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Review

An overview of dermatological and cosmeceutical benefits of *Diospyros kaki* and its phytoconstituents

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ABSTRACT

Diospyros kaki L.f. belonging to family Ebenaceae, commonly known as persimmon is used as a medicinal plant in Chinese traditional medicine since many years for different ailments including cosmetics and dermatologic applications. Traditionally this plant is used to treat different skin conditions including pimples, skin eruptions and eczema. Present interest has been focused toward use of natural bioactive compounds in various curative and beautifying applications in dermatological and cosmeceutical disciplines. The objective of this article is to present cumulative data on potential use of *D. kaki* for its possible role in dermatologic and cosmetic applications. Scientific data has revealed an excellent position of *D. kaki* in both dermatology and cosmetic discipline making it a valuable choice in respective field. Active principles from different plant parts have shown to possess anti-inflammatory, antiallergic, photo-protective, and anti-wrinkle effects with appreciable activities against tyrosinase, elastase, and collagenase enzymes. Promising antioxidant activity and skin whitening potential, augmented by reduction in sebum contents, and reduction in size and number of skin pores make it a suitable choice as cosmetic ingredient. Data has been summarized and presented on available molecular mechanism that can contribute toward phytoconstituents usage in cosmetics and dermatology mediated by different cellular pathways. Crude extracts and some of phytochemical obtained from this plant such as isoquercitrin and hyperin have better reported activities than well-known cosmetic ingredients viz., arbutin, kojic acid and hydroquinone with possibility of having no side effects. Photo protection against degenerative effects of UVA, UVB and gamma radiation can help skin to fight well against oxidative stress and reactive oxygen species. Further investigation need to be directed toward human subjects for evaluation of these reported activities for obtaining optimum commercial and industrial benefits from this valuable plant.

Introduction

Different factors contribute toward changing skin and beauty-care product industry including a strict regulatory control, cost and enhanced customer expectation with minimal side effects of active constituents in cosmetics. During the first decade of 21st century total expenditure on beauty and personnel care products increased from 166.1 billion USD to 382.3 billion (Łopaciuk and Łoboda, 2013) with a 25.9% sale share of Asia at the end of 2007. Ingested or applied bioactive molecules interact with different targets in our body modulating different biological functions. As the skin ages, these metabolic processes also change resulting in cellular damage and poor maintenance of skin. Cellular damage and aging is linked with a change in certain metabolic enzymes, amino acids, lipids, antioxidants and nutrients levels. The natural bioactive molecules present in botanical extract are shown to have positive regulating effects on aging process and other skin and dermatological conditions (Mukherjee et al., 2011; Ye et al., 2014; Shin et al., 2015). Currently the research in field of skincare and other dermatological conditions have been shifted considerably toward use of natural products and their bioactive constituent after establishing scientific validation, assuring safety and efficacy.

Diospyros kaki L.f. commonly called as persimmon or Japanese persimmon, is a deciduous plant native to China, Korea and Japan, however now it is being grown in many East Asian countries and southern Europe. *D. kaki* belongs to family Ebenaceae and is considered as one of most important species from genus *Diospyros* because of yielding exotic fruits (Zhu et al., 2016). This plant can

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Table 1
Production statistics of *Diospyros kaki* in 2014 and various varieties produced by top 10 producer countries.

Country	Production in 2014 (million tons)	Persimmon cultivars produced
China	3.804	Hachiya, Tamopan, Tanenashe, Ormond, Fuyu, Imoto
Korea	0.428	Hongosi, Hachiya, Dan Gam (Fuyu)
Spain	0.245	Homan red
Japan	0.241	Hachiya, Tamopan, Tanenashe, Taubata, Fuyu, Imoto, Jiro, Suruga
Brazil	0.182	Sibugaki, Hachiya, Trakoukaki, Hatemya
Azerbaijan	0.140	Gosho, Ghibrid-27235, Kiakume
Uzbekistan	0.066	Hachiya,
Italy	0.039	Kaki Tipo, Vaniglia, Cioccolatino, Zellonafuyu
Israel	0.037	Triumph
New Zealand	0.003	Fuyu, Jiro
Others	0.006	–
World Total	5.191	–

be categorized into two distinct varieties including astringent (*e.g.* "Hachiya, Tamopan, Tanenashi, Triumph, Homan Red, Ormond, and Taubata") and non-astringent (*e.g.* "Fuyu, Imoto, Izu, Jiro, Okugosho, Suruga and others") based on chemical nature of tannins present in respective variety (Martinez-Las Heras et al., 2017). International commercial producers of *D. kaki* and various product varieties produced are presented in Table 1. According to Food and Agriculture Organization Statistics (FAO-STAT) department of United Nations, 5.191 million tons of *D. kaki* was produced globally in 2014 with 73.27% share of China alone in 2014 (FAOSTAT, 2014). This plant is not endemic to Brazil, however it is being cultivated with good propagation rate having a total growth of 0.182 million tons in 2014 (see Table 1). In Brazil *D. kaki* is cultivated in southeast, northeast and central-west regions (Janeiro, 2017).

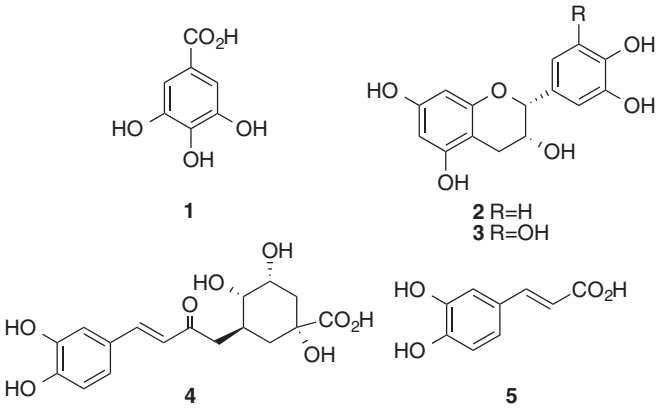
Persimmon is enriched with many nutritious and bioactive components including proteins, sugar, lipids, vitamin A, vitamin B6, vitamin B12, vitamin D, ascorbic acid (AA), vitamin E, polyphenols, flavonoids and carotenoids (Kim and Kim, 2003). Elemental micronutrients present in persimmon fruit include potassium, sodium, iron, calcium and many others. The fruit have been used as a key ingredients in some marketed cosmetic products including soaps, deodorizing and purifying body lotion, body wash, skin toner and body serum (Mirai Clinical, 2017). Different reviews have been published about reported pharmacological activities and phytoconstituents profile of various parts of this plant, with very limited or no emphasis on its potential use in dermatology and cosmetics (Piretti, 1991; Giordani et al., 2011; Xie et al., 2015). This review describes available data about potential utilization of different parts of *D. kaki* and its bioactive phytoconstituents in different dermatological and cosmeceutical applications.

