas pathological breast tissue samples are measured. Operating frequency is chosen as 13 GHz because of antenna radiation values. Antenna structures are obtained from laboratory equipment. They belong to Feedback brand [12].

There are four different breast tissue samples: two normal breast and two tumorous breast tissues. These samples were taken from Medical Pathology Laboratory at Selcuk University. Firstly, the setup is designed and simulated by using the free-space measurement method [8], [13]–[16] in HFSS (High Frequency Structural Simulator) from ANSYS. Then the real-time measurements are done like simulation model. In the measurements, Keysight PNA-L Series Vector Network Analyzer is used in an anechoic chamber. Standard calibration techniques are applied (Open, Short, Load), auto scale property is done and pathological tissue samples are fixed in measurement set-up to enhance the accuracy and sensitivity of measurements. Then, scattering parameters (S-parameters) are obtained both simulations and measurements. The measuring distance between the antennas to the samples is kept within the near field zone boundary. Near field measurement is generally selected in the biomedical applications because of electromagnetic radiation effects [17]–[22]. It should be ensured that all possible electromagnetic energy sent with horn antennas with high directivity falls on the MUT (Material Under Test).

Normalization preferred in various measurements is used to eliminate the effects of some setup [23], [24]. Here, by applying normalization approach to S-parameter values, the differences between normal and tumorous breast tissue are compared. Differences of compared values reveal the success of the study. In the literature, there is no detail information about pathological breast tissues with free-space antenna applications. This increases the importance of the study. Details of the work are presented below.

System Design and Antenna Structure

Like every material, every part of human body has electrical properties. Each body tissue has a different electrical value. To simulate the system, normal and tumorous breast tissue values are implemented in HFSS. These values are obtained in [25]. Dielectric value of normal and tumorous breast tissue is 6.3 and 50.0 for 13 GHz, respectively [26]–[28].

The designed system is showed in Fig. 1. There are two identical horn antennas. These antennas are placed at an equal distance from each other. This method called Free-Space measurement is used for various applications in the biomedical field [8], [29]–[31]. The distance is quarter of wavelength. The glass slide is placed in the center of the system [8], [13], [32], [33]. Also, MUT is fixed in the system.

Horn antennas used in simulations have the gain of 22.5 dB. Fig. 2 shows the gain of the antenna structures obtained from HFSS. The dimensions of them are 38.1x48.26x102.87 mm^3.

Antennas used for measurements are from communication applications laboratory equipment from [12]. Operating frequency is 13 GHz with rectangular waveguide feed the antenna. The distance between horn antennas is quarter of wavelength, in the near field region, which is about 6 mm [8], [30]. The distance is in near field radiation region. This radiation region is widely used because of no need to larger test distance [22], [34]. Directivity is important because of related with gain parameter. The directivity of the antenna is directly proportional to the maximum radiation intensity which explained in (1).

$$D_{max} = 4\pi \frac{U_{max}}{P_{rad}} \qquad (1)$$

Where Dmax is the maximum directivity of the antenna (unitless), Umax is the maximum radiation intensity of the antenna (W/unit solid angle) and Prad is the total power of radiation (W) [35]. In the light of all these data, the importance of horn antenna structures is expressed. In order to express the difference between tissues, almost all electromagnetic radiation reflected from the antennas should fall on the tissues, so that the difference between normal and tumor tissue can be expressed.

Why Normalization?

Normalization is a principle to compare variables with each other and is done differently depending on the measurement level of the variables. It is related to the uniqueness properties of the measurement level [36]. In the literature, it is used for several aims [37]–[39]. In this work, it is used to minimize the effects of set-up, environment noise, cable noise etc.

With this work, the differences between normal and tumorous breast tissue are expressed by using S-parameters, S_{11}, S_{21}, S_{12} and S_{22} [16], [40], [41]. These parameters express the radiation and propagation values of the antenna structures. Return and transmission loss are explained with them. Firstly, as seen in Fig.1, while there is only air (MUT) in the center, simulations and measurements are done and obtained S-parameters are saved. Secondly, while MUT is only glass slide, simulation and measurements are done and obtained S-parameters are saved. Then each parameter is subdivided by itself to be included in the parameter. It is explained in (2).

$$\frac{(S_{ij})_{empty\ glass\ slide}}{(S_{ij})_{air}} \quad i,j = 1,2,... \qquad (2)$$

where Sij expresses the values of S-parameters (for i,j=1,2). That ratio is used to obtain the differences between normal and tumorous breast tissue samples. After that, while MUT is normal breast tissue on the glass slide, simulations and measurements are done and parameters are saved. The measurement setup of designed system is shown in Fig. 4. For the tumorous breast tissue, the same procedure is performed. The obtained parameter values are divided by the above ratio for normal and tumorous tissue samples. It is explained in (3) and (4).

In this work, especially S-parameters are emphasized and examined. Because, S-parameters are used to obtain complex permittivity values of the materials. S_{11} and S_{21} express reflection and transmission coefficient values, respectively [8]. Differences of S_{21} values are important to show the value of the work because transmission coefficient values. This value gives the complex permittivity value in the literature [30], [42]. Complex permittivity is an important electrical variable. It represents the electrical conductivity of the medium and particles by depending on the angular frequency of the electric field applied. Here, complex permittivity values were not obtained because of not extracting the effect of the glass layer in the measurement. Tissue samples are evaluated with glass layer. Differences of S_{21} values are also important due to a new research issue of pathological tissue samples with antenna structure applications. By using normalization procedure to get more sensitive this process, the accuracy of the work is improved.

Differences of normal and tumorous tissue samples are obtained and compared with each other. Then evaluation is done.

$$\frac{(S_{ij})_{normal\ breast\ tissue}}{\frac{(S_{ij})_{empty\ glass\ slide}}{(S_{ij})_{air}}} \quad i,j = 1,2,\ldots \qquad (3)$$

$$\frac{(S_{ij})_{tumorous\ breast\ tissue}}{\frac{(S_{ij})_{empty\ glass\ slide}}{(S_{ij})_{air}}} \quad i,j = 1,2,\ldots \qquad (4)$$

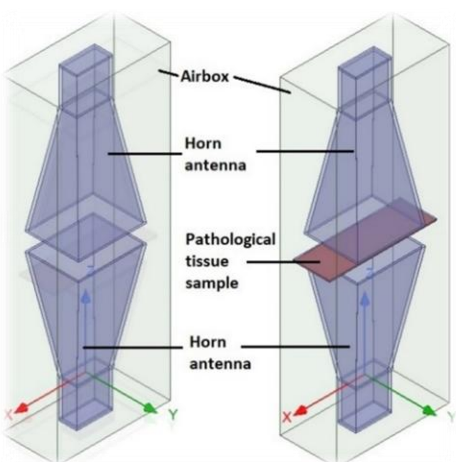

Fig. 1. The designed system.

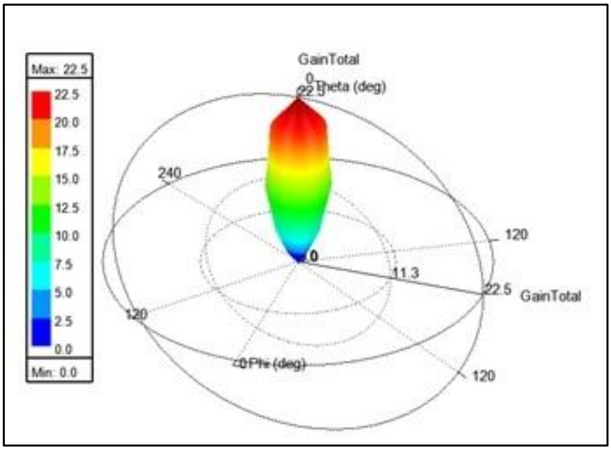

Fig. 2. The gain graph of the antenna structure.

Fig. 3. The pathological breast tissue samples.

Results of Simulations/Measurements and Evaluation

Results of Simulations and Measurements

Parameter values obtained from VNA in dB are converted without units. Fig. 5-8 show the difference graphics of normalized S_{11}, S_{21}, S_{12} and S_{22} values between normal and tumorous breast tissues from simulation results. Fig. 9 and 10 show the difference graphics of normalized S_{21} values between normal and tumorous breast tissues from measurements for first and second tissue samples, respectively. Fig. 11 and 12 show the difference of S_{21} values between normal and tumorous breast tissue according to measurement points (201 points) for first and second tissue samples, respectively. That is, they show the removal of normal breast tissue from tumorous tissue sample. Fig. 13 shows the comparison graphic between simulated and measured normal and tumorous breast tissue samples of normalized S_{21} values.

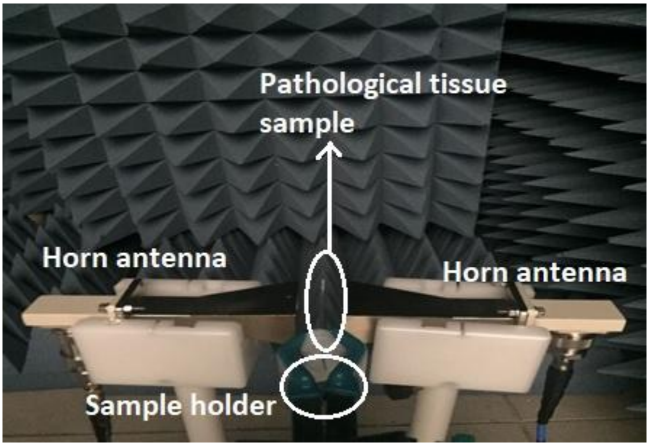

Fig. 4. The measurement setup of designed system.

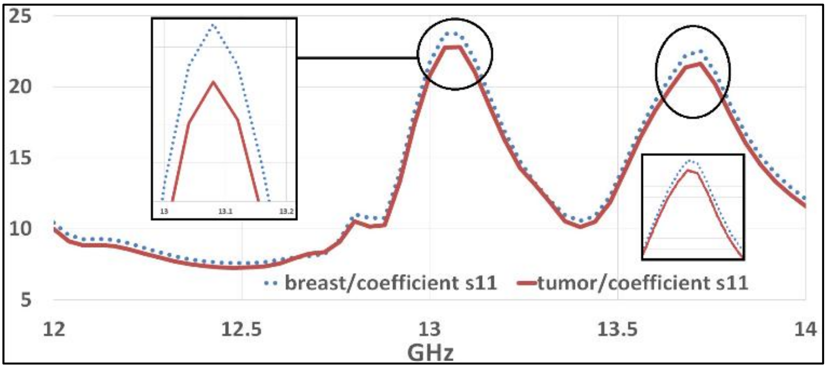

Fig. 5. Normalized S_{11} values after simulations.

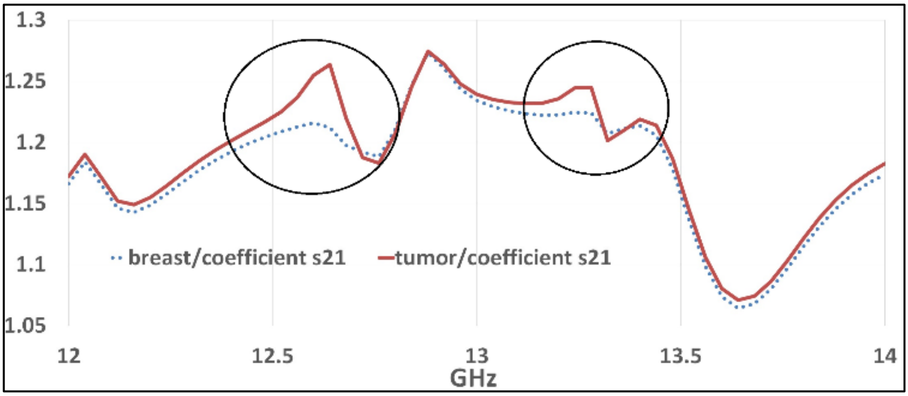

Fig. 6. Normalized S_{21} values after simulations.

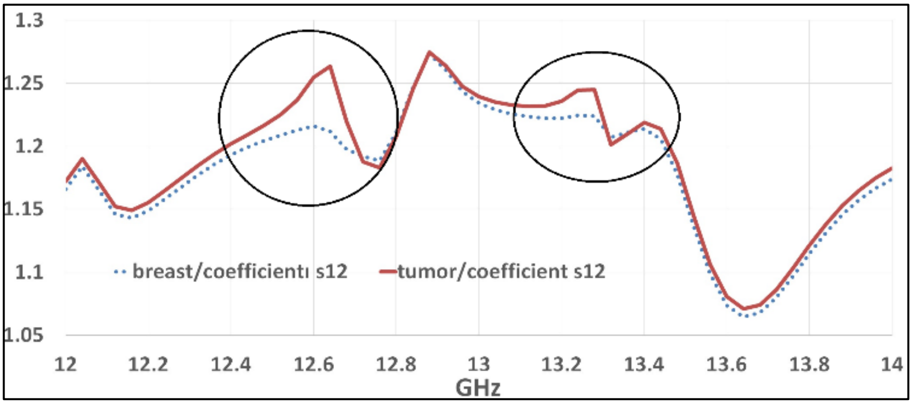

Fig. 7. Normalized S_{12} values after simulations.

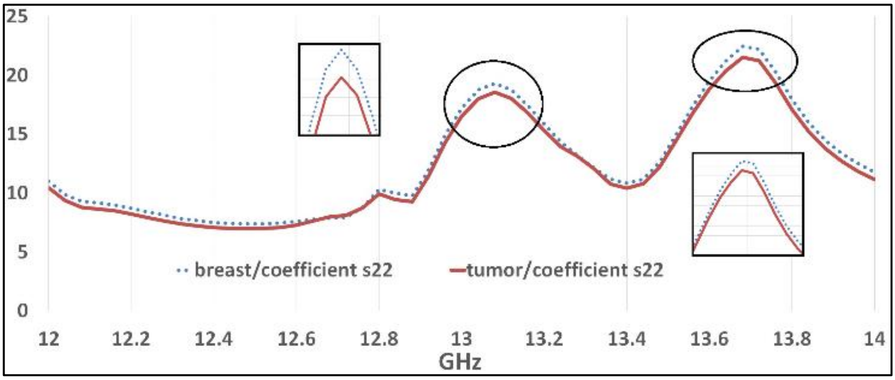

Fig. 8. Normalized S_{22} values after simulations.

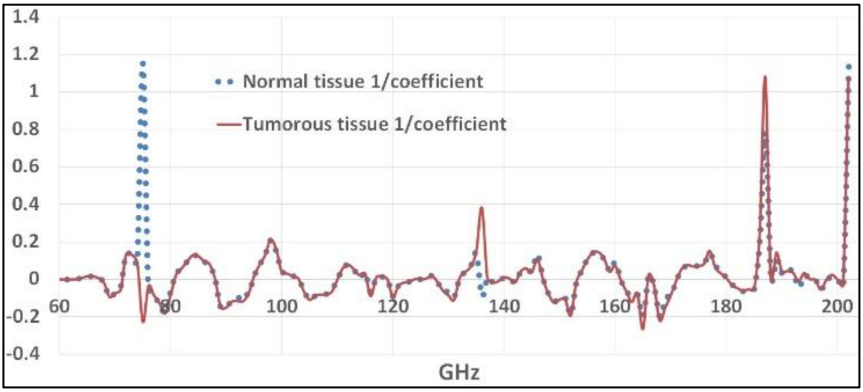

Fig. 9. The differences of normalized S_{21} values after measurement for first tissue sample.

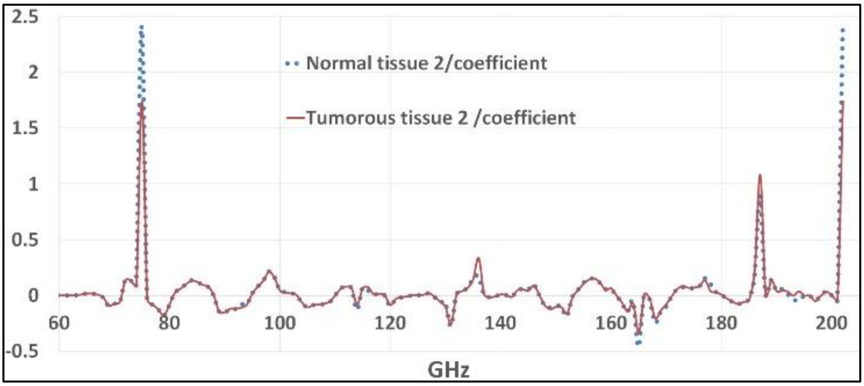

Fig. 10. The differences of normalized S_{21} values after measurement for second tissue sample.

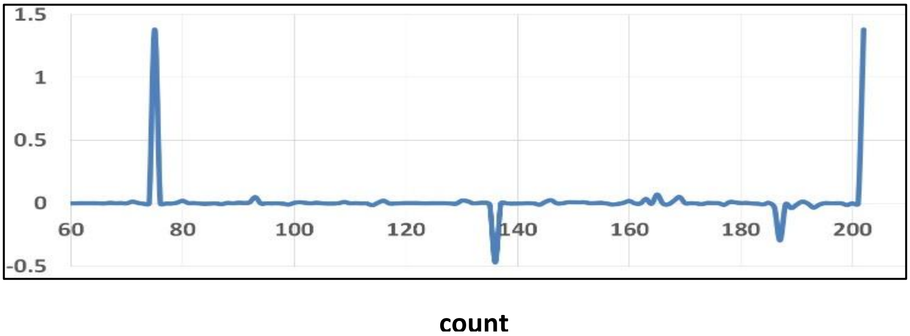

Fig. 11. The difference between first normal and tumorous tissue sample for S_{21}.

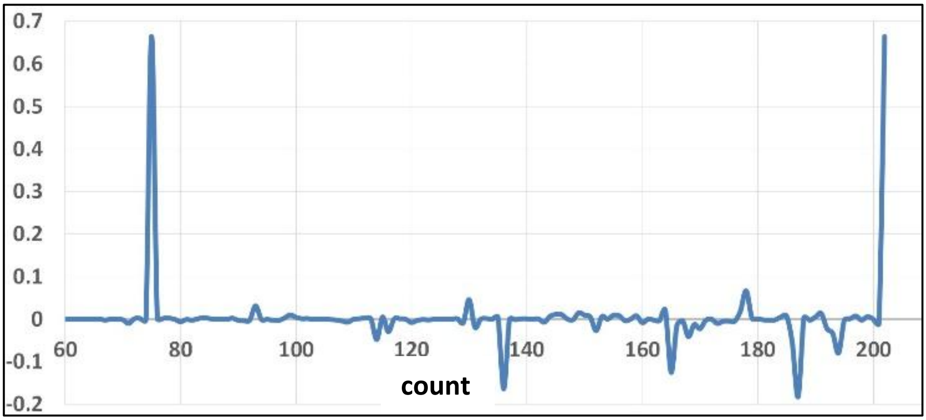

Fig. 12. The difference between second normal and tumorous tissue sample for S_{21}.

Evaluation

It is shown that for the S_{11} value, the normal breast tissue value is 23.75, while the tumorous tissue value is 22.80 after normalization at 13.04 GHz in the Fig. 5. When compared to normal tissue, the value of tumor tissue decreased by 4%.

Fig. 6 and 7 show that the maximum differences of S_{21} and S_{12} values about 0.05 and at 12.68 GHz. The rate of change is about 1% when it is compared with tumorous tissue.

Fig. 8 shows that for the S_{22} value, the normal breast tissue value is 22.47, while the tumorous tissue value is 21.53 after normalization at 13.70 GHz. When compared to normal tissue, the value of tumor tissue decreased by 4%.

Measurements have been done between 10 MHz and 20 GHz. There are 201 measurement points in this scale. The values between 60 and 201 are taken to show the figures more clearly. Here, the S_{21} values, which express the maximum difference according to the measurement results, is examined. Also, S_{21} is an important parameter because of expressing the transmission coefficient. When Fig. 9 and 10 are examined, the differences in measurements are shown to be more pronounced for first and second tissue samples. The maximum normalization values are about 20% for first tissue sample and 27% for second tissue sample at 7.41 GHz. The minimum normalization values are about 32.8% for first tissue sample and 27% for second tissue sample at 16 GHz. When the percentages are examined, it is possible to say that the measurement results are more efficient than the simulation results.

The difference in normalization values between normal and tumorous breast tissue for the first tissue sample is shown in Fig. 11. For second tissue sample, the difference in normalization values is shown in Fig. 12. The fact that both graphics vary at a similar rate is important in expressing the accuracy of data of the measurement results. The difference of simulated and measured of normalized S_{21} values is shown in Fig. 13. The difference ratios of the measurement results are given more clearly.

Conclusion

Access period to pathological reports is increasing day by day. Ways to shorten this period with technological development are being researched. For this purpose, the use of antenna structures is an alternative. This alternative is presented in this study.

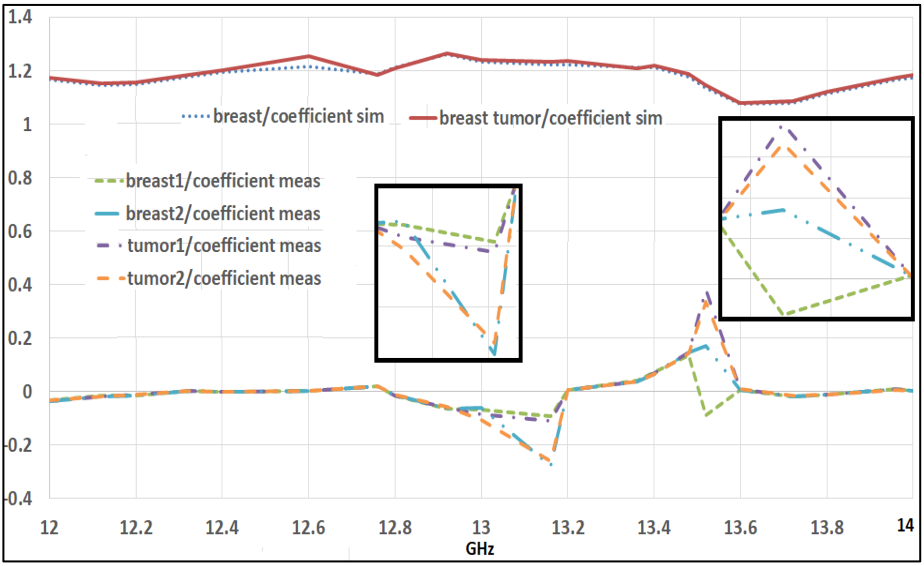

Fig. 13. The comparison graphic between simulated and measured normal and tumorous tissue sample for normalized S21.

Horn antenna structure is selected to determine the differences of obtained S-parameter values because of its gain value. Both simulations and measurements have been done. Normal and tumorous breast tissue are introduced in HFSS. Also, two each normal and tumorous breast tissue samples are measured in the setup from Faculty of Medicine, Pathology Laboratory at Selcuk University. The obtained S-parameter values are evaluated after normalization. Normalization has been done for increasing the accuracy of setup in the measurements. Thus, the reflection and scattering of the environment and the setup are minimized. Normal breast tissues have differences than tumorous breast tissues. Different values are obtained as a result of the analyzes. For example, S_{21} values have changed 1% in the simulation and 20% and 32.8% in the measurements, when normal tissues are compared with tumorous tissues. It is seen that the measurement results are better than the simulation results. These percentages express the success of the study.

References

[1] R. E. Nakhleh, “What is quality in surgical pathology?,” Journal of Clinical Pathology, vol. 59, no. 7. BMJ Publishing Group, pp. 669–672, 01-Jul-2006.

[2] H. M. Kamel, “Trends and Challenges in Pathology Practice Choices and necessities,” vol. 11, no. 1, pp. 38–44, 2011.

[3] N. K. Khitrov and A. B. Saltykov, “[Diseases of civilization and a nosological principle of medicine in terms of general pathology],” Klin. Med. (Mosk)., vol. 81, no. 1, p. 5—12, 2003.

[4] H. A. Wheeler, “Formulas for the Skin Effect,” Proc. IRE, vol. 30, no. 9, pp. 412–424, 1942.

[5] K. Ouerghi, N. Fadlallah, A. Smida, R. Ghayoula, J. Fattahi, and N. Boulejfen, “Circular antenna array design for breast cancer detection,” 2017 Sensors Networks Smart Emerg. Technol. SENSET 2017, vol. 2017-Janua, no. 1, pp. 1–4, 2017.

[6] H. Kurose, D. Miyagi, N. Takahashi, N. Uchida, and K. Kawanaka, “3-D Eddy current analysis of induction heating apparatus considering heat emission, heat conduction, and temperature dependence of magnetic characteristics,” IEEE Trans. Magn., vol. 45, no. 3, pp. 1847–1850, Mar. 2009.

[7] O. B. I. et al Daniyan O.L., Opara F.E., “Horn Antenna Design: The Concepts and Considerations,” Int. J. Emerg. Technol. Adv. Eng., vol. 4, no. 5, pp. 706–708, 2014.

[8] D. K. Ghodgaonkar, V. V. Varadan, and V. K. Varadan, “A Free-Space Method for Measurement of Dielectric Constants and Loss Tangents at Microwave Frequencies,” IEEE Trans. Instrum. Meas., vol. 38, no. 3, pp. 789–793, 1989.

[9] W. He, B. Xu, M. Gustafsson, Z. Ying, and S. He, “RF Compliance Study of Temperature Elevation in Human Head Model Around 28 GHz for 5G User Equipment Application: Simulation Analysis,” IEEE Access, vol. 6, pp. 830–838, 2017.

[10] Z. Shen and C. Feng, “A new dual-polarized broadband horn antenna,” IEEE Antennas Wirel. Propag. Lett., vol. 4, pp. 270–273, 2005.

[11] C. A. Balanis, “Horn Antennas,” in Anten Teorisi: Analiz ve Tasarım, 3th ed., 2013, pp. 739–805.

[12] “Microwaves in the free space - physical principles - Micro wave technology - High frequency technology - Communications technology - Electrical Engineering - Technology.” [Online]. Available: https://www.feedback-shop.co.uk/ve5-4-1-1.html. [Accessed: 21-Apr-2022].

[13] S. Alhuwaidi, K. Zubair, H. Song, Y. Shellman, W. Robinson, and S. Robinson, “Disease diagnostics of biological tissues using free-space technique in te-

rahertz frequency range," in IEEE Biomedical Circuits and Systems Conference: Engineering for Healthy Minds and Able Bodies, BioCAS 2015 - Proceedings, 2015.

[14] K. N. Ketavath, D. Gopi, and S. S. Rani, "In-vitro test of miniaturized CPW-fed implantable conformal patch antenna at ISM band for biomedical applications," IEEE Access, vol. 7, pp. 43547–43554, 2019.

[15] C. Schmidt, F. Casado, A. Arriola, I. Ortego, P. D. Bradley, and D. Valderas, "Broadband UHF implanted 3-D conformal antenna design and characterization for in-off body wireless links," IEEE Trans. Antennas Propag., vol. 62, no. 3, pp. 1433–1444, 2014.

[16] T. Ozturk, M. Hudlička, and İ. Uluer, "Development of Measurement and Extraction Technique of Complex Permittivity Using Transmission Parameter S 21 for Millimeter Wave Frequencies," J. Infrared, Millimeter, Terahertz Waves, vol. 38, no. 12, pp. 1510–1520, 2017.

[17] A. Ren, M. Qing, N. A. N. Zhao, M. Wang, and G. E. Gao, "Nano-Ferrite Near-Field Microwave Imaging for In-Body Applications," vol. 6, pp. 29551–29557, 2018.

[18] M. S. Israel and P. D. Chobanov, "Evaluation of the measurement equipment for electromagnetic fields in the near-field and far-field zones," p. 35, Nov. 2002.

[19] A. P. Tran, F. André, C. Craeye, and S. Lambot, "Near-field or far-field full-wave ground penetrating radar modeling as a function of the antenna height above a planar layered medium," Prog. Electromagn. Res., vol. 141, pp. 415–430, 2013.

[20] J. Notaros, C. V Poulton, M. Raval, and M. R. Watts, "Near-field-focusing integrated optical phased arrays," J. Light. Technol., vol. 36, no. 24, pp. 5912–5920, 2018.

[21] K. M. Labus, B. M. Notaroš, M. M. Ilić, C. J. Sutherland, A. Holcomb, and C. M. Puttlitz, "A Coaxial Dipole Antenna for Passively Sensing Object Displacement and Deflection for Orthopaedic Applications," IEEE Access, vol. 6, pp. 68184–68194, 2018.

[22] X. Zhao, L. Zhao, L. Zhang, Z. Fan, and Z. Su, "Application of Quad-Ridge Horn Antenna in near Field Measurement System," 2020 Cross Strait Radio Sci. Wirel. Technol. Conf. CSRSWTC 2020 - Proc., Dec. 2020.

[23] H. S. Jin, B. H. Choi, J. K. Kang, S. I. Kim, J. H. Lim, and S. Y. Song, "Measurement and Normalization Methods to Provide Detailed Information on Energy Consumption by Usage in Apartment Buildings," Energy Procedia, vol. 96, no. October, pp. 881–894, 2016.

[24] G. Alexander, I. L. Klavsuts, D. A. Klavsuts, and M. V. Khayrullina, "AC voltage normalization - Conception and technology for smart grid system," Proc. -

2016 51st Int. Univ. Power Eng. Conf. UPEC 2016, vol. 2017-Janua, pp. 1–5, 2016.

[25] C. Gabriel, "Compilation of the Dielectric Properties of Body Tissues at RF and Microwave Frequencies.," Environ. Heal., vol. Report No., no. June, p. 21, 1996.

[26] R. I. H. A.Kahwaji, H.Arshad, S.Sahran, A.G. Garba, "Hexagonal Microstrip Patch Antenna Simulation for Breast Cancer Detection," -, vol. 5, no. 1, pp. 1–4, 2016.

[27] J. J. Susila and H. R. Fathima, "A Slot Loaded Rectangular Microstrip Patch Antenna for Breast Cancer Detection," Int. Res. J. Eng. Technol., vol. 4, no. 4, pp. 3394–3397, 2017.

[28] R. Çalışkan, S. S. Gültekin, D. Uzer, and Ö. Dündar, "A microstrip patch antenna design for breast cancer detection," Procedia-Social Behav. Sci., vol. 195, pp. 2905–2911, 2015.

[29] C. Orlob, T. Reinecke, E. Denicke, B. Geck, and I. Rolfes, "Compact unfocused antenna setup for X-band free-space dielectric measurements based on line-network-network calibration method," IEEE Trans. Instrum. Meas., vol. 62, no. 7, pp. 1982–1989, 2013.

[30] G. L. Friedsam and E. M. Biebl, "A broadband free-space dielectric properties measurement system at millimeter wavelengths," IEEE Trans. Instrum. Meas., vol. 46, no. 2, pp. 515–518, 1997.

[31] J. Matlacz and K. D. Palmer, "Using offset parabolic reflector antennas for free space material measurement," IEEE Trans. Instrum. Meas., vol. 49, no. 4, pp. 862–866, Aug. 2000.

[32] K. N. Paracha et al., "A Low Profile, Dual-band, Dual Polarized Antenna for Indoor/Outdoor Wearable Application," IEEE Access, vol. 7, pp. 33277–33288, 2019.

[33] R. Toprak, "Detection of Cancerous Tissues Fixed with High Gain Microstrip and Horn Antenna Structures," Konya Technical University, 2022.

[34] F. Las-Heras, M. R. Pino, S. Loredo, Y. Alvarez, and T. K. Sarkar, "Evaluating near-field radiation patterns of commercial antennas," IEEE Trans. Antennas Propag., vol. 54, no. 8, pp. 2198–2207, Aug. 2006.

[35] C. A. Balanis, "Anten teorisi : analiz ve tasarım," 3rd ed., Nobel Akademik Yayıncılık, 2013, p. 843.

[36] H. Aguinis et al., "Recommendations for Improved Methods and Analysis in Management Research," Acad. Manag. Proc., vol. 2019, no. 1, p. 17367, Aug. 2019.

[37] S. Lu, Z. Liu, and Y. Shen, “Automatic Fault Detection of Multiple Targets in Railway Maintenance Based on Time-Scale Normalization,” IEEE Trans. Instrum. Meas., vol. 67, no. 4, pp. 849–865, Apr. 2018.

[38] S. Golemati et al., “Carotid artery motion estimation from sequences of b-mode ultrasound images: Effect of scanner settings and image normalization,” IEEE Trans. Instrum. Meas., vol. 58, no. 7, pp. 2102–2112, 2009.

[39] D. Karakos et al., “Score normalization and system combination for improved keyword spotting,” 2013 IEEE Work. Autom. Speech Recognit. Understanding, ASRU 2013 - Proc., pp. 210–215, 2013.

[40] F. Caspers, “RF engineering basic concepts: S-parameters,” CAS 2010 - Cern Accel. Sch. RF Accel. Proc., no. June, pp. 67–93, 2011.

[41] R. TOP, S. S. GÜLTEKİN, and D. UZER, “Evaluation and Comparison of Electromagnetic and Scattering Parameters Data of Two Microstrip Patch Antennas Operating in ISM Band for Cancer Detection,” Eur. J. Sci. Technol., pp. 237–244, Oct. 2020.

[42] T. Tosaka, K. Fujii, K. Fukunaga, and A. Kasamatsu, “Development of complex relative permittivity measurement system based on free-space in 220-330-GHz range,” IEEE Trans. Terahertz Sci. Technol., vol. 5, no. 1, pp. 102–109, Jan. 2015.

Chapter 8

MICROMORPHOLOGICAL FEATURES OF *TARAXACUM MICROCEPHALOIDES* SOEST, A MEDICINAL AND EDIBLE SPECIES BELONGING TO THE ASTRECEAE

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1. INTRODUCTION

Nature has long been a fertile source of medicinal agents, and manifold progress has been made by researchers worldwide in the use of medicinal plants for new drug discoveries. However, the overuse of known medicinal plants poses a serious threat to their survival, and it is clear that substitutes for these resource plants are becoming increasingly urgent. Wild herbs are one such group of plants traditionally known to have medicinal properties. Leaves, flowers (flower tops and flower heads), aerial parts and fruits are the parts of plants most used for medicinal purposes. Before this knowledge is lost, data on the medicinal uses of wild herbs must be obtained from traditional repositories (Jayasundera et al., 2021). The Asteraceae family includes important taxa from many medicinal species (Doğan 2007; Kırpık et al. 2019). In Türkiye some of the medicinal plants belonging to this family are also cultivated and cultivated (Demir 2020a; Demir 2013; Demir 2021).

The Asteraceae family is represented by approximately 1100 genera and 25000 species in the world and is the most widely distributed family of flowering plants with the highest number of species (Seçmen et al., 2000). In Türkiye , this family is represented by a total of 1438 taxa including 152 genera, 1230 species, 133 subspecies and 75 varieties (Yıldırımlı, 1999). Most of the Asteraceae family is composed of herbaceous forms distributed in temperate regions. Members of the family are widely distributed in almost all parts of the world except Antarctica (Attar and Ghahreman, 2006). It is especially abundant in the southwestern United States and Mexico, southern Brazil, along the Andes Mountains, Mediterranean Region, Southwest Asia, Central Asia, South Africa and Australia (Bremer, 1994). The majority of members of the Asteraceae family have therapeutic applications and have a long history in traditional medicine: Some members have been edible and cultivated for medicinal purposes for more than 3000 years. They are most common in arid and semi-arid regions of subtropical areas, but are known and distributed worldwide. Members of the Asteraceae family show a wide range of anti-inflammatory, antimicrobial, antioxidant and hepatoprotective activity (Rolnik and Olas 2021). Members of the family have an important place in Turkish agriculture and make a great economic contribution (Demir 2020b; Demir 2020c).

The genus *Taraxacum* is distributed in the Northern Hemisphere and all countries of Europe with approximately 2500 species and 43 sections. In Türkiye, they are latex-bearing perennial herbaceous plants represented by 50 species (Davis et al. 1988, Güner et al. 2000). It is a perennial plant with yellow flowers that can grow in meadows and roadsides in April-May. *Taraxacum* *microcephaloides* (Dandelion) is a common plant that contains many important compounds such as terpenoid, sterol, calcium, potassium, vitamin A, nicotinic acid and vitamin C and has nutritive value (Hu, 2018). Due to these properties, it has been stated that eating 5-6 flower stalks freshly, especially in liver and gallbladder diseases, provides improvement in chronic liver inflammation and fatty liver and regulates the work of the gallbladder. In addition, although it has a great effect on diabetes, skin diseases, vitamin deficiency, arteriosclerosis, lowering blood sugar, increasing appetite, cleaning the blood, anemia, rheumatism and gout diseases, protecting bone integrity, regulating gastric fluids and cleaning the stomach from waste substances and some types of cancer, it is not recognized by many people and is known as a harmful herb (Koç et al. 2015. Dandelion is known to have anti-inflammation effect thanks to sesquiterpene lactones and phenyl propanoid in its composition. At the same time, the terpenes and polysaccharide components it contains regulate the immune system, prevent platelet accumulation and protect the liver (Sigstedt et al., 2008). It is a very important plant in terms of containing vitamins B, C, D, E as well as choline, inositol, lecithin, minerals and oligoelements (calcium, sodium, magnesium, iron, copper, phosphorus, zinc, manganese). Dandelion is also one of the best natural sources of potassium due to its high potassium content (Gallaher et al., 2006).

Micromorphological characteristics obtained using electron microscopy reveal very important information about these plants. In recent years, micromorphological findings have been utilized for taxonomic, ecological and physiological purposes. The aim of this study is to determine the micromorphological characteristics of medicinal and edible *Taraxacum microcephaloides* Soest (Dandelion).

2. MATERIAL AND METHOD

The species *Taraxacum microcephaloides* Soest was collected from Pazar district of Tokat in April and May 2016-2017. Electron microscope photographs were taken from the fruits, leaf sepals and petals of the species. For electron microscope photographs, the specimens were fixed on stubs with double-sided carbon tape. The fixed specimens were coated with 12.5-15 nm gold-palladium (SEM coating system, SC7620). Examination and images were taken on a JEOL JMS-7001F Scanning Electron Microscope (SEM) with a voltage of 5-15 KV.

3. RESULTS

Fruit

The fruit type of *T. microcephaloides* is cypsela. The papuses of the cypsela are sparse. The epidermal cells of the fruit are square, rectangular or polygonal. The general The ornemantation is ribbed. Papillae can be seen on the surface close to the pappus. The ornamentation in this region is sulcate (Figure 1). The cells on the pappus are elongated rectangular. Sulcate ornamentation is observed. Hairs are seen on the surface towards the pappus. There are two seeds together at the end of the stalk of the fruit (Figure 1).

Seed

Seeds are elliptical in shape. There are long covering hairs on the basal part of the seed. The cover hairs have a foveolate pattern. The seed surface is also sulcate-tuberculate patterned. Sem-shots of the seed show that the surface cells are square, rectangular or polygonal. The ornemantation type is reticulate- striate (Figure 1).

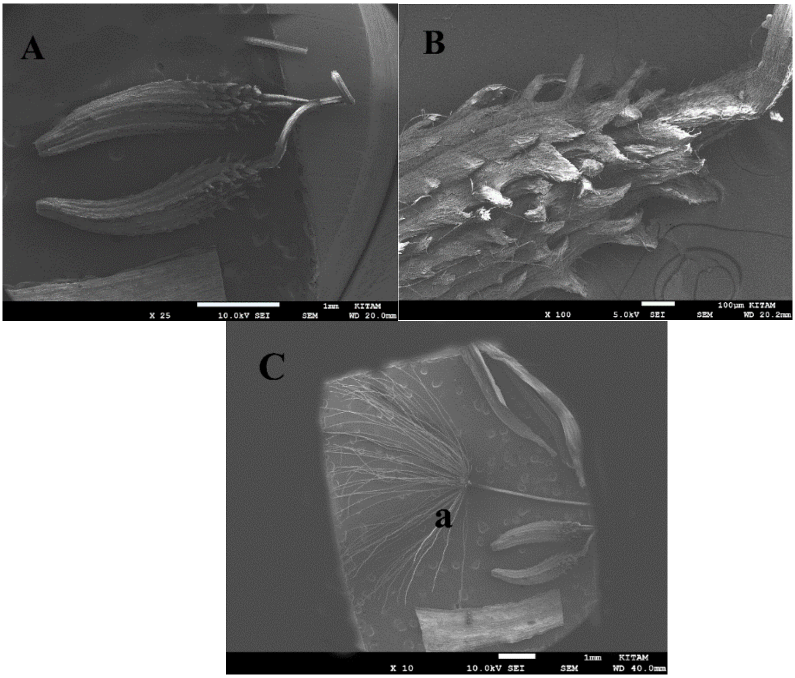

Figure 1. SEM images of *T. microcephaloides* fruit and seed. A-B seed, C fruit. a cypsela.

Leaf

The taxon has very dense stomata on the lower leaf surface. Stomatal aperture is quite wide and dorsal walls are thickened. The ornemantation of leaf lower surface is rugose. The patterning type on the upper surface of the leaf is rugose as on the lower surface. Stomata are densely arranged. Hairs are absent on both the upper and lower surfaces (Figure 2). No glandular or non-glandular hairs were found on the leaves.

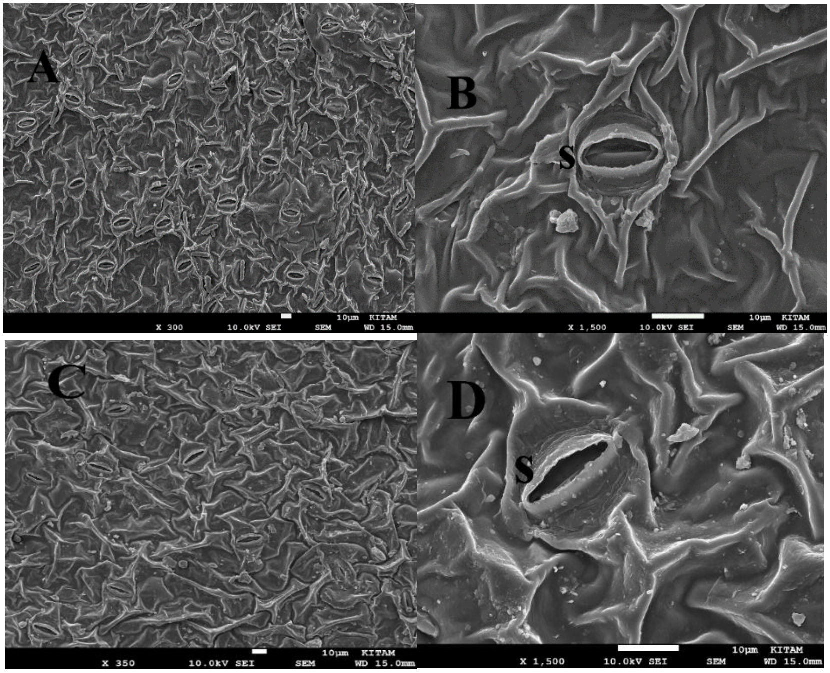

Figure 2. SEM images of *T. microcephaloides* leaves. A-B leaf lower surface, C-D Leaf lower surface. s stomata.

Sepal and petal

Sparse stomata were observed on the sepals in SEM images. The ornemantation type is lineolate. The ornemantation on the petals is lineate (Figure 3). No glandular or non-glandular hairs were found on the sepal and petal.

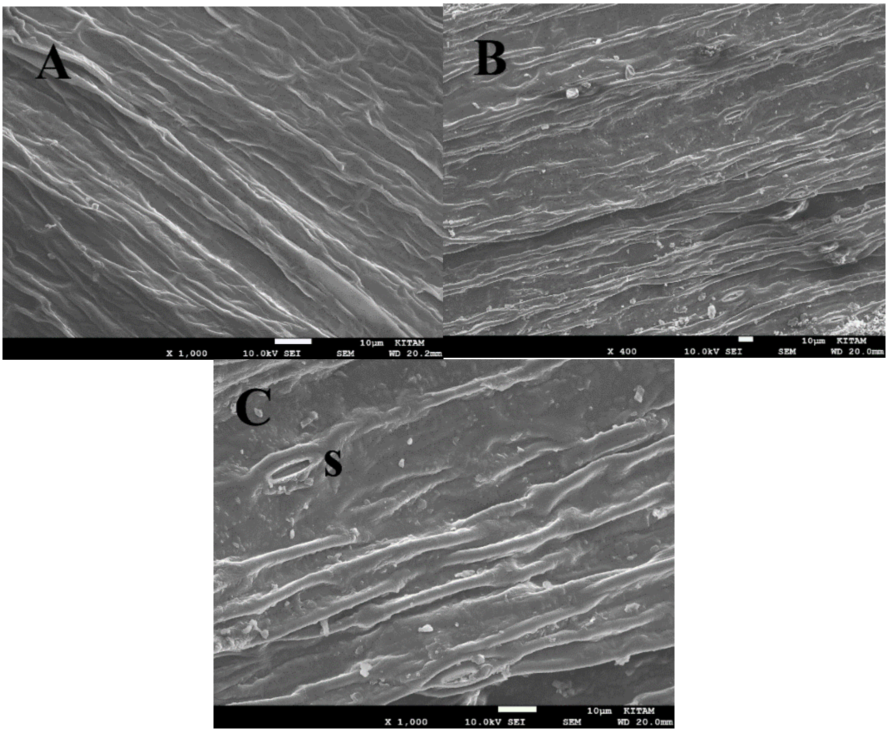

Figure 3. SEM images of *T. microcephaloides* sepal and petal. A sepal, B-C petal. s stomata

In this study, the micromorphologies of the plant's fruit, seed, and leaf have been examined in detail. Micromorphological characters can be important criteria for plant identification (Adedeji and Jewoola 2008). Micromorphological traits of leaves, involucral bracts (Gavrilović et al. 2019), flowers (Torres and Galetto 2007, Erbar and Leins 2015, Erbar et al. 2018), and particularly cypselae (Kalmuk et al. 2018, Ozcan and Akinci 2019) have offered valuable insights for the classification and evolutionary relationships of specific groups within the Asteraceae family. Leaf venation patterns have also been utilized for identifying and distinguishing species (Teixeira & Gabrielli, 2000).

The leaf of *T. microcephaloides* exhibits a rugose ornamentation. The fruit of this species is a cypsela, characterized by ribbed ornamentation. Reports have noted undulate and rugose ornamentations in the fruits of members of Cardueae (Asteraceae) (Ozcan and Demir 2022). Additionally, a striation pattern has been observed in the leaf of *Centaurea glaberrima* subsp. *divergens* Tausch. (Asteraceae) (Gavrilović and Janaćković 2022).

In conclusion, the micromorphological characteristics of the fruit, seed, and leaf of the species are distinctive. It is anticipated that these findings will serve as a resource for future studies related to the genus.

REFERENCES

Adedeji, O., & Jewoola, O.A., (2008). Importance of leaf epidermal characters in the Asteraceae family. Notulae Botanicae Horti Agrobotanici Cluj-Napoca. 36, 7–16.

Attar, F., & Ghahreman, A. (2006) A synopsis of sect. Cynaroides (Cousinia, Compositae), distribution patterns and diversity centers. - Rostaniha 7(Suppl. 2): 315-342.

Bremer, K. (1994). Asteraceae. Cladistics and classification. Portland (OR): Timber Press.

Borisova, A.G. (1964). Tragopogon. In: Shishkin BK, editor.Flora of the USSR. vol 29. Moscow: Nauka; p. 115–196.

Davis, P.H., Mill, R.R., & Tan, K. (1988). Flora of Turkey and the East Aegean Islands. vol 10. Edinburgh: Edinburgh University Press.

Demir, İ. (2020a). Inter and intra row competition effects on growth and yield components of sunflower (Helianthus annuus L.) Under rainfed conditions. JAPS: Journal of Animal & Plant Sciences, 30(1).

Demir, İ. (2020b). Comparing the performances of sunflower hybrids in semi-arid condition. Turkish Journal of Agriculture and Natural Sciences, 7(4), 1108-1115.

Demir, I. (2020c). Improving seed and oil yield of sunflower (Helianthus annuus L.) by using different inter and intra row space combinations. J. Glob. Innov. Agric. Soc. Sci, 8, 147-153.

Demir, I (2013) Oilseed crop cultivation in TR71 region and effects of climate change. Turkish Journal of Agriculture-Food Science and Technology 1, 73–78.

Demir, I. (2021). The evaluation of confectionery sunflower (Helianthus annuus L.) cultivars and populations for yield and yield components. International Journal of Agriculture, Environment and Bioresearch, 6(01), 179-186.

Dogan, B., Duran, A., & Hakki, E. E. (2007, January). Phylogenetic analysis of Jurinea (Asteraceae) species from Turkey based on ISSR amplification. In Annales Botanici Fennici (pp. 353-358). Finnish Zoological and Botanical Publishing Board.

Erbar, C., & Leins, P. (2015). Cuticular patterns on stylar hairs in Asteraceae: a new micromorphological feature. International Journal of Plant Sciences, 176(3), 269-284.

Erbar, C., Eichelser, C., & Mögerle, S. (2020). Styles in Carduoideae (Asteraceae)–diversity in the uniformity. Plant Diversity & Evolution, 132(1).

Gallaher, R. N., Gallaher, K., Marshall, A. J., & Marshall, A. C. (2006). Mineral analysis of ten types of commercially available tea. Journal of Food Composition and Analysis, 19, S53-S57.

Gavrilović, M., & Janaćković, P. (2022). Micromorphology of endemic Centaurea glaberrima subsp. divergens (Asteraceae). Acta Botanica Croatica, 81(1), 23-31.

Gavrilović, M., Jacas, N. G., Susanna, A., Marin, P. D., & Janaćković, P. (2019). How does micromorphology reflect taxonomy within the Xeranthemum group (Cardueae-Asteraceae)?. Flora, 252, 51-61.

Güner A, Özhatay N, Ekim T, Başer KHC. 2000. Flora of Turkey and the East Aegean Islands. vol 11. Edinburgh: Edinburgh University Press.

Hu, C. (2018). Taraxacum: Phytochemistry and health benefits. Chinese Herbal Medicines, 10(4), 353-361.

Jayasundera, M., Florentine, S., Tennakoon, K. U., & Chauhan, B. S. (2021). Medicinal value of three agricultural weed species of the asteraceae family: A review. Pharmacognosy Journal, 13(1).

Kırpık, M. A., Altunoğlu, M.K., Yıldız Asker, Y., Altunkalem, S. (2019). Evelik Bitkisi (Rumex patientia L.) ve Karahindiba (Taraxacum officinale L.) kullanılarak doğal yolla baklagil yaprak biti (Aphis fabae Scop.)'nin hedef konukçusunun değiştirilmesi. KAUFBED 12 (1), 1-8.

Aksu Kalmuk, N., Inceer, H., & Imamoglu, K. V. (2018). Achene micromorphology of 26 Crepis L.(Asteraceae) taxa from Turkey with notes on its systematic and ecological significance. Botany Letters, 165(2), 292-306.

Koc, S., Isgor, B. S., Isgor, Y. G., Shomali Moghaddam, N., & Yildirim, O. (2015). The potential medicinal value of plants from Asteraceae family with antioxidant defense enzymes as biological targets. Pharmaceutical biology, 53(5), 746-751.

Ozcan, M., & Demir, K. (2022). Pappus and fruit micromorphology and fruit anatomy in some members of the tribe Cardueae (Asteraceae) from Turkey with their contributions to systematics. Microscopy Research and Technique, 85(2), 641-666.

Ozcan, M., & Akinci, N. (2019). Micromorpho-anatomical fruit characteristics and pappus features of representative Cardueae (Asteraceae) taxa: Their systematic significance. Flora, 256, 16-35.

Teixeira, S. P. & Gabrielli, A. C. (2000). Anatomia do eixo vegetativo de Dahlstedtia pinnata (Benth.) Malme e D. Pentaphylla (Taub.) Burkart (Leguminosae, papilionoideae). Brazilian Journal of Botany, 23, 1-11

Torres, C., & Galetto, L. (2007). Style morphological diversity of some Asteraceae species from Argentina: systematic and functional implications. Journal of Plant Research, 120, 359-364.

Rolnik, A., & Olas, B. (2021). The plants of the Asteraceae family as agents in the protection of human health. International journal of molecular sciences, 22(6), 3009.

Seçmen, Ö., Gemici, Y., Görk, G., Bekat, L., & Leblebici, E. (2000). Systematics of seed plants. Ege University Faculty of Science Book Series, 116, 394.

Sigstedt, S. C., Hooten, C. J., Callewaert, M. C., Jenkins, A. R., Romero, A. E., Pullin, M. J., ... & Steelant, W. F. (2008). Evaluation of aqueous extracts of Taraxacum officinale on growth and invasion of breast and prostate cancer cells. International journal of oncology, 32(5), 1085-1090.

Yıldırımlı, Ş. (1999). The chorology of the Turkish species of Asteraceae family. Journal of Systematic Botany. 6(2), 75-123.