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REVIEW

Medical and Cosmetic Applications of Persimmon (*Diospyros kaki* L.) and Their Toxicity Assessment-A review

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Abstract

In this review study, it is aimed to summarize the information cited about medical and cosmetic applications of the date persimmon (*Diospyros kaki* L.f.) and accordingly the toxicity assessment. For this purpose, the information cited about medical and cosmetic applications of the date persimmon (*Diospyros kaki*) and accordingly the toxicity assessment were summarized. Persimmon (*Diospyros kaki*), which is cultivated in tropical/subtropic regions such as China, Korea, Japan and Brazil, especially in the Far Eastern countries with more hot climate conditions, has been named as Trabzon Persimmon because it entered Turkey through the Black Sea region. This fruit type has a very important role on the immune system thanks to vitamins and some active ingredients. Although it is mostly consumed as fresh fruit and dried in our country, there are also formulations developed as medical support products (dematological and cosmetic applications etc.) in different countries worldwide. However, toxicity assessment studies on natural plants/herbal products are also very few. Since there is scientific evidence on the phytotherapeutic effects of *Diospyros kaki*, and the product scale on the market is very narrow, this is highly promising for future healthcare products.

Keywords: *Diospyros kaki*, Persimmon, Medical Applications, Cosmetic Applications, Toxicity

INTRODUCTION

Fruits and vegetables play a very important role in human nutrition and diet. Consumption of these nutrients plays a role in the development of health with the presence of potentially bioactive components, and also the phytochemicals they contain are various bioactive compounds that are widely accepted for their useful roles in human physiology [1]. The number of plants has gained popularity as healthy food ingredients, but researchers' attention is still required in many respects.

Persimmon (*Diospyros kaki* L.f.) is one of these nutritious fruits given with strong antioxidant activity [2,3]. Persimmon is a pulpy/fibrous tropical and deciduous fruit belonging to the Ebenaceae family. The world's regions with hot climates, such as China, Korea, Japan, Brazil, Turkey and Italy are known to grow it widely [4,5]. The Mediterranean region has a manufacturing potential of up to 110,000 tons per year. The worldwide persimmon (*Diospyros kaki*) manufacturing was found as about 5.75 million tons in 2017, and China is the leading country (2.36 million tons) followed by Korea (0.32 million tons) and Japan (0.25 million tons) [6]. Persimmon is not very popular in European countries, but due to its awareness of its potential for consumer health development, the demand needed increases [2,7,8]. There are more than 400 species of persimmon grown globally. *D. kaki, D. virginiana, D. oleifera and D. lotus* are some of the most important species of them [9]. However, it is interesting that Diospyros kaki is the most promising species. Popular types are widely cultivated in Japan in general [10,11].

Today, nutrition and health-related issues are intertwined, and researchers have focused on a diet-based regimen strategy that has emerged to combat various physiological threats, including

cardiovascular disorders, oxidative stress, diabetes mellitus, etc. At this point of view, consumption of fruits and vegetables is of great importance in protecting human health. However, phytochemicals and bioactive molecules have also become popular as promising therapeutic agents for a variety of ailments. According to the some studies in the literature, persimmons and components of them are thought to be effective because of their rich phytochemistry in reducing oxidative damage caused by reactive oxygen species (ROT). Anti-malignant and anti-melanogenic compounds, which are among the functional components of persimmon, show antioxidant potential. There is, however, evidence that pharmacological administration of persimmon and functional compounds such as proanthocyanidin may help against hyperlipidemia and hyperglycemia. However, the astringent effect and diospirobezoar formation create a gap to increase vitality. Persimmons and their ingredients have the potential to be one of the fully effective modules effective in diet-based therapy; however, meticulously integrated research and meta-analysis are still required [12]. Therefore, it is of great importance to investigate and carry out toxicity studies related to the use of persimmon fruit and related products. For this reason, in this review study, it is aimed to summarize the researches related to the toxicity studies with medical/pharmacological and cosmetic applications of the persimmon (*Diospyros kaki*).

General features of the persimmon

Diospyros is a member of the genus Ebenaceae family and consists of 400 species that have spread in tropical and subtropical regions of the world. However, only 4 of these species have commercial importance (*Diospyros kaki, Diospyros lotus, Diospyros virginia, Diospyros oleifera chen*). Among these 4 species, the most cultivated species in the world is *Diospyros kaki* [13].

The word Diospyros is derived from the words Mythological Jupiter (Dios) and dane (Pyros) in the mythological period, meaning the food of the gods due to the beautiful appearance and taste of the fruit[14].

Place in Systematic:

Kingdom: Plantea
Division: Magnoliophyta
Class: Magnoliopsida
Order: Ebenales
Family: Ebenaceae
Genus: *Diospyros*
Species: *Diospyros kaki*

Persimmon, whose homeland is China, was brought from Japan before. It has been started to be called "Japanese Apple" among the people [15].

In Figure 1, ripe and unripe versions of the fruit of Persimmonare given. Commercially recognized varieties and properties of *Diospyros kaki* are given in Table 1.

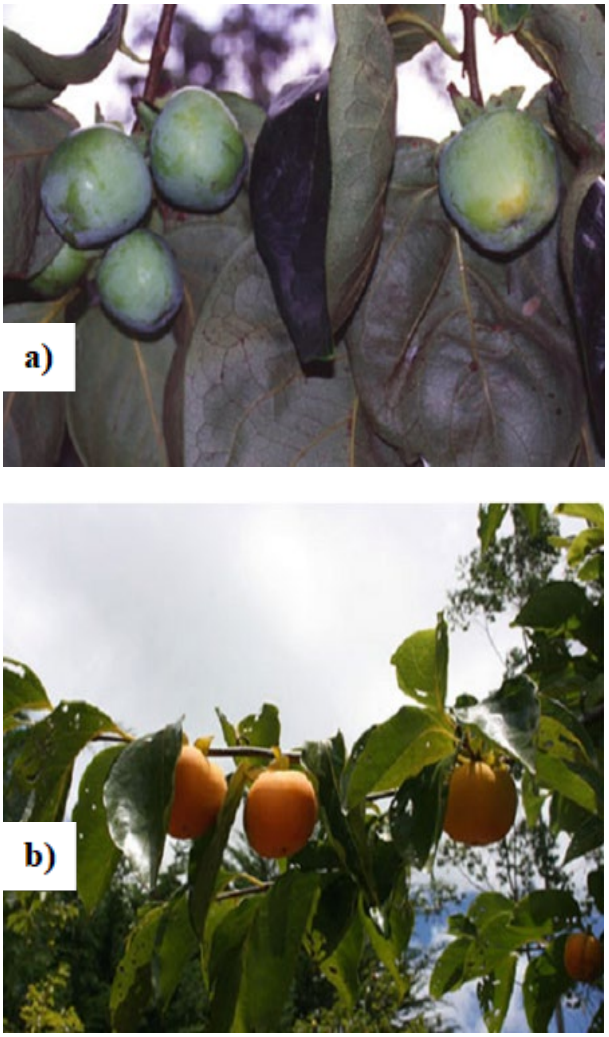

Figure 1. Ripened and unripe versions of the fruit of Persimmon **a)** immature form (stringent form) **b)** ripe form (non-stringent form)

Table 1. Commercially recognized varieties and properties of *Diospyros kaki*

Types	Characteristic
Hiratanenashi	stringent
Ishibashi-ves	bitter pulp and high-soluble tannins
Ton-ves	
Maekawa-jiro (MJ)	non stringent
Matsumoto-wasefuyu (MF)	sweet pulp and low-soluble tannins

Persimmon, which is grown also in economic field in the countries with tropical and subtropic climates such as China, Korea, Japan, and Brazil, is grown economically in the Mediterranean, Aegean, East Black Sea, Southeastern Anatolia and Marmara in our country, Turkey [16]. Persimmon plays very important roles in the immune system in humans thanks to vitamins and some special nutrients. In addition, since it has a rich content in vitamin c, dietary fiber, carotenoids and polyphenols, it has been consumed both fresh and dried since ancient times [7]. In the food industry, it has different uses such as marmalade, cake, puree, various sauces, ice creams, cream and custard making. In addition, fresh or dried leaves are considered as tea in some countries [15]. *Diospyros kaki* species, which enters our country from the Black Sea region, is therefore called the Persimmon, and is also known as paradise fruit, Japanese persimmon and public in some places. Today, due to the changes in consumption habits of the societies and demands for alternative products, the interest in subtropic climate fruits is increasing. Persimmon cultivation, which is mostly cultivated in tropical and subtropic climates, has also started to become widespread in our country (Turkey). Although there is no information about when it was brought to our country, it is known among people as the Trabzon fruit because it first entered our country through Trabzon. Due to the suitability of the climatic conditions in our country, it is a fruit that is cultivated intensively in the Mediterranean region, especially in Hatay, Mersin and Adana, and that the people of the region gain economically. Figures 2, Figure 3 and Figure 4 persimmon production volume in the world, producing country in the world and the number of Persimmon trees in Turkey, area, yield and production quantities are given. When the date of persimmon production in our country is analyzed according to the data in 2017, Adana (9100 tons), 2nd place İzmir (4179 tons), 3rd place Mersin (3403 tons), 4th place Hatay (3172 tons) and 5th place Adıyaman (2991 tons) is located (http://www.tuik.gov.tr/)[17].

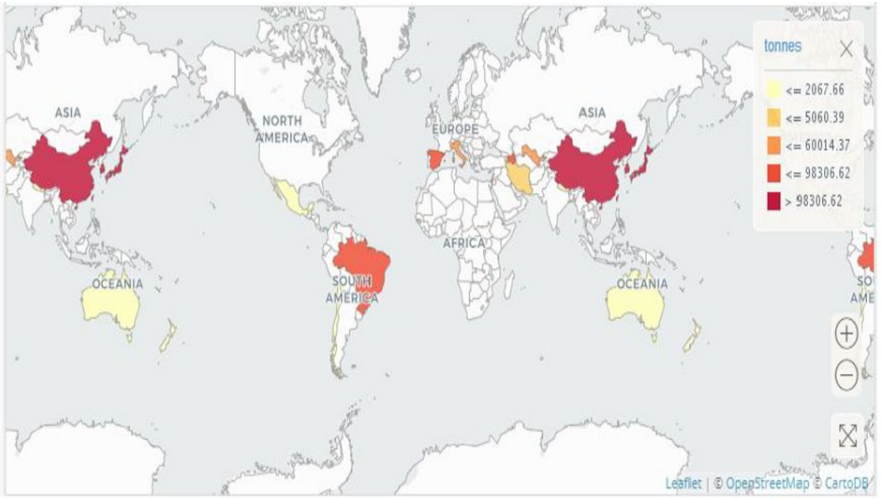

Figure 2. Persimmon production in the world (https://www.mapsofworld.com/world-top-ten/persimmon-producing-countries.html)[18]

The main phytochemicals found in persimmon

Compounds such as proanthocyanidin, flavonoid oligomer, tannins, phenolic acid, carotenoid and catechin are commonly found in persimmon and leaves [2,14,19,20]. Dried fruit is known to consist of 0,16-0,25g/100g polyphenol, 0,002g/100g

carotenoid and 0,64-1,3g/100g proteins. Dried fruit leaves are known to contain 1,15g/100g of phenolic compounds and 63,48g/100g of fiber, and it is thought to have a beneficial effect [19].

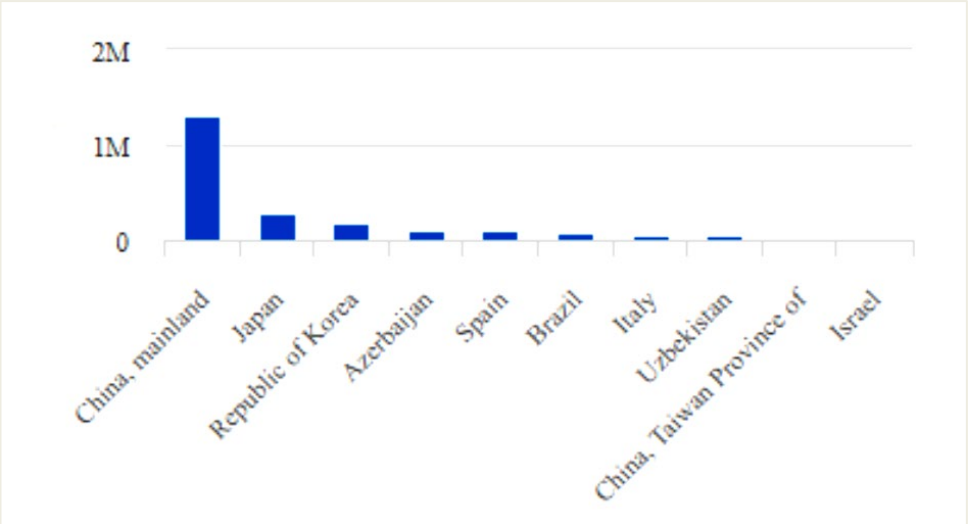

Figure 3. Persimmon manufaturing countries in the world (https://www.researchgate.net/figure/trnL-F-region-and-primers-This-figure-shows-the-coding-and-non-coding-portions-of-the_fig1_8346824)[21]

Years	Number of trees fruiting	Number of trees does not bear fruit	The area of fruit bulk (decares)	Efficiency (kg/trees fruiting)	Production amount (tons)
2010	733.563	194.329	19.741	36	26.277
2011	800.898	197.141	20.900	35	28.295
2012	857.840	188.454	21.317	38	32.392
2013	883.235	172.778	226.42	38	332.32
2014	873.755	184.245	206.19	38	334.70
2015	860.177	197.067	207.89	39	337.25
2016	865.242	275.655	230.24	40	346.50
2017	883.449	303.467	239.32	43	380.43

Figure 4. Number of *Persimmon* tree in Turkey area, yield and production quantity (https://www.mapsofworld.com/world-top-ten/persimmon-producing-countries.html)[18]

Evaluation of the date persimmon in terms of health benefits

It has been found that persimmon leaves have beneficial effects against oxidative stress, hypertension, diabetes mellitus and its complications and atherosclerosis [22,23]. Its bioactive components, especially carotenoids and tannins, are effective in damping free radicals, reducing

cardiovascular risk factors (blood pressure and cholesterol), and reducing the risk of diabetes mellitus, but also against cancer formation [19,24]. The tannins found in persimmon are ultimately responsible for the improvement of physiological threats. It is responsible for antibacterial, anti-allergic, free radical hunt, lowering blood pressure, anticancer and antioxidant activities [20,22,25-27]. The antioxidant activities of the diagnosis depend on the presence of nucleophilic groups with some antimutagenic properties by inhibition of nitrogen reactive compounds [28]. They are also effective in reducing the incidence of stroke and in hypertensive disorders [26]. Similarly, flavonoids inhibit the activity of the angiotensin converting enzyme, which raises blood pressure, and inhibits cyclooxygenase, which forms prostaglandins. Some in vitro studies have illustrated the inhibitory effects of flavonoids in preventing platelet aggregation and thrombosis formation. According to research conducted in the USA, there is an inverse proportion between persimmon consumption and coronary heart disease [19]. Carotenoids and catechins also carry anticancer perspectives against various cancer cell lines [28,29]. Anthocyanidins are similar to other flavonoids for carrying out in vivo and in vitro antioxidative activities and in vivo anti-mutagenic properties. In addition, persimmon fruit has a hypocholesterolemic and antioxidant potential [30-32].

Pharmacological and dermatological applications of persimmon (*Diospyros kaki*)

Persimmon (*Diospyros kaki*) is applied and formulated in the market in dermatological and cosmetic applications, in the form of extraction variations and creams. In Table 2. the dermatological and cosmetic formulations and effects of various active ingredients of *Diospyros kaki* were given.

Jung et al. (2015) [33] applied to melanoma cells B16F10 of mouse stimulated with MSH in the form of acetone-water (70%) extract (10-100 µg/ml) by purifying quercetin-3-O-β-dglucopyranosyl- (1 → 6) -β-dglucopyranoside active substance from *Diospyros kaki* fruit, they encountered results such as hypopigmentation effects, inhibition of melanin synthesis, inhibition of tyrosinase activity and decreased expression of melanogenic proteins. Xue et al. (2011) [34] observed antithrocinase activity (moderate) by in-vitro L-DOPA oxidation, which obtained the active ingredient of chrysontem from the leaves of persimmon as a methanolic extract. Ohguchi et al. (2010) [35] obtained the active substances of isoquercitrin (quercetin-3-oglucoside) and hyperin (quercetin-3-ogalactoside) as acetone extract from the peel of the fruit, and found that the on the mouse it inhibits melanin biosynthesis on b16 melanoma cells (kojic acid and arbutin). Fukai et al. (2009) [36] extracted 2-methoxy-4-vinylphenol from the shell, methanolic and aqueous, and observed antithrosinase activity (higher than arbutin). Thuong et al. (2008) [37] provided rotungenic acid, 24-hydroxyursolic acid, ursolic acid, oleanolic acid and spathodic acid substances from the leaves as methanolic extract and obtained inhibitory effects on protein tyrosine phosphatase 1B (PTP1B). Tiechi et al. (1999) [38] tested the in vitro antithyrosinase activity in ethanolic form of the crude extract of the fruit and observed antithelrosinase activity comparable to the arbutin. An et al. (2005) [39] tested the inhibitory activity against ethanolic extract and their purification from fractions I, II and III xanthine oxidase, collagenase and elastase enzymes, found antithrocinase activity, collagenase inhibition, collagen synthesis in culture-promoted fibroblasts, xanthine oxidase activity and elastase inhibitory effects. Tsang et al. (2016) [40] obtained gallic acid in form of gallic acid dilutions and topical preparation from leaves and fruits, and observed anti-inflammatory, anti-microbial, histamine release inhibition effects by application of eiosinophil-dermal fibroblast. The method used by Kumar et al. (2013) [41] and Tsang et al. (2016) [40] was experienced on Swiss albino rats, zebrafish and UV-B mice tested in skin model, and it was observed suppressing the release of eosinophils-dermal fibroblasts of pro-inflammatory cytokines (IL-6) and chemokines (CCL7 and CXCL8) - oxidants and with modulating of MMP-2/MMP-9 two-stage skin carcinogenesis, depigmentation and skin lightening effect and anti-aging effects were

Table 2. Dermatological and cosmetic formulations and effects of various active ingredients of *Diospyros kaki*

		Effects of dermatologically/cosmetically;
Dermatological and cosmetic formulations of various active ingredients of *Diospyros kaki*:	• Fraction purified from acetone-water (70%) extract • Acetone extract • Methanolic extract and purified fractions • Ethanolic extract • Purified fractions of ethanolic extract • Gallic acid dilutions and topical preparation • Diluted samples • Topical cream • Aqueous methanolic extract [42]	• Hypopigmentation effects • inhibits melanin synthesis • Prevents tyrosinase activity • Decreased expression of melanogenic proteins • Antityrosinase activity (medium) • Inhibitory effects on protein tyrosine phosphatase 1B • Collagenase inhibition • Collagen synthesis promoted in fibroblasts • Xanthine oxidase activity • Elastase inhibitory effects • Anti-inflammatory, • Anti-microbial • Prevents histamine release • 7,12-DMBA/Croton oil from two-stage skin is suppressed by modulatiın of anti-oxidants and MMP- 2/MMP-9 in Swiss albino mice • Depigmentation and skin lightening effect • Anti-aging effects (in-vivo and in-vitro) • Attenuation of oxidative damage from UVA to human skin fibroblasts • Photo protector (UV-B) • Anti-inflammatory • Reduces melanin synthesis • Inhibits tyrosinase activity and suppresses melanogenesis in B16 melanoma cells • Protects skin against UV-ind. oxidative damage • Anti-inflammatory effects • To give the skin “Golden Yellow” color • Protection against UV-skin damage • Suppress release of pro-inflam. cytokine and chemokine from eosinophil-dermal fibroblast[42]

observed induced by 7,12-DMBA/croton oil (in-vivo and in-vitro), modulated by 7,12-DMBA / croton oil. Domingo et al. (2010) [43] and Jeon et al. (2010) [44] extracted the active ingredients of epicatechin and epigallocatechin from fruits and leaves, diluted samples and cultured human skin fibroblasts in topical cream, and healthy human volunteers used split face study design applications, as a result, reducing UVA-induced oxidative damage in human skin fibroblasts, photo protector (UV-B) have achieved anti-inflammatory, melanin synthesis-reducing effects. Li et al. (2014) [45], Kitagawa et al. (2011) [46] and Tsang et al. (2016) [40] obtained chlorogenic acid from fruits and leaves and applied it to B16 melanoma cells with 0-500 µM dilution, as a result, they found tyrosinase activity inhibition and suppression of melanogenesis in B16 melanoma cells. Zaghdoudi et al. (2015, 2016) [47,48] obtained the β-carotene by purifying it from fruit pulp and peel, and determined the effects of giving the skin a "golden yellow" color and protection against UV-skin damage. Anunciato and da Rocha Filho (2012) [49] purified lycopene from the fruit part and determined the effects of reducing the level of skin erythema and regulating cholesterol. Kaulmann et al. (2014) [50] obtained leutin and xeaxanthin fruit, providing protection against UV damage and ROS. Gu et al. (2008) [30] and Zhou et al. (2016) [51] provided tannins and procyanidinoellagitanin,

including flavanoellagitan, as aqueous methanolic extract from fruit pulp, and obtained findings such as lowering ROS levels of exposure to gamma radiation in HEK 293T cells and lowering ROS levels in HEK 293T cells. Kim et al. (2016) [52] purified coussaric and betulinic acid from leaves, applied lipopolysaccharide-induced RAW 264 macrophages and observed anti-inflammatory effects. Xue et al. (2011) [34] obtained reports that chrysontem, isolated from persimmon leaves, shows moderate inhibitory activity for tyrosinase and that chrysontem inhibits carcinogenesis and tumor metastasis caused by the tumor promoter in vivo. Also in the same study, antifungal activity of hyperoside and trifolin; anti-inflammatory activity of isoquercitrin; antiallergic activity of astragalin; and angiotensin converting enzyme inhibitory activity of astragalin, isoquerycrine has also been reported. According to Wang et al. (2011) [53], the vomifoliol 9-O-a-arabinofuranosyl-(1-6)-β-D-glycoranorano side from persimmon leaves may increase peripheral glucose as an insulin sensitizing agent against type 2 diabetes mellitus. According to Chen et al. (2002) [54], ursolic acid (UA), 19-hydroxy ursolic acid and 19, 24-dihydroxy ursolic acid (DHU), stimulated superoxide production and tyrosyl phosphorylation release could help to pharmaceutical applications. Some reports have proved that persimmon leaves increase coronary artery blood flow in the hearts of rabbits and frogs in vitro and coronary blood circulation in anesthetic dogs [55]. Huang et al. (1983) [55] evaluated the effects of alcohol extract from palm leaves on various cardiovascular indices in anesthetic dogs. In addition, it has been reported that persimmon leaves show protective activities against injuries caused by myocardial ischemia. In the experiment of Deng et al. (2004) [56], the acute myocardial ischemia model was stimulated by ligation of the left anterior descending coronary artery in the distal third segment in rat open breast rats. Also, persimmon with its leaves flavonoids can reduce AST, CK and LDH release and MDA production, as well as increased activities of SOD, Naş-ATŞ enzyme and ATP. There are studies showing that Ca2-enzyme PLF has myocardial protective effects against I/R damage in rats [57]. Persimmon leaves showed potential antioxidant activity in in vitro studies. Ethanolic extracts from leaves (600 mg/kg) were effective in delaying lard deterioration, which showed slightly higher antioxidative activity than hesperidin (100 mg/kg) and tea polyphenol (100 mg/kg) [55]. Total flavonoids from persimmon leaves significantly reduced the level of reactive oxygen species and malondialdehyde with increased catalase, SOD and glutathione peroxidase (GSH-Px) activity in E1 cells [31]. This indicates that persimmon extract and palm leaf tea leaves have an oxygen-free radical and antioxidant cleaning effect. To investigate the mechanisms in osteoblast cells injured by oxidative stress, Sun et al. (2014) [58] discussed potential therapeutic or toxic effects on MC3T3-E1 cells stimulated with H_2O_2 and found that flavonoids from persimmon leaves (FPL) reduced H_2O_2-induced apoptosis in MC3T3-E1 cells via the NF-kB pathway. The results suggest that the molecular mechanism of FPL in antiapoptosis is associated with the suppression of the translocation of NF-kB/p65 into the nucleus. The protective effect of FPL can provide a promising approach for the treatment of osteoporosis. Some studies have proven that palm leaves have free radical scavenging activity [26,59]. Han et al. (2002)'s [59] experiment showed that the IC 50 value of the methanol extract of persimmon leaves was 0,11 mg/mL against the DPPH radical. The effect of PLF on DPPH's free radical clearance is not routine as the EC50 is 96,367, 2,63 and 41,567 1,96 µg/mL, respectively [31].

In the study of Ercisli et al. (2008) [60], the highest antioxidant activity was observed in the 08 TH 10 genotype with 91,6%, while the lowest antioxidant activity was found as 14 TH 01 (51,7%), respectively. The antioxidant activities of butylated hydroxyanisole and butylated hydroxytoluene were 93,4% and 91,8%, respectively. A low correlation (R = 0,711) was obtained between total phenolic content and antioxidant activity between genotypes. The results showed that the antioxidant activity in palm fruits is strongly managed by the genotype. Jang et al. (2010) [61] found that palm seed and calyx extracts showed higher antioxidant

activities and phenolic contents than shell and pulp extracts when evaluated with DPPH (1,1-diphenyl-pyridylhydrazyl) radical scavenging activity and reducing power (RP). Ethanol has been found to be more effective on extraction of antioxidant compounds than other solvents (acetone, methanol and water). Antigenotoxic effects of persimmon extracts on DNA damage induced by H_2O_2 in human leukocytes were evaluated by Comet test. All persimmon extracts inhibited DNA damage caused by 200 µM H_2O_2. Calyx and seed extracts showed stronger inhibition activity than shell and meat extracts. The results suggested that persimmon extracts may have protective toxins against beneficial antioxidant and protective effects. Akter et al. (2010) [62] has shown that palm kernel extracts can potentially be used as a cheap source of natural antioxidants in the food and pharmaceutical industries. EC50 values of persimmon seeds were found in the radical hunter assay, while extracts from absolute ethanol and methanol were 49,71 and 51,15 µg/ml, respectively, while the EC50 of butylated hydroxyanisole extract was found as 70,82 mg/ml. The EC50 value of reducing power for absolute acetone extract was higher (210.06 µg/ml) than butylated hydroxyanisole extract (212,67 µg/ml). Absolute methanol extract has the highest antioxidant activity, but it has the lowest total phenolics and flavonoids. In contrast, the antioxidant activities of aqueous solvent extracts showed good correlation with total phenolics and flavonoids compared to absolute solvent extracts.

Kim et al. (2010) [63] reported that treatment of human leukemia HL-60 cells with zero to 100 mg/ml D. kaki leaves (KV-1) for 72 hours caused a small increase in cell differentiation. When HL-60 cells were treated with all-trans retinoic acid (ATRA) and persimmon leaf extract, a synergistic differentiation induction was observed. Protein kinase C (PKC) (a and b I) and extracellular signal regulated kinase (ERK) inhibitors, but phosphoinositide 3-kinase (PI3-K) and c-Jun N-terminal kinase (JNK) inhibitors ATRA or 1.25 HL-60 differentiation induced by the extract with the combination of (OH) 2D3 indicates that PKC and ERK are involved in the development of cell differentiation by the extract. The results showed that acetone extract of *D. kaki* leaves has the ability to increase HL-60 cell differentiation and may be useful in the treatment of acute promyelocytic leukemia.

Diets supplemented with dried and powdered young and ripe fruits of persimmon Fuyu-kaki and Hachiya-kaki varieties significantly reduced plasma lipids, including total cholesterol, triglyceride and LDL cholesterol [64]. The fruit-supported young diets of both varieties evenly regulated the three-fold expression of the cholesterol 7 α-hydroxylase (CYP7A1) gene in the liver. CYP7A1 plays an important role in maintaining cholesterol homeostasis by regulating bile acid synthesis, suggesting that increased conversion of cholesterol to bile acids may cause cholesterol-lowering effects of young fruits. The results showed that young palm fruits are useful in the development of protective and therapeutic agents against dyslipidemia. In a follow-up study, young persimmon fruit treatment was found to significantly reduce plasma chylomicron, very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) cholesterol and triglyceride, with increased fecal bile acid excretion [64].

Matsumoto et al. (2006)[64], diets supplemented with dried and powdered young and mature fruits of persimmon Fuyu-kaki and Hachiya-kaki varieties significantly reduced the increase in plasma lipids, including total cholesterol, triglyceride and LDL cholesterol. The fruit-supported young diets of both varieties evenly regulated the three-fold expression of the cholesterol 7 α-hydroxylase (CYP7A1) gene in the liver. CYP7A1 plays an important role in maintaining cholesterol homeostasis by regulating bile acid synthesis, suggesting that increased conversion of cholesterol to bile acids may cause cholesterol-lowering effects of young fruits. The results showed that young palm fruits are useful in the development of protective and therapeutic agents against dyslipidemia. Matsumoto et al. (2008)[65] found in a follow-up study that young persimmon fruit therapy reduced plasma chylomicron, low-density lipoprotein and low-

density lipoprotein cholesterol and triglyceride with increased fecal bile acid excretion.

According to the study of Fukai et al. (2009) [36], it was found that triterpenoids with 3b-hydroxy group inhibit protein tyrosine phosphatase 1B (PTP1B) activity while IC50 values ranged from 3,1 to 18,8 mM, while those with 3a-hydroxy moiety were inactive. 2-methoxy-4-vinylphenol, which is a component of persimmon bark, has been found to have high antioxidant activity on DPPH (1,1-diphenyl-2-picrilhydrazyl) radical scavenger and SOD (superoxide dismutase) assays. The compound exhibited higher tyrosinase-inhibiting activity than that of arbutinin using both L-tyrosine and L-DOPA as substrates. In addition, the synthesized 2-methoxy-4-vinylphenol glycoside exhibited tyrosinase-inhibiting activity, suggesting its potential as a cosmetic component with a whitening effect. The acetone extract (*Diospyros kaki* 'Fuyu') of the Japanese persimmon bark has been found to inhibit melanin biosynthesis in mouse B16 melanoma cells [35]. Two active compounds were isolated and flavonoid glycosides were defined as isocercitrin (quercetin-3-O-glucoside) and hyperin (quercetin-3-O-galactoside). It has strongly inhibited the production of isoercitrin and hyperin, melanin with IC50 values of 21,7 and 18,2 mM, respectively. Inhibitory effects were mediated by the suppression of tyrosinase expression.

***Diospyros kaki*'s current formulations on the market**

The formulations of *Diospyros kaki* available worldwide are very limited and some of the products are shown in Figure 5. In Figure 5a, there is a patented sedative with content (camellia leaf, persimmon and carob bean) that plays a role in hair growth produced in South Korea and soothes skin irritation. In addition, in Figure 5b, acol-based/non-alcoholic extracts, teas, food supplement products and skin care products produced from plants made in Japan consisting of persimmon (*Diospyros kaki*) and dry sepals as liquid extracts. Persimmon in Turkey found in the form of that more fresh fruits and dried fruits in the market and is known to be consumed.

Figure 5. Some of *Diospyros kaki*'s existing formulations on the market **a)** a patented skin soothing developed in South Korea **b)** supplement food product.

Toxic effects of medicinal plants and herbal products

The interest in herbal products has started to increase especially in recent years for preventive/therapeutic purposes. Incomplete information in the market creates a perception that herbal products are completely harmless, and this situation may have harmful consequences. Plants/herbal products can have unexpected adverse effects due to their different content. In addition, some of them may have toxic effects or interact with medicines taken together. Therefore, it can cause other conditions or increase the size of the condition. Scientific studies regarding the side effects that can be seen in treatment with plants

should be increased and necessary legal arrangements should be completed in this regard. Plants/herbal products on the market as supplementary products could be sold unsupervised. However, it is legally mandatory to have the necessary information on the drugs. In plant treatment/phytotherapy, the systematic identification and naming of the plant inaccurately leads to undesired results. For example, only the diagnosis based on the appearance may cause serious results due to morphological similarity (the very poisonous hemlock leaf is compared to parsley). However, the subspecies of the plant can be of very different structures, so scientific diagnosis on the subspecies basis is important besides the species base [66].

Plants and herbal products used for therapeutic purposes can be found contaminated with pesticides, heavy metals, toxic substances, synthetic drug residues and microorganisms (plants irrigated with well-treated recycled wastewater, etc.) [67]. There are very few herbal products, such as vinblastin, vincristine and paclitaxel, among the cancer drugs that are being used. However, the tobacco plant causing cancer creates a contradiction with the aforementioned situations. Some slimming teas in the market have been found with high amounts of diuretics and laxatives. In addition, some of the ingredients in these teas may have blood pressure-increasing or sodium, potassium, plasma aldosterone and lowering effects, and may even lead to death.

In the formulation of products sold in the market as vitamin supplements, stimulant foreign active ingredients not mentioned on the label were found. It is also known that some athletes who consume herbal products containing ephedrine active ingredient in the sports sector are also disqualified as a result of doping controls [66].

Toxicity studies on persimmon (*Diospyros kaki*)

Xie et al. (2015), according to their research, the toxicity studies conducted in the literature related to the fruit of persimmon are mostly related to leaves, and there have been no cases of toxicity in various uses of the leaves during the last hundred years [55]. Modern toxicity studies on animals have not been toxic in leaves. Studies on the fruit portion are very limited and no toxicity has been found. While this appears to be reliable in widespread use, further studies of toxicity are essential and necessary to fill the literature gap today, especially in different effective extracts (stem, fruit).

According to Wu et al. (2012) [68], in the acute toxicity test, after pretreatment of leaves with water extract, both LD50 in male and female mice were higher than 21,5 g/kg (equal to 597,2 g/kg in raw medicinal material), which suggested that the extract was non-toxic. In the mouse bone marrow micronucleus test (MNT), the ratio of polychromatic erythrocytes/normrochromatic erythrocytes (PCE/NCE) drops to 10 g/kg in the normal range compared to 20 mg/kg cyclophosphamide. It is implied that palm leaf extracts do not have a mutagenic effect on somatic cells. Therefore, 10,0 g/kg palm leaf extracts did not show the effect of sperm malformation. In the study of Chen et al. (2005) [69], subchronic toxicity test was performed on 100 SD rats by oral administration of 0,5, 1,0, 3,0, 6,4 g/kg preparations (ethanol extract of leaves) for 90 days. The blood and physiological indices of the rats were not significantly different from the normal diet control group. Teratogenicity was evaluated using 100 pregnant rats at preparation doses of 1,0, 3,0, 6,4 g kg and compared to negative and positive (control group). No significant changes were observed in weight gain at each dose. The mean live fetus, absorbent fetus, and dead fetus amount were not significantly different in the negative control group. Anomaly of physiological features was also not observed at all doses. Therefore, NOAEL ethanol extract from leaves was 6,4 g/kg, no maternal toxicity, embryo toxicity and teratogenesis were observed at this dose.

Xie et al. (2015) [55], the long-term toxicity of Naoxinqing Tablets (persimmon leaf extract) was investigated in an experimental study on rats. Rats sat intragastric administration Naoxinqing tablet at doses of 35, 70, 140 g/kg once daily for 180 days. There was a slight decrease in food intake of the high dose group (140 g/kg), compared to the control group for serum total bilirubin, medium

dose group (140 g/kg) and high dose group (140 g / kg), no abnormal changes were observed for other indicators. The safe dose for persimmon leaf extract was 35 g/kg.

El-Hawary et al. (2019) [70] and the results of the study and results for the leaf and fruit part of the fruit are detailed below; fifteen male Wistar rats (200-220 g) were used. Conventional laboratory conditions: temperature with free access to water and food (20-25 °C). Kits for plasma albumin, total protein, alkaline phosphatase, GOT and GPT, creatinine, urea, total cholesterol, HDL cholesterol, LDL-cholesterol, total lipids, triglycerides, malondialdehyde and catalase were obtained from Biodiagnostic Company, BIODIAGNOSTIC. Blood glucose was recorded by Accu-Chek Go and strips purchased from Roche. Drabkin reagent was taken from Vitro Scientific for hemoglobin testing. Rats were randomly divided into three experimental groups. All groups were fed a balanced diet, 15% casein (80% protein), 5% cellulose, 8% corn oil, 10% sugar, enough vitamins and mineral mixtures for a week. Then, the control group: only a balanced diet was applied to the rats. Fruit group: rats received a balanced diet, but were fortified with fruit powder (10%). Fresh fruits were collected, dried in an oven, then ground into powder (as specified in plant material), then added to a balanced diet at 10:90. Leaves group: rats received a balanced diet, but supplemented with leaf powder (10%) Fresh leaves were collected, dried in an oven, then ground into powder (as specified in plant material) and then added to a balanced diet (10:90). All diets were completed to 100 g using starch. Diets were prepared and stored frozen for the duration of the experiment (4 weeks). At the end of the experiment, the mice were fasted overnight, total food intake, final rats body weight gain recorded. Food efficiency rate was calculated according to the equation: food efficiency rate=body weight gain/food intake. Blood samples were drawn from the retro-orbital venous plexus in heparinized tubes under light ether anesthesia and serum was separated by centrifugation at 3000 rpm for 15 min. Plasma was liquefied and stored at -20°C until used for biological analysis. Blood glucose levels (mg/dl) were measured in a glucometer using the Accu-check Go strip (Roche) test using the albumin function (g/dl). Total proteins (g/dl) were measured and Globulin (g/dl) was calculated by the difference between the total protein level and the albumin level. Liver functions such as alkaline phosphatase (ALP), GOT and GPT activities were determined by Reitman and Frankel (1957) method [71]. For kidney function; creatinine and urea levels were measured. Serum lipid profile containing total cholesterol, total lipids, triglycerides, HDL and LDL-cholesterol was determined. Antioxidant enzymes; Catalase activity and malondialdehyde (MDA) were measured. The results showed that there was no significant difference in overall food intake or food efficiency rates across all experimental groups. In addition, at the end of the experiment period, the group fed the fruit diet showed a significant decrease in blood sugar level and also a significant increase in blood hemoglobin level. The results obtained for liver and kidney functions did not show a significant difference in all parameters evaluated, in all values determined by the control group fed with a balanced diet. The healthy effect of *Diospyros kaki L.* fruits and leaves on the plasma lipid profile showed a significant reduction ($p<0,05$) in plasma total cholesterol and triglyceride values, but not a significant reduction in total lipids. Therefore, there was an insignificant increase in HDL/LDL ratio. For antioxidant enzymes; catalase and MDA did not show a significant reduction in activities when comparing the results of the fruit and leaf groups with the control group.

CONCLUSIONS

In this study, the pharmacological/cosmetic applications and toxicity assesment of the persimmon (*Diospyros kaki*) fruit and leaves were evaluated with the existing phytochemical content. Various active ingredients obtained with crude extracts, purified fractions have been found to have great potential for dermatological and cosmetic applications. In addition, it has been proved that the leaves of the persimmon are rich in bioactive substances with rich nutritional values as well as of

the fruit. Some significant evidence-based scientific studies for microbial inhibition have been conducted in Asian countries such as China, Korea and Japan, and most importantly, despite many years of research, no side effects or toxicity reports have been found on these plants. As a result of the study, persimmon fruits and leaves are traditionally consumed as a support product, but health-related products are not common in the market worldwide. Since there is scientific evidence on the phytotherapeutic effects of *Diospyros kaki*, and the product scale on the market is very narrow, this research area is highly promising for future healthcare products.

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