Phytochemicals of dermatological and cosmetics interest obtained from *Diospyros kaki*

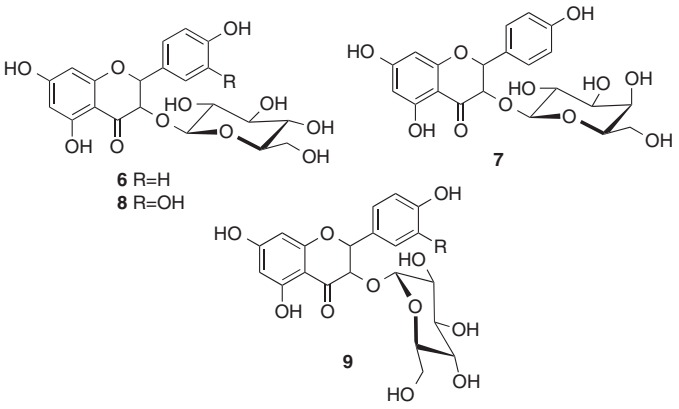
Phenolic acids

Phenolics (or phenolic acids) are widely distributed aromatic secondary metabolites in plant kingdom. They contain an aromatic hydrocarbon and one or more than one functional hydroxyl (or carboxylic acid) group attached to it. They can be categorized into simple phenols bearing one phenol unit or polyphenols having multiple phenol units in chemical structure. They perform a range of different functions in plants and human being including structural maintenance and protection against oxidative stress disorders such as coronary heart disease, stroke and cancer (Robbins, 2003). Phenolic acids are present in fruits, vegetables, seeds, grains, leaves, roots and stem (Robbins, 2003).

In a recent report 32 low molecular weight phenolics have been detected from the pulp of persimmon and most important ones include gallic acid (**1**) (its glycoside and acyl derivatives), glycosides of *p*-coumaric, vanillic and cinnamic acids and different flavone di-*C*-hexosides. Catechin (5.81 ± 0.12 mg/100 g of dry sample: DW), epicatechin (**2**) (0.61 ± 0.023 mg/100 g DW), epigallocatechin (**3**) (0.28 ± 0.02 mg/100 g DW) chlorogenic acid (**4**) (3.67 ± 0.07 mg/100 g DW), caffeic acid (**5**) (2.83 ± 0.07 mg/100 g DW), and gallic acid (19.11 ± 0.61 mg/100 g DW) were separated from ethanol extract of Mopan persimmon and their antioxidant activity was found to be higher than that of white apple, grapes, and tomato (Chen et al., 2008). Among these six phenolics (contributing not more than 20% of total phenolic), gallic acid showed highest antioxidant activity.



The other polyphenolics investigated from persimmon fruits include ferulic acid, tannic acid, protocatechuic acid, vanillic acid, epicatechin gallate and catechin gallate (Lee et al., 2012). These and other polyphenolic compounds have a potential role in prevention of oxidative stress damage by scavenging reactive oxygen species (ROS) (Fu et al., 2015; Zhou et al., 2016), prevention of lipid peroxidase (Toschi et al., 2000) and may be helpful in prevention of different skin pathological conditions. In another study different polyphenol have been separated from methanolic extract of leaves of persimmon and their tyrosinase inhibitory effects were elucidated. The separated compound includes hyperoside, isoquercitrin (**6**), trifolin (**7**), astragalin (**8**), chrysontemin (**9**), quercetin-3-*O*-(2″-galloyl-β-D-glucopyranoside), and kaempferol-3-*O*-(2″-*O*-galloyl-β-D-glucopyranoside) (Xue et al., 2011). Among these polyphenols, chrysontemin has shown moderate activity against tyrosinase enzyme while other compounds have already been reported to possess different activities. For example hyperoside and trifolin have antifungal activity (Li et al., 2005), isoquercitrin has anti-inflammatory activity (Rogerio et al., 2007) and astragalin shows antiallergic effects (Kotani et al., 2000). These and many other reported effects from different active constituents and crude extracts from fruit and leaves of persimmon makes it a valuable choice for different dermatological and cosmetic applications. Box 1 summarizes some important phytoconstituents and their respecti dermatological and cosmetics functions.



Flavonoids

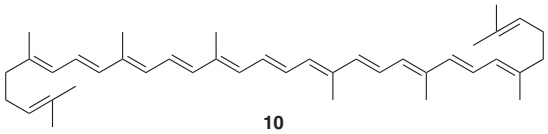
Flavonoids, also called bioflavonoids are naturally occurring secondary metabolites of botanical origin having a general structure of 15-carbon skeleton comprised of two phenyl rings and one heterocyclic ring. More than 8000 phytoconstituents have been identified with this characteristic flavonoid structure. Basic benzo-γ-pyrone ring is subjected to different combinations of hydroxyl, methoxyl, and *O*-glycosyl group substituents resulting in numerous individual flavonoids (Benavente-Garcia and Castillo, 2008).

Flavonoids are further classified into twelve different subgroups, however six of them have gained a significant dietary importance, including anthocyanidins, flavan-3-ols, flavonols, flavones, flavanones, and isoflavones (Manach et al., 2004). In *D. kaki* following examples are found in different parts of the tree including (I) anthocyanidins *e.g.* cyanidin, (II) flavan-3-ols *e.g.* (+)-catechin, (−)-epicatechin and (−)-epigallocatechin, (III) flavonols *e.g.* kaempferol (H), quercetin and their glycosides. Persimmon fruit contains high molecular weight condensed proanthocyanidins in vacuoles of tannin cells. The astringency of the fruit is mainly attributed to their presence specially during unripe stages. Catechin, gallactocatechin, gallic acid, epigallactocatechin and epigallactocatechin-3-*O*-gallate are the major subunits of condensed proanthocyanidins in the fruits (Akagi et al., 2011).

Persimmon leaves contain many beneficial flavonoids including quercetin and its glycoside complexes (*i.e.* hyperin and isoquercitrin), kaempferol and its glycoside (astragalin) along with catechin (Ohguchi et al., 2010; Sun et al., 2011, 2014). Total flavonoids present in persimmon leaves per 100 g of sample is equal to 19.2 μg catechin equivalent. The flavonoids present in the extracts were shown to have potent antioxidant activity, being capable to scavenge superoxide anions, hydroxyl radicals with good reducing power and iron chelating activity superior than that of rutin (Sun et al., 2011). Naoxinging, a patent and authorized traditional Chinese medicine used in management of stroke and apoplexy syndrome contains flavonoids extract from leaves of persimmon (Bei et al., 2009). In another study five flavonoids were separated and identified from the leaves of *D. kaki* with following names kaempferol 3-*O*-β-D-galactopyranoside, kaempferol 3-*O*-β-D-glucopyranoside, isorhamnetin 3-*O*-β-D-glucopyranoside, quercetin 3-*O*-β-D-galactopyranoside, quercetin 3-*O*-β-D-glucopyranosyl-(6→1)-a-L-rhamnopyranoside (Chen et al., 2002b). The potential use of these listed flavonoids in dermatology and as a possible cosmetic ingredient has been described briefly in Box 1.

Carotenoids

Carotenoids are colored, fat soluble pigments generated as secondary metabolites in fruits, vegetables, algae, fungi, and some microbes. Most important carotenoids include beta-carotene, lycopene (**10**), lutein, and zeaxanthin (Anunciato and da Rocha Filho, 2012). Carotenoids can be categorized into two groups *i.e.*, "xanthophylls" which are oxygenated carotenoids and "carotenes" being non-oxygenated. Approximately 700 carotenoids have been identified with around 100 being considered for their dietary benefits (Kaulmann et al., 2014). They have wider applications in food, cosmetics and nutrition because of their color producing tendency and free radical scavenging activity (Kaulmann et al., 2014; Chang et al., 2015). Peroxyl radicals, singlet molecular oxygen and superoxide anions are the major ROS formed in human skin exposed to UV irradiation, which may result in degradation of lipids, proteins and nucleic acids. Such degradation outcomes in various skin pathological conditions such as erythema, pre-mature skin aging and even dermatological carcinomas. β-Carotene also known as "provitamin A" which resides in the skin imparting a golden yellow color, have no doubt a selective cosmetic value. Lutein and zeaxanthin provide protection to retina against oxidative damage to UV light. Lycopene can reduce erythema induced by UV light.



Persimmon fruit contains different types of carotenoids including both xanthophylls and carotenes. Lutein, zeaxanthin, β-cryptoxanthin and β-carotene have been separated and optimized using response surface methodology recently (Zaghdoudi et al., 2015, 2016). So the persimmon can be used as a source of important polyphenolic constituents and carotenoids as a suitable candidate for inclusion into cosmeceuticals.

Hydrolysable tannins

Another group of bioactive phytoconstituents present in persimmon are tannins (MW = 1.12×10^4 Da). Tannins are comprised of either gallic acid subunits (e.g. hydrolysable tannins), flavone subunit (non-hydrolysable or condensed tannins) or phloroglucinol subunits (phloro-tannins). Tannins from different sources have been studied for their antiviral (Ueda et al., 2013), antibacterial (Akiyama et al., 2001), antioxidant (Gu et al., 2008; Tourino et al., 2008), pediatric dermatoses (Fölster-Holst and Latussek, 2007), anti-inflammatory (Mota et al., 1985; Liu et al., 2015) and radioprotective effects (Zhou et al., 2016). Tannins have been used medically for many years and their importance in dermatological application have gained significant importance because of their astringent effects, management of superficial skin condition, weeping, inflammation and itching with acceptable tolerability.

Astringent feeling upon eating persimmon fruit is due to soluble tannins which are released from tannin vacuoles making complex with protein in oral cavity. When these tannins are transformed into insoluble form, the fruit loses its astringent nature considerably. In persimmon major tannin present include flavanoellagitannin (molecule of flavan-3-ol attached with hydrolysable tannin through C-C linkage), procyanidinoellagitannin (proanthocyanidins and ellagitannins) and their degraded products such as gallo-catechin, catechin, catechin-gallate and gallocatechin-gallate (Özen et al., 2004; Gu et al., 2008). In a recent study, tannins from persimmon have been extracted by ultrasound-assisted extraction (39.56% as catechin equivalents) and shown to possess radio protective effects against gamma radiations induced ROS (Zhou et al., 2016).

Box 1: Dermatological and cosmetics application of various active principles of *Diospyros kaki* and its extracts

Active principle/or crude drug	Plant part used	Pharmaceutical form	Test subject/experimental condition	Pharmacological action of dermatologic and/or cosmetics	Reference
• Quercetin-3-*O*-β-d-glucopyranosyl-(1→6)-β-d-glucopyranosid	Calyx	Purified fraction from acetone-water (70%) extract	(10–100 μg/ml) α-MSH-stimulated B16F10 mouse melanoma cells	• Hypopigmentation effects • Inhibit melanin synthesis • Inhibit tyrosinase activity • Reduced expression of melanogenic proteins	(Jung et al., 2015)
• Chrysontemin	Leaves	Methanolic extract	*In-vitro* L-DOPA oxidation	• Antityrosinase activity (moderate)	(Xue et al., 2011)
• Isoquercitrin (quercetin-3-*O*-glucoside) • Hyperin (quercetin-3-*O*-galactoside)	Peel	Acetone extract	B16 Melanoma cells	• Inhibits melanin biosynthesis in mouse B16 melanoma cells (higher than kojic acid and arbutin)	(Ohguchi et al., 2010)
• 2-Methoxy-4-vinylphenol	Peel	Methanolic extract and its purified fractions	Aqueous, methanolic and acetone purified fractions	• Antityrosinase activity (higher than arbutin)	(Fukai et al., 2009)
• Rotungenic acid • 24-Hydroxyursolic acid • Ursolic acid • Oleanolic acid • Spathodic acid	Leaves	Methanolic extract	Protein tyrosine phosphatase 1B (PTP1B)	• Inhibitory effects on protein tyrosine phosphatase 1B	(Thuong et al., 2008)
• Crude extract	Fruit	Ethanolic extract	*In-vitro* antityrosinase activity	Antityrosinase activity comparable to that of arbutin	(Tiechi et al., 1999)
• Ethanolic extract and their purified fractions I, II & III	Leaves	Purified fractions of Ethanolic extract	Inhibitory activity against xanthine oxidase, collagenase, and elastase enzymes	• Antityrosinase activity • Collagenase inhibition • Collagen synthesis promoted in cultivated fibroblasts • Xanthine oxidase activity • Elastase inhibitory effects	(An et al., 2005)
Gallic acid	Leaves and fruit	Gallic acid dilutions and topical preparation	Eiosinophil-dermal fibroblast, Swiss Albino rats Zebrafish, UV-B induced mice skin model	• Anti-inflammatory, • Anti-microbial • Inhibits histamine release • Suppress release of pro-inflammatory cytokines (IL-6) and chemokines (CCL7 & CXCL8) from eosinophils-dermal fibroblast • Suppresses the 7,12-DMBA/Croton oil induced two-step skin carcinogenesis by modulating anti-oxidants and MMP-2/MMP-9 in Swiss albino mice • Depigmentation and skin lightening effect • Anti-aging effects (*in-vivo* and *in-vitro*)	(Tsang et al., 2016) (Kumar et al., 2013)
• Epicatechin	Fruit and leaves	Diluted samples	Cultured human skin fibroblast	• Attenuation of UVA-induced oxidative damage to human skin fibroblasts	
• Epigallocatechin	Fruit and leaves	Topical cream	Healthy human volunteers Split face study design	• Photo protective (UV-B) • Anti-inflammatory • Reduces melanin synthesis	(Domingo et al., 2010; Jeon et al., 2010)
• Chlorogenic acid	Fruit and leaves	0–500 μM dilution	B16 melanoma cells	• Inhibits tyrosinase activity and suppresses melanogenesis in B16 melanoma cells • Protect skin against UV-induced oxidative damage • Anti-inflammatory effects	(Li et al., 2014) (Kitagawa et al., 2011) (Tsang et al., 2016)
• β-Carotene	Fruit pulp and peel	–	–	• Imparting "Golden Yellow" color to skin • Protects against UV-skin damage	(Zaghdoudi et al., 2016; Zaghdoudi et al., 2015)
• Lycopene	Fruit	–	–	• Reduces skin erythema level • Regulates cholesterol	(Anunciato and da Rocha Filho, 2012)
• Leutin and xeaxanthin	Fruit	–	–	• Protection against UV damage and ROS	(Kaulmann et al., 2014)
• Tannins including flavanoellagitannin, • Procyanidinoellagitannin	Fruit pulp	Aqueous methanolic extract	HEK293T cells	• Potent antioxidant properties • Reducing the ROS levels of Gamma-radiation exposure in HEK 293T cells. • Reducing cell apoptosis	(Gu et al., 2008; Zhou et al., 2016)
• Coussaric acid and betulinic acid	Leaves	Purified fractions	Lipopolysaccharide-stimulated RAW 264.7 macrophages	• Anti-inflammatory effects with suppression of NO, PGE2, TNF-α, IL-6 and IL-1β	(Kim et al., 2016)

Proanthocyanidins

Proanthocyanidins (PA), secondary metabolic bioactive constituents are colorless polymers resulting from condensation of flavan-3-ol monomeric units. They get deposited in persimmon fruits during early developmental stages. Astringent specie of persimmon contains higher amounts of PA even after fruit maturation. While in non-astringent fruit types these bioactive moieties disappear on maturation of fruits (Ikegami et al., 2007). According to Ikegami et al. (2007) PA present in persimmon usually comprise of flavan-3-ol units, and they result in production of bioactive components like xavonols and glycosylated anthocyanidins. Multiple catechin units are present in PA obtained from persimmon with approximate MW of 1.38×10^4 Da.

Terpenoids

Different triterpenoids have been separated from leaves of *D. kaki* including ursolic acid, 19-hydroxy ursolic acid and 19,24-dihydroxy ursolic acid, which demonstrated suppressive activity against stimulus induced super oxide generation and tyrosyl phosphorylation (Chen et al., 2002a). In 2009, another report indicated identification and separation of 18,19-secoursane novel triterpenoids (kakisaponin B and kakisaponin C) along with an ursane type 28-nortritepne (kakidiol) and rosamultin from leaves of *D. kaki* (Chen et al., 2009). Kakisaponin A was also previously identified by the same researchers (Chen et al., 2007). Other terpenoids reported from leaves of *D. kaki* include lupeol, betulinic acid, betulic acid (Yoshihira et al., 1971) and pomolic acid (Thuong et al., 2008). Coussaric acid and betulinic acid have been separated from leaves of persimmon plant (Kim et al., 2016).

Ascorbic acid, vitamins A, D and E

Ascorbic acid (AA) is hexuronic acid lactone micronutrient being lipophobic in its nature. It cannot be synthesized by human being and hence should be supplied externally from food. AA performs different biochemical functions inside the body including synthesis and maintenance of collagen (Esteban-Pretel et al., 2013; Kishimoto et al., 2013; Findik et al., 2016), immunostimulant (Tewary and Patra, 2008), anti-aging (Xu et al., 2012), and skin rejuvenating agent (Zahouani et al., 2002; Crisan et al., 2015), skin whitening effects (Smith, 1999; Traikovich, 1999), neuromodulator (Rebec and Pierce, 1994), anti-oxidant, free radical scavenger (Cathcart, 1985; Erb et al., 2004) and antiviral (Jariwalla and Harakeh, 1996). In the skin AA plays a vital role as a substrate for oxidative stressors and hence prevents damage to skin caused by ROS and other reactive oxidants produced as a result of UV exposure. Topical application of AA can provide objective and subjective improvements in photo-damaged facial skin as confirmed by quantitation of skin surface texture changes (Traikovich, 1999). Amount of AA in persimmon fruit is ranged between 180 to 200 mg per 100 g of fresh weight (FW), which is subjected to variation during ripening stages (Del Bubba et al., 2009). Total AA contents in fruits have a mean value of 47 ± 39 mg/100 g FW with 3.5 mg/100 g FW in the astringent variety Costata to 146 mg/100 g FW in the non-astringent cultivar Hana Fuyu (Del Bubba et al., 2009). Persimmon leaves are also tested to be enriched with AA contents localized in cytosol of palisade parenchyma tissue cells (Kusunoki et al., 1998).

Vitamin A has been used widely in cosmetic industry and dermatology for it beneficial effects in skin care products including normalization of keratin, reduction in sebum production in acne patients, and curing photo damaged and aged skin (Shapiro and Saliou, 2001). Vitamin D has shown to down-regulate epithelial growth and facilitates its differentiation. Vitamin E being used in experimental and clinical dermatology for more than 50 years (Thiele and Ekanayake-Mudiyanselage, 2007), is an important membrane antioxidant, provide protection against oxidative damage, and when combined with AA, it can act as a photoprotective agent. These vital vitamins are present in appreciable amount in fruits and leaves of persimmon, strengthening its value as a cosmetic ingredient.

Dermatological and cosmetics benefits

Anti-inflammatory effects

Inflammation is a vital immune mechanism of innate immunity that protects body against various harmful factors. Inflammation is usually mediated by different exogenous and endogenous stimuli that may activate cellular immune system, which intern can produce some pro-inflammatory cytokines. Cyclooxygenase-2 (COX-2) in human skin, is a main key player in UV-induced inflammation, wrinkle formation (Lim et al., 2013), edema, epidermal hyperplasia and carcinogenesis. Lipopolysaccharide (LPS), in an exogenous bacterial endotoxin that can activate macrophages resulting in release of pro-inflammatory cytokines such as tumor necrotic factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), nitric oxide (NO), and prostaglandin E2 (PGE2). Inflammation is regulated by heme oxygenase-1 (HO-1) which inhibits synthesis of pro-inflammatory cytokines and mediator in activated macrophages. Nuclear factor-kB (NF-kB) has been considered an important factor involved in immune and inflammatory response. These cytokines can cause an expression of vascular and dermal adhesion molecules, chemoattraction of inflammatory cells, and activation of other inflammatory mediators like leukotrienes and PG.

Coussaric acid (CA) and betulinic acid (BA), (triterpenoids obtained from leaves of *D. kaki*), has shown to possess anti-inflammatory effects by inhibition of NF-kB pathway. Both of these two acids (Kim et al., 2016) and quercetin-3-*O*-β-D-(2″-galloyl)-glucopyranoside and quercetin (Cho et al., 2016) (separated from calyx of *D. kaki*) can inhibit NO and PGE2 along with a marked suppression of TNF-α, IL-6 and IL-1β in LPS-activated RAW 264.7 macrophages. They were also found to suppress protein expression of inducible nitric oxide synthetase and COX-2. BA was also shown to have a positive impact on HO-1 while CA was having no significant effects. It is commendable to note that in different skin condition manifested by inflammation, like "inflammatory acne vulgaris", pro-inflammatory cytokines such as IL-1α, IL-1β and TNF-α are associated in pathophysiology of acne (Basal et al., 2004). Acne vulgaris affects about 80% of young population aged between 11–30 years, manifested by formation of microcommodeness (Bergler-Czop and Brzezinska-Wcislo, 2014). It is believed that activation of toll like receptors-2 (TLR2) by *Propionibacterium acnes*, causes an increase in IL-8 and IL-12 (Zouboulis et al., 2005). So the potential activity of phytoconstituents of *D. kaki* against these inflammatory mediators can be of interest against acne and other related inflammatory skin disorders. More over epigallocatechin (Domingo et al., 2010; Jeon et al., 2010), gallic acid (**1**) and chlorogenic acids (Tsang et al., 2016) have shown to possess good anti-inflammatory activities in literature. Oligomeric proanthocyanidins have anti-inflammatory effects and can inhibit melanin synthesis by tyrosinase inhibitory activity (Tatsuno et al., 2012). Which correlates PA use in management of certain dermatological conditions including dermal inflammation and excessive melanogenesis. Tannins have also been used for their anti-inflammatory effects for different dermatological applications. Flavonoids from natural sources and those identified from *D. kaki* (Hougee et al., 2005) indicated anti-inflammatory activity *in-vivo* and *in vitro*

(Chen et al., 2016; Hougee et al., 2005; Vezza et al., 2016; Wu et al., 2016).

Antiallergic properties and potential use in prevention of dermatitis

Skin is the largest protective organ at the interface between host and environment. It protects from pathogens as a physical barrier and defends our body against different allergens by activating immune system (Skabytska et al., 2016). Mast cells are widely distributed in mammalian tissues and play an important role in regulation of allergic inflammation in different immune mediated disorders. Mast cells upon activation can release histamine and other inflammatory mediators, for example eicosanoids, proteoglycans, and other pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6 and IL-13 (Kim et al., 2013). Dermatitis is a common skin condition characterized by inflamed, red, itchy skin that may become blistered and weepy. There are different types of dermatitis and all of them are precipitated onto the skin by reacting with allergens or irritants. When allergens or irritants become in contact with skin, they may lead to a skin reaction, this condition is termed as contact dermatitis. A skin damage is usually seen with an irritant while an allergen initiates immune response advancing to allergic reaction. Atopic dermatitis or eczema occurs due to hypersensitivity to certain types of food (*e.g.* cow's milk) and/or allergens. Neurodermatitis is because of irritation to nerve endings down the skin, leading to sever itchy sensation and an irresistible desire to scratch the skin repeatedly resulting in thickening and redness of the skin. There are some other types of dermatitis as well including statis dermatitis, seborrheic dermatitis, perioral dermatitis and dermatitis herpetiformis. Recent advances in immunological screening of atopic dermatitis has resulted in understanding that activated mast cells and increased T-helper-2 lymphocytes (Th2) cells via chemical mediators and cytokines might play a vital role in development of dermatitis and IgE production. Topical steroid therapy is useful in management of this condition, however prolong use of these medicinal substances is of concern to some patients.

Botanical extract from leaves of *D. kaki* contains some antiallergic substances than can inhibit histamine release from human basophilic cell lines KU812. Oral administration of persimmon leaves extract and a flavonoid fraction called astragalin, to models of passive cutaneous anaphylaxis and atopic dermatitis mice has resulted in suppression of dermatitis development, scratching behavior, and serum IgE levels. Inflammatory cell infiltration, specially degranulated mast cells, thickening of epidermis and hyperkeratosis were reduced significantly. Moreover, production of IL-4 and IL-13 by spleen cells was reduced (Kotani et al., 2000). In another report polyphenolic compounds from persimmon leaves were shown to possess antiallergic properties and their potential use in contact dermatitis was reported (Park, 2000). Aqueous extract of *D. kaki* was investigated for its protective effects on mast cell mediated allergic reaction by *in-vivo* and *in-vitro* mast cell based models. The extract was found to inhibit the release of histamine and β-hexosaminidase from the mast cells by modulating cAMP and intracellular calcium levels. The release of pro-inflammatory cytokines such as TNF-α, IL-1β was also reduced by inhibition of NF-kB (Kim et al., 2013). It was established that the aqueous extract can inhibit systemic and cutaneous allergic reaction in a similar way as that of sodium cromoglycate. Different phenolic compounds including gallic acid, ellagic acid, hyperin, isoquercitrin, astragalin, quercetin and kaempferol from a herbal extract has revealed a dose dependent inhibitory action against edema induced by allergic contact dermatitis (Fu et al., 2015).

Anti-radiation activity (protection against photo damage)

Electromagnetic radiation emitted from sun, is comprised of ultraviolet radiation (UVR; 200–400 nm), visible light (400–780 nm), and infrared (IR; 780 nm to 1 mm). International commission on illumination (CIE) divides UVR into three categories: UVA (315–400 nm), UVB (280–315 nm) and UVC (100–280 nm). UVC portion being most dangerous for skin, is entirely absorbed by the upper atmospheric layers. Human body needs a very limited UVA and UVB photons for vitamin D synthesis (Holick, 2008; Rivas et al., 2015), longer exposure to UVR may lead to various skin abnormalities including photoaging and photocarcinogenesis through production of ROS, DNA damage, immunosuppression, photo-inflammation, altered remodeling of extracellular matrix (ECM) and/or angiogenesis (Bickers and Athar, 2006; Nishigori, 2006). ROS are produced as a result of UVR exposure to the skin (Bickers and Athar, 2006), which can activate cell surface receptors resulting in stimulation of mitogen-activated protein kinases (MAPK) (Wang et al., 2013). Cell proliferation, cell death and cell survival is regulated by activator protein (AP-1), and NF-kB. Moreover NF-kB also regulates inflammation, oncogenesis and apoptosis (Muthusamy and Piva, 2010). UVR exposure causes the release of arachidonic acid from oxidized lipid membranes, which is converted into prostaglandin (PG) by cyclooxygenase enzyme (COX). The newly produced PG may attract inflammatory cells. The activation of AP-1 by UVR helps promote photo-carcinogenesis and destruction of ECM. The activated AP-1 also interferes with collagen synthesis and block the effects of transforming growth factor-β (TGF-β) which is responsible for collagen transcription. The activation of AP-1 by UVR leads to overexpression of matrix metalloproteinases (MMP) in human skin and ECM destruction (Cooper and Bowden, 2007).

Longer exposure to UV light (particularly UV-A portion) can result in premature skin aging (photo-aging) because of higher degree of oxidative stress in human skin. The antioxidant defense mechanism in the skin protects it from harmful effects of ROS, however the overproduction of ROS generated from prolonged exposure to UV-A light can cause an increase in oxidative stress damage and results in degradation of certain molecules like, DNA, proteins, and fatty acids. This situation may lead to destruction of cellular and interstitial structure promoting tissue necrosis or apoptosis of skin cells, and skin may develop pathological conditions like skin aging, wrinkles or even cancer. UV radiation leads to a marked decrease in epidermal Langerhans cells, resulting in T helper-1 lymphocytes (Th1) clonal anergy. This results in immunosuppression, anergy, and immunological tolerance (Simon et al., 1991). Isomerization of urocanic acid (UCA) from trans-UCA into cis-UCA changes UV radiations into bioactive recognizable signal that initiates immune suppression (Prater et al., 2003).

Non UV radiations such as visible light and IR have not much been focused for their any possible role in photo-aging as opposed by UVA and UVB radiations. However recent studies demonstrate their possible role in pathogenesis of photoaging (Sklar et al., 2013). Ionizing radiation have been used broadly in medicine for radiodiagnostic and radio-therapeutic purposes. These radiations can produce ions and cause an imbalance in free radicals in human. As result cell phospholipids and DNA damage may happen (Zhou et al., 2016).

Ethanolic PLE was tested for its protective effects against UVB induced skin inflammation in HaCaT keratinocytes and mice. UVB radiation leads to reduced cell viability with enhanced production of chemokines. PLE was capable to regain cell viability and also suppressed generation of chemokines (CCL2 and CCL27) in HaCaT keratinocytes. There was significant reduction in skin damage upon oral administration of PLE to UV irradiated mice. Microscopic

studies revealed a reduction in infiltration of inflammatory (degranulated mast) cells, thickening of epidermis, and hyperplasia (Cho et al., 2011). UVB induced production of CCL2 and CCL27 is firmly regulated by activation of NF-kB. AP-1 and NF-kB, regulated by intracellular redox state, are increased by UVB irradiation. Oxidative stress and mitochondrial dysfunction plays a major function in apoptotic events. Flavonoids from the leaves of *D. kaki* have shown to reduce hydrogen peroxide induced apoptosis like injury to NG108-15 cells (Bei et al., 2005), implicating their possible use in reversing oxidative stress caused by ROS.

Quercetin, kaempfetol, rutin, astragalin, hyperin and isoquercitrin were thought to play a major role in improving the redox status, inhibiting apoptosis, and increasing cell viability under oxidative stress in NG108-15 cells (Bei et al., 2005). In another study involving MC3T3-E1 cells, induced with oxidative stress by hydrogen peroxide, flavonoid from PLE were shown to protect cells against oxidative stress related cellular injuries. Flavonoids from PLE can inhibit apoptosis in H2O2 activated MC3T3-E1 cells with suppression of NO, inducible nitric oxide synthetase (iNOS), COX-2, melanone dialdehyde (MDA), indicating that anti-apoptosis activity is mediated by suppression of translocation of NF-kB/p65 into the nucleus (Sun et al., 2014).

Collagenase (a matrix metalloproteinases; MMP) regulates photoaging process of skin due to ROS generated as a result of UVA exposure. Efficacy of different flavonoids including myricetin, quercetin, kaempferol, luteolin, apigenin and chrysin, on capturing ROS and inhibition of MMP have been studied earlier in 2007 by Sim and Lee et al. It was concluded that flavonoids can inhibit collagenase activity in UVA induced human dermal fibroblasts in dose dependent manner and can result in lower expression of MMP. The degree of antioxidant property and inhibition of collagenase was linked with numbers of hydroxyl groups in flavonoid structure (Sim et al., 2007). Phenolic acid and their amide derivatives can help protect skin against UV-A induced oxidative stress damage and sebum peroxidation (Ley, 2001). Chlorogenic acid, loaded in o/w heterogeneous emulsified topical formulation, can help to protect against UV induced oxidative damage (Kitagawa et al., 2011).

Tannins extracted from persimmon were shown to possess radio protective effects against different doses of gamma radiations (2–20 kGy) exposed to HEK 293T cells. Radiation protection was wielded by an increased cells lifespan, reduction in cell apoptosis and a decrease in ROS levels in HEK 293T cells exposed to Gamma-radiations. Recently in another report restorative effects of PLE against Gamma radiation induced oxidative stress and liver damage, was evaluated in irradiated mice and was found to reduce severity of radiation induced liver damage and other metabolic parameters (Ashry et al., 2016). Some types of skin cancers are hard to treat with chemotherapeutic agents, and of course, such agents have profound side effect profile. Polyphenol enriched extracts have been evaluated for their efficacy toward skin cancer with greatly promising outcomes (Wang et al., 2012a) indicating their potential role in preventing or curing different skin cancer condition.

Effects on sebum contents, oil contents, number and size of skin pores

Excessive sebum production and accumulation on the skin may increase the skin pore size. An effective skin cleanser is capable to reduce skin pore size by reducing production rate of sebum and promoting its removal from skin, hence reducing chances of comedones development. Careful face washing helps improve skin lesions and prevents acne development by washing away excessive sebum and avoiding hair follicular obstruction (Isoda et al., 2015). Many cosmetic ingredients used in skin cleansers have some unwanted effects, such as sodium lauryl sulphate may irritate the skin. Similarly, retinoid and its derivatives are known to be sever local skin irritants. Natural products usually have lesser side effects, that is why cosmetics industry is going through a shift from synthetic to natural cosmetic ingredients.

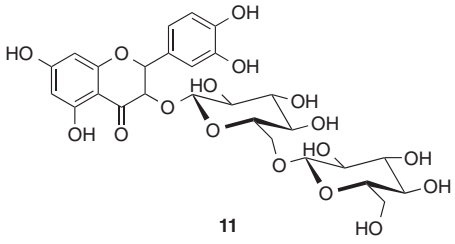
Extract from *D. kaki* folium, *Polygonum cuspidatum*, and *Castanea crenata* (DPC) loaded to cosmetic cleanser formulation was evaluated for its effects on skin parameters including number and size of skin pores and removal of sebum from the skin in 23 healthy volunteers. On application of test formulation containing DPC extract, oil contents decreased by 77.3%, number of skin pores were reduced by 24.83% and skin pore size was reduced by 71.43% as compared to the control formulation (Isoda et al., 2015). The preparation was also capable to remove solidified sebum from skin and can facilitate removal of *Demodex mites* (causative microbe for rosacea and seborrheic dermatitis) from the skin. Further studies can be directed for evaluation of different formulation containing persimmon extract for their effects on other skin parameters using non-invasive *in-vivo* evaluation techniques.

Inhibition of melanogenesis (skin whitening effects)

Skin color is usually determined by four chromophoric substances known as carotenoids, hemoglobin, oxyhaemoglobin and melanin, the last being most abundant (Hearing, 2005) relatively. Melanin is produced by melanosomes which are present in the skin, eyes, inner ear, and hairs (Jung et al., 2015). In human being pigmentation may increase as a result of UV or solar light exposure to the skin, which intern, stimulates melanin production by melanosomes (Coelho et al., 2013). Melanin provides protection against UV radiations, skin burn and cancer. Melanogenesis is the production of melanin from melanocytes in basal epidermal layer. Every individual usually have a particular number of melanocyte, however the skin color in not determined by the number of melanocytes, rather its being determined by melanin producing genes. In melanocytes, melanogenesis is usually regulated by certain enzymes such as tyrosinase-related protein-1 (TRP-1), tyrosinase-related protein-2 (TRP-2) and tyrosinase (TYR) (Kameyama et al., 1995; Wang et al., 2012b). Transcription of TRP-1, TRP-2, and the TYR family genes is controlled by microphthalmia-associated transcription factor (MITF), that is why it is believed that MITF is a master regulator in melanocyte proliferation, development, survival and melanoma formation (Wang et al., 2012b). Recently it is reported that mitogen activated protein kinases (MAPK) including p38 MAPK is mainly involved in MITF regulation. Activation of p38 MAPK increases transcription of TYR, stimulating melanogenesis (Galibert et al., 2001). cAMP, the second messenger derived from ATP, plays a vital role in intracellular signal transduction. Increased cAMP concentration affects protein kinase A (PKA), cAMP response element-binding protein (CREB) and cAMP response element (CRE). PKA has direct effect on melanogenesis and its activation leads to MITF expression by phosphorylation of CREB, which increases melanin synthesis (Busca and Ballotti, 2000). So, for an agent to efficiently reduce hyperpigmentation and produce whitening effects, it should act by regulating MITF, CREB, PKA and MAPK pathways.

Many different compounds have been isolated from persimmon and their antityrosinase activities have been reported as outlined in Box 1. Quercetin-3-*O*-β-D-glucopyranosyl-(1→6)-β-D-glucopyranosid (QCGG) (**11**) separated from the calyx of persimmon, inhibits melanogenesis and tyrosinase activity in B16F10 cells by suppressing expression of MITF, TRP-1, TRP-2, TYR via p38 MAPK and CREB pathway (Jung et al., 2015). It was pointed out that QCGG acts by reducing intracellular cAMP levels. QCGG can be used as a suitable natural cosmetic ingredient for different hyper pigmentary disorders. Two flavonoids glycosides identified as isoquercitrin and hyperin, isolated from acetone extract of persimmon

fruit peel, were found to be potent inhibitors of melanin production by suppressing tyrosinase expression in mouse B16 melanoma cells (Ohguchi et al., 2010). 2-Methoxy-4-vinylphenol (and its glycoside) isolated from peel of persimmon has antityrosinase activity higher than that of arbutin (Fukai et al., 2009). Seven different polyphenols separated from leaves of persimmon have been tested for their antityrosinase activities and chrysontemin was reported to contain moderate antityrosinase activity (Xue et al., 2011). Crude ethanolic extract of persimmon has antityrosinase activity comparable to that of arbutin with anti-wrinkle effects (Tiechi et al., 1999). Similarly among fraction I, II, and III of ethanolic PLE, fraction III (82% total phenols) showed significant antityrosinase activity (higher than that of green tea leaves, mushroom, garlic and black tea extracts) along with inhibition of xanthine oxidase and collagenase enzymes (An et al., 2005).



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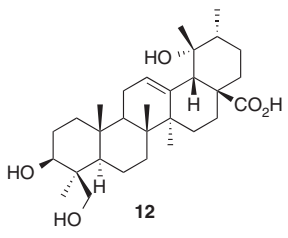
The other isolated phytoconstituents from persimmon have been reported for their antityrosinase/anti-melanogenic and other useful activities for cosmetic and dermatological interest include, rotungenic acid (**12**), gallic acid, epicatechin, epigallocatechin, chlorogenic acid, β-carotene, lycopene, lutein, zeaxanthin, coussaric acid and betulinic acid. Gallic acid, a major polyphenolic content from persimmon leaves and fruit have shown to reduce UVB induced hyperpigmentation in rats (Kumar et al., 2013). Gallic acid has shown to suppress melanogenesis by down-regulating melanogenic regulatory genes in TYR, TRP-1 and dopachrome tatamerase expression at level of transcription and translation (Kumar et al., 2013). Moreover, gallic acid inhibits MITF expression by reducing cAMP-mediated PKA/CREB signaling cascade. Similarly chlorogenic acid acts as a substrate for melanin and its metabolic products of are shown to suppress melanogenesis in B16 melanoma cells by inhibiting TYR activity (Li et al., 2014). Skin lightening effects of PLE are promising and comparable to that of hydroquinone (An et al., 2005), without any associated side effects. PLE being enriched with many valuable phytoconstituents can serve an efficient ingredient for different cosmetics formulations.



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Collagenase and elastase inhibition (prevention of wrinkle formation)

Collagen represents 30% of total protein in man with almost same weightage in other animals. Collagen can exist in 27 different types however, type I, II, and III are most prominent in man, comprising approximately 80–90% of total collagen in the body. Some body organs are relatively richer in collagen type-I including dermis, bones, tendon, and ligament while skin, blood vessels and intestine are enriched with type-III (Findik et al., 2016). In the skin collagen may be degraded by aging or by activity of collagenase, producing wrinkles. Collagen is produced by mature cells called fibroblasts. Firstly, procollagen is produced by fibroblasts, which is subjected to different modifications including proline and lysine hydroxylation. Cross linkage occurs as a result of proline hydroxylation producing strong collagen fibers (Roach et al., 1985).

Skin aging is usually estimated by wrinkles on the face. In wrinkled skin, usually there is deposition of altered elastic fibers and/or degraded or degenerated collagen bundles in the dermis (Antonicelli et al., 2009) resulting in reduced skin elasticity (Tsuji et al., 2001). Prolonged exposure to sunlight is considered to be the most probable cause for evoking skin wrinkles. Insoluble elastin is the major part of skin elastic fiber. Elastin fibers produces a delicate dispersed network between the collagen (Oxlund et al., 1988). Elastin plays a vital role in maintenance and restoration of skin elasticity and its degradation may result in wrinkles and loss of elasticity. Higher levels of elastase enzyme, diminished elastin generation and reduced skin regeneration with increased aging results in reduced skin elasticity. There are two main types of elastases in the skin; neutrophil elastase (serine proteinase) and skin fibroblast elastase (metalloproteinases). Neutrophil elastase can degrade all types of elastin fibers while fibroblast elastase affects oxytalan and elaunin fibers with a minimal effects on mature elastin fibers (Tsuji et al., 2001). Overproduction of elastase enzyme induced by UV irradiation affects elastic-fiber network. Skin fibroblast elastase released by fibroblasts upon UV exposure (even at suberythmal levels) contributes at large toward degradation of elastic fiber resulting in wrinkle formation. Topical application of synthetic elastase inhibitor (*N*-phenethylphosphonyl-L-leucyl-L-tryptophane) in hairless mouse induced with wrinkles by UV irradiations, has resulted in significant suppression of wrinkle formation (Tsuji et al., 2001).

PLE fractionated into three parts have been studied for its anti-elastase activity and it was demonstrated that fraction having more flavonoids contents (fraction II) showed better inhibition of elastase than fraction having more polyphenolic contents (fraction III) (An et al., 2005). It was concluded that flavonoids may have a better activity against elastase enzyme. Flavone from the leaves of *D. kaki* have shown to inhibit proliferation of advential fibroblasts stimulated by advanced glycation end-products (Ouyang et al., 2003), and advanced oxidation protein products (Ouyang et al., 2004). PLE separated into three fractions (*i.e.* I, II, and III) have been studied for its anti-collagenase effects. Results revealed that fraction III being more enriched with polyphenols showed higher activity against collagenase enzyme. The activity of PLE against collagenase enzyme was compared with reported activities of soybean trypsin inhibitor (46% at 4 mg/ml) and green tea extract (100% at 0.2 mg/ml). Purified fraction of PLE indicated 30% inhibition of enzyme at 20 ppm concentration, which was, relatively considered as a higher level of inhibition of collagenase enzyme (An et al., 2005). AA being an important constituent of persimmon leaves and fruit extract, acts as a co-factor for prolyl and lysyl hydroxylase and is indispensable for biosynthesis of collagen. AA also causes provocation of collagen gene expression. Human skin fibroblasts when exposed to AA for a longer duration in vitro, showed higher ratio of collagen type I and type IV with increased procollagen synthesis (Kishimoto et al., 2013). So extract of *D. kaki* can be used in cosmetic preparation as a natural whitening and anti-wrinkle agent. Persimmon leaves have a long been used in Chinese medicines to treat different skin conditions traditionally including pimples, skin eruption and eczema. These traditional uses can be appreