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Antioxidant Effective Phenolic Compounds Naturally Found in Various Plants

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Introduction

Free radicals are highly reactive molecules with one or more unpaired electrons in their outer orbital. Reactive molecules can occur endogenously and exogenously. The conversion of 10% of oxygen to superoxide anion radicals or hydrogen peroxide during physiological respiration and metabolism processes in aerobic respiration organisms causes the endogenous formation of free radicals. Smoking, radiation, alcohol, stress, drugs, pesticides, environmental pollutants, malnutrition, infections and many different factors are exogenous factors that cause free radical formation (Wojtunik-Kulesza et al., 2016).

Free oxygen radicals are formed in the organism by three main mechanisms: energetic, reactive and metabolic. Metabolic reactions are the most important source of free oxygen radicals. The free oxygen radicals formed cause harmful effects on cells due to their highly reactive nature (Pellegrini et al., 2009). Free radicals are one of the main causes of disease formation and the natural aging process in the person (Harman, 2009). Lipids, proteins, enzymes, carbohydrates and DNA can be damaged due to oxidative stress. As a result of damage to the membranes, random breaks and bindings in the DNA chain may occur. Damage to enzymes and structural proteins can result in cell death. These phenomena form the molecular basis for the development of cancer, neurodegenerative and cardiovascular diseases, diabetes and autoimmune disorders (Cemeli, Baumgartner & Anderson, 2009).

Antioxidant compounds increase the antioxidant capacity of the body with their unique mechanism of action and they show this in two basic ways. The first of these involves inhibitory mechanisms such as the removal of initiating reactive compounds such as hydrogen peroxide and of metals that catalyze reactions such as free iron, and the reduction of oxygen concentration. The second involves direct mechanisms such as scavenging free radicals, suppressing their activity by adding protons to them, regenerating and repairing radicalized antioxidants or molecules, and breaking auto-oxidation (Benzie, 2003). Antioxidant substances reduce the harmful effects of free radicals on health, which are known to have a role in processes and diseases such as cardiovascular and pulmonary system diseases, cancer, cataracts, aging, by affecting all cells in the body. They show these effects by stopping the reactions of free radicals, preventing damage caused by oxidation by binding oxygen and metals, or preventing low-density lipoprotein and lipoprotein oxidation (Harman, 2009).

It has been determined by in vivo studies that some food antioxidants may be beneficial in atherosclerosis, malaria, rheumatoid arthritis and diabetes by inhibiting oxidation, and that they also have antitumoral, antimutagenic, antimetastatic, antithrombic, antiulcer, anticarcinogenic, antihypertensive, antibacterial, antifungal, antiviral and antiaging effects (Pellegrini et al., 2009).

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Factors Affecting the Antioxidant Content of Foods

The antioxidant content of foods and the bioavailability of antioxidants can vary according to the type of food, harvest time and methods, climate, the temperature, humidity and light of the storage and preservation environment, preparation of the food, and even the consumption habits of people and societies. In addition, inappropriate storage conditions, poor solubility, poor permeability of the digestive tract and other factors mentioned above are important in the bioavailability of antioxidants (Pellegrini et al., 2009). Nutrient losses, known as hidden losses in vegetables, occur in the period between post-harvest and consumption stage, and in some cases result in the loss of all nutritional value (Kalkan & Yücecan, 2014). The maturity of fruits and vegetables, harvest time, storage conditions and duration, and processes such as pre-consumption cooking affect their vitamin C content. It has been determined that different factors such as food storage conditions and preparation methods negatively affect the phenolic compound content and antioxidant properties of the food (Berno et al., 2014).

Velioğlu et al. (1998) found a good correlation between total phenolic values and total antioxidant activities in cereal products and flax seeds. In a study on industrial microwave exposure of sage, basil and black pepper, no change in the antioxidant properties of these plants was observed (Lopez-Bote et al., 1998). Nursal (2001) determined that the ascorbic acid content decreased by 47.9% in okra, 55% in potatoes, 42.4% in beans, 66.5% in broccoli and 64% in spinach after 6 months of storage at -18 °C; and found that the difference between the vitamin C values determined after cooling and freezing processes was statistically significant. Hunter & Fletcher (2002) found that freezing peas and spinach at -20 °C and storing them for 25 days reduced their antioxidant activities by 30% and 50%, respectively.

Natural Antioxidants

Phenolic compounds such as vitamin E, vitamin C, and beta carotene are the leading protective nutrients with antioxidant properties, and they protect cells against aggressive oxygen radicals by different mechanisms (Finley et al., 2011). In the elimination of free oxygen radicals endogenous antioxidant enzymes (glutathione peroxidase, superoxide dismutase and catalase), some vitamins (A, C, K and E) and minerals (Se and Zn) can be functional as well as exogenous antioxidants (lycopene, resveratrol, β-carotene, lutein, zeaxanthin) and precursors with antioxidant properties (benzoic, gallic and vanillic acid) are also needed (Cornelli, 2009).

The most important sources of antioxidant components are natural nutrients of plant origin (Güleşci & Aygül, 2016). Among the antioxidants contained in vegetables, phenolic compounds such as ascorbic acid, tocopherols, carotenoids, flavonols and phenolic acids can be counted (Kalkan & Yücecan, 2014). Sufficient and continuous consumption of herbal antioxidants (carotenoid, vitamin C, folic acid, retinol) prevents DNA damage from oxidative stress, while preventing the growth, tumoral formation and metastasis of advanced damaged cells. It is known that some active substances in aromatic plants and essential oils, which have natural antioxidant effects, show very strong antioxidant activity (Yeşilbağ, 2009). The compounds with the highest antioxidant effect are gallic acid, phloroglucinic acid, caffeic acid and gentisic acid (Kolaç, Gürbüz & Yetiş, 2017). Many plant-derived foods contain phenolic phytochemicals, which are the strongest antioxidants, and contribute to the body's defense against oxidative damage (Güleşci & Aygül, 2016).

Antioxidant Effects of Phenols

Phenolic compounds are substances containing one or more hydroxyl groups, including functional derivatives attached to an aromatic ring. Phenolic compounds are also called bioflavonoids due to their positive effects on nutritional physiology. More than eight thousand phenolic compounds have been identified until the beginning of the 2000s, and this number is

increasing day by day (Kolaç, Gürbüz & Yetiş, 2017). Phenolic substances form the most important groups of natural antioxidants. The most common herbal phenolic antioxidants are flavonoids, cinnamic acid derivatives, coumarins, tocopherols and phenolic acids (Deveci et al., 2016). Of these, important as antioxidants are phenolic acids and flavonoids (Fernandez-Panchon et al., 2008). Peanut flavonoids, soybean phenolic acids and isoflavone glycosides, rice hull phenolic, oat phenolic, sesame seed phenolic, wheat bran phenolic, tea phenolics and rosemary phenolics can be given as examples of phenolic substances showing antioxidant activity (Güleşci & Aygül, 2016). The phenols with the most effective antioxidant activity were determined as rosemary and sage (Rice-Evans et al., 1995). Akgül & Ayar (1993) determined that rosemary had the strongest antioxidant effect, followed by sage, sumac, thyme, marjoram, and zahter, respectively.

Phenolic compounds and some of their types are very effective in preventing autoxidation (Scalbert et al., 2005). Since the chemical composition of aromatic plants differs depending on many factors, their antioxidant effects can also change (Yeşilbağ, 2009). Studies have shown that certain phenolic antioxidants prevent cell death that occurs as a result of oxidative pressure (Deveci et al., 2016). It is stated that plant phenolic compounds are multifunctional antioxidants and play a role in many steps of oxidative reactions. The antioxidant effect of phenolic compounds is due to their properties such as scavenging free radicals, forming compounds with metal ions, preventing or reducing singlet oxygen formation and inhibiting lipoxygenase enzyme (Rice-Evans et al., 1995).

Consumption of foods with high phenolic content has the power to prevent many ailments in the body. Phenolic antioxidants have a preventive role in coronary heart failure by their effects on Ca^{+2} homeostasis (Deveci et al., 2016). Studies show the antiallergic, anti-inflammatory, antidiabetic, antimicrobial, antipathogenic, antiviral and antithrombotic properties of phenolic compounds and their protective effects in cardiovascular diseases, cancer, osteoporosis, diabetes mellitus and neurodegenerative diseases. Effects of anthocyanins such as reducing the risk of chronic heart diseases and improving visual and antiviral activity in humans have been observed (Scalbert et al., 2005).

Polyphenols, which are among the phenolic compounds, are antioxidants that break the bonds of lipid and reactive oxygen species and can scavenge radicals by binding them with bonds like chelates made by metal ions (Cemeli, Baumgartner & Anderson, 2009). The main groups of polyphenols are flavonoids, phenolic acids, tannins, stilbenes (resveratrol) and lignans. Polyphenolic substances, named according to the number of rings and structural elements they contain, generally have a phenol ring, as in phenolic acids and alcohols (D'Archivio et al., 2007).

Most Important Polyphenols: Flavonoids, Phenolic acids and Stilbenes

Flavonoids are low molecular weight compounds comprising 15 carbon atoms arranged in the C_6-C_3-C_6 configuration. The differences between the different flavonoids are due to the number of hydroxyl groups attached, the degree of unsaturation, and the oxidation level of the triple carbon segment. Changes in the heterocyclic ring C divide flavonoids into 6 main compound groups, the most common being flavonols and flavones, flavonols, flavones, flavanones, isoflavones, flavan-3-ols and anthocyanidins (D'Archivio et al., 2007). Flavonoids found in leaves, flowers and woody parts of plants can donate hydrogen in the hydroxyl group of their aromatic rings in order to prevent lipids, carbohydrates and proteins from being oxidized by free radicals (Fernandez-Panchon et al., 2008). The main foods containing flavonoids with proven antioxidant effects are green tea, strawberries, raspberries, blackberries and broccoli (Yağcı, Toker & Toker, 2008). Due to their antioxidant properties, flavonoids are one of the most important anticarcinogens in the diet (Fernandez-Panchon et al., 2008).

The flavonol group compounds, which are in the structure of 3-hydroxyflavone, are commonly found in foods in the form of glycosides. The main flavonols are kaempferol, quercetin, myricetin and isorhamnetin. It has been shown that kaempferol helps prevent DNA oxidative

damage with its antioxidant effect and reduces the risk of fatal heart disease, especially in women. It has been seen that kaempferol is especially effective together with quercetin, and it has been found that it inhibits cancer cell formation and growth in laboratory studies (Aherne & O'Brien, 2002). Quercetin positively affects performance by increasing genes that control mitochondrial biogenesis. Studies have shown that quercetin reduces the risk of prostate, ovarian, breast, stomach and bowel cancer. The anti-inflammatory activity of isorhamnetin and its positive effect on various types of cancer have been demonstrated (Kim et al., 2011). The main flavones are apigenin, luteolin, tangeretin, chrysin, baicalein, scutellarein, and wogonin (Aherne & O'Brien, 2002). Apigenin is found in hair sprays and shampoos. It has been shown that it may also be effective in the treatment of leukemia. It is thought that luteolin, which is abundant in *Terminalia chebula*, may be beneficial in patients with acute lymphoblastic leukemia (Ko et al., 2002).

The most abundant flavanones in nature are butin, eriodictyol, hesperetin, hesperidin, homoeriodictyol, isosakuranetin, naringenin, naringin, pinocembrin, poncirin, sakuranetin, sakuranin and sterubin. Flavanones such as naringin, hesperidin, and naringenin are commonly found in citrus fruits (Cemeroğlu, 2004). Isoflavones, known as phytoestrogenics, are found in a variety of legumes, most notably soybeans. Among the isoflavones, daidzein, genistein and glycitein come to the fore. When genistein interacts with the estrogen receptor beta, it produces effects similar to estrogen in breast, ovary, endometrium, prostate, vascular and bone tissues, with an effect of one third of the strength of estrogen. It has been shown that isoflavones reduce the risk of endometrial and breast cancer in short-term applications (İnanç & Tuna, 2005).

Taxifolin, the most important member of the flavan-3-ol group, has been reported to be beneficial in ovarian cancer as well as its antioxidant and anti-inflammatory effects (Nam et al., 2015). Catechins, which are found in almost every fruit, take place as intermediates in the flavonoid biosynthesis and fall into the flavan-3-ol group. It has been shown that catechins can prevent lipid hydroperoxide formation and the toxicity, and scavenge superoxide, peroxynitrite and other free radicals (Deveci et al., 2016). It has also been reported that catechins significantly inhibit the increased malondialdehyde level due to the formation of lipid peroxidation and increase the catalytic activity of antioxidant enzymes (Goldberg, Yan & Soleas, 2003). (+)-Epicatechin, which prevents the formation of histamine from histidine, was found to be five hundred times more effective than the flavone compounds in lemon when used in capillary cracks and caused a remarkable increase in capillary wall resistance (Fidan & Cenik, 1976).

In general, phenolic acids, which are not found in free form, are examined in two groups as hydroxycinnamic acids and hydroxybenzoic acids. Among the hydroxycinnamic acids, ferulic acid, caffeic acid, coumaric acid and sinapic acid come to the fore (Kolaç, Gürbüz & Yetiş, 2017). Plants such as coffee, thyme, sage, mint, ceylon cinnamon, anise, red wine, apple, apricot, plum and prune are the main sources (Pokorny, 1991). Caffeic acid shows suppressive, immunomodulatory, anti-inflammatory and nephroprotective activity against lipid peroxidation and tissue damage. Sinapic acid is localized near the husk in cereal grains (Kolaç, Gürbüz & Yetiş, 2017). It has been shown that sinapic acid has antimicrobial, anti-carcinogenic and anti-inflammatory effects and has antihyperglycemic effects in diabetic animals (Cherng et al., 2013). Among the hydroxybenzoic acids, the most well-known are salicylic acid, p-hydroxybenzoic acid, protocatechuic acid, syringic acid and gallic acid. The most well-known of the stilbenes is resveratrol. The powerful antioxidant property of resveratrol found in grape skin, which is thought to have an anti-aging and life-expanding effect, is 50 times more than vitamin E and 30 times more than vitamin C (Kolaç, Gürbüz & Yetiş, 2017).

Plants Containing Phenolic Compounds with Antioxidant Effects

Rosemary (*Salvia rosmarinus*)

Figure 1. Rosemary (Salvia rosmarinus)

The antioxidant property of rosemary (Figure 1) is due to the carnosol, carnosic acid and rosmarinic acid found in its leaves. It has been reported that carnosic acid in rosemary is three times higher than carnosol and seven times higher than BHT and BHA. Carnosic acid and carnosol, which are abietatriene-derived diterpenes, are responsible for 90% of the antioxidant effect of rosemary. It is known that carnosic acid is the strongest antioxidant for animal fats. Other compounds with similar action are rosmanol, epirosmanol, isorosmanol, rosmaridiphenol, rosmadial, and miltirone (Richheimer et al., 1996). It has been reported that the antioxidant effect of rosemary primarily depends on the species, variety, harvest time, type of processing and environmental and ecological characteristics of the growth environment, which is one of the most important factors. In a study examining the antioxidant effect of 31 kinds of aromatic plants, it was seen that the rosemary plant had the strongest antioxidant effect, followed by plants such as sage, sumac and thyme, respectively (Akgül & Ayar, 1993).

Thyme (*Thymus vulgaris*)

Figure 2. Thyme (Thymus vulgaris)

The common feature of thyme (Figure 2) species is that they contain essential oils and the main components of these essential oils are thymol and carvacrol. Thymol and carvacrol make up 78-82% of essential oils in thyme. Thymol and carvacrol are phenolic compounds that give thyme its distinctive smell and give it antibacterial and antioxidant properties (Botsoglou et al., 2003). Öztürk, Konyalıoğlu & Baykan, (2002a) reported that the antioxidant capacity is *Thymus brachychilus*, *Thymus leucotrichus var. leucotrichus* and *Thymus leucostomus var. argillaceus* from the lowest to the highest. It has been observed that the antioxidant effect of thyme essential oil is not as strong as vitamin E (Botsoglou et al., 2003).

Clove (Syzygium aromaticum)

Figure 3. Clove (Syzygium aromaticum)

It is the essential oil called eugenol that gives cloves (Figure 3) its odor and flavor. The main components of cloves are eugenol and eugenol acetate. Eugenol forms a large part of the clove extract and is the antioxidative element of the plant (Lee & Shibamoto, 2001).

Sage (*Salvia officinalis*)

Figure 4. Sage (Salvia officinalis)

The most important phenolic components in the structure of sage (Figure 4), which have an antioxidant effect, are carnosol, carnosic acid and rosmanol, as in rosemary. It was determined that chloroform extract of clary sage (*Salvia sclarea*) had higher antioxidant activity than acetone extract and total antioxidant activities of both extracts were higher than α-tocopherol (Gülçin et al., 2004). Pizzale et al. (2002) determined that the antioxidant activity of sage species (*Salvia officinalis* and *Salvia fruticosa*) was higher than that of thyme species (*Origanum onites* and *Origanum indercedens*).

