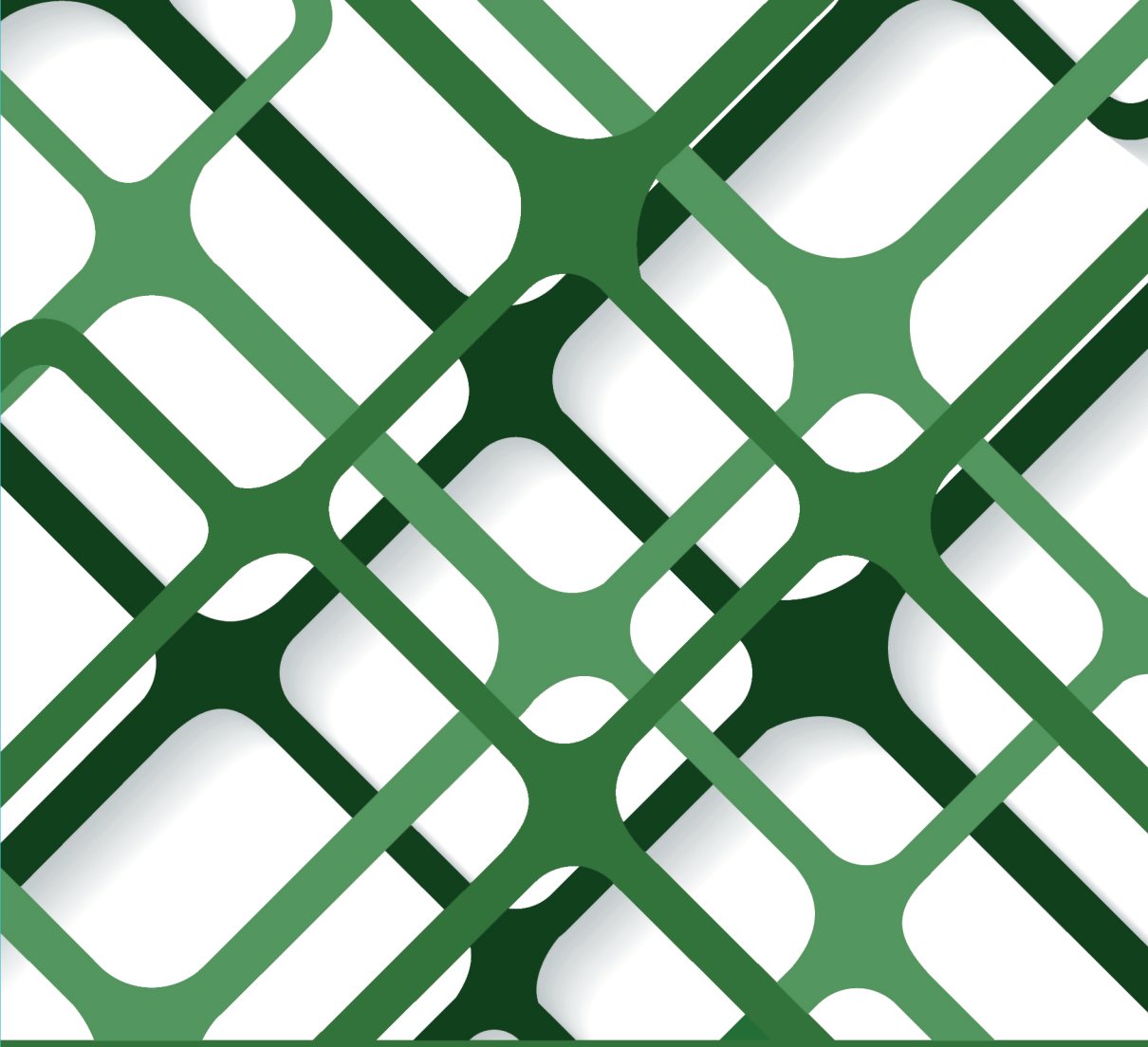

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SEPTEMBER/2021

EDITOR
PROF. DR. CEM EVEREKLİOĞLU

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Research & Reviews in Health Sciences - II

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gece kitaplığı

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Chapter 1

ANALYSIS OF L- CARNITINE IN FOOD SUPPLEMENTS

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INTRODUCTION

In our developing world, the term food, hunger relief problem, carbohydrate, protein, fat, vitamin and mineral etc. It is defined as a lack of nutrients. Apart from this, it is evaluated with its beneficial effects on mental and physical health. It reduces the risk of chronic diseases such as cancer, heart disease and obesity. An important part of this definition is the definition of 'nutrition for health'. In this approach, the physiological, biochemical or pathological effects of food are better evaluated. Many chronic diseases and communicable diseases related to nutrition and proper food consumption by 25-70% is possible to avoid these diseases. (Er, 2019).

Today, people; Due to factors such as the increasing awareness about healthy lifestyles, the high prominence of health in the media, and the relatively easy access to health services, they tend to take the decision-making authority more and more into their own hands every day (WHO, 2004).

Before consuming or purchasing food supplements, FAO and WHO standards, and in institutions where there are no criteria, national regulations should be taken into account. In Turkey, products are allowed to be sold with the approval of the Ministry of Agriculture and Rural Affairs (Atalay and Erge, 2018).

With the increase in demand in recent years, it is necessary to consult a specialist and analyze these products before using thousands of products on the market.

GENERAL SECTIONS

1. Definition of Food Supplements

In the Turkish Food Codex Complementary Foods Communiqué, food supplements include other substances of plant, vegetable and animal origin that have nutritional or physiological effects and are bioactive, such as vitamins, minerals, proteins, carbohydrates, fibres, fatty acids, amino acids. Substances and the like may be defined as products expressing daily intake by preparing concentrates or extracts in capsules, tablets, lozenges, sachets, disposable powder, liquid ampoules, dropper bottles and other similar liquid or powder forms, alone or in mixtures (Turkish Food Codex Supplementary Supplements Foods Communiqué, 2013) .

2.Types of Food Supplements

Food supplements; It is examined under three groups as vitamin-mineral, plant-based and animal-derived food supplements.

Herbal food supplements are obtained from various parts of plants such as roots, fruits, flowers, stems or leaves and have many elemental contents. There are 20,000 medicinal plants registered by WHO. Mostly ginseng, echinacea, soy, grape seed, green tea and their extracts are frequently used in the production of food supplements (Dolan et al. 2003, Garcia-Rico et al. 2007).

Food supplements of animal origin are obtained from seafood as well as bees and their products, and food supplements obtained from seafood contain many components such as omega-3 fatty acids, protein, enzymes, carotenoids. Seaweed, dried crustacean molluscs and fish oils are the most used products in the production of food supplements. It is known that fish oils are very rich in terms of EPA and DHA, which are polyunsaturated fatty acids (Covaci et al. 2007).

It is known that consuming food and food supplements containing these fatty acids, known as essential fatty acids, have important effects on human health. (Mol, 2008). Propolis, a bee product; It is used as a food supplement due to its antibacterial, antifungal and antioxidant effects. It is recognized as a registered drug in Romania and Germany (Moret et al. 2010).

3. Use of Food Supplements

The frequency of use of food supplements has been increasing in recent years. In a study conducted in 2001, 61.2% of 376 adults randomly selected used food supplements; on the advice of some of these patients from their doctor; it is reported that many of them use food supplements through their family, friends or the internet (Harnack et al., 2001).

In the study conducted by Durante et al. (2001) among 118 patients, 73% of women and 44% of men used vitamin, mineral or herbal supplements, 70% of patients under 50 years of age and 26% of patients over 50 years of age had no medical advice. Food supplements are found to be safer and more effective than the drugs recommended by doctors, especially in young patients. The use of food supplements has become widespread and popular, especially in recent years, thanks to sales strategies, advertisements and the internet. (Halsted, 2003).

In a study conducted in the USA, it is stated that half of adults use one or more food supplements. People who use food supplements usually; It is stated that they are elderly, have a low body mass index, are physically active, have low smoking rates, and have good education and socioeconomic status (Bailey et al., 2013; Dickinson et al., 2014).

4. Legal Regulations in Food Supplements

Contact and transmission of the contaminants of food supplements can occur during the process from the procurement and processing of the raw material to the packaging and storage of the product (Raman et al. 2004, Petroczi et al. 2011).

It is reported that the non-conformities identified regarding food supplements increased 6 times between 2004-2011 in the inspections carried out by the European Union's Rapid Alert System in Food and Feed (RASFF). Unauthorized or false label statements, contaminants such as heavy metals, PAHs, pesticides, unauthorized radiation applications, unauthorized use of additives to increase their effectiveness, and the presence of genetically modified organisms are among some of the identified nonconformities (Petroczi et al., 2011).

Fish oils obtained from fish caught in waters containing heavy metal pollution or from fish fed with feed contaminated by fish farms may also contain dioxins, polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs) and toxic metals. When the pollution risks related to all food supplements are examined, it is very important to carry out chemical controls of food supplements used to improve their health or support their nutrition, believing that they are natural and safe by the society. When examined in terms of element contents, it is necessary to determine the levels of elements such as As, Cd, Hg and Pb, which have high toxicity. They pose a risk to all living organisms because of their long-term toxic effects that accumulate in water and sediments (Castro-Gonzalez et al., 2008).

Consumption in food supplements has increased all over the world in recent years. However, studies on the elemental contents of these products are very few in our country. Studies have gained importance for the safe consumption of food supplements and for the determination of their elemental and organic content. Maximum limits for these elements have been determined by the European Union Directive EC 629/2008 for the protection of public health. The maximum limits for all food supplements are 3 mg/kg for Pb and 0.1 mg/kg for Hg. For cadmium, it has been determined as 3 mg/kg for food supplements produced from dried seaweed, seaweed product or dried crustacean molluscs or whose basic components are these, and 1 mg/kg for others. It has been stated that the boundaries have not been determined yet due to the lack of studies, but the studies are still continuing (Baer et al., 2011).

The title of food supplements was included for the first time in the Turkish Food Codex Contaminants Regulation published in Turkey in 2011, and the maximum limits were determined to be equivalent to the

values in the European Union Directive no EC 629/2008.

The Veterinary Services, Phytosanitary, Food and Feed Law No. 5996 entered into force on 13 June 2010, and the Regulation on the Import, Production, Processing and Placing of Supplementary Foods was published on 2 May 2013 and entered into force on 2 August 2013. Turkish Food Codex Communiqué on Supplementary Foods was published on 16 August 2013. Turkish Food Codex Regulation on Nutrition and Health Claims was published on January 26, 2017. When the relevant horizontal legislation published within the scope of the law is examined, the following list is reached:

Additives; • Flavorings and Food Ingredients with Flavoring Feature, Contaminants, Pesticide Residues, Hygiene, Veterinary Drugs Tolerance Levels, Packaging, Transport and Storage, Sampling and Analysis Methods.

As of June 24, 1995, when the Decree-Law on Production, Consumption and Inspection of Food No. 560 was published, a protocol was made between the Ministry of Agriculture and Forestry and the Ministry of Health in 2000 regarding these substances, all inspection and permit procedures of which were carried out by the Ministry of Agriculture and Forestry. The authorization has been given to the Ministry of Health for one year. In the process since 2002, the authority and responsibility rests with the Ministry of Agriculture and Forestry. The procedures and principles regarding the production, import, export and inspection of supplementary foods and baby foods are determined by the Ministry. ” With this provision, the authority of the Ministry of Agriculture and Forestry regarding food supplements continued (Tokay, 2017).

5.L-Carnitine

5.1. Definition and Structure of L-Carnitine

L-carnitine (3-hydroxy-4-N-trimethyl aminobutyric acid) is a water-soluble, thermostable (200°C) white-colored substance with a polar structure, which plays an important role in the conversion of nutrients entering our body into energy. Although L-carnitine is likened to vitamins due to the role it plays in the body, it is not included in the class of vitamins because it can be produced in low amounts in our body. Form D, which is not found in pure form in nature, can be produced by the organism as a result of chemical synthesis. L-carnitine has the ability to form internal salts and is capable of holding 3 significant levels of water due to its betaine-like structure. The molecular distance between the acid and basic groups of this molecule, which has a zwitterionic nature, is almost the same as that of lecithin. This chemical property of L-carnitine, along with some other structural similarities between lecithin and L-carnitine; explains why

acyl-L-carnitines can pass quickly across lipid membranes (Zeyner and Harmeyer 1999).

L-carnitine is also recognized as a natural amino acid that plays an important role in free fatty acid metabolism and glucose oxidation. However, there are some differences regarding the definition of L-carnitine. With a simple definition, L-carnitine can be explained as an amino acid and vitamin-like nutritive element associated with B group vitamins. It is an essential element that is mainly involved in the conversion of fatty acids into energy. In another definition; L-carnitine is a quaternary ammonium compound found in living metabolism as free L-carnitine and acyl-L-carnitines and obligatory for energy metabolism (Umutlu, 2012).

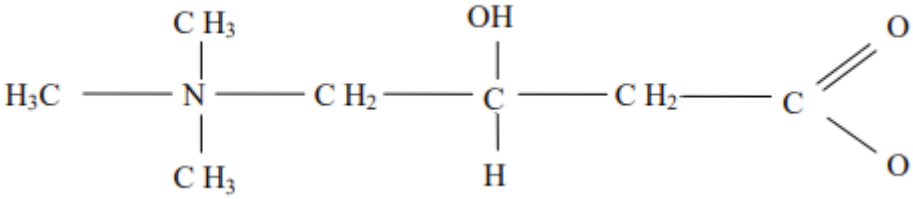

Figure 1. L-carnitine (L-3-hydroxy 4-N-trimethylamino butyrate) (Zeyner and Harmeyer, 1999)

5.2. History of L-Carnitine

L-carnitine was isolated from muscle tissue in 1905 and given the name carnis, which means meat in Latin. In 1927, it was determined that the hydroxyl group of L-carnitine was in the β-position, and the first comprehensive article was published in 1935. The first findings of the biological function of L-carnitine were found in 1948 on mealybug larvae demonstrated in a vitamin study. In the aforementioned study, it was observed that the development and metamorphism of these larvae in the adult insect was significantly impaired when they were kept in the presence of 9 types of B vitamins and in a salty environment. However, it was observed that the said development was significantly improved with the addition of liver preparations to the medium. Researchers named this active structure present in the liver extract as a different vitamin called vitamin BT. The letter T comes from the abbreviation of the name of the mealworm (Tenebrio molitor), while the letter B is used to show that this biological substance is another vitamin B. In 1952, this biological active substance, which was found to be an essential substance and needed in the growth environment of mealworms, was defined as a nutritive element and it was reported to be similar to L-carnitine. In 1958, L-carnitine increased the burning of fats in the mitochondria and played an important role

in the oxidation of fatty acids. In 1962, it was shown that the naturally occurring form of L-carnitine from two enantiomers is L-carnitine. Thus, the D and L classification of L-carnitine was made in 1962 for the first time. The naturally occurring L-form has been identified as physiological L-carnitine. In 1973, studies were carried out for the first time on the diagnosis of primary disorders caused by L-carnitine deficiency. It has become a commercially available product after the 1980s, and research on its effect continues today (Umutlu, 2012).

5.3. Sources of L-Carnitine

While plant food sources contain small amounts of L-carnitine, animal foods are important sources of L-carnitine. Vegetable and animal origin oils do not contain L-carnitine. In the human body, skeletal muscle, heart, liver, kidney and brain tissues can biosynthesize L-carnitine. However, there is a higher concentration of L-carnitine in skeletal and cardiac muscle. The richest sources of exogenous dietary L-carnitine can be listed as red meat, fish, chicken and dairy products. Fruits, vegetables and cereals have much less L-carnitine content compared to these products. In a recent study, the level of free L-carnitine in foods commonly consumed in many western countries was determined. In the study determined by radioisotopic measurement, the content of L-carnitine in pure and processed foods was revealed. The study clearly showed that meat products are the best source of L-carnitine. Other seafood and fish are generally partially lower in carnitine, while vegetables are found to contain very little carnitine. While the omnivorous regimen allowed intake of the recommended amount of L-carnitine, the vegetarian diet was clearly observed well below this amount. While L-carnitine is found only in the L-form in nature, the D-form is produced chemically, and the D-L form carries 50% of these two active substances. Cooking processes applied to raw foods can cause a partial loss of carnitine level according to the cooking method, such as some heat-sensitive vitamins. It is also stated that smoking and changing the storage conditions also affect the L-carnitine level (Tuna, 2014).

5.4. L-Carnitine Synthesis

L-carnitine is synthesized endogenously in the body, and its intake is provided exogenously with the diet. The organs where it is synthesized the most in the body are liver, kidney and brain. After L-carnitine is synthesized, it is transported through the bloodstream to tissues and organs that need this bioactive compound for energy production (Vaz et al., 2002).

These are mainly muscle and heart tissues. For the synthesis of L-carnitine, besides the essential amino acids lysine and methionine, vitamin C, iron (Fe2+), vitamin B6 and niacin in the structure of nicotinamide adenine dinucleotide (NAD) are needed. In addition, the

function of L-carnitine is impaired in the deficiency of vitamin B12, which is required for methionine synthesis. Therefore, L-carnitine is defined as a vitamin-like substance (Sharma et al., 2009).

The biosynthesis level of L-carnitine in the human body ranges from 0.16 mg/kg to 0.48 mg/kg body weight/day, as a result, 11-34 mg of L-carnitine per day can be synthesized in a 70 kg person (Rebouche, CJ, 2012).

5.5. Absorption, Transport and Excretion of L-Carnitine in the Body

L-carnitine is actively and passively absorbed in the intestines. Its transport capacity is low compared to glucose and amino acids. L-carnitine is thought to be esterified in the small intestine before being released into the blood. Approximately 54-87% of the oral dose is absorbed. Dietary L-carnitine is absorbed from the duodenum and jejunum by active transport. The small intestine cells acetylate the L-carnitine that comes into the intestinal lumen and gives it to the blood as both free and ester. In the blood serum, 80% is free and 20% is ester (Umutlu, 2012).

Carnitine reabsorption may decrease according to various physiological factors such as adiposity, and it is in close relationship with enzyme activities such as carnitine acetyltransferase, CPT1A and CPT2. The intestinal absorption of carnitine, its reabsorption in the kidneys, and its distribution to tissues are regulated by the organic cation transporter OCTN2. OCTN2 (Na+ dependent, high affinity transporter) is the most important physiologically important carnitine transporter. L-carnitine and acyl carnitines are transported by mitochondrial OCTN1 (organic cation transporter 1), plasmalemmal OCTN2 and peroxisomal OCTN3. OCTN2 is very important in keeping the amount of carnitine in the serum at normal levels. it is also responsible for carnitine reabsorption in the kidneys (Yavuz, 2013).

In the kidneys, more than 90% of the part that passes into the glomerular filtrate undergoes tubular reabsorption. In addition, L-carnitine is not completely metabolized after being used in the body and is excreted in milk and urine. A very small part of it is excreted in the faeces. The amount of reabsorption in the kidney tubules is regulated depending on the amount of L-carnitine taken with food, the needs of the organism and the plasma carnitine concentration (Umutlu, 2012).

5.6 .L-Carnitine Deficiency

Carnitine deficiency was first demonstrated in skeletal muscle in humans as lipid-accumulating myopathy. It can happen in two ways:

1) Primary carnitine deficiency: It is a rare autosomal recessive disorder of fatty acid oxidation. It has been defined by the low level of L-carnitine in plasma red blood cells and tissues. For this reason, as a result of insufficient use of fatty acids in energy production, energy deficit occurs and metabolic balance is disturbed. An increase in free fatty acids and triglyceride levels, a decrease in ketogenesis, and fat infiltration in the liver and muscles occur. In this case, carnitine supplementation is a life-saving treatment.

2) Secondary carnitine deficiency: There are genetic and acquired forms. In secondary carnitine deficiency, carnitine stores in the tissues are decreased. Long-term antiepileptic treatments may also cause secondary carnitine deficiency. Secondary carnitine deficiency has been detected, especially in clinically diagnosed metabolic diseases (such as diabetes, acidosis).

In carnitine deficiency;

• Fatty acids cannot be used in energy production, as a result, energy needs of especially heart and skeletal muscles are revealed.

• An increase is observed in free fatty acids and triglycerides.

• Fatty acids accumulate in the cytoplasm.

• Fat occurs in the muscles.

• Metabolic disorders occur due to toxic effect.

• Hypoglycemia occurs due to excessive use of carbohydrates.

• As a result of the deterioration of carbohydrate metabolism, lactic acid accumulation occurs and fatigue and pain occur in the body due to this accumulation.

• Growth and development retardation and recurrent infections occur in children.

• Free Co-A deficiency required for β-oxidation occurs (Köklü, 2013).

5.7 Effects of L-Carnitine

5.7.1. Effect of L-Carnitine on Myocardial Functions

Carnitine is a transporter for β-oxidation of activated fatty acids across the mitochondrial membrane. In the absence of carnitine, β-oxidation is affected. After β-oxidation is adversely affected, fats cannot be used, accumulate and eventually organ dysfunction occurs. In some special conditions, such as myocardial ischemia, cardiac hypertrophy and hemodialysis, a decrease in secondary myocardial carnitine levels has been detected. When the heart cannot synthesize carnitine, the post-ischemic

myocardium cannot maintain normal fatty acid metabolism without adequate plasma carnitine levels. It can be said that blood cardioplegia supplemented with carnitine affects myocardial endothelial functions indirectly by entering into energy metabolism. Carnitine stimulates the production of ATP in the mitochondria and contributes to the protection of endothelial functions and contractile functions by helping the myocardium to meet its energy requirement. Therefore, carnitine gains importance in patients with impaired myocardial functions (Furat et al., 2006).

5.7.2. L-carnitine in the Sports Performance Effect

In light and moderate intensity exercises, the energy requirement is provided from free fatty acids. The highest oxidation of fatty acids occurs in exercises performed up to 50-60% of maximal oxygen consumption. Theoretically, carnitine increases the use of fatty acids as an energy source during exercise and ensures the sparing use of muscle glycogen. Carnitine acts as a necessary mediator in the transport of long-chain fatty acids to the mitochondrial matrix. Due to this feature, it helps to produce more energy from fats and economical use of muscle glycogen stores by taking a role in increasing the oxidation of fatty acids. Carnitine intake also reduces lactic acid production. is indicated. In the studies, it was determined that it slightly increased the maximum oxygen consumption, and it was suggested that this increase could be a determinant in the results of important encounters. Jeff et al. examined the effect of total serum carnitine and muscle pain by applying the squat exercise protocol to the study participants by giving 2 g of carnitine per day for 3 weeks. They stated that carnitine has an effect on muscle pain and recovery after exercise (Yılmaz and İbiş, 2006).

5.7.3. The Effect of L-Carnitine on Broiler Performance and Visceral Weights

Although L-carnitine is synthesized endogenously, it is recommended to be given to animals with ration. This is due to the fact that plant feed materials contain much lower L-carnitine than animal feeds. In studies using experimental animals. It has been found that adding L-carnitine to feeds reduces fat accumulation in the body, especially in grain-based animals. It is also reported that L-carnitine inhibits lipogenesis by providing fat burning. In its deficiency, it has been stated that fat accumulation in the form of fat droplets in the muscles (myolipidosis), muscle weakness, fatigue in the heart muscle and muscle pain are observed. It has been reported that the need for carnitine has increased. Different results have been obtained from studies conducted to determine the effects of L-carnitine supplementation in broiler diets on the fattening performance of broilers. Contrary to studies reporting that adding L-carnitine to balanced diets increases body weight gain and decreases abdominal fat, there are also reports that L-carnitine

does not affect body weight, feed conversion and abdominal fat ratio. In some of the studies examining the effect of L-carnitine supplementation on diets containing different levels of energy on broiler performance. It has been reported that L-carnitine increases the body weight gain and feed conversion ratio, while it decreases the abdominal fat ratio, while in some studies it does not affect the body weight gain, feed conversion ratio and abdominal fat ratio. Rabie et al. In their study where they added L-carnitine to diets containing the same energy levels but 18%, 20% and 22% crude protein, respectively, regardless of crude protein levels. It was determined that L-carnitine supplementation significantly improved the body weight gain and feed conversion ratio of broilers and reduced abdominal fat weight. (Gezen et al., 2003)

5.7.4. Effect of L- Carnitine on Lipid Metabolism

It has been reported that L-carnitine plays a key role in lipid metabolism and has a positive effect on plasma lipids and lipoprotein, which are cardiovascular risk factors. Studies have shown that L-carnitine reduces serum cholesterol and triglyceride levels, and it has been interpreted that this may be due to the decrease in triglyceride and VLDL synthesis, as well as the increase in oxidation of fatty acids. Count et al. They found that plasma total cholesterol concentration decreased proportionally with the increase in L-carnitine level. In the study investigating the effect of L-carnitine on sportive performance, it was determined that L-carnitine caused a statistically significant decrease in cholesterol levels, but no significant result was observed in triglyceride levels.

5.7.5. Antioxidant Effect of L-Carnitine

Fe++'s increase the synthesis of free oxygen radicals in the organism. L-carnitine, on the other hand, reduces lipid peroxidation with the compounds it creates by binding to Fe++. L-Carnitine chelates the iron required for the formation of the hydroxyl radical and exerts an antioxidant effect by suppressing this radical production in the Fenton reaction. In the study of Kalaiselvi and Panneerselavam, it was stated that L-carnitine exerts an antioxidant effect by contributing to the regulation of the activities of enzymes that help to balance the amount of nitric oxide, regulate cellular respiration, and defend against oxidative damage. L-carnitine provides the transport and transformation of long-chain fatty acids into the mitochondrial matrix, and with the inclusion of acetyl CoA in the tricarboxylic acid circle, a significant part of the oxygen required for this reaction is removed from the environment. ATP is formed by oxidative phosphorylation in the electron transport chain, and at the end of this cycle, oxygen is converted to H2O, reducing the free oxygen concentration and partially preventing oxygen radical damage. It also shows antioxidant

properties by catching and binding free radicals. L-carnitine also has an antioxidative effect on the gastric mucosa. By providing membrane stabilization, L-carnitine can prevent membrane damage caused by free radicals and also prevent mitochondrial defects. Thus, it can save energy by minimizing the leakage from radicals. It has a suppressive effect on the formation of reactive oxygen species that occur as a result of the xanthine/xanthine oxidase system. Moreover, in recent studies, L-carnitine has been found to be effective as a mediator for apoptosis. It is also thought that it may be effective by preventing a widespread damage to the oxygen-damaged cell (Karaçetin, 2020).

5.7. 6. Anti-Inflammatory Effect of L- Carnitine

In many studies on the anti-inflammatory mechanism of action, it has been determined that there is a close relationship between oxidative stress, antioxidant mechanisms and inflammation. Measurement of free oxygen radicals in the pathogenesis of many diseases determines the severity of tissue damage. While oxidants play a role in wound healing at every stage of regeneration, it has been determined that the amount of oxygen radicals is highest in the inflammatory phase. Therefore, in the light of these studies, considering the relationship between antioxidant and inflammation; We can conclude that L-carnitine has a positive effect on the response of the organism against inflammation, either directly or by inhibiting free oxygen radicals, through the above-mentioned antioxidant properties (Karaçetin, 2020).

5.7.7. Effect of L-Carnitine on Fertility

Within the human body; In the male reproductive system, L-carnitine is found free and highest in epididymal fluid. L-carnitine has an important role in the sperm cell mechanism. Its free and acetylated form directly affects sperm metabolism and maturation process. It was determined by Matalliotakis et al. (2000) that carnitine is concentrated in the epididymis, conversion of carnitine to acyl carnitine has an important place in sperm metabolism, and acyl carnitine is found at much higher rates than carnitine in normal spermatozoa. Recently, it has been reported in some publications that carnitine and its acetylated form may be a treatment option that can be used in erectile dysfunction in men. It has also been reported that carnitine supplementation increases sperm quality and quantity in patients with asthenozoospermia. Seminal carnitine concentration; In addition to sperm count, it is positively related to sperm motility and morphology. In infertile patients, the low level of seminal plasma total carnitine and the detection of improvements in reproductive functions with carnitine supplementation support the hypotheses in this regard. After L-carnitine applications in infertile men, increases in sperm concentration and motility, and sperm amount were observed (Yavuz, 2013).

5.7.8. Other Effects of L-Carnitine

Catherine M. Crill et al. investigated the total carnitine and developmental status of premature infants by feeding with carnitine supplement. They reached the desired reference plasma carnitine level by giving 2 mg/kg/day carnitine supplementation with enteral nutrition for 4 weeks. As a result, it was concluded that early carnitine supplementation in premature newborns has positive effects for restoring birth weight and improving periodic breathing in premature newborns (Crill et al., 2006).

Aliye Özenoğlu et al. in their study, it is explained that people with bipolar disorder form more long-chain fatty acids as a result of weight gain due to the use of valproic acid, increased food intake, decreased thermogenesis and competitive binding to serum albumin. In the study, L-carnitine (1 g/day) was added to the treatment, considering that carnitine deficiency might be due to the fact that the fat rate detected in the body analysis of the patient was much higher than expected, and the patient lost 13.3% of his weight compared to the baseline, and his body fat decreased by 7.7% (Özenoğlu et al., 2009).

REVIEW OF ANALYTICAL METHODS

Vendula Prokoratova et al. Three capillary electrophoresis modes are tested for the determination of l-carnitine in food supplements. Compared with HPLC, CE analysis was faster from HPLC solvent consumes less and has lower overall operating costs. For capillary electrophoresis and capillary isotachophoresis using indirect photometric sensing a kinin buffer has a very simple method of sample preparation and the two other complex also allows derivatization reactions directly without the use of L-carnitine to be identified. Direct UV-sensing capillary zone electrophoresis can be used for carnitine analysis after derivatization (Prokoratova et al., 2005).

Andrea C. Isaguirre et al. developed an online surfactant-mediated extraction method using the bile salt NaTDC as the coacervate agent with fluorimetric detection for the determination of L-carnitine in dietary supplements. The proposed method reported for the first time the use of the natural origin surfactant, the bile salt taurodeoxycholate, as a clouding phenomenon promoter. Automation of the methodology was achieved using a flow injection analysis scheme, achieving a sample throughput of 30 samples per hour (not taking into account the time required for L-carnitine derivation). The developed method resulted in simple, fast, reliable and economical results and showed low detection limits compatible with the concentration of this compound in complex matrix as pharmaceutical formulations. In addition, the proposed methodology has been determined

to be environmentally friendly as well as representing a suitable alternative to traditional carnitine analysis methods (Isaguirre et al., 2016).

Although numerous reports have been published on analytical methods for the determination of L-carnitine in biological samples, food supplements and pharmaceutical formulations, there are few reports on the determination of impurities in L-carnitine. 3-Carboxy-N, N, N-trimethylprop-2-en-1-aminium (crotonoylbetaine) was detected in pharmaceutical formulations of L-carnitine by HPLC-UV ion pairs with content <1%. CE–MS/MS was used for the determination of D-carnitine in pharmaceutical formulations of L-carnitine with 10 ng mL LOD. CE with UV detector was used with 0.5–4.4 μg mL_1 LOD for the determination of carnitine in food supplements. A chiral-achiral tandem column with a UV detector and HPLC separations with 640 ng mL_1 LOD were also used. Although the method established in the study has advantages in terms of detection limits and analytical speed, it is concluded that it is suitable for the identification and measurement of impurities in various L-carnitine samples during actual production. (Wang and Xie, 2017).

Aikaterini Kakou et al. A new method was developed for the determination of l-carnitine in food supplement formulations and validated using ion pair chromatography with indirect conductivity detection. L-carnitine, an agent administered as a dietary supplement for carnitine deficiency and various chronic diseases, was determined using TFA nonpolar (C18) aqueous octane sulfonate, indirect conductivity detection and an analytical column by ion-pair chromatography. The proposed method has been applied for the determination of carnitine in oral solutions and capsules. There was no interaction required from the excipient and one pretreatment step is appropriate dilutions with mobile phase. Recovery of the added sample in the range of 97.7% to 99.7%, accuracy (RSD%, n = 3) were between 0.01-2.1%. When it comes to the safety of the method, special care is required for the preparation and handling of the mobile phase as TFA is a strong acid and corrosive reagent. As deduced from the literature, this is the first study of a conductivity-measured LC method for l-carnitine and can be applied to the assay of other substances with a similar (carboxylate inert salt) structure. (Kakou et al., 2005).

In their research, Monika Dabrowska and Małgorzata Starek concluded that the most popular techniques for carnitine separation are based on chromatography, capillary electrophoresis, mass spectrometry, and more recently electrochemistry, which offer some advantages such as simplicity, low cost and high efficiency. Although spectrophotometric methods are quite common, it has been determined that the results obtained (especially for the diagnosis of metabolic disorders) are not precise enough. Despite the wide availability of equipment, their use is limited, especially

with a complex matrix. Prior chromatographic analysis L-carnitine and its esters require a derivatization to reduce their polar properties and to ensure proper chromatographic separation and detection. Therefore, chromatographic techniques are difficult to use and require samples to be pre-treated. When ESI – MS is applied, component separation is not mandatory with this method, which involves time-consuming derivation. As a multi-component methodology, MS/MS replaces traditional testing as more sensitive, specific, reliable and comprehensive. (Dabrowska and Starek, 2013).

Worapan Pormsila et al. A CE method with capacitively coupled non-contact conductivity detection was developed and tested for the determination of the amount of carnitine in food supplements. When conductivity detection is used, sample preparation is minimal as no chemical or enzymatic conversion of the non-UV absorbing compound to the analyte is required. Optimized work buffer with 0.05% Tween-20 pH 2.6 500 mmol / L acetic acid solution was used. Analysis time was about 4 min, and the correlation coefficient of 0.9996 with 5-500 mmol / L in the concentration range of linearity was obtained. LOD (3 signals/noise) was determined as 2.6 mmol/L. Intra-day and inter-day variability of both the transit time and less than 10% for peak area method and the results show a good precision (Pormsila et al., 2010).

CONCLUSION

Food supplements are products of plant and animal origin, which are used as supplements in addition to basic nutritional elements by the society recently. These products are known to be used in cases where normal nutrition is insufficient or for support purposes. The recommendation of food supplements, which have increased in popularity with social media in recent years, by authorized and unauthorized persons, causes the use of these products to increase. However, it should not be forgotten that the unnecessary use of these products can also cause negative effects on human health.

The misconception that food supplements are natural, safe and have no side effects pushes consumers to these products more. Therefore, ensuring the quality of these products and determining their contents are very important for human health. In our country and in the world, the regulations regarding this issue are being investigated to the extent determined by the necessary institutions and individuals.

L-carnitine, one of the food supplements we mentioned, is found in many plant and animal food sources. L-carnitine, which causes many metabolic disorders in its deficiency, is also known to have many positive effects on human health. It also has many positive effects such as its use in

disorders of myocardial functions, increase in sports performance, increase in weight gain, increase in HDL level in lipid metabolism and decrease in LDL level, antioxidant and anti-inflammatory effects, increase in sperm concentration, motility and fertility, depending on the amount.

Finally, in our study, the analyzes of l-carnitine in food supplements are mentioned. Capillary electrophoresis, which is one of the analysis methods, has been found to be cheaper and faster than HPLC, which is one of the other methods. By developing an extraction method using NaTDC as a coacervate agent with fluorometric detection, the method used for the determination of L-carnitine was determined to be both suitable for the traditional carnitine analysis method and environmentally friendly. In the method with UV detector, it is a suitable method for identifying and measuring the impurities of products containing L-carnitine, as it has the advantages of detection limits and analytical speed. Indirect conductivity determination and ion pair chromatography are also among the methods used for the determination of L-carnitine.

In conclusion, it is concluded that the most popular techniques for L-carnitine analysis are based on high performance liquid chromatography, capillary electrophoresis, mass spectrometry and more recently electrochemistry, as they offer advantages such as simplicity, low cost and high efficiency.In addition to the analysis methods, there is a need for more economical, reliable, high-efficiency new analysis methods with today's technology. In addition to the analysis methods, there is a need for more economical, reliable, high-efficiency new analysis methods with today's technology.

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Chapter 2

THE USE OF *NIGELLA SATIVA* IN LIVESTOCK

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Introduction

Nigella sativa Linn is a yearly spice that has a place with the family Ranunculaceae and is most widely explored for its remedial purposes (Aggarwal et al., 2008; Kamal et al., 2010). It is a local plant from the Mediterranean territory and it is likewise discovered filling in some different districts on the planet, for example, in Saudi Arabia, Syria, Middle Eastern, North Africa and furthermore has been broadly developed all through South Europe, Asia, Turkey, Pakistan, and India utilized for culinary and clinical purposes by the Romans (Randhawa and Al-Ghamdi, 2002; Rifat-uz-Zaman and Khan, 2004; Kamal et al., 2010; Rifqi, 2012). There are a few names credited towards *Nigella sativa* in different nations of the world. In Arabic nations they are called as Al-habbah, Al-Sawda, Habbet el-Baraka and Kamounaswad. In Iran, it is known as Shonaiz, dark cumin in America, Ajenue in Europe, Kalonji in India and Pakistan, and Schwarz kummel in Germany (Zahoor et al., 2004). In Islamic instructing, the plant is of incredible importance because of its wide scope of employments especially for mending purposes. Prophet Muhammad (PBUH) has referenced *Nigella sativa* explicitly that the dark seeds of the plant which can recuperate a wide range of infections aside from death (Ilaiyaraja and Khanum, 2010; Hajra, 2011). In the book "Cannon of Medicine", Avicenna has expressed that Nigella helps recuperation from weakness and misery just as animates energy in the body. It is additionally one of the common medications utilized by Prophet Muhammad, and is called Tibb-e-Nabavi. In the Ayurvedic medication, the utilization of its seed was coordinated as energizer, diuretic, anthelmintic, discontinuous fever, jaundice, dyspepsia, heaps, skin illnesses and numerous others. As indicated by Unani Tibb medication, *Nigella sativa* is seen as a medication that could recuperate various sicknesses (Paarakh, 2010; Singh, 2011). The employments of natural enhancements have been expanded significantly in the course of recent many years since this sort of restorative plants is locally accessible and modest (Amin and Nagy, 2009). These days utilization of therapeutic spices is the best answer for fix an illness when contrasted with other treatment and unfortunate items in light of its regular properties, which are less poisonous (Al-Attar and Wafa'a, 2010). Home grown prescriptions got from plant separates were likewise progressively used to treat a wide assortment of clinical infections (Lee et al., 2004).

Morphology

Nigella sativa is a little spice with length around 45 cm; having slim leaves pinnatisect whose length 4cm cut into a direct section. It is a spice with pale blossoms, blue peduncles, and dark trigonous seeds. It is portrayed by the firmness of its stem, which has grayish green leaves bearing a terminal grayish blue bloom that has toothed seed vessels with

packed three-cornered seeds. They have scent, which is like that of nutmegs and a taste that is hot and sharp. Its blossoms, with 5-10 petals, are blue in shading. Other morphological highlights of *Nigella sativa* are huge and expanded case that is made out of 3-7 joined follicles, the organic product which contains countless seeds and has harsh and impactful tastes and a smell that is just about as weak as that of strawberry (Varghese, 1996; Randhawa and Al-Ghamdi, 2002; Dwivedi, 2003; Rifat-uz-Zaman and Khan, 2004). Kinds of *Nigella sativa* Linn: is found in Iraq and particularly developed around there (Chakravarty, 1976). *Nigella arnvensis*: dispersed in Iraq especially in the north of Iraq and this sort is portrayed by little seeds and leaves as contrasted and *N. sativa* Linn. (Chakravarty, 1976). *Nigella orientales*: circulated in Syria and has pale greenish leaves and blossoms are yellowish, ruddy touched (Sayed, 1980). *Nigella damascenna*: appropriated in Syria and it has huge size and greenish shading leaves (Ansari et al., 1988).

Nutritive composition of *Nigella sativa* seeds

The seeds of *Nigella sativa* showed lavishness and variety in its substance sythesis. Starches, proteins, amino acids, unstable and fixed oils are contained in the seeds (Rajsekhar and Kuldeep, 2011). Thymoquinone end up being the fundamental dynamic constituent of the unstable oil of the dark seed (Gali-Muhtasib et al., 2006). The carbonyl polymer of thymoquinone have therapeutic properties that incorporate enemy of microbial, antitumor, hostile to viral, calming, decrease in glucose, muscle unwinding and against oxidation (Janfaza and Janfaza, 2012). *Nigella sativa* is additionally a decent hotspot for high carbs, fats and protein.

Anti-microbial and anti-parasitic action

Suresh et al., (2010) have completed a few examinations on *Nigella sativa* antibacterial properties. The fundamental examinations on the impacts of in vitro antimicrobial on various phases of developing of *Nigella sativa* removes have shown not many essential outcomes with respect to its enemy of microbial impact (Al-Khalaf and Ramadan, 2013). Islam et al., (2013), demonstrated that contrasting and seed separate; the methanol concentrates of *Nigella sativa* has incredible controlling impact on Gram-negative and Gram-positive clinical bacterial strains during germination stages. It can introduce a greatest movement from 5th to 11th day of germination the mixtures of separated saponin from *Nigella sativa* (seeds) delivered critical impact of hindrance on the development of certain microscopic organisms. They include: *Staphylococcus aureus, Bacillus subtilis, Salmonella typhi, Klebsiella pneumoniae, Proteus vulgaris* and *Pseudomonas aeruginosa* (Mohammed, 2009). *Nigella sativa* oil has been proved to have functioning antibacterial properties wherein it works

viably on injuries contaminated by microorganism that was segregated. The oil from *Nigella sativa* extricate has great hindrance consequences for *S. aureus* and *Streptococcus* spp. (Khuder, 2012). The investigation likewise showed that thymoquinone and thymohydroquinones have antibacterial action, which could be potentiated by anti-toxins particularly in the event of *S. aureus* contamination (Halawani, 2009). *Nigella sativa* concentrates and its constituents were generally concentrated because of their antimicrobial effect on a wide scope of parasitic life forms, bacterial, and contagious. Notwithstanding, *Nigella sativa* seeds have been appeared to have antiparasitic activity in which the schistosomicidal properties of *Nigella sativa* seeds against *Schistosoma mansoni* (in vitro), showed that *Nigella sativa* has a solid biocidal impact against all phases of the parasite and uncovered an inhibitory impact on egg-laying of grown-up female worms (Gilani et al., 2004; Mohamed et al., 2005). Methanol concentrate of *Nigella sativa* seeds shows hostile to plaque activity through successfully hindering *Streptococcus mutans* and, hence, staying away from dental caries (Namba et al., 1985). Examination of the plant seeds by electron turn reverberation (ESR), has uncovered the presence of a high substance of thymohydroquinones which showed action against *Bacillus subtilis, Klebsiella pneumonia, Mycobacterium phlei*, and methicillin touchy and safe *S. aureus*. Likewise, the fluid concentrate has appeared to display an inhibitory impact against candidiasis brought about by *Candida albicans. Nigella sativa* additionally has a huge adjuvant impact on the reaction of *Brucella melitensis* immunization in rodents (Hailat et al., 1998; Mouhajir et al., 1999; Khan et al., 2003). The alcoholic concentrate of *Nigella sativa* has suppressive impact on practicality of *Ecchinococcus granulosus protoscoleces* from sheep starting point in vitro and moreover, the alcoholic concentrate was found to actuate a similar remedial impact as metronidazole in the treatment of trial giardiasis (Sawsan and Somia, 1992; Al-Roubaee, 2006).

Effect on Immune System

By utilizing the unstable oil in the treatment of typhoid-antigen-tested rodent, it showed an immunosuppressant activity as proven by the critical diminished in the immunizer titer and the splenocytes and neutrophils check (El-Tahir and Bakeet, 2006). The alluring impacts of *Nigella sativa* have been tried generally on safe frameworks (Al-Ghamdi, 2001; Al-Naggar, Gómez-Serranillos, Carretero, and Villar, 2003; Alsaif, 2008). *Nigella sativa*, oil or seeds, are taken by individuals as a solution for the prophylaxis of cold and asthma. As indicated by El-Kadi and Kandil (1986), *Nigella sativa* affects the insusceptible framework and it has resistant potentiating attributes in vitro in human T-cells. In a comparative report, Haq et al. (1995) reasoned that T-lymphocyte could be initiated by

the seeds of *Nigella sativa* by creation of IL-3, IL-1B and interleukin. In extra investigation, it was noticed that in the cleaning of the proteins of the entire seeds of *Nigella sativa* has been proved that they have suppressive and other stimulatory properties in lymphocyte culture in certain proteins (Haq et al., 1999).

Nigella sativa is annual herbaceous herbal emerging to 30 cm besides has an upright increasing stem, deeply cut leaves, blue flowers besides seed pots. The shrub is native to the Mediterranean zone. The seeds comprise 40% static oil, a saponin and about 1.4% random oil (Chevallier, 1996). Dioscorides, a Greek surgeon of the era, verified that black cumin seeds were engaged for treatment of migraines, nasal mucus, tooth pain, and intestinal larvae (Chevallier, 1996). The seeds of *Nigella. sativa* have been used usually for fairly a extensive time in the North Africa for the cure of diverse illnesses (Brutis and Bucar, 2000; Gilani et al., 2004). The herbal important oil indicated a extensive range of pharmacological effects (Fararh et al., 2002; Benhaddou-Andaloussi et al., 2010), spasmolytic and bronchodilator (Gilani et al., 2001; Boskabady et al., 2008), hepatoprotective (Al-Ghamdi, 2003; Coban et al., 2010), ache releasing (Hajhashemi et al., 2004; Bashir and Qureshi, 2010), tumor anti (Khan et al., 2003; Majdalawieh et al., 2010) and stomach defensive (El-Dakhakhny et al., 2000) influences in diverse examinations. The essences moreover seemed in vivo and in vitro against microbial (Mashhadian and Rakhshandeh, 2005; Salem et al., 2010), and against cestodal effects (Akhtar and Riffat, 1991). It is misused normally in Iran to enhance urination and celiac antiprotozoal medicine (Amin, 1990).

The seeds of *Nigella Sativa* must be consumed usually for relatively a extensive time in the Middle Asia for the dealing of diverse diseases such as chest pain, lungs infection, brain pain, muscle stiffness, stomach problem, flu and skin problems (Burits and Bucar 2000; Gilani et al. 2004). The distillates moreover seemed in vivo and in vitro antimicrobial effects (Mashhadian and Rakhshandeh 2005). Many investigations have complete cancer inhibition cause deed of *Nigella Sativa* essence and its vibrant components in contradiction of certainly dangerous oxygen species (Houghton et al. 1995).

The high gentle strong stage proteins are haptoglobin and serum amyloid A protein in cows, and APPs are body fluid proteins that can be used to assess the intrinsic insusceptible central reaction to adulteration, augmentation, wound and pressure. Albeit a limited reconnoitres detailing a significant run down of copies declaring the usefulness of *Nigella Sativa* in medicine occurs, not many surveys have proclaimed its impression on the conceptive outline and everyone have zeroed in on the male recreating outline (Aggarwal et al. 2008; Gilani et al. 2004). In count, the effect of *Nigella Sativa* seeds on female reformative abilities kept usually unclear

(Kabir et al. 2001). In entirely investigations, the galactagogue impact of *Nigella sativa* was determined based on these four limitations, as monitors: milk creation, serum prolactin; litter's weight; and variations of bosom matter as obvious through tisse studying. Other limitations, one study measured blood and biological assessments of the individuals took care of with *Nigella sativa* (Abo El-Nor et al. 2007), and one more inquiry obvious its destructiveness (Hosseinzadeh et al. 2013). Three surveys exploited *Nigella sativa* in powder arrangement (Abo El-Nor et al. 2007; Al-Snafi et al. 2014; Nurdin et al. 2011), however one exploited the fluid and the seeds (Hosseinzadeh et al. 2013). *Nigella sativa* distinct was focused to the individuals by oral mean (AlSnafi et al. 2014; Hosseinzadeh et al. 2013) and as food increment (Abo El-Nor et al. 2007; Nurdin et al. 2011). Besides of four studies, just one (Nurdin et al. 2011) used milking cows assumed with inflammation of udder. The three others research exploited solid milking individuals (Abo El-Nor et al. 2007; Al-Snafi et al. 2014; Hosseinzadeh et al. 2013). Although the numerous practices comprised in each inquiry, the results exposed optimistic galactagogue influence in individuals cured with *Nigella sativa* discriminated and the control one. The galactagogue action of *Nigella sativa* was obviously revealed in totally comprised inspections by assessing serum prolactin amount, bosom tissue modification, milk organization, and the weightiness of litter. Prolactin is a biochemical that is comprised directly in breast feeding. In pregnancy, the mark of prolactin in blood additions. In case, milk discharge is delayed by the great serum estrogen levels. Rapidly subsequent labor and placental expulsion, estrogen and progesterone decrease meaningfully, and milk release continues as of the action of prolactin and is restored by treatment of the litter.

The galactagogue action of *Nigella sativa* by assessing the serum prolactin dose of female milking mice profited from diet improved with N. sativa (Al-Snafi et al. 2014). The serum prolactin amount of the lactating mice took care of with the ingestion schedule was basically established standard group. The origination period of lacto genesis similarly elegant deviations in bosom muscle, which remember an increase for total number of lobules and development of epithelial cells. Between the comprised surveys, one inspected the histology of bosom matter of milking mice (Al-Snafi et al. 2014). One side of bosom tissue in female mice tookcare of with *Nigella* sativa comprising food had larger acini, denser skin cells, and secretory weighed and the standard cluster. The high action of bosom tissue of mice helped from *Nigella sativa* identical with the development in serological prolactin. This result can be as of the portion of prolactin in energizing bosom tissue growth and development throughout pregnancy.

Milk formation was evaluated in three of the inspections. Three

studies measured the milk amount, and inspections displayed basically extended milk amount compared and the standard group. Out of the three surveys that *Nigella sativa* seeds can be properly used Hosseinzadeh et al. (2004) and consumed the ethanol distillates of seeds, while the remaining three surveys exploited the genuine seeds. The consumption of little mice allowable organization of the distillates by oral means (Hosseinzadeh et al. 2005) nevertheless, in massive cow and wild oxen, *Nigella sativa* was presented as feed increments (Abo El-Nor et al. 2007; Nurdin et al. 2011). One study observed extended milk creation (Hosseinzadeh et al. 2013), while reading (Abo El-Nor et al. 2007) noted extended milk raises from the 2nd week to the 6th 7th day bounce of cure. Nurdin et al. (2011) didn't direct the time of milk collection.

Hosseinzadeh et al. (2013) displayed a serious extension in milk formation in the assemblies accommodating the fluid essence at amount of 0.5 g kg^{-1} and ethanolic distinctive at a fraction of 1 g kg^{-1} weighed and the control. The milk formation evidence was assembled 23 hours after gavage usage. A serious extension in milk revenue was perceived afterwards *Nigella sativa* association massive individuals, in specific, cows, as well as wild oxen.

Nurdin et al. (2011) obvious milk fat, milk lactose and milk protein. Abo ElNor et al. (2007) measured equivalent limits with the development of complete strong, strong non/fat, lactose, debris, and sharpness. Milk tests were assembled twice day, and all data were documented every day for 12 weeks (Abo El-Nor et al. 2007). The milk checking plan used by Nurdin et al. (2011) was not simply articulated. Fat of milk didn't distinction completely in the two meetings; nevertheless, a vast lessening in milk protein about 2.56% was recognized in the *Nigella sativa* bunch treated and the control one about 3.56% in the investigation showed by Nurdin et al. (2011). Total Solid, acridity, debris, and lactose displayed no vast differences observed between the treated and control group. Milk lactose was overall upper in the treated than control group in an examination directed by Abo El-Nor et al. (2007). Two inspections discovered the safety of *Nigella sativa* consumption in the individuals (Al-Snafi et al. 2014; Hosseinzadeh et al. 2013).

One study played out an deep deadliness revision to pick the wellbeing of *Nigella* sativa (Hosseinzadeh et al. 2013), while alternative study exploited blood samples get from the hepatic cell and GIT system, which were furthermore equipped for tissue calculations (Al-Snafi et al. 2014). Galactagogue action of *Nigella sativa* characteristics in the selected revisions might be attributed to two main essentials. To initiate with, *Nigella sativa* stimulates prolactin, a serious chemical in breastfeeding that cover bosom tissue improvement. *Nigella sativa* seeds contains estrogenic

items (Huchchannanavar et al. 2019). It may be increase cycle of month, labour during birth, and incrase milk ejection. Anethole has a relatively contain dopamine and might be go about foe at the dopamine receptor place. Dopamine inhibits prolactin, which limit anethole at dopamine receptor may works as inhibitory effect of dopamine over prolactin. So, other amount of prolactin is dispatched. In other aspect, the components in the *Nigella sativa* seed improve rumen physiology (Nurdin et al. 2011). *Nigella sativa* seeds has 28 to 36 % of oil and proteins and also about 0.4 to 2.5 % of basic oil (Hajhashemi et al. 2004). Saponin achieve equil microplora in the rumen envirnoment by lowering the amount of pathogenic microrganisms. The amount of rumen microplora and the sum of volatile fatty acids increase causing the lowering of NH_3. Different rumen microplora can caused for volatile fatty acids creation, further expanding the production of milk and meat in cows. *Nigella sativa* oil contains about 35% starches, 35 to 38 % of total fats, and about 21% total proteins (AI-Jassir 1992.). These components contains a high fuel that may work as a part in the galactagogue effect of *Nigella sativa* (Al Snafi et al. 2014).

Conclusions

Studies have demonstrated that the seeds of *Nigella sativa* are sensibly ok for utilization and they have likely therapeutic qualities. The instruments by which the seeds of *Nigella sativa* apply their helpful impacts are an issue that requires more definite exploration. With the expanded comprehension of the instrument of its bioactivity, the fuse of this therapeutic spice as integral medication into standard clinical science can be accomplished later on. The valuable impacts of *Nigella sativa* were not characteristic on their strategy for arrangement (for example ether extraction, oil) and their method of organization (oral) as it has a high wellbeing and adequacy towards the host.

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Chapter 3

PRESEPSIN LEVELS AT NEUTROPENIC PATIENTS

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INTRODUCTION AND PURPOSE

Chemotherapy has an effective role in cancer treatment[1]. Especially at advanced stage cancers, great possibility exists that there is disseminated microscopic cancer. That is why adjuvan chemotherapy has an important place in cancer treatment[2]. Neutropenia is when peripheral blood neutrophil count is lower than 1500 cell/microL and it is one of the most important side effects of chemotherapy. Neutropenic patients are prone to infections. These infections mostly originate from patient's own skin or intestinal flora. The duration and severity of neutropenia determines the risk of developing neutropenic fever[3]. Although GC-SFs are effective at neutropenia treatment, neutropenic fever is the most common reason for decreasing or delaying of chemotherapy dose. Mortality of patients who are hospitalized is 10 %, while with multiple or severe morbidity, it increases to 20 %. In long term, it increases cancer mortality by decreasing dose, delaying or sometimes changing chemotherapy protocol[4].

Presepsin is a subtype of soluble component of CD14. CD14, is a glycoprotein receptor which has a high affinity towards lipopolysaccharides and found on surface of monocytes/macrophages. It has two components; membranous and soluble[5]. Since presepsin emerges from monocytes fagocyting bacterias , the idea of using presepsin for early diagnosis of bacterial infection and sepsis come up and caused studies to be made on subject[6]. Interaction between presepsin and molecules like hemoglobin, bilirubins, lipids, romatoid factor is not founded[7].

