RECENT DEVELOPMENTS IN SCIENTIFIC RESEARCH I

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PREFACE

Multidisciplinary approach is inevitable in academic studies. In recent years there has been a significant development in science. This book is a compilation of six chapters relating to different areas of scientific research. In the first chapter of this book, Secondary Metabolites in Medicinal Plants And Production in Plant Tissue Cultures, in the second chapter Synthesis and theoretical studies of quinoline-based triazole compound, in the third chapter Tropone-Carbazole Hybrid Structures For Potential Oled And TADF Systems, in the fourth chapter Effects On Florosis And Cell Mechanisms, in the fifth chapter Gonadotropine Hormones and in the sixth chapter Giardiasis is examined.

The efforts of our extreme contributors of this book are highly commendable. I would especially like to express my gratitude to the İKSAD Publishing family, scientific committee, authors and readers who contributed to the preparation, layout and printing of the book.

Prof. Dr. Ayşegül GÜMÜŞ
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CHAPTER I

SECONDARY METABOLITES IN MEDICINAL PLANTS AND PRODUCTION IN PLANT TISSUE CULTURES

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INTRODUCTION

For centuries, human beings have used plants as therapeutic as well as food and beverage, cosmetics and chemical industry. The main reason why the demand for herbal resources has continued to increase in recent years is that synthetically produced drugs cause negative effects that will harm different organs of the body while curing the disease in question. Plants gain an increasing value due to the primary metabolites they produce as well as the secondary metabolites that give them therapeutic properties. Collecting medicinal plants from the environment where they naturally grow, harms their habitat and negatively affects genetic diversity. Micropropagation of continuous, high-quality plant cultures in tissue culture is an effective way to prevent the extinction of medicinal plants and damage to their habitats (Murch et al., 2000). Plant tissue cultures currently present a different strategy for the synthesis of significant secondary metabolites. Cell culture technology enables both secondary metabolite production and analysis. Plant cells convert natural or artificial compounds added to cultures into metabolites by subjecting them to a wide variety of reactions such as hydroxylation, glycolysis, hydrogenation, and dehydrogenation. The majority of secondary metabolites as naturally occurring antioxidants have a variety of biological effects, particularly anti-allergic, antibacterial, anti-inflammatory, antithrombotic, antiviral and vasodilatory ones. An essential component of life is antioxidant activity (Velioğlu et al., 1998). The cancer, diabetes, Alzheimer's disease, stroke, heart attack, and atherosclerosis are just a few of the more than sixty diseases that have been determined to have a strong connection to free radicals. The likelihood that our body may experience health issues caused by free radicals can be decreased (Shovan, 2017) by reducing exposure to them and increasing consumption of foods high in antioxidant enzymes or antioxidant enzyme supplements. Plant tissue cultures, an emerging technique, has had a significant impact on both industry and agriculture by supplying necessary plants to fulfil the growing global demand. It has recently made significant contributions to the development of agricultural sciences and has emerged as a key area of contemporary agriculture. Agricultural applications of biotechnology are being developed at an unprecedented rate. The creation and propagation of genetically uniform, disease free plant material is made possible via plant tissue cultures.

1. THE THERAPEUTIC USES OF PLANTS

The emergence of humanity onto the historical scene marked the beginning of the utilization of plants for medicinal uses. It is reported that plants were used in the treatment of diseases in Old China Medicine, in Ancient Egyptian papyrus (Shovan, 2017) Early Roman inscriptions, and Islamic and Ottoman medicine (Ağırakça,2015). Today, modern medicine continues to add plant-based raw materials to many of the drugs it produces. People have been using the plants in their environment for food, drink, cosmetics, and the chemical industry for thousands of years all over the world. Even today, the use of medicinal plants in folk medicine continues widely in almost every country. The main reason why the demand for herbal resources continues to increase in recent years is that synthetically produced drugs cause negative effects that will harm different organs of the body while curing the disease in question. The World Health Organization (WHO) reports that 80% of the world's population primarily benefits from medicinal plants for the prevention and healing of diseases, and the number of medicinal plants used for treatment is around 20,000 (Faydaloğlu and Sürücüoğlu, 2011). Despite the developments in technology and medicine in the modern world, the demand for medicinal plants continues to increase day by day.

2.PLANT SECONDARY METABOLITES

Plants synthesize two kinds of basic chemicals as primary and secondary metabolites. Vitamins, proteins, lipids, carbohydrates, and minerals are examples of primary metabolites, which are chemicals produced during plant metabolism and utilised in metabolic processes. Secondary metabolites are compounds that are helpful to the plant as a whole but are not necessary for the survival of plant cells. In contrast to primary metabolites, secondary metabolites may not cause instant mortality; instead, they may cause long-term declines in the organism's survival, fertility, or aesthetics, or they may have no effect at all (Tiwari, 2015). These are sophisticated phytochemicals with messaging properties that influence metabolic processes and promote plant growth by shielding the plant from alterations in its environment. Bioactive molecules accumulate as secondary metabolites in specialized plant cells or organs, but their amounts vary according to plant parts, season, climate and growth phase. Bioactive molecules accumulate as secondary metabolites in specialized plant cells or organs, but their amounts vary according to plant parts, season, climate and growth phase. By supporting the functions of organs,

they increase the body's defense power and accelerate healing. All metabolic pathways required for the survival of the cell, such as lipid and nucleotide biosynthesis, energy transfer with ADP, ATP and other nucleotide triphosphates, proton and electron acceptors, glycolysis and citric acid cycles, respiratory chain, carbohydrate cycle, enzyme reactions, are the main elements of primary metabolism. All basic metabolic processes in primary metabolism are related to the transformation of cell components during energy production and growth. In secondary metabolism, components responsible for plant defense are produced. Secondary metabolites can be classified as alkaloids, isoprenoids/terpenes, rubber like polymers/polyisoprene, phenolic compounds, rare amino acids, plant amines and glycosides (Güven and Gürsul, 2014). These are sophisticated chemicals with signalling properties that influence metabolic processes and promote plant growth by shielding the plant from alterations in its environment. Secondary metabolites are not indispensable for plant life, but they are organic compounds that plants may encounter in their life cycle, which are outside the optimum living conditions and are produced in every situation that requires self-defense (drought, salinity, herbicide, etc.) (Güven and Knorr, 2011). Although the emergence of secondary metabolism under stress conditions seems to be negative for plants, it is perceived as a positive effect because it encourages secondary metabolite production.

2.1.Classifying Secondary Metabolites

According to their chemical formation (possessing a ring or having sugar), constitutent (having nitrogen or not), solving ability in different solvents, or the metabolic pathway through which they are formed, secondary metabolites can be categorised (Harborne and Williams, 2000). Three large families of molecules are generally accepted: Terpenes, Nitrogenous Compounds (Alkaloids), and Phenolic Compounds (Bourgaud et al., 2001).

2.1.1. Terpenes

The largest family of plant secondary metabolites, terpenes, are produced through the glycolytic or acetyl-CoA pathways. They typically don't dissolve in water. They are created by combining five units of carbon isoprene. Certain terpenes are crucial for growth and development. For example, gibberellins, which constitute an important group of growth hormones, are diterpenes. Because terpenes are toxic, they take part in plant defense against plant-feeding organisms. Many

plant species synthesize mono- and sesquiterpene mixture molecules, known as essential oil or ethereal oil with a distinctive odor (Taiz and Zeiger, 2008). Terpenes make up essential oils which are important chemicals and are derived from different plant parts. The aromatherapy, scent, and food industry sectors all use essential oils. Essential oils have a significant function in safeguarding plants in nature. They protect against herbivore activity and act as antifungal, insecticides, antiviral, and antibacterial. Sometimes they draw insects that aid in pollen transmission or deter other undesirable insects. They have a lower density than water, are liquid, flammable, opaque, rarely coloured, soluble in organic solvents, and are hardly tinted. All of the plant's organs produce and transport them to different organs for preservation (Nunes et al., 2012).

2.1.2. Alkaloids

Alkaloids are defined as pharmacologically active, nitrogen-containing essential compounds of plant origin. They can block ion channels and neurotransmission, inhibit enzymes, cause hallucinations, loss of coordination, convulsions, vomiting and death. Generally, there are malic, tartaric, citric, limonic, etc. in the structure of plants. exists in the form of salts with acids. alkaloid salts; They are white, crystalline, water - soluble, insoluble in organic solvents, or only sporadically soluble in them. They are used as a nitrogen source in plants due to their nitrogen transport. They protect plants against grass-eating animals. Thanks to the salts they form by bonding with organic acids, they regulate the pH and ion balance of the cell (Mammadov, 2014). In addition to carbon, hydrogen, and nitrogen, alkaloids may have different molecules such as phosphorus, sulfur, bromine, oxygen and rarely chlorine.

2.1.3. Phenolic compounds

Phenolic compounds dye the tissues in which they are synthesized, and also give the distinctive acrid taste and color of vegetables and fruits. While some phenolics are soluble only in organic solvents, another group is water-soluble thanks to their carboxylic acids and glycolisides. The third group of phenolics are large polymers and are insoluble in water. High amounts of phenolic chemicals are present in plants and promote antioxidant potential. By giving hydrogen or electrons, they can neutralise free radicals such as reactive oxygen species (ROS) (Fernandez-Pachon et al., 2006). The redox characteristics of phenolic compounds, which

can be useful in adsorbing and neutralising free radicals, reducing singlet and triplet oxygen, or breaking peroxides, are primarily responsible for their antioxidant effects (Rice et al., 1995). Plant phenolics add rigidity to the cell wall by forming molecular bridges between cell wall components. They are precursors of lignin and phytoalexin. They affect the nitrogen and humus content of the soil as a result of the breakdown of microorganisms. They are synthesized in chloroplasts under the influence of light and stored in vacuoles. Some form lignins in the secondary cell wall. Since it affects the light synthesis, there is more phenolic content in the spring leaves than in the autumn. Derivatives of phenolics such as cinnamic acid, coumarin and narinjenin have the ability to inhibit growth. In some plants, phenolic derivatives have allelopathic properties (eg, isosalipurposide, the naringenin derivative produced by Salix rubra and Salix viminalis).

2.2.Free Radicals and Antioxidants

Living things use the energy generated as a result of the breakdown of organic molecules by glucolysis in order to maintain their vital activities. Oxygen metabolism produces highly damaging reactive oxygen species (ROS) by cells. Increased ROS/RNS levels in the cell lead to impaired cell function, aging or disease. The continual production of free radicals and reactive oxygen species by cells plays a significant role in tissue damage in living things (Gümüş and Okumuş, 2018). Oxidizing agents and antioxidant defences are in equilibrium in a physiological environment. Enzymes including, glutathione peroxidase, superoxide dismutase, glutathione, and catalase as well as non-enzymatic antioxidant defence chemicals like vitamin C and E, can be produced or imported by living cells. Reactive oxygen and nitrogen species may react with lipids, proteins, and DNA, causing structural and functional damage to the cell's enzymes and genetic material, if the creation of free radicals exceeds the capacity of a living system's antioxidants (Nunes et al., 2012). The dominance of oxidants and the resulting damage is called oxidative stress (Magder, 2006). As the oxidant-antioxidant balance works in favor of reactive species, oxidative damage levels increase and cause tissue destruction in some chronic diseases (Halliwell, 2001). Due to the unpaired electron in free radicals, they must capture electrons from other molecules in order to neutralise themselves. Although the free radical is neutralised by the initial attack, another free radical is created as a result, setting off a series of events. Within seconds following the original reaction, thousands of subsequent free radical reactions may

take place until the subsequent free radicals are deactivated. Due to its extreme reactivity, oxygen can form potentially harmful molecules known as free radicals or reactive oxygen species (ROS). A substance that prevents other molecules from oxidising is known as an antioxidant. Antioxidants give electrons to the free radical, which causes them to oxidise themselves, but they also prevent oxidation reactions by stabilising the free radical (Shovan, 2017). Before free radicals assault cellular components, antioxidants can neutralize or stop them. By lowering their energy or allowing several of their electrons to be used, they give free radicals the ability to act. Consuming antioxidants from plants helps prevent degenerative diseases brought on by oxidative stress, such as cancer, Parkinson's disease, and Alzheimer's disease (Young and Woodside, 2001).

2.3.Phenolics as Antioxidants

Phenolic compounds can bind an electron and hydrogen atom in their hydroxyl groups to a free radical (Dai and Mumper, 2010). They prevent lipid and other molecule oxidation by quickly attaching a hydrogen atom to radicals. Phenolic substances gain resonance properties due to their double bonds in the benzene ring. When they encounter ROS, they donate their electrons to stabilize the radical. However, since they have a circular structure (benzene) and have double bonds in this structure, they stabilize themselves by circulating their only remaining electrons in the benzene ring. Phenolics have been blamed in part for the negative correlation between fruit and vegetable consumption and oxidative stress-related illnesses including cardiovascular disease, cancer, or osteoporosis (Dai and Mumper, 2010).

3. PLANT TISSUE CULTURES

The increasing world population has led people to seek answers to the question of how they can use the living things around them more efficiently. Until decades ago, agricultural yield could be obtained as a result of using modern breeding methods with appropriate breeding techniques. However, the increase in yield was insufficient in the face of the rapid increase in the world population. It has been revealed that studies to improve the genetic codes of plants with classical plant breeding methods are not sufficient to collect all desired characteristics in a single genotype. While efforts to increase product quality and quantity are the basis of classical plant breeding studies, gaining resistance against diseases and pests,

which are among the most important causes of agricultural product loss, has always been left in the background. High priced plant protection chemical residues represent a major risk to the health of people, animals, and the environment since they persist in products, soil, and water for a very long period of time without decomposing. The use of chemicals also brings high costs. Classical plant breeding studies that benefit from genetic diversity in nature cover a very long time period. For this reason, studies on plant tissue cultures and plant genes in improving the agricultural characteristics of plants will eliminate the difficulties of plant breeding (Mansuroğlu and Gürel, 2002). Plant tissue cultures are cultures obtained by using an intact plant or a part of the plant (explant) in sterile conditions, using artificial nutrient media. The ability of plant cells to alter their metabolism, growth, and development is equally significant and essential for the regeneration of the entire plant, in addition to the pluripotent potential of the cell. In addition to the plant cell's totipotency, the ability of the cells to change their growth, metabolism, and development is equally important and necessary for the regeneration of the entire plant. The plant tissue culture media has every nutrient required for plants to grow and develop normally. Macronutrients, micronutrients, vitamins, other organic ingredients, plant growth regulators, carbon sources, and gelling agents are the key components of solid media. The nitrogen source and plant hormones in particular, as well as the nature of the medium, have a significant impact on how the initial explant reacts. Plant growth regulators (BBD) are key players in influencing how plant cells and tissues develop in the culture medium. The three plant growth regulators that are most frequently utilized are auxins, cytokinins, and gibberellins. The plant species, tissue, or organ, as well as the goal of the experiment, are the key determinants of the type and concentration of hormones utilized. The basic system used in plant tissue cultures is plant regeneration. Plant regeneration is generally studied under three subheadings:

1. Regeneration from somatic tissues composed of meristematic cells; In this system, because the plant is propagated from the end and side meristems, it is called clonal propagation by meristem culture. The resulting cells are completely similar to the donor plant.
2. Regeneration from non-meristematic somatic cells: Under the control of plant growth regulators, a portion of somatic cells on the cut surface of a plant explant proliferate and organize to create the plant. If the dividing

and organized somatic cells first form organs and then the plant, it is called direct organogenesis, and if it continuously divides to form an embryo and then a whole plant, it is called direct somatic embryogenesis. If both conditions occur after a certain state of callus, proto-callus or cell suspension, it is called indirect regeneration.

3. Regeneration from gametic cells that have undergone meiosis. In this case, steril haploid plants with half the chromosome number of the donor plant are obtained (Mansuroğlu and Gürel, 2002).

Micropropagation can be defined as the obtaining of new plants from plant parts (embryo, seed, stem, shoot, root, callus, single cell or pollen grain, etc.) taken from a plant that have the potential to form a complete plant, in artificial nutrient media and under aseptic conditions (Mansuroğlu and Gürel, 2002). The process of micropropagation starts with the choice of healthy plant tissue (explant). Explants are any healthy parent plant component, including the leaves, apical meristems, buds, and roots. Since many secondary plant metabolites cannot be chemically manufactured and can only be derived from plants, micropropagation is a crucial method for the synthesis of these secondary metabolites. Advances in plant tissue culture will guarantee the quick reproduction and long-term viability of therapeutic plants. To minimize the contamination of the main plant in *in vitro* culture, *in vitro* growing the plant from seed under optimal conditions increases the probability of success. An explant's surface is sterilized and moved to nutritive media at this point. For sterilization, it is typically advised to apply fungicide and bacteriacide chemicals together. The choice of product depends on the kind of application being made. It is crucial to the surface of the explant in chemicals to prevent contamination from even slightly harming plant cells. The most often used disinfectants include ethyl alcohol, sodium hypochlorite, mercury chloride, and calcium hypochlorite. Depending on the propagation strategy, cultures are either incubated in the climate room under light or dark circumstances (Husain and Anis, 2009). Subcultures are repeated until the required (or intended) amount of plants is obtained. The process of rooting can take place concurrently in the same culture media that is employed to propagate explants. To encourage the formation of roo-ting and robust root growth, it is occasionally essential to alter the media, including nutrient alteration and plant growth regulators. Acclimatization is a transitional stage between in vitro and ex vitro conditions, and abnormalities in in vitro conditions must be

corrected during the acclimation stage to ensure normal plant growth. At this point, *in vitro* plants are carefully taken out of their lab surroundings. The acclimatization is done gradually from high to low moisture and from low light density to a high one. In time, the plants are slowly acclimatized in the greenhouse by transferring them to a suitable substrate (sand, peat, compost, etc.). An increase in plant cell number and cell volume indicates growth in plant cells. The growth-time graph in plant cell cultures is a sigmoidal curve, as in microorganisms. Cell development in plant tissue cultures exhibits a sigmoidal behavior, consisting of five growth phases. Lag Phase: The stage in which cells prepare to divide. Log or exponential Phase: Rapidly dividing cells cause exponential increase. Linear Phase: The phase in which the fresh and dry weights of the culture increase with the linear increase in the number of cells. Deceleration Phase: Gradual reduction of cell division in plant tissue culture due to decreased nutrient content and accumulation of cell wastes in the medium (Güven and Gürsul, 2014).

4. SECONDARY METABOLITE PRODUCTION BY TISSUE CULTURES

Increasing environmental pollution with modern urbanization has led to the restriction of the habitats of plants, the increasing market need to become unmet and the danger of extinction. Medicinal plants carry more and more herbicides, insecticides and heavy metal contamination to humans and animals as side effects. For the growth of the pharmaceutical business globally, the study of secondary metabolite synthesis from medicinal plants using tissue cultures has become more and more crucial (Tiwari, 2015). Four times as many chemicals, including medications and pigments, are generated by plants than by microbes. Plant cell culture is not constrained by climatic factors, ecological, or environmental therefore cells can multiply more quickly than in cultured plants (Zhon, 2001). Attempting to obtain secondary metabolites directly from plants brings with it a series of problems. Particularly, it is costly and difficult to collect plants from their natural environments, their descendants gradually decrease, the quality and amount of secondary metabolites change according to the season, the production of phytochemicals very little in certain developmental stages, the difficulties of cultivating the target plant, the need for quite large arable land for the production of the desired secondary metabolite, are some of them. Limited production due to such difficulties cannot meet consumer demands arising from the interest in secondary metabolites. While

efforts to increase product quality and quantity are the basis of classical plant breeding studies, gaining resistance against diseases and pests, which are among the most important causes of agricultural product loss, has always been left in the background. In addition to their high costs, plant preservatives significantly threaten human and environmental health because they maintain their toxic effects in plant soil and water for a long time. On the other hand, classical plant breeding studies, have been undesirable despite benefiting from genetic diversity since they cover a very long period of time. For this reason, studies on plant tissue cultures and plant genes in improving the agricultural characteristics of plants will eliminate the difficulties of plant breeding (Mansuroğlu and Gürel, 2002). The inadequacy of classical agricultural methods in order for plant active substances to meet the demands in food, chemistry, cosmetics, paint, pharmacy, has also opened the door to studies on secondary metabolite production and increase through tissue cultures (Erkoyuncu and Yorgancılar, 2015). As an alternative option for producing active secondary metabolites, cell and tissue culture of medicinal plants has distinct advantages; The culture system does not need a lot of space that can be used to grow crops; The process is not restricted with season. Regardless of weather fluctuations or soil conditions, useful chemicals can be synthesised under regulated settings. It is possible to control secondary metabolism to increase the production of desired chemicals. Since no pesticides or herbicides are utilised during system upgrades, human health won't be negatively impacted. As a result, tissue culture might be characterised as environmentally beneficial. Once the system is in place, the amount of advantageous compounds in plants collected from various locations would be less unstable, making it easier to ensure product quality (Tiwari, 2015). One of the factors affecting secondary metabolite biosynthesis is environmental stress. However, since the target secondary metabolite is in the cell, it is very difficult to obtain. Secondary metabolite production in plant tissue cultures cannot be sustained simply by inducing secondary metabolite activity. Secondary metabolites must be removed concurrently from cells. Therefore, in actuality, stress factors that stimulate the creation of secondary metabolites should ideally also enhance product improvement (Güven and Knorr, 2011). Plants taken into tissue culture can produce chemicals that they do not produce under normal conditions. As one of the reasons for this, Plant cells contain much more than the amount of DNA necessary for their normal functions, and that this excess DNA can only carry genes and gene groups that function "structural" and encode enzymes

that are not normally found in the mother plant (Fowler, 1982). The biosynthetic pathways catalyzed by these enzymes, which can be produced in plants taken into tissue culture, may also lead to the synthesis of new metabolites. On the other hand, some undifferentiated and unorganized cells in the tissue culture medium may have a different phenotype from the mother plant although they are of the same genotype as the parent cell (Sökmen and Gürel, 2002). It states that any one or more of the components of the culture medium will suppress the biosynthesis pathway of any secondary metabolite, causing the precursor to shift to another pathway and produce new biosynthetic products.

9.CONCLUSION

Herbal materials represent an important part of the global pharmaceutical market, used as over the counter medicinal goods and immature substances for the pharmacy in developed and developing countries. The therapeutic activity of plants, which usually do not have serious side effects, is associated with biologically active organic compounds such as oils, proteins, secondary metabolites, minerals and vitamins. Plant production by agricultural methods can limit the secondary metabolite production because it depends on the geographical location, climate and growing conditions for many plants. Since plant tissue cultures develop independently of environmental factors, production conditions can be controlled. Ensuring optimum growth conditions with supervision accelerates cell division. Morphological diversity in the tissue culture medium can be discerned by visual selection. In addition, some plant enzymes can be secreted effectively in the culture medium. Biotechnological researches have accelerated the use of *in vitro* cell cultures in the medicine, cosmetics, paint, chemistry and food industries as well as providing secondary product augmentation. It is possible to accomplish yields based on demand-supply equilibrium and irrespective of environmental impacts by manufacturing secondary goods in a tissue culture environment. When the secondary metabolite production is carried out with cell cultures, various interventions can be made to the cultures in order to provide as much or more production as in the plant. Addition of precursors of these substances to the culture medium, elicitation, selection of high productive strains from culture and metabolic engineering studies are some of these interventions. The desired amount of production can be made with constant efficiency and stabilityIt is possible to reduce land use and the degradation of the environment. It might be possible to acquire fresh secondary

goods. Secondary products obtained in this way are not contaminated with other compounds as in the plant and the amount of purity may increase. Endangered species can be protected. Metabolic pathways can be illuminated and thus the necessary information is obtained for the transition to mass production. In today's modern medicine applications, where secondary metabolites of medicinal plants gain more importance, plant tissue cultures play a very important role in order to obtain the desired amount of product without the limitation of time and space.

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CHAPTER II

SYNTHESIS AND THEORETICAL STUDIES OF QUINOLINE-BASED TRIAZOLE COMPOUND

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INTRODUCTION

Heterocyclic compounds are fundamental scaffolds for organic synthesis of biologically active natural compounds and advanced materials (Welch et. al. 2010.; Fryatt et. al. 2004; Michael, 2008). Among the heterocycles, quinoline and its derivatives have always attracted the researcher's attention with medicinal benefits in drug chemistry, especially antitubercular and anticancer activities (Matada et. al. 2021). In recent studies, quinoline-based compounds are usually employed as fluorescence sensors due to their significant spectroscopic properties, biocompatibility, and coordination properties toward central metals (Gao et. al. 2013; Weng et. al. 2009; Meng et. al. 2012).

Fluorescent metal sensors have broad application area both in environmental monitoring and biological researches since fluorescence has important benefits such as generally non-destructive character, high efficiency, high sensitivity, and real time monitoring capability (Xu et. al. 2010; Carter et. al. 2014; Cheng et. al. 2017). Fluorescent probes designed for sensing are composed of two parts ionophore and fluorophore. The latter fluorophore unit converts the occurrence of diagnosis received from ionophore part to analytical signals while the former unit chelates with metal ions. Anthracene is one of the most useful skeleton for molecular sensor due to its rigid characteristic and sensitive emissions from both the monomer and the excimer emission. Receptors based on anthracene derivatives for anion and cation recognition have been widely investigated (Chang et. al. 2007; Zu et. al. 2007; Kim et. al. 2003). Lee et al. (2014) published a novel receptor with anthracene unit **1**, which shows highly sensitive and selective fluorescence "off–on" sensation to Zn^{2+}, and the resulting ligand-Zn^{2+} complex displays recognition to Cu^{2+} with very high selectivity through "on-off" fluorescence (Figure 1). In other study, Anthracene moiety with 2-hydroxy-1-benzaldehyde unit **2** was reported as selectively detecting Hg^{2+} via absorption and Al^{3+} ions via fluorescence emission spectroscopy in methanol (Figure 1) (Kaur, 2017). A highly selective, cost-effective and simple, anthracene-based chemical sensor **3** displying an Hg^{2+}-selective "on–off" fluorescence quenching behavior has been developed (Figure 1) (Kaur et. al. 2015).

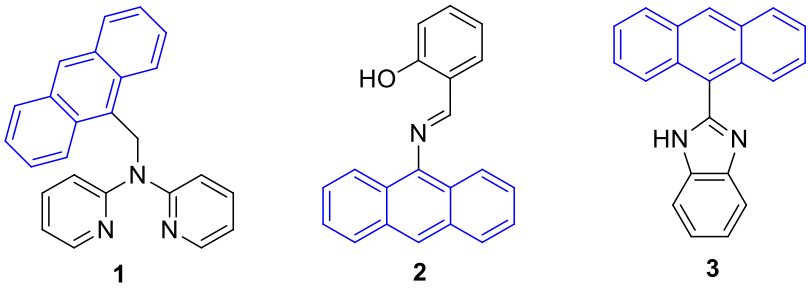


Figure 1. Anthracene-based chemosensors

Compounds bearing 8-Hydroxyquinoline (8-HQ) unit is ubiquitous in various fields ranging from medicinal chemistry (as antimicrobial, anticancer and antiviral drugs) to supramolecular chemistry. They have found many application areas in chemistry such as strong metal complexation (with many transition metals), fluorescence markers, dye-sensitized solar cells (DSSC), organic light emitting diodes (OLED), and various other applications (Rohini, 2020). A selective fluorescent sensor based on 8-hydroxyquinoline **4** was reported to determine Fe^{3+} ions selectively (Figure 2) (Hu et. al. 2013).

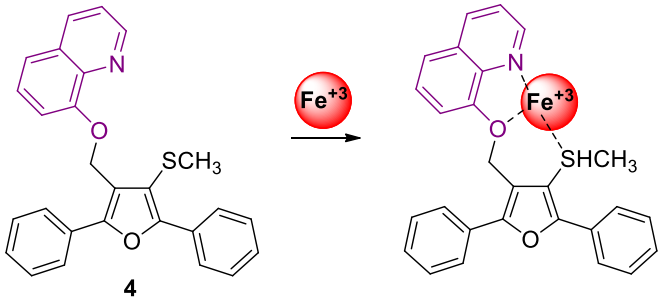


Figure 2. Anthracene-based chemosensor

Triazole, an important building block is five-membered heterocyclic system containing three nitrogen atoms and exists in two isomeric forms known as 1,2,3-triazole and 1,2,4-triazole. The synthesis of 1,2,3-triazole derivatives has attracted attention in the last few years due to its wide application in chemical and bioactive materials science. The Huisgen 1,3-dipolar cycloaddition of organic azides to alkynes giving a mixture of regioisomers 1,4- and 1,5-disubstituted 1,2,3-triazole, is one of the most important

transformations in organic chemistry, as evidence a wide variety of triazoles with structurally diverse and functionalized groups (Huisgen, 1963). This reaction suffered from disadvantages such as heat requirement and long reaction time for complex formations, lack of selectivity in products, and difficulty in separation of the two regioisomers using classical chromatographic techniques. Despite the high versatility, for more than 40 years, Fortunately, representing a milestone in this field, Meldal and Sharpless independently reported the application of Cu(I) salt as the catalyst (Meldal et. al. 2002 and Kolb et. al. 2001). In this method, the Huisgen reaction worked well under mild conditions furnishing exclusively the 1,4-regioisomer with minimal work-up and purification. Since then, the "click chemistry" has been extensively researched and recognized as an epoch-making progress for the synthesis of 1,2,3-triazole derivatives as synthetic intermediates for bioactive compounds, chemotherapeutic agents (Huisgen 1984 and Agalave et. al. 2011), agrochemicals, photostabilizers, optical brighteners, anticorrosive agents, and metal chelators (Krivopalov et. al. 2005 and Yet, 2004).

Triazole skeleton is an important binding unit because of their great stability against metabolic transformations, aromatic character, high dipole moment and H-bonding abilities (Seo et. al. 2003 and Hota et. al. 2006). Poonam et al. (2020) reported the synthesis of 1,2,3-triazole derivative **5** exhibiting high selectivity and sensitivity Hg^{2+} ions.

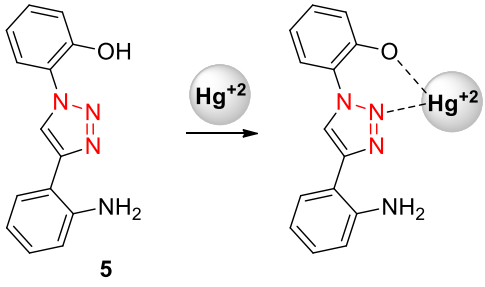


Figure 3. 1,2,3-Triazole-based Hg^{2+} sensor

Molecular conjugation consists of many processes applied in pharmachology, advanced materials and nanotechnology to collaborate two partners (Truong et. al. 2015). Over the past two decades, the click chemistry

has emerged to provide us new and powerful methods for molecular identification. Herein, we aimed to synthesize quinoline-anthracene conjugates connected by a triazole bridge and compute three-dimensional geometries and get some data on electronic properties (Figure 3).

1. RESULTS AND DISCUSSION

The 2-amino 8-hydroxyquinoline group, which acts as a receptor in molecules, was bind to anthracene, a highly fluorescent and stable fluorophore, by 'click' reaction, forming a triazole bridge. Meanwhile, the 1,2,3-triazole linker with H-bond acceptor part could be operated for the binding of cations that might be practical in the sensing of metal ions. Based on this description, fluorescence sensor candidate **8** was designed (Figure 4).

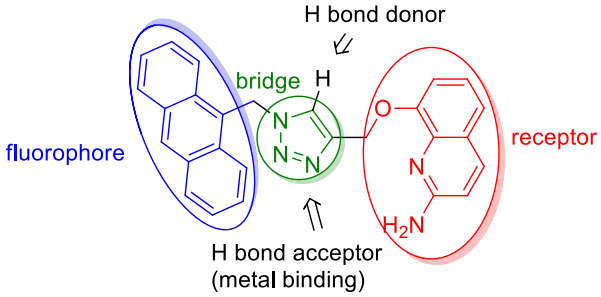
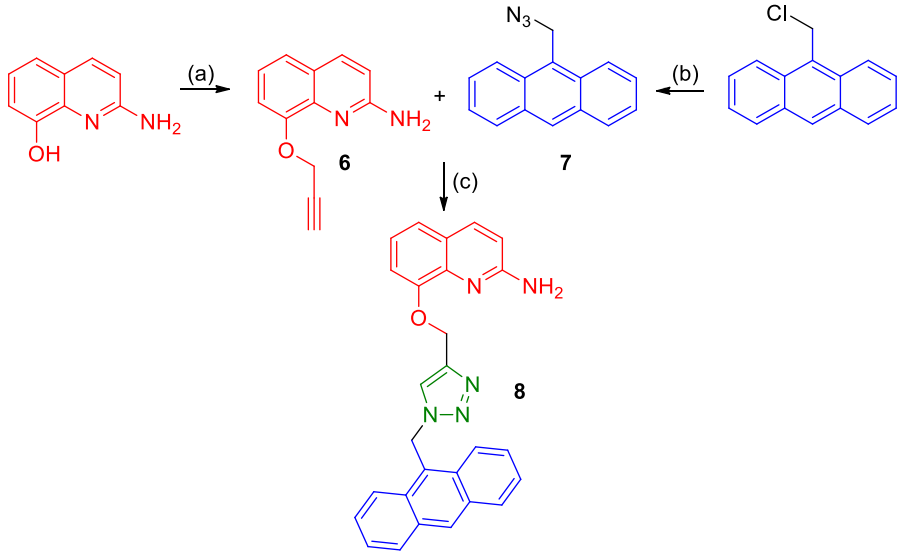


Figure 4. Quinoline-triazole-anthracene system

The (prop-2-ynyloxy)quinoline moiety **6** was used as key compound for the construction of 1,4-disubstituted 1,2,3-triazole derivative via Huisgen dipolar cycloaddition method using click chemistry. 2-Aminoquinolin-8-ol was subjected to O-propargylation reaction by the addition of propargyl bromide in the presence of K_2CO_3 and alkyne-substituted quinoline 6 was obtained (Scheme 1).



Scheme 1. Synthesis of target compound; (a)Propargyl bromide, K2CO3, THF; (b) NaN3, THF; (c) CuSO4, sodium ascorbate.

Chloromethyl anthracene was sbjected to the reaction by NaN_3 and transformed to azidomethyl anthracene **7** needed for Click reaction (Scheme 1).

The most useful method for the formation of triazole is to form Cu(I) in situ by the addition of $CuSO_4$ and a reducing agent like sodium ascorbate in an aqueous solution. Alkyne-substituted quinoline **6** and azidomethyl anthracene **7** units were reacted in this solution and desired hybrid molecule **8** was obtained in good yield (Scheme 1).

Together with the experimental synthesis of the target compound, we have also performed some theoretical calculations on compound **8**. Some structural and electronic properties of the compound has been computed by the use of Density Functional Theory at B3LYP/6-31G(d,p) level of theory. The optimized three-dimensional geometry of the compound has been found to locate triazlo unit directing out of the central cavity where complexation with metal cations can take place.

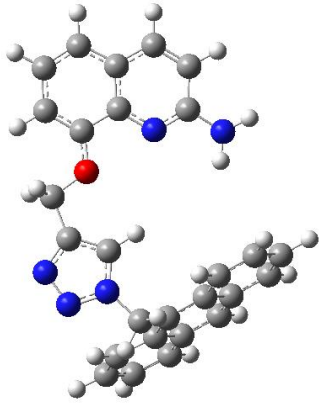
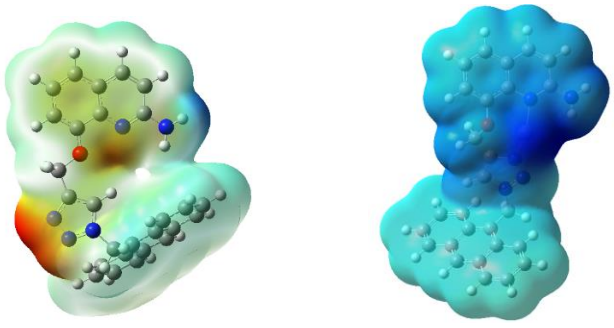


Figure 5. Geometry optimized structure of target compound **8**.

Thereafter we have performed a scan coordinate computation to be sure about the stability of the compound as if it is representing a global minimum or just a local minima on the potential energy surface. The output of the scan process resulted in triazole unit directing outwards is more favorable than directing opposite inside the cavity. Actually, it is not only steric effects but also some π-π or π -lone pair electrons' interactions via anthracene moiety and nitrogen of amine group may be effective.

Molecular electrostatic potential map is a nice tool to indicate the positions where electron locatization is more or less in a complex system. The electronegative atoms or strongly electron withdrawing or donating groups are effective on the electron distribution throughout the structure. It is useful to guess the points in the structure for nucleophilic attact or electrophilic interactions. Electron rich sides are suitable for cation chelation as in our case.

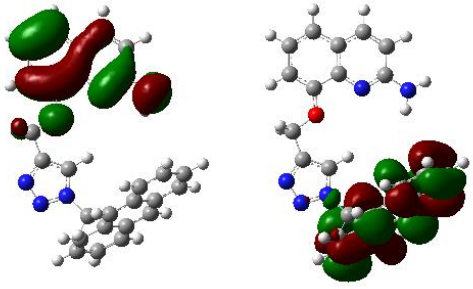


8 **8_Zn**

Figure 6. Molecular electrostatic potential maps of **8** and **8_Zn**

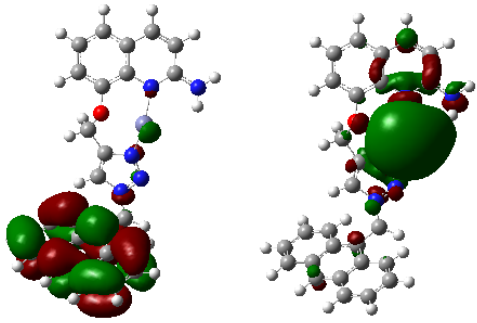
3D-electrostatic potential maps of **8** and **8_Zn** are given in Figure 6. They clearly show that electron distribution of the parent compound has been altered completely upon chelation with Zn^{2+}. The electron deficiency on the cation has been compensated through electron donation from the nitrogen lone pairs of triazole and quinoline units. Thus, a more uniform electron distribuion has been obtained after metal cation interaction. Moreover, it was not only electron distribution that effected after complexation but also there happened very striking structural changes. The triazole unit turned inside the complexation cavity to join chelation.

Another important variable effecting the structures structural and electronic properties is their HOMO and LUMO orbitals. HOMO and LUMO are located on quinoline and anthracene parts of the parent molecule, respectively, whereas HOMO is located on anthracene and LUMO is mostly formed on the metal which is expected since LUMO represents the electron deficient sites in a structure (Figure 7). The energy difference between HOMO and LUMO is also an important variable to indicate whether the compound is insulator, conductor or semiconductor. Our parent structure can be considered as an insulator or at most a semi conductor, while the complex has shown conductor property with an only 0.71 eV HOMO-LUMO energy gap (ΔE).



-5.30 eV -2.02 eV

8

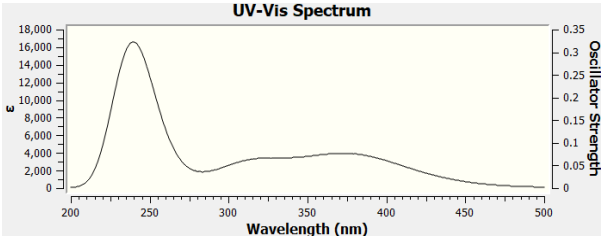


-9.82 eV -9.11 eV

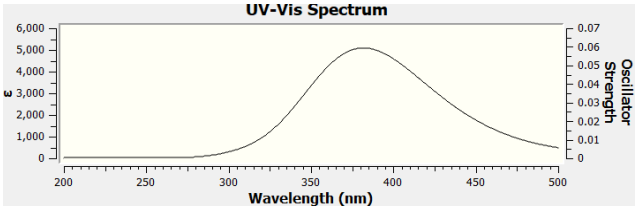
8_Zn

Figure 7. HOMO and LUMO orbital schemes of **8** and **8_Zn.**

As a result of metal coordination, the electronic properties of the structure change enormously. One way of observing this change and proving the coordination is to calculate the absorption spectra by applying the Time-Dependent Density Functional Theory (TDDFT-Time Dependent Density Functional Theory). TDDFT application was performed with B3LYP/6-311G(d,p) calculation method. 20 excitation levels were taken into account to obtain UV-VIS spectra. The absorption spectrum of the **8** structure has one sharp band at 230 nm (Figure 8). In addition, two weak bands were calculated at 320 nm and 370 nm. When the structure **8** is coordinated with Zn^{2+}, a very broad band replace the two broad bands in the absorption spectrum of the molecule. Moreover, the sharpest band has disappeared. In addition, a red shift is observed in the bands. The redshift in the pass bands may be due to the decrease in the HOMO-LUMO energy gap due to the conductivity of the metal to the structure.



8



8_Zn

Figure 8. UV-VIS spectra for **8** and **8_Zn.**

2. EXPERIMENTAL

2.1. Synthesis of 8-(prop-2-yn-1-yloxy)quinolin-2-amine, 6.

2-aminoquinolin-8-ol was reacted with propargyl bromide in the presence of K_2CO_3 according to the protocol we published in our previous study (Gümüş et al. 2018).

2.2. Synthesis of 9-(azidomethyl)anthracene, 7.

9-(Chloromethyl)anthracene (2.27 g, 10 mmol) were dissolved in 50 mL CH_3CN. Then NaN_3 (1.30 g, 20 mmol) was added and refluxed overnight at 85 °C. Reaction was followed by TLC and terminated accordingly. Reaction mixture was filtered and solvent was evaporated under vacuum. Flash column chromatography by EtOAc:Hexane mixture (1:15) was applied to purify the crude product.

Yellow solid. (2.28 g, 98% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.51 (s, 1H), 8.32-8.28 (m, 2H), 8.07-8.06 (m, 1H), 8.05-8.04 (m, 1H), 7.62-7.58 (m, 2H), 7.54-7.50 (m, 2H), 5.33 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 131.4, 130.7, 129.3, 129.0, 126.8, 125.8, 125.2, 123.5, 46.3.

2.3. Synthesis of quinoline-triazole-anthracene Derivative, 8.

8-(prop-2-yn-1-yloxy)quinolin-2-amine, **6** (198 mg, 1 mmol) and 9-(azidomethyl)anthracene (233 mg, 1 mmol) were dissolved in 5 mL THF:H_2O (4:1). $CuSO_4.5H_2O$ (25 mg, 0.1 mmol) and sodium ascorbate (40 mg, 0.2 mmol) were added to form Cu (I) catalyst in reaction medium. The reactions were monitored by TLC and stopped after 24 h with the addition of water (5 mL). The reaction mixture was extracted with EtOAc. The combined organic phase

was dried over $MgSO_4$ and evaporated in vacuo. The crude product was purified by flash column chromatography using ethyl acetate/hexane as the eluent.

Pale yellow solid. (310 mg, 72% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.55 (s, 1H, Ar-H), 8.29-8.26 (m, 2H, Ar-H), 8.06-8.03 (m, 2H, Ar-H), 7.76 (d, $^3J_{orto}$=8.8 Hz, 1H, AB system, Ar-H), 7.56-7.47 (m, 4H, Ar-H), 7.37 (s, 1H, Ar-H), 7.16 (dd, $^3J_{orto}$=7.6 Hz and $^4J_{meta}$=1.7 Hz, 1H, Ar-H), 7.11-7.04 (m, 2H, Ar-H), 6.63 (d, $^3J_{orto}$=8.8 Hz, 1H, AB system, Ar-H), 6.51 (s, 2H, CH_2N), 5.29 (s, 2H, CH_2O), 4.99 (bs, 2H, NH_2) (Figure 9). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.4, 151.8, 144.4, 139.0, 138.0, 131.4, 130.8, 129.8, 129.4, 127.6, 125.3, 124.4, 123.7, 123.0, 122.9, 122.2, 120.4, 112.0, 111.5, 63.2, 46.4 (Figure 10). LC-MS/MS. Anal. Calcd. for $C_{27}H_{21}N_5O$ $[M+H]^+$: *m/z* 432,18189. Found: *m/z* 432,18082.

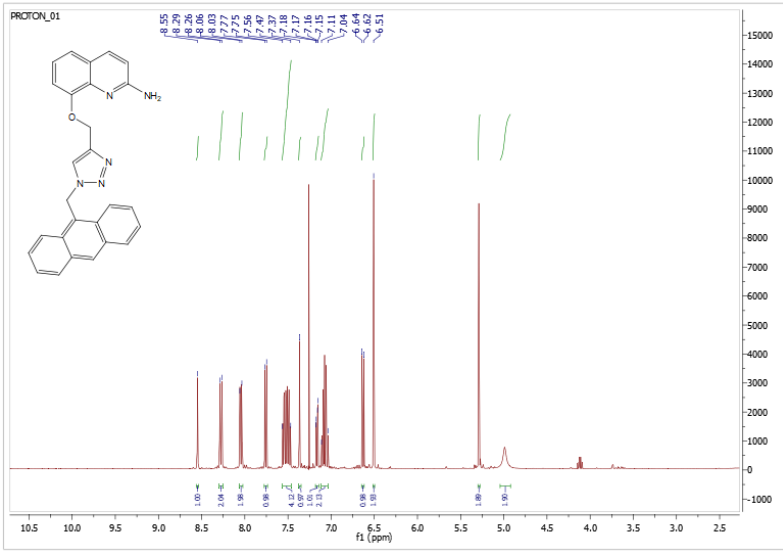


Figure 9. ^{1}H NMR spectrum of compound **8**.

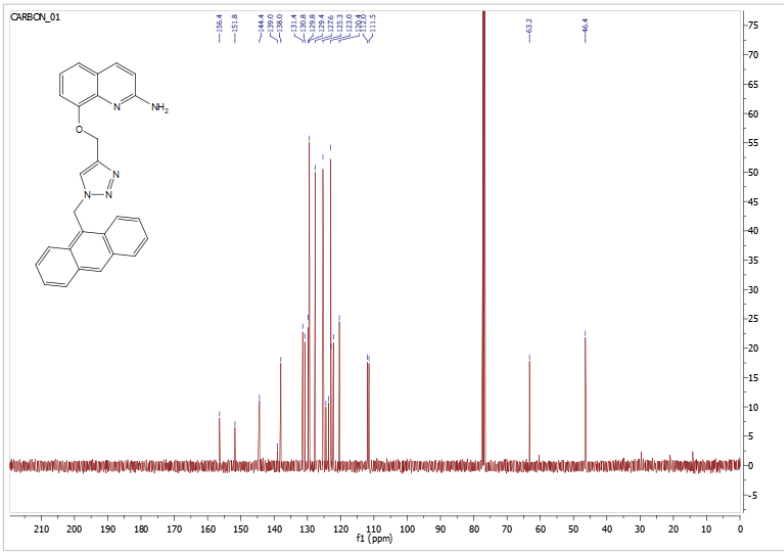


Figure 10. ^{13}C NMR spectrum of compound **8**.

3. CONCLUSION

In conclusion, quinoline and anthracene rings were conjugated by alkyne-azide cycloaddition named as 'click chemistry'. Amino-substituted 8-hydroxyquinoline was subjected to O-propargylation reaction to bind alkyne moiety. Azide part of te cycloaddition was obtained from the reaction of chloromethyl anthracene with sodium azide. In the last step, alkyne-substituted quinoline and anthracene-azide were coupled in the presence of Cu(I) catalyst by forming triazole bridge and a novel fluorescent sensor was isolated in good yield.

Theoretical calculations with B3LYP/6-31G(d,p) level of theory were applied to gather structural and electronic data about the target compound and its complex with Zn^{2+}. While in the initial geometry triazole was looking out of the central cavity, it turned towards the complexation site and interact with the cation to form a chelate. The molecular electrostatic potential maps revealed well complexation, since the charge distribution of the molecule has been altered entirely upon interaction with the metal cation. Negative charge development on some

electronegative atoms was pushed towards the cation to get a more uniform charge distribution. The contribution of the atoms and groups to frontier molecular orbitals has also changed via complex formation. The final complex structure's LUMO is mostly formed on Zn atom. And finally, absorption spectra for for **8** and **8_Zn** were computed with the same method. Some absorption bands of the target structure has disappeared and new bands are formed after complexation.

ACKNOWLEDGEMENT

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CHAPTER III

TROPONE-CARBAZOLE HYBRID STRUCTURES FOR POTENTIAL OLED AND TADF SYSTEMS

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INTRODUCTION

The photovoltaic effect was first discovered by Becquerel in 1839 (Becquerel, 1839). Becquerel discovered the photovoltaic effect by observing the photoelectrochemical process. When a silver bromide or silver chloride-coated platinum electrode was placed in a solution, it produced a photocurrent when it irradiated (Spanggaard and Krebs, 2004). Photoconductivity was reported for the first time in history by Smith in 1873 (Smith, 1873) and Adams in 1876 (Adams 1876) with their work with selenium. Studies in the field of organic luminescent molecules begin in the early 1900s with the discovery of the photoconductive property of solid anthracene. In 1959, Kallman and Pope (Kallman and Pope, 1959) observed the photovoltaic effect by placing anthracene between two electrons and sending light to one side of the electrodes; however, they could not fully explain this phenomenon and suggested that there are different exciton separation mechanisms in the light and dark electrodes (Benanti and Venkataraman, 2006). Then, they observed the photovoltaic effect in the terracene-water system. In this system, they stated that exciton dissociation in the symmetrical device takes place by moving the electron through the water and the vacuum by moving over the organic material. In the mid-1900s, studies on the use of organic materials as photoreceptors began to be focused on.

Compared to devices created with inorganic materials, the most striking advantages of devices created with organic molecules are; They can be coated on plastic substrates, soft and flexible structures can be obtained with the bonds between neighboring organic molecules in interaction thanks to van-der Waals forces, and coating can be made by methods that can be applied using low-cost and low-temperature methods such as melting method, printing technique and solution deposition (Carpick et al. Salehi, 2019; Burke, 2012; Sellner, 2005). Therefore, photoconductivity and related issues have become the focus of attention, from a scientific as well as a commercial point of view. In the early 1960s, it was discovered that many commonly used dyes, such as methylene blue, have semiconductor properties. In the following years, it was revealed that these paints exhibit photovoltaic effect. Although organic semiconductors are interesting for researchers; The first use of organic electronics in the production of organic luminescent molecules, organic field effect transistors, organic light emitting diode and organic solar cell was found in mid-1980s (Gustafsson, 1992; Malenfant, 2002; Forrest, 2004). Despite all these developments, since the efficiency of the devices made using organic materials is incomparably lower than inorganic ones, they could not take their place in the world market

at the desired level in those years. Research in the field of organic luminescent molecules has increased exponentially, especially after 2005. Some of the organic structures used in this area are shown in Figure 1. Small organic molecules are materials used in polymers as well as OGH (Bredas, 2004). These organic structures can be used alone or mixed with fluorine derivatives, which are strong electron withdrawing groups (Benanti and Venkataraman, 2006). The aim of research groups and R&D departments of companies is to produce electricity with high efficiency by designing organic materials with high impact value, stable and can be used for many years. In a study conducted in 2012, the effect of different electron withdrawing groups on the photovoltaic effect was shown in detail and it was found that the efficiency increases exponentially if there is a strong electron withdrawing group in the structure (Chen et al., 2015).

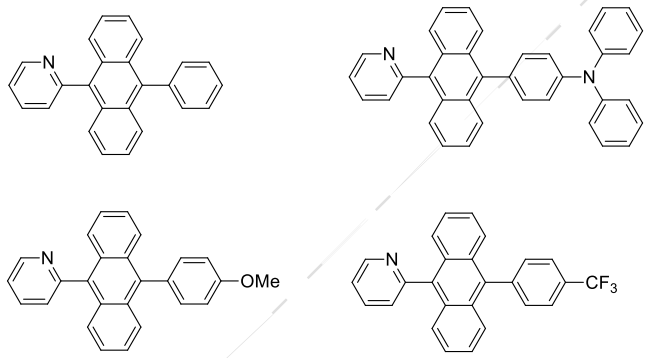

Figure 1. Some synthesized structures from the literature.

Organic electronic materials have many uses. Some of these are electrochromic devices, capacitors, organic solar cells and OLEDs.

Organic electrochromic devices have low energy processing, optical contrast adjustment and wide field of view. They have the potential to be used as smart glasses to control solar radiation in buildings and cars. Molecules with low molecular weight have the ability to give multiple colors. Polymer films are particularly attractive in this regard. They have a long lifespan as they exhibit memory properties.

Capacitors are used to store energy. Energy storage takes place between the electrode and the electrolyte interface. Capacitors are called by different names. Some of them are ultracapacitors, supercapacitors and gold capacitors. Among them, capacitor with double layer is the general name of the basic energy storage unit. Electrochemical capacitors can be divided according to the

electrode material used. They basically fall into three categories: organic-based, ozides of metals, and polymers.

In organic solar cells, energy of light from the sun has been converted to electrical power by using a light-absorbing material. The light-absorbing material absorbs sunlight to form excitons. The excitons formed are distributed on active surfaces that offer and withdraw electrons. Therefore, the electron donating surface and the electron withdrawing surface are important for the device performance of the organic solar cell (Cassida, et al. 1995).

The organic electroluminescence phenomenon was first discovered by Pope using an anthracene crystal. The OLED obtained in the study with the anthracene crystal did not work at very high voltages and did not become commercial. Later, Tang and VanSlyke developed a high-efficiency double-layer OLED. The developed OLED has reached 1% efficiency. Since the discovery of double-layer OLEDs, Tang and VanSlyke have used different properties of cavity injection layer (HIL), cavity conduction layer (HTL), cavity blocking layer (HBL), and electron conduction layer (ETL). As a result of the studies, it has been seen that the electroluminescence efficiency of OLEDs is high in multilayer devices (Figure 2).

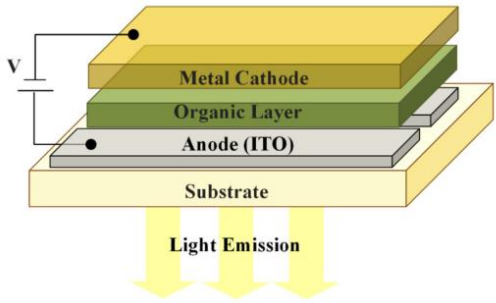

Figure 2. OLED structure.

Organic electroluminescent molecules (OLED) have recently been a common research topic in both science and industry, due to their full color monitor capability, flexibility, and light source applications. Considering that metal-containing compounds, which are widely used in the evaluation of sunlight as an energy source, are toxic and are found in very small amounts on earth, it will be extremely economical to start using organic structures. Organic structures are also preferred due to their price, ease of shaping and production. New OLED design and applications are important in terms of increasing

efficiency and material lifetime. The electronic and structural properties of these pyrido[2,3]quinoline-based potential organic electroluminescent structures will be designed and examined theoretically.

In recent studies, it is planned to produce and apply structures that contain both electron donor and acceptor groups in their structure, and therefore that can realize electronic transitions at the intramolecular level. The HOMO level increases in molecules containing electron donating groups in their structures, and the LUMO energy level decreases in structures containing electron withdrawing groups in their structure. When this situation is evaluated together in the same structure, the difference between HOMO and LUMO energy levels decreases and the design of potential semiconductor materials can be realized.

In addition, during electronic excitation from the ground state to the excited state 75% of the excited electrons to the singlet level in the pass to the triplet energy level and reduce the fluorescence efficiency up to 25%. It is not possible to prevent this situation. However, with the transition between levels (ISC), the idea of returning electrons that have passed to the triplet energy level back to the singlet energy level has emerged. This situation is called inverse transition between levels (RISC). In this way, the recovery of 75% lost is achieved. Another aim of our thesis work is to realize the singlet-triplet energy (ΔE_{ST}) gap low structure design.

In this study, tropone unit is combined with a donor carbazole group to examine theoretically, and the positional effect of electron donor group will be investigated. Since the study will reflect the optoelectronic properties of tropone-carbazole-based structures before synthetic procedures are performed, it will shed light on synthetic organic chemistry studies. B3LYP/6-31G(d,p)) basis set will be applied in electronic property calculations.

Photoluminescence

Scientists has been studying fluorescence and phosphorescence experimetally for the last 15 years. The popularity of photoluminescent compounds comes from their need for low-cost instrumentation with very powerful output of these methods. Photons directly excited by a suitable energy source emit light and the fraction of molecules in number to those who emit after absroption is called the luminescence quantum yield (Demasa and Crosby, 1968).

With the absorption of photons by a molecule, as a result of light absorption, the atom or molecule changes from the ground state to the excited energy state. In this energy level state, it returns to the ground state, which is

the stable state, by transferring the remaining atomic or molecular energy for about 10-9 seconds to the environment without radiation or radiation (with light) (Figure 3).

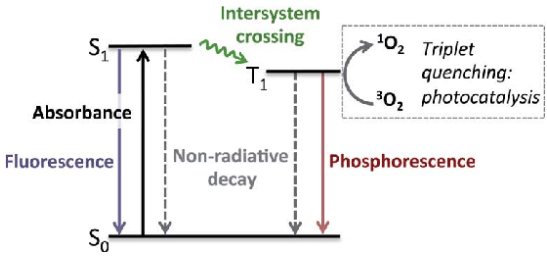

Figure 3. Ground and exited states

The phenomenon of radiating its energy to the environment as a result of excitation by radiation is called photoluminescence. Photoluminescence can take two forms, either fluorescence or phosphorescence, depending on the excited energy level. The diagram of fluorescence or phosphorescence mechanism energy levels was first tried to be interpreted by Alexander Jablonski and began to be defined as the Jablonski energy diagram. Photoluminescence event can be basically studied as fluorescence and phosphorescence event (Çapan, 2008).

Flourescence

Light emission is only possible for singlet excitons using fluorescence emitters, but phosphorescent materials can be created using singlet and triplet excitons via inter-system transition (ISC) (Baldo et al., 1998; Ha et al., 2022).

An organic molecule at the ground level is in the S_0 state, known as the ground electronic state. After excitation, one electron in a high energy orbital and another electron in a low energy orbital have opposite spins. These electrons in the excited singlet state are called "paired". Fluorescence is the glow emitted by a light-excited aromatic molecule as it transforms from the excited singlet state to the ground singlet state. Electrons in the excited singlet state become fundamental singlet and opposite spins do not change direction, whereas spin direction change is required for the triplet state. The recombined electron-hole pairs are called excitons. Spin statistics show that only 25% of excitons can be produced in the singlet state and the remaining excitons will be in the triplet state (Pope et al., 1963). Emission of light energy during decay from the singlet level to the ground level is called fluorescence and is usually very fast. On the

other hand, direct degradation of excitons of the triplet level to the lowest level called phosphorescence is usually slow and only occurs at lower temperatures, so it is considered a forbidden process (Baldo et al., 1998; Uoyama et al., 2012; Egidi et al., 2018). This means that conventional fluorescent OLEDs can have a maximum internal quantum efficiency of 25% (Dias et al., 2013; Esme Baş, 2021) (Figure 4).

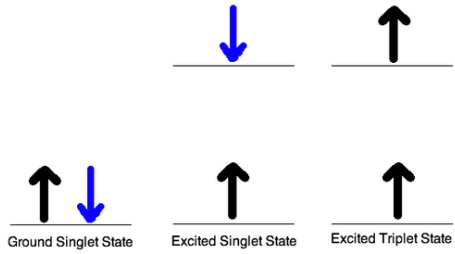

Figure 4. Ground, singlet and triplet state electronic configuration

Phosphorescence

According to the Pauli Exclusion Principle, it is forbidden for two electrons to have a spin orientation in the same direction. However, the electrons in the triplet state are not "paired", in which case the spins are in the same direction and the radiation emitted is called phosphorescence (Figure 5).

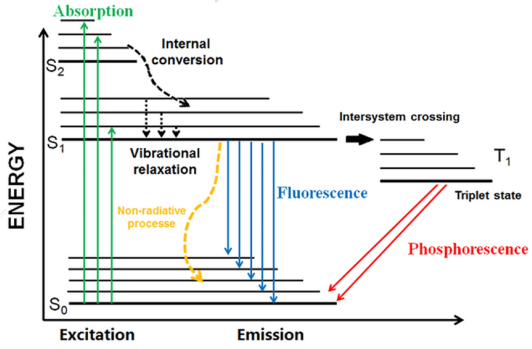

Figure 5. Jablonski diagram

Molecules, which are generally in solid phase, transfer some of their energy to the environment as heat or vibration as a result of excitation, and in this way they return to the S_1 energy level. This process is called internal conversion and takes place in 10-12 seconds. Molecules that pass from the S_1 level to the T_1 level can have the property of emitting light. This process is called a crossover (Çapan, 2008).

Traditional OLED structures have commercial limitations. Because singlet excitations are reported to produce 1:4 spin statistics due to weak emissions and triplet excitations (Jankus et al., 2013). It has been explained that the use of TADF-featured materials in the emission layer of OLEDs enables the conversion of triplet excitons into singlet excitons with the help of low singlet-triplet energy difference, thus increasing the efficiency. As a result, it has been reported that 100% efficiency can be obtained in OLED devices with the use of TADF molecules. Molecular design strategies are important for an effective TADF structure. The small singlet-triplet spacing is required for intramolecular charge transfer (ICT) to occur. For this reason, they emphasized the importance of correctly understanding the relationship between structure and photochemical properties (Dos Santos et al., 2016).

In a published article, the photophysical properties of a series of emitters and the molecular structure was investigated, with theoretical calculations, how a strategy should be followed to design a suitable molecule for use as a semiconductor (Shizu et al., 2015). In the aforementioned study, the structures of molecules with TADF properties were compared with structures with weak TADF properties. The dihedral angle between neighboring electron donor (D) and electron withdrawing (A) units and the energy difference (ΔE_{ST}) relationship between singlet energy level (S_1) and triplet energy level (T_1) were studied over an index. After that scientist tried to find new ways to gather back the lost efficiency due to loss through intersystem crossing. Thermally activated delayed fluorescence compounds have recently been the focus of attention, as they effectively recycle triplet excitons into singlet excitons. Using conventional organic molecules increases the electroluminescence (EL) efficiency of OLEDs. They stated that toxicity is reduced by the lack of heavy metals in phosphorescent emitters and that high quantum efficiencies can be obtained with TADF light emitters, therefore they are considered as highly innovative designs. The orbitals that make up the HOMO and LUMO are sufficiently far apart within the molecule, resulting in a small ΔEST. They reported that this is possible with steric hindrance (preventing rotation around a single bond), which causes a large dihedral angle between intramolecular groups (Shizu et al., 2015).

Designing TADF emitters is generally done by applying planar donor and acceptor groups together. In this way, bending between the donor and acceptor groups is provided and a more rigid structure is obtained. This increases efficiency. (Wang et al., 2017; Özek, 2019).

The creation of organic light emitting diodes is by hybrid use of two types of units: a) donors (D) and b) acceptors (A). Organic molecules with simultaneous Donor-Acceptor units can have important optical and photophysical properties. Intramolecular charge transfer occurs to the LUMO of the acceptor from the donor's excited state. During the design of TADF compounds it is very importnt to achieve as small energy gap as possible between singlet and triplet energies (ΔE_{ST}). In a study on benzophenone-based butterfly type molecules, computational applications were used and electronic properties of new compounds were investigated theoretically. According to the results of the study, it has been shown that the investigated compounds can be potential candidates for OLEDs or organic solar cell applications (Gümüş and Gümüş, 2017).

In this study, derivatives using phenanthroline as acceptor were examined. The π bridge is provided with benzene, thiophene and furan. Benzene, thiophene, furan, anthracene, pyrene and triphenylamine are the most common in the literature.

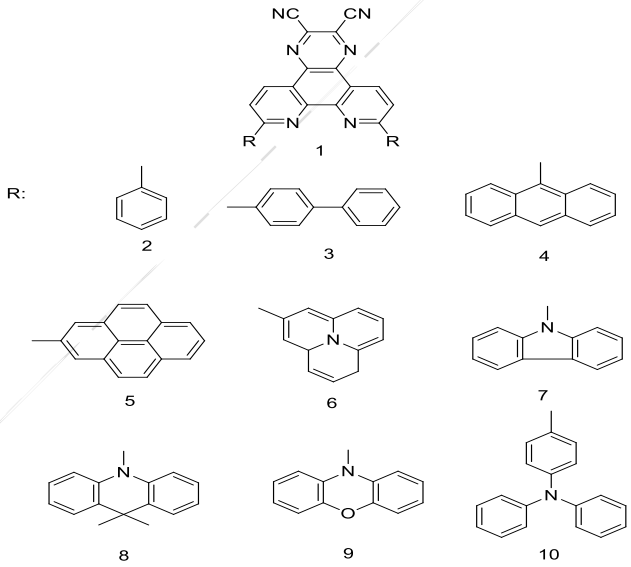

Figure 6. TADF structures

The combination of the parent structure, which contains a strong acceptor unit in its structure, with the donors enables potential TADF compounds (Figure 6). Moreover, distribution of HOMO and LUMO orbitals on different sites can be achieved within the molecule by design. This causes the singlet and triplet

energy gap ΔE_{ST} to decrease. The structural and electronic properties of the designed compounds were calculated theoretically. As a result of the calculations, it has been reported that they have the potential to be used as TADF, since the singlet and triplet energy gaps for new structures are determined to be quite small. As a result, it has been stated that some pyrazine derivatives are the most suitable candidates for the purpose. Calculated ΔE values for all compounds are below 4 eV. Thus all compounds have semiconductor potential. In fact, compound 6 has a significant OLED material potential, with a band gap of 0.90 eV HOMO-LUMO (Turhan Irak et al., 2019).

In that study, computational chemistry was applied on 105 selected organic compounds. With the TD-DFT results, promising candidates were named for the three structures (Tavakoli et al., 2021).

In this study, dithienosilole (DTS) and its derivatives were investigated, the structural and electronic properties of a series of organics were investigated. As a result, it has been shown that it is possible to create significant differnces in the optical and electronic properties of the DTS compounds with two phenyl groups and various functional groups attached at the silicon atom (Van Trang et al., 2020).

Highly efficient transmission of charges from neighboring charge-carrying layers to the emission layer results in the expansion of exciton recombination sites, which is directly related to the efficiency of OLED structures (Wagner et al., 2013; Kang et al., 2016; Hwang et al., 2020). In general, molecules with carbazole (Cz) units are known to have high triplet energy levels (T1) (Brunner et al., 2004; Jiang et al., 2011). A fluorine atom or a cyano group binds to the Cz unit, leading to a significant yield change in the structure (Mizuno et al., 2012; Kim and Lee, 2014; Hwang et al., 2020). In another study published in the literature, it is reported that the highest possible yield of TADF properties can be obtained from simple aromatic compounds (Uoyama et al., 2012).

In the study where CzPy2TCz and CzPy3TCz materials were designed, high efficiency TADF-OLEDs were also synthesized. In the design, a pyridine group is attached to the central unit as the electron withdrawing unit and the position of tercarbazole (TCz) is changed. The two synthesized base materials have strong thermal stability and high triplet energy level. As a result, it has been emphasized that the synthesized base materials play an important role in the application of high-performance, TADF-OLED structures (Hwang et al., 2020).

CONCLUSION

In this research study, the need for more efficient motivated us to investigate novel potential OLED materials. Tropone based electroluminescent compounds are very rare in the literature as far as our knowledge. The hybrid structure of tropone with carbazole unit has been thought to be a good starting point for generation of new D-A type organic fluorescent molecules. The tropone is a unique structure with the carbonyl making the seven membered ring aromatic. However, it is 6 electrons-7 centered aromatic structure which make the ring electron deficient. This fact was a good point for us in search of a suitable acceptor moiety. Carbazole, on the other hand, is a well-known donor which has wide applications for OLED use. In Figure 7, the geometry optimized structures can be seen. The dihedral angle between the two major units lead to separation of the HOMO and LUMO in the molecule. There are three possible derivatives of the present compounds (Figure 7).

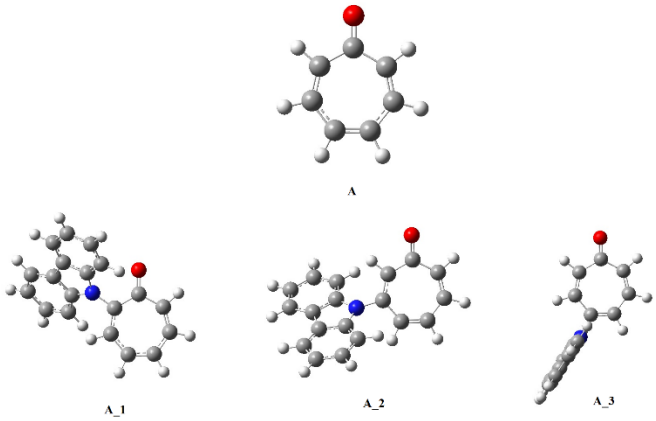

Figure 7. Geometry optimized tropone-carbazole hybrid systems

As donor and acceptor groups in the structures of the molecules examined theoretically carbazole and tropone are used, respectively. Conjugation-enhancing bridging groups such as benzene, furan, thiophene derivatives have not been applied here. The electron withdrawing tropone group was chosen as the acceptor group. Organic compounds with Donor-Acceptor (D-A) structures exhibit important optical and photophysical properties. In the field of molecular electronics D-A compounds find wide use of applications and interesting properties can be obtained upon scientific search.

In this study, a comprehensive conformational investigation was applied to the ground states of all the structures studied. Ground state optimizations were performed at B3LYP/6-31G(d,p). The sameF calculation method was preferred for excited state calculations. Hybrid systems having conjugations worth studying for their potential interesting capacities as photoluminescent structures. Density Functional Theory (DFT) level has been applied to investigate structural and molecular properties theoretically. The unit of carbazole acts as a donor. Strong electron withdrawing tropone on the other hand, form the acceptor moiety. In addition, various electron-withdrawing bridge groups based on benzene, furan, thiophene derivatives form the π system by bonding with pyridoquinoline. As a whole, the three derivatives here have two aromatic cites. Extended conjugation is provided for all compounds. In some cases, bends are expected due to the planarity, as the acceptor units create steric hindrance. The structures are designed as D-A type organic systems. D-A type organic compounds are considered to be serious potential candidates for organic light emitting diodes.

The components of the designed structures are given in Figure 8. The carbazole-tropone hybrid system structure was used for the first time for OLED research without benzene, thiophene and furan bridges, to achieve the investigation of donor-acceptor type OLED systems in contrast to literature. D-A type OLED structures used in this thesis project have not been found in the literature. The designed molecules are completely original designs.

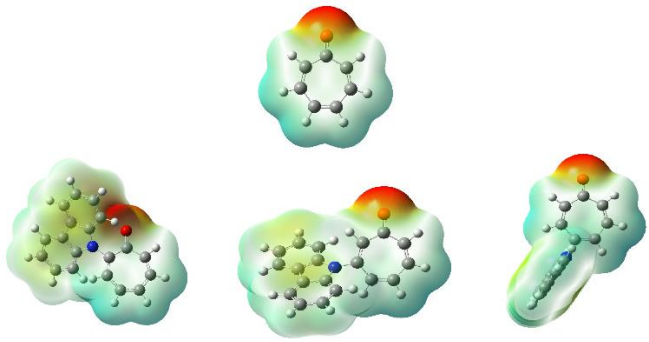

Figure 8. Molecular electrostatic potential maps for tropone-carbazole hybrid systems

Molecular electron potential maps represent the distribtion of charge in a molecule and indicate the electron poor and rich parts. Therefore, we can decide where to attact electrophiles and where to receive attacts from nuclephiles. In

our present case, carbazole forms the electron rich moiety and in contrast, tropone part forms the electron poor area of the structure.

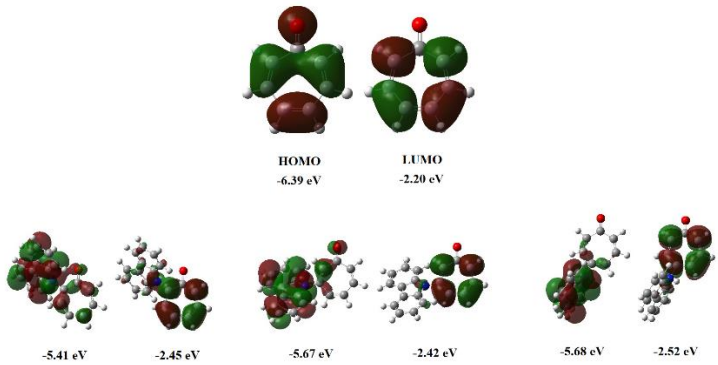

Figure 9. HOMO and LUMO maps for tropone-carbazole hybrid systems

OLED structures have been differentiated from others with separated HOMO and LUMO distributions in the molecular structure. When HOMO and LUMO are well-separated that molecule can be considered for a potential OLED system. It can be observed from Figure 9 that, HOMO and LUMO are both located on parent structure. However, the attachment of carbazole unit replaced HOMO on itself and HOMO and LUMO are very well separated in these novel compounds. Moreover, interfrontier molecular orbital energy gap for semiconductors should be between 2.00-4.00 eV. According to literature, compounds with less than 2.00 eV HOMO_LUMO gap are said to be conductors and vice versa compounds with greater than 4.00 eV HOMO_LUMO gap ($\Delta E = e_{LUMO} - e_{HOMO}$) are said to be insulators. In our case, parent tropone structure which had 4.19 eV HOMO-LUMO difference (an insulator) has been converted to a semiconductor via connection with carbazole unit. The hybrid structures possess around 3.0 eV ΔE for each. Another criteria for an organic structure to be candidate for OLED systems is that transition energy from singlet to triplet (be below 0.50 eV in order to be able to achieve reverse intersystem crossing. These type of structures can achieve thermally acticated delayed flourescence (TADF) to regain the lost energy through intersystem crossing which then lead to phosphorescence. The potential TADF systems studied here possess 0.02, 0.06 and 0.12 eV ΔE_{ST} data, respectively which make them strong candidates for OLED use.

In the last century, there has been a great worldwide need for the use of digital screens. With the resources owned, the most effective efficiency is provided by the materials obtained by using inorganic additives. It does not seem possible to meet this need with the underground riches of the world. Because the elements to be used are very few in the earth's crust. As a result, scientists have started to conduct research within the framework of new searches. Organic compounds are considered as a good alternative because of their ability to be synthesized in large quantities, their easy synthesis and their abundance. In addition, organic semiconductor products are a cheaper alternative to their silicon-containing counterparts. Therefore, organic-containing semiconductors can be strong potential candidates for digital applications. Compounds with D-A structure have been taken into consideration much more than expected for more than a decade resulting from narrow HOMO-LUMO band gaps and possessing special electro-optical properties. The properties of all organic semiconductors are effected by their π-electron conjugation or non-conjugated structure as well. Single bonds are σ-bonds and are associated with dormant electrons, while double bonds consist of a σ-bond and a π-bond. LUMO represents the lowest energy vacant orbital and HOMO represents the highest energy occupied orbital. These orbitals are called precursor molecular orbitals. Because if an electron is to be given during a reaction, the HOMO orbital comes into play, if the electron is to be accepted, the LUMO orbital comes into play. The energy difference (ΔE) between these two terrestrial orbitals gives information about the conductivity of the compounds.

In the present study, compounds that are thought to have the potential to be TADF active were designed and examined with theoretical calculation methods. Care was taken that the selected constructs contain both donor and acceptor groups. Thus, intramolecular charge transfer can occur. The effect of diversity of donor, acceptor and π groups on TADF efficiency was investigated. Photophysical and optical properties for these structures were also investigated. The TD-DFT method was used in the excited state calculations with the B3LYP/6-31G(d,p) method.

Among the studied molecules, the structures with the potential to display the best semiconductor properties were evaluated as 2, 3 and 4. Literature information states that structures with an energy difference of less than 4.0 eV between two orbitals can be considered as semiconductors. The three mentioned compounds have HOMO-LUMO energy ranges of 1.96, 2.25 and 2.16 eV, respectively. These results make 2, 3 and 4 potential candidates for OLED use.

The secondary condition is to examine whether they have TADF properties for these structures. In order for a molecule to show TADF property, the singlet-triplet energy gap must be lower than 0.5 eV, and the lower this value, the more positive it is considered. All three molecules 2, 3 and 4 were calculated to have zero or almost zero ΔE_{ST} values. On the other hand, in these molecules, HOMO and LUMO are completely separated from each other and determined in accordance with intramolecular charge transfer.

As a result, computational calculations were performed for the four structures considered and the results were evaluated. It was determined that all of the new designs showed the potential to be semiconductors when the energy gap between the precursors was evaluated. However, since the quantum efficiency is aimed to approach 100%, it is expected that the target molecules will also have TADF properties. TDDFT calculations allowed us to show that molecules 2, 3 and 4 have very very low singlet-triplet energy gaps and are suitable for inverse inter-system transition and are the strongest candidates for OLED applications. In order for a structure to be suitable for OLED use, structures that meet all three criteria (HOMO and LUMO are located in different regions, HOMO-LUMO band gap is less than 4.0 eV, and singlet-triplet energy gap is less than 0.5 eV) 4a were identified for 2, 3 and 4.

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BÖLÜM IV

FLOROZİS ve HÜCRESEL MEKANİZMALARA ETKİSİ

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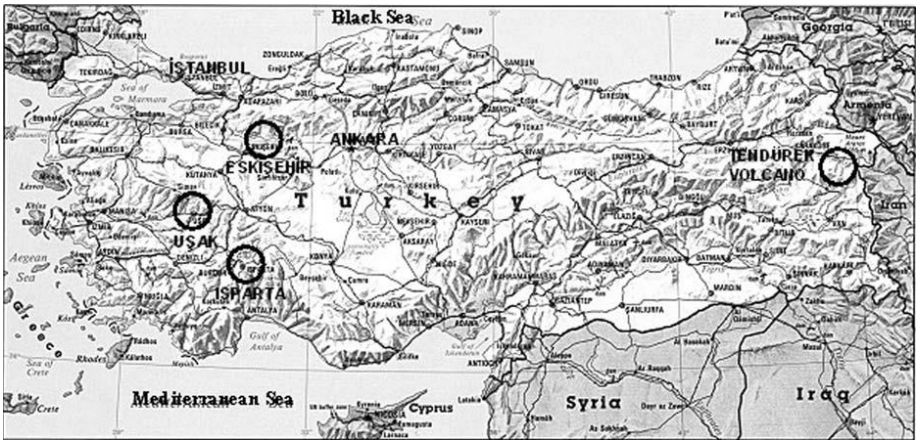
GİRİŞ

Flor halojenler içerisinde elektronegativitesi en yüksek olan elementir. Bu özelliğinden dolayı tüm elementlerle kolayca birleşik oluşturabilmektedir ve doğada birleşik halinde bulunmaktadır. Flor başta içme suları olmak üzere besinler, diş macunları, çeşitli ilaçlarda kullanımı ve solunum yollarıyla vücuda alınmaktadır. Özellikle jeolojik olarak volkanik bölgelerde yoğun şekilde yer almaktadır. Vücuttan atılımı düşük olduğunda, özellikle kemiklerde birikmesi sonucu zamanla toksik bir hal almaktadır. Uzun süre yüksek dozda flora maruz kalınması nedeniyle, iskelet ve dişlerde flor birikmesi sonucu florozis hastalığına neden olmaktadır. Bu hastalık başta dişlerde olmak üzere benekli kahverengi bir durum ve kemiklerde ise ortopedik şekil bozuklukları ve çabuk kırılmalarla kendini göstermektedir. Kronik olarak görülmekle beraber, ani olarak yüksek seviyelere maruz kalmak suretiyle akut toksisite olarak da görülebilir. Bu durum vücutta bir toksikasyona neden olmaktadır. Son zamanlarda yapılan önemli araştırmalar florun gerek insanlarda gerekse hayvanlarda alımı ve vücuttan atılımı esnasında yumuşak doku hasarına da neden olduğu bilinmektedir.

1. FLOR

Flor gibi iz elementlerin miktarlarının tespiti insan sağlılğı açısından önem teşkil ettiği bilinmektedir (Görmez, 2022). Flor (F) peryodik cetvelde 7A grubunda bulunan bir halojendir. Reaktivitesi yüksek olmasından dolayı bütün elementler ve asal gazlarla kolaylıkla bileşikler oluşturabilmekte (Rafique ve ark., 2015).

Bu özelliği sebebiyledir ki doğada serbest halde değil, bir takım bileşikler halinde bulunmaktadır (Wei ve ark., 2014). Flor, doğada çoğunlukla CaF_2, MgF_2, $Ca_5(PO_4)_3F$, Na_3AlF_6, NaF bileşikler halinde bulunmaktadır. (Rafique ve ark., 2015). Flor ülkemizde Van/Çaldıran, Ağrı/Doğubeyazıt, Eskişehir ve Isparta Yörelerinde daha fazla yer almaktadır. Dünyanın farklı bölgelerinde de doğal olarak yüksek miktarda yer almaktadır (Şendil ve Bayşu, 1973; Küçükeşmen, 2008; Narsimha ve Sudarshan, 2017).



Şekil 1: Türkiye'de flor ve florozis hastalığının yoğun bulunduğu bölgeler (Varol ve Varol, 2010)

Florlu yapılar jeoljik dağılıma bağlı olarak değişen oranlarda yayılmış bir elementir. Florlu bileşikler yeryüzünü oluşturan topraklarda, kaya parçalarında, madden yataklarında, bitkilerde ve birçok canlı türünün yapısında doğal olarak bulunmaktadır. Bunula birlikte, yer kürede en fazla bulunan yapılardan biridir (Gutiérrez ve ark., 2010). Yeryüzünün takriben %0.06-0.09'unu oluşturmakta. Bilhasa volkanik alanlarda yeralan yer altı ve yer yüzü sularında fazla bulunmakta (Kahraman ve ark., 2011).

Flor sanayide birçok alanda kullanılmaktadır. Bu kullanımından dolayı yoğun çevre kirliliğine ve kontaminasyonuna neden olmaktadır. Elektronik araçlarda, soğutuculardа, teflon üretiminde, izolasyon ürünlerinde, fiberlerde, yüzey aktif maddelerde, yangın söndürme gereçlerinde, membranlarda, ilaç yapımında ve diş ürünlerinde v.s. bulunmaktadır (Kurtdede ve ark., 2017).

Flor, başta su olmak üzere, hava, bitkiler ve hayvanlarda bulunduğundan insanlara çok rahatlıkla geçebilmektedir (Wei ve ark., 2014). Oranı değişmekle birlikte, çoğunlukla yer altı su kaynaklarındaki miktarı yeryüzündekinden daha fazladır (Kahraman ve ark., 2011). İçme sularında flor kontrolü CaF_2 bileşiğiyle miktarı azaltılmakta (Mondal ve ark., 2016).

2. FLOR METABOLİZMASI

2.1. Sindirim ve Birikmesi

Florun yaklaşık %85'i basit düfizyon aracılığıyla sindirim sisteminden emilimi gerçekleşir. Florlu bileşiklerin türüne, çözünebilirliğine, konsantrasyonuna ve sindirim sisteminin içeriğine göre emilen flor oranı değişim göstermektedir. Böbrek, terleme ve bağırsak yoluyla vücuttan atılır (Buzalaf ve Whitford, 2011).

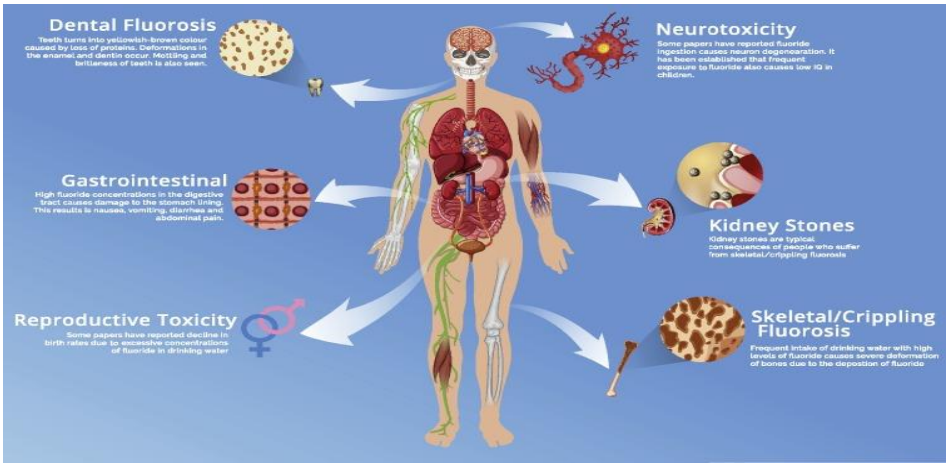
Flor emildikten sonra dolaşım yoluyla kolayca vücuda dağılır. Plazmada yer alması 3-10 saat kadardır. Plazma florür yoğunluğu vücutta dengeli değildir, artması ve azalması alınan flor konsantrasyonuyla ilişkilidir. Flor çoğunluğu böbrek yollu ile atılmaktadır. Florun vücutta birikmesi %99 oranında kemik ve dişlerde meydana gelmektedir. Florun canlılarda bilinen en iyi etkisi kemik yapısında apatit yapılarda OH^- iyonlarıyla yer değiştirerek, yapısal sağlamlığı desteklemesidir (Aoba, 1997). Kemik mineralizasyonun hızlı oluşmasında etkili olduğu düşünülen flor iyonu, hidroksiapatiten daha dayanıklı ve daha az çözülebilen mineralizasyon kompleksi olan floroapatitin bileşimine girebilmektedir. Deneysel çalışmalar, mineral katılmasında etkili olması, flor yoğunluğu yüksek olan kobaylarda diş dolgusunun büyümesinin yükseldiğini göstermektedir (Mondal ve ark., 2015). Flor diş macunlarında yer alan bir antibakteryel yapı olarak da kullanılmaktadır. Flor iyonu, kemiklerin mineralizasyonu ve kalsifikasyonunda görev alan bir mikro besin elementidir. Ayrıca osteoporosis hastalığının tedavisinde de kullanılmaktadır (Mondal ve ark., 2015).

Dünya Sağlık Örgütü tarafından kabul gören flor miktarı, içme sularında ortalama 1 ppm oranında olmasıdır. Bu tavsiye edilen flor miktarının halk sağlığı bakımından problem yaratmadığı ve diş sağlığı ve diş estetiği açısından önemli görülmektedir. Dental florozisin meydana gelmemesi ve diş çürüklerinin önlenmesi için 0,6-1,1 ppm aralığında yer alacak şekilde suya flor katmak gerektiği rapor edilmiştir (Mondal ve ark., 2016).

2.2 Toksisitesi

Çevre açısından flor potansiyel bir tehlikeye sahiptir. İnsanlar, su ve diğer besin maddeleri ve solunum yoluyla uzun zaman flordan etkilenebilmektedir. Tüm gıda maddeleri ve içme suyu yoluyla flor iyonun

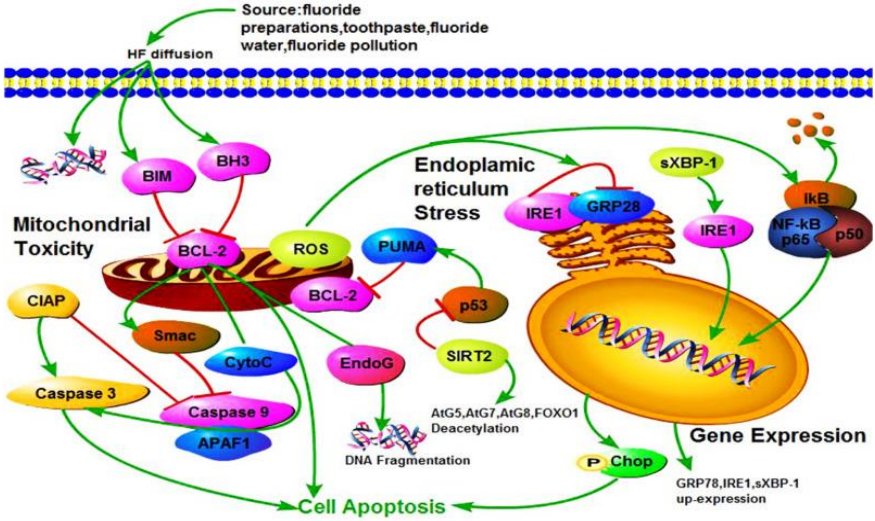
geniş bir alanda bulunması sağlık yönünden çoğu zaman bir yan etki oluşturmaktadır (Song ve ark., 2014). İnsanlarda florün en belirgin toksisitesi, florün yüksek oranda görüldüğü yerleşim alanlarında yaygın görülen endemik kemik ve diş florozisidir (Guney ve ark., 2007). Flor iyonlarının hücre membranından geçişi ve kemik dışındaki diğer dokulara girişi bilinmektedir (Guney ve ark., 2007). Uzun zamanda düşük konsantrasyonda florlu bileşik tüketilmesi sonucunda azda olsa yan etki meydana gelmesine rağmen, yüksek konsantrasyondaki maruziyet önemli akut toksisite meydana getirmektedir (Li ve ark., 2005). Yüksek konsantrasyonda flor, doku gelişiminin gerilemesi ve yavaşlaması sonucu anormal diş minesi oluşmasına neden olmaktadır (Yang ve ark., 2013). Uzun süre yoğun flor alınması dişlerin rengini değişmesine, inme, osteoporosis ve damar sertliği gibi durumların sonucu ile alakalı kronik florozis oluşmaktadır (He ve ark., 2015). Farelerde deneysel olarak florür uygulanmasından dolayı, tiyobütirik aktif maddesi, üre, kreatin, T3, T4, PTH, fosfor, magnezyum düzeyleri, ALT, AST, ACP ve GGT (gamma glutamil tranferaz) aktiviteleri yüksek oranda artış gösterirken, serum östradiol, kalsiyum ve glutatyonda azalma gösterdiği tespit edilmiştir (Mohamed, 2016). Florun toksik etkisinin sonucu olarak, lipid peroksidasyonu ile birlikte serbest radikallerinin oluşmasına çok fazla etkisi olduğu düşünülmektedir (Guney ve ark., 2007).



Şekil 2: İçme suyundan aşırı florür alımı nedeniyle insanlar üzerinde sağlık olumsuz etkileri (Kashyap ve ark., 2021)

3. FLORUN HÜCRESEL ETKİLERİ

Flor iyonlarının, bağırsak hücreleri içine geçişleri hidrojen florür (HF)'ün difüzyonuyla meydana gelir. HF suyun geçişine benzer bir durumla hücre zarını süratli bir şekilde geçtiği rapor edilmekte. Florlu bileşiklerin ayrıca anyon kanaları aracılığıyla geçiş yaptığı da bilinmektedir. Florun, süre ve miktarla alakalı olacak şekilde, hücre türüne göre de etki yaptığı bilinmektedir. Florlu bileşiklerin hücre içi yapılara en önemli etkisi enzimlerle etkileşimidir. Florun enzimlerle etkileşimi çoğu zaman inhitör, nadiren de olsa enzim aktivatörü olarakta da davranabilmesidir. Gerçekleştirilen bilimsel çalışmalarda, florürün proliferatif veya toksik olmayan miktarları etkili anabolik bir molekül gibi davranırken, toksik oranlarda önemli bir enzim inhibitörü olabileceği raporlanmıştır (Barbier ve ark., 2010, Korkmaz ve ark.,2022).



Şekil 2: Hücresel seviyede flor toksitesi (Zuo, 2018)

Florun solunum sistemlerinde epitel hücrelerden geçmesi anyon geçiş kanaları ile gerçekleşir. Natriyum florür (NaF) ve natriyum fluorosilikat (Na_2SiF_6) gibi suda çözünen flor bileşikleri gastro intestinal sistemlerde çok iyi geçerken, natriyum aluminofluoroaluminate ve kalsiyum diflorine gibi daha az çözünebilen florlu yapılar bağırsaklardan orta düzeyde geçebilmektedir (Gutknecht ve Walter,1981).

Flor iyonlarının kana geçişiyle birlikte, bütün vücuda dağılması kolaylaşır. Florürün en fazla yer aldığı doku kemik ve dişlerdir. Flor kemik hasarlarının oluşması döneminde kemikten fazla miktarda ayrılan kalsiyum ve fosforla birleşerek idrarla daha fazla atılmasına neden olmakta. Flor iyonlarının vücuda girişi azalmaya başlamasıyla birlikte, kemik ve dişte bulunan flor kana geçiş yapar. Florun idrarla atılımı pH göre değişkenlik göstermektedir. Bu durum pH ile ters orantılıdır (Elbek ve Sabah, 2000).

Florürün çeşitli biyokimyasal ve hücresel etkileri, GTP'azlar ve ATP'azlar gibi fosforil transfer aktivitesine sahip enzimatik sistemlerle etkileşimleri ile açıklanmaktadır. Florla etkileşim, protein oluşumunu ve salınmını durdurarak proteinlerin bir membran bölümünden bir diğerine geçişini etkilediği tespit edilmiştir (Mendoza ve ark., 2009).

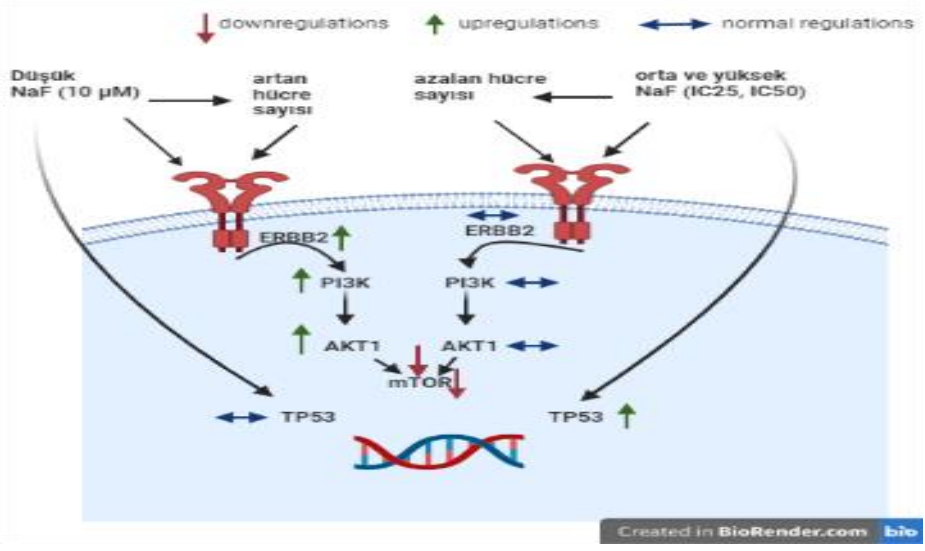
3.1. Hücre çoğalması ve bölünmesine etkisi

Forlu bileşikler farklı insan ve fare kökenli hücre serilerine uygulandığında süreye bağlı olarak düşük konsantrasyonlarda (0,001-0,1µM) genellikle hücre canlılığını değiştirmediği veya çoğalmasını kontrol gruplarına göre artırdığı, daha yüksek konsantrasyonlarda (0,25-5,0 µM) ise yine uygulama zamanına bağlı olmakla birlikte (6-72 saat) hücre canlılığı ve proliferasyonunu azaltığı tespit edilmiştir (Yüksek ve ark., 2017; Korkmaz ve ark., 2022). İnsan PBMC hücre serisinde düşük miktarda (<1µg/ml) NaF'ın hücre döngüsünün ilerlemesini yavaşlattığı ortaya konulmuştur (Jothiramajayam ve ark., 2014). HePG2 hepatosellüler hücre hattından yapılan çalışmada, hücrelerde 48 saat uygulandıktan sonra NaF ve PbAc maddelerinin hücre çoğalmasına etkilerinin ortaya konulduğu çalışmada, düşük konsantrasyonda hücre çoğalmasını artırırken, yüksek konsantrasyonlarda ise azalmasına sebep olduğu tespit edilmiştir. Sitotoksik konsantrasyonda NaF ile birlikte mineral, vitamin ve bitki ekstraktlarının aynı anda uygulandığı çalışmalarda NaF'ın toksik etkisini azaldığı tespit edilmiştir (Yüksek ve ark., 2017; Çetin ve ark., 2019).

3.2. Hücre Metabolizmasına Etkileri

Flor iyonları fonksiyonel olan aminoasit gruplarına bağlanarak bir enzimin aktif merkezini inhibeye neden olacak şekilde kerbs siklüsünü ve glikolitik yollun enzimlerini inhibe edebilir. Hücre içi metabolizmalara olan

etkisiyle alakalı çok sayıda çalışma yapılmıştır. Flor, ester oluşumu sağlayan enzimler, hidrolazlar ve fosfatazlar gibi çok sayıda enzim yapılarını inhibisyonunu ve ayrıca tirozin kinaz aktivitesine etki eden bir nükleofilik reaktiftir (Viñals ve ark., 1993). Flor iyonları başta apoptozis olmak üzere otofajik ve nekrotik ölüm yolaklarında bulunan birçok enzimin artışına neden olarak hücre ölümüne neden olmaktadır (Urut ve ark., 2018). Aynı zamanda oksidan antioksidan dengesini değiştirmektedir (Efe et al., 2020). Hücresel değişimleri, çoğalmaları ve işlevselliğinin devamı, invazyon ve bunlar gibi bir çok hücresel olayları düzenleyen bir sinyal yolağı olan PI3K/AKT/mTOR, florun neden olduğu hücre hasarının patogenezinde önemli bir sinyal yolağıdır. Flor konsantrasyonuna bağlı olarak bu yolakta yer alan önemli genlerin mRNA ekspresiyonun artış gösterdiği (şekil 2) tespit edilmiştir (Korkmaz ve ark., 2022)



Şekil 3: Florun PI3K/akt1/mTOR yolağına etkisi (Korkmaz ve ark., 2022)

3.2.1 DNA'ya Etkisi

Flor iyonlarının DNA yapısına olan etkisi, canlıların içme suları ve diğer besin kaynakları ve solunum yoluyla etkilenmelerinden dolayı önemlidir (Jothiramajayam ve ark., 2014). Birçok çalışma, florun farelerde özellikle yüksek konsantrasyonlardaki etkisi DNA hasarını indüklediği göstermiştir (Song ve ark., 2015). Fare kemik hücrelerinde yapılan *in vivo* flor uygulamasında; kontrol grubuna göre değerlendirildiğinde yüksek

konsantrasyondaki florun DNA hasarını tetiklediği ortaya konulmuştur (Zhang ve ark., 2006). Sistotoksik konsantrasyonda flor uygulanan sıçan renal epitelyal hücrelerinin DNA zincir kırıklarına sebep olduğu rapor edilmiştir (Yüksek ve ark., 2020). Fare lenfo ve insan fibroblast hücre serilerinde, NaF'ın farklı yoğunluklarının uygulanmasıyla her iki hücre serisinde de, komet assayle yapılan çalışmada, DNA fragmentlerinin oluşmadığı rapor edilmiştir. Hücre canlılığının her iki hücre serisi için ortalama %95 olduğu tespit edilmiştir (Ribeiro ve ark., 2006). Birkaç farklı konsantrasyonlarda sodyum florür verilen HL-60 hücre serisinde, 5000 μM ve üzerindeki konsantrasyonlarda bileşiğin internükleozimal DNA fragmentlerinin tetiklendiği rapor edilmiştir (Otsuki ve ark., 2005).

3.2.2. Translasyona etkisi

Flor iyonlarının protein sentezinin inhibisyonuna neden olduğu rapor edilmiştir (Lee ve ark., 2008). Fibroblastlarda Arhgap geni, RhoA olarak isimlendirilen küçük G proteinini düzenleyen bir RhoGAP'ı kodlar. Fibroblasta flor uygulanması RhoGAP'ı baskılar, böylelikle filamentli aktinin (F-aktin) artışına yol açan RhoA'yı aktive eder. (Li ve ark., 2005). Kemik yapısını gelişiminde önemli bir protein grubunun üyesi BMP-2 ve BMP-3 translasyonu human osteosarkoma hücrelerinde yüksek miktarda flor iyonu uygulanan hücrelerde azaldığı tespit edilmiştir (Wei ve ark., 2014). Human RPMI8226 hücreleri konsantrasyona bağlı olarak florun etkisinde kalmaları sonucunda, birkaç farklı proteinin translasyonunda değişiklik meydana getirmiştir, özellikle de yüksek konsantrasyonda flor uygulaması yapılan gruplarda (He ve ark., 2015).

3.2.3. Mitokondriyal sisteme etkisi

Düşük konsantrasyondaki flor iyonları toksik olmamasına rağmen, lipit peroksidasyon düzeyinde bir artıştan dolayı oksidatif strese neden olmaktadır. Lipit oksidayonu, mitokondriyal iyon geçiş sistemi gibi apoptozisin oluşmasına sebep olacak hücre içi ve hücre dışı mitokondriyal membran taşıma düzenini düşürebilir. Diğer bir önemli ilişki ise, apoptozis ve mitokondri fizyolojisi arasındaki Bcl-2 ailesi proteinleridir. Flor uygulanmış hücre serilerinde Bcl-2 ekspresiyonunda düşüş olduğu rapor edilmiştir. Bcl-2'nin ekspresiyonun düşmesi, Bcl-2 ilişkili apoptotik direncinin azalmasına sebep olmaktadır (Guney ve ark., 2007). Ayrıca Bax/Bcl-2 arasındaki oran

mitokondriyal apoptozis için önemli olabiliyor. BaX/Bcl-2 oranı artıkça apotozis yönlü bir artış meydana gelmektedir (Raisova ve ark.,2001). Florlu bileşik verilmiş PBMC hücre serisinde 24 saat sonunda inert mitokondriyal membranın depolarizasyonu meydana geldiği tespit edilmiştir (Jothiramajayam ve ark., 2014). Flor uygulanmış H9c2 hücrelerde flor miktarının artışıyla birlikte mitokondri membran geçiş pontansiyeli azalma göstermiş (He ve ark., 2015), HL-60 hücrelerinde ise mitokondri membran geçiş potansiyelinin yok olmasına sebep olduğu rapor edilmiştir (Otsuki ve ark., 2005).

SONUÇ

Tüm halojenler içerisinde en yüksek elektronegatifliğe sahip olan flor bu özelliğinden dolayı hem cansız hem de canlı organizmalarda bileşik halinde bulunur. Özellikle jeolojik yapı bakımından volkanik bölgelerde yüksek konsantrasyonda bulunmakta. Bu da, gerek direk içme sularında olmak üzere gerekse, besin maddeleriyle insanlara geçmektedir. Flor, vücuda girdikten sonra atılımı diğer iyonik bileşiklerin aksine düşük olmakta. Özellikle kemiklerde kalsiyum ile yer değiştirerek hidroksiapatit oluşturması bunun kemiklerde zamanla birikmesine neden olmaktadır. Dünya Sağlık Örgütü'ne göre her ne kadar düşük konsantrasyonda tüketimi tavsiye edilse de flor zamanla vücutta birikerek toksik bir orana yükselebilir. Florlu bileşikler, dünyada artan ilaç tüketimi, diş bakım ürünlerinde kullanılması, çeşitli sanayi bölgelerinde atık olarak havaya verilmesi ve artan hazır gıda tüketimine bağlı olarak vücuda giriş yolları artmış bulunmaktadır. Yapılan tüm çalışmalarda florun hücre içi metabolizmaları ciddi anlamda olumsuz etkilediği sonucu çıkmakta. Biyolojik zararlarının yararlarından çok fazla olduğu tespit edilmiştir. Sonuç olarak gerek içme sularında gerekse tüm gıda maddelerinde flor bileşiklerinin mümkün mertebe en düşük seviyede olmasının, insan sağlığı açısından daha önemli olabileceği sonucuna varılmıştır.

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BÖLÜM V

GONADOTROPİN HORMONLAR

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GONADOTROPİN HORMONLAR

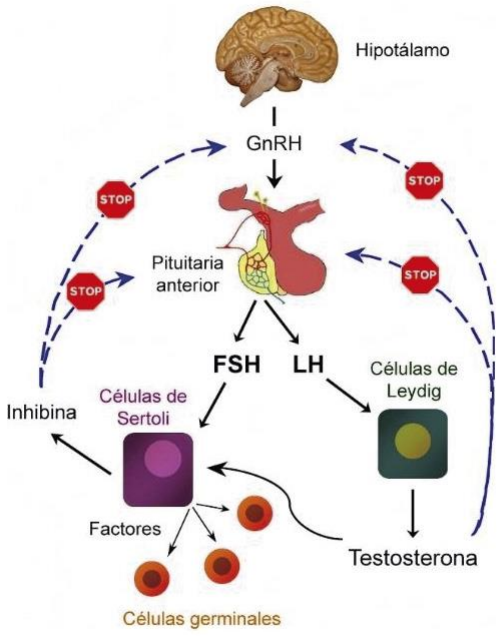
1. Hipotalamik-Hipofiz-Gonadal Ekseni Ve Erkek Cinsel Fonksiyonun Kontrolü

Erkek hipotalamus-hipofiz-gonadal eksen iki temel işlevi kontrol eder (Şekil 1).

(1) seminifertübüllerde erkek gamet (spermatogenez) Üretimi

(2) testislerdeki Leydig hücrelerinde androjen sentezi.

Hipotalamustan salgılanan gonadotropin serbestleştirici hormon (GnRH), ön hipofizin gonadotrop hücrelerinden Luteinize Edici Hormon (LH) ve Follikül Uyarıcı Hormon (FSH) salgısını uyarır. LH ve FSH kontrolü, sırasıyla testislerdeki Leydig ve Sertoli hücreleri tarafındandır. Bu olay kısaca aşağıdaki gibidir(1).



Şekil:1 Erkek Hipotalamus-Hipofiz-Gonadal Ekseni (2)

Hipotalamus-Hipofiz-Testis ekseninde, hipotalamusun Arkuat çekirdek ve Preoptik alanda küçük gövdeli nöronlar, GnRH salgılarlar. Salgılanan GnRH uzun portal venlerle ön hipofizdeki gonadotoplara ulaşırlar. GnRH tarafından uyarılan gonadotroplar, FSH ve LH'ın sentezlenmesi ve salgılanmasına neden olur. LH, Leydig hücreleri üzerindeki reseptörlere bağlanır. Bu şekilde testosteronun biyosentezini de içeren çok sayıda protein transkripsiyonunu uyarır. FSH Sertoli hücrelerinin bazolateral zar üzerinde reseptörlerine bağlanarak gen transkripsiyonunu ve protein sentezini uyarır. Bu proteinler, Androjen Bağlayıcı Proteinin (ABP), aromataz, büyüme faktörleri ve inhibindir(3).

Hipotalamus-Hipofiz-Testis ekseninde negatif geri besleme iki yolla meydana gelir. Birincisi testosteron, hipotalamus nöronları tarafından GnRH'ın salınmasını inhibe eder ve ön hipofiz gonadotroplar tarafından LH salınımını inhibe eder. İkincisi inhibin, ön hipofiz gonadotroplar tarafından FSH salınımını inhibe eder.

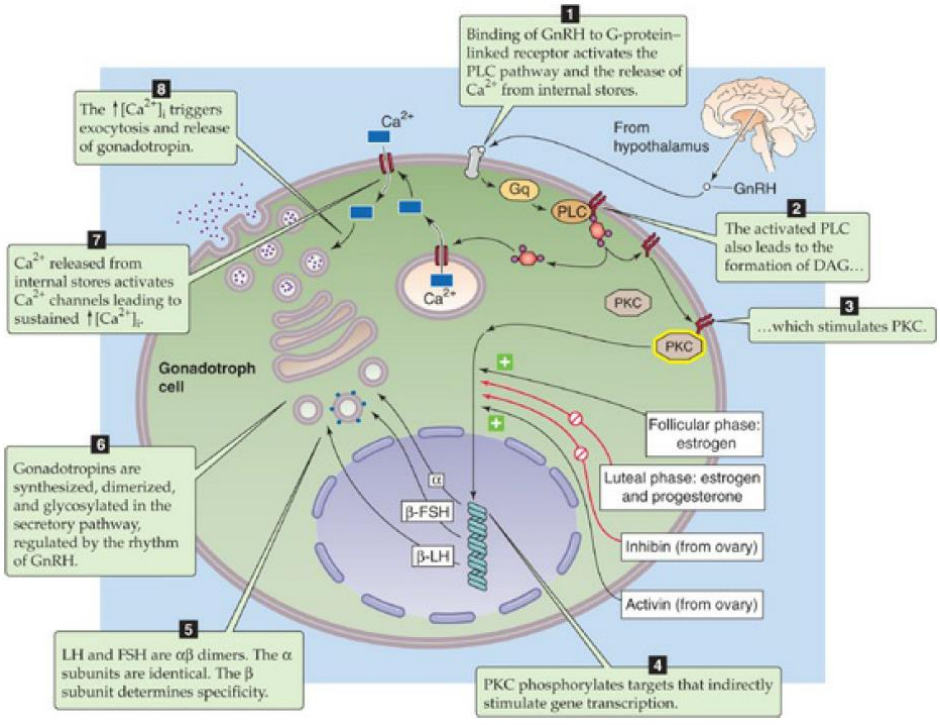
1.1. Hipotalamusta GnRH Salgılanmasıyla, Ön Hipofiz İçindeki Gonadotroplar Üzerine Etkisi

Hipotalamusta küçük gövdeli peptiderjik nöronlar tarafından sentezlenen GnRH, ön hipofiz gonadotrop hücreleri tarafından gonadotropinlerin sentezi, depolama ve salgılanmasını uyarır(3). Nöronlardan GnRH'ın sentezlenmesi depolanması ve serbestleşmesi hipotalamus boyunca dağılmıştır. Fakat esas Arkuat çekirdek ve Preoptik alanda yer almaktadır. Sıçanlarla ilgili yapılan çalışmalar GnRH'ın üretimi hipotalamus dışındaki bölgelerde de (limbik sistem gibi) seks davranış kontrolünde katılabilir olduğunu gösterdi. Beynin diğer bölgelerinden kaynaklanan nöronal sistemler hipotalamik GnRH salan nöronlarla bağ kurarak ve böylece fonksiyonel nöronal ağı oluşturur.

Diğer peptid hormonları gibi GnRH 69 aminoasitli tek zincirden bir prohormondur ve enzimatik bölünme ile elde edilir. Saf hali 10 aminoasitlik bir dekapeptittir. Salgılanan GnRH uzun portal venlerle ön hipofize ulaşırlar. GnRH, hipofiz ön gonadotop hücrelerinden hem FSH hemde LH salınımını uyarır.

Hipofiz gonadotrop hücre zar yüzeyinde GnRH için yüksek afinite reseptör alanıdır. Bu reseptörler fosfolipaz C (PLC) aktive eden G protein ailesinin Gαq çiftidir(4). G protein αq alt ünitesi; Fosfotidil İnozitol Bifosfat (PIP2)'ı membran bağımlı diaçilgliserol ve stozolik IP3 olmak üzere iki farklı hücre içi haberciye

ayıran fosfolipaz C'yi aktifler(Şekil 2). Diaçilgliserol protein kinaz C'yi uyarır. İnositol 1, 4, 5-Trifosfatı (IP3) ise endoplazmik retikulum üzerindeki reseptörüyle birleşir ve Ca^{+2}'un hücre içi depolarından serbestleşmesini tetikler. Sonuçta gonadotroplardan hem LH hem de sentez FSH ve serbest bırakılır. Portal sisteme GnRH salgılanması aralıklı olduğundan, gonadotroplardan hem LH hem de FSH sekresyonu aralıklıdır. Erkeklerde LH aralıklı deşarj frekansı ~24 saatlik süre içinde 8 ila 14 kadardır. Dolaşımdaki FSH'ın hem miktarı hemde yarılanma süresinden dolayı salgılanma aralığı, LH'ın salgılanma aralığı gibi belirgin değildir.



Şekil:2 GnRH Salgılanması ve Ön Hipofiz İçinde Gonadotroplar Üzerinde Etkisi(5)

Testisler, özellikle seks steroidleri ve inhibin ürünleri, hipotalamus ve ön hipofiz bezinin negatif geri besleme ile kontrol uygulamaktadır. Arkuat çekirdekteki nöronlar seks steroidlerine cevap verir. Seks steroidleri hem erkeklerde hem de kadınlarda LH salgılanma sıklığını değiştirir. Seks davranışındaki değişiklikleri ile kanıtlandığı gibi androjenler de, yüksek beyin fonksiyonu üzerinde güçlü etkileri vardır(6).

1.2. GnRH Kontrolü Altında, Ön Hipofiz Gonadotropları LH ve FSH Salgılar

Ön hipofiz gonadotroplar tarafından salgılanan LH ve FSH, testis fonksiyonlarının birincil düzenleyicileridirler. LH ve FSH, İnsan Koryonik Gonadotropin (hCG) ve Tiroid Uyarıcı Hormon (TSH) gibi hormon ailesinin aynı üyeleridir. Tüm bu glikoprotein hormonları α ve β olarak gösterilen iki polipeptid zincirinden oluşur. Tam bir biyolojik aktivitesi için iki alt ünite olan α ve β gereklidir. LH ve FSH α alt birimi gibi hCG ve TSH α alt birimi aynıdır. İnsanlarda, ortak bir α alt birimi 92 amino asit ve ortalama 20000 bir moleküler ağırlığa sahiptir. β alt birimi ise dört hormonda farklıdır ve böylece sağlam moleküllerin imünolojik özellikler ve özel işlevsellikler kazandırır. FSH ve LH eşsiz β alt birimlerinin her birinin uzunluğu 115 amino asit. LH ve hCG β alt birimi, aynı fakat hCG β alt birimi dışında bir C-terminali uca ilave 24 amino asit ve daha fazla glikozilasyon alanı vardır. hCG plasenta tarafından salgılanır fakat bazı raporlarda bu maddenin küçük miktarlarda testis, hipofiz bezi ve diğer plasenta dışı dokularda yapılmış olduğu gösterilmiştir. LH ve hCG'nin biyolojik aktiviteleri çok benzerdir(7).

Ön hipofizden salınan gonadotropin her bir oranı ve özelliği gelişimsel yaşına ve de mevcut hormonal ortama bağlıdır. Gebeliğin ilk trimesterin sonunda erkek fetüsün hipofiz bezi fonksiyonel gonadotroplar içerir. Daha sonra, gonadotropin salgı hızlı ve platoları artar. Gonadotropin salgısı uterusta fetal yaşamda geç döneminde azalmaya başlar ve doğum sonrası erken dönemde tekrar artar.

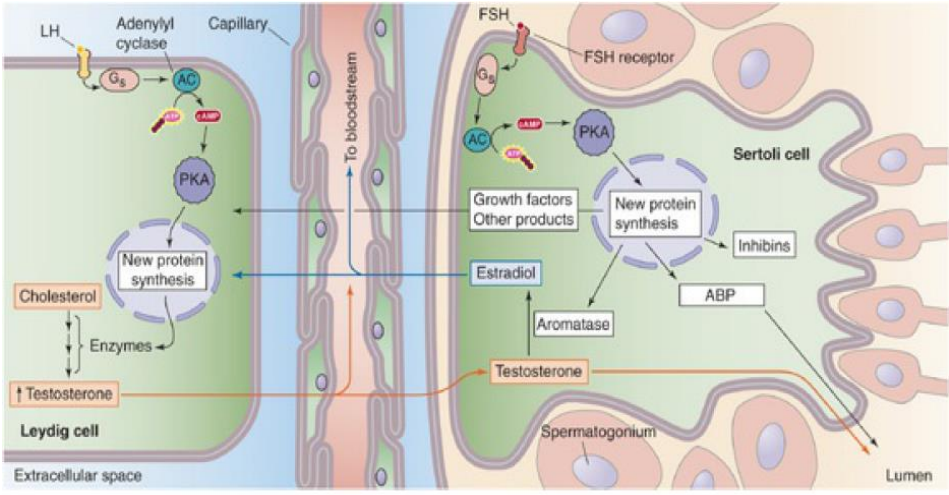
FSH salınımı puberte öncesi dönemde, LH'dan daha yüksektir, puberteden sonraki dönemde ise tam tersine döner. GnRH erkeklerde tercihen LH salınımını tetikler. LH tercihi testislerde salgılanan inhibin ile testis olgunlaşmasını yansıtıyor olabilir ve ayrıca inhibinin ön hipofiz bezi FSH salgı seviyesinde, belirli bir baskılayıcıdır. Hipofizde artmış gonadal steroid üretimi FSH salgısının sınırlamasından sorumlu olabilir(8).

1.3. LH'ın Testislerin Leydig (İntestinal) Hücrelerini Uyarmasıyla Testesteron Üretimi

LH adını kadınlarda gözlenen etkilerinden yani luteal fonksiyonları uyarabilme yeteneğinden almaktadır. Başlangıçta erkeklerde karşılaştırılabilir madde İnterstisyel Hücre Uyarıcı Hormon (ICSH)'du. Daha sonra araştırmacılar, LH ve ICSH aynı madde olduğunu fark edip ortak ad LH oldu. Erkeklerde testesteron salgılanması hipofizektomiden sonra azalır. Bu olay testesteron

üretimi için ön hipofizden LH'ın salgılanması gerektiğini bizlere gösterir. Testisin intestinal hücleleri (Leydig hücreleri toplam testisin %20'sini oluştururlar) erkeklerde birincil testesteron kaynağını oluşturur. Leydig hücreleri steroid biyosentetik yolların parçası olan enzimlerin bir dizisini kullanarak kolesterolden androjenler sentezler.

LH, Leydig hücrelerinin plazma membran üzerindeki spesifik yüksek afiniteli yüzey reseptörlerine bağlanır (Şekil 3). LH'ın Leydig hücresinin membran üzerindeki G-protein bağlı reseptöre bağlanması cAMP oluşumunu katalize eden Adenilsiklazı (AC) uyarır ve sonuçta Protein Kinaz A (PKA) yolu aktive edilir. Aktive edilmiş PKA, gen transkripsiyonu ve testesteronun biyosentezi için gerekli olan diğer protein ve enzim sentezini arttırır. Bu diğer iki proteinlerin Sterol-Taşıyıcı Protein olan (SCP-2) ve Steroidogenik Hızlı Düzenleyici Protein ya da (StAR veya STARD1)(8). SCP 13500 molekül ağırlığında ve plazma membran ya da organel membranlardan diğer organel membranlara kolesterol taşıyan bir protein gibi gözükür ve mitokondriyal membranlarda da gözükür.



Şekil:3 LH ve FSH'ın Leydig ve Sertoli Hücreleri Üzerine Olan Etkleri(9)

Yukarıdaki şekil özeltlenecek olursa: Leydig hücresi (solda) LH reseptörüne sahiptir. Sertoli hücresi (sağda) FSH için reseptörler vardır. FSH Sertoli hücrelerinin bazolateral zar üzerinde reseptörlerine bağlanarak gen transkripsiyonunu ve protein sentezini uyarır. Bu proteinler, Androjen Bağlayıcı Proteinin (ABP), aromataz, büyüme faktörleri ve inhibindir. Leydig ve Sertoli

hücreleri arası karşılıklı madde alışverişi oluşur. Leydig hücreleri testesteron yapar ve bunu sertoli hücresine gönderir. Sertoli hücresi testesteronu aromataz enzimini kullanarak östradiole çevirerek tekrar leydig hücresine gönderir. **[**Erkeklerde östrojenin oluşumu testesteronun sertoli hücrelerinde östradiole dönüşmesi sonucu oluşur.**]** Sertoli hücreleri ayrıca ürettikleri büyüme faktörlerinide Leydig hücrelerine gönderir(8).

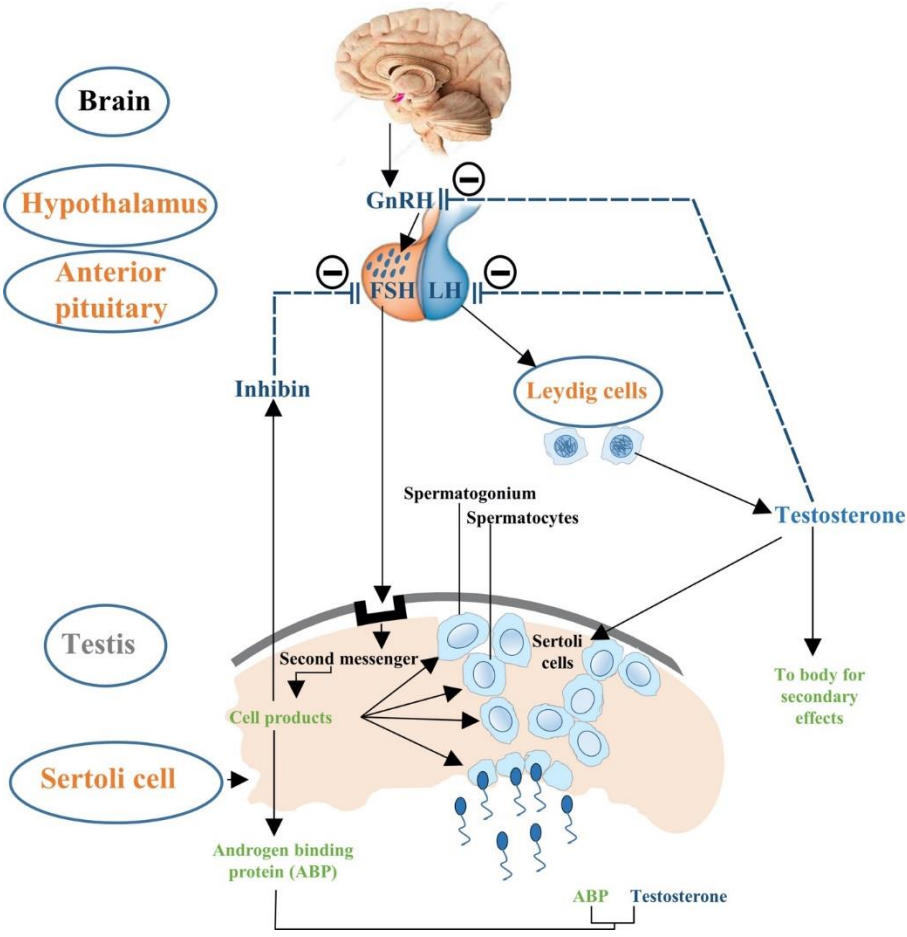
1.4. FSH Hem Leydig Hücrelerinin Hemde Spermatogenezin Gelişmesinde İhtiyaç Duyduğu Belirli Ürünleri Sentezlemek İçin Sertoli Hücrelerini Uyarır

FSH'ın etki ettiği testislerdeki Sertoli hücre alanı görünmektedir (Şekil 4). FSH Sertoli hücrelerinin üzerindeki etkileri ile Leydig hücre fizyolojisini düzenler. FSH bağlama sonrası görülen erken biyokimyasal olaylar, LH'ın Leydig hücre için tarif edilenlere benzerdir. Bu yüzden FSH'ın G protein reseptörüne bağlanması sırayla Adenilsiklaz (AC) uyarılmasını siklik adenozinmonofosfat (cAMP) miktarında artışa, protein kinaz A (PKA)'nın uyarılmasına, belirli genlerin transkripsiyonuna ve protein sentezinde artış gibi bir dizi reaksiyon zincirini başlatır. FSH'a cevap olarak birkaç protein sentezlenir. Bazıları steroid eylemler için önemlidir:

1. FSH, seminifer tübüllerin luminal alanına salgılanan ve sperm hücrelerinin gelişimine yardımcı olan Androjen Bağlayıcı Proteinin (ABP) sentezine yol açar. ABP ayrıca yerel testesteron seviyesinin yüksek tutulmasına yardımcı olur.
2. FSH Sertoli hücrelerinin içinde P-450 aromataz enziminin sentezini neden olur. Bu enzim Leydig hücrelerinden difüzyonla Sertoli hücrelerine gönderilen testesteronu östradiole çevirerek tekrar Leydig hücresine gönderir.
3. FSH, sperm hücreleri ve spermatogenezi destekleyen Sertoli hücreleri tarafından büyüme faktörleri ve diğer ürünlerin üretimine yol açar. Bu maddeler testislerde spermatogonium, spermatositler ve Spermatidlerin sayısını önemli ölçüde artmıştır. Bu yüzden, spermatogenez üzerinde FSH'ın uyarıcı etkisi spermatogenez üzerinde FSH doğrudan bir eylem olmadığı görülür. Aslında spermatogenez uyarımı Sertoli hücreleri üzerine FSH'ın doğrudan hareketiyle oluşur. FSH spermin kesin sayısında artışından ziyade ayrıca spermlere kazandırdığı motilite etkisi ile spermin doğurganlık potansiyelini arttırır.

4. FSH Sertoli hücrelerinden inhibin sentezine neden olur. Bu inhibinler Transforme Edici Büyüme Faktörü β (TGF-β) olarak adlandırılan gen ailesinin üyeleridir ayrıca Aktivinlerin ve Antimullerian hormonu içerir. İnhibinler kovalent biçimde bağlanmış bir α, bir β alt birimi içeren glikoprotein heterodimerlerdir. Bayanlarda overlerdeki Granüloza hücreleri ve erkeklerin testisindeki Sertoli hücreleri insanlardaki inhibinin esas kaynağıdır. İnhibinler Seminifer tübül sıvısına ve testisin interstisyel sıvısına salgılanırlar. İnhibinler hem Parakrin hemde Endokrin eylemlere sahiptirler. İnhibinler Leydig hücreleri üzerinde etki gösterdiği düşünülen Sertoli hücreleri tarafından salgılanan büyüme faktörlerinin bazılarıdırlar. Daha önemlisi erkeklerde hipotalamus-hipofiz-testis ekseni üzerinde negatif feedback mekanizmasında önemli bir rol almasıdır(10).

Leydig ve Sertoli hücreleri arası karşılıklı madde alışverişi oluşur. Örneğin; Leydig hücreleri testesteron yapar ve bunu sertoli hücresine gönderir. Sıçanlarda fetal Leydig hücreleri tarafından β-Endorfin üretilir ve Sertoli hücrelerindeki Afyon Reseptörlerine bağlanırak onları çoğalmasını durdurur. Leydig hücreleri tarafından β-endorfin sentezi Sertoli hücre sayısını ayarlamada yerel bir geri besleme mekanizması temsil edebilir. Bunun aksine, Sertoli hücreleride Leydig hücrelerini etkiler. Örneğin; Leydig hücreleri tarafında üretilen testesteronu Sertoli hücreleri östradiole dönüştürür ve daha sonra östradiol Leydig hücreleri üzerine etki eder(11).



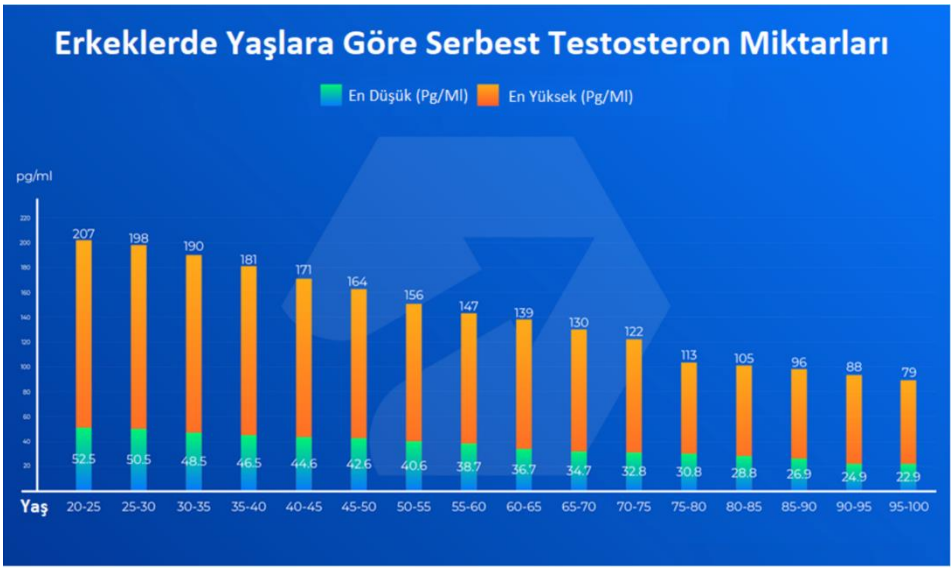
Şekil:4 FSH'ın Etki Ettiği Testislerdeki Sertoli Hücre Alanı (12)

Öyleyse en uygun spermatogenez meydana gelmesi için ne gereklidir? İki testis hücre tipleri (Leydig hücreleri ve Sertoli hücreleri) iki gonadotropin (LH ve FSH) ve bir androjen (testosteron), gerekli olduğu görülmektedir.

İlk olarak, LH ve Leydig hücreleri testosteron üretmek için gereklidir. Bu yüzden LH ya da onun yerine insan koryonik gonadotropin (hCG), Azospermik veya oligospermik adamlarda spermatogenez başlatmak için tedavi edici olarak kullanılabilir(7).

İkinci olarak, FSH ve Sertoli hücreleri sperm hücrelerinin geliştirme ve bakım için önemlidir. Ayrıca Leydig etkisi ile inhibin ve büyüme faktörlerinin üretimi içinde önemlidir. Böylece, FSH spermatogenez için yeterli testosteron seviyeleri gibi Leydig hücrelerinin uygun sayıda gelişimini düzenlenmesinde başlıca rolü oynar. Erkeklerde erken ergenlik döneminde hem FSH hem de LH

düzeyleri artış gösterirken aynı zamanda Leydig hücreleri çoğalmaya ve plazma testosteronunda (Yetişkinlerde 6 ng/ml'dir) artış da görülmektedir (Şekil 5).



Şekil:5 Erkeklerde Yaşa Göre Salgılanan Testosteron Oranı(13)

1.5. Hipotalamus-Hipofiz-Testis Eksen Testiküler Hormonlar Ve İnhibin Tarafından Karşılıklı İnhibisyonu

Hipotalamus-hipofiz-testis ekseni sadece testosteron ve inhibin üretmez aynı zamanda bu maddelerden negatif geribildirimde alır. Erkeklerde testosteron ve estradiolün her ikisinin normal dolaşım seviyeleri, LH salgılanması üzerine baskılayıcı etkisi vardır. Testosteron muhtemelen hipotalamus tarafından GnRH pulsatil salınımını inhibe ederek LH'ın pulsatil salınımını baskılar. Testosteron ayrıca Hipofiz gonadotrop düzeyinde LH salınımı üzerinde negatif feedback etkiye sahip olduğu görülüyor.

FSH salgılanması üzerinde bir testis hormon geribildirimi vardır. Testislerde germinal elementlerin kaybı ile orantılı olarak plazma FSH konsantrasyonları artış FSH salınımı üzerinde bir testiküler madde tarafından negatif geri besleme olduğunu kanıtlar. FSH baskılayıcı madde olan İnhibin hem testis hem de Sertoli hücre kültürlerinde steroid olmayan bir maddedir. Böylece, FSH özellikle inhibin üretmek için sertoli hücrelerini uyarır ve inhibin FSH salgılamasını engeller. İnhibin ön hipofiz bezi seviyesinde etki ederek FSH salınımını azaltan (hipotalamus seviyesinde değil) bir etki gösterdiği görülüyor.

2. Hipotalamus-Hipofiz-Gonadal Eksen ve Kadın Menstrual Ritminin Kontrolü

2.1. Menstrual Döngüsü Hem Over Hem De Endometriyum Döngülerini İçerir

Menstrüel Döngü aslında Yumurtalık ve Rahim organlarında döngüsel değişiklikler içerir. Yumurtalık (ovulasyon) döngüsü; foliküler faz, luteal faz ve yumurtlama ile overlerden ayrılmayı içerir. Endometrial döngüsü; Menstrual (Adet), proliferatif (çoğalma) ve salgı aşamalarını içermektedir(34).

Menstrual döngüsü üreme yıllarda genellikle normal olmakla birlikte, Menstrual döngüsünün uzunluğu nöroendokrin fonksiyonlarındaki rahatsızlıklarından dolayı yüksek değişiklikler gösterebilir. Esas döngü 28 gün olmasına karşın hem perimenapozal dönemde hem de erken üreme yılı sırasında önemli değişmeler oluşur(14).

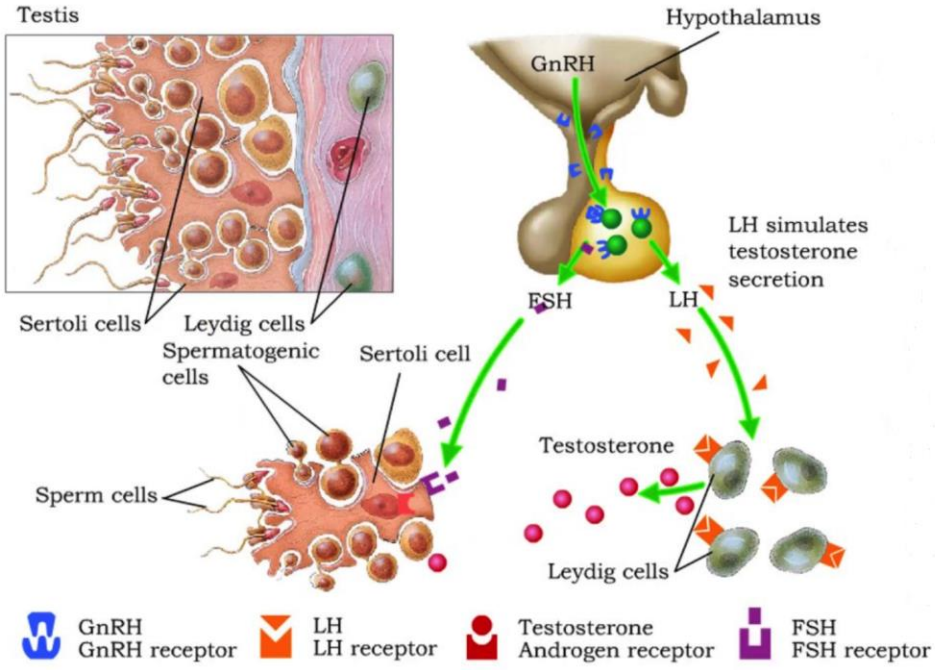
Ovulasyon döngüsünün ilk aşaması FSH'ın foliküler faz sırasında bir folikülün gelişmesini (yani follikülogenez) tamamlamasıdır. Foliküler faz mestürasyonun başlaması ile başlar ve ortalama 14 gün uzunluğundadır. Foliküler faz süresi döngüsünün en değişkenidir. follikülogenez sırasında östrojen, östradiol üretimi artmıştır. Foliküler granüloza hücreleri endometrium uyararak folikülün hızlı ve sürekli büyüme ve olgunlaşmasını sağlar. Bu dönem endometriyal döngünün proliferatif faz aşamasıdır. Overde östradiol salgısındaki hızlı bir artış sonunda ovulasyona neden olan LH'ta bir artış tetikler(11).

Ovulasyon döngüsünün ikinci aşaması ovulasyondan (yumurtayı bıraktıktan) sonra, folikülün kalan kısmı corpus luteum dönüştüğü luteal faz dönemidir. Luteal hücreler progesteron ve östrojen üreterek endometrial büyüme ve gelişmeyi uyarır. Bu periyod endometriyal döngünün salgı fazıdır.

Bilinmeyen nedenlerden dolayı korpus luteum progesteron ve östrojen üretimini durdurur ve bu yüzden mestrüal kanamaya neden olan endometriumun katastrofik dejenerasyonu ile sonuçlanır. Bu periyot endometriumun dönemin Menstrual faz dönemidir.

2.2. Hipotalamus-Hipofiz-Over Eksenin Menstrual Döngüyü Sürdürmesi

Hipotalamusta ki Nöronlar GnRH'ı sentezler depolar ve salgılar. Uzun portal damarlarla GnRH hormon ön hipofize taşınır ve gonadotrop hücrelerin yüzeyinde ki özgül reseptörlere bağlanır (Şekil 6). Sonuç olarak gonadotrop hücrelerden FSH ve LH hormonları sentezlenir ve salgılanır.



Şekil:6 GnRH Hormon Ön Hipofize Taşınır ve Gonadotrop Hücrelerin Yüzeyinde Reseptöre Bağlanması (15)

Bu trofik hormonlar olan FSH ve LH, seks steroidleri olan östrojenler ve progestin sentezlemek ve salgılamak için overleri uyarır. Overler ayrıca Aktivinler ve İnhibinler gibi peptitleride üretir. Overiyel steroid ve peptitler hem hipotalamusu hem de ön hipofizi negatif ve pozitif feedback mekanizmasıyla uyarırlar. Bu karmaşık etkileşim hormon dalgalanmaları aylık desen üretir gibi vücudun endokrin sistemleri arasında eşsizdir. Birincil endometrial olgunlaşmasını kontrol için östrojenler ve progestinlerin siklik salgılanması, menstruasyon hormon salgısının bu döngüsel değişiklikleri yansıtır(8,11).

Yukardaki şekil hipotalamus hipofiz ve over eksenini gösteriyor. Hipotalomusun Arkuat çekirdek ve Preoptik alanda küçük gövdeli nöronlar, bir dekapeptit olan GnRH salgılarlar ve bu GnRH ön hipofiz gonadotroplara ulaşır uzun portal venler yoluyla. Bu reseptörler fosfolipaz C (PLC) aktive eden G protein ailesinin Gαq çiftidir. G protein IP3/ Diaçilgliserol yolu ve Ca^{+2}'un hücre içi depolarından serbestleşmesini tetikler. Sonuçta gonadotroplardan hem LH hem de FSH sentezler ve serbest bırakırlar. LH Teka hücreleri üzerindeki reseptörlere bağlanırlar. G proteine bağlı olan adenilsiklazı uyarır. [cAMP]

artışın sonucu olarak çeşitli proteinlerin fosforile olmasına ve sonuç olarak PKA yolunu harekete geçirir. Böylece progestin ve androjen biyosentezinide içine alan birkaç protein transkripsiyonunu arttırır. Androjen granüloza hücrelerine girer ve androjeni östrojene dönüştürür. FSH granüloza hücrelerinin bazolateral membranındaki reseptörlerine bağlanır. PKA aktivitesini başlatarak böylece gen transkripsiyonu, ilgili enzimler (aromataz gibi) aktivin ve inhibin sentezini uyarır. Birkaç yol ile Hipotalamus-Hipofiz-Over Ekseni üzerinde negatif feedback oluşur. Aktivin ve İnhibin ile sadece ön hipofiz üzerinde negatif feedback kontrolü vardır. Östrojen ve Progestinler ile hem hipotalamus hem de ön hipofiz üzerinde pozitif ve negatif feedback mekanizması ile kontrol oluşur(14).

2.3. Hipotalamus Nöronların Ritmik Bir Tarzda GnRH Salgısı

Hipotalomusun Arkuat çekirdek ve Preoptik alanda küçük gövdeli nöronlar, GnRH salgılarlar. Onlar GnRH sonraki depolama ve salgı için kendi sinir terminallerine taşırlar. Bahsi geçen iki grup nöronların her biri GnRH salgılama ritminin çok farklı bir türünden sorumludurlar. GnRH nöronların aksonları median eminensi doğrudan (hipotalamusun aşırı bazal kısmı) yakın portal damarlarla sonlandırır. Bu damarlar GnRH ön hipofiz içinde ki gonadotrop hücrelere taşır.

GnRH kodlayan gen kromozom 9 üzerinde yer almaktadır. mRNA GnRH için 92 amino asitten oluşan bir preprohormonu kodlar. 23-amino asit sinyal peptit çıkarıldıktan sonra (N ucu sinyal peptit 1-23), nöron bir Prohormon (C ucu GnRH ilişkili pepetit) üretir. Bu prohormon yarılması dekapeptit (GnRH) verir (1-10 amino asit). 56 amino asit peptidi (14- 69 amino asit) GnRH-ilişkili peptid (GAP) olarak adlandırılır. Portal dolaşıma salgılanması için nöronlarda aksonlardan aşağıya hem GnRH hem de GAP taşınır. GAP'ın önemi bilinmiyor ancak prolaktin sekresyonunu inhibe edebilir.

GnRH 14 ila 16 gebelik haftasında hipotalamusta bulunur ve gonadotropin ihtiva eden hücrelerdir. Hipotalamik-hipofizer sistem fonksiyonel olarak gebeliğin 23. haftasında tamamlanır. GnRH nöronları sürekli ritmik dalgalarla GnRH salgılamazlar. GnRH saat başı bir kez portal damarlar içine patlama tarzında salınır bu yüzden ön hipofizdeki gonadotropları hızlı bir şekilde uyarır. GnRH'ın kandaki yarılanma önrü sadece 2 ila 4 dakika olduğu için GnRH saatlik patlamaları gonadotroplardaki LH ve FSH saatlik salgılanmasındaki dalgalanmalar Portal plazma GnRH düzeylerindeki salınımlar açıkça ayırt edilebilir. döngünün erken foliküler fazda gonadotroplar GnRH duyarlılığı çok fazla değildir. GnRH saatlik her patlamada LH'ta sadece küçük bir artış ortaya

çıkar. Follikül fazdan sonra ön hipofizdeki gonadotroplar portal kandaki GnRH'a çok duyarlı hale geldikleri zamandır ve GnRH saatlik her patlamada LH'ta çok büyük bir artış ortaya çıkartır.

GnRH saatlik patlamalarının kontrol mekanizmaları tam olarak bilinmemesine rağmen, GnRH için patlama üreten bölge medial bazal hipotalamusun arkuat çekirdeğinde yerleşmiş GnRH nöronlarının bulunduğu yer düşünülmektedir. Patlama üreten mekanizma döngüsel üreme fonksiyonu ve mestrual döngü düzenlenmesi için kontrollü anahtardır. GnRH salgılanmasının sıklığı ve böylece LH salınımı gonadların özel cevaplarını belirler. Patlama 60 ile 90 dakika arayla gonadotropların GnRH reseptörlerini düzenleyebildiğini ve böylece gonadotropinlerin (FSH ve LH) salgılanmasını uyardığı görülmektedir. Ancak, GnRH sürekli yönetimi gonadotropların GnRH reseptörlerinin aşağı düzenlemesine neden olur ve Gonadotropin salınımını ve gonadal fonksiyonların bastırılmasına neden olur(16).

GnRH saatlik salgılama ritimine ek olarak, arkuat çekirdek tarafından düzenlenmiştir, GnRH salgısının aylık bir ritim de oluşur (rhesus maymunlarında)(3). Orta döngüde GnRH salgılamasında büyük bir artış, kısmen ovulasyona yol açan LH yükselmesi sorumludur. GnRH'taki büyük dalgalanma üreten nöronların hangisi LH dalgalanmasına yol açar? Bunlar arkuat çekirdekte bulunan GnRH nöronları değil, Preoptik alanda olanlardır. Preoptik GnRH nöronları inhibitör γ-aminobütirik asit (GABA) reseptörlere sahipler oysa arkuat GnRH nöronlar inhibitör opioid reseptörleri vardır.

2.4. GnRH Anterior Hipofiz Gonadotrop Uyarır FSH ve LH Salgılanmasını ve FSH ve LH'ta Over Hücrelerini Uyararak Östrojen Ve Progestin Salgılanmasına Neden Olur.

GnRH, hipofiz ön gonadotop hücrelerinden hem FSH hemde LH salınımını uyarır. Hipofiz gonadotrop hücre zar yüzeyinde GnRH için yüksek afinite **reseptörleri** alanıdır. Bu reseptörler Fosfolipaz C (PLC) aktive eden G protein ailesinin Gαq çiftidir. G protein αq alt ünitesi; fosfolipaz C'yi aktifler bu da fosfotidil inozitol 4,5- bifosfat (PIP2), İnositol 1, 4, 5-trifosfatı (IP3) ve Diaçilgliserol hidrolizine yol açar. Hem IP3 hem de DAG ikinci habercilerdir. IP3 ile Ca^{+2} endoplazmik retikulumdan salınır ve Ca^{+2} artışına neden olur. Bu Ca^{+2} 'un sebep olur Ca^{+2} kanallarından hücre membranın içine sitoplâzmaya Hücre dışı Ca^{+2} bir akınla hücreiçine girmesine ve hücre içi Ca^{+2} artmasına neden olur. Bu Ca^{+2} ekzositozu tetikler ve gonada tropinlar hücre dışana salgılanır (Şekil 8).

IP3 yolunun yanı sıra GnRH ayrıca DAG yolu ile de hareket eder. Fosfolipaz C (PLC) tarafından oluşturulan DAG, Protein kinaz C'yi uyarır ve dolaylı bir şekilde gen transkripsiyonunu arttırır. Net etki gonadotropinlerin FSH ve LH sentezinde bir artış olmuştur. GnRH reseptörü içsel ve kısmen lizozomlar tarafından parçalanır. Bununla birlikte, GnRH reseptörü bir kısmı, hücre yüzeyine geri gönderilmeleridir. Hücre membranına GnRH reseptörü geri reseptör ikmal olarak adlandırılır ve reseptör aktivitesinin üst düzenlemesi ile ilişkilidir. Mekanizma tam olarak bilinmemektedir(17).

FSH ve LH; TSH ve hCG hormonlarını aynı ailesine üyesidirler. FSH ve LH farklı salgılanması ayrıca çeşitli diğer hormonal aracılar etkilenir (İnhibinler ve aktivinler gibi).

Ovülasyon öncesi, gonadotroplardan salgılanan LH ve FSH gelişmekte olan folikül hücrelere hareket ederler. folikülün Teka hücreleri, LH reseptörleri var buna karşılık Granüloza hücreleri hem LH hem de FSH reseptörlerine sahiptir. Östrojen üretimi için hem LH hem de FSH gereklidir. Çünkü ne teka hücreleri ne de granüloza hücreli gerekli tüm adımları taşımaz. Ovulasyon sonra LH korpus luteum hücreleri üzerinde hareket eder.

Hedef hücrelerin yüzeyi üzerinde çok özel reseptörlere LH ve FSH bağlanır. Hem LH hem de FSH, Gα protein reseptörüne bağlanarak adenilsiklaz (AC) yolunu ATP nin katalizi ile cAMP ye dönüşümünü aktive eder. Bu olay Protein kinaz A yolunu aktive eder. Sadece steroid biyosentezinide içeren enzim uyarılması değil aynı zamanda belirli protein sentezini ve artmış hücre bölünmesinide içerir. Sentezlenen proteinler arasında gonadotropinler tarafından düzenlenen düşük yoğunluklu lipoprotein (LDL) kolesterol alımı için gerekli reseptör ve östrojen sentezi için gerekli olan aromataz vardır(14,16).

2.5. Yumurtalıklar Da Peptid Hormonları Üretmek İnhibin; FSH Sekresyonunu İnhibe Eder, Ve Aktivin; FSH Sekresyonunu Aktive Eder.

İnhibin ve Aktivin gonadotrop tarafından FSH salgısını ayarlayan peptidlerdir. İnhibinler folikül granüloza hücreleri ve de diğer dokular (hipofiz, beyin, adrenal bezler böbrekler, kemik iliği, korpus luteum ve plesenta) tarafından üretilir.

FSH özellikle granüloza hücrelerinde inhibin üretimini uyarır. Ayrıca inhibin üretiminin düzenlenmesine katılan hormonlar ve büyüme uyarıcı dâhil olmak üzere bazı diğer faktörler vardır. Estradiol bir intraovaryan aracılığıyla inhibin üretimini uyarabilir. Ovulasyon öncesi ve sonrası granüloza hücreleri LH reseptörleri içerirler, LH ayrıca granüloza hücreleri tarafından inhibin üretimini

uyarır. İnhibinler biyolojik etkileri esas olarak üreme sistemi ile sınırlıdır. İnhibinler gonadotrop tarafından FSH üretimini baskılar(18).

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BÖLÜM VI

GİARDİAZİS

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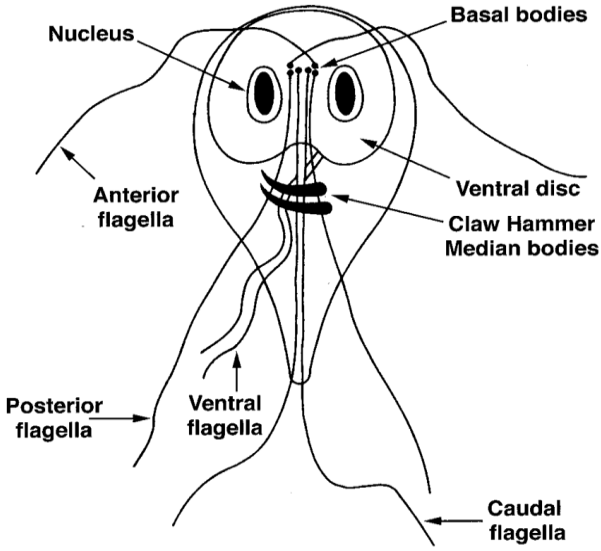
GİRİŞ

Giardia lamblia (syn. *G. duodenalis, G. intestinalis*), dünyada yaygın olarak görülen, fekal-oral yolla bulaşan bir protozoon parazittir (Adam, 2001). *Giardia lamblia*, insanlarda değişen şiddette ishale sebep olan flagellalı protozoon parazittir (Şekil1).



Şekil 1. *Giardia duodenalis'*in trofozoiti (WEB1)

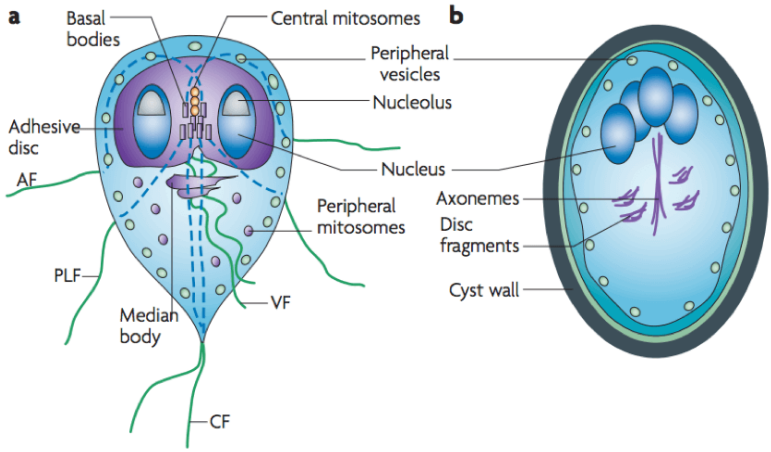
Giardia instestinalis'in Sınıflaması

Yaygın olarak kullanılan 1980 sınıflandırmasında Protozoa, yedi Phylumlu bir alt bölge olarak kabul edilir. Sarkomastigophora (Mastigophora ve Sarkodina içeren), Apikomplexa, Mikrospora, Miksozoa ve Siliofora önemli parazitler içerir. En son sınıflandırma, Protozoayı bazal ökaryotik krallık olarak belirler ve 13 Phylumu tanır. Eski Mastigophoraya ait kamçılılar şimdi dört Phylum, Metamonada, Parabasalia, Percolozoa ve Euglenozoa arasında dağılmıştır. Bu yeni anlayışlar sadece moleküler dizi çalışmalarından değil, genetik, yapısal ve biyokimyasal olmak üzere diğer birçok kanıtla bütünleştirilerek elde edilmiştir Bu nedenle, morfolojiye dayanan eski sistematik *Giardia*, Phylum Sarkomastigophora, Subphylum Mastigophora (= Flagellata), Zoomastigophora Sınıfına, Diplomonodida takımına ve Hexamitidae Familyasına aittir (Plutzer ve ark. 2010).

Giardia duodenalis; insan ve diğer memelilerde, *Giardia muris*; rodentlerde, *Giardia agilis*; amfibilerde, *Giardia ardea*; balıkçıl kuşlarda, *Giardia psittaci*; ötücü kuşlarda görülmektedir (Cacciò, 2005; Thompson, 2004; Xiao ve Fayer, 2008).

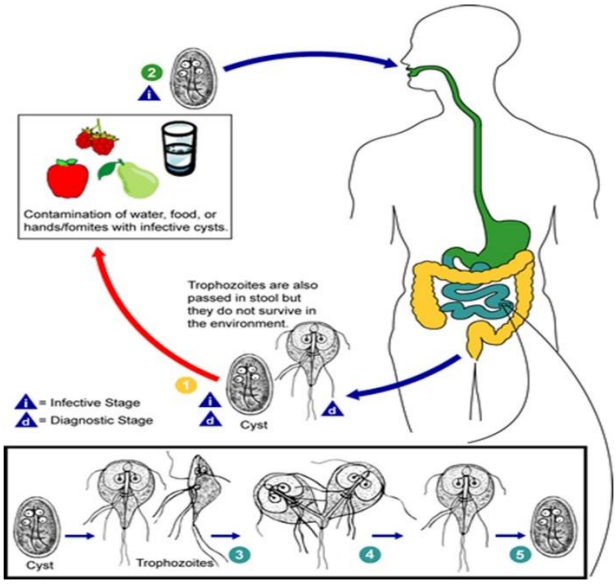
Bu parazit, A-H asemblajları olarak adlandırılan 8 genetik gruba ayrılır. A ve B asemblajlarının insanları enfekte ettiği bilinmektedir. (Monis ve ark. 2009), ancak son yıllardaki çalışmalarda asemblaj E'ye ait insan enfeksiyonları tanımlanmıştır (Zahidi ve ark. 2017). Asemblaj A1; İnsan, köpek, kedi, çiftlik hayvanları, rodentler, kunduz ve diğer vahşi memelilerde, Asemblaj A2; İnsanlar, Asemblaj A3; İnsanlar ve Hayvanlar, Asemblaj B; İnsan, köpek, diğer primatlar, şinşila, fare ve bazı vahşi memelilerde, Asemblaj C ve Asemblaj D; Köpek ve diğer Kaninlerde, Asemblaj E; Koyun, keçi, domuz, Sığır ve diğer çift tırnaklı hayvanlarda, Asemblaj F; Kediler, Asemblaj G; Rodentler, Asemblaj H; Fok balığı ve martıda bulunmaktadır (Weese ve Fulford, 2011; Caccio ve ark. 2008; Lalle ve ark. 2005; Lasek-Nesselquist, 2010).

Giardia spp.'nin iki formu vardır. Bunlar trofozoit ve kist formudur. Trofozoit piriformdur ve yaklaşık 20 µm'dir; önemi bağırsaktaki enfeksiyonla ilgilidir. Kist ovaldir ve 8 ila 18 µm arasındadır ve parazitin bulaşma şeklidir (Ryan ve ark. 2019). Her kist, iki tur bölünmenin ardından dört adet trofozoit oluştururur. Trofozoitler, konağın bağırsak yolunu, özellikle üst bağırsağı veya duodenumu kolonize edecek ve eşeysiz ikili fisyon yoluyla çoğalacaktır. Sonunda bazı trofozoitler, enfektif kistler olarak konakçılardan dış ortama döküldükleri alt bağırsağa doğru göç ederek sistemleşme sürecini başlatır (Fink ve Singer, 2017). İnsan *Giardia* enfeksiyonları (Giardiazis) küresel olarak bulunur ve prevalansı gelişmekte olan ülkelerde % 20-30 ile sanayileşmiş ülkelerde% 3-7 arasında değişmektedir (Roxstrom-Lindquist ve ark. 2006, Halliez ve Buret, 2013).



Şekil 2. *Giardia* spp.'nin trofozoit ve kist formu (WEB2)

Giardiosis'in bulaşması fekal oral yol ile olmaktadır. Kistlerle kontamine yiyecek ve suların ağız yoluyla alınmasıyla bulaştığı bilinmektedir (Şekil 3). Ayrıca cinsel yolla da bulaştığı da bildirilmektedir. *Giardia* kistlerinin bulaşması fekal oral yolla veya kontamine olmuş su ve yiyeceklerle gerçekleşmektedir (Roxstrom-Lindguist ve ark 2006; Üner ve Ertuğ 1997).



Şekil 3. *Giardia intestinalis*'in yaşam döngüsü (WEB3)

Ne yazık ki, insan kullanımı için koruyucu aşı mevcut değildir ve ilaç tedavisi seçeneklerinin farklı etkileri vardır (Ansell ve ark. 2015). *Giardia*'nın akut enfeksiyonları tipik olarak birkaç hafta içinde düzelse de, enfeksiyonlar kronik enfeksiyonlar olarak birkaç ay da sürebilir. Semptom olarak diyare, kramp, mide bulantısı ve bağırsak emilim bozukluğu ortaya çıkabilir, ancak asemptomatik enfeksiyonlar çok yaygın görünmektedir. Bazı raporlar, muhtemelen gıda antijenlerinin enfeksiyon sırasında bağırsak lümeninin dışına translokasyon yapabilmesi nedeniyle *Giardia* enfeksiyonları ile gıda duyarlılıkları ve alerjileri arasında bir ilişki olduğunu belirtmiştir (Di Prisco ve ark. 1998, Di Prisco ve ark. 1993). Ek olarak, *Giardia*'ya maruz kalma, insanlarda algılanan gıda intoleransı prevalansının artmasına neden olabilir, ancak bu reaksiyonun nedeni tanımlanmamıştır (Litleskare ve ark. 2015). Bunun nedeni tam olarak anlaşılamamıştır, ancak çapraz koruyucu immün yanıtların gelişimi, azalmış inflamatuar yanıt veya mikrobiyotanın değiştirilmiş bileşimi gibi çeşitli faktörlere bağlanabilir. Bununla birlikte, *Giardia*, 1 yaşından küçük çocukların dışkılarında bulunan en yaygın 4. patojen ve 1 ila 2 yaş arasındaki çocuklar arasında en yaygın ikinci patojen olarak bulunmuştur (Platts-Mills JA,ve ark.2015). *Giardia* enfeksiyonları ayrıca enfeksiyon sonrası sendromlara da yol açabilir. Son çalışmalar, irritabl bağırsak sendromunun (IBS) ve kronik yorgunluk sendromunun (CFS) bu parazitin ortadan kaldırılmasından yıllar sonra geliştiğini göstermiştir (Hanevik ve ark. 2017). Son zamanlarda, yenidoğan sıçan enfeksiyonu modeli kullanılarak enfeksiyon sonrası irritabl bağırsak sendromu (IBS) için potansiyel bir mekanizma incelenmiştir. Enfeksiyonlar, enfeksiyondan 50 gün sonra sıçanların jejunum ve rektumunda viseral aşırı duyarlılığa yol açtı ve villöz atrofi, kript hiperplazisi ve artmış immün hücre sayıları ile ilişkiliydi. Bu çalışma aynı zamanda kommensal bakterilerin epitel bariyeri boyunca translokasyonunu ve enfeksiyon sonrası irritabl bağırsak sendromu (IBS) ile de ilişkili olan nöronal c-fos'un ekspresyonunun arttığını bildirmiştir (Halliez ve ark. 2016).

Giardiazis tedavi yöntemleri

Giardiazis, özellikle çocuklarda yüksek prevalansı ve patojenitesi nedeniyle epidemiyolojik ve klinik önemi olan paraziter bir hastalık olmasına rağmen, bu enfeksiyon için en uygun tedaviye dair net bir kanıt yoktur (Addis ve ark. 1992). Kreş ve ilkokullar, tuvaletlerin yetersiz hijyeni Giardiazisin

bulaşabileceği potansiyel yerlerdir. Diğer risk gurupları ise kontamine suların içilmesi ile enfekte olabilecek kişilerdir. (Martínez-Gordillo ve ark. 2014). Günümüzde Giardiazisin tedavsinde en yaygın kullanılan ve test edilen ilaçlar Metronidazol, Albendazol ve Furazolidondur ancak bu ilaçların etkinliği ile ilgili yeterince çalışma yapılmamıştır. Bu nedenle Giardiazis tedavisine yeni yaklaşımlar klinik uygulamaya giriyor (Escobedo ve ark. 2007; Lalle, 2010). Günümüzde Metronidazol, Giardiazis tedavisinde yan etkilerinin az olması ve diğer tedavi yöntemlerine nazaran daha etkili olması bakımından dünya çapında en çok kullanılan ilaçtır (Adam, 2001, Gardner, 2001). Ayrıca, Giardiazis'in, tedavisinde, Kinakrin, 5-Nitroimidazoller (5Nİ), Tinidazol, Seknidazol, Ornidazol, Albendazol, Menbendazol, Nitazoksanid, Paromomisin, Furazolidon, Auranofin'in, Basitrasin çinko kullanılır (Addiss ve ark. 1992).

Giardiazisin tedavisinde güncel yaklaşımlar olarak bazı esansiyel yağlar laktobasilus bakterileri hünnap balı, fitokimyasal bileşikler gibi güncel yaklaşımlar mevcuttur (Vivancos ve ark. 2018).

Sonuç

Giardiazis çocuklarda başta olmak üzere bağışıklığı yetersiz bireylerde de sorun olmakta, özellikle yetersiz hijyen koşularının olduğu okullar fekal oral yolla bulaşım bakımımndan en riskli bölgelerdir. Giardiazis'in enfeksiyonu, bulaş yolları ve korunma yöntemleri hakkında sağlık personeline ve topluma, eğitim verilmelidir. Gıda sektöründe de çalışan kişilerin özellikle konu hakkında bilgilendirilmesi, gerekli görülürse portör muayenelerine Giardiazis dahil edilebilir. Enfekte kişilerin sadece kendileri değil yakın temasta olduğu kişiler ve aileleri de tedaviye dahil edilmelidir. Hastalığın bulaşmasını engellemek için hijyene daha fazla dikkat edilmeli. Giardiazis'in tedavisinde kullanılan ilaçların etkinliği konusunda daha fazla çalışma yapılmalı ve farklı tedavi yöntemlerinin kullanılması için sağlık personeline eğitim verilmeli ve casaretlendirilmelidir. Giardiazis gelecek vaat eden yeni tedaviler, yüksek etkinlikleri ve güvenlikleri nedeniyle fitokimyasallar, uçucu yağlar ve Laktobasiller ar-ge programlarına dahil edilmelidir. Giardiazis'in bulaşıcı olduğu ve halk sağlığına tehdit olabileceğinin farkında olunmalı ve önlem alınmalıdır.

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