Black pepper (*Piper nigrum)*

Figure 5. Black pepper (Piper nigrum)

Black pepper (Figure 5) contains five phenolic acids (piperettin, piperanine, piperyline A, piperolein B and pipericine) amides with antioxidant properties. These compounds are oil-free, odorless and tasteless, and show stronger antioxidant activity than α-tocopherol. Black pepper has antioxidant, antimicrobial and antipyretic properties (Ravindran & Kallupurackal, 2001).

Turmeric (*Curcuma longa*)

Figure 6. Turmeric (Curcuma longa)

Curcuminoids (curcumin, demethoxycurcumin, and bisdemethoxycurcumin) form the main component of turmeric (Figure 6). Turmeric contains tetrahydrocurcumin, an antioxidant compound. It has been stated that the antioxidant property of turmeric is due to the phenolic components it contains. It has been determined that the components isolated from *Curcuma longa* have strong antioxidant effects and are very important on lipid oxidation. It has been determined that the antioxidant capacity of curcuminoids is equivalent to ascorbic acid (Jayaprakasha, Rao & Sakariah, 2005).

Green tea (*Camellia sinensis*)

Figure 7. Green tea (Camellia sinensis)

Polyphenols, which are antioxidant compounds of tea, make up 35% of dry tea. Green tea (Figure 7) is especially rich in flavonoids, including catechins and catechin derivatives. It has been reported that fresh tea sprouts contain epigallocatechin gallate, epicatechin gallate, epigallocatechin and epicatechin. Of these, 60% of the total catechin is epigallocatechin gallate (Yılmaz, 2010). The antioxidant activity of green tea, which is rich in catechin and polyphenol compounds, is several times higher than that of vitamins C and E. It has been reported that tea catechins inhibit the initiation, progression and transformation stages of cancer. It has also been stated that tea consumption provides protection against chemical carcinogens that cause pancreatic, liver, lung, esophagus, duodenum, breast and colon cancers, is protective against arthritis and coronary heart diseases, and prevents or delays the formation of cardiovascular disorders (Cemeli, Baumgartner & Anderson, 2009).

Common Nettle (*Urtica dioica*)

Figure 8. Common Nettle (Urtica dioica)

Common nettle (Figure 8) contains flavonoids, formic acid, high levels of chlorophyll, plant sterols, plant enzymes, phenylpropanes, coumarins, terpenoids, potassium salts, calcium and

vitamin C. It has been reported that common nettle has anti-inflammatory, anticarcinogenic, antiviral and antioxidant effects and acts as an immune system stimulator through its many flavonol glycosides. Aqueous extraction of *Urtica dioica* has been shown to be effective on free radical scavenging and metal scavenging activities (Fijalek et al., 2003). Cetinus et al. (2005) reported in their study that *Urtica dioica* has a potential antioxidant effect on ischemic muscle tissues in rats, thus preventing lipid peroxidation by reducing malondialdehyde levels. Kanter et al. (2003) reported that *Urtica dioica* and *Nigella sativa* strengthened the weakened antioxidant defense system and reduced the elevated lipid peroxidation in rats treated with carbon tetrachloride, and that aqueous extraction of *Urtica dioica* exhibited more effective antioxidant activity than α-tocopherol on the peroxidation of linoleic acid.

Aloe vera

Figure 9. Aloe vera

Aloe vera (Figure 9) belongs to the Liliaceae family and contains anthracene derivatives as an active ingredient. The antioxidant property of *Aloe vera* is due to the abundant amounts of vitamin A (β-carotene), vitamins C, E and B_{12}, as well as choline and folic acid (Surjushe, Vasani & Saple, 2008). Studies have shown that *Aloe vera* has strong antioxidant properties and significantly inhibits lipid peroxidation by increasing the activity of antioxidant enzymes such as glutathione-S-transferase, glutathione peroxidase, catalase and superoxide dismutase (Deveci et al., 2016). *Aloe vera* has antioxidant properties as well as antiviral, anti-inflammatory and antitumor properties (Surjushe, Vasani & Saple, 2008).

Mint (*Mentha x piperita*)

Figure 10. Mint (Mentha x piperita)

As the active compounds of the mint (Figure 10) plant, the leaves contain 0.8-4% essential oil, flavones, rosmarinic acid, caffeic acid, chlorogenic acid and triterpenic substances. The essential oil contains 45-50% menthol, 5-20% menthol esters and lesser amounts of menthone, eucalyptol, limonene and β-caryophyllene. The amount and components of essential oil vary according to the breed and growing conditions. *Mentha longifolia* subsp. *typhoides* has the highest antioxidant capacity (Öztürk et al., 2002b).

Mountain Tea (*Sideritis syriaca*)

Figure 11. Mountain Tea (Sideritis syriaca)

Mountain tea (Figure 11) contains essential oil, diterpenoid, fatty acid, coumarin and flavonoid group compounds. Mountain tea shows antioxidant and antimicrobial properties because it contains flavonoids, phenolic glycosides, phenolic acid derivatives and essential oils (Deveci et al., 2016). Tunalıer et al. (2002) reported that some sideritis species with high total phenol content have free radical scavenging effects and are effective in preventing lipid peroxidation.

St. John's Wort (*Hypericum perforatum*)

Figure 12. St. John's Wort (Hypericum perforatum)

St. John's Wort (Figure 12) contains 6.5-15% catechin, tannin and proanthocyanidins (eg catechin, epicatechin, leukocyanidin), flavonoids (eg hyperoside) (up to 2%), rutin (up to 1.6%), quercetin (up to 0.3%), biflavonoids (0.26% biapigenins), phloroglucinol derivatives (eg hyperforin) (up to 4%), essential oil, naphthodianthrones (hypericin and pseudohypericin), xanthones, sterols, and vitamins A and C. The phenolic compounds in St. John's Wort are responsible for the antioxidant activity (Mahady, Fong & Farnsworth, 2001).

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The Effect Of Body and Environmental Temperature on Embrionic Development During Pregnancy

Emre AYDEMİR
İnci BİLGE

1.INTRODUCTION

During pregnancy, embryonic development takes place within 42 weeks, and normal birth occurs between 38 and 42 weeks. Babies of mothers who gave birth normally are born with a live weight of 2500-4000 grams (g). But; low birth weights, miscarriages, various health problems, and deaths occur due to genetic and environmental conditions (Manning 1991; Norwitz and Fisher 2001; Simpson 2007; Larsen et al. 2013; Regan and Rai 2000). Among the causes of embryonic deaths, genetic and environmental factors draw attention (King 1991; Mieusset et al. 1987). Environmental factors; during pregnancy, it can cause some structural and functional disorders in the embryo depending on its sensitivity to environmental teratogens such as light, chemical (drugs and nutrients), temperature, radiation. This is because, in prenatal development, susceptibility to teratogen is relatively high. It is known to cause differentiation during cell division and even cell death (apoptosis) by being sensitive to heat in neo-natal and post-natal periods during embryo development during pregnancy. For example, exposure to high temperatures during the period until the embryo settles on the uterine wall can cause embryonic death. Cell division due to high temperature during organogenesis can cause developmental disorders in specific organs or structures. Various physiological disorders that occur, the mother's sensitivity to heat (threshold value), genetic, age, psychological, physical and chemical, etc. it differs depending on the circumstances (Tilbrook et al. 2000). In some studies, when exposed to heat stress between 20 and 28 days of organogenesis; During the neural plate and neural tube formation stages, malformations are seen in the brain, eye, heart, and face regions of the embryo (Konermann 1989; Pleet et al. 1981; Khursheed et al. 2021). It is also stated that problems such as defective spinal cord development, small or missing fingers, tooth defects, abdominal wall defects, cataracts, coloboma, and blindness are observed (Tikkanen and Heinonen 1991; Pleet et al. 1981; Khursheed et al. 2021; Tamás and Gábor 2021; Edwards et al. 2003). When studies on humans and animals are examined, similar results are observed (Carleton 2016; Mora et al. 2018). However, the reasons for the different results encountered between species differ due to the genotypic structure of the species, sensitivity to environmental conditions, and adaptation process (Webster et al. 1984; Finnell et al. 1986; Kimmel et al. 1993).

2.EFFECTS OF TEMPERATURE ON EMBRYONİC DEVELOPMENT

2.1.The Effect Of Body Temperature On Embryonic Development During Pregnancy

Body temperature; It is kept in balance within a limited range with the heat output and loss. This balance is 37 ^{0}C for humans. This temperature may differ due to disease, malnutrition, and severe environmental temperature. In addition to the increase in body temperature during pregnancy, disruption of gene expression, DNA replication stage, damage to blood vessels and placenta, structural, functional, and physiological disorders, it also causes many embryonic defects

such as a slowdown in embryo development, apoptosis and even embryo death due to environmental temperature. For example, in a study conducted, embryonic maternal heat exchange is prevented as a result of decreased placental blood flow due to heat stress during long-term hyperthermia periods. Accordingly, it was stated that fetal body weights decreased and embryonic development slowed down (Bell 1987; McMurray and Katz 1990). The fetus is not capable of regulating its temperature, heat; blood flow is provided by the mother's body temperature through the umbilical circulation and fetal skin, amniotic fluid, and uterine wall (Schro¨ve Power 1997). In addition, any abnormality in the mother's body can affect the fetus.

2.2.The Effect Of Environmental Temperature On Embryonic Development During Pregnancy

Various health problems arise due to environmental factors such as light, temperature, and humidity (Parsons 2002; Kjellstrom 2009). One of these problems is the negative effects on the mother and the fetus due to the high environmental temperature during pregnancy. Depending on the exposure time to high ambient temperature; it causes various physiological disorders, permanent disorders, embryo deaths, and miscarriages (Berkman et al. 2002).

3.STUDIES DONE

3.1.Studies On Body Temperature And Embryonic Development

Although the number of studies on the effects of hyperthermia during pregnancy is limited; It is accepted that heat stress is an influencing factor in childbirth. As a result of the increase in body temperature; it is known to have significant effects on perinatal morbidity and mortality (Niswander and Jordan, 1972; Cefalo and Hellegers, 1978). Kline et al. (1985) in a study carried out by; investigated the effects of the mother's body temperature of 37.78 ^{0}C and above at the 28th week of pregnancy. In the findings obtained from the study, they concluded that high body temperature is an influencing factor for spontaneous abortion. In another study; Tikkanen and Heinonen (1991) studied the relationship between conditions that may cause hyperthermia and the occurrence of cardiovascular malformations. In the findings obtained from the study, it was stated that there was a statistically significant relationship between first-trimester fever (> 38.8 ^{0}C) and atrial septal defects (p <0:01). In addition, they observed a statistically significant relationship between first-trimester fever and hypoplastic left heart and upper respiratory tract infections (p <0: 001). In another study, Pleet et al. (1981) examined the effects of a fever higher than 38.9 ^{0}C at least once a week between the 4th and 14th weeks of pregnancy on the embryo to be born. In the study, the researchers stated that there were negative effects on mental development in children exposed to high temperatures between 4-14 weeks of pregnancy. They also stated that seizures, neuronal heterotopies, defects, microphthalmia, micrognathia, midface hypoplasia, and facial physical defects occur in those exposed between 4-7 weeks. In the study conducted by Shiota (1982), it was observed that it caused significant malformations in fetuses obtained from mothers who had an abortion due to high fever in the early stages of pregnancy. They also reported that it causes physical disorders such as anencephaly, heart defects, cleft lip, and hypospadias. Edwards et al. (2003), it was stated that a sudden high-temperature change causes hyperthermia during pregnancy, miscarriage, and various disorders in embryonic development. It has also been reported to cause embryonic deaths. In the study conducted by Tamás and Gábor (2021), they examined the effects of different ambient temperatures (15 ^{0}C, 20–25 ^{0}C, and–20 ^{0}C) on pregnancy during early pregnancy. As a result of the findings obtained without clinical observation in the study, the embryonic death rate increased with the increase in temperature, however; Researchers observed

that embryonic death rate decreases at low temperature. In the results of another study, Khursheed et al. (2021) stated that exposure to heat stress as a result of high temperature adversely affects embryo fertilization, oogenesis, oocyte maturation, and implantation.

3.2.Studies On Embryonic Development With Environment Temperature

Strand et al. (2011) investigated the effects of different seasonal temperatures in the embryonic period. In the results of the study, they stated that exposure to high temperatures before birth had negative effects on birth weight, preterm birth, and stillbirth (Strand et al. 2011). Studying environmental temperature and birth weight, Jonathan and Tim (2002) examined the effects of various factors such as ethnicity, maternal size, maternal nutritional status, and different environmental temperature on birth weight. In the study, it was reported that the variance between 108 different ethnicities and birth weight was 9.6%, and heat stress was inversely proportional to birth weight.

3.3. Studies on other species

Effects of temperature in the embryonic period; Apart from humans, there are many studies on experimental animals such as mice and rats, and various farm animals such as cattle and sheep with economic value (Al-Ghetaa 2012; Oviedo et al. 2008; Wolfenson et al. 2000). In a study on rats, Shiota and Kayamura (1989) stated that during the 12-15 days of pregnancy; investigated the differences between the behavioral characteristics of the puppies obtained by keeping them in a heated water bath for 10 minutes once or twice, and the control group (not treated). In the results of their study, they observed that the activation of the puppies was slower at the age of 5 weeks compared to the control group, and they had difficulty in learning at the age of 7 weeks. They also stated that at the age of 11 weeks, their brains were smaller than the control group. In another study, Edwards (1969b) pigs between the 4th and 67th day of pregnancy; He applied heat at 38 ^{0}C or 43 ^{0}C for 1 hour a day. In the study, 14-31 days of pregnancy. observed that high-temperature application on consecutive days (2 days) increased the incidence of mycencephaly following hyperthermia and decreased the mean brain weight. Researchers found that brain weight gains if the body temperature rises more than 2.5 ^{0}C above normal for the 16-17, 20-21, 22-23 and 24-25 days of the study; reported that for every 1 ^{0}C increase in body temperature, brain weight decreased by 8.4% compared to the control group. As a result, it was reported that the brain weight of the heat-treated groups was statistically lighter than the control group ($p < 0: 001$). In addition, the researcher stated that the incidence of microcephaly in the group to which heat treatment was applied was 54.6%. In another study by Edwards (1969a), she applied high temperature for 90 minutes 2, 4, and 8 times a day on days 4-32 of pregnancy. In the study, the researchers found that there was no effect on fetal development at 4-11 days of pregnancy; He stated that fetal resorption occurred in 11-15 days. High temperature is applied; 11-32. and 18-25 days reported that were observed developmental abnormalities in newborn puppies. Also, 15-27. days mycenacephaly, due to abnormalities in bone development; determined that there was amyoplasia, reduction in cervical size, affecting the neck, forelimbs, rib cage, and abdominal muscles. As a result, both studies by Edwards (1969a,b) reported that the application of high temperatures with different frequencies above normal added embryonic development. Wolfenson et al. (2000) in the study by; reported that the effects of exposure to high temperature (heat stress) in cows on embryogenesis, uterus–oviduct, follicular dynamics, oestrus determination, conception rate, steroid and gonadotropin concentrations are seen in 60% of cows worldwide. In a study on poultry, Oviedo et al. (2008) were investigated the effects of four different (36, 37, 38, or 39 ^{0}C) incubation temperatures on chick weight. Researchers reported that going outside the optimum conditions in terms of temperature adversely affected chick weight and chick quality. In another study, İpek et al. (2014) control group

was 39.4 ^{0}C, low temperature 38.7 ^{0}C, and high temperature 40.5 ^{0}C; The effects of 3 different incubation temperatures on chick quality were investigated. While the average chick weight in the study was estimated to be 39.5 g, 42.5 g, and 41.0 g, respectively; chick length averages were determined as 18.5 cm, 19.1 cm, and 21.4 cm, respectively. As a result; They observed that chick weight and length, high and low-temperature application were lower than the control group. As a result of this; reported that chick quality deteriorated.

4.CONCLUSION

In the literature, the number of studies on the relationship between environment and body temperature in embryonic development is limited. However, various clinical studies have been carried out on many models such as experimental, farm animals. In the studies carried out; it was concluded that body temperature causes gene expression, DNA replication, neuronal heterotopies, defects, microphthalmia, micrognathia, heart defects, physical disorders on the face, placental damage, embryo development, oogenesis, fertilization, implantation, physical disorders such as hydrocephalus, hypospadias, many embryonic defects such as apoptosis, low birth weight and embryo deaths during pregnancy. It has been stated that environmental temperature causes various physiological disorders, permanent ailments, embryo deaths, and miscarriages. It has been reported that similar results were obtained in studies conducted in other model animal species.

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Aromatic Compounds With Antiviral Effects and Covid-19

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Zeliha Nur Özdemir

INTRODUCTION

Aromatic Compound

The word aromatic means "fragrant" according to the definition of the Turkish Language Association. The concept of aromatism in the chemical sense; It is used for compounds with conjugated double bonds in the planar, compound ring structure. In addition, compliance with the Hückel's rule is checked today for the aromatic compound requirement. Hückel's rule is that the ring carries (4n+2) a number of p-electrons. Here; n = 0, 1, 2, 3, 4..... or a greater positive integer. According to this definition; Planar rings with conjugated double bonds with 2, 6, 10, 14 and 18 p-electrons are aromatic. Benzene, naphthalene and anthracene are examples of hydrocarbons that meet the aromatism requirements.

Virus

Viruses are disease elements that cause systemic or regional diseases in the human body. The most common diseases caused by viruses in humans; flu, AIDS, hepatitis, measles, smallpox, chickenpox and covid-19, which is becoming common today (Saricaoğlu, 2011).

<table>
<tr><td colspan="2">Herpes virüs enfeksiyonları</td><td colspan="2">İnsan papilloma virüs (HPV) enfeksiyonları</td></tr>
<tr><td>Herpes simpleks virüsü tip I
Herpes simpleks virüsü tip II
Varisella-zoster virüsü (VZV)
Epstein-Barr virüsü (EBV)
Sitomegalovirüs (CMV)
İnsan herpes virüsü tip 6
İnsan herpes virüsü tip 7
İnsan herpes virüsü tip 8</td><td>HSV1 Mukokütanöz herpes
HSV2 Genital herpes
HHV3 Suçiçeği, Zona
HHV4 Enfeksiyöz mononükleoz, Giannotti crosti snd
HHV5 Sitomegalik inklüzyon hastalığı
HHV6 Ekzantema subitumeritema enfeksiozum
HHV7
HHV8 Kaposi sarkomu</td><td colspan="2">İnsan papilloma virüs (HPV) enfeksiyonları
Verrukalar (Siğiller)
Epidermodisplazia verrüsiformis
Reküren respiratuar papillomatoz
İmmünosupresyonda HPV</td></tr>
<tr><td>Pox virüs enfeksiyonları</td><td>Aıds</td><td colspan="2">Diğer viral hastalıklar</td></tr>
</table>

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Çiçek Molluskum kontagiozum Sütçü nodülleri Orf		**Enterovirüsler** Coxsackie (el-ayak-ağız hast, herpanjina,farenjit) ECHO (rubella bezeri ekzantem,makülopapüler ekzantem,Eruptive psödoanjiomatöz) Aphtovirus (ayak - ağız hast.)

Altı hastalık	**Diğer viral ekzantemler**
Rubeola (1.hastalık-Kızamık): Paramyxovirus Kızıl (2. hastalık): streptokok Rubella (3. hastalık-kızamıkcık, alman kızamığı): togavirus Rubella scarlatinosa(4 hastalık): - Eritema enfesksiyozum (5. Hastalık) Parvovirüs B19 Ekzantema subitum (6. Hastalık-Roseola infantum): HHV6	Enfektif dermatit X Papüler purpurik eldiven-çorap sendromu: Parvovirus B 19, HHV6 vd.) Asimetrik perifleksural ekzantem X Giannotti-Crosti: HHV4, CMV, coxsackie, vd. Rubeola scarlatinosa(4.hastalık): X Eritema enfeksiozum (5. Hastalık): Parvovirus B19 Ekzantema subitum (6.hastalık-Roseaola infantum): HHV6

Flu

It is a highly contagious disease caused by influenza viruses. Influenza viruses, an RNA virus from the Orthomyxo viridea family, are of two types, A and B, which cause disease in humans. The virus undergoes various mutations every year, causing question marks in the mind about vaccines and drug treatment. With the adhesion of influenza viruses to the cell surface, the effect of the virus on the body begins to appear. The virus that attaches to the cell is taken in and releases its own genetic material into the cell. The material forms a new component with the nucleus of the cell. Components collect on the host cell surface and manage to infect the cell. The side effects that seem most common in patients infected with the influenza virus are fever, headache, exhaustion, runny nose, sneezing. For the diagnosis of the disease, nasal swab samples, throat swab can be used. In addition, hemagglutination inhibition test, PCR or ELISA techniques are also used. Analgesics, antipyretics, sometimes antihistamines are the most commonly used types of drugs in the treatment of the disease. (Tosun, 2017)

AIDS

The HIV/AIDS disease that emerged in the 1980s has been called the "plague of the age". In 2014, 78 million people had experienced this disease and 39 million people's lives ended from this disease. Although it is stated that it is unlikely to be seen in Turkey, it is thought that 75% of people in 15 countries around the world have HIV/AIDS in total. It is thought that in the years when the disease was first discovered, it was only seen in homosexual men. The cases that emerged in the following years showed that they also occurred in heterosexual men. It has been shown to be passed on to women and to babies through infected pregnant women. Thus, the disease began to spread. Studies show that it is transmitted vertically from mother to baby through sexual contact, intravenous drug use. When HIV-infected patients were examined, destruction of CD4+T lymphocytes, which have an important place in the immune system, was detected. Infection usually lasts 8-12 years and proceeds in some stages. These phases are; acute primary HIV infection, chronic asymptomatic stage, is the most severe stage of AIDS. Tests for the diagnosis of the disease are; screening and verification tests to detect antibodies and tests to detect virus antigen and virus DNA/RNA. Prevention of the disease is considered a more important issue than the treatment of

the disease and some measures that can be taken in this direction; monogamy, the use of condoms during sexual intercourse, the use of common needles in drug users. In addition, as in all matters, it is aimed to prevent the disease by informing individuals correctly. Although the mortality rate of the disease was very remarkable at first, there has been a significant decrease in the annual frequency of death from AIDS-related diseases with the increase in access to treatment recently. The fact that the disease can be transmitted sexually has led to it becoming a taboo in society. With the breaking of these taboos in the future, the disease is expected to have a very low value in terms of risk potential. (War, 2015)

Hepatitis

Hepatitis disease is a viral disease and has been a risk for many years in the world. Various studies have tried to determine the viruses that cause viral hepatitis. Today, hepatitis A, B, C, D and E viruses, which are known to cause viral hepatitis, are known. However, the causative agent of some types of hepatitis has still not been identified. (Kaya and Akçam 2005)

Hepatitis A

It is classified in the genus Hepatovirus in the family Picornaviridae. There is only one serotype. The virion is composed of linear RNA with a capsid layer consisting of four repetitive building blocks. Once in the body, it develops a replication mechanism in the liver cells. During the period of spread of the virus, its excretion from feces occurs. Heptatit Avirus has been shown to cause destruction in hepatocytes. In vitro studies have shown that cells carrying hepatitis A virus become targets of natural killer cells and CD8 cytotoxic T lymphocytes. The immune system is responsible for the distribution of the virus throughout the body. Serological tests were developed and started to be used in the 1970s in order to recognize the disease. In 1995, the hepatitis A vaccine was licensed. It has generally been found to be transmitted orally. it is likely to occur in developing countries. Apart from the liver, no serious destruction of the body has been observed. (Comrade et al. 2012)

Hepatitis B

It is known that an average of 2 billion people in the world have encountered hepatitis B virus (HBV) and 400,000 people have chronically experienced the disease. In our country, when HBsAg, known as the surface antigen of hepatitis B virus, is examined, a rate of 0.8-5.7% is determined. When HBsAg positivity is compared between geographical regions in Turkey, it has a higher rate in Southeastern Anatolia and Eastern Anatolia Regions than in other regions. The identified genotypes of this virus have reached 10 with recent research. The transmission pathways have been determined parenterally, vertically and horizontally. It has been observed that the disease is more common in high age groups. The disease progresses through two different periods, acute and chronic. With the disappearance of HBsAg antigen, the healing process of the disease begins. (Akhan et al. 2012)

Hepatitis C

Hepatitis C is a virus-induced infectious disease that causes serious problems, especially in the liver. According to the estimated data, 130-170 million people are thought to carry hepatitis C virus (HCV). The spread and transmission routes of the disease vary between countries and regions. The highest risk modes of transmission are transfusion of blood and blood products, solid organ transfusion from an infected donor, IV drug use, unsafe therapeutic injections, occupational

percutaneous contacts such as needle prick, transmission from infected mother to baby, sexual intercourse with an infected partner and multiple partners. (Barut and Günal 2009)

Measles

The virus that causes measles is a virus in the form of single-stranded RNA with polarity in the genome structure belonging to the family Paramyxoviridae. Symptoms of the disease include high fever and skin rashes. Although it is a disease for which there is a vaccine, there is still an intense prevalence worldwide. This is because it is extremely contagious. Mortality rates due to the disease are around 25%. The age distribution is wide. This means that people of all age groups can get this disease. The most common complications due to measles are otitis media, pneumonia and encephalomyelitis. (Sünnetçioğlu et al. 2015)

Chickenpox

It is a virus-borne disease that can be seen mostly in childhood but also in later ages. The virus that causes the disease is called varicella zoster. This virus has a double-stranded DNA structure and 7 specific glycoproteins belonging to the virus have been shown in the cell membrane. The disease usually heals on its own in the range of 7-14 days and also has c iddi mortality and morbidity rates. During the course of the disease, symptoms such as nystagmus, vomiting, tremor, headache, rigidity and hypotonia were observed. The most observed symptom is the rashes that appear on the skin. (Dilek et al. 2015)

COVİD-19

Although the Covid-19 outbreak that emerged in China was tried to be prevented by the measures of the World Health Organization, it turned into a pandemic and spread all over the world. As a result of the researches, it was determined that the disease was caused by the new coronavirus SARS-CoV-2. It is among the information discovered so far that this virus can infect a wide variety of animals, especially humans. However, when examined, the resulting images were called coronaviruses (Latin: corona = crown) based on their morphology as virions due to their core shell and sun-like surface protrusions. When coronaviruses with subspecies are classified, they are called alpha, beta, gamma and delta. When the genome of SARS-CoV-2, which causes today's pandemic, was examined, it showed 96% similarity with bat-borne alpha and beta subspecies. (Velavan and Meyer 2020)

What is the Source of COVID-19 Disease and Ways of Transmission?

Although studies on the source of the disease are ongoing, studies so far suggest that wild animals sold illegally at the Huanan Seafood Wholesale Market cause this virus. Domestic animals such as cats and dogs were also examined, but no evidence was found that these animals were carriers. As a result, the source of the disease has not yet been clearly concluded. (Til, 2020).

As for the ways of transmission, research has proven that the disease is mainly transmitted by droplets. These droplets are known to be effective within a distance of two meters. The droplets are scattered around by coughing and sneezing of sick individuals and remain suspended in the air for up to three hours. In addition, the virus has also been seen in blood and urine samples of positive people. The exact number of days after which the sick individual becomes contagious is still a subject that is being investigated. Studies on parameters such as these, which vary from person to person, are ongoing. (Türken & Köse 2020).

Covid-19 Clinical Findings:

It is known that the incubation period of the disease is from 1 to 14 days. When the reported cases were examined, it was seen that the smallest patient was 1.5 months old. The disease can be seen symptomatically or asymptomatically. Symptoms vary between patients. Some of these symptoms are as follows; runny nose, sore throat, dry cough, nausea, vomiting, diarrhea. The most common of these symptoms is dry cough with a rate of 50%. PCR tests are applied in patients with symptoms. In suspicious cases, chest X-ray should be examined. The frosted glass-shaped structures seen on the graphs are evidence that the fault is covid-19. In addition, another issue that has attracted attention in clinical studies has been related to the transmission of the virus to breast milk. In the examinations, it was reported that there was no vertical transmission of SARS-CoV-2 from 9 mothers with SARS-C oV-2 infection to their infants. (Özdemir & Ayşegül 2020)

The researches on the effects of SARS-CoV-2 on humans and the pathways it follows in the body are as follows; As a result of the examination of human respiratory tract epithelial cells, Vero E6 and Huh7 cell lines, it was learned that this virus causes severe acute respiratory syndrome. In addition, as a result of the same study, when the viral load on the nasopharyngeal swabs was detected, a direct link was detected between the severe transmission of the disease and the viral load. Biochemical researches have brought clarifications to the changes that this virus creates in the body. As a result, SARS-CoV-2 has been shown to bind to the human receptor for angiotensin-converting enzyme 2 (ACE2). The spike protein of SARS-CoV-2 contains two subunits, S1 and S2. On the border between the two subunits there is a polybasic zone of furin division. This region of division is important for virus infectivity and host range (Ciotti et al. 2020).

Prevention of the spread of the disease:

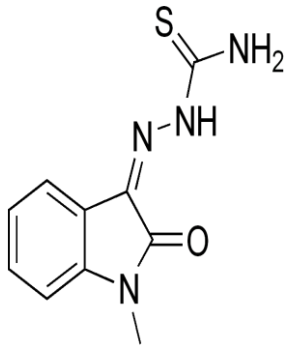
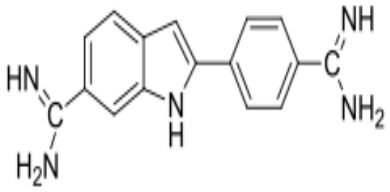
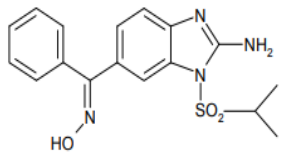
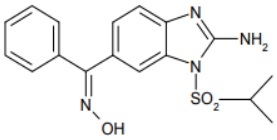
First of all, exposure should be reduced to a minimum. For this purpose, public areas should be avoided and the mask rule should be observed. As much as possible, it should be in airy environments. Touching and consuming wild animals that are considered to be the source of the disease should be avoided.

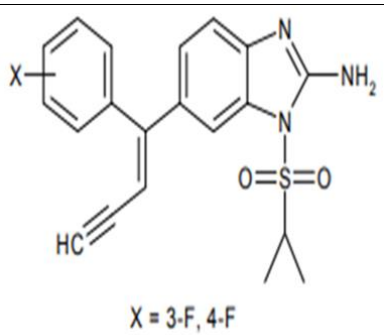
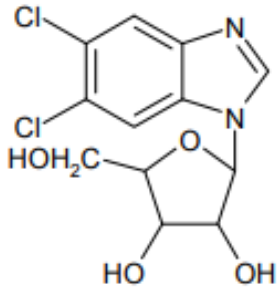
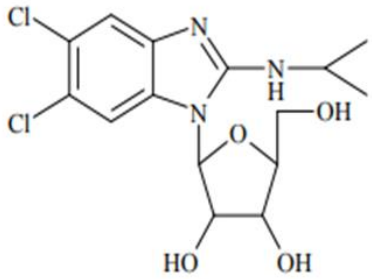
Caution should be exercised against droplets that have proven to be a contact route. It should be remembered how simple it is to stick droplets from any media. For this reason, in order to protect ourselves, hands should be washed frequently, and the health suitability of clothes and other items should be given importance. In order to protect others, precautions should be taken against droplets that may come out of our mouths when talking and coughing.

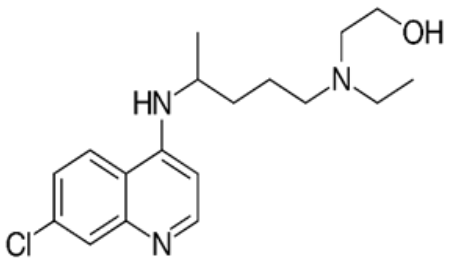
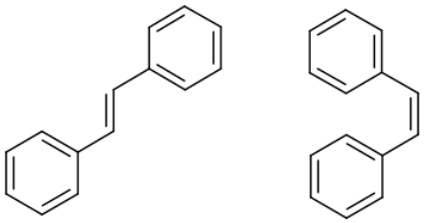
Antiviral Effect

Antiviral effect; is the effect that occurs with the help of pharmacological agents in order to cure infections caused by viruses in the body. The drugs that produce this effect show their effects by killing, reducing or neutralizing the viruses in the body.

Viruses are particles defined as the transition of the inanimate form consisting of DNA and RNA particles to the living form. It enters the host creature in various ways, leading to changes in the body of the creature it has entered. The most known diseases caused by these changes are as follows; flu, AIDS (Acquired Immunodeficiency Syndrome), chickenpox, measles, mumps. (Öksüz and Algül 2019)

Antiviral Effective Compounds Chemical Structures	Pharmacological Activity
Metisazon 	One of the first antiviral agents synthetically used in the clinic was methiscalone (N-methylsatin-β-thiosemicarbazone). Experimental results have shown to be effective for inhibition of HIV-1 replication. (Selvam et al. 2008)
DAPI (4',6-diamidino-2-fenilindol) 	DAPI (4',6-diamidino-2-phenylindole), which is used as a colorant in DNA studies today, was developed primarily as an antitrypanosomal agent. With the increase of studies in the future, the antiviral activity of this compound has been proven. (Göker et al. 2014)
Benzimidazole Derivatives **Enviroksim (son)**  **Enviraden (anti)** 	Rhinoviruses are the type of virus that most commonly cause colds and acute respiratory infections. Benzimidazole Derivatives have been synthesized and their effect on rhinovirus, which causes these common diseases, has been investigated. Tests have been conducted for two isomers of two different isomers (syn and anti) of the same compound. These compounds have been reported to be effective against all known rhinovirus types. (Wikel et al. 1980)
Enviroksim-p-flower	Some side effects of the anti-isomer enviroxime compound have been reported. Being vomiting is one of these side effects. However, its poor bioavailability led Victor et al. to synthesize a series of vinylacetylene benzimidazole derivatives that are analogous to enviroximim. Among the derivatives they synthesized, fluorine-bearing derivatives in the position of money inhibited viral RNA synthesis by showing high

	bioavailability orally in experimental animals. (Victor et al. 1997)
DRB (5,6-dikloro-1-β-D-ribofuranozilbenzimidazol) 	Some improvements have been made to strengthen the effect of DRB (5,6-dichloro-1-β-D-ribofuranozil benzimidazole) and its analogues, which have been proven to have antiviral activity in previous years. The new synthesized derivatives showed a good level of inhibitory activity in general. However, one of the derivatives is both the most effective and the least cytotoxic. (Devivar et al. 1994) These compounds show their antiviral activity on HCMV (Human Cytomegalo Virus). These viruses are very common in diseases due to immune system deficiency such as AIDS and can have fatal consequences. (Göker et al. 2007)
Benzimidavir 	Benzimidavir is a compound synthesized in 2002 with the chemical name 5,6-dichloro-2- isopropylamino-1-(β-L-ribofuranozil)-1H-benzimidazole. Its effect against HCMV is more potent and less toxic than many FDA-approved drugs. In addition, the effect of benzimidavir has been proven on resistant strains. oral bioavailability varied in various experimental animals. Although Phase and Phase studies of the compound have been conducted, Phase III studies are ongoing as of 2021. (Evers et al. 2002)

Hidroksiklorokin 	Hydroxychloroquine is a drug that was used mainly as an antimalarial, receiving FDA approval on April 18, 1955. It is also frequently prescribed in the treatment of rheumatoid arthritis, chronic discoid lupus erythematosus and systemic lupus erythematosus. It has received emergency use authorization from the FDA for the treatment of SARS-CoV-2, which emerged all over the world in the early twenty-first century. However, the authorization for use was revoked on June 15, 2020, after a death was reported in a group treated with hydroxychloroquine. (Law et al. 2020)
Stilben and **derivatives** 	Stilbene derivatives have become a chemical species that has attracted attention in recent years. When examined in terms of their effects, stilbens are thought to have a wide place in pharmacology. Some of these effects are antimicrobial, antioxidant, antileukemic, anticarcinogenic and viral aspects of anti-HIV and anti-herpes simplex effects. As a result of the investigations, only two derivatives of the approximately 20 synthesized compounds were found to have inhibitory ability on the coronavirus. (Li et al. 2006)

Other Compounds:

In addition to the compounds whose structures are given above, research is also continuing on some compounds. In a study conducted in 2007, a series of heterocyclic benzimidazole structures carrying amidino derivatives at the 5th carbon of the benzimidazole ring were prepared. Pyridine, N-methyl-pyrrol or imidazole were added to the 2nd carbon of the structure. The antiviral activities of the synthesized molecules were evaluated. As a result of the research, a surprising selectivity against Coxsackie viruses and ecoviruses was determined. In particular, the molecules bearing pyridine structure in the 2nd carbon are powerful molecules in terms of their antiviral effect (Starcevic et al. 2007).

The antiviral activity of 2 ***H-3*-(4-chlorophenyl)-3,4-dihydro-1,4-benzo-thiazin-2-carbonitryl 1,1-dioxide,** another compound whose structure is not given above, and its anthalogin fused with thiophene has also been studied. This compound was synthesized based on previous experience with arylsulfone derivatives. With this structure, which exhibits antiherpetic activity, several analogues have been synthesized in which the sulfonyl group is part of a bicyclic

structure. Derivatives combined with benzene have been reported to have positive activity and selectivity against betaherpesviruses and human cytomegalovirus. (Naesens et al. 2006)

CONCLUSIONS AND RECOMMENDATIONS

Thisresearch includes a summary screening of antiviral drugs containing aromatic structure used in viral infections and treatment. Virus infections are diseases that exist today as in the past. The fact that it will always pose a risk to human life has been understood more closely with the recent Covid-19 pandemic. As an individual or as a society, minimizing this risk is of great importance in terms of health. This study draws attention to the antiviral effect of substances containing aromatic structure and emphasizes the importance of developing new antiviral drugs by increasing biological activity studies.

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Alzheimer and Periodontal Health

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Introduction

Periodontal diseases are infectious diseases characterized by chronic inflammation and destruction of teeth and tooth support tissues. It has been understood that immunological reactions against bacterial colonization have an important role in the progression of periodontal disease. In the etiopathogenesis of periodontal diseases, microorganisms, immune response, environmental and genetic factors include many mechanisms arising from the multifaceted interaction (Slots, 2013).

There are studies reporting that oxidative stress plays a role in the pathogenesis of many chronic diseases such as diabetes, hypertension, neurodegenerative diseases, rheumatoid arthritis, cancer, obesity, atherosclerosis, as well as periodontal diseases (Cullinan and Seymour, 2013; Bullon et al, 2014; Southerland et al, 2006).

In recent years, it has been emphasized that oxidative stress, which occurs as a result of the disruption of the balance between free radicals and the protective antioxidant system, is an inflammatory marker associated with both Alzheimer's and periodontitis. It is now an accepted fact that periodontitis is a risk factor for many systemic diseases, and there is evidence of an increasing association between periodontitis and Alzheimer's disease.

Despite long-term research, no disease-modifying drug has been found to date for the treatment of Alzheimer's (Norton et al, 2014; Bateman, 2015). Therefore, in recent years, studies have been intensified to identify modifiable risk factors that aim to develop preventive strategies that can reduce the prevalence of dementia. (Barnes and Yaffe, 2011; Norton et al, 2014). The main preventable risk factors identified for Alzheimer's worldwide are low education level, smoking, physical inactivity, depression, hypertension, diabetes mellitus, and early-onset obesity. (Norton et al, 2014). If these risk factors can be controlled, it is predicted that Alzheimer's cases will decrease by 30%-50% (Barnes and Yaffe, 2011; Norton et al, 2014).

Neurodegenerative Diseases and Alzheimer's

Neurodegenerative diseases are diseases characterized by cognitive-behavioral disorders and movement problems (Dugger and Dickson, 2017). Neurodegenerative diseases are typically specific protein deposits and share many essential processes associated with progressive neuronal dysfunction, such as oxidative stress, apoptosis, and neuroinflammation. In these diseases with

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complex clinical features; only a very small group of patients show symptoms of the disease (Dugger and Dickson, 2017).

The most important of the neurodegenerative diseases is Alzheimer's disease. Apart from Alzheimer's disease, other most important neurodegenerative diseases; Parkinson's disease (PD), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), multiple system atrophy (MSA) and Huntington's Disease (HD) (Davis et al, 2018). All these diseases; The time between the onset of symptoms and the final stage of the disease is highly variable, although it is progressive and can lead to death as a result of primary dysfunction of the central nervous system or related medical complications.

Despite the many differences in the clinical components and epidemiology of neurodegenerative diseases, the anatomical regions affected and the cell types involved, there are several common aspects that can aid in understanding the pathophysiology of the diseases. One of the most conspicuous of these common features is the insoluble accumulation of endogenous proteins. In many neurodegenerative diseases, specific proteins begin to collect in characteristic regions early in the course of the disease, and spread to other regions is observed in later stages. This observation led to the hypothesis that protein deposits could spread from one cell to another, from one brain region to other brain regions (Davis et al, 2018). It has been reported that protein anomalies that define neurodegenerative diseases may occur before the onset of clinical symptoms (Adler et al, 2010; Evidente et al, 2011; Schmitt et al, 2000).

Alzheimer's Disease

Alzheimer's disease is a progressive neurodegenerative disease of the central nervous system that accounts for 50-80% of all dementia cases; It is a disease characterized by the deterioration of mental functions such as learning, memory, language, personality and orientation. Alois Alzheimer (14 June 1864 - 19 December 1915), a German psychiatrist and neuropathologist, published the first case of "presenile dementia". Later, this disease was defined as "Alzheimer's disease" by the famous psychiatrist Emil Kraepelin (Selekler, 2010).

Alzheimer's disease (AD) is also the most common cause of dementia, which starts with recent memory impairment, and with the progression of the disease, attention and executive functions, language, spatial functions, cognitive dysfunctions and disorders in activities of daily living, cognitive weakness, depression accompanied by significant behavioral changes and psychiatric symptoms, It is a progressive neurodegenerative disease accompanied by anxiety, apathy, phobia of being alone, aimless wanderings, agitation, aggression, hallucinations, delusions and sleep disorders (Cerajewska et al, 2015; Kamer et al, 2008).

Alzheimer's disease (AD) is a neurodegenerative brain disease that develops as the most common cause of dementia (Wilson et al, 2012). AD is characterized by slowly progressive cognitive decline Lane et al, 2018). While AD mostly occurs in advanced ages, it has been reported that its familial form is seen at an early age and is associated with various gene mutations (Bateman et al, 2011). Alzheimer's Disease is a dementia syndrome with an insidious onset, slow-progressed tempo, in which other cognitive functions are impaired with the addition of neocortical involvement (Bhat et al, 2015).

AD is actually a proteinopathy. The inflammatory state that occurs due to the accumulation of proteins causes functional disorders in neurons. The most important pathological markers in

AD are amyloid-β (Aβ) deposition, a degenerative protein, and neurofibrillary tangle (NFT) formation (9). Although the mechanisms in the pathogenesis of AD have not been clarified, it is thought that inflammatory conditions may contribute to the progression of the disease. It has been determined that oxidative stress is an important factor leading to the onset and progression of AD (Bhat et al, 2015). It has been reported that overexpression of reactive oxygen species can induce Aβ accumulation (Bhat et al, 2015). It has also been shown that the number of iNOS positive neurons accompanying neuronal damage in AD patients is increased (Wolk and Klunk, 2009). It is thought that long-term chronic inflammatory diseases, including periodontitis, may play a role in the pathogenesis of AD by increasing oxidative stress. (Holmes and Butchart, 2011; Holmer at al, 2018).

AD, which is a neurodegenerative disease, starts with recent memory impairment in the majority of cases. In the following period, various behavioral disorders and neuropsychiatric symptoms occur as a result of cognitive dysfunctions such as language, visuospatial functions, executive functions, attention and praxis, and disorders in daily living activities are added to the clinic (Querfurth and LaFerla, 2004). Behavioral changes such as agitation, depression, delusions, and hallucinations usually appear from the middle stage of the disease, but may occur at any time during the course of the disease. Memory impairment is initially in the form of inability to learn and form new memory, and distant memory is relatively preserved. The same question can be asked over and over again. In the future, distant memory also deteriorates. Language disorder is in the form of difficulty in finding words, saying the wrong word or the word instead. Especially from the middle stage, there are deteriorations in daily life activities such as finding way and direction, shopping, watching television-radio, cooking, calculating money, solving problems related to home and work, choosing clothes, reading books and remembering appointments (Bhat et al, 2015).

Etiology of Alzheimer's Disease

The age of onset is generally important in terms of showing whether the disease is inherited or not. Alzheimer's disease, which is not familial but also starts at an advanced age, constitutes approximately 95-98% of all cases. Familial Alzheimer's disease is less common and the exact cause of the disease is unknown. However, the most important factor in both groups is thought to be genetic. Dominant mutations in three different genes have been identified in early-onset Alzheimer's disease and a small number of familial inherited cases. ApoE was found to be one of the susceptibility genes in late-onset Alzheimer's patients, which is more common. (Cerajewska et al, 2015; Gatz et al, 2006). The impact of many of the factors in Alzheimer's disease, their interaction with the disease, and their significance on the disease are still not fully understood.

Alzheimer's Disease Pathophysiology and Genetics

A healthy brain has about 100 billion neurons and about 100 trillion synapses. The proper functioning of the neuron-synapse allows signals to flow rapidly through the circuits of the brain, laying the foundation for thoughts, feelings, sensations, memories, movements and skills. It is thought that beta amyloid protein, which is believed to be responsible for the pathogenesis of AD development, acts by disrupting synapse neuron functioning with accumulation of beta amyloid protein outside of neurons (senile plaques-SP) and accumulation of an abnormal form of tau protein inside neurons (neurofibrillary tangles-NFT) (Jones-Davis and Buckholtz, 2015).

Brain atrophy due to loss of neurons and synapses in the cerebral cortex and subcortical areas in Alzheimer's disease is the most important pathological feature of the disease (Hardy, 1997). These extracellular and intracellular accumulations cause oxidative stress by negatively affecting

axonal transport, signal transmission and neurotrophic factor production in neurons (Dursun et al, 2011).

AD, which is a polygenic/multiallelic disease with heterogeneity, arises with many different mutations of gene loci in more than one chromosome. It has been found that 3 different genes are responsible for autosomal dominant inheritance in this disease. These are the 2 genes of presenilin on chromosome 1; It can be listed as the presenilin 1 gene on the 14th chromosome and the amyloid precursor protein gene on the 21st chromosome (Howard, 2004).

Although the normal functions of these 3 transmembrane proteins are not well known; There are studies showing that they play a role in neuronal plasticity. In such people, the symptoms of the disease tend to develop before the age of 65. The majority of AD cases start at a later age (Cerejewska et al, 2018).

Age is the most determining factor in the prevalence and incidence of Alzheimer's disease. If the disease is seen before the age of 65, it is called early-onset Alzheimer's, and if it is seen at the age of 65 or later, it is called late-onset Alzheimer's (Hebert et al, 2003; Bekris et al, 2010). Early-onset cases are less common and mostly have an autosomal dominant inheritance linked to a single gene. Late-onset cases, on the other hand, have a complex inheritance that occurs with the small contribution of many genes and the effect of environmental factors (Bekris et al, 2010; Alonso et al, 2012). It has been determined that there is a strong relationship between Alzheimer's disease and the ε4 allele of the apolipoprotein E gene, especially in late-onset cases (Namba et al, 1991).

Risk Factors for Alzheimer's Disease

The most important risk factor for Alzheimer's Disease is old age. Apart from old age, genetic and environmental problems are also important risk factors for Alzheimer's disease (Ganguli et al, 2000). Hypertension, presence of hypercholesterolemia, smoking, diabetes mellitus, which are modifiable factors, increase the likelihood of the disease and its course rate (Gao et al, 1998). Unchangeable factors are age, gender, genetic factors, familial predisposition, Down syndrome and head circumference. In addition to non-modifiable factors, modifiable risk factors also have a significant impact on the onset and course of the disease. Environmental factors affecting the development of the disease; physical and mental activity, alcohol use, head trauma, socioeconomic status, education level and occupation. Other risk factors are sleep disorders, depression, eating habits, diet and exposure to toxic substances (Barnes and Yaffe, 2011; Ceraewska et al, 2015). (Table 1)

FACTORS PLAYING ROLE IN ALZHEIMER'S DISEASE	
Risk Factors	***Protective Factors***
• Age	• Higher education
• Family history of dementia	• APOE-ε2
• Down syndrome	• Use of antioxidants
• Female gender	• Nonsteroidal antiinflammatory use
• Low education	• Statin use
• Head trauma with loss of consciousness	• Red wine
• History of major depression	• Mediterranean diet
• Vascular events and risk factors	• Physical and mental activity
• Genetic factors (APOE-ε4)	
• Plasma homocysteine level	
• Hypothyroidism	
• Exposure to certain toxic and harmful conditions	

Table 1. Factors Playing Role in Alzheimer's Disease.

Alzheimer's Disease Epidemiology

Age is the most important risk factor for AD, and the prevalence of the disease increases exponentially every five years after the age of 65 (Cerajewska et al, 2015). The prevalence of AD was found to be 4-5% between the ages of 65-70 in studies, and the highest prevalence is observed in the 8th decade (Tonetti et al, 2015; Maiotti, 1999).

According to WHO data, AD is the fifth cause of death worldwide. AD is more common in women than men. It has been stated that one out of every 6 women aged 65 and over has Alzheimer's disease, and this rate is one in 11 men in men (Altmann et al, 2014). The duration of AD varies between 2-16 years from the onset of the disease. It is known that the average life expectancy for cases diagnosed with Alzheimer's varies from 3 to 7 years. (Fitzpatrick et al, 2005).

Alzheimer's Disease Stages

Alzheimer's disease is a disease that usually progresses slowly over the years, and this progression also varies according to the patients. Dr. Barry Reisberg has staged the disease in seven stages;

STAGE 1: There is no biological damage in the patient, there is no abnormality in their memory and behavior, and no change is noticed by their environment.

STAGE 2: Cognitive change can be felt less and current events can be forgotten. Cases of forgetting personal belongings in different places are frequent in patients.

STAGE 3: Cognitive change is felt at a moderate level. Changes are noticed by the patient's relatives. The patient ignores these problems and starts to hide them. It is difficult to diagnose the disease at an early stage.

STAGE 4: It is considered as the onset of Alzheimer's. The patient has problems with calculations, disruptions in routine work, becoming withdrawn, and on the contrary, an increase in moodiness and irritability. The patient continues to get to know the people around him.

STAGE 5: It is considered as moderate-severe level between dementia stages. The patient begins to lose his ability to solve personal problems, to confuse the plots, to blame the other person due to serious forgetfulness and forgetfulness.

STAGE 6: It is considered as the severe level between the stages of dementia. He starts to encounter psychological problems such as not being able to realize his actions, not being able to remember the names of his relatives, having difficulty in fulfilling basic needs, needing help, remembering something that did not happen, and hallucinating.

STAGE 7: It is considered as a very severe level between dementia stages. The patient loses his motor skills, cannot fulfill his basic needs without assistance, cannot meet his toilet needs, and incontinence becomes more frequent. As the disease progresses, the patient forgets to sit and eat and becomes bedridden (Reisberg et al, 2011).

Periodontal Health

According to the classification revised in 2017, absolute periodontal health is not frequently observed in the clinic, but it is a rare condition that can be seen and all diagnostic parameters such as bleeding on probing, presence of pockets, attachment loss, radiographic bone loss, edema, pus formation are negative. There is no inflammation at the histological level and no anatomical changes are observed in the periodontium. The absence of inflammatory periodontal disease is referred to as clinical periodontal health. Intact clinical health is defined as the absence of attachment loss and no bleeding on probing, no probing pocket depth exceeding 3 mm, no redness, edema and pus, and no histopathological inflammation. The absence of clinical periodontal inflammation in an intact periodontium or reduced periodontium is defined as clinical health (Lang et al, 2018).

Absence of bleeding on probing, which is the best indicator of gingival inflammation, represents periodontal health. Studies have also shown that the assessment of bleeding or attachment levels on probing alone should not be used as evidence of gingival health or disease, and that with regular maintenance treatment, deep pockets can remain stable for a very long time without any signs of inflammation. (Knowles et al, 1979).

One of the most important indicators in the clinical evaluation of the periodontium is radiographic findings. An intact lamina dura at the alveolar crest, no bone loss in the furcation areas, and a 2 mm distance between the alveolar bone crest and the enamel-cementum junction in the most coronal part; form the radiographic features of a healthy periodontium. Clinical periodontal health in the decreased periodontium should not be determined by radiographic findings alone, but clinical findings should be combined with radiographic findings and evaluated together (Lang et al, 2018).

Periodontal diseases

The defense of periodontal tissues is of great importance in meeting and adapting functional forces. Periodontal diseases characterized by irreversible tissue damage; They are inflammatory diseases that affect the periodontal ligament, alveolar bone and gingiva surrounding the tooth and are characterized by periodontal pocket formation and alveolar bone resorption (Papapanou et al, 2018). Although the incidence of periodontitis in underdeveloped or developing countries is much higher than in developed countries; The worldwide prevalence of periodontitis accounts for 10-15% of the adult population. It is also reported that the sixth most common chronic disease in humans is periodontitis, and periodontal diseases are the precursors and markers of many systemic chronic diseases (Kassebaum et al, 2018). (Figure 1)

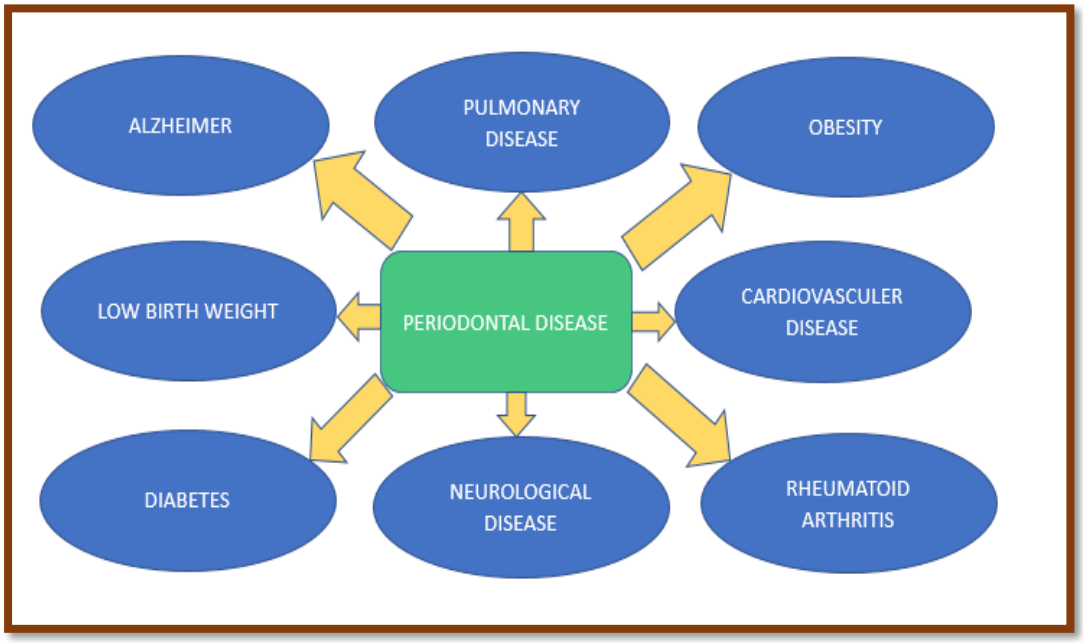

Figure 1. Interaction of periodontal diseases with systemic diseases.

The primary cause of periodontal disease is microbial dental plaque that accumulates on hard structures such as teeth and restorations. Local factors make mechanical plaque removal difficult and cause dental plaque accumulation at the gingival margin or apical, which facilitates the biofilm to adhere more tightly and mature in the following processes. (Chapple et al, 2018).

Microscopic and clinical signs of gingival inflammation become evident within 4-7 days, and these inflammatory changes can be reversed when adequate oral hygiene is provided. It was observed that there were differences between microorganisms in subgingival plaque samples taken from periodontally healthy and diseased areas, and it was determined that bacteria in these different biofilms were closely related among themselves (Kinane et al, 2017).

Gingivitis is a periodontal disease that occurs with the formation of dental biofilm on the teeth, in which there is gingival redness, edema, post-probing or spontaneous bleeding, an increase in gingival groove fluid and no radiographic bone loss. Bleeding on probing and increased gingival groove fluid are the two earliest signs of the disease, and dental plaque accumulation and microbial changes are considered to be two of the main causes of gingivitis (Chapple et al, 2018).

Periodontal diseases are complex diseases in which pathogenic bacteria in dental plaque induce an immune response in the host. Periodontal diseases are diseases characterized by the

destruction of teeth and the hard and soft tissues that support the teeth as a result of long-term chronic systemic inflammation and immune reactions (Garcia et al, 2001). Periodontal tissue destruction; The amount of microbial dental plaque varies in proportion to host defense and other associated risk factors (Kinane et al, 2017). The main features of periodontal disease are loss of periodontal tissue support resulting from clinical attachment loss, presence of periodontal pockets, gingival bleeding and radiologically detected alveolar bone loss. (Papapanou et al, 2018). In recent years, it has been stated that it is possible to predict the progression of periodontitis and the risk of tooth loss by associating the presence of individual risk factors with validated risk assessment tools and tooth loss (Tonetti et al, 2018).

According to the new classification made by Tonetti et al (2018), Periodontitis is divided into 4 stages.

Stage I periodontitis is the stage in which the maximum probing depth is 4 mm or less, the interdental clinical attachment loss is 1-2 mm, the alveolar bone loss is less than 15% in radiographic examination, and mostly horizontal loss is observed. Initial periodontitis is considered the boundary between gingivitis and periodontitis and represents the first stage of attachment loss. (Tonetti et al, 2018; Hayta et al, 2014).

Stage II periodontitis refers to established periodontitis, which is defined by the characteristic damage of periodontitis to the tooth support tissues as a result of clinical periodontal examination in which the pocket depth is 5 mm or less on probing, the attachment loss is 3-4 mm, and the radiographic bone loss is between 15-33%, mostly horizontal bone loss is observed (Tonetti et al, 2018).

Stage III periodontitis is the stage with pocket depth of 6 mm or more on probing, vertical bone loss of 3 mm or more, loss of attachment greater than 5 mm, and radiographic bone loss extending to the middle or apical third of the root, and class 2 or 3 furcation problems are present (Tonetti et al, 2018).

Stage IV periodontitis, attachment loss is more than 5 mm and radiographic bone loss extends to the middle or apical part of the root, and tooth loss occurs due to destruction of the supporting tissues. There is mobility of class 2 or more due to secondary occlusal trauma in the teeth and chewing dysfunction is observed in the patients (Tonetti et al, 2018).

Periodontitis is classified with 3 different gradings in addition to these staging;

In patients with grade A periodontitis; The rate of bone loss and age is less than 0.25 percent. Although there is a large amount of biofilm, there is a low level of bone resorption and the disease progresses slowly. Modifying factors such as smoking and diabetic symptoms are not observed in the patients.

In patients with grade B periodontitis; , the rate of bone loss and age is between 0.25 and 1 percent. There is bone destruction due to biofilm accumulation and a moderate progression rate is observed. They smoke less than 10 cigarettes a day, and people with diabetes have HbA1c less than 7.

In patients with grade C periodontitis; The rate of bone loss and age is greater than 1 percent. Rapidly progressive bone destruction is observed. Daily cigarette use is more than 10 in patients and HbA1c is greater than 7 in diabetes patients (Tonetti et al, 2018).

The Relationship between Alzheimer's and Periodontal Disease

Two mechanisms have been proposed to explain the relationship between periodontitis and Alzheimer's.

a. According to the first mechanism, periodontopathogenic microorganisms and the host response cause an increase in the levels of proinflammatory cytokines. This causes the release of excessive amounts of cytokines and pro-inflammatory agents into the systemic circulation, which increases the systemic inflammatory load, resulting in systemic or peripheral inflammation. These proinflammatory molecules have the ability to cross the blood brain barrier and invade cerebral regions. This, in turn, leads to activation of microglial cells and neuronal damage (Lee et al, 2009).

b. The second mechanism is that the microorganisms in the dental plaque biofilm invade the brain. Microorganisms in dental plaque can enter the brain through the bloodstream or peripheral nerves. These microorganisms and their products reveal an inflammatory mechanism in the central nervous system. It is generally accepted that the presence of inflammation in the central nervous system causes cognitive disorders such as Alzheimer's disease. This inflammatory degradation is attributed to interactions between neurons and glial cells mediated by cytokines. Among the cytokines released due to inflammation are IL family, TNF-a, TGF-β and chemokines, and since these cytokines are detected in both serum and plasma, they are considered to play an important role in the pathogenesis of Alzheimer's disease. (Lee et al, 2009). TNF-α, one of the cytokines released during inflammation, plays a major role in neurodegenerative disease. TNF-α accelerates the inflammatory process resulting in gliosis, demyelination, disruption of the blood-brain barrier and cell death. Therefore, TNF-α has been considered to play a crucial role in the neurodegenerative process (Park and Bowers, 2010; Montgomery and Bowers, 2012). Anti-inflammatory agents indicated during any inflammatory state significantly reduce the effects of these cytokines and other pro-inflammatory molecules. Studies in mouse models have revealed the beneficial effects of anti-inflammatory agents in improving neuroinflammation and amyloid plaque deposition. In addition, significant reductions in IL-1β levels and glial fibrillary acidic protein levels have also been reported in mice treated with a nonsteroidal anti-inflammatory agent. (Yan et al, 2003; Heneka et al, 2005).

Alzheimer's disease causes gradual disorientation of the person in time and space, preventing daily living activities. Difficulty developing in motor skills paves the way for the development of periodontal disease as a result of not fulfilling oral hygiene habits (Ghezzi and Ship, 2000). Periodontal diseases are chronic inflammatory diseases that can affect the periodontal ligament, alveolar bone and gingiva surrounding the tooth and are characterized by periodontal pocket formation and alveolar bone destruction. Microbial dental plaque accumulating on hard surfaces such as teeth and restorations is the most important factor in the etiology of periodontal diseases (Loe, 1969). It has been determined that the bacterial endotoxins and enzymes in the plaque cause direct destruction in the periodontium (Loe, 1969). With the stimulus, the entire cytokine network in the organism is activated, and the activation of one cytokine triggers other cytokines. Accordingly, proinflammatory cytokines (TNF, IL-1, IL-6, IL-12, IFN etc.) and anti-inflammatory cytokines (IL4, IL-10, IL-13 etc.) are released. Periodontal disease can stimulate systemic inflammation as well as the local response that occurs with the release of cytokines (Hotamisligil and Spiegelman, 1994; Okada and Murakami, 1998). It is thought that this systemic effect may affect the pathophysiology of Alzheimer's disease. According to the relationship between periodontitis and cognitive loss; during chronic periodontitis, periodontal bacterial component containing IL-1β, TNF-α and lipopolysaccharide and flagellin secreted from macrophages; It activates microglia, the phagocytic cell in the brain, by activating IL-1 receptor/TNF receptor and Toll-like receptors localized on the leptomeninges. After cellular activation, microglia secrete

proinflammatory molecules such as IL-1β, which increase BACE1 (β-secretase enzyme) expression and activation, resulting in increased Aβ accumulation. In addition, IL-1β secreted from activated microglia accelerates tangle formation resulting from tau hyperphosphorylation. This pathological condition can damage neuronal functions and facilitate cognitive loss (Wu and Nakanishi, 2014).

As the course of Alzheimer's disease progresses, oral hygiene deteriorates due to the decrease in motor functions and due to decreased motor skills, periodontal diseases are prepared. In addition, higher serum TNF-α and antibody levels in Alzheimer's patients compared to healthy controls were associated with poor oral hygiene in Alzheimer's patients (Ship, 1992). There are studies showing that Alzheimer's patients have worse oral health than healthy but older control groups, and that oral health worsens as the disease becomes more severe. (Kmaer et al, 2012; Martande et al, 2014). Studies show that Alzheimer's patients have high plaque index, high gingival bleeding and higher periodontitis scores and they need help with oral care (Delwel et al,2018).

Serum levels of pro and anti-inflammatory cytokines can be evaluated in the examination of host defense, and cytokines can also be preferred to determine the systemic inflammatory status of periodontitis patients (Hınz and Geschwind, 2017; Lopez and Kuller, 2019). Increased levels of IL-1β, which occurs in response to stimuli during inflammation, have been detected both in neuroinflammation in Alzheimer's disease and in periodontal diseases.

Oxidative stress also plays an important role in the pathogenesis of Alzheimer's. Accumulation of reactive oxygen species damages major cell components, especially mitochondria, in certain brain regions (Chen and Zhong, 2014). Inflammation has an important role in the pathogenesis of Alzheimer's. Activated microglia and reactive astrocytes settle into fibrillar plaques and the level of biochemical markers increases. Initially, phagocytic microglia engulf and degrade beta-amyloid protein. Chronically activated microglia initiate the cytokine cascade after chemokine release. As a result of fibrillary Aβ and glial activation, the classical complement pathway is activated. There is acute phase reactant release from stimulated astroglia, which can lead to both worsening and improvement of patients' clinical condition (Pan et al, 2010).

Smoking and alcohol use are accepted as risk factors for AD. Recent studies have shown that the risk of AD is significantly increased in middle-aged smokers who smoke two or more packs/day. Similarly, neuroimaging studies have shown that smoking results in gray matter tissue loss. It has been reported that heavy alcohol use increases the risk of AD three times in middle age, especially in those carrying the APOE-ε4 allele. In another study, it was shown that heavy alcohol and cigarette use increased the age of onset of AD in those carrying the APOE-ε4 allele. (Querfurth and Laferla, 2010).

In the light of the results obtained from many epidemiological, neuroimaging and neuropathological studies conducted to date, vascular risk factors (obesity, smoking, high total cholesterol level) and vascular morbidity (diabetes, myocardial ischemia, high blood pressure, stroke, silent brain infarctions and white matter) lesions) have been found to be a risk factor for AD as well as dementia. Alzheimer's Disease has been associated with endothelial dysfunction, the first step of atherosclerosis (Dede et al, 2007). In addition, high homocysteine level, which is a stroke risk factor, has also been shown to be an independent risk factor. The association of hypothyroidism with both dementia in general and AD has been demonstrated, although the mechanism is unclear (Kivipelto et al, 2001; Launer at al, 2000).

Oxidative stress is one of the mechanisms thought to be involved in the pathogenesis of AD. The accumulation of free radicals and oxidative stress play a role in the pathology of AD by causing lipid peroxidation and neuronal degeneration in the brain (Sano et ai, 1997, Yavuz et al, 2008). Alzheimer's Disease has been associated with oxidative stress in many studies. Oxidative stress

markers were found to be high in the brain, neurons, NFYs and APs of Alzheimer's patients. In addition, disorders in the mechanisms of protection from oxidative stress have been detected (Zhu et al, 2004; Zhu et al, 2007).

Özçaka et al (Ozcaka et al, 2011) found the serum IL-18 level to be similar in chronic periodontitis and healthy controls, the serum IL-18 level did not change compared to the periodontitis level, the higher serum IL-18 level in Alzheimer's patients was found in Alzheimer's patients, it suggests that it may be related to the pathology of the disease.

In addition to neutrophils in the production of ROS in periodontal disease; It is thought that pocket epithelium and epithelial attachment, which constitute the first line of defense, play a direct role in the formation of oxidative stress in periodontal tissues and O2 produced by epithelial cells is a local ROS source (Chamulitrat et al, 2004). As a result of evaluating the correlation between periodontal disease and systemic ROS level, a significant relationship was found between oxidative stress level in plasma and periodontal attachment loss (Tamakki et al, 2008). In addition, as a result of the examination of antioxidant levels, antioxidant levels were compared with healthy controls and it was seen that both local and systemic antioxidant levels were higher in healthy controls (Brock et al, 2004).

Alzheimer's Disease and Periodontopathogens

Porphyromonas gingivalis, Tannerella forsythia, Prevotella intermedia, Campylobacter rectus, Eikenella corrodens, Fusobacterium nucleatum, Aggregatibacter actinomycetemcomitans, Peptostreptococcus micros ans many species of Treponema and Eubacterium via, which are accepted as periodontopathogens, are known to reach the systemic circulation of tissue and organ circulation (Genco et al, 2002). It is known that P. gingivalis, one of the periodontopathogens, has the ability to disrupt the barrier function of the host and potentially affect the junctional epithelial attachment of the gingival and blood brain barrier (Cerajewska and West, 2019). Therefore, it is possible for periodontopathogenic bacteria to reach the brain via systemic circulation.

Sparks Stein et al. (Sparks Stein et al, 2012) obtained initial serum samples from 158 neurologically healthy individuals with a mean age of 72 years and after approximately 10 years of follow-up, 29.1% (N=46) had mild cognitive impairment and 22.2% (N=35) had Alzheimer's disease developed. When the serum samples taken at the beginning were examined, it was determined that F. nucleatum and P. intermedia antibodies were higher in individuals with Alzheimer's disease compared to healthy individuals. In studies using molecular techniques in Alzheimer's brain tissues, DNA or components of periodontopathogens have been detected. Firstly, Riviere et al. in their study, they examined postmortem brain tissues of 16 patients with Alzheimer's disease and 18 without Alzheimer's disease, and they detected Treponema species in 87.5% (N=14) of Alzheimer's brains and only 22.2% (N=4) of healthy brains (Riviere et al, 2002). Poole et al (Poole et al, 2013) showed the presence of P. gingivalis lipopolysaccharides only in 40% (N=4) of Alzheimer's brains in their study on postmortem brain tissue, 10 with Alzheimer's and 10 without Alzheimer'sIn these two studies, the presence of periodontopathogens in Alzheimer's brain tissues was found to be significantly higher than in healthy brain tissue.

In an animal study in which mice were orally infected with P. gingivalis, neuroinflammation, neurodegeneration, Aβ 1-42 secretion and tau hyperphosphorylation were detected in the infected group in brain samples collected after 22 weeks. In addition, amyloid precursor protein and BACE1 gene expression were found to be significantly higher in the infected group (Ilievski et al, 2018).

Conclusion

The incidence of Alzheimer's disease and periodontal diseases increases with age, and Alzheimer's disease may affect the development of periodontal diseases with the decrease in motor skills, and periodontal diseases may affect the physiopathological process of Alzheimer's disease with the inflammation it causes. In the light of current studies, neuronal tissues can be affected both by periodontal inflammation triggering systemic inflammation, and by periodontopathogens and their products entering the systemic circulation and reaching the brain by passing the impaired blood-brain barrier caused by possible Alzheimer's disease.

Locally or systemically reduced antioxidant capacity and formation of oxidative stress and higher susceptibility to periodontal disease suggest that there may be a pathophysiological link between them for Alzheimer's disease. Studies have shown that neurodegenerative diseases are associated with systemic chronic oxidative stress and are associated with various chronic diseases, including periodontal diseases.

Although the possible mechanism between periodontitis and Alzheimer's, which are accepted to share similar etiological and pathophysiological back ground in the literature, is the subject of many studies, the pathophysiology of the relationship between both diseases; the oxidative mechanism should also be considered and examined in more detail.

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Isolated Avulsion Fracture of the Lesser Trochanter

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Avulsion fractures are most common in adolescents between 11 and 17 years of age and in boys due to trauma, and in adults, it is almost always seen as pathological fracture due to metastasis. The two main causes of fractures of the lesser trochanter are stated as excessive stretching of iliopsoas muscle with strong flexion in the hip and bone metastases (Ruffing et al., 2019). Isolated fractures of the lesser trochanter are extremely rare (Fasting, 1978; Harding et al., 2019; Homma et al., 2014; Uzun, 2016; Vazquez, Kim & Young, 2013; Wilson, Michele & Jacobson, 1939). Since it is a rare case, studies are limited to case reports. Therefore, difficulties arise regarding the diagnosis and treatment of the fracture.

The inability of the patient to lift his thigh in the sitting position is known as the Ludloff sign. Although it is an important finding for lesser trochanter fractures, if the fracture is not complete, it can be found negative (Vazquez, Kim & Young, 2013). Although there is no definite consensus about the treatment, Mc Kinney et al determined a classification in order to determine the treatment option. Accordingly, non-operative treatment is recommended for all acute apophyseal avulsion fractures (types I-III). In type IV cases, surgical intervention may be considered in case of symptomatic association and painful exostosis.

Case Presentation:

A 14-year-old male patient applied to the emergency department with a complaint of pain in his left hip due to a simple fall during walking. An antalgic gait was observed in his examination. There was tenderness in the medial aspect of the left inguinal region. Active and passive hip movements were painful. Raising the thigh in the sitting position was painful (Ludloff sign). A metaphyseal bone avulsion fracture was seen in the lesser trochanter on X-ray (Fig.1). Computed tomography and magnetic resonance imaging were requested to rule out underlying pathologies. A separation greater than 2 cm was observed in the tomography of the patient (Fig.2). On magnetic resonance imaging, there was marked edema around the left iliopsoas muscle. No finding that might raise suspicion for malignancy was found (Fig.2).

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The patient was recommended to rest in a neutral position and to use a thigh corset. Analgesic and NSAID treatment was initiated. He was allowed to use crutches as pain permitted. It was aimed to be able to return to his daily life without restriction at the end of 6 weeks. At the end of the 4th week, he was allowed to walk without crutches. In the control performed at the end of the 6th week, it was observed that full recovery was achieved patient (Fig.2). On magnetic resonance imaging, there was marked edema around the left iliopsoas muscle. No finding that might raise suspicion for malignancy was found (Fig.2). The patient was recommended to rest in a neutral position and to use a thigh corset. Analgesic and NSAID treatment was initiated. He was allowed to use crutches as pain permitted. It was aimed to be able to return to his daily life without restriction at the end of 6 weeks. At the end of the 4th week, he was allowed to walk without crutches. In the control performed at the end of the 6th week, it was observed that full recovery was achieved.

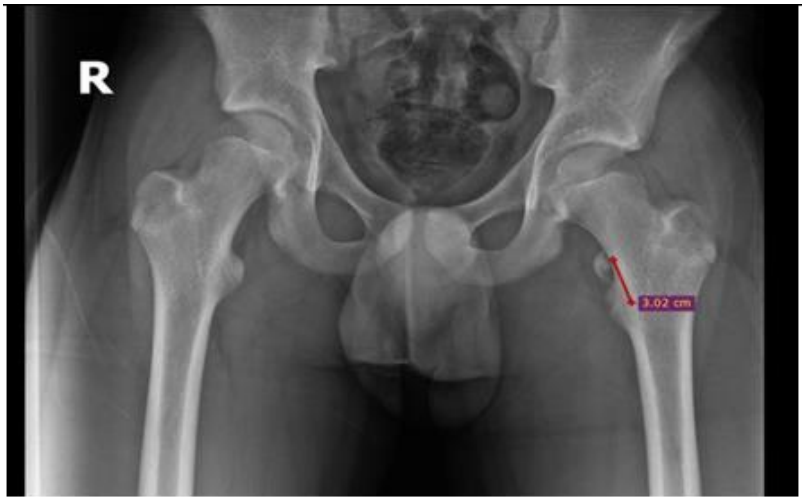

Fig. 1. More than 2 cm separation avulsion fracture of the left lesser trochanter on X-RAY.

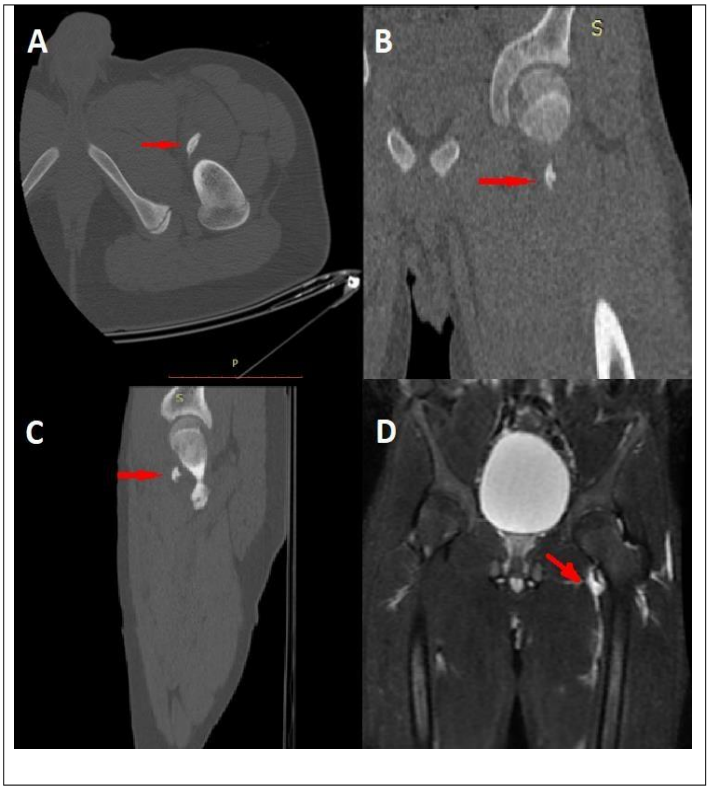

Fig. 2. A: Avulsion fracture in axial CT image B: Avulsion fracture in coronal CT image C: Avulsion fracture in sagittal CT image D: Edema around trochanter minor on MRI.

When the literature is scanned, there is no comprehensive study on isolated fractures of the lesser trochanter (Table I). Hosli and Von Laer identified 3 lesser trochanter fractures in their 20-year study (Hösli & Von Laer, 1995). Theologis et al retrospectively examined patients with 1116 proximal femur fractures and identified isolated fractures of the lesser trochanter in only 3 children (Theologis et al., 1997).

Avulsion fractures have often been reported during running, jumping, playing football and basketball. In addition, isolated avulsion fractures of lesser trochanter that occur in long-distance runners due to long-term stress and during tonic-clonic seizures have also been reported (Kewenter, 1932; McMillan, Rehman & Mitchell, 2016; Michael, 2019; Obi, 2014; Papacostas, Bowe & Strout, 2013; Ruffing et al., 2012). Probably all of them occurred due to the sudden stretching of the iliopsoas muscle or the damage it inflicted on the lesser trochanter due to chronic stress.

In adolescents, muscles are more resistant to injury than bones. While sudden and strong contractions can cause avulsion fractures in adolescents, it can cause muscle sprains in adults. Thus, fractures in adolescents usually present as avulsion fractures due to trauma or prolonged stress, whereas in adults they almost always present as pathological fractures due to malignancy (Ruffing et al., 2018).

Khemka et al. stated that arthroscopic intervention to 3 lesser trochanter fractures with displacement of more than 2 cm and fractures with displacement of more than 2 cm may lead to muscle weakness and ischio-femoral impingement syndrome in the future (Khemka et al., 2014). Ruffing et al. treated isolated fractures of 2 type II, 3 type III Lesser trochanter with non-surgical method and stated that complete recovery was achieved in all patients after an average of 4.9 years of follow-up (Ruffing et al., 2018). Cengiz et al. and Karaduman et al. reported that they successfully treated an isolated lesser trochanter fracture of a 14-year-old male patient with nonsurgical method (Cengiz, Küçükdurmaz & Pulatkan, 2015; Karaduman, Aydın & Kınık, 2017).

As a 15-year-old male patient, our case complies with the literature in terms of age and gender. On physical examination, the Ludloff sign is positive. X-ray radiography was used to diagnose the patient, and computed tomography and magnetic resonance imaging were used to rule out another underlying pathological fracture cause. Non-surgical method was used in the treatment, and was treated with rest and analgesic in the neutral hip position. In the controls performed, no pathology was detected at the end of 6 weeks, and complete recovery was achieved. At the end of 6 weeks, he was allowed to continue her daily life without any restrictions.

Age, gender, history, physical examination and radiological imaging have an important place in isolated fractures of the lesser trochanter. In adults, underlying malignancy should almost always be considered, and this should not be overlooked in adolescents. The fact that itis a rare case and there is no clear physical examination finding can make it difficult to diagnose. In such cases, computed tomography and magnetic resonance imaging will be useful to exclude an underlying malignancy besides X-ray imaging. As in our case, although non-surgical treatment is an effective method in isolated fractures of lesser trochanter, controlled studies are needed in more patient groups.

Table 1. Literature review for trochanter minor avulsion fractures.

Author and Year	**Article Type**	**Way of Being**	**Time to Occur**	**Age and Gender**	**Treatment**	**Result**
Vazquez et al. (2012)	Case report	Football, sprint	Acute	15, M	Non-surgical	Successful
Papacostas et al (2013) [7]	Case report	Basketball	Acute	15, M	Non-surgical	Successful
Khemka et al. (2014)	Case series	Rugby, sprint Football, sprint Football sprint	Chronic Acute Acute	15, M 16, M 15, M	Surgical	Successful
Obi et al. (2014)	Case report	Football	Chronic	15, M	Non-surgical	Successful
Homma et al. (2015)	Case report	Football	Acute	14, M	Non-surgical	Successful
Cengiz et al. (2015)	Case report	Football	Acute	15, M	Non-surgical	Successful
Uzun (2016)	Case report	Football	Acute	13, M	Non-surgical	Successful
McMillian et al. (2016)	Case report	Tonic-clonic seizure	Acute	16, M	Non-surgical	Successful
Karaduman et al. (2017)	Case report	Football, minor trauma	Acute	14, M	Non-surgical	Successful
Ruffing et al. (2018)	Case series	a. Athletics, sprint b. Football, sprint c. Long jump, sprint d. Football, sprint e. Football	Acute	a.12, F b.13, M c.13, M d.14, M e.14, M	Non-surgical	Successful
Ruffing et al. (2019)	Case report	Youth games, sprint	acute	13, F	Non-surgical	Successful
Harding et al. (2019)	Case series	a. Simple fall b. falling from lap c. Falling off the kitchen counter d. Falling from 6 meters	Acute	a., F b.8 months, F c.7 months, F d.23, F	Non-surgical	Successful
Our case	Case report	Simple fall	Acute	14, M	Non-surgical	Successful

F Female, *M* Male

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The Role of Beverages in the Prevention of Dental Caries

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Introduction

Dental caries is the most chronic disease seen in both children and adults; it is about five times more common than asthma and seven times more common than hayfever (Ramos-Gomez, 2010). It is not a self-limiting disease, such as ear infections or colds, which can only be limited by antibiotics. Dental caries; is an infection disease that characterized by destruction of organic and inorganic parts of the enamel, dentin and cement.

For more than 115 years, it is known that the dental caries process is a process mediated by the bacteria. Since then, it has been discovered that caries formation is a multifaceted disease process. It is now known that the host, bacteria and food triplets are required to produce organic acid production and subsequent demineralization activity (Figure 1). According to this model, it is necessary to have all three elements for the initiation and progress of the disease process, it may suffice to eliminate at least one factor in order to prevent the disease process.

Probiotic and prebiotic beverages to prevent dental caries

The word "probiotic" comes from Greek and means "for life". Over the years, the term "probiotic" has been given several definitions. "Probiotic" is used to refer to cultures of live microorganisms that affects the health of the environment positively when taken orally in sufficient quantities. Prebiotics are nutrients that are not digested but fermented in the intestines and improve the health of the host by affecting the proliferation and effectiveness of the bacteria in the vicinity in a positive way. Synbiotics, probiotics and prebiotics coexist (Gupta, 2009). The most important probiotic source for humans is yoghurt and fermented dairy products. Dairy products usually contain Streptococcus, Lactobacillus or Bifidobacterium.

It is essential that commercialized probiotic products which make health claims meet the minimum criterion of one million viable probiotic cells per milliliter of product at the expiration date. Accordingly, the minimum dosage of probiotic cells per day for any beneficial effect on the consumer is considered to be 108–109 probiotic CFU ml-1 or CFU g-1, which corresponds to an intake of 100 g product containing 106–107 CFU ml-1 or CFU g-1 per day (Lourens-Hattingh, 2001). Prebiotics include substances such as inulin, fructo-oligosaccharides, galactooligosaccharides and lactulose.

Some researchers are working on a probiotic treatment method to intervene in the oral colonization of cariogenic pathogens in order to overcome deficiencies in conventional disease

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prevention strategies and to treat the dental caries caused by the infection (Lee, 2014; Saha, 2014; Burton, 2013; Terai, 2015). Although there are a few studies, the results are encouraging in this area. To be useful in preventing or slowing dental caries, probiotic bacteria must be able to adhere to tooth surfaces and be incorporated into biofilm-forming bacterial populations. However, probiotic bacteria must compete with and harmful to cariogenic bacteria, and therefore prevent their replication. Finally, probiotic bacteria should be able to reduce acid production by affecting sugar metabolism. The activation of probiotics used in caries prevention are shown in Figure 2. This can be done by adding probiotics to the daily dairy products.

In a study of 23 bacterial species used in dairy products, it has been reported that Streptococcus thermophilus NCC1561 and Lactobacillus lactis NCC2211 bacteria may adhere to the biofilm on the hydroxyapatite surface and prevent the development of cariogenic strains of S. Sobrinus (Comelli, 2002). In some other studies, L. rhamnosus and L. casei bacteria have been shown in vivo and in vitro to suppress the development of two important pathogens, S. mutans and S. Sobrinus (Chuang, 2011).

Such as Lactobacillus, Bifidobacteria is another probiotic that is frequently used for the development of intestinal microbial balance. In one study, the researchers were evaluated whether short-term consumption of yoghurt containing Bifidobacteria in young adult subjects may have an effect on salivary levels of S. mutans and Lactobacillus. As a result, it was observed that the amount of saliva S.mutans decreased significantly in the intake of bifidobacterium-containing yogurt, but the amount of Lactobacillus did not change (Caglar, 2005) .

Ayran (yoghurt drink)

Yogurt contains probiotics, living beneficial microorganisms with an inhibitory effect on pathogenic bacteria. Yogurt and other fermented milk-based products have been demonstrated to be beneficial for general health, especially because of their probiotic content. They were proposed as an alternative to manage many disorders such as infectious diseases, cancers and gastrointestinal problems in particular (Ghasempour, 2015).

Ayran is the most known traditional Turkish fermented non-alcoholic beverages. (Figure 3). It is a drinkable fermented milk product produced by the addition of water to yoghurt (homemade) or by the addition of Streptococcus thermophilus and L. delbrueckii subsp. bulgaricus to standardized milk for fermentation (industrially produced). The microbiota of homemade ayran is similar to the microbiota of yoghurt which is used for its production. Yoghurt bacteria which are S. thermophilus and L. delbrueckii subsp. bulgaricus are used in the fermentation of milk in industrial production. The numbers of yoghurt bacteria in industrially produced ayran are higher than homemade ayran (Altay, 2013).

Studies have shown that lactobacilli can stick to the enamel, but when they are given with yogurt they do not have the possibility of colonizing in the mouth. Especially, in the subjects who consumed biofeedlons containing L. rhamnosus GG daily, they were able to isolate the saliva L. rhamnosus for 2 weeks after leaving yoghurt consumption. Ayran should be made from the yoghurt formulated to be 108 probiotic bacteria at approximately every g / ml with 1.5-2 dL intake.

Kefir

Kefir is an acidic-alcoholic fermented milk product with little acidic taste and creamy consistency that was first made by the Turks in Central Asia, then spread to Central Europe, Scandinavian countries and other countries (Figure 4).

Kefir is a product obtained by the combination of acid and alcohol fermentation (Prado, 2015). Depending on the length of the fermentation period, a classification was made according to the alcohol content.

After 24 hours fermentation → sweet kefir,

48 hours → medium hard kefir,

Fermentation result up to 3 days → hard kefir

At the end of fermentation longer than 3 days → very hard kefir

Fermentation occurs in the milk which is fermented with kefir grains, and a beverage that resembles aromatic buttermilk is formed. Sheep and goat milk can be used as milk as well as any kind of cow's milk, coconut milk, soya milk and rice milk can also be used. Kefir has the property of being easily digested and the whole of the proteins of kefir can be used by the body.

In the kefir composition, about 1% milk acid and 0.5-2.0% ethyl alcohol. Kefir has a bubbling structure due to the CO_2 it contains and has a pH of about 4.0. The sensory qualities of kefir were formed by lactic acid, oxalic acid, α-ketoglutaric acid and some essential fatty acids, as well as some other aromatic compounds (acetaldehyde and acetone) that are released after fermentation; small amount of CO_2, alcohol and lactic acid bacteria and yeast. Kefir has a sharp acid taste and a yeast flavor stemming from the CO_2 produced by yeast. In fact, yeast flora that gives a typical flavor to the kefir. Containing all the nutrients in milk and the effect of microorganisms in the structure of kefir granules, the increase of nutritive value and the better absorbility by the body reveal the importance of kefir (Wszolek, 2001; Güzel-Seydim, 2000).

The first scientific studies on kefir were made in Russia at the end of the 19th century. The medical doctors then gave kefir as a practical drug for the treatment of cough diarrhea and stomach discomfort. It is an easily digestible nutritious food that will be ideal for children, infants, pregnant women, healing people, elderly people, constipation and other people suffering from digestive problems.

In the kefir, not only bifidobacteria and lactobacilli are present, but also bacterias such as L. caucasus, Leuconostoc, acetobacter and streptococcus, fungi such as Saccharomyces kefir and Torula kefir. The use of more than one probiotic organism synergistically with each other brings the kefir to more precious food than ayran. In addition, microorganisms in kefir can be colonized in the intestinal tract and also kefir is rich in Ca and Mg from the minerals.

Data are lacking about the efficacy of kefir on dental caries risk factors. In one study it was suggested that short-term consumption of kefir might inhibit the growth of high levels of salivary mutans streptococci and lactobacilli (Cogulu, 2010).

Ayran is prebiotic so it increases the proliferation of probiotics. Kefir is probiotic, it is itself a useful microorganism.

Milk

Human milk contains an average of 7%, cow's milk contains 4% lactose. When rinsed with pure lactose solution in this concentration, the enamel pH rapidly drops below 5.5. However, milk is not a pure lactose solution and is a complex solution with casein, Ca, lactate, phosphate, fat and vitamins in its structure (Grenby, 2001). These ions in the milk structure inhibit demineralization

of enamel and accelerate remineralization. The cariostatic effects of whey proteins in milk have been shown, but casein has been reported to cause a significant reduction in caries development relative to whey proteins. Casein is a phosphopeptidase found in milk. In fact, there is no direct effect on caries prevention. However, it has a binding function for Ca and phosphate that passing through to plaque from enamel due to the action of the acid and prevents Ca and phosphate from moving away from the medium. Ca and phosphate, which bind to caseine, form the amorphous Ca-phosphate complex. This formation means converting demineralization into remineralization. Casein in milk also prevents plaque formation, because it selectively modulates the binding of bacteria to plaque, it reduces the formation of caryogenic plaque.

In a variety of clinical trials, regular consumption of probiotic milk, has been shown to decrease in the number of cariogenic bacteria in the saliva and in the plaque (Rodriguez, 2016). However, the sugar added in the milk, is turned the milk into a cryogenic structure.

Teas

Tea is obtained from the leaves of Camellia sinensis plant. Depending on the production process, tea is divided into 3 major groups; non-fermented (green tea), semi-fermented (oolong tea) and fermented (black tea). In addition to the proteins, enzymes, carbohydrates, elements and many vitamins it contains, polyphenols are the most noteworthy ingredient of tea. The basic polyphenols in the tea are the katesins. The katesins are separated in four. The most commonly found catechin epigallocatechin-3-gallate (EGCG) accounts for 59% of all catechins, 20% epigallocatechin, 14% epicatechin-3 gallate (ECG) and 7% epicatechin. These catechins can interact with biological molecules such as proteins, fats and nucleic acids in a variety of ways. It has been reported that the polyphenol content of tea is an inhibitory effect of growth of several pathogenic bacteria such as Helicobacter pylori, methicillin resistant Staphylococcus aureus, Streptococcus mutans, Streptococcus sobrinus, Salmonella typhi, Shigella dysentery, Shigella flexneri and Vibrio cholera (Goenka, 2013).

Green Tea

Tea is one of the most consumed beverages. Especially green tea has been recommended as a healthy drink since 2000 years. For the last 20 years, the interest in green tea has been increasing due to the positive effects on human health. Green tea has biological effects of antifungal, antimicrobial and antioxidant activity that reduce the incidence of cardiovascular disease, obesity and oral cancer.

Dental caries; is a multifactorial infectious disease that is linked to diet, nutrition, localized oral flora and host response. The metabolism of the carbohydrates by bacteria leads to the demineralization of the enamel by decreasing the pH of the enamel with the resulting acid. Despite the microbial diversity of oral flora, S. mutans and S. sobrinus are accepted as the primary etiologic factor of dental caries. It is shown that green tea has inhibitory effect on S. mutans and S. Sobrinus (Goenka, 2013). The researches examined the effects of iran black tea and green tea on S. mutans and showed that iran black tea inhibited S. mutans at concentrations of over 100 mg / ml and iran green tea at concentrations of 150 mg / ml and over. In studies of the effect of green tea's on S. mutans' virulence activity, it was reported that epigallocatein gallate content of green tea showed antimicrobial activity against S. mutans and also suppressed virulence factors related to caries development. The α-amylase found in saliva facilitates the digestion of carbohydrates, while increases the caries potential of the cariogenic bacteria. Polyphenols reduce the digestive activity of α-amylase. Another beneficial effect of polyphenols in green tea is to prevent microorganisms'

sticking to the hard tissues. This prevents dental plaque formation and helps reduce acid production of microorganisms on the tooth surface.

The preventive effect of fluor has been known for many years. For this purpose, the daily use of low-release fluoride preparations has been recommended and various products are presented to the market. Green tea has a high fluoride concentration. Thanks to this feature, its use in anti-caries preparations is on the agenda. In a study of the remineralization activity of gums containing green tea extracts, it was reported that these gums were shown to be protective against dental caries and acid attacks, and their use may be widespread for this purpose.

Sage Tea

Sage has one of the longest histories of use of any culinary or medicinal herb. Greek physician Dioscorides reported that the aqueous decoction of sage stopped

the bleeding of wounds and cleaned ulcers and sores. He also recommended sage juice in warm water for hoarseness and coughs. It was used by herbalists externally to treat sprains, swelling, ulcers, and bleeding (Ayoubi, 2016).

Sage tea used by herbalists for rheumatism, excessive menstrual bleeding, to treat throats and coughs, strengthening the nervous system, improving memory, and sharpening the senses (Ayoubi, 2016). Just like green tea, sage tea prevents antibacterial effect and caries formation. The findings of a study support the view that the hydroalcoholic extract of *sage tea* has growth inhibitory effect on dental caries causing bacteria such as *Streptococcus mutans*, *Lactobacillus rhamnosus*, and *Actinomyces viscosus* (Behesti-Rouy, 2015).

Coffee

Coffee is classified in the Rubiaceae family, Coffea genus, and the species cultivated in Brazil are Coffea arabica and Coffea canephora, known as "arabic coffee" and "robust coffee", respectively. Arabic coffee represents more than 75% of the world-wide trade. Coffee grain is composed by water, mineral substances, glucides, lipids, organic acids, alkaloids, tanic acids, theobromine, cafein and several vitamins (0). Some components in coffee such as caffeine, volatile, and non-volatile organic acids, phenols and aromatic compounds are reported to have antimicrobial activity. Few studies on the antimicrobial activity of coffee-based solutions are found in the literature. It was reported that the effects of coffee on microbial species such as Staphylococcus aureus, Salmonella thiphi, Shigella dysenteriae, Vibrio cholerae, Vibrio parahaemolyticus and Yersinia enterocolitica and attributed this bactericide effect to the tanic acid. In vitro studies showed that extracts of coffee may inhibit glucosyltransferase in several oral streptococci and anti-cariogenic property of coffee is related to anti-adhesive effect of coffee on the adherence of Streptococcus mutans (da Silva Brandão, 2005; Landucci, 2003).

Owing to its α-dicarbonyl compounds content, roasted coffee, showed antibacterial activity against Streptococcus mutans. Green and roasted coffee extracts interfere with Streptococcus mutans adsorption to Hydroxylapatite. Both the roasted coffee dialyzable and non-dialyzable (melanoidin) fractions had anti-adhesive properties. Low molecular mass components, that is, trigonelline, and nicotinic and chlorogenic acids, proved active as anti-adhesives. Coffee also promoted anti-adhesive properties of dental surfaces (Anila Namboodiripad, 2009).

Wine

Wine is s an alcoholic beverage made from fermented grapes, generally Vitis vinifera or its hybrids with Vitis labrusca or Vitis rupestris (Figure 5). Wine is produced by fermenting crushed grapes using various types of yeast which consume the sugars found in the grapes and convert them into alcohol.

Grapes and wines are sources of polyphenolic compounds, including hydroxybenzoic and hydroxycinnamic acids, phenolic alcohols, flavan-3-ol monomers, oligomeric and polymeric procyanidins, flavonols, stilbenes and anthocyanins. Although there are many studies in the literature about the antimicrobial properties of polyphenols against bacteria species, the number of studies which investigate the effect on oral pathogens of polyphenols is limited. In one study it has been found that wine and grape phenolic extracts were able to inhibit the growth of different Streptococcus spp. strains associated with dental caries (Furiga, 2009). In addition wine was found to interfere strongly with Streptococcus mutans adhesion to and detachment from Hydroxylapatite and to strongly inhibit biofilm formation (Daglia, 2007). The main responsible substances for these activities were found to be the PAC fraction. It was also demonstrated that red wine could inhibit ex vivo Streptococcus mutans biofilm formation on the occlusal surface of extracted human teeth.

Pomegranate Juice

Pomegranate (Punica granatum), an important member of the punicaceae family; is a fruit known since the ancient times and has mystical features (Figure 6). It is the symbol of the Productivity, abundance and luck in many religious books. Pomegranate was used healing in various diseases in ancient times. In Ayurveda medicine pomegranate was called as 'pharmacy plant', and used for oral aft, diarrhea, ulcer, parasitosis treatment in the old periods.

Pomegranate juice has been shown to support antioxidant and antiinflammatory effects by inhibiting oxidative destruction of nitric oxide. The researchers have shown that many of the antioxidants in Pomegranate juice can inhibit the formation of the plaque polysaccharide matrix, block the adherence of bacteria, prevent acid formation and reduce acid tolerance of cariogenic microorganisms. Recent studies demonstrate that pomegranates can support oral health and is a successful remedy for strengthening gums and fastening loose teeth (Kote, 2011).

Cranberry juice

Cranberry is a type of evergreen shrub that grows in wet areas, such as bogs or wetlands. The shrub has small, dark green leaves, pink flowers, and dark red fruit that are egg-shaped. It was shown that, the polyphenols in cranberries may influence the formation of dental caries by affecting the colonization of dental surfaces and the production of acids by cariogenic bacteria.

Certain constituents of cranberries may limit dental caries by inhibiting the production of organic acids by cariogenic bacteria, the formation of biofilms by S. mutans and S. sobrinus, and the adhesion and coaggregation of a considerable number of other oral species of Streptococcus (Bonifait, 2010).

It has also been reported that the polyphenols in cranberries led to the desorption of S. sobrinus from an artificial dental biofilm. These observations suggest that cranberry polyphenols can inhibit the colonization of dental surfaces by oral streptococci and thereby slow the development of cariogenic dental plaque.

Conclusion

In recent years, several researchers have tried to identify edible, nontoxic compounds that could interfere with formation of the cariogenic biofilm. As a result of these studies antibacterial and antioxidant-containing beverages prevented the formation of caries. These beverages can be used in place of synthetic and toxic substances which used in caries prevention. The advantages of these products are that they would be perceived as a natural product, and their use does not raise any toxicological problems.

Acknowledgements

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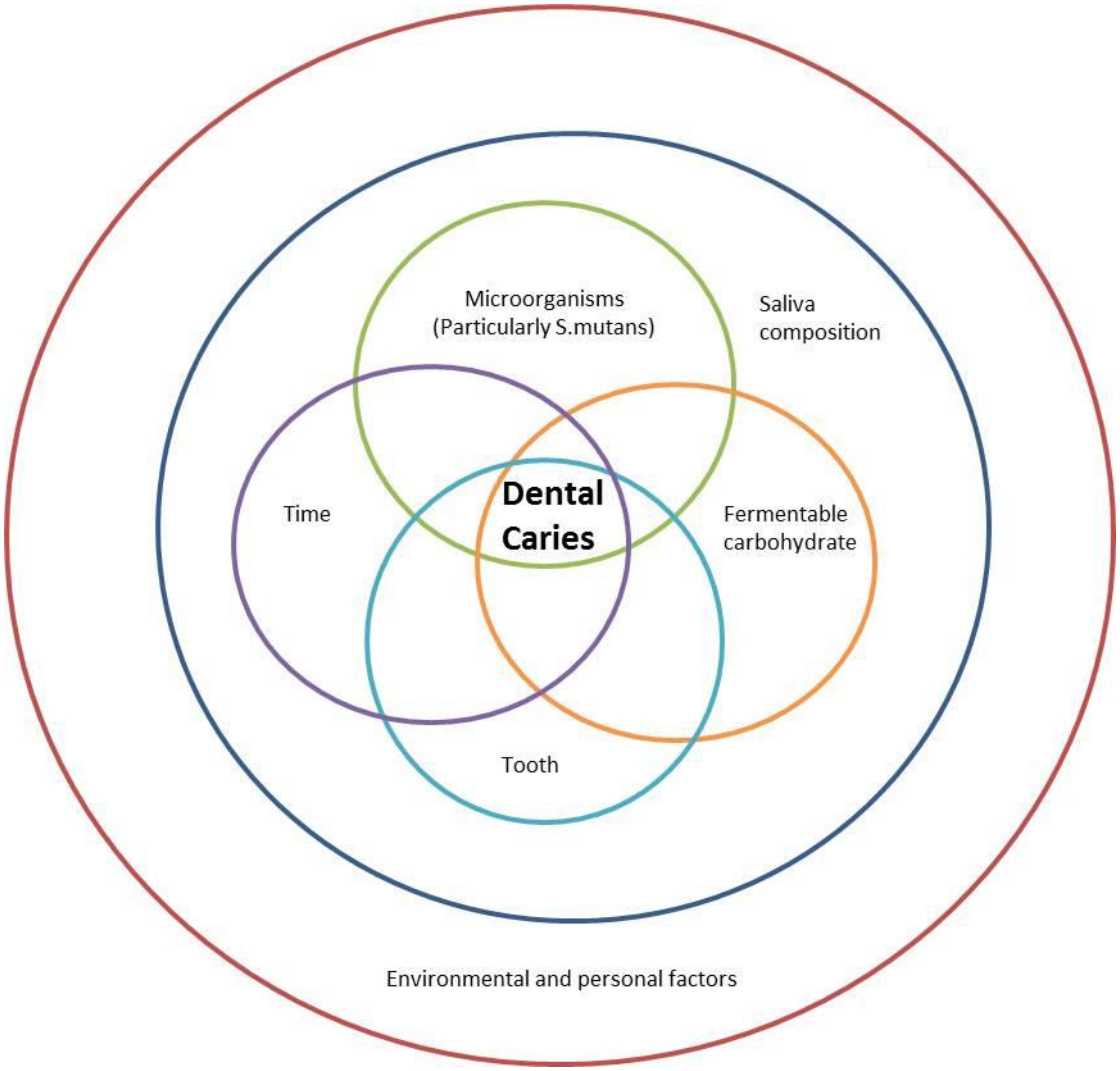

Figure 1. Dental caries mechanism

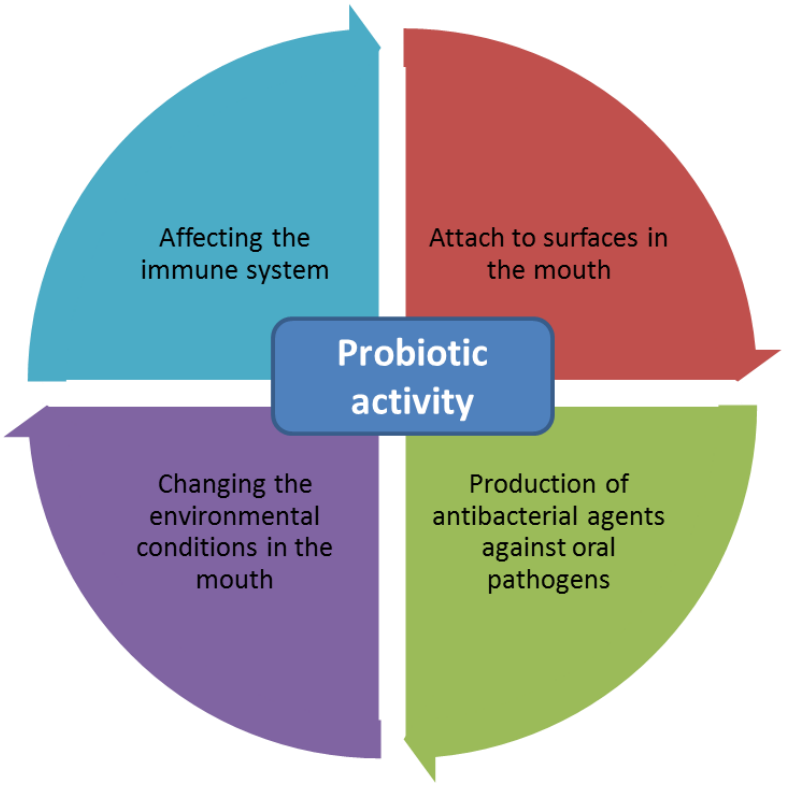

Figure 2. Preferred probiotic activity in caries prevention

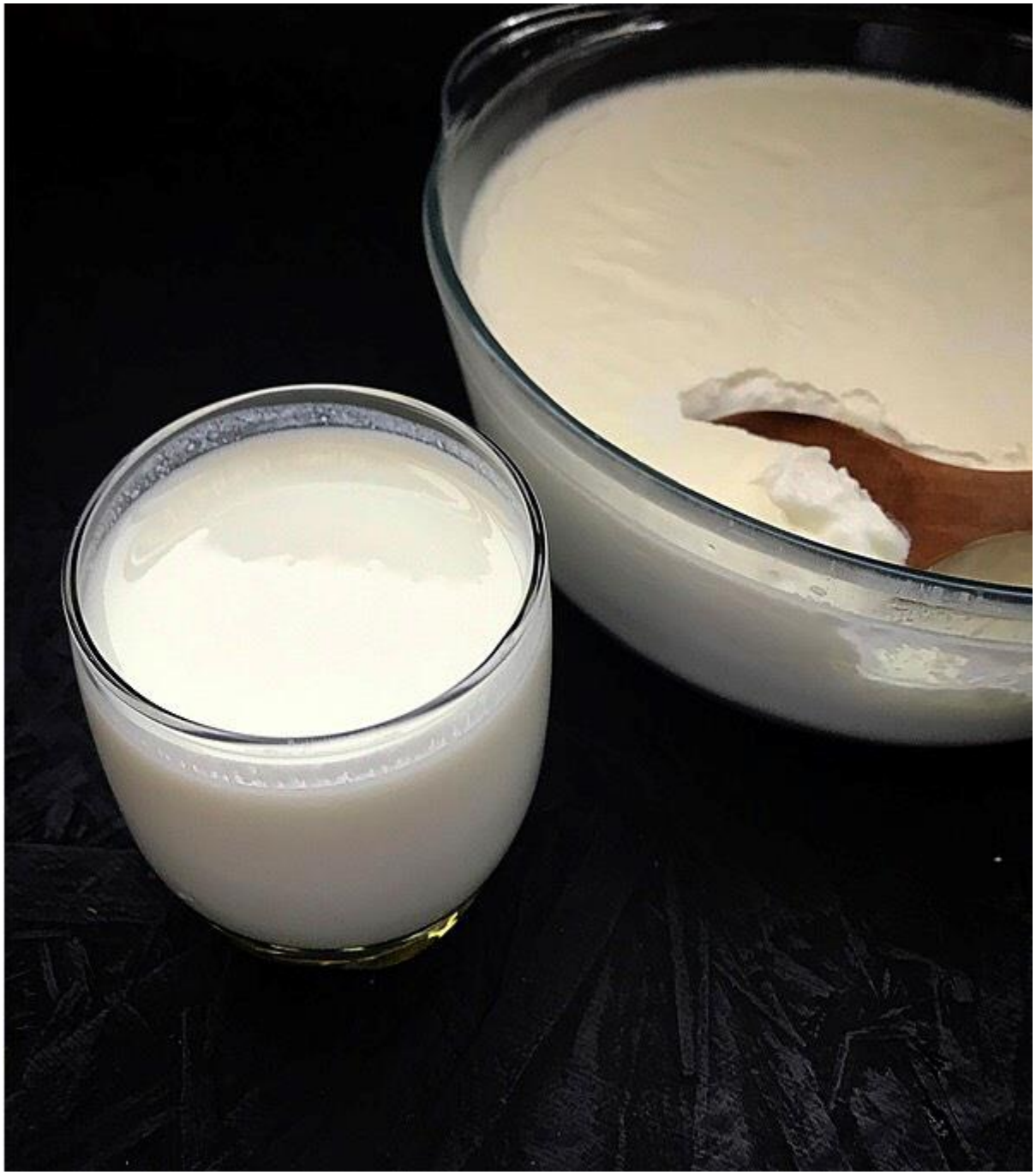

Figure 3. Ayran is obtained by dilution of yoghurt.

Figure 4. Kefir is a probiotic.

Figure 5. The health effects of wine are mainly determined by its active ingredient alcohol.

Figure 6. Pomegranate juice is being studied for its many health benefits.

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Macular Hole Surgery

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Introduction

The first person to reveal the name of the macular hole is considered to be Ogilvie (Ogilvie, 1900). The first reported case of macular hole was traumatic, reported by Knapp in 1869 (Knapp, 1869). While trauma was the most common cause in the beginning, it is reported that these cases constitute 9% of the cases (David et al, 2001).

Gass Classification

Stage 1a: As a result of flattening of the fovea, the foveal depression disappears and a yellow spot appears. The inner retinal layers separate from the photoreceptor layer and form the schisis cavity.

Stage 1b: Yellow ring appearance is observed in the fovea. It attaches to the posterior hyaloid fovea, separates the sensory retinal and retinal pigment epithelium layers in the foveolar region, and intraretinal cystic changes occur.

Stage 2: The diameter of the macular hole is less than 400 μm. The hole center may be slightly off-center or crescent-shaped.

Stage 3: The diameter of the macular hole is greater than 400 μm. The roof of the schisis cavity is separated and the operculum is formed. The parafoveal adhesion of the vitreous is preserved. The base of the macular hole is red. Depending on the subretinal fluid accumulation, a gray ring surrounding the hole and the operculum above the hole can be observed clinically.

Stage 4: Full thickness macular hole and total posterior vitreous detachment (AVD). The Weiss ring is observed (Gass, 1995).

Classic Pars Plana Vitrectomy (PPV)

After sclerotomy entries are made, the first step in PPV surgery is to perform central (core) vitrectomy. For this purpose, the light probe and vitrectomy cutter are advanced from the sclerotomies to the middle vitreous cavity and kept as fixed as possible. The vitreous is expected to come to the tip of the cutting probe by itself. When vitreous flow stops, core vitrectomy is completed and the condition of the posterior vitreous is checked. The appearance of the Weiss ring is an important indicator of posterior hyaloid separation.

Separation of the posterior vitreous cortex from the retinal surface with PPV is one of the most important and careful steps in macular hole surgery. In the presence of adhesions, the traction force during aspiration may be transmitted to the vitreous base and cause tears (Penha et al, 2008)

The condition of the posterior hyaloid has become easily controllable with the widespread use of triamcinolone in chromovitrectomy. Triamcinolone acetate is injected into the vitreous after core vitrectomy and is expected to stain the vitreous fibers to an opaque-white color. An attempt

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is then made to lift the posterior vitreous from the optic nerve nasal, where it has the lowest potential for retinal damage.

After making sure that the cortical vitreous is completely separated from the retinal surface, the active aspiration phase is started. The posterior vitreous is completely excised. In order to detect iatrogenic retinal tears and/or detachment, peripheral retinal imaging with an indirect ophthalmoscope or scleral depression should be performed. During the removal of the posterior hyaloid, the tears around the hole can be easily noticed, but especially during vitrectomies involving the vitreous base, tears that occur in these peripheral retinal quadrants where there is tight adhesion can easily be overlooked. In addition, tears may occur after surgery on the vitreous basis. The main reason for this is that the posterior hyaloid continues to separate.

Staining and Peeling of the Internal Limiting Membrane (ILM)

Staining or visualizing the internal limiting membrane for peeling is beneficial as it will shorten the duration of surgery and reduce surgical trauma. For this reason, it is currently used as a standard procedure by many vitreoretinal surgeons. After the appropriate dye is injected into the vitreous cavity, the ILM is waited for staining, and then the dye is washed away from the vitreous fluid within seconds-minutes.

There are different surgical procedures for ILM peeling. The first of these; it is performed by making a small hole on the ILM with a toothed myringotomy knife, one disc diameter from the macular hole. Alternatively, extra-fine forceps can be used. The aim is to circularly separate the ILM from the underlying retina parallel to the retinal plane. It is peeled circularly with the help of forceps, similar to capsulorhexis in cataract surgery. This technique is also called maculorhexis. When the ILM is extensively peeled, the inner retina temporarily becomes pale in the peeled part. This color difference helped to complete the peeling process by distinguishing the peeling and non-peeling areas, especially during the periods when vital dye was not used.

The second technique for ILM peeling is drawing the ILM with a curved needle and entering between the ILM and the retina, lifting the membrane and peeling it off. When ILM peeling is completed, the diameter of the hole decreases in a significant part of the cases compared to the situation before the surgery.

Fluid-Air Exchange

At the end of the operation, the fluid in the posterior pole is removed by passive aspiration. On the other hand, it is not necessary to aspirate the fluid inside the hole. The fluid inside the hole will be absorbed by the retina pigment epithelium (RPE) shortly after surgery. In addition, the possibility of damaging the RPE during this procedure, which will be performed with a very thin cannula, is extremely high.

Shortly after fluid aspiration, rapid diffusion of fluid from the vitreous base, ciliary body and anterior segment structures to the retinal surface occurs due to the effect of gravity. This technique is thought to be performed to obtain maximum size gas bubbles after closure of sclerotomies and air-gas exchange (Rubin et al, 1995)

Use of Internal Tamponad

Internal tamponades are substances that are self-resorbable, other than silicone oil, which are injected into the vitreous cavity after fluid-air exchange in order to keep the retina attached in the postoperative period.

There are 3 types of tamponade materials used in vitreoretinal surgery. These substances are gas, perfluorocarbon fluids and silicone oil. Gas tamponades are the most commonly used tamponades in macular hole surgery. Intraocular gases are injected through the pars plana, by passive or active aspiration, following fluid-air exchange.

Frequently preferred gas tamponades during surgery are sulfur hexafluoride (SF6), perfluoroethane (C2F6), C3F8 and air. All gas tamponades are colorless and odorless. When injected into the vitreous cavity, non-air expands to a certain extent.

Gases have a higher surface tension than silicone oil and perfluoropropane. This can be explained by the fact that the density of gases is lower than that of water and the buoyancy is high at the top of the gas bubble. This buoyancy force effect is utilized while the retina is adhered to. The high surface tension between the gas and the liquid facilitates the absorption of the subretinal fluid that occurs after surgery by the RPE.

The role of intraocular gas tamponades in macular hole surgery is to prevent the passage of fluid from the vitreous to the macula by providing surface tension between the macula and the vitreous, and to act as a bridge over the joining hole edges.

In the postoperative period, patients are placed in a prone and lying position to ensure the closure of the hole by creating maximum surface tension on the macular hole. The duration of the lying position is recommended to be approximately 1 month in C3F8, 1-2 weeks in SF6 and approximately 1 week in air.

Silicone oil can be used to reduce the dependence of surgical success on position. Silicone oil is infused after liquid gas exchange and taken 6-12 weeks postoperatively. There are many limiting factors in the use of silicone tamponade. Some of these can be counted as requiring a separate surgery for silicone oil removal, increasing the risk of glaucoma and cataracts, and preventing closure of the silicone oil droplets by entering the hole (de Juan et al, 1985)

Inverted internal limiting membrane flap technique

The prognosis of idiopathic macular holes mainly depends on the duration, stage and diameter of the hole. The reverse ILM-flap technique was introduced in 2010 by Michalewska et al. for the treatment of large holes (Michalewska et al, 2010).

In this technique, the peripheral ILM is peeled off and an ILM flap loosely attached to the edge of the hole is created, then inverted into the hole using forceps. The zero-vacuum trimming technique reduces the risk of accidental ILM-flap avulsion. Various variations of the technique have been proposed to reduce the postural requirement, duration of surgery, and risk of retinal trauma. However, recent reports suggest that these variations do not increase success rates.

The technique is believed to work with both a scaffolding effect and the presence of Muller cell fragments on the peeled ILM that act to stimulate a glial cell response that aids in closure. Although occlusion rates increase, visual acuity does not increase due to the presence of a non-neural retinal layer in the hole.

Internal limiting membrane–free flap

A free flap can be used in patients with a permanent macular hole after previous surgery. A free flap of peripheral peeled ILM is placed over or inside the hole. Some surgeons fill the hole with ILM, sometimes using viscoelastic materials as "glue" to hold the ILM in place, while others attempt to lay the ILM across the hole. It can be used to hold the throttle in place during heavy liquids, gas exchange and fluid-air exchange before positioning face down for a few days.

Internal limiting membrane abrasion technique

In the ILM abrasion technique, which is an alternative technique, it is tried to stimulate glial cell activation by loosening the adhesion of the ILM to the underlying retina. In a study by Mahajan et al., with a diamond dust-coated membrane scraper, the ILM in a disc-diameter area gently brushed from the macula towards the periphery with both circumferential and radial movements. A closure rate of 94% was achieved in 100 eyes performed with this technique (Mahajan et al, 2015)

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