The aim of this study is to investigate the usability of presepsin for diagnosing bacterial infection at patients who become neutropenic after chemotherapy.

MATERIAL AND METHOD

For study, 25 patients with a solid malign neoplasm who have neutrophil levels less than 1500 cell/microL and 22 individuals as control group without any chronic disease or active infection who applied to Kirikkale University Medical Faculty Hospital between November 2019-April 2020 are included.

Those under the age of 18, pregnant women, those with active infection, those with kidney or liver failure, neutropenic patients due to a reason other than malignancy, those who did not consent to the study were not included in the patient group while those who did not consent to the study, those with any additional disease and pregnancy were not included in the control group.

Anamnesis was taken from all individuals included in the study, physical examinations were performed, their fever was measured, and

their backgrounds were questioned. Of the individuals, the patient group routinely performed complete blood count, biochemistry, CRP, erythrocyte sedimentation rate (ESR), procalcitonin, blood and urine culture, lung film examinations, and the control group has been selected among those whose complete blood count, biochemistry, CRP and ESR values were measured for any reason. Ten cc of blood from both groups was taken into a biochemistry tube, centrifuged, their serums were separated and stored in a freezer at -24 ° C. Later presepsin level was measured from these serums.

RESULTS:

While there were 12 women and 13 men in the patient group, there were 14 women and 8 men in the control group. The average age of the patient group was 57,76, while the average age of the control group was 57,64. While 10 of the patients had fever, 15 of them had no fever.

At least one culture result of 4 patients was positive.

While the presepsin level of the patients was higher than the control group ($p < 0,001$), there was no significant difference in terms of presepsin levels between men and women in all groups ($p = 0.614$).

In self-evaluation of neutropenic patients; The presepsin level of those with fever was statistically significantly higher than those with no fever, and those with positive culture higher than those with negative culture.

While the CRP level was found to be higher in the patient group compared to the control group ($p < 0.001$); it was found to be statistically significantly higher in both culture positive patients than negative ones and in those with fever than those without fever.

Procalcitonin level was found to be statistically significantly higher in those with positive culture than negative ones, and those with fever compared to those without fever.

ESR levels were found to be statistically significantly higher in those with positive culture than those with negative culture, and those with fever than those without fever.

There was a significant positive correlation between presepsin levels and sedimentation, CRP and procalcitonin values ($p=0.027$ $r=0.443$, $p<0.001$, $r= 0.594$, $p=0.02$ $r=0.462$, respectively.).

DISCUSSION

The presented study is an important study since it shows that the measurement of serum presepsin level in the group of neutropenic patients can detect bacterial infection at an earlier stage. Serum presepsin level was found to be higher in patients compared to the control group. It was

also higher in patients with fever than without fever and higher in culture positive patients than negative patients. Procalcitonin, CRP, and ESR each were higher in those with fever than without fever and those with positive cultures than those with negative cultures. Presepsin value was positively correlated with procalcitonin, CRP and ESR values.

In a study conducted with children with neutropenic fever, CRP and procalcitonin values were found to be higher in culture-positive patients, while there was no difference in presepsin values. In the same study, it was observed that although patients were neutropenic, presepsin values could still increase in the patient group[8].

Again, in a study conducted in pediatric, chemotherapy-induced neutropenic patients, the presepsin level was found to be higher in culture positive patients compared to negative patients and patients with fever compared to patients without fever[9].

In another study, presepsin values were compared in healthy individuals with patients who have positive SIRS (systemic inflammatory response syndrome), sepsis, severe sepsis, and septic shock, and it was found that the presepsin value increased as the patient's condition worsened[10].

In a study conducted to show the effectiveness of presepsin in recognizing fungal infection, procalcitonin and presepsin were examined in 11 patients with fungemia, and the SOFA (sequential organ failure assesment) score was calculated. As a result, both presepsin value and procalcitonin value were found to be positively correlated with SOFA score. It was observed that the presepsin of the patients decreased whose fungi had treated and their general condition improved[11].

In a study conducted in Japan, serial presepsin measurements were made in patients with hematological malignancies who received chemotherapy. While monocyte, neutrophil and white blood cell counts were monitored one by one, white blood cell count and presepsin level were not found to be related. The reason for this has been interpreted as the release of the presepin mostly from the monocyte and the macrophages in the tissues and bringing the presepin to a certain level. Presepsin levels increased in the early period in most patients with bacteremia and in all patients with gram-negative growth[12].

In a study conducted in Slovenia to measure the usability of presepsin in sepsis, which was decided by two separate cultures and procalcitonin values, the value of presepsin in patients with sepsis and patients with aseptic meningitis was compared. As a result, the presepsin value was higher in patients with sepsis. There was no difference in gram negative and positive ones[13].

In a recently published study, blood culture and SeptiFast tests were performed in patients with suspected sepsis and compared with presepsin and procalcitonin levels. SeptiFast is a test that measures bacteremia and fungemia in the blood. In conclusion, while procalcitonin and presepsin were significantly higher in those who were positive for SeptiFast, there was no significant difference in blood culture positive and negative patients[14].

In this presented study, the higher presepsin levels in patients with positive cultures and the increase in presepsin in bacterial infection in neutropenic patients are consistent with the results of most studies in the literature. In some studies, the lack of significant difference in the positive cultures may be the result of the culture results affected by reasons such as the amount and quality of the sample, the severity of the infection or the insufficiency of the laboratory[6].

The most important limitation of this study is the small number of patients. The factors that cause the small number of patients are the limited duration of the study, the fact that it is a single-center study, and the prophylactic use of GC-SF to some of the patients receiving chemotherapy. Another limitation is that patients are not homogeneous. There are patients from different cancer groups in the patient group and many of these patients have additional diseases.

The strength of the study is that there are no other studies, as seen in the literature, in which the value of presepsin in neutropenic fever in solid tumors, especially in adults, was examined.

CONCLUSION:

As a result; the results we have obtained from this study are generally compatible with the data in the literature.

Presepsin is a quick, easy-to-look parameter that is measured from serum. According to the results of our study, presepsin can be used in the diagnosis of bacterial infection. However, it is necessary to conduct studies with a larger patient population with presepsin in adult solid malignant tumor patients by ensuring the homogeneity of the patient group.

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Table 1. Demografic Findings

		Neutropenic (n=25)	Control (n=22)	p
Age(years)		57,76±8,44	57,64±11,46	0,966
Sex				
	Female	12(48 %)	14(64 %)	0,292
	Male	13(52 %)	8(36 %)	
Body heat≥38 °C				
	Yes	10(40 %)	0(0 %)	
	No	15(60%)	22(100 %)	
Culture				
	Positive	4(16 %)	-	
	Negative	21(84 %)	-	
Cancers				
	Lung	9(36 %)		
	Breast	5(20 %)		
	Ovary	3(12 %)		
		2(8 %)		
Neurendokrine				
	Urinary	2(8 %)		
bladder				
	Cerviks	2(8 %)		
	Peritoneum	1(4 %)		
	Stomach	1(4 %)		

Table 2. Presepsin levels in the patient group

	Presepsin düzeyi(mg/L)	p
Body heat ≥38 °C		<0,001
Yes	0,695(0,16-1,82)	
No	0,19(0,09-1)	
Culture		<0,001
Positive		
	0,755(0,62-1,82)	
Negative	0,2(0,09-1)	

Table 3. CRP levels in the patient group

	CRP level(mg/L)	p
Body heat≥38 °C		
Yes	213,6±70,819	<0,001
No	24,935±46,867	
Culture		
Positive		0,003
	202±58,737	
Negative		
	52,34±86,204	

Table 4. Procalcitonin levels in the patient group

	Procalcitonin level (ng/mL)	p
Body heat ≥38 °C		
Yes	0,546(0,05-21)	0,019
No	0,65(0,02-0,84)	
Culture		
Positive	0,754(0,05-21)	<0,001
Negative	0,081(0,02-4,98)	

Table 5. ESR levels in the patient group

	ESR level(mm/h)	p
Body heat ≥38 °C		<0,001
Yes	93,6±21,077	
No	45,4±28,147	
Culture		0,026
Positive	87,25±14,127	
Negative	60,429±36,038	

Chapter 4

VASCULAR-INDUCED LEG PAIN: CAUSES, SYMPTOMS, AND TREATMENT

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1. Introduction

Thanks to the advancing noninvasive and invasive research techniques and radiological tests, our approaches to the diagnosis and treatment of lower extremity vascular diseases have become much easier today. Many vascular diseases can now be treated with percutaneous methods with the inevitable developments in the field of angiography (Stoner, 2016). Knowing and distinguishing the current vascular pathology well by general practitioners and non-vascular surgeons in terms of the treatment and the physician to be referred is very important for the patient's health and the success of the treatment because time is very important for the success of the treatment in lower extremity vascular diseases. It covers a wide range of diseases, including arterial (acute or chronic peripheral arterial disease, etc.), venous disease (venous insufficiency and venous thrombosis, etc.), and lymphatic diseases. An accurate definition of leg pain occurring in these diseases is important in making the diagnosis. Although leg pain of vascular origin is frequently encountered in the elderly population, it can also be seen in young and even athletes (Abid, 2016). A good understanding of the underlying pain mechanisms to manage both acute and chronic vascular pain provides the rationale for treatment. It is an undeniable fact that more research is needed to better understand the pathophysiological mechanisms underlying vascular pain (Serenty, 2016). Multiple comorbidities must be considered in order to accurately diagnose vascular pain. Cardiac problems, diabetes mellitus, obesity, renal dysfunction, and cognitive impairment are major contributors to morbidity (Bosma, 2013). In this section, approaches to understanding the etiology and pathophysiology of a patient presenting with leg pain as a result of vascular disease are presented in a language that appeals to all our physicians. Some cornerstones are tried to be shown to the physicians who will treat the patient.

2. Definition of pain related to vascular diseases

2.1. Nociceptive pain:

Nociceptive pain results from stimulation of peripheral nociceptors on unmyelinated C fibers. It produces a physiological response to actual or threatened non-neuronal tissue damage and reflects the normal adaptive functioning of the somatosensory (Leffler, 2006). Typically, it is a reversible type of pain that subsides when the cause is removed. An example of nociceptive pain in vascular patients is intermittent claudication (pain and cramping after repetitive muscle movement or exercise) (Rüger, 2008).

2.2. Inflammatory pain:

Inflammatory pain is a somatosensory response to tissue damage and inflammation in the nervous system. An increase in inflammatory mediators

and chemokines sensitizes local nociceptors and increased responsiveness results in potential stimulation (Costigan, 2009). Pain modulated by the inflammatory response is an inevitable consequence of tissue trauma that occurs rapidly as a result of changes in local blood flow, chemical and electrical activity as a result of interactions between peripheral immune cells. It normally resolves as tissue healing occurs. Insufficient resolution of these changes also reveals the transition of acute pain to the chronic process (eg chronic deep venous thrombosis) (Woolf, 2007).

2.3. Neuropathic pain:

In simple terms, pain caused by a disease of the somatosensory nervous system is called neuropathic pain. Molecular or cellular changes in the somatosensory nervous system have an impact on function. With the combination of sensory loss and increased sensitivity, neuropathic pain types such as allodynia, hyperpathy, and hyperalgesia occur as a result of mild or high adaptations. Examples include phantom pain that may occur in critical limb ischemia and after amputation (Gröne, 2014).

Etiology and management options in vascular diseases causing leg pain are presented below.

3. Arterial leg pain

It occurs as a result of acute or chronic diseases of the peripheral arterial system.

3.1. Acute lower extremity arterial occlusive diseases

It is an emergency vascular disease that can result in loss of limb with sudden occlusion of the leg arteries. This condition is defined as acute limb ischemia. The causes are, in order of frequency, acute arterial embolism, acute arterial thrombosis, arterial injuries, phlegmasia caerulea dolens, and dissecting aortic aneurysms. In any case, a thrombus forms in the occluded artery, and this thrombus travels up and down, causing further occlusion of the artery (Ramos, 2009).

3.1.1. Symptoms

Patients complain of sudden onset of severe and sharp pain in the leg fed by the vein with acute arterial occlusion, which does not go away with painkillers. The extremity is cold and pale. Although the pain continues within hours, loss of sensation occurs in the extremity. The situation is urgent and carries a significant risk of amputation and even death if not treated on time (Conte, 2015).

3.1.2. Causes - Differential diagnosis

3.1.2.1. Acute arterial embolisms

It constitutes the primary frequency of acute limb ischemia causes. Acute arterial embolism is in the 1st frequency and is secondary to heart disease with a rate of 95% (Lyaker, 2013). The causes of development of thromboembolism can be grouped under a wide spectrum as cardiac and vascular. The definition of paradoxical emboli is pathological processes that rarely occur in the venous system and are caused by embolisms from there to the arterial system. Embolisms originating from the heart are thrown into the body as a result of sudden changes in heart rhythm. The primary finding in the diagnosis is the anamnesis of ischemia symptoms in the area supplied by the occluded artery. In the extremities, there is a classic 6P finding in arterial occlusions, which Pratt detected in 1954. Pain is the first of these symptoms. Since the nerve tissues will be affected first by the developing anoxia, neurological findings appear immediately. Pale and blue ischemia phases to be determined in the clinical picture are related to the duration and are important in terms of treatment in arterial occlusions in the extremities (Rutherford, 1997).

Clinically, the 6P sign is important in the diagnosis. Auscultation, ECG, chest X-ray and, if possible, echocardiography can be routinely performed to detect the origin of the embolism. The most important antecedents of the anamnesis are the history of embolism with rheumatic or coronary heart disease. Determination of the absence of peripheral pulse should be detected by Doppler USG as well as palpation. Angiography in arterial embolism comes to the fore in the presence of suspected thrombosis (Stoner, 2016).

The main factors determining the prognosis are; the condition and stage of the actual disease, the age of the patient, the localization of the obstruction, the timing and form of the treatment applied. After the use of the catheter developed by Thomas Fogarty, a 4th-year student at the Faculty of Medicine in 1963, the success rate of the surgical procedure approaches 100% in cases that are caught at an early stage and have not yet developed muscular rigidity (Fogarty, 1963). In emergencies, besides embolectomy, correction of the embolism source, bypass, endovascular methods, amputation, sympathectomy, and fasciotomy are other surgical methods that can be applied. It should be known that the duration of the surgical intervention should be short and that it should contain minimal trauma. As an anesthesia modality, it should generally be started with local anesthesia and it should not be forgotten that general anesthesia may be required (Beyersdorf, 1989).

3.1.2.2. Acute arterial thrombosis

It ranks second as the cause of acute arterial occlusion. They develop with the provocation of local, hemodynamic, and hemopathological causes in a previously pathological place in the arterial lumen. The most common cause of acute thrombosis is atherosclerosis obliterans. The most common localizations are the region of the femoral artery within the Hunter canal and the fossa poplitea. Although the clinic of rapidly developing thrombosis is similar to that of embolism, it may not be as noisy. If it is slowly located, there may not even be any obvious finding other than claudication. The most important element in the diagnosis is hidden in the anamnesis, and the patient describes claudication. On physical examination, pathological murmur is detected on auscultation of the artery, and degenerative changes and collaterals are conspicuous on angiography. In the treatment protocol, the type of intervention is determined with the help of angiography. If the thrombosis has caused complete ischemia in the extremities, surgical intervention is performed as an emergency. In addition, conservative procedures such as heparinization, hemodilution, adding agents that increase tissue perfusion, and wrapping the extremity with cotton (protects from trauma and prevents heat loss from the skin) can be added to medical treatment (Norgren, 2007; Rutherford, 1997).

3.1.2.3. Artery injuries

Since injuries can be direct or indirect (penetrating, blunt, interventional surgical procedures), classification is made accordingly.

Contusion: It occurs as a result of narrowing of the arterial wall due to intramural hematoma. There is eccentric or concentric stenosis.

Intimal separation: It occurs as a result of the traction of the vessel due to blunt trauma. In angiography, a linear defect due to intimal separation is observed in the vessel.

Puncture: Appears with piercing tools. Most of the time, pseudoaneurysm can also occur as it can heal on its own.

Lateral separation: There is a tangential injury. Only a portion of the vessel is divided laterally. It is the type that causes the most bleeding. Pulsatile hematoma or pseudoaneurysm often develops.

A-V fistula: It occurs as a result of the combined destruction of the artery and vein with a sharp instrument.

Transection: There is a complete separation (incision) in the artery. The artery is retracted and prone to constriction and thrombosis. Surgical exploration of the artery is indicated.

The aim of treatment in acute arterial injury covers the principles of

restoring vascular restoration by repairing the injured area (Bonanni, 1993). Finally, if we talk about 'Causalgia' in the injuries section, the findings in this pathological process, which is defined as the late resolution of pain after a traumatic event, are due to sympathetic nerve hyperactivation. These are burning pain, sympathetic dysfunction, leg atrophy, hyperhidrosis and decreased skin temperature. Pale thin skin, muscle atrophy, and bone demineralization are the main trophic changes. Sympathectomy can be applied in its treatment and it responds well (Shah, 2011).

3.1.2.4. Phlegmasia caerulea dolens

Massive thrombosis in the superficial and deep veins of the lower extremity and pelvic veins is the primary event. Secondary arterial occlusion is added. The cause of arterial occlusion here is the compression of the thrombosed vein to the adjacent artery, reflex artery spasm, and the development of flow arrest in the capillary region. The main difference from arterial occlusion is the finding of 'edema'. In addition, the veins that are seen as empty in arterial occlusions are enlarged and painful here. In this pathological event, systemic findings such as fatigue and fever are also noteworthy. Emergency thrombectomy and additional conservative treatment should be urgently planned considering that venous gangrene and necrosis will develop (Bindsbergen, 2009).

3.1.2.5. Dissecting aortic aneurysm

It is remarkable that sudden retrosternal pain, acute abdomen, shock, hemiplegia, or paraplegia are the main clinical signs added to acute onset leg pain. There is a weakening or resetting of the pulse amplitude. Its treatment is emergency surgery and CT findings are important (Parve, 2017).

3.2. Chronic lower extremity arterial occlusive diseases

Peripheral arterial disease (PAD) is a chronic and often atherosclerotic disease of the peripheral vascular system. It ranges from intermittent claudication, which is the classic manifestation of the disease, to ischemic resting pain. PAD is a condition that affects 220 million people worldwide and has an increasing prevalence (Selvin, 2004).

3.2.1. Symptoms

In the PAD group, where the ankle-arm pressure index (AKI) was accepted as ≤0.9, 10-30% of the patients have pain in the lower extremities that increases with exercise and improves with rest, that is, 'intermittent claudication', the classic symptom of peripheral arterial disease. These patients may only experience deep ischemic pain, such as claudication and ischemic rest pain in the calf region, as the superficial pain sensation may

change. In the vast majority, foot pain is too serious to bear and may respond only to opiates. Ischemic rest pain typically occurs at night but maybe continuous in severe cases. They often sleep with their ischemic legs hanging over the edge of the bed or sitting in a chair (Davies, 2014). The aim here is to use the effect of gravity. Although the pain symptom is usually located in the calf region, it can also affect the hips, thighs and soles of the feet. It causes pain in the hip-thigh in aortoiliac occlusion, in the calf in femoral occlusion, and in the plantar area in infrapopliteal occlusion. In patients with intermittent claudication, resting blood flow is normal and there are no symptoms in the leg. During exercise, as the occlusive lesions do not allow sufficient flow to the leg muscles, a mismatch occurs between the metabolic demand of the muscles and the oxygen support provided, and intermittent claudication occurs. Therefore, it is important to understand intermittent claudication and make its differential diagnosis. There are possible non-vascular pain syndromes related to the musculoskeletal system such as nerve root compression, symptomatic Baker's cyst, spinal stenosis, hip or foot arthritis that can be confused with intermittent claudication, but in this section, arterial lesions that may potentially cause claudication in the lower extremity arteries are examined in the differential diagnosis (Sigvant, 2016).

3.2.2. Causes - Differential diagnosis

3.2.2.1. Atherosclerosis

It is the most common cause of peripheral arterial diseases in Western society. Atherosclerosis is a disease that involves the arteries and creates changes that lead to complete occlusion in the future. The incidence increases with advancing age, starting from the age of 40. It is one of the most common diseases in the elderly population (Norgren, 2007)

3.2.2.2. Thromboangiitis obliterans (Buerger's disease)

Buerger's Disease is a vascular disease that affects medium and small vessels without atherosclerosis and causes narrowing and blockages as a result of inflammation of arteries and veins. Since it involves small vessels, it often causes non-healing wounds and gangrene on the fingers. Although it is not known exactly why it develops, it has been proven to be very closely related to smoking. There is probably a direct toxic effect of tobacco on the cells in the inner surface of the vessel or hypersensitivity of these cells to tobacco. Therefore, it is common in the Mediterranean, the Middle East, and Asia, where cigarettes are consumed heavily. It is more common in men, especially between the ages of 40-45 (Piazza, 2010).

3.2.2.3. Abdominal aortic coarctation

It constitutes 10% of all aortic coarctations. It appears as a non-hereditary isolated lesion in 2-3 decades. In addition, neurofibromatosis may

develop as a result of radiation therapy, Takayasu arteritis, atherosclerosis, focal calcific aortic obstruction, homocystinuria, and pseudoxanthoma elasticum (Scott, 1979).

3.2.2.4. Endofibrosis of the external iliac artery (Cyclists iliac syndrome)

Usually, in the middle segment of the external iliac artery of the dominant leg, intimal hyperplasia causes 4-5 cm in length, 40-50% luminal stenosis. Later, it may cause complete cessation of flow with thrombotic occlusion. Obstruction increases with the flexion of the thigh. Mostly, there is elongation in the external iliac artery (Rensburg, 2014).

3.2.2.5. Fibromuscular dysplasia

It is an idiopathic, segmental, non-atherosclerotic, and non-inflammatory arteriopathy affecting small and medium-sized arteries. Although it is most common in middle-aged women, it can occur in any age group. It can cause stenosis, aneurysm, dissection, occlusion and tortuosity in the affected artery. Its etiopathogenesis is not known exactly, but it is thought that environmental and genetic factors may be effective in the development of the disease (Brinza, 2016).

3.2.2.6. Popliteal artery aneurysm (with secondary thromboembolism)

It accounts for 85% of all peripheral artery aneurysms. Atherosclerosis is the most important factor. It is bilateral in 50-60% of cases. They are frequently thrombosed and are a source of subclinical embolism (Varino, 2015).

3.2.2.7. Primary vascular tumors

Vascular tumors give symptoms according to their location.

3.2.2.8. Pseudoxanthoma elasticum

The primary pathology is elastin rather than collagen. It is generally seen in the 4th-6th decade, but arterial findings may occur under 10 years of age (Zhang, 2014).

3.2.2.9. Takayasu's disease

Takayasu arteritis is included in giant cell vasculitides and is an obliterative arteriopathy. Its etiology is not fully known. It is most common in eastern countries. 80-90% of the patients are women and the age of onset of the disease is usually between 10-30 years of age. Granulamatory inflammation affecting the entire artery wall is the typical finding of the disease. It often involves the branches of the aortic arch. Although the clinical symptoms are nonspecific at the beginning, vascular insufficiency

findings may be seen in the later period depending on the involved area of the artery (Tann, 2008).

3.2.2.10. Adventitial cystic disease of the popliteal artery

It is the formation of popliteal artery stenosis or occlusion due to cyst formation under the adventitia. It is usually seen in men, unilaterally and aged 50-60 years. While the distal pulses are palpable when the leg is in extension, the pulses disappear in flexion (Scobie, 1975).

3.2.2.11. Popliteal artery entrapment syndrome

There are 2 types, anatomically and functionally. Anatomically, there are 5 most common types and it develops as a result of compression of the popliteal artery between the gastrocnemius and popliteal muscles. It should be kept in mind if there is a pain when walking in young people, but the pain disappears while running. In the functional type, there is no positional anomaly with the muscles. The main pathology is a chronic overuse injury. It is common in young women and athletes. Pain symptoms are exacerbated by running. It is suspected if the distal pulses disappear during plantar flexion in young patients without signs of general vascular disease (Hicks, 2019).

3.2.2.12. Chronic compartment syndrome

It is an overuse injury observed in young men and especially in runners. Normal resting compartment pressure is less than 15 mmHg. A pressure of 16-20 mmHg is considered borderline. Compartment syndrome above 25 mmHg is mentioned. In normal individuals, the compartment pressure increases 3-4 times during exercise but returns to normal within 1-2 minutes after exercise. In chronic compartment syndrome, the pressure increase is evident during running and decreases to baseline value more than 10 minutes after exercise (Vajapey, 2017).

3.2.2.13. Persistent sciatic artery thrombosis

The persistent sciatic artery is a very rare embryological vascular variant with a prevalence of 0.05% according to angiographic studies. In the presence of persistent sciatic artery (its normal remnant gluteal artery), the femoro-popliteal artery segment may be agenetic and the sciatic artery continues with the popliteal artery. In this case, the femoral artery pulses cannot be obtained, while the distal pulses are normal. (Cowie sign) Depending on the relationship between the sciatic artery and the femoral artery, two different types of this anomaly may occur, either complete or incomplete. Although most of these patients are asymptomatic, they pose a threat to lower extremity viability due to atherosclerotic changes resulting in occlusive thrombosis or embolic events with distal complications (Santaolalla, 2010).

3.2.3. Treatment

The goals of treatment are to relieve symptoms, improve exercise performance and daily functional abilities. After the differential diagnosis of the disease is made, treatment should be planned. In cases where exercise or drug therapy fails, the next step should be taken and revascularization should be considered. However, in patients with a suspected proximal lesion (hip claudication, decreased or absent femoral pulses) without starting intensive medical treatment initially; direct revascularization may be considered (Sigvant, 2016). The prescription for treatment is summarized in Table 1.

Table 1: *Prescription of peripheral arterial disease*

Heart attack, stroke, and cardiovascular requirements to reduce the risk of death	*Correction of symptoms and quality of life ; prevention of amputation*
- Quitting tobacco products	- Quitting tobacco products
- Walking exercise program	- Walking exercise program
- Blood pressure control	-Medical treatment (cilostazol)
- High-dose statin therapy	-Daily good foot care
-Antiaggregant treatment	-Revascularization

3.3. Phantom pain

Phantom pain is defined as severe pain felt by amputees in the lost part of their extremities. Phantom pain has been reported in up to 80% of amputees. This type of pain, which usually decreases in intensity over time, is caused by various mechanisms, and the severity of the pain is affected by some factors. Although the mechanisms of the central and peripheral nervous system are reported as the source of pain, pain is also affected by physiological factors. To effectively treat phantom pain, which is still being discussed today, it is necessary to better understand the mechanisms that cause pain. There is no specific medication that treats phantom pain. Calcitonin, various antidepressants, epilepsy drugs, and morphine-derived pain relievers have been tried in drug treatment. Apart from many drugs, it is tried in psychotherapies (Erlenwein, 2021).

4. Vein-induced leg pain

It is the pain that occurs as a result of insufficiency or thrombosis of the superficial and deep venous system.

4.1. Chronic venous diseases

The chronic venous disease of the lower extremities is a disease that occurs as a result of persistent venous hypertension, which, if left untreated, can cause varicose veins, skin inflammation, discoloration, and ulceration. This disease is characterized by symptoms such as swelling in the legs, cramps, burning, heaviness, throbbing, itching, soreness, and pain even pain with exertion. These symptoms show a prevalence of 50% in the general population. However, these symptoms are reported with the same frequency in patients without the identifiable venous disease. Pain symptoms have a nonspecific character and are relatively benign in the patient. There is a cause-effect relationship between the increase in the volume of the leg venous system and pain. In clinical and laboratory studies, short periods of sitting or standing still cause these symptoms, which can be attributed to venous hypertension. With the effect of gravity, the superficial and deep veins remain under pressure and as a result, the leg venous volume increases. Macrohemodynamic causes are stretching of the vessel walls, decreased arterial flow, and blood stasis. As a result, sudden chemical changes occur in the microcirculation. Deviations that threaten homeostasis are converted into neuronal signals. Signals are transmitted to the subcortical region and a feeling of tension and pressure is felt, indicating pain (Blättler, 2016).

4.1.1. Diagnosis

We can classify chronic venous disease diagnosis methods in three steps:

Level 1: History, physical examination

Level 2: Continuous wave Doppler, color Doppler ultrasonography (USG), plethysmography

Level 3: Computed tomography (CT) venography, magnetic resonance (MR) venography, ascending venography, descending venography

The purpose of these examinations is to detect the presence of venous reflux, superficial or deep vein thrombosis (Gloviczki, 2012).

4.1.2. Treatment

Treatment of chronic venous insufficiency ranges from drug therapy and simple compression stockings to very complicated venous reconstructions. Patient education is the most important step of treatment. This diversity in

treatment options requires an accurate diagnosis. Which treatment method will be applied may vary according to the level of venous insufficiency and personal characteristics of the patient (Rasmussen, 2013).

4.2. Thrombophlebitis

Thrombophlebitis is a disease that especially affects the leg veins. This disease is characterized by an infection in superficial veins, especially varicose veins, followed by thrombosis in the same veins. During the course of the vein, it causes symptoms such as redness, pain, fever, burning, stinging, and tenderness on the skin when touched, and even a feeling of stiffness in the vein. Antibiotic, anti-inflammatory and blood thinning treatments are recommended for treatment (Kerstein, 1977).

4.3. Deep venous thrombosis

Deep vein thrombosis (DVT) is a sudden thrombus occlusion of the deep venous system, mostly in the lower extremities. It is an important public health problem due to its frequent occurrence, high risk of recurrence, reduced quality of life and survival, and high costs. The clinical picture in DVT shows different features depending on the location. The left lower extremity is more frequently affected by the disease due to the anatomical course of the iliac vein. Thrombosis of the calf veins usually has calf pain and tenderness, but edema is at the ankle level. In more proximal thromboses, edema is high and the extremity is extremely painful. Hanging the leg down, standing, and muscular activity increase the pain. The patient states that the calf hurts in a tearing manner. The Homan's sign is often positive (Tritschler, 2018).

4.3.1. Causes - Differential diagnosis

Calf pain and unilateral leg edema occur as the initial symptoms of venous thrombosis in the patients. The clinical picture of the patient is important in the diagnosis. However, it is beneficial to perform laboratory and radiological tests that will guide the optimal treatment and help the real diagnosis. There are some diseases that should be considered in the differential diagnosis. These are muscle tear, ruptured Baker's cyst, hematoma, lymphatic obstruction, advanced venous reflux, superficial venous thrombosis, knee diseases, leg muscle abscesses, lymphangitis, cellulitis, vasomotor changes, and postphlebitic syndrome (Tritschler, 2018).

4.3.1.1. Postphlebitic syndrome

Since the venous system is blocked after DVT, circulation is provided by superficial or side branches. Pain and swelling in the leg continue until recanalization and enlargement of the collateral veins occur. These veins are

not competent and edema continues to occur in the leg. For the problematic extremity, the patient spends more effort while walking. Therefore, fatigue pain due to effort begins to appear. Over the years, complications with chronic edema secondary skin findings occur (Kahn, 2000).

4.3.2. Treatment

The aim of DVT treatment is to prevent pulmonary embolism, chronic pulmonary hypertension, recurrence of venous thromboembolism and postthrombotic syndrome. Virchow triad (venous stasis, hypercoagulability, and endothelial damage) in the formation of venous thromboembolism has been valid since the 19th century. Genetic and acquired risk factors are very important in the formation of venous thromboembolism and show special features in prophylaxis and treatment. The main lines of treatment are anticoagulant therapy and compression stockings used to reduce symptoms (Tritschler, 2018).

5. Leg pain due to lymphatic diseases

The lymphatic system and the vascular system show parallelism. The lymph vessels of the lower extremity consist of superficial and deep lymph systems. Edema is the pathognomonic finding of lower extremity lymphatic system diseases. This edema is firm, non-marking, and particularly painless. Over time, with the collapse of the proteins in the edema fluid and fibrosis, subcutaneous stiffness increases and does not soften at rest. Hyperkeratosis develops in the skin, and eczematiform skin lesions are observed on the skin over time. This situation prepares the ground for skin infection. After the infection in the lymph vessels, tenderness and pain occur in the extremity (Borman, 2018).

5.1. Lymphangitis

Lymphangitis is an infection picture that occurs as a result of the invasion of bacteria into subcutaneous tissues. Conditions such as traumas, heel cracks, skin wounds, ingrown nails predispose to lymphangitis. Infection often involves the superficial lymphatic system. Bacteria spread rapidly along the lymphatic vessels in the subcutaneous tissue. There are exuding and hyperemic areas around the lymphatics. These areas are very sensitive and painful. There is an increase in temperature both in this area and systemically (Kano, 2020).

5.1.1. Treatment

Immobilization and elevation of the extremities, local dressing, and broad-spectrum antibiotics are indicated. If there is an accompanying fungal infection, it should be treated simultaneously.

6. Conclusion

The risk of pain in patients with vascular disease is quite high. Pain has the potential to become chronic. Although analgesic treatments are possible in acute lesions, the chance of success is low in chronic pain. Multidisciplinary pain management and treatment of the disease should be considered in terms of the patient's functionality and quality of life. In this context, it is recommended that studies of vascular surgery outcomes include both acute and chronic pain measures to understand the progression from acute to chronic. These results are very valuable in terms of controlling pain in the future.

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Chapter 5

UP-TO-DATE ARTIFICIAL INTELLIGENCE IN ORTHODONTICS

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1. Introduction and History

The artificial intelligence is a term that denotes computer or computer-driven robots with ability to perform human behaviors. The AI consists of software and hardware systems that build many skills to a computer including image recognition, sound perception, mobility, prediction and reasoning (Ucuzal & Gündoğdu, 2020).

In an article published by Alan Turing in 1950, it has began to investigate whether machines will have thinking skill as with human. By a test proposed by Turing, a machine could be tested whether it is intelligent or not. The test has become foundation of artificial intelligence. In Turkey, Professor Cahit Arf gave a lecture a conference "Can machine think? How a machine think?" in 1958. Professor Arf depicted the concept of designing a machine that can think independently, proposing that it is possible (Arf, 1959).

After introduction of artificial intelligence concept in 1950s, the term machine learning has been introduced in 1980s; followed by the terms deep learning and artificial neural networks (Figure 1). To understand artificial intelligence, one should know relevant terms of machine learning, deep learning and artificial neural networks.

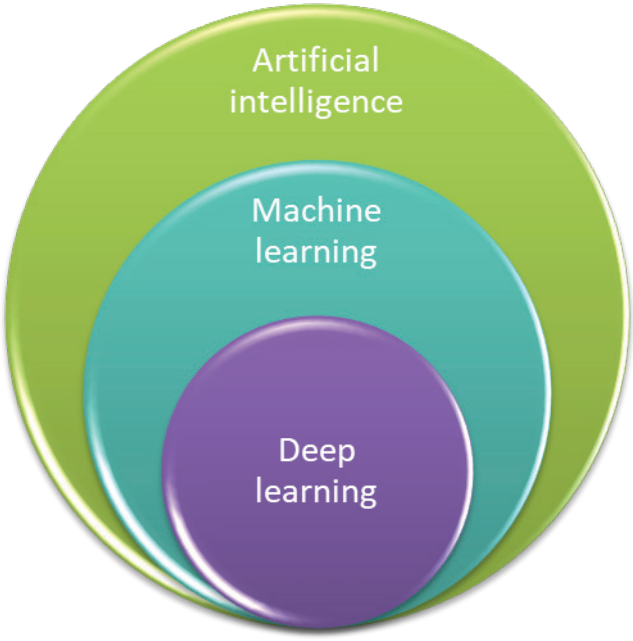

Figure 1: *Artificial intelligence is a field that encompasses and is related to deep learning and machine learning.*

2. Overview

2.1 Machine Learning

The machine learning is an image recognition and process system that aims to build skills of recognizing complex patterns and making reasonable decisions based on data. In the machine learning, first step is to design a training set. In this form of learning, data and expected responses are defined to computer by human skills. Thereafter, classification algorithms should have to be created, which can predict using these data. The algorithms used are support vector machines (SVM), random forest, k-nearest neighbors (k-NN), logistic regressor (Log Regr) and decision among others. Thus, computers acquire ability to learn from experiences and previous data. There are several types of machine learning, including controlled learning, uncontrolled learning, reinforcement learning, offline learning and online learning (Society, 2017).

2.2 Deep Learning and Artificial Neural Networks

The deep learning, a subdomain of machine learning, encompasses several complex tasks such as image classification, object recognition, voice recognition and language translation. The deep learning systems can accept multiple data types as input, which is particularly important health data (J. Yu & Liu, 2020). The systems that can inferential prediction based on data can be build by machine learning and deep learning methods (Figure 1).

The artificial neural network is a technology that is basically inspired by neural network in human brain. The artificial neurons (knots) comprises an interconnected network as similar to neurons in human brain, providing data transfer *(https://teknoloji.org/derin-ogrenme-nedir-yapay-sinir-aglari-ne-ise-yarar/*). Thus, it mimics mode of operation of the biological nervous system.

The machine learning uses algorithms to learn from data and conscious decisions using the things they have learned. It is required to model characteristics of data desired to be extracted in a manual manner. The deep learning configures algorithms within layers in order to create an artificial neural network which can make independent decisions and learn (*https://teknoloji.org/derin-ogrenme-nedir-yapay-sinir-aglari-ne-ise-yarar/*) (Figure 2). Many non-linear process layers are used in the deep learning (Deng & Yu, 2013). Many distinct deep learning architectures have been created by variations in the number and structure of layers in the artificial neural network. The deep learning architectures include convolution neural network (CNN), recurrent neural network (RNN), long short-term memory networks (LSTM), deep belief network (DBN) and generative adversarial network (GAN) (Ucuzal & Gündoğdu, 2020).

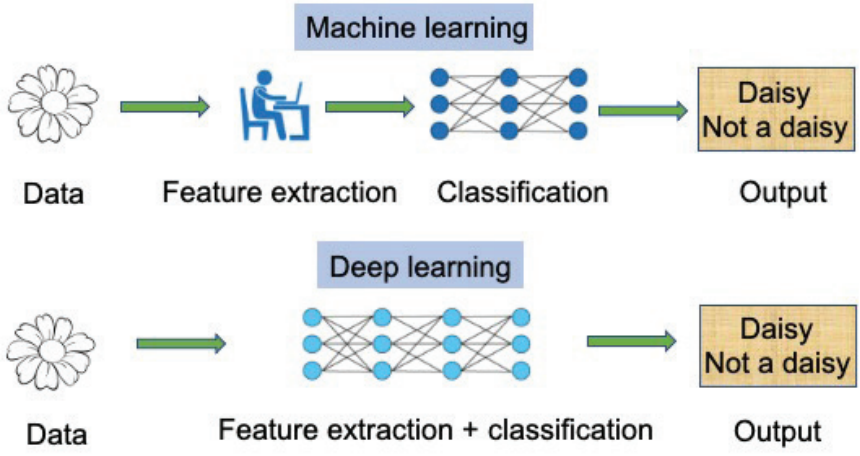

Figure 2: *Differences between machine learning and deep learning.*

The learning is of importance in health data. The well-established models, CNN and RNN, have become popular in dentistry. The CNN includes convolution layers, max pooling layers and fully-connected layers. It can use image as input and has ability to extra characteristics on the image. Thus, it is used to process data from medical images and videos in healthcare services. The RNN is a neural network with repeated connections. It takes available input and output learned from previous input into consideration for decision-making. It is widely used to model time series data by recognizing short- and long-term temporal dependency. As such, the prediction of next time step is affected by previous time step. As a result, the RNN has an excellent ability to memorize dependency between two adjacent time steps (Murata et al., 2017)· (Ucuzal & Gündoğdu, 2020). Based on these features, they are preferred as clinical aid in medical image analysis.

3. Artificial Intelligence in Orthodontics

While the artificial intelligence is pivotal in many sectors, it is also increasingly used in orthodontics. It has become an important aid in the orthodontic diagnosis and treatment-planning. The artificial intelligence is primarily used for face analysis, tooth and mandible segmentation, identification and analysis of cephalometric landmark, bone age determination, decision-making for tooth extraction, prediction of orthognathic surgery, temporomandibular bone segmentation and airway segmentation.

3.1 Artificial Intelligence Applications in Orthodontic Diagnosis

The orthodontic diagnosis is a time-consuming process that includes dynamic examination the patient, review and analysis of photograph ad radiographic recordings and model analyses. The examination is clinically performed in a comprehensive manner. The other diagnostic tools use data gathered from patient. Today, photographs and radiographs are assessed in computer environment while model analysis can be performed either on model plaster or digital models. In orthodontics, the diagnosis process, in which many data are assessed, is time-consuming with higher likelihood of measurements that are performed by millimetric sensitivity. As a result of this complicated assessment process, different treatment plans can give rise among orthodontists. Thus, there is need for automatization in orthodontic diagnosis in order to improve expedition, consistency and accuracy (Murata et al., 2017).

3.1.1 Face Analysis

In orthodontics, Murata et al. (2017) first offered a deep learning model to automatize diagnostic step in orthodontics. In the study, a hybrid CNN and RNN model was used. The model was trained based on facial images of patients to predict assessments for face and maxillomandibular proportions. The CNN uses facial images as input and extracts their characteristics while the RNN predicts a classification based on prior predicted classes. These models used labeling such as “left deviation”, “normal” or “right deviation” for mandible while “normal or mild impairment”, “moderate impairment” and “severe impairment” for facial assessment. The orthodontists can automatize assessment process for new patients using the trained models.

The artificial intelligence studies have also been performed to assess facial attractiveness. In a study, 69 orthodontists assessed pretreatment and post-treatment photographs of the patients, ranking from “most attractive” to “least attractive” (X. Yu et al., 2014). Then, superposition was performed through landmarks defined on photographs in order to eliminate errors which may be resulted from variation in image size and inappropriate head positioning. A support vector regression function was structured based on coordinates of defined landmarks and corresponding grading. It was found that support vector functions were highly reliable in assessment of facial attractiveness when prediction ability was tested.

3.1.2 Tooth and Mandibular Segmentation

Dental models play an important role in orthodontics. Three-dimensional anatomy as well as shape and distribution of localization of teeth can be demonstrated by using artificial neural networks. Thus, it is

possible to move teeth and re-align teeth on the image or reduce number of teeth, allowing accurate treatment planning (Li et al., 2007; Wongwaen & Sinthanayothin, 2010).

There are 3 functional component of computer-assisted design and computer-assisted manufacture (CAD/CAM) systems used in dentistry practice since 1980s: scanner which collects data; software which provides design; and milling machine and abrasion machine (Kalaycı & Bayındır, 2015). The CAD/CAM systems initially used for prosthetic restorations; today, it is intensively used in orthodontics. The CAD/CAM systems are currently used in aligner treatment, lingual orthodontic treatment and Herbst apparatus design. Many commercial CAD/CAM software have been introduced by advances in computer and software technology, including Clear Aligner Studio (3shape, Denmark), Implant3D (Media Lab S.p.A, Milano, Italy) and OrthoCAD (Align Technology, Inc, USA), and automated tooth segmentation is somewhat achieved (Tian et al., 2019).

Grzegorzek et al. proposed a multi-step approach from dentition to tooth segmentation based on a 2-dimensional (2D) model-based contour retrieval algorithm (Grzegorzek et al., 2010). Ponstri et al. (2017) proposed a model to identify tooth region and segment teeth on panoramic radiograph by template matching. However, these methods aren't reliable to identify tooth margins and segment tooth in complicated dental arcs. Thus, many 3D model-based segmentation methods have been introduced (Tian et al., 2019).

Miki et al. (2017) achieved successful tooth segmentation by using pre-trained AlexNet artificial neural network. Xu et al. (2017) designed a segmentation-based artificial neural network, improving accuracy of segmentation. Tian et al. (2019) reported a success rate of 89.81% in their study in which 3Shape laser scanner (D700, Denmark) was used to generate digital dental model and convolutional neural network for segmentation. Authors suggested that the segmentation network employed can be used in different malformations and patients with missing teeth. In a study, by Yau et al. (2014) segmented crowns using data from intraoral scanner while roots from cone-beam computerized tomography (CBCT) images. They combined these data using Delaunay-based region-growing algorithm. They reported that orthodontists were able to control direction and contact of roots together with crowns. Thus, currently, ability to simulate and re-arrange tooth movements from models obtained using CBCT and intraoral scanners has become an important aid in prediction of treatment.

3.1.3 Identification and Analysis of Cephalometric Landmark

Cephalometric analysis is an orthodontic diagnostic tool. The cephalometry was first introduced by Broadbend (Broadbend, 1931) and

Hofrath (Hofrath, 1931) in 1930s and it has currently become a routine method in identification of malocclusion. It is generally used for 3 purposes:

1. Sagittal assessment of hard and soft tissues in head and face based on available norms

2. Identification of changes during treatment and reinforcement process

3. Determination of changes by growth and development

The cephalometric analyses can be performed via manual tracing landmarks or computer-assisted approaches. Manual tracing is a most widely employed method which has been long used; however, it is time-consuming and associated with errors. This methods may take 15-20 minutes to perform in average based on experience of orthodontist, quality of cephalogram and number of parameters to evaluate (Chen et al., 2004). However, the variations in tracing is common depending on quality of radiography and experience of operator (Leonardi et al., 2008). According to Dean et al. (1998), mean variation is 3.3 mm in landmark positioning among experts, which is large enough to alter treatment plan. Automated cephalometric analysis transfers landmarks to a computer-attached digitizer; then, cephalometric analysis is completed via measurement of distances and angled by a software after tracing landmarks to be used in design (Richardson, 1981) (Leonardi et al., 2008). The cephalometric analyses using artificial intelligence aim to reduce analysis duration and improve diagnostic value of analyses by decreasing subjective errors (Leonardi et al., 2008).

The primary challenge is detection of landmarks in automated cephalometric analysis. In this issue, the first study was performed by Cohen (Cohen et al., 1984) in 1984 and 2 landmarks (sella and menton) were traced in an automated manner. In subsequent years, several approaches have been developed for automated tracing of cephalometric landmarks, which can be classified into 3 groups based on approaches used:

1. Informatics-based systems: Levy-Mandel et al. (1986) were first investigators who used informatics-based systems for automated cephalometric landmark tracing. In the study, the landmarks were traced according to geometric definition. The software developed accurately positioned 23 of 36 landmarks on 2 high-quality radiographic images. Parthasaraty et al. (1989) improved the software used by Levy et al. and tested on 5 cephalometric radiographs. In the study, it was reported that 58% of 9 landmarks were positioned by deviation of ±2 mm whereas 18% by ±1 mm and 100% by 5 mm. However, the software was unreliable in the presence of artifacts and poor-quality images as it was tested in a training set.

2. Template matching: This method relies on detection of parts in source image resembling template image. The template image is scanned on source images and similarity is measured by matching in each pixel. The coordinates of resembling pixels are recorded (Özekeş & Çamurcu, 2006). Cardillo et al. (Cardillo & Sid-Ahmed, 1994) developed a template matching algorithm based on mathematical morphology to determine landmarks. In the study, 20 different images were tested and 66% of landmarks were traced with a deviation of ±2 mm. Grau et al. (Grau et al., 2001) developed study by Cardillo et al. using line detection module. They used 20 images for training and test and reported that 90% of 17 landmarks were traced by a deviation of ±2 mm. These studies were tested in limited number of training set. Thus, they are unreliable in the presence of artifacts and poor-quality images.

3. Statistical modeling: Statistical models is one of the appropriate option for assessment of alterations in cephalograms since they takes variation of image quality into consideration (Rueda & Alcañiz, 2006). Rudolph et al. (1998) used statistical model recognition method to position landmarks in an automated manner. In the study, authors compared automated and manual landmark tracing on images with lowest resolution where cephalometric structures can be identified. It was found that there was no statistical significance between manual and computerized landmark tracing methods for 15 landmarks.

Hutton et al. (2000) applied Active Shape Model (ASM) to identify landmarks on 63 random cephalograms. It was found that 13% of 16 landmarks were traced by a deviation of ±1 mm whereas 35% by ±2 mm and 74% by ±5 mm. In the study, it was concluded that ASM had greater deviation rate for landmark identification; thus, it was insufficient for landmark identification in the clinical practice but it may be used as a starting point. In subsequent years, Cootes (Cootes & Taylor, 2004),(Cootes et al., 2001) proposed Active Appearance Model (AAM) which can model both shape and tissue variability. S. Rueda and M. Alcañiz (Rueda & Alcañiz, 2006) applied AAM, reporting mean sensitivity of 2.48 mm and mean standard deviation of 1.66 mm for each landmark. In the study, 50.04% of landmarks were traced by a deviation of 2 mm whereas 72.62% by 3 mm and 91.44% of 5 mm.

In a study, Jia-Kaung Liu et al. (Liu et al., 2000) evaluated accuracy of automated, computerized landmark identification system. The landmarks selected (n=13) were tested 10 cephalometric radiographs and it was shown there was no significant difference in 5 of 13 landmarks (sella, nasion, porion, orbitale and gnathion) between manual and computerized identification systems. The authors reported that accuracy of automated, computerized identification system was acceptable for only certain landmarks.

In 2014, IEEE International Biomedical Imaging Symposium organized a competition for automated cephalometric analyses. In the meeting, 300 cephalometric radiographs were used in Automated Cephalometric X-Ray Landmark Tracing Contest. In the assessment, 19 landmarks were traced by manually and evaluated by two experienced orthodontists (Yu et al., 2006). It was reported the team with best performance achieved a success rate of 71.48% by a sensitivity range of 2 mm; in addition, it was reported that identification of porion, gonion and articulare marks were particularly challenging (Wang et al., 2015).

Currently, there are ongoing studies on automatization of cephalometric analyses in recent studies. In 2020, Hye-Won Hwang et al. (2021) used 200 cephalograms as test data in their cephalometric analysis study using a novel deep learning method. In the study, reference points were manually identified by an orthodontist; then, same points were traced in the test data by another orthodontist and trained artificial intelligence. It was found that the success rate was 81.53% for accurate tracing of landmarks in novel artificial intelligence which was also found to be more successful than orthodontist in 3 of 19 landmarks.

Lee JH et al. developed a novel model to identify cephalometric landmarks with safety regions using Bayesian convolutional neural networks (B-CNN). Authors reported that the model showed a error rate of 1.53-1.74 mm in landmark placement and that it may be helpful with safe regions identified for inexperienced dentists (J.-H. Lee et al., 2020).

Automated landmark tracing and cephalometric analysis can use 2D imaging modalities as well as 3-dimensional (3D) imaging modalities by training landmarks via artificial intelligence. Lee SM et al. used Vgg-net neural network for landmark tracing and reported that the mean deviation was 1.5 mm for 7 landmarks. The mean deviation for Vgg-net was lower than those in 2D images.

Currently there are ongoing studies about automated cephalometric analysis and landmark tracing using 2D cephalometric radiographs or 3D CT images. Planmeca Romexis (Planmeca, Finland), CephX (ORCA Dental Al, Las Vegas, NV) and AudaxCeph (Ljubljana, Slovenia) are widely used automated cephalometric analysis software in the market.

3.1.4 Automated Bone Determination

Age at time of treatment is of importance for successful outcome in patients undergoing functional jaw orthopedics (Baccetti et al., 2002; Franchi et al., 2008). In patients, growth status can be assessed by chronological age and skeletal age. However, chronological age is not always reliable. thus, hand-wrist radiography and lateral cephalometric

radiographs are most commonly preferred methods for determination of post-pubertal growth period in orthodontics.

The bone age determination on lateral cephalometric radiographs was first investigated by Lamparski (1972), suggesting that cervical vertebra can be used for this purpose. This system has advantage of reduction in ionizing radiation since it is routinely obtained before orthodontic treatment (Aguiar et al., 2013) (Baccetti et al., 2005); however, it is unable to provide information as detailed as hand-wrist method due to limited number of bones evaluated (Tarvade (Daokar) & Ramkrishna, 2015).

Hand-wrist radiograph is readily available, cost-effective tool which can evaluate post-pubertal growth in a detailed manner. The Greulich and Pyle (GP) or Tanner or Whitehouse (TW2) method is used for determination of skeletal age on hand-wrists radiographs. Although GP method is older, it is most widely used method today (Reynolds, 1950). In this method, hand radiograph of patients is compared with a group of hand radiographs classified according to age and gender, determining bone age. The TW2 method analyzes and scores each bone in a detailed manner. Bone age is determined according to total score. Since the technique is complex and time-consuming, it is used by up to 20% (Chang et al., 2003) (Milner et al., 1986).

In traditional bone age determination, there may be some variability among orthodontists with disadvantages such as longer duration and difficulty in application. Thus, clinical decision-support systems (CDSS) have been developed to help orthodontists in determination of bone age.

In a study, cervical maturation stages were assessed on 188 cephalogram in either manual or computer-assisted manner (Baptista et al., 2012). It was reported that computer-assisted approach can contribute orthodontic treatment planning with high accuracy.

In 2015, Dzemidzic et al. (Dzemidzic et al., 2015) developed a software (Cephalometer HF V1) in order to determine maturation stage of cervical vertebra. It was reported that the software could accurately predict maturation stages of C1, C2 and C4 by automatically drawing their shapes.

In 2019, Kök et al. (Kök et al., 2019) compared performances of artificial intelligence algorithms including k-nearest neighbors (k-NN), Naive Bayes (NB), decision tree (Tree), artificial neural networks (ANN), support vector machine (SVM), random forest (RF) and logistic regression (Log. Regr.) which are commonly used to determine growth and development according to maturation stages of cervical vertebras. Authors reported that kNN and Log. Regr algorithms had lowest accuracy values while ANN was most stable algorithm.

In 2020, Amasya et al. (Amasya et al., 2020) developed an artificial intelligence system to determine cervical maturation stages and compared the system with human observer. In addition, 5 distinct machine learning algorithms (ANN, Tree, Log.Reg, SVM, RF) were used to compare success in classification. Authors reported that ANN was most successful model in classifying lateral cephalograms with performance closer to human observer.

In their study, Van Rijn et al. used BoneXpert (Visiana, Holte, Denmarky) which determine bone age according to GP atlas in an automated manner. In the comparison involving 405 hand-wrist radiographs, it was reported that the difference was 0.71 years between manual and automated bone age determination (Van Rijn et al., 2009).

Pietka et al. (2005) reported that the algorithm which they developed could determine bone age when assisted by image processing method of electronic atlas (e-atlas). Authors reported that evaluation can be made through " Image Archiving and Communication System".

Chang et al. (2003) carpal bone assessment is required for bone age determination in children aged <10 years but it cannot provide sufficient data in older children. Thus, authors developed a fuzzy logic-based system which can assess both carpal bones and phalanges, reporting that the hybrid system used can age determine by combining data from carpal bones and phalanges.

In 2016, Çelik and İçer (Çelik et al., 2016) developed an automated system using artificial neural network to determine bone age on hand-wrist radiograph. Authors found quadratic error as 0.52 years for the system. They reported that, by the system, bone age determination can be performed without need for an expert or use of high-quality images.

In 2018, Tajmir et al. (2019) investigated effects of supporting radiologists by artificial intelligence on accuracy and variability of bone age determination and reported that the use of artificial intelligence by radiologist improved accuracy in bone age determination with reduced error rate.

The automated bone age determination system can be used as clinical aid as they are fast and objective. Currently, these systems can determine bone age by support of clinicians and it is predicted that they can perform these procedures without human support (İzgi&Kök, 2020).

4. Artificial Intelligence in Orthodontic and Orthognathic Surgery Planning

Accurate treatment planning is one of the most important stages of orthodontic treatment. Treatment decision with or without tooth

extraction and identification of tooth to be extracted are key points in treatment planning. Tooth extraction is one of the irreversible procedures in orthodontic treatment; inaccurate applications can lad many problems such as suboptimum occlusion, insufficient over-jet, loss of anchorage, poor patient profile and failure to close space created by tooth extraction.

Orthodontist reaches a decision based on his/her experience and knowledge and data from clinical assessment, photographs, plaster model and 3D intraoral models and radiographs when developing a treatment plan(Ribarevski et al., 1996). The use of different tools and experience of clinician may result in differences in treatment plan. Thus, no standardization can be achieved during treatment planning (Devereux et al., 2011; Durão et al., 2015). In recent years, computer systems have been developed to formulate treatment planning in an objective manner, which mimics decision-making process of clinicians (Yagi et al., 2010).

In a study by Takada et al. (Takada et al., 2009), a template matching-based decision-making model was used for orthodontic treatment planning, reporting success rate of 90%. Similarly, Xie et al. (2010) used an artificial neural network-based artificial intelligence model to decide whether tooth extraction is required before orthodontic treatment. The model evaluated 25 indices to decide tooth extraction. The study showed success rate of 80%. In addition, authors estimated relative contribution of 25 indices to tooth extraction and found that the greatest contribution was provided by "anterior teeth appearing with insufficient lips" and "incisor mandibular plane angle while smallest contribution was provided by Frankfort-mandibular plane angle.

In a similar study using artificial neural network, it was reported that the model showed success rate of 93% in decision of treatment with or without tooth extraction (Jung & Kim, 2016). In the study, authors assessed decision-making for tooth to be extracted including maxillary/mandibular and first/second premolar and reported success rate of 84%.

The available studies showed that artificial intelligence models can be used as a novel approach for orthodontic treatment planning. These models can be used as reference by inexperienced orthodontists as they mimic decision-making processes of experienced orthodontists (Jung & Kim, 2016).

Orthognathic treatment is a mode of surgery-assisted orthodontic treatment that corrects skeletal deficits in patients completed their growth and development. In patients assigned for orthognathic surgery, malocclusion becomes more severe due to impairment of dental compensation during fixed orthodontic treatment; thus, the inaccurate positioning of jaws is corrected by surgery and treatment is completed. Thus, treatment planning

is of important in decision-making of orthognathic surgery.

Choi et al. (2019) developed an artificial intelligence model which can decide tooth extraction in orthognathic surgery. In the study, an experienced orthodontist gave decision of orthognathic surgery in 160 while orthodontic treatment without surgery in 156 of 316 patients. In the study comparing orthodontist and artificial intelligence model, it was reported that the success rate of the model was 96% for decision of orthognathic surgery and 91% for decision of orthognathic surgery with or without tooth extraction.

The field of use of artificial intelligence applications in orthognathic surgery protocol can be summarized in 4 topics:

a) Diagnosis: The artificial intelligence technology can be used in acquisition of data to be used diagnosis of orthodontic anomaly and to create a virtual patient in which can be used by clinician for planning. The field of use of artificial intelligence includes generation of 3D dental models, acquisition of 3D images of tooth and bone tissues by CBCT and acquisition of images of facial soft tissues by 3D camera (3dMd) and generation of facial and dental structures in 1:1 scale by combining above-mentioned data (Rasteau et al., 2020).

b) Cephalometric analysis: Automatization of cephalometric analysis in orthognathic surgery protocol allows 2D analysis as well as 3D analyses on CBCT images. As such, the clinician can interpret 3D dentofacial characteristics. The automated analysis software allows rapid and detailed analysis/interpretation of patient (Faure et al, 2016).

c) Treatment planning: Currently, several software are being used for 3D digital orthognathic treatment planning, including Dolphin 3D (Patterson Dental, USA), Nemoceph (Orthopia, Eskişehir, Türkiye), Clin Check (invisalign, US), Insigna (Ormco,US), Orthoanalyzer (3shape, Denmark). The model surgery used in traditional orthognathic treatment planning has been replaced by these software. Treatment predictions by Virtual Surgery Planning (VSP) allow effects of interventions on the patient and accurate communication between orthodontist and surgeon. In addition, it is used to explain orthognathic treatment to patient and to discuss outcome (Pagani et al., 2016). In their study, Steinhuber et al. (Steinhuber et al., 2018), reported that VSP is more rapid than traditional planning. In the study, it was suggested that digital surgical planning can be used to aid clinicians in challenging situations such as facial asymmetry. By widespread use of VSP, novel techniques have been developed for hand-made acrylic surgical splints used in orthognathic surgery. Today, surgical splints manufactured using CADD/CAM can be used as alternative to hand-made acrylic splints by eliminating human factor (Pascal et al., 2018).

d) Monitoring prognosis: The artificial intelligence technology allows detailed measurements with superposition of digital images. Superposition on 2- and 3D radiographic images are used in the assessment and follow-up of treatment (Bouletreau et al., 2019).

The artificial intelligence technology can provide 3D dental arc, skeletal profile and soft tissue profile of patients; in addition, automated cephalometric analysis can be performed using these data and surgical splints can be produced using CADD/CAM system. The data obtained can be used for virtual surgical planning and postoperative analysis. It is known that artificial intelligence is increasingly used for orthognathic treatment planning. However, complexity of procedures employed, need for special training and costs hamper its use in routine practice (Rasteau et al., 2020).

5. Conclusion

The artificial intelligence technology has shown a rapid progress in recent years and has been used in novel and different areas. In the health sector, presence of substantial data ready to process is one of the factors that accelerates advances in this technology. It is thought that artificial intelligence will become an important technology in planning healthcare services against pandemics in addition to diagnosis and monitoring of treatment.

In dentistry, artificial intelligence applications are being used in diagnosis and treatment planning. The studies on radiology have brought forward due to advances in image-processing technology. By increasing number of studies, clinical decision support systems will become an important component in dentistry practice.

In orthodontics, artificial intelligence has primarily focused onface analysis, tooth-jaw segmentation, cephalometric landmark tracing and cephalometric analysis, automated age determination, treatment planning and orthognathic surgery protocol. The artificial intelligence models reduce burden and time consumed by clinicians in diagnosis, treatment planning and treatment monitoring stages of orthodontic treatment. It was observed that the models used in the studies were generally trained via data input from clinicians. In subsequent years, by advances in the technology and increasing number of studies, the procedures achieved by orthodontist in diagnosis and treatment planning can be performed by artificial intelligence.

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Chapter 6

THE IMPORTANCE OF PHOTODYNAMIC THERAPY IN DENTISTRY

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Photodynamic Therapy

Photodynamic therapy is defined as the termination of the viability of target cells by generating reactive oxygen species in the presence of a photosensitizing agent with an appropriate wavelength and dose of light.[1,2]

The foundations of modern phototherapy were laid at the beginning of the 19th century. Oskar Raab proved that some chemical compounds such as acridine and eosin have toxic effects under light.[2]

The biggest step in the destruction of living microorganisms by light was taken with the production of the photosensitizing substance called Photofrin and the treatment protocol in many countries including the United States of America. This approach, which is effective on many microorganisms such as bacteria, viruses, protozoans and fungi, is particularly effective in localized and superficial infections.[3] For this reason, photodynamic therapy, also called "Photodynamic Antimicrobial Therapy", is a potential treatment approach in the field of dentistry, especially for infections in the oral cavity such as mucosal and endodontic infections, periodontal diseases, caries and periimlantitis.[1, 2, 4]

It is reported as a promising treatment because it is localized and non-invasive. While bacteria cannot develop resistance against photodynamic therapy, the application has no genotoxic or mutogenic effect.[5] It has been reported that the treatment, which is effective on both Gr (+) and Gr (-) bacteria, has a higher effect especially on Gr (+) bacteria.[5]

Mechanism of Action of Photodynamic Therapy

The basic principle of photodynamic therapy is the "killing effect" that occurs by a series of mechanisms. Photodynamic therapy includes three components: photosensitizer, light and oxygen.[1, 6] Photosensitizers are light-sensitive agents that absorb visible light, causing electron transfer or transferring light energy to its environment. In the presence of oxygen, they cause oxidative reactions that are toxic to microorganisms.[7] Toxic products resulting from a series of photochemical reactions occurring in the presence of photosensitizers with the effect of light at the appropriate wavelength and dose cause target cell death through oxidative damage.[1,8]

The first step of photosensitization reactions is the absorption of photon energy from the light source by the photosensitizer. Photosensitizers have a stable electronic configuration at the lowest energy level. When the light sensitive drug is exposed to light energy in the target area, the energy level rises after some energy distributions.[1, 9]

The photosensitizer, which absorbs light at the appropriate wavelength, changes from the singular state having a low energy level to the excited

singular state. Later, the photosensitizer can return to singular state as a result of the emission of light from the excited singular state, or it switches to the excited triple state with a high energy level. The stimulated triple state causes rapid and selective destruction in the target tissue by creating singular oxygen and other free radicals with high reactivity. Two mechanisms occur in the interaction of the photosensitizer with the biomolecules of the excited triple state.[1, 2]

In the Type I reaction, free radicals are formed by direct electron / hydrogen transfer from the photosensitizer, formation of ions, redox reactions or electron / hydrogen separation from the substrate molecule. As a result of the rapid reaction of these radicals with oxygen, reactive oxygen species such as superoxide, hydroxyl radicals and hydrogen peroxide are formed.

In the Type II reaction, the photosensitizer is electronically stimulated as a result of transferring the energy of its excited ternary form to molecular oxygen and single oxygen, known as the highly reactive form of oxygen, is formed. Photodynamic therapy is also very difficult to distinguish between these two mechanisms. However, it should be known that the damage caused by both mechanisms depends on the oxygen and the concentration of the photosensitizer.

Type II reactions are considered to be the main mechanism leading to photooxidative microbial cell damage. The photodynamic effect describes type II photoreactions that are mainly dependent on oxygen.[1, 2, 7, 10]

Sensitivity to photodynamic therapy varies depending on the cell wall structures of bacteria. Photosensitizer penetrates sensitive areas inside the cell thanks to the peptidoglycan and lipoteiotic pores in the cytoplasmic membrane of Gram positive bacteria. The outer membrane of Gram-negative bacteria acts as a physical and functional barrier between the cell and its external environment.[1, 11, 12]

Photodynamic inactivation can be achieved in both gram-positive and gram-negative bacteria with cationic photosensitizers.[12] In Gram-negative bacteria, the strong negative charge arising from the lipopolysaccharide layer on the outer membrane prevents neutral or anionic photosensitizers from entering the gram negative bacterial cell.[9]

Neutral or anionic photosensitizers are effective only on gram positive bacteria.[9,12]

Photodynamic therapy in bacteria creates a cytotoxic effect by affecting intracellular organelles and biomolecules through photodamage. Mitochondria, lysosome, cytoplasmic membrane and nucleic acid are potential targets for photodynamic therapy.[1] Two mechanisms are

proposed regarding the cellular damage caused by photodynamic therapy. The first is DNA damage, the second is cytoplasmic membrane damage or inactivation of cell membrane permeability and enzymes.[13]

The individual oxygen and free radicals that emerge as a result of photodynamic therapy affect many cell structures and show their effectiveness by following different metabolic pathways. In the use of antibiotics, resistance to this antibiotic may develop over time, while microbial cells cannot develop resistance to Photodynamic therapy.[1, 2]

Another advantage of photodynamic therapy over antibiotics is that it does not cause the secretion of proinflammatory cytokines. It has been observed that the damage to the cell membrane with photodynamic therapy is through lipid peroxidation and protein damage.[13]

However, antibiotics cause the development of a series of pathological events that result in tissue damage by causing the release of proinflammatory cytokines from cells.[14]

Photosensitizing Substances

The substances that initiate the photochemical reaction are photosensitizers and light sensitive agents. Photosensitizers, one of the three components of photodynamic therapy, absorb light and create a toxic effect for the cell. Thousands of photoactive compounds consisting of various natural and synthetic substances are known as photosensitizers. An ideal photosensitizer should be non-toxic, show local toxicity and be activated only under light.[1-3]

More than 400 compounds consisting of dyes and various natural substances are known as photosensitizers. The agents to be used in the treatment of microbial infections are required to have sufficient photophysical (maximum absorption wavelength, light absorption amount) and physicochemical (lipophilicity, ionization) properties, and to create a high amount of long-lasting oxygen. These agents, while killing microbial cells, are expected to cause minimal damage to host tissues and prevent the reproduction of pathogenic microorganisms after treatment. In addition, an ideal Photosensitizer should be stable during storage and application.[14]

Photosensitizing agents most commonly used in dentistry; toludine blue, methylene blue, rose bengal, malachite green and hypericin. However, with the increasing interest in natural materials in the new period, dyes obtained from natural plants; Hypericum perforatum, curcuma longa (turmeric) and oligomeric proanthocyanidins have been tried and successful results have been obtained.

Toluidine Blue

Toludin blue and methylene blue, which have the same chemical properties, are often used in antimicrobial photo-active disinfection. Toluidine blue is a basic drug that has been used in the antimicrobial field for many years. It is a blue cationic dye. Toluidine has the ability to kill a wide range of bacteria, including blue methicillin-resistant Staphylococcus aureus. Toluidine blue shows its effect by producing singular oxygen under light in the wavelength range of 630 nm.[7, 16]

Toluidine blue can be applied topically in the treatment of oral infections. In topical application, it has been shown that toluidine blue penetrates all layers of the epithelium, but in amounts negligible to the connective tissue. Toludin blue is a thiazine dye from the quinone-imine family. Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Fusobacterium spp. and more effective on lipopolysaccharides.[17]

Hypericin (Hypericum perforatum L.)

It is thought that Hypericin, which is naturally obtained from plants of the Hypericum type, is the strongest Photosensitizing agent found in nature. Hypericin is a phenanthroperylene quinine pigment naturally found in plants and is a natural photoactive. Hypericin can be synthesized naturally from plants of the hypericum type and is activated at 590-600 nm.[18]

Hypericum perforatum L. (Hypericaceae) plant has been used since ancient times for its antidepressant properties. It is also known to speed up wound healing. There are creams, ointments and extracts of the plant containing phenylpropane, flavanol derivatives, biflavones, proanthocyanidins, xanthons, chloroglycins, some amino acids, naphthodyantrons and essential oils. Two compounds called hypericin and hyperforin can be synthesized from the plant.[18]

Rose Bengal

Rose bengal is a structure with an oxygen atom in the middle of three aromatic rings and generates long-lived radicals. It is a xanthene dye that is activated at 450–600 nm. Rose bengal is an anionic compound especially effective against gram (+) bacteria.[19]

Rose can form singular oxygen, known as the highly reactive form of bengal oxygen. The high rate of halogen in the structure of rose bengal and its high molecular weight in these halogens enable this Photosensitizer to be more effective than other halogenated derivatives. This is because the increase in the amount of halogen and the fact that the photosensitizer contains higher halogens by weight facilitates the formation of an induced

triple state that will generate high reactivity single oxygen and other free radicals that cause rapid and selective destruction of the target tissue.[20]

Malachite green

The dye from the triarylmethane family absorbs red light. The material, which is mostly studied in periodontology, has been shown to be effective on Staphylococci, Enterobacteria and Candida with the study of Junqueira et al. (2010).

Proanthocyanidins

Proanthocyanidin, also known as procyanidin, is a group of polyphenolic compounds found naturally in fruits, vegetables, nuts, seeds, and flowers.[21]

In 1987, thanks to Jack Masquelier's powerful free radical scavenging ability at the same time obtaining oligomeric proanthocyanidins from apples, blueberries, avocado seeds, immature cocoa beans, horse chestnut, hawthorn fruit, birch flower, immature strawberry / blackberry, grape seed and red wine. It has been reported that proanthocyanidins claim to have an important therapeutic effect. The phenolic hydroxyl group in its structure acts as a hydrogen donor, effectively scavenging free radicals. It has been recognized to be effective in preventing many diseases such as hypertension, allergies, cardiovascular diseases and various infections. It is also thought to be anticarcinogenic, anti-inflammatory and vasodilator.[21,23]

Turmeric (Curcuma longa L.)

Turmeric (Curcuma longa L.) is one of the most recently prominent plant-derived Photosensitizer substances. The extract of the plant, which was used as a medicine in liver diseases, in the treatment of inflamed joints and wound healing in ancient times, is yellow pigmented and activated at 430 nm.[14, 22]

However, the low water solubility capacity of turmeric has been reported as a disadvantage. [23]

Rumex cristatus DC. (Labada)

Plants are used for medicines or dietary supplements due to their antioxidant, anti-inflammatory and antimicrobial properties. It is a plant from the Polygonaceae family, with more than 200 varieties all over the world, twenty three of which are found in Turkey. It has been used in traditional medicine for its anti-inflammatory and constipating effect. As a result of phytochemical screening, Labada derivatives were found to contain flavonoids, terpenes, organic acids and naphthalene.[24]

Light in Photodynamic Therapy

Photodynamic therapy requires a low-power visible light source that is compatible with the absorption spectrum of the Photosensitizer and can activate the Photosensitiser.[1]

Photosensitizers used today are activated with red light between 630-660 wavelengths.[17] Lasers, which are used as a standard light source in photodynamic therapy, provide superiority to ordinary light because of their ability to provide high energy, produce monochromatic light, and ease of access to the desired area by means of fiber optics. Complicated dye laser systems were used as a light source before, but in recent years, diode lasers, which are portable, much cheaper and extremely easy to use, have been developed. In addition, non-laser light sources have come into use.[17]

The wavelength of the light used and the activation peak of the Photosensitizer must be compatible with each other.[25] In this sense, the use of LED and filter lamps with a wide wavelength range in this area will allow the activation of many Photosensitizers. [26] In photodynamic therapy, various high-energy filter lamps are used in the clinical environment other than laser sources.[25] Light sources such as tungsten filament, quartz halogen, xenon arc and phosphor-coated sodium lamps are used in the treatment of large areas.[1]

Although these light sources are inexpensive, their general maintenance is also easier. Compared to lasers, filter lamps have a much wider wavelength range. Combined with various filters, they emit light of specific wavelengths. However, this situation causes a decrease in light power. Therefore, its use is limited in skin lesions.[25]

LEDs and halogen light sources, which are routinely used in dentistry, also constitute the basic light sources to be used in the activation of the Photosensitizer.[12] Halogen light sources have been used in dentistry for many years for the polymerization of fissure sealants, bonding agents, resin cement and composite resins. It is sufficient that the wavelength of the light used to polymerize these materials is around 400-500 nm.[27]

With the development of LEDs in recent years, these light sources have started to be used in Photodynamic therapy. LEDs, which have various advantages in clinical environment, provide ease of use in difficult to reach anatomical areas.[25] Although these light sources are cheaper and smaller, they are also lighter and easier to use.[1] Wavelength range ranges from 350 nm to 1100 nm.[25] In a study by Lima et al.,(2009) microorganisms in dentin caries were eliminated by activating the photosensitizer using an LED device.

Photodynamic therapy also depends on the depth (penetration) the light can reach in the tissue, the wavelength of the light used, and the penetration of the light into the tissues increases as the wavelength of the light increases. Although red light is mostly used in photodynamic therapy, the intensity of this light decreases in the tissue and can penetrate up to 1 cm. When near infrared light (700-850 nm) is used, tissue penetration approximately doubles. For this purpose, the development of new Photosensitizers that can be activated at this wavelength continues.[2, 3, 17]

Oxygen in Photodynamic Therapy

For photodynamic therapy to take place, the presence of oxygen is required and the inactivation of microorganisms occurs by photo-oxidation of biomolecules in cells.[28] In the type I reaction that occurs after the interaction of the triplet form of the photosensitizer with biomolecules, direct electron / hydrogen transfer from the photosensitizer results in the formation of ions, redox reactions, or the formation of reactive oxygen species such as hydroxyl radicals, superoxide and peroxide anions by the formation of electron / hydrogen from the substrate molecule. In the type II reaction, single oxygen, which is electronically excited and known as the highly reactive form of oxygen, is formed. The damage caused by these two reactions in the target tissue depends on both the energy level of oxygen and the concentration of photosensitizer.[1, 2]

The primary toxic product involved in the type II reaction is single oxygen. Single oxygen causes microbial cell death by acting on viruses, fungi, protozoa and bacteria. In addition, while anti-oxidant enzymes such as superoxide, dismutase and catalase can protect the cell against some oxygen radicals, they cannot protect it against singular oxygen.[1, 8, 29]

Dentistry and Photodynamic Therapy

The oral cavity is complex, relatively specific, and contains gram-positive and gram-negative bacteria, fungi, mycoplasma, protozoa and viruses, which are highly associated with microorganisms.[1,12]

Bacteria, fungi, viruses and single-celled microorganisms can be eliminated by photodynamic therapy by creating singlet oxygen derivatives. Photodynamic therapy is recommended as an alternative or addition to existing disinfection methods in root canal treatments and treatment periodontal issues. The biggest advantage of using photodynamic therapy in endodontic treatments and periodontal treatments are that it eliminates harmful microorganisms without damaging the cells in the surrounding tissues and is successful even against bacteria that have developed resistance to many drugs.[2-4]

Biofilm is a complex organization formed by microorganisms in the extracellular matrix that live together in a certain structural integrity by adhering to the tooth surface and communicate with each other to fulfill the functions necessary for the continuation of their existence. Photosensitizer, which has direct effect on extracellular molecules, shows its antimicrobial effect through singular oxygen with high chemical reactivity. The fact that the photosensitizer is also effective on the polysaccharides in the extracellular matrix of the plaque is among the advantages of Photodynamic therapy compared to antibiotics. In this way, resistance developed against antibiotics against Photodynamic therapy, which inhibits plasmid change by breaking down the biofilm, does not develop.[1, 2, 4]

As is known, antibiotics show their effects by damaging certain parts of microorganisms. In contrast, Photodynamic therapy causes destruction in more than one part of the cell through oxidative damage. For this reason, it is very unlikely that all damaged areas gain resistance to Photodynamic therapy.[12, 13] Photodynamic therapy, which targets microorganisms in plaque in dentistry, can be used as a preventive method and as a noninvasive method by eliminating bacteria in the carious cavity. Photodynamic therapy, which performs a rapid bacterial death after a short light activation process, also has a short half-life of reactive oxygen species and a limited diffusion distance. In addition, the irradiation area is limited. This enables Photodynamic therapy to be applied in a specific area.[1, 30]

It is a matter of discussion that bacteria may remain inactive in the area where dentin is minimally affected in deep caries. In this context, using Photodynamic therapy to take advantage of its lethal effect on bacteria may be an appropriate approach.[4, 31]

There are many studies on oral microorganisms. It was found that toluidine blue applied to dentin caries created in situ by Lima et al. (2009) was effective on microorganisms and it was concluded that Photodynamic treatment would be a useful approach that can be used to eliminate microorganisms in dentin caries before restoration. In another study, photogem, hematoporphyrin and toluidine blue applied on L. acidophilus and S. mutans were activated with an LED light source and toluidine blue was reported to be the most effective photosensitizer among these three materials.[32]

Hypericin and Foslipos (FOS) were applied on S. mutans and S. sobrinus. In this study, halogen light source used for polymerization in dentistry was used to activate Photosensitizer and effective results were obtained.[33]

It is a promising treatment option due to the lack of resistance of

bacteria against photodynamic therapy and also because it is localized and non-invasive.

In order for photodynamic therapy to be a reliable alternative to conventional antibiotics, the destructive effect of photodynamic therapy should be minimal, especially on tissues damaged by infection. Therefore, it is necessary to evaluate the results of well-planned controlled clinical studies in order to determine the optimum conditions.

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Chapter 7

PROTECTIVE EFFICACY OF NOBILETIN AND PHYSIOLOGICAL PATHWAYS IT USES

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Introduction

Nobiletin, which is especially concentrated in the peel of citrus fruits (Li *et al*., 2006), is an active ingredient that attracts the attention of researchers because it has very high bioactive properties, is easily accessible and is thought to be affordable in terms of cost. The name nobiletin is thought to be inspired by *Citrus nobilis*, most likely referring to citrus fruits such as tangerines that peel easily. It was stated by Li *et al*. (2014) that the commonly used other names for nobiletin are 2-(3,4-dimethoxyphenyl)-5,6,7, 8-tetramethoxy-4H-1-benzopyran-4-one, and 5,6,7,8,3′,4′ – hexamethoxyflavone. In other studies, it was determined that the content of nobiletin was the highest in *Citrus sinensis* and *Citrus aurantium* (Li *et al.,* 2006, Li *et al.,* 2014). It has been stated that nobiletin can be easily absorbed due to its high permeability and most likely the mechanism of absorption is facilitated diffusion (Kimura *et al.,* 2014). Nobiletin, one of the major components of the polymethoxyflavone family, has been shown to have anti-carcinogenic (Ma *et al.,* 2014), antioxidant (Zhang *et al.,* 2016), antidepressant (Yi *et al.,* 2011), antimicrobial (Yao *et al.,* 2012) and, cardioprotective (Parkar *et al.,* 2016) effects in addition to its strong anti-inflammatory properties. In addition, There has effects of nobiletin serious on the central nervous system. Some of these effects can be listed as follows. alleviating memory disorders, improving neurogenerative disorders, protecting against neurotoxicity induced by various chemicals, protecting brain cells against ischemia and reperfusion injury, and preventing cerebral edema (Nagase *et al.,* 2005; Yasuda *et al.,* 2014).

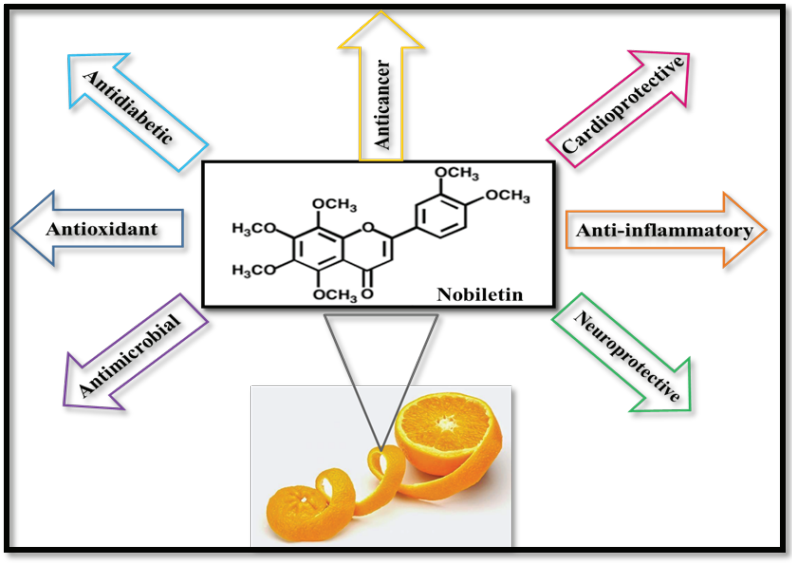

Figure 1. *Protective effects of nobiletin*

Anti-inflammatory Effect

In a study investigating the chondroprotective activity of nobiletin, it was stated that this active ingredient may be among strong anti-inflammatory agents as it inhibits PGE2 production, matrix degradation and pannus formation (Ishiwa *et al.,* 2020). Inhibition of iNOS and COX-2 is considered as one of the mechanisms underlying the anti-inflammatory activity of nobiletin, and depending on these inhibitions, it is accepted to prevent or reduce the formation of N-nitroso compounds and peroxynitrides (Li *et al.,* 2007). As another anti-inflammatory mechanism of action, nobiletin has been shown to decrease IL-1a, IL-1b, TNF-a and IL-6 levels, as well as decrease the production of pro-matrix metalloproteinases and increase the expression of TIMP-1. In addition, it has been suggested that it may be a unique anti-inflammatory due to its effect on TIMP-1 expression (Lin *et al.,* 2003). It was determined that nobiletin nanoemulsion caused a decrease in the levels of various cytokines and mediators that are effective in initiating the inflammation process in RAW 264.7 macrophages stimulated with lipopolysaccharide (Liao *et al.,* 2018). Similar to this study, it was reported that the combination of nobiletin and sulforaphane showed a synergistic effect on the inhibition of lipopolysaccharide-induced inflammation (Guo *et al.,* 2012). It has been stated that nobiletin can be used as a nutraceutical supplement in the treatment of inflammatory bowel diseases because it is very successful in reducing intestinal inflammation and fibrosis (Hagenlocher *et al.,* 2019). Nobiletin has also been reported to be effective on neuroinflammations. For example, it has been shown to play an active role in suppressing excessive microglial activation induced by LPS and causing brain damage, reducing proinflammatory cytokine levels and inhibiting the nuclear factor kB pathway (Cui *et al.,* 2010). Bi *et al.* (2016) determined that nobiletin significantly reduced the levels of NF-κB and proinflammatory cytokines in a model of isoflurane-induced cognitive impairment in aged rats. According to Xiong *et al.* (2015) reported that nobiletin causes a decrease in the expression of proinflammatory cytokines, iNOS and COX-2 in an experimental colitis model, and therefore may be effective in alleviating the increased inflammation in colitis. It was determined by Li *et al.* (2018) that nobiletin reduced proinflammatory cytokine levels and inhibited the NF-kB pathway in mice with acute lung injury, and reduced pulmonary edema. In a study published in 2006, it was suggested that nobiletin could create a synergistic effect with standard drugs (glucocorticoids and H2 receptor agonists) used in the treatment of allergic inflammation and asthma, and could be a new therapeutic agent (Wu *et al.,* 2006). In another study, it was determined that nobiletin decreased proinflammatory cytokine levels, inhibited the MAPK pathway and increased the PGE2 level in ethanol-induced gastric injury (Li *et al.,*

2017). According to Xie *et al.* (2019), nobiletin is a potent therapeutic agent that can be used in the treatment of osteoarthritis because it inhibits the IL-1β-stimulated phosphorylation of PI3K/Akt and the NF-κB pathway, and decreases the levels of proinflammatory markers. Wang *et al.* (2019) stated that brain infarction developing due to ischemia and reperfusion injury is relieved by the application of nobiletin, which its anti-inflammatory activity is known. They also suggested that the mechanism underlying this effect is the inhibition of p-p38, MAPKAP-2 and inflammatory marker production. In another study, in which an acute pancreatitis model was created, it was found that nobiletin reduced pp38MAPK and p-AKT expression and accordingly significantly reduced tissue damage and inflammation (Liu *et al.,* 2016).

Anticancer Effect

It would not be wrong to say that nobiletin shows its anticancer activity in various ways and as a result of the literature reviews, ways such as inhibiting cell proliferation, preventing angiogenesis and preventing apoptosis are at the forefront. The findings obtained in a study on liver cancer are quite striking, and it has been suggested that nobiletin inhibits the cell cycle in the G2 phase, has antiproliferative effects, and is a good candidate to be used in cancer treatments in the future (Ma *et al.,* 2014). In a study investigating the efficacy of various flavonoids in human breast cancer and colon cancer cell lines, the efficacy of nobiletin was also investigated, and it was found that proliferation decreased and apoptosis was not induced in cell lines exposed to flavonoids. It has even been suggested that it may be advantageous in the treatment of tumors due to these effects (Morley *et al.,* 2007). In the in vitro study of Chen *et al*. (2014) on breast cancer, it was determined that nobiletin inhibited cell cycle progression in the G0/G1 phase, suppressed ERK1/2 activity and Bcl-xL expression. It has been stated that nobiletin prevents cell proliferation and induces apoptosis in a dose-dependent manner in ovarian cancer (Zhang *et al.,* 2020). In another study on ovarian cancer, it was determined that nobiletin inhibited angiogenesis and limited tumor growth by inhibiting the expression of Akt, HIF-1α, NF-κB and vascular epithelial growth factor (Chen *et al.,* 2015). It is declared that nobiletin inhibits increased cell proliferation in the G1 phase on gastric cancer and has a synergistic effect with 5-fluorouracil, which is used in cancer treatment (Moon *et al.,* 2013). In a study conducted in 2014, it was determined that the application of nobiletin in acute myeloid leukemia inhibited the cell cycle in the G0/G1 phase and prevented cell proliferation, induced apoptosis with activation in the caspase cascade, and due to these effects, it had a strong potential to be used in cancer treatment (Hsiao *et al.,* 2014). Similar to other cancer studies, it was been shown in another cancer study that nobiletin inhibits

cell cycle by ERK and AKT pathways, prevents cell proliferation and induces apoptosis in osteosarcoma cells (Niu *et al.,* 2014.). Sp *et al.* (2018) stated that nobiletin affects CD36, which plays a role in angiogenesis, with STAT3 activator and inhibits angiogenesis and even prevents tumor metastasis in breast cancer. It has also been determined that the CD36/STAT3/NF-kB pathway is used in this inhibition. Li *et al*. (2019) applied nobiletin together with a chemotherapeutic drug in a colorectal cancer cell line, and it was determined that nobiletin increased the antiproliferative and apoptotic efficiency of the standard drug by activating the PI3K/Akt/mTOR pathway.

Antioxidant Effect

Since oxidative stress plays an important role in the pathogenesis of many diseases, another feature sought in substances that can be used for treatment is antioxidant effect. Malik *et al.* (2015) reported that in cisplatin-induced kidney damage, nobiletin causes a decrease in MDA levels, which increases due to oxidative damage, and an increase in antioxidant levels such as GSH, SOD and CAT. It has been determined that nobiletin has cytoprotective, anti-apoptotic, anti-oxidant and insulinotropic effects against oxidative stress-induced damage in isolated pancreatic islets (Keshtkar *et al.,* 2019). It has been declared that the administration of nobiletin in rats with McFarlane flap model has been reported to control oxidative stress by increasing blood flow, vascular endothelial growth factor and SOD levels and decreasing MDA levels. (Jiang *et al.,* 2020). It was determined that MDA levels increased significantly and GSH and SOD levels decreased significantly in ethanol-induced gastric damage, and it was shown that this negative picture was reversed depending on the dose in the nobiletin administered groups (Li *et al.,* 2017). It has been stated that cell death caused by oxidative stress induced by hydrogen peroxide in the HT22 hippocampal cell line is prevented by the application of nobiletin, but it can be used in neurodegenerative diseases after its antiapoptotic mechanisms are fully elucidated (Cho *et al.,* 2015). The increased in GSH level, glutathione peroxidase and manganese-superoxide dismutase activities and decreased in tau phosphorylation in mice with experimental aging model (SAMP8) after nobiletin administration reveals that nobiletin has a strong antioxidant activity (Nakajima *et al.,* 2013). Liu *et al*. (2018) evaluated the effectiveness of nobiletin against the damage induced by hydrogen peroxide in retinal pigment epithelial cells (ARPE-19), and found that nobiletin showed antioxidant activity by stimulating Akt signaling pathway. It has been stated that nobiletin, which is used in the treatment of brain ischemia injury, increases Nrf2, HO-1, SOD1 levels, while decreasing NF-κB and MMP9 levels, thus showing antioxidant and anti-inflammatory effects (Zhang *et al.,* 2016). It has been reported that

nobiletin inhibits the JNK/ERK1/2 and Akt/mTOR pathways in cadmium-induced neurotoxicity, thus reducing free radical production. This effect is due to its strong antioxidant properties (Qu *et al.,* 2018). It has been suggested that as a result of exposure to nonylphenol, a decrease in antioxidant levels, an increase in oxidant levels and an increase in sperm abnormalities, a decrease in motility-viability-numbers and testicular steroidogenic enzymes occur in rats, and these negative effects was significantly reduced with nobiletin supplementation (Ijaz *et al.,* 2021).

Cardiovascular Effect

In vitro study investigating the cardioprotective efficacy of nobiletin, it has been reported that the pathophysiological chart that occurs due to hypoxia/reoxygenation damage in H9c2 cells is corrected with the application of nobiletin, therefore it has the potential to be used in ischemic heart diseases in the future (Liu *et al.,* 2019). Due to increased oxidative stress and inflammation in diabetes, cardiomyopathy, which is one of the most important chronic complications, is triggered. In the experimental diabetic cardiomyopathy model, it was determined that nobiletin reduces oxidative stress and inflammation and accordingly improves myocardial dysfunction (Zhang *et al.,* 2016). A significant decreased in oxidant levels and an increased in antioxidant levels were observed as a result of intragastric administration of nobiletin in rats with trimethylamine oxide and oxidative stress-induced aortic inflammation. As a result of these results, it was been shown that nobiletin is a powerful antioxidant source in the elimination of vascular inflammations (Yang *et al.,* 2019). In rats which hypertension was induced by L-NAME, vasodilation responses in the mesenteric vascular beds and aorta were improved and oxidant marker levels decreased as a result of treatment with nobiletin. Considering these findings, it would not be wrong to say that nobiletin has antihypertensive properties (Potue *et al.,* 2019). Myocardial damage induced by coronary microembolization was healed by nobiletin treatment and returned to the physiological state; it for this effect was been stated that it stimulates the PI3K/Akt pathway, increases Bcl-2, one of the apaoptosis markers, and inhibits the expression of caspase-3 and Bax, and finally, it performs its cardioprotective activity by reducing oxidative stress (Mao *et al.,* 2019). It was been declared that these adverse effects, in which TGF-β1 is over-synthesized as a result of feeding with a high-fat diet, and vascular and renal function disorders occur, can be alleviated by nobiletin treatment (Bunbupha *et al.,* 2020). Cardiac dysfunction after acute myocardial infarction was improved by nobiletin treatment, accelerates the elimination of impaired and damaged cells due to ischemia (LC3BII and P62 protein levels have been tested), and it is stated that this active substance has a strong potential in myocardial protection (Wu *et al.,* 2017).

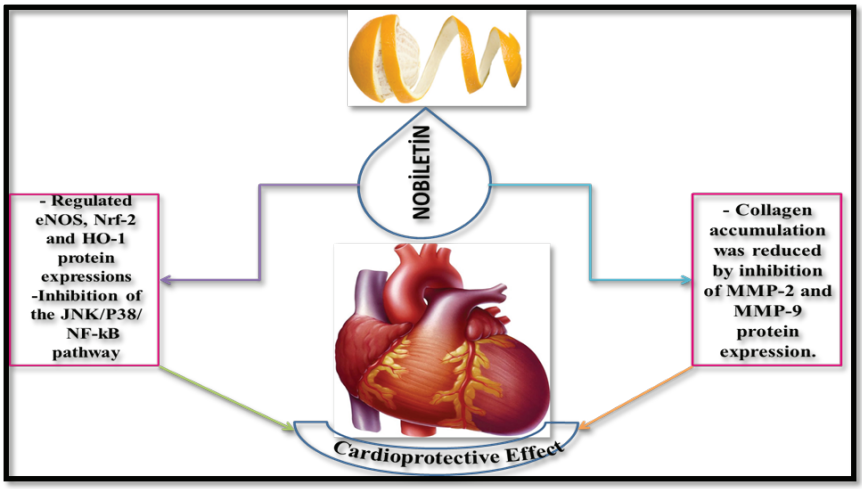

Figure 2. *Pathways of cardioprotective action of nobiletin*

Antidiabetic Effect

Diabetes is one of the leading metabolic diseases with serious economic burden and complications, the number of which is increasing unabated worldwide. Currently, the lack of a definitive treatment for diabetes and the fact that the protocols applied are aimed at keeping hyperglycemia under control, lead researchers to search for new active substances. Nobiliten is one of these substances. In a study on gestesyanol diabetes mellitus mice, nobiletin was found to cause a decrease in fasting blood glucose levels and inflammation. However, it was emphasized by the researchers that more studies are needed to determine the long-term effects (Nguyen-Ngo *et al.,* 2020). It has been determined that nobiletin increases glucose uptake by PI3K/Akt/protein kinase A pathway in adipose tissue, which is one of the most important tissues where insulin-mediated glucose uptake takes place in the periphery. It was thought that the mechanism underlying this effect might be due to its antidiabetic properties (Onda *et al.,* 2013). Takii *et al*. (2017) also mentioned two important mechanisms underlying the antidiabetic activity of nobiletin. It has been suggested that the first of these mechanisms is to increase glucose-induced insulin secretion by the exchange protein activated by cAMP (EPAC), and the second is to prevent beta cell apoptosis by the JNK/PKA pathway. It was been determined that testicular damage due to increased hyperglycemia and oxidative stress in diabetes is reduced by nobiletin treatment because nobiletin increases insulin sensitivity compared to the diabetes control group, as well as decreases proinflammatory cytokine and oxidant levels and increases FSH, LH and testosterone levels (Salah, & Ismail 2021). The administration of nobiletin was effective in improving hyperglycemia by reducing plasma

glucose levels in obese diabetic mice, and insulin resistance by regulating Glut1 and Glut4 expression in white adipose tissue and muscle tissue (Lee *et al.,* 2010) Insulin resistance and atherosclerosis inducedIn an animal model, it has been shown that nobiletin decreases VLDL-triglyceride secretion, increases peripheral insulin sensitivity, decreases aortic atherosclerosis, and even does not stimulate phosphorylation of insulin receptor substrate-1 and lipogenesis (Mulvihill *et al.,* 2011). One of the common chronic complications of diabetes is retinopathy, and it has been stated that nobiletin treatment reduces blood retinal barrier permeability and improves the thickness of retinal layers in rats induced type 1 diabetes by streptozotocin (Parkar & Addepalli, 2014).

Neuroprotective Effect

In the cerebral ischemia/reperfusion model, nobiletin was showed a neuroprotective effect by reducing infarct volume and brain edema, reducing brain cell death by showing anti-apoptotic effect, and reducing motor functional disorders (Yasuda *et al.,* 2014). Since the physiology of the nervous system has not been fully resolved, the physiopathology of neurodegenerative diseases, the incidence of which has increased in recent years, has not been fully understood. This, in turn, hinders the full success of practices aimed at preventing or treating these diseases. Nobiletin has been identified as a potential neuroprotective agent for the treatment and/or prevention of neurodegenerative diseases, as it inhibits the accumulation of amyloid beta peptides and the hyperphosphorylation of tau protein, preventing taupathies, reducing ischemic damage and cholinergic deficiencies (Braidy *et al.,* 2017). Nobiletin treatment against oxidative stress in HT22 cells inhibited caspase 3 and Bax expression while stimulating Bcl-2 expression, in addition, as it was inhibited the expression of phospho-Jun N-terminal kinases and p-p38 proteins, as a result of these results, it was determined that nobiletin had a neuroprotective effect in the hippocampal neuron model (Cho *et al.,* 2015). In another study, nobiletin was administered to rats for 9 days before ischemic brain damage was created. When the results were examined, it was reported that nobiletin inhibited the TRL4/NF-κB pathway and activates the Akt/mTOR pathway with propofel-mediated treatment, thus showing neuroprotective and anti-inflammatory effects (Zheng *et al.,* 2017). In a study investigating the efficacy of nobiletin on mitochondrial dysfunction in cortilal neurons, it was suggested that it may decrease mitochondrial free radical production and show neuroprotective activity by increasing the expression of antioxidants such as Nrf2 and HO-1 (Amarsanaa *et al.,* 2021). As a result of the application of nobiletin, apoptosis was prevented in hippocampal CA1 neurons in carotid artery occlusion ischemia, an increasing in calcium/calmodulin-dependent protein kinase II (CaMKII), ERK and

CREB phosphorylation, considering these results, it has been declared that nobiletin is a neuroprotectant that can be used in the treatment of ischemia-induced learning and memory disorders (Yamamoto *et al.,* 2019). It has been determined that the administration of nobiletin in rats with cerebral artery occlusion protected the brain from ischemic damage by stimulating the Akt/CREB/BDNF pathway and increasing the expression of Bcl-2 and claudin-5 (Zhang *et al.,* 2013). Kazak *et al*. (2021), in the neurotoxicity model induced by cisplatin, showed that the administration of nobiletin increased BDNF expression and G6PD activity in experimental animals, and caused a decrease in neuronal degeneration, edema and apoptosis.

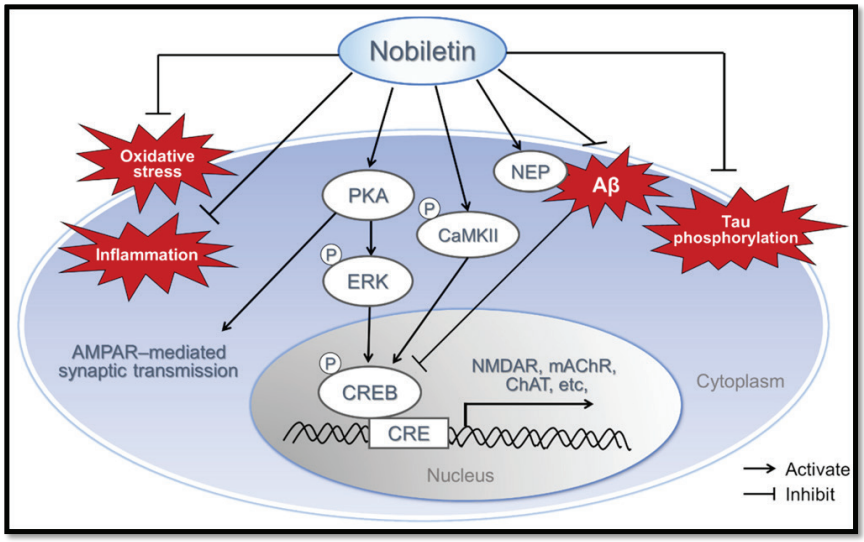

Figure 3. *Some of the neuroprotective action pathways of nobiletin (Matsuzaki & Ohiz, 2021).*

Antimicrobial effect

It would not be wrong to say that nobiletin is a highly bioactive active ingredient and has a protective effect in a wide range. Considering its antimicrobial activity, Yao *et al*. (2012) investigated the effectiveness of nobiletin on Pseudomonas fluorescens and Pseudomonas aeruginosa. The highlights of their results can be listed as follows; firstly, nobiletin inhibits succinate dehydrogenase, malate dehydrogenase and protein synthesis, secondly, it impairs cell membrane permeability, and thirdly, it causes plasmolysis and death. Yi *et al*. (2008) evaluated the efficacy of various flavonoids in six different strains of microorganisms (E. coli, S. aureus, S. epidermidis, E. faecalis, S. typhi and E. cloacae). Among the flavonoids, it has been suggested that nobiletin has a lower antimicrobial activity in these bacterial strains, which may be due to its polymethoxylated structure.

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Chapter 8

THE MAIN PHYSIOLOGICAL EFFECTS AND BE EFFECTIVE METABOLIC PATHWAYS OF CHLOROGENIC ACID

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Introduction

Chlorogenic acid, a member of the hydroxycinnamic acid family, consists of a combination of a caffeic acid part and a quinic acid part. Although some researchers have called chlorogenic acid 3-CQA, in reality this nomenclature is incorrect. In fact, chlorogenic acid is called 5-O-caffeoylquinic acid, or 5-CQA for short (Naso *et al.,* 2014; Wang *et al.,* 2016; Santana-Gálvez *et al.,* 2017). Despite the chloro prefix in the name of chlorogenic acid, it does not contain chlorine. The chloro suffix here actually comes from the Greek and is used to mean light green (Kremr *et al.,* 2016). Although the presence of chlorogenic acid in sunflower seeds was first reported by Ludwig and Kromeyer in 1854; It was first isolated from green coffee beans by Gorter in 1909 (Lu *et al.,* 2020). Chlorogenic acid is a polyphenolic component that must be taken with daily nutrition due to its antiviral, antibacterial, antimicrobial, anti-inflammatory, antipyretic, hepatoprotective, cardioprotective, antihypertensive, neuroprotective, antidiabetic, antiobesity, anticancer and free radical scavenging effects. Because of these activities, it was produced in crystalline form and commercially sold before other hydroxycinnamic acid family members (Naveed *et al.,* 2018; Lukitasari *et al.,* 2018). Chlorogenic acid is a polyphenolic compound produced in many plants. With the highest rate in green coffee beans; It is found in many herbs and vegetables, including roasted coffee beans, potatoes, sunflower seeds, artichoke leaves, apples, sweet potato leaves, prunus fruit, pears, peaches, nectarines, blueberries, carrots, tomatoes, broccoli, and sweet bell peppers (Fazel *et al.,* 2017; Lu *et al.,* 2020).

1. Structure, absorbtion and mechanism of action

As mentioned before, chlorogenic acid is occurs by esterification between the COOH and 3-OH groups of caffeic acid and quinic acid (figure 1) (Olthof *et al.,* 2001). Chlorogenic acid can be found in many isomers in many fruits and vegetables, especially in coffee beans. Neochlorogenic acid (3-CQA), Cryptochlorogenic acid (4-CQA), 3,5-Dicaffeoylquinic acid (3,5-diCQA = Isochlorogenic acid A), 4,5-Dicaffeoylquinic acid (4,5-diCQA = Isochlorogenic acid C), and Chlorogenic acid (5-CQA) are the main ones (Liang *et al.,* 2019). It is reported that chlorogenic acid is absorbed in humans in two ways. First, about 33% of the chlorogenic acid taken with nutrition is absorbed from the stomach and upper parts of the digestive system without being broken down. Secondly, approximately 7% is absorbed from the small intestine after being broken down into quinic acid and cafeic acid (Lu *et al.,* 2020). Olthof *et al.* (2001) administered 2.8 mmol chlorogenic acid and the same amount of caffeic acid orally to 7 ileostomy subjects (4 females and 3 males) on separate days and collected ileostomy fluid and urine samples of these subjects for 24 hours. They

determined that chlorogenic acid was absorbed at a rate of 33 ± 17% and caffeic acid at a rate of 95 ± 4%. They also stated that approximately 11% of orally taken caffeic acid is excreted in the urine. Again, they determined only 0.3% of the level of caffeic acid, which is the breakdown product of chlorogenic acid, in the urine. Based on this information, they reported that the second pathway (caffeic acid + quinic acid) in the absorption of chlorogenic acid is not very important. Lafay *et al.,* (2006) in their study on rats, determined that less than 1% of chlorogenic acid has been metabolized in the stomach and small intestine, and 15-32% of dietary chlorogenic acid was has been metabolized into caffeic acid in the cecum. In addition, they stated that caffeic acid and chlorogenic acid arised in both plasma and urine in a short period of 1.5 hours, indicating that chlorogenic acid was absorbed into the upper part of the digestive system. Chlorogenic acid metabolism and absorption of products take place through the microbiota in the colon. Undegraded chlorogenic acid and its other metabolites taken into the bloodstream are transported to the liver and processed there (Lu *et al.,* 2020).

Many investigators reported that chlorogenic acid inhibits inflammatory pathways such as JAT/STAT, PI3K/Akt/mTOR, TLR4/MyD88/RELA, NLRP3, HIF-1α/AKT, and COX-2/NLRP3/NF-κB moreover activates antioxidant pathways such as NFE2L2 and MAPKs. (Zhang *et al.,* 2018; Park *et al.,* 2015; Chen *et al.,* 2018; Shi *et al.,* 2016., Wang *et al.,* 2019). Chlorogenic acid is thought to show its effectiveness by inhibiting the inflammatory pathways mentioned above and even more so and activating the anti-inflammatory pathways.

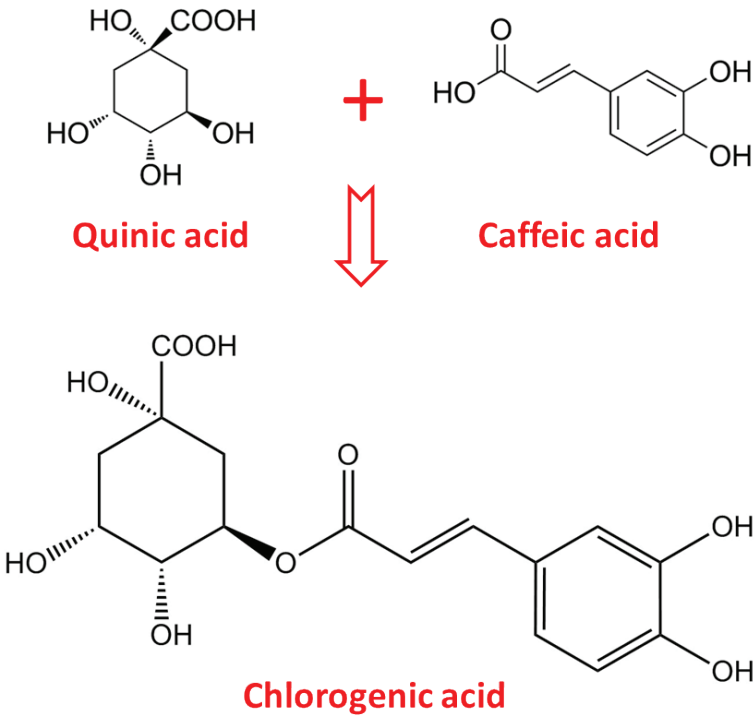

Figure 1. *Chemical structure of chlorogenic acid (5-CQA)*

2. Antiviral effects

Ding *et al.* (2017) stated that 100 mg/kg of chlorogenic acid administered intravenously to mice reduced the death rate against H1N1 and H3N2 by 60% and 50%, respectively, and effectively attenuated lung inflammation. In the same study, it was stated that chlorogenic acid acts as a neuraminidase blocker against influenza A virus. In yet another study, in vivo and in-vitro experiments showed that chlorogenic acid almost completely inhibits the activity of neuraminidase, one of the important antigenic structures of the influenza virus (Liu *et al.,* 2016.). In another study, it was determined that chlorogenic acid showed strong antiviral activity on enterovirus 71 infected cell line (Li *et al.,* 2013). It was expressed that administration of high doses of chlorogenic acid in chickens infected with bronchitis virus is effective in regulating innate immunity via TLR7, MDA5 and NF-kB signaling pathways. It was also been reported that it can regulate innate immune mechanisms against gamma coronavirus (Abaidullah *et al.,* 2021). In infectious bursal disease in chicken embryos, it was shown that chlorogenic acid application reduces histamine production, greatly reduces NF-κB activation, and inhibits TNF-α and IL-1β production (Li *et al.,* 2021.). It was reported that chlorogenic acid has an inhibitory

effects against hepatitis B virus in both in-vivo and in-vitro experiments (Zuo *et al.,* 2015).

3. Antibacterial effects

Jeong *et al.* (2014) showed that chlorogenic acid has antibacterial activity against *P. Aeruginosa, S. aureus, B. cereus* and *S. epidermidis* bacteria. Similarly, Lou *et al.* (2011) stated that its significantly inhibited the growth of both gram - (*Salmonella Typhimurium, Escherichia coli, Shigella dysenteriae*) and gram + (*Bacillus subtilis, Streptococcus pneumoniae, Staphylococcus aureus*) bacterial pathogens. It has believed that chlorogenic acid achieves this effect by binding to the outer membrane of the bacterium, increasing its permeability and causing the loss of its barrier property, and also by releasing cytoplasmic macromolecules that cause apoptosis. In a study, it was determined that nanoparticles produced as chlorogenic acid-loaded silica mesoporous can enter the cell by breaking the cell wall of *Escherichia coli* and *Bacillus subtilis*, and as a result, prevent bacterial proliferation. It is thought that this effect is probably due to reactive oxygen radicals induced by chlorogenic acid (Wang *et al.,* 2020). In many studies, it was determined that chlorogenic acid effectively prevent the proliferation of *Staphylococcus aureus* and *Escherichia coli* species (Li *et al.,* 2014; Lee & Lee, 2018; Zhu *et al.,* 2020; Zheng *et al.,* 2016). In a study examining the effects of chlorogenic acid both in-vivo and in-vitro in *Klebsiella pneumonia* infection, it was reported that it had a similar effect to the standard drug, levofloxacin (Tan *et al.,* 2020). While chlorogenic acid applied in the obesity model created in mice fed a high-fat diet significantly reduced the proliferation of bacteria belonging to the Ruminococcaceae, Desulfovibrionaceae, Erysipelotrichaceae and Lachnospiraceae family; It significantly increased the growth of Lactobacillaceae and Bacteroidaceae family members (Wang *et al.,* 2019).

4. Anti-inflammatory effects

It was reported that chlorogenic acid inhibits TNF-α and hydrogen peroxide-induced IL-8 production in Caco-2 cells, and also inhibits dextran sulphate sodium-induced MIP-2 and IL-1β mRNA expression. In addition, it has been stated that it acts as an anti-inflammatory against inflammatory bowel disease (Shin *et al.,* 2015). It was expressed that chlorogenic acid greatly inhibits the production of COX-2 and iNOS without causing any toxicity besides nitric oxide, and also reduces the levels of proinflammatory cytokines like IL-1β and TNF-α. In addition to all these, it was stated that it suppress the nuclear translocation of NF-kB and may be a potential source for the cure of inflammatory diseases such as sepsis (Hwang *et al.,* 2014). Dos Santos *et al.* (2006) reported that chlorogenic acid applied to rats at dosage of 50-100 mg/kg inhibited experimentally induced edema

and formaldehyde-induced pain, but did not prevent fever induced by lipopolysaccharides. They attributed this to the fact that prostaglandin E2 has no effect on its synthesis or release, or that it cannot cross the blood-brain barrier due to its high polarity. It has been stated that chlorogenic acid can decrease the increased serum TNF-α, NOS and COX-2 levels and mRNA expression in liver ischemia-reperfusion. It was thought that this positive regulation was probably due to the inhibition of the inflammatory answer and the potentiation of the anti-oxidant system (Yun *et al.,* 2012). Uslu and Atila Uslu determined that the ethanol extract obtained from *Prunus laurocerasus* fruits showed significant gastroprotective effects in the indomethacin-induced ulcer model. They stated that it showed this effect by reducing the levels of CRP, COX-2 and TNF-α, as well as the % of ulcerative area. They stated that the extract obtained from the fruits of *Prunus laurocerasus* realizes these strong anti-inflammatory effects thanks to the phenolic compound chlorogenic acid, which is abundant in its structure. Similarly, Shimoyama *et al.* (2013) reported that chlorogenic acid prevented gastric mucosal damage by activating neutrophil flow, inflammatory mediators and antioxidants in the mouse ulcer model they created with EtOH/HCl – piroxicam. Zhang *et al.* (2018) put forward to chlorogenic acid inhibited ear, paw and granuloma swelling in a non-infectious inflammation model and also reduced intraperitoneal capillary permeability. It has also been stated that it reduces serum PGE2 and IL-1β in lung injury induced by its lipopolysaccharides. In addition, it has been shown to be effective in blocking the COX-2/NLRP3/NF-κB inflammatory signaling pathways. In a study, a paw edema model was created by injection of carrageenan in mice. It was statement that when chlorogenic acid is given orally 1 hour before the administration of carrageenan, it reduces paw edema, liver TNF-α expression, and increases antioxidant enzymes. However, it was also stated that it did not show any effect when administered 1 hour after the carrageenan injection (Chauhan *et al.,* 2011).

5. Hepatoprotective, cardioprotective and antihypertensive effects

Chlorogenic acid can reduce hepatocyte damage and inflammatory cell infiltration in liver damage induced by lipopolysaccharides, and also prevent the decrease in mitochondrial Nicotinamide adenine dinucleotide dehydrogenase and ATP synthase activities, and thus the decrease in AMP and ATP (Chen *et al.,* 2019). In one study, was revealed that chlorogenic acid protected the liver against damage that may be caused by alloxan (Ali *et al.,* 2016), while in another it was reported that it reduced neurophile infiltration and necrosis in hepatocytes in liver damage induced by lipopolysaccharides. In addition, in the same study, it was emphasized that chlorogenic acid decreased AST and ALT levels, decreased TLR4, NF-kB p65 subunit and TNF-α mRNA expression (Xu *et al.,* 2010).

Tian *et al.* (2019) statement that chlorogenic acid may inhibit NF-kB signaling by preventing NF-kB/p65 phosphorylation, and also exerts a strong cardioprotective effect by inhibiting the activation of the JNK pathway. According to these results, they claimed that it can be used for the prevention and even treatment of heart failure. It has been stated that chlorogenic acid provides a preventive effect opposite myocardial infarction induced by isoproterenol (Akila *et al.,* 2017), and also exhibits an antihypertensive property by reducing the levels of hypertension-related E-NTPDase, 5′-ectonucleotidase, arginase, AChE, ADA, and ACE enzymes (Agunloye & Oboh, 2018). Chlorogeninic acid was reported that reduce heart rate, systolic blood pressure, arginase, butrylcholinesterase, and angiotensin-1-converting enzyme. It is believed that chlorogenic acid achieves this effect by binding to the outer membrane of bacteria, increasing its permeability and releasing cytoplasmic macromolecules that cause loss of barrier property as well as apoptosis. Acetylcholinesterase activity in a cyclosporine-induced hypertension model (Agunloye *et al.,* 2019). Atsushi *et al.* statement that a single dose of chlorogenic acid applied to rats reduced blood pressure, and when administered for 8 weeks, it reduced the development of hypertension. In addition, they reported that it improved Ach-mediated endothelium-dependent vasodilation in the aorta (Suzuki *et al.,* 2008).

6. Neuroprotective effects

It was statement that intranasal application of chlorogenic acid 10 mg/kg in cerebral ischemia rats reduces the cerebral infarct area compared to the ischemia group, and also significantly reduces the levels of i-NOS, Caspase-3 and TNF-α in the hippocampus, cerebellum, CSF and cerebral cortex (Kumar *et al.,* 2019). Chlorogenic acid prohibits the formation of senile plaques related with Alzheimer's disease (Han *et al.,* 2010), and also prolongs the duration of action of acetylcholine and butyrylcholine by inhibiting acetylcholinesterase and butyrylcholinesterase. (Oboh *et al.,* 2013). It has been stated that the control of motor activities of chlorogenic acid administered to mice in the MPTP-induced Parkinson's model was significantly improved. Moreover, it has been suggested that it exerts strong neuroprotective effects by re-activating Akt and ERK1/2 signaling pathways, whose activity is decreased by the effect of chlorogenic acid MPTP, and consequently, by increasing GSK3β phosphorylation (Singh *et al.,* 2020). Rebai *et al.* (2017) emphasized that in glutamate-excitotoxicity, which plays an important role in the pathogenesis of various neurodegenerative diseases, chlorogenic acid is effective in preventing cortical neuron damage by preventing the accumulation of ROS and re-activating the mitochondrial membrane potential. Mikami and Yamazawa (2015) stated that when chlorogenic acid is applied to mouse cerebral cell

culture, it prevents glutamate-induced cell death and also protects neurons from glutamate toxicity by regulating intracellular calcium influx. Liu *et al.,* (2020) determined that chlorogenic acid reduces cerebral ischemia-reperfusion-induced nerve and brain damage, and has important effects on learning and spatial memory development. It has also been stated that it has a neuroprotective effect by increasing various antioxidant activities, decreasing oxidant levels and regulating the Nrf2 pathway associated with oxidative stress (Liu *et al.,* 2020).

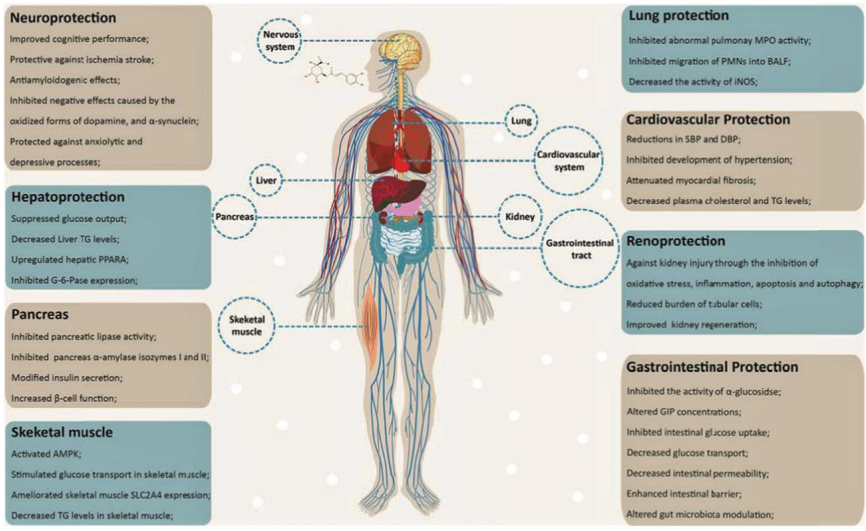

Figure 2. *Physiological effects of chlorogenic acid (Lu et al., 2020)*

7. Antidiabetic effects

In genetically mutated Leprdb/db mice, acute practice of chlorogenic acid decreases the $AUC_{glucose}$ in the OGTT, and chronic administration inhibits Glucose 6 phosphatase activity, reduces hepatosteatosis, improves lipid profile and skeletal muscle glucose uptake, thereby improving glucose tolerance, dyslipidemia and insulin sensitivity through activation of AMPK (Ong *et al.,* 2013). It was statement that the extract obtained from *Morus alba* leaves contains abundant chlorogenic acid and when this extract is administrated to type II diabetic rats, remarkably reduced in postprandial blood glucose levels are observed (Hunyadi *et al.,* 2012). It has been suggested that the administration of extracts obtained from *Cecropia peltata* and *Cecropia obtusifolia* plants, which are determined to have high chlorogenic acid content, to healthy mice have a hypoglycemic effect by reducing plasma glucose levels (Nicasio *et al.,* 2005). *Smallanthus sonchifolius* extract, which is used in conventional medicine for its antidiabetic properties, and one of its main components,

chlorogenic acid, have been reported to have a hypoglycemic effect when administered orally for 6 weeks in diabetic rats STZ-induced, and also reduced total cholesterol and triglyceride levels. In addition, DPPH test results showed that chlorogenic acid has a similar free radical scavenging effect to vitamin E (Jeong Sook *et al.,* 2009). Karthikesan *et al.* (2010) expressed that together application of tetrahydrocurcumin and chlorogenic acid for 45 days in the insulin-dependent diabetic rat model reduced HbA1C, whereas increased insulin, hemoglobin, glycogen and C-peptide levels. In one study, it was reported that chlorogenic acid administered 60 minutes after feeding remarkably decreased the blood glucose levels (Tunnicliffe *et al.,* 2011), while in another study, it was determined that chlorogenic acid administered at 400 mg for twelve weeks significantly reduced the postprandial blood glucose level in patients with disturbed glucose tolerance (Zuniga *et al.,* 2018).

8. Antipyretic and antinociceptive effects

Dos Santos *et al.* (2006) reported that chlorogenic acid at dosage of 50-100 mg/kg inhibited formaldehyde-induced pain in rats, but did not inhibit fever induced by lipopolysaccharides. In a study investigating the effects of chlorogenic acid applied in STZ-induced diabetic neuropathic pain in rats, it was stated that chlorogenic acid treatment as a one dose (100 mg/kg) didn't show antinociceptive feature, on the contrary, it showed antinociceptive effects in non-diabetic animals when administered for 14 days (Bagdas *et al.,* 2014). Gao *et al.* (2014) wanted to determine the efficacy of chlorogenic acid in rectal temperature difference stimulated by baker's yeast, they reported that plasma chlorogenic acid levels were higher in febrile rats, and as a result, they reported that fever may play an major role in the pharmacokinetic process of chlorogenic acid. In the burn model caused by ultraviolet radiation, extracting the avocado fruit and applying it to the burn area in gel form showed an antinociceptive effect; this effect was attributed to phenolic components such as chlorogenic acid in its compound (Deuschle *et al.,* 2019). Hara *et al.* (2014) experimentally created chronic constriction injury of the sciatic nerve in rats and investigated the effectiveness of chlorogenic acid in this neuropathic pain model they created. They determined that spinally applied chlorogenic acid relatively improved mechanical and cold hyperalgesia by activating GABAergic transmission in animals exposed to plantar test, cold plate test, von Frey test, and rotator test.

9. Antiobesity effects

Cho *et al*. showed that chlorogenic acid improved lipid metabolism, body weight, and obesity-related hormone levels in mice fed a high-fat diet (Cho *et al.,* 2010). Kumar *et al.,* (2020) on the other hand, stated that

chlorogenic acid inhibits the 3-hydroxy 3-methylglutaryl coenzyme-A reductase enzyme and activates AMP-activated protein kinase, and in addition, it increases the activity of carnitine palmitoyltransferase to keep obesity under control. Wang *et al.,* (2019) showed that 150 mg/kg dose of chlorogenic acid administered orally to rats treated with a fatty diet for 6 weeks reduced body weight, could improve plasma lipid levels associated with high-fat diet feeding, and can regulate lipolysis and lipogenesis in white adipose tissue by controlling gene expression. In another study, it has been reported that the leaves of Houttuynia cordata contain high levels of chlorogenic acid and thus show anti-obesity effects (Wang *et al.,* 2018). He *et al.* (2021) determined that chlorogenic acid at a dosage of 100 mg/kg administered for 13 weeks in a high-fat diet-induced obese C57BL/6J mouse model reduced food intake, elevated body temperature and the activity of brown adipose tissue, and also improved glucose tolerance. It was showed that the together application of chlorogenic acid and caffeine can suppress the increase in body weight in mice by regulating liver lipid metabolism-related enzyme activities, mRNA and protein expression. Moreover, it has been emphasized that the combined use of chlorogenic acid and caffeine has a more effective antiobesity effect than their separate use (Zheng *et al.,* 2014). Song *et al.* (2019) stated that the extract obtained from peach blossoms provided a reduction in hyperglycemia and spleen-liver damage caused by obesity in male C57BL/6 mice, to which they applied for 8 weeks, and thus showed an antiobesitic effect. In addition to all these, they reported that it may be effective in increasing fatty acid oxidation and reducing lipogenesis in liver tissue. Chlorogenic acid applied to 3T3-L1 white fat cell cultures stimulated the transformation into brown fat cells; In this way, it has been shown that it can be effective in burning fat and, as a result, in reducing fat stores. During this mechanism, AMPK and PPARγ/PRDM16 pathways are effective (Sudhakar *et al.,* 2020).

10. Antioxidative effects

Chlorogenic acid administered to mice at 20 mg/kg diminished anxiety-related behaviors in the elevated + maze test, free exploration test and light-dark test; In addition, chlorogenic acid protected granulocytes from oxidative damage (Bouayed *et al.,* 2007). Sato *et al.* (2011) statement that caffeic acid has more antioxidant activity than chlorogenic acid in in vitro tests. They also stated that both substances have positive effects on preventing intestinal ischemia-reperfusion injury. Kwon *et al.,* (2010) determined that in a mouse model of scopolamine-induced amnesia, chlorogenic acid suppressed AChE activity in the frontal cortex and hippocampus, and also reduced MDA levels in the same tissues. According to these results, chlorogenic acid has an antiamnesic effect (Kwon *et al.,* 2010). Uslu *et al.* (2018) statement that the extract obtained from the

leaves of *prunus laurocerasus*, the main phenolic component of which is chlorogenic acid, decreased oxidant levels and increased antioxidant levels in type 1 diabetic rats, and also increased HDL levels while decreasing LDL and triglyceride levels. They also stated that it may be effective in suppressing the main complications of diabetes by showing strong antioxidative and antihyperlipidemic effects. In a study investigating the antioxidant effects of Flos lonicerae extract, the plant contained high levels of chlorogenic acid and the results of the DPPH radical scavenging test and Fe reduction test showed that it had strong antioxidant activity (Wu, 2007). Chlorogenic acid administered to rats in It has been suggested that chlorogenic acid can be effective in preventing paraquat-induced oxidative stress and cell damage through its superoxide anion scavenging activity. It suggests that chlorogenic acid may be effective in preventing paraquat-induced oxidative stress and cell damage, thanks to its superoxide anion scavenging activity (Tsuchiya *et al.,* 1996). Bao *et al.* (2018) determined that chlorogenic acid can prevent experimentally induced diabetic nephropathy in rats by arrangement Nrf2/HO-1 and NF-κB pathways and suppressing inflammation and oxidative stress. Chlorogenic acid has been specified to have protective properties against oxidative stress and cell damage caused by ultraviolet radiation in human HaCaT cells exposed to ultraviolet radiation (Cha *et al.,* 2014).

11. Anticancer effects

In a study investigating the effecttiveness of chlorogenic acid on the viability of human liver tumor (hepatoma) cells, it was shown that MTT tests applied could inhibit the activity of Huh-7 and Hep-G2 and, however, it was stated that it didn't affect the activity and growth of normal human hepatocytes. In another study, it was been reported that chlorogenic acid activates the mitochondrial apoptotic pathway by prevent the non-canonical NF-κB pathway and upregulating the level of Bcl-2 binding component 3 (BBC3) (Jiang *et al.,* 2021). Accordingly Lukitasari *et al.* (2018) suggested that chlorogenic acid may prevents the proliferation of cancer cells by suppressing VEGF, HIF, EGFR/PI3K/mTOR and MAPK/ERK pathways. In addition, they stated that it induced the genesis of TOP1 and TOP2 DNA complexes associated with apoptosis and cellular DNA damage. Santana-Gálvez *et al.* (2020) showed that dihydrocaffeic acid, a metabolism product of chlorogenic acid, has high cytotoxic effects on cancer cell lines HCT-116, PC-3 and MCF-7. In a study conducted on the lung cancer cells, it was found that chlorogenic acid induced JNK, MAPK, p38, and JNK gene expression and also decreased gene expression of stem cell-associated markers SOX2, POU5F1 and NANOG. As a result, it was expressed that stem cell markers regulate gene expressions and apoptosis in lung A549 cancer cells (Yamagata *et al.,* 2018). It was stated that the

chlorogenic acid complex formed by the combination of 7 isomers (3-, 4-, and 5-caffeoylquinic acid, 3,4-, 3,5-, and 4,5-dicaffeoylquinic acid and 5-feruloylquinic acid) at a ratio of 3/3/1 activates proapoptotic proteins caspase-9 and PARP-1, as well as decreases Bcl-2 levels and increases Bax levels. It has been suggested that these changes in Bax and Bcl-2 levels indicate that the intrinsic pathway mechanism of apoptosis is activated following chlorogenic acid administration. In the light of all these data, it can be said that chlorogenic acid can have an inhibitory effect on colon cancer (Gouthamchandra *et al.,* 2017).

Conclusion

As a result, as many researchers have reported, chlorogenic acid is a very important poliphenolic compound in terms of health. Intake of chlorogenic acid during daily nutrition is very useful in eliminating many health problems and returning to normal physiological state, as it is tried to be expressed in this article. However, it should not be ignored that acute and chronic use of chlorogenic acid may have possible side effects, as can be the case with any compound. In addition, many detailed studies are still needed for its use in the treatment of diseases in the clinic.

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Chapter 9

APPLICATION OF OREM SELF-CARE MODEL IN NURSING MANAGEMENT OF PATIENTS WITH RHEUMATOID ARTHRITIS

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LOGIN

Rheumatoid arthritis (RA) is a chronic inflammatory disease that causes joint pain, swelling (synovitis), stiffness, and muscle wasting around the affected joints. RA is one of the most common inflammatory painful diseases in the world. Its worldwide prevalence is between 1-2% and one million people in the USA suffer from RA (Wasserman, 2011). The prevalence of RA in our country was found to be 0.49% to 0.38% (Akar et al., 2004). Women are affected by RA 2.5 times more often than men. RA can occur at any age, but the most common incidence is between the ages of forty and sixty (Helmick et al., 2008). The proportion of geriatric RA patients is increasing worldwide, and approximately 30% of RA cases occur in the geriatric category (Yathish, 2015). Since the proportion of individuals aged 65 and over in the population has increased in Western societies, morbidity, mortality, and disability rates due to RA are likely to increase in the future (Helmick et al., 2008).

RA that occurs in old age may differ significantly from other young-adult RA patient groups in terms of disease progression and functional outcomes. Geriatric patients may have a more functional disability than younger RA patients due to the increase in disease severity (Tutuncu, Reed, Kremer, & Kavanaugh, 2006). Some studies on RA have shown that geriatric patients have worse functional status (Calvo-Alen et al., 2005); In another study, it was stated that RA that occurs at an advanced age causes more functional disability than patients with inflammatory polyarthritis (Tutuncu et al., 2006). Pain, stiffness, swollen joints, insomnia, fatigue, and joint deformities are seen later in the disease are common symptoms of RA. The painful, stiff, and deformed joints of the affected joints cause patients with RA to have more physical impairment than a healthy person (Combe, 2007; Steultjens et al., 2002). These conditions affect patients physically, mentally, and socially from the early stages of the disease (Salaffi, Carotti, Gasparini, Intorcia, & Grassi, 2009). Therefore, prevention of inflammation and relief of pain in treatment is important for symptom control (Kwoh et al., 2002). Disease-Modifying Antirheumatic Drugs (DMARDs) are started first in pharmacological treatment in RA. Agents such as corticosteroids and NSAIDs are used in the treatment of inflammation and pain, which is the second focus of treatment (Kwoh et al., 2002).

In recent years, it has been emphasized that care in health is more important than treatment (Ovayolu, Ovayolu, & Karadag, 2012). For this reason, the role of the nurse has also changed and the concept of self-care has been more focused (Ovayolu et al., 2012). The concept of self-care was first defined by Orem (Taulbee, 2009). Orem's nursing model is a model that explains the relationship between individuals' self-care needs and their

ability to meet them (Simmons, 1990; Taulbee, 2009). Orem reported that everyone needs self-care and helping people to meet these needs is at the core of nursing. In addition, Orem suggested that nursing develops because there are situations in which people are not self-sufficient (Taulbee, 2009).

According to the Orem self-care model, when patients cannot meet their own care needs, there is a need for nursing systems to protect health (Mahmoudzadeh-Zarandi, Hamedanizadeh, Ebadi, & Raiesifar, 2016). Many patients with RA have symptoms in both hands. symptoms; It is related to the activities of patients performing daily tasks such as combing hair, brushing teeth, opening the door, turning something in the hand, holding a key or a glass. These symptoms cause problems with the home, work, and entertainment in patients. Many patients experience stiffness, inability to perform daily activities, frustration, and distress due to hand pain. After the diagnosis of RA, patients may become completely unable to carry out life activities within five years (Conditions, 2009). According to Orem, with care, it can also be ensured that the patient continues his life activities independently. This situation is the nurse's direct responsibility (Habibzadeh, Ghofranipour, & Ahmadi, 2007). Helping patients with RA is possible by maintaining self-care (Taal, Rasker, & Wiegman, 1996). Since RA mostly affects the small joints of the hands and feet (Combe, 2007; Steultjens et al., 2002), approximately 80% of patients with RA have difficulties in maintaining their life activities and 35% have a permanent disability. (Allaire et al., 2009; Choy & Panayi, 2001; Wasserman, 2011). Therefore, to increase the effectiveness of self-care in RA patients, care interventions in this area and more focus on the content of self-care programs are required (Baker & Denyes, 2008).

Empowering people experiencing chronic pain using self-care methods is more effective than other methods (Barlow, Williams, & Wright, 1999). Nurses' being together with the patient for a long time, learning the patient's previous pain experiences and methods of coping with pain and benefiting from them when necessary, guiding the patients, applying the treatment planned for the patients, monitoring the effects and results of the treatment, and their empathetic approach to the patient constitute the basis of nursing care (Jezewski, Scherer). , Miller, & Battista, 1993).

In the literature; According to Orem, the effect of care on drug use in patients with hypertension (Ahmadi, Taheri Tanjani, & Qolami Fesharaki, 2018), its effect on sleep quality in patients with multiple sclerosis (Dahmardeh et al., 2016), its effect on the prevention of osteoporosis due to RA (Sharifi, Majlessi, Montazeri, Shojaeizadeh, & Sadeghi, 2017), the effect of self-care on self-care activities and quality of life in patients with systemic lupus erythematosus (Kusnanto, Sari, Harmayetty, Efendi, & Gunawan, 2018; Yang, Xie, Song, Nie, & Chen, 2018), its effect on

the quality of life in patients with thalassemia (Madmoli et al., 2019), its effect on organ function in patients with cirrhosis (Gao, Chen, Wenhui, & Chen, 2017), its effect on the quality of life in patients with migraine (Mahmoudzadeh-Zarandi et al. ., 2016) on quality of life in patients receiving chemotherapy (Karbaschi, Zareiyan, Dadgari, & SIADATI, 2015). In the study of Saeedifar et al. (2018), the effect of Orem on pain management in female patients with RA was examined and it was found that care according to Orem was effective in reducing pain in patients with RA (Saeedifar, Memariyan, Akhyani, Fatahi, & Ghelichkhani, 2018). In the systematic review of Zuhur and Özpancar (2017) on the use of nursing models in chronic diseases in our country, it was emphasized that the use of theories and models in chronic disease management is limited (Zuhur & Özpancar, 2017).

Rheumatoid Arthritis and Self Care

Orem Self Care model

The concept of self-care was first published by Orem in 1956. Orem explained that everyone needs self-care and that the essence of nursing is helping people meet their needs. Self-care is one of the main concepts in Orem's theory and is defined as "activities initiated and performed by individuals to maintain life, health, and well-being". She argued that nursing develops because there are situations where people are not self-sufficient (Burnside & Burnside, 1988). Self-care is individuals doing their part to protect their authentic life, health, and well-being. self-care; is associated with many concepts such as people, environment, culture, and life activities.

The concept of human; According to Orem, a person can combine motivation for self-care behavior with functions (Hartweg, 1991). Patients with RA need the support of nurses to overcome the burden of their disease and maintain their self-care (Ebrahimi et al., 2015; Saeedifar, Memarian, Fatahi, & Ghelichkhani, 2018).

The concept of the environment; Man adapts his needs to his environment. People have developed and used various technologies in their environment to meet their needs (Koç, Keskin Kızıltepe, Çınarlı, & Şener, 2017). For individuals to continue their lives due to RA, their living environment should be reviewed and they should live in cooperation with a multidisciplinary team.

The concept of culture; The individual's way of meeting his needs for self-care is a learned behavior from cultural sources rather than instinctive. The family is the first institution that teaches the individual cultural measures. Environmental factors such as friends, teachers, television,

and society participate in cultural learning later in life. Individuals with a diagnosis of RA can first identify their self-care needs or eliminate their deficiencies from healthcare professionals and then from patients in similar situations or mass media (Koç et al., 2017).

Orem explains the concept of the values of life as follows; Self-care is not only concerned with the individual's position in the family, it is also affected by the role played by the individual, age, and health status. A person's system of values determines their priorities in self-care. In Orem's theory, human is seen as a "self-care agent". With a change in the health status of the individual, if he or she has become fully or partially dependent on others for sustaining and supporting his or her life and well-being, then the person has shifted from the position of "self-care agent" to "receiver of care". Infants, children, the elderly, the sick, and those with disabilities need help in meeting self-care activities (Demoro, Fontes, Trettene, Cianciarullo, & Lazarini, 2018). Individuals with RA may also become semi-dependent in the first years of their illness, and then become completely dependent if complications cannot be prevented. In this case, the individual begins to move towards the position of self-care agent with the support of the nurse.

Self-care is a positive action that includes both a practice and a therapeutic approach. Self-care is therapeutic as long as it serves to achieve the following:

- Supporting life processes and normal functions,

- Maintaining normal growth, development, and maturation,

- Providing care, treatment, and supervision in the processes of illness and disability,

- Protection from disability (injury) or compensating for it in other ways (Blodgett, 2017; Fawcett & Desanto-Madeya, 2012).

Self Care Requirements

Self-care needs, which are the constant involvement of one's health, are basic human needs that everyone must meet. When these needs are not met and care cannot be sustained, health is adversely affected. Self-care needs are grouped into three groups.

1. Universal self-care requirements

2. Self-care requirements in health deviations

3. Developmental self-care needs (Fawcett & Desanto-Madeya, 2012).

Universal Self-Care Requirements

Universal self-care needs are defined as meeting all life activities that protect the integrity of human structure and functions and cover the basic wishes and needs of the human being related to the life process (Blodgett, 2017; Fawcett & Desanto-Madeya, 2012).

Orem listed the demands and actions of universal self-care as follows:

- Maintaining adequate air, water, and nutrient intake,
- Providing functions related to unloading operations,
- Maintaining the balance between activity and rest,
- Maintaining loneliness and social interaction,
- Threats to life and well-being,
- It is not in normal condition.

When needs are met effectively, self-care promotes health and well-being. For a healthy individual to meet his basic needs, he must have sufficient self-care skills. In a healthy individual, there is a balance between self-care ability and universal self-care needs (Fawcett & Desanto-Madeya, 2012). Individuals with RA need help in meeting some of the universal self-care needs, especially for activities of living.

Self-Care Needs in Health Deviation

When the individual cannot meet their universal care needs, the need for self-care increases in deviations from health. Orem defines self-care in health deviations as "needed only in the event of ailments, disability or illness" (Alligood, 2013).

Some additional self-care needs may arise for the individual who has experienced an injury, illness, or illness in his or her life. These are self-care requirements associated with medical treatment, deviations in human structure and functions, genetic and structural defects. For example, a person with diabetes may need a special self-care activity that corrects the pathology, such as making his insulin. Orem named these needs as self-care needs in deviance from health. Orem's individual nursing care model helps the individual to determine what kind of needs they have and to plan appropriate interventions (Blodgett, 2017; Fawcett & Desanto-Madeya, 2012). If adults can meet their self-care needs in cases of health deviation, they will not need a nurse. If individuals are competent in maintaining their self-care, they will be able to demonstrate the ability to seek relevant medical information and assistance for their care. In this case, intervening nursing interventions will create activities that help balance between self-care abilities and needs (Alligood, 2013; Blodgett, 2017; Chinn & Kramer, 2013; Fawcett & Desanto-Madeya, 2012).

In patients diagnosed with RA, self-care insufficiency occurs due to joint destruction. During this period, people should both use the prescribed drugs and monitor the symptoms specific to the complications and perform the necessary intervention to prevent possible complications and to prevent joint deformities. For this reason, individuals need nursing interventions to take on their self-care responsibilities after their needs are met.

Developmental Self-care Requirements

They are self-care needs that cope with or reduce the harmful effects of conditions affecting human development and support developmental processes such as pregnancy and adolescence (Fawcett & Desanto-Madeya, 2012).

Developmental self-care needs are divided into two groups. First; These are the needs that emphasize the impact of the developmental process on the universal self-care needs and are associated with each of the universal self-care needs. E.g; During a normal developmental period such as old age, the need for food will change. Due to the occurrence of many events and conditions that can adversely affect human development in various periods of life, these needs are defined as universal self-care needs that are specific to developmental processes. Developmental self-care needs are to protect people from harmful effects of conditions such as "educational deprivation, social incompatibility, loss of relatives, friends, and friends, problems with social status, disability, challenging living conditions, terminal illness or being under the threat of death". requires. It also requires the ability to cope with these situations or to provide care so that they are minimally affected (Hartweg, 1991).

Problems may also occur in the developmental self-care needs of individuals with RA. For example, there may be difficulties in meeting developmental self-care needs such as getting married for a single person, fulfilling a role for a parent, and an inability to perform a job for an artisan.

Self-Care and the Role of the Nurse

Orem nursing has been defined as "an applied science that includes both theoretical and practical knowledge". Nursing can be seen as a tool in assisting individuals with partial or complete disabilities and in practicing their daily health care. A nurse's ability to help the individual in need depends on her ability or strength (Alligood, 2013; Chinn & Kramer, 2013; Fawcett & Desanto-Madeya, 2012). This power and practice are influenced by the nurse's educational preparation and experience as well as the individual's self-care power. The purpose of nursing power is to help people identify and meet their therapeutic self-care needs (Manojlovich, 2007).

This goal has three elements:

1. Helping the individual to cope with therapeutic self-care,

2. To try to direct the individual in a way that will increase his independence and responsibility in self-care actions,

3. To assist the family or other important persons in providing and maintaining the care of the individual with appropriate nursing supervision and counseling.

The selection of the appropriate nursing system also requires the selection of appropriate helping methods. In Orem's theory, five different helping methods are defined. These;

- Acting or doing on behalf of the individual

- Guiding the individual

- Supporting the individual physically or psychologically

- Creating an environment that provides personal development

- To teach the individual.

Thus, nurses help to meet the self-care needs of sick and healthy individuals by choosing one of the three nursing systems and using five helping methods (Alligood, 2013; Fawcett & Desanto-Madeya, 2012; Simmons, 1990).

Helping the family or other important people in providing and maintaining the care of the individual with RA with appropriate nursing supervision and counseling, the nursing system is selected, starting immediately after the diagnosis of the disease, and continuing after the discharge, with the nursing care support, the individual gains independence and fulfills self-care behaviors. should be provided.

The Effect of Self-Care on Movement Function

It is recommended that patients with RA use a wide variety of self-care methods to maintain or improve their functions (Veitiene & Tamulaitiene, 2005). In a randomized controlled study in which Lamb et al. examined the effectiveness of exercise in increasing hand function in patients with RA, they concluded that exercise was effective in increasing hand functions (Lamb et al., 2015). In the study of McHugh et al., in which the self-care program applied to geriatric RA patients evaluated the effect on the patient's hand symptoms, they found that the self-care program was effective in improving hand symptoms (McHugh et al., 2018). In the meta-analysis of Bobos et al. to examine the effectiveness of joint protection programs applied to increase hand function in patients with RA, the level

of evidence for the effectiveness of joint protection programs in improving hand functions was found to be low (Bobos et al., 2019). In the study of Çalışkan Uçkun et al. with geriatric patients with RA, it was found that the hand activities scale score increased with increasing age (Çalışkan Uçkun et al., 2019). However, no study has been found examining the effect of nursing care given according to the Orem Self-Care Model on hand function in patients with RA. However, in the literature, the Orem self-care model; is seen that it is also applied in different diseases such as heart failure, coronary artery diseases, colorectal cancers, osteoporosis, asthma problems in adolescents, postpartum complications. The results of these studies conducted in various fields are similar, and the results of the study; The patients who applied the Orem Self-Care Model improved significantly (Abbasi, Ghezeljeh, & Farahani, 2018; Ghiasvand, Riazi, Hajian, Kazemi, & Firoozi, 2017; Hua et al., 2017; Sharifi et al., 2017; Wong, Ip. , Choi, & Lam, 2015).

The effect of self-care on life activities

Studies examining the effect of self-care power on life activities have been found in the literature. In the study of Thyberg et al., in which they examined the effect of assistive devices on RA in patients with RA, they found that assistive devices affect RA (Thyberg, Hass, Nordenskiöld, Skogh, & Research, 2004). In the study of Tokem et al. in which they examined the relationship between self-care power and functional status in RA patients, it was found that patients with high self-care power had better functional status (Tokem, Akyol, & Argon, 2007). Similarly, Chen et al. In their study to examine the relationships between physical function and self-care behavior in patients with RA, it was found that patients with low self-care behavior were more affected by the dysfunction caused by the disease (Chen & Wang, 2007). In the study of Hizmetli et al., in which they examined the relationship between self-care power and GA in geriatric patients with osteoarthritis, they concluded that patients with good self-care power were more successful in performing GA (Hizmetli, Tel, Tel, & Yıldırım, 2012). In line with this information, it is seen that increasing self-care power has a positive effect on OA in patients with arthritis. Studies evaluating the effectiveness of care in patients with arthritis have also been found in the literature. Lorig et al. As a result of the study in which the internet-based arthritis self-care program examined the effect of symptom management in patients, it was determined that the health-based behaviors of the patients improved and their self-care skills increased (K. R. Lorig, Ritter, Laurent, & Plant, 2008). As a result of Anvar et al.'s study examining the effectiveness of the arthritis self-management program in geriatric patients with arthritis, it was concluded that the arthritis symptoms of the patients decreased and their self-care skills increased (Anvar, Matlabi, Safaiyan,

Allahverdipour, & Kolahi, 2018). In the experimental study of Gurjar et al. to examine the effectiveness of nursing care on self-care behavior and GI in arthritis patients, they concluded that nursing interventions are effective in improving the self-care efficacy of arthritis patients. In addition, in this study, it is recommended to increase nursing practices to improve the self-care competence of patients with RA (Gurjar, Thomas, & Tiwari, 2018).

Loring et al., in their study to determine the strengths and weaknesses of the arthritis self-management program, concluded that a 6-week arthritis self-care program was more effective than a 3-week program and this program was effective in increasing the pain control of patients (K. Lorig et al., 1998).). In Barlow's study, it was found that the self-care training program given to osteoarthritis and RA patients reduced the pain of the patients by 20% (Barlow et al., 1999). In the study of Cherkin et al., the arthritis self-management program was found to be effective in reducing pain (Cherkin et al., 2001). Warsi et al., in a systematic review of 71 experimental articles on the effect of self-care education in chronic patients, reported that self-care education is effective in reducing pain associated with chronic diseases (Warsi et al., 2003). Miaskowski et al., in a study on pain management, concluded that nursing care for patients within the framework of self-care is effective in reducing pain (Miaskowski et al., 2004). The study of Shariff et al. showed that self-care practice is effective in reducing RA-related pain (Shariff et al., 2009). In the study of Ovayolu et al., it was stated that patients with low self-care scale scores had higher pain scores (Ovayolu et al., 2012). Mc Hugh et al., in a study examining the effect of a self-care program on geriatric RA patients, reported that a self-care program can reduce pain in geriatric adults living with arthritis (McHugh et al., 2018). Saeedifar et al., in their clinical study on 60 patients with RA to measure the effectiveness of the Orem self-care model, stated that the 12-week Orem self-care model on RA patients was effective in reducing pain (Saeedifar, Memarian, et al., 2018).

Problems Detected in Rheumatoid Arthritis Patients and Solution Suggestions for Orem Self-Care Model

Chronic Pain

- Use various comfort measures (eg heat or cold application, massage, position changes, rest, foam mattress, supportive pillow, splints, relaxation techniques, distracting activities).

- Use your prescribed anti-inflammatory, analgesic, and slow-acting antirheumatic drugs regularly.

- You can apply hot or cold. The warm application can give you comfort in 20 minutes and make your exercises easier.

- If there is acute inflammation, you should apply cold.

- You can use walking aids as they will reduce the weight on the joints.

Having shower

- You must use an auxiliary tool.

- You should do your body cleaning and oral care daily.

- You can take painkillers before taking a bath.

- Use the auxiliary tools recommended by the physiotherapist.

- You should act independently in maintaining bathroom and oral hygiene.

- You can set your own pace during your self-care.

- Your family can support you in providing and maintaining your care.

- Towels, soap, deodorant, shaving materials, and other necessary materials should be placed where you can easily reach the bathroom.

- Your family will support you in brushing your teeth when necessary.

Toilet Relief

- You should increase your ability to act independently and safely.

- You should increase your ability to fix your clothes.

- Sensory, cognitive, and physical inadequacies that can limit the need to meet the toilet needs should be eliminated.

- Adaptation activities and the use of auxiliary tools were applied to you by the physical therapist. You should improve yourself in this regard.

- You can take your pain medication before you go to the toilet.

- When necessary, your family will help you to meet your basic care and toilet needs.

- You should choose clothes that are easy to manage.

- Periodically, your family can help you go to the toilet, sit on the potty chair, use the slider and the duck.

- Toilet cleaning should be facilitated after emptying is completed.

- Items that prevent going to the toilet should be removed (eg loose carpets and small movable furniture).

- To prevent reluctance and fatigue, sufficient time should be allocated to meet the toilet needs.

- You should not delay your strength-enhancing exercises.

Nutrition

- It is recommended to have sea fish dishes on your table once or twice a week. It is known that the unsaturated Omega-3-fatty acids contained in fish oils have an anti-inflammatory effect.

- Be sure to avoid excess weight in order not to overload the joints.

- If you are losing weight, you need to reduce your weight gradually.

- A moderate diet can reduce disease activities.

- Avoid alcohol consumption as alcohol is an inflammatory trigger.

- Avoid smoking. Smokers; carry a risk in terms of blood circulation complications and the formation of rheumatic nodules.

- You can use alternative methods during the meal (such as using a straw, using a spoon that can go to the wrist).

- Nutrients should be taken in small quantities in each bite.

- To increase your independence, meals that are eaten by hand (eg fruit, bread) can be preferred.

- A pleasant environment should be created while eating.

- Processes such as cutting the meat and peeling the eggs are done on the tray and the food is arranged.

- Auxiliary tools such as long handles, large round handles, or small-strapped utensils can be used to improve your self-feeding.

Suit up

- One item of clothing should be selected at a time during dressing.

- Dressing should be started as you can easily do it in the same order every day.

- Velcro fasteners and fasteners should be used on your clothes.

- Easy-to-wear and loose-fitting clothes should be chosen.

- The clothes must be within reach in the order required for dressing.

- During dressing, extension materials such as a long-handled shoehorn, button hook, zipper pull should be used.

Movement

- Thanks to targeted exercises, bones, cartilage, and muscles gain better blood circulation. Thus, the strength and endurance of the muscles increase.

- You can use mobility aids (eg cane, walker, crutches, or wheelchair).

- Non-slip and supportive shoes are required for walking.

- You can take your painkillers before starting the exercises.

- You should not delay your exercises to increase strength, balance, and flexibility.

- You should increase your walking distance every day.

Maintaining the Home

- You can benefit from home cleaning services when necessary.

- Support can be obtained from pest control services when necessary.

- Support can be obtained from home renovation services when necessary.

- Make sure that family members are aware that the patient needs help to continue living at home.

- With a positive and confident outlook, you can better overcome the many pressures and restrictions that come with illness and treatment.

- The phone numbers of institutions/businesses providing foodservice, home care nurses, and social resources that will help with food service to homes should always be easily accessible.

- Try to think positively.

- Don’t let the disease put restrictions on you in your daily life, on the contrary, you can direct your life in a way that you can enjoy it, spend your spare time with your family and friends, and go on travels.

Tiredness

- You should record your sleeping hours and sleeping times.

- You should pay attention to your diet for sufficient energy sources.

- You should arrange your daily activities in order of priority.

- With the support of your family, it is necessary to organize the home environment in a way that reduces fatigue.

Sleep

- Environmental factors such as noise and light that affect your sleep should be limited.

- You should do activities (taking a warm shower, quiet environment, etc.) that will facilitate your transition to sleep.

- You should discuss your fears and unresolved problems with your family.

- You should not sleep during the day, you can do activities that will keep you awake and energetic.

- You can do relaxing movements such as massage, lying position.

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Chapter 10

ANTIOXIDANT AND PHARMACOLOGICAL PROPERTIES OF SUMAC

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INTRODUCTION

Sumac is a shrub or tree with a height of 0.5 to 3 m. The twigs are dark brown with a hairy colour. The fruits, 4-6 mm in diameter, formed in clustered flowers, are single-seeded and spherical, hairy and red at maturity. The fruits of sumac are round or slightly flattened lentils with a single surface. The seed is flat and kidney-like, greyish brown and extremely hard. The flesh of the fruit, which contains a thick juice with a slightly spicy acid taste, surrounds the seed. At maturity, the fruits are dark red and hairy on the upper surface (Başoğlu and Cemeroğlu 1984). It grows in dry, stony and rocky locations, in bushes, on the slopes of roads and in forests, at an altitude of 600-1900 m. The flower blossoms in June - July (Baytop 1999). Rhus coriaria Linn (Sumak) is a spice used as a spice and aromatizing, particularly in Iranian, Turkish and Middle Eastern dishes.

Sumac (Rhus coriaria L., family Anacardiaceae), a popular flower herb extract. It contains phytochemical compounds like anthocyanins, terpenes, phenolic acids, tannins, vitamins, minerals and fatty acids. Persian medicine (PM) Cold and astringent and tonic properties together with dry temperament for sumac. Sumac was mostly prescribed for strengthening the stomach and gums, bloody diarrhea, infectious, severe uterine bleeding, and gout. Today, the hepatoprotective effect of Sumac is known through its free radical and antioxidant recovery activities. Also, it has been demonstrated that Sumac inhibits the growth of cancer cells (Zakeri and. al 2020).

Sumac, a natural source of bioactives; contains components such as organic acids, fatty acids, essential and non-essential amino acids, vitamins, carbohydrates, minerals, tannins, anthocyanins, flavonoids, terpeneoids and phenolics. Sumac shows a strong anti-oxidant effect due to the phenolic compounds it contains, in particular gallic acid and its derivatives (Chakraborty et al. 2009, Kossah et al. 2009, Kossah et al. 2010, Abu-Reidah et al. 2015, Demchik et al. 2015).

The sour flavour of sumac is dependent on organic acids (malic, citric, etc.) It contains, and the taste of the fruit is oily, spicy and kind of like cumin (Brunke et al. 1993a).

Numerous studies examine sumac's antioxidant effect. Although different types of sumac were used in the studies, the researchers concentrated mainly on R. Coriaria species and concluded that the sumac has shown a powerful antioxidant effect. Some of the studies are described below. Özcan (2003) investigated the antioxidant effects of peanut oil stored at 65°C for 35 days by adding different levels of sumac extract and butylhydroxyanisole (BHA).

It was determined that sumac extracts (1%, 3% and 5%) inhibited hydroperoxide formation for 7 days after its addition to hazelnut oil, but after 28 days of storage, the antioxidant potential of sumac extract decreased compared to BHA. This decrease may be attributable to a reduction in polyphenol components in sumac extract.

It has been reported that the antioxidant effect of sumac extract can increase with the application of higher levels. Altiok et al. (2006)(in English only) identified the total phenolic compounds and antioxidant capacities of certain spices used in the production of functional foods in a study they conducted.

Based on this research, the highest total amount of phenol (235.3 mg EAG/g) and the highest antioxidant capacity (10.5 TEAK) were found in the sumac spice. As a result of various studies, it has been understood that sumac exhibits remarkable antioxidant behaviour and has a commercially important place as a natural antioxidant source (Rayne and Mazza 2007).

The fruits and leaves of the sumac plant contain significant substances and are therefore used as a raw material for medicine for many years. Sumac; It is recognized that it has protective and beneficial effects against various diseases like diabetes, certain types of cancer, inflammation, dysentery and digestive tract disorders. It also has antivirals, antibacterials, antifungals, antioxidants and hypolipidemics (Abu-Reidah et al. 2014; Alsamri, 2021).

Many herbs and spices such as sumac have been shown to have health benefits, including antioxidant and antidiabetic properties, due to their high polyphenol content (Mirhadi et al., 2011; Koşar, 2007).

Previous phytochemical studies have reported that the leaves of this plant contain flavones, tannins, anthocyanins and organic acids (Mavlyanov et al., 1997). Since the fruits contain more tannin, essential oil, organic acid, anthocyanin and fixed oil, studies have generally been on the tannin and flavonoid content of sumac leaves (Brunke et al., 1993). The chemical (phytochemical) compounds contained in the sumac plant are antioxidant and antimicrobial. It is emphasized that regularly consumed sumac has a protective effect on atherosclerosis, oxidative stress and liver enzymes caused by high-fat foods (Setorki et al., 2012).

Chemical make-up of Rhus coriaria. The presence of important minerals like iron (Kastamonu, 610.99 ppm) was highlighted. Calcium was found in large quantities (Iskenderun, 1062.14 ppm) in their cores, while copper, aluminum and iron were found in very small quantities (Özcan, 2007; Under and Zerrin, 2019).

In phytochemical studies on the aerial (leaf, fruit, bark, seed) and underground (root) parts of Rhus coriaria, the presence of important

commercial, particularly guillotine, attracts attention. Besides tannin, the amount of water (approximately 7%) and carbohydrates (5%) were also determined (Abu-Reidah et al., 2014; Kaysers et al., 2015; Ünder and Zerrin, 2019).

In the last detailed study conducted in 2015; It is reported that more than 200 phenolic compounds are found in sumac fruits by the 'HPLC-DAD-ESIMS/MS method' (Abu-Reidah et al., 2015). In mice, R. Javanica gal and garlic acid extracts were tested to prevent acute hepatic damage from CCl4 (carbon tetrachloride). It was emphasized that the protective function is due to the effect of compounds on cell membranes rather than the sweeping effect of oxygenated radicals (Kanai and Okano 1998).

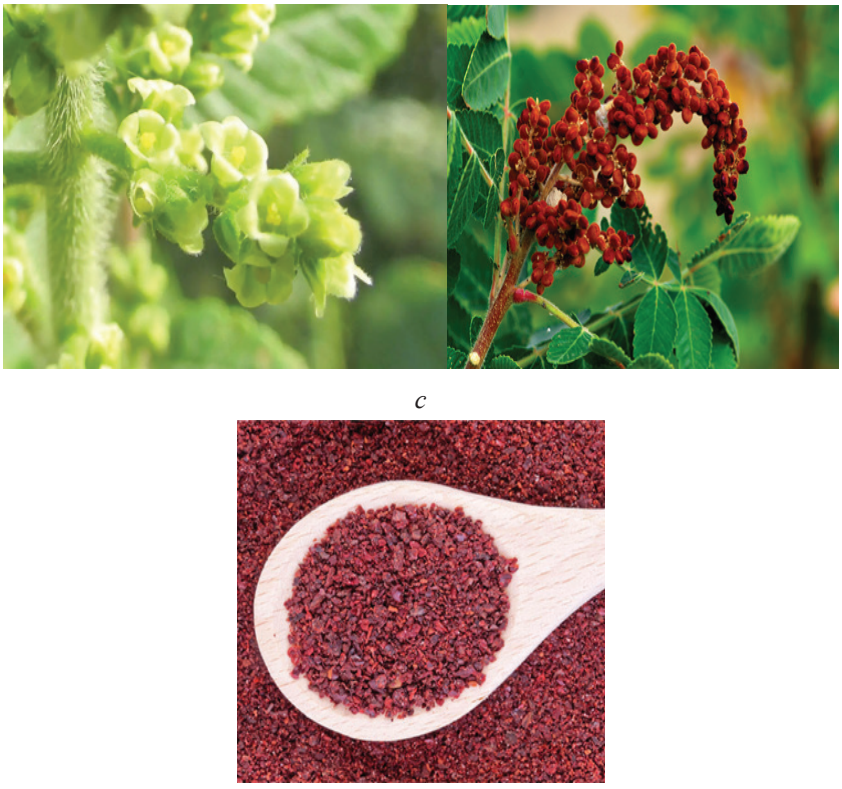

Figure showing sumac plants and fruits (Abu-Reidah et al. 2014). (a) The flower, the leaf of the sumac plant, (b) The sumac fruit c) The powder of the sumac fruit.

RESULT

Anthocyanins and phenolic compounds are known to be involved in the physiological effects of functional foods. Anthocyanins and phenolics in sumac were clarified in our study and demonstrated antimicrobial and antioxidant effects. Koşar et al. [2002] reported that methanol extracts from sumac fruit had a high antioxidant effect and separated the extracts obtained into their fractions. In terms of the structure of its chemical components, sumac has numerous physiological properties. Studies have found antioxidants and antimicrobial effects (Wildman, 2001; Koşar, 2007). The high antioxidant effect in herbal extracts is of course caused by the antioxidant molecules contained in the extract. Antioxidant compounds can carry out their antioxidant activities through a variety of mechanisms (binding of transition metals, decomposition of peroxides, prevention of hydrogen sequestration, elimination of radical properties of molecules, etc.) (Koşar et al., 2007). The fact that many different factors can affect the antioxidant activity of an extract makes it difficult to determine the main source of antioxidant activity and the contribution of other factors. A large amount of data (reducing power, free metal binding, radical scavenging, peroxide scavenging, superoxide scavenging abilities) is needed for each compound in the extract to determine what the main factor is. To this end, the determination of the total amount of phenolics and their reducing power will give us information on the source of the antioxidant activity. DNA protective effect Study of the DNA protective effect of powdered Rhus coriaria ethanol extracts in internal organs and lymphocytes, application of 3 g per day in humans for 3 days, the addition of 0.02 g/kg drinking water for each animal in animals internal organs (colon, liver and lung) and has been proven to inhibit the formation of oxidized DNA bases in lymphocytes. It has been determined by lesion-specific enzymes that sumac reduces tail elongation due to the formation of oxidized purine and pyrimidine bases in human lymphocytes under standard conditions by 52% and 36%, respectively. In addition, the formation of hydrogen peroxide (H2o2) and anti-benzo[a]pyrene-7,8-dihydrodiol-9,10-epoxy (BPDE) reduced DNA damage by 30% and 69%. All this evidence shows that Rhus coriaria is an effective antioxidant that can protect humans from oxidative damage to DNA (Chakraborty et al.). Recent epidemiological studies have shown that consumption of plant materials containing antioxidants may reduce the risk of a variety of diseases. The anticancer activity of Rhus coriaria ethanol extract on cervical cancer using HeLa cells was determined. Indeed, the non-cytotoxic concentrations of Rhus coriaria decreased HeLa cell migration in the wound healing assay. It has also been demonstrated that Rhus coriaria resin extract induces cytotoxic and antiangiogenic effects against the retinoblastoma Y79 cell line. Unfortunately, studies have been

conducted to conclusively evaluate the anticancer activity of Rhus coriaria against cancer of the uterus, cervix and retinoblastoma. Therefore, in vitro and in vivo studies are recommended to define the potential anticancer effects of this plant against both forms of cancer (Alsamri et l., 2021). Several studies have shown Rhus coriaria to have antioxidant activity. Shafiei et al. Studied the antioxidants and free radical scavengers as well as lipid peroxidation inhibition effects of methanol Rhus coriaria fruits and also indicated chronic disease prevention such as atherosclerosis by the plant extract. Rhus coriaria is proven to have a significant antioxidant property due to its rich phenolic compounds, in particular, gallic acid and its derivatives. (Zuhair Abdul-Jalil, 2020).

The antioxidant capability of the ripe fruit of Rhus coriaria was estimated using DPPH and the disappearance of dark purple assays by Mahdavi et al. Their study revealed that the antioxidant potential of Rhus coriaria was relatively elevated (Mahdavi and. Al. 2018). In another research (Gabr et.al., 2014; Soleymani et l., 2017), demonstrated that phenols derived from Rhus coriaria fruits had strong scavenging activities in vitro on β-carotene-linoleic acid and 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH) scavenging power assessment when compared to glycosides, alkaloids and terpenoids respectively. The use of this plant as a source of novel bioactive compounds, as well as toxicological studies and clinical trials are required to develop better alternative natural products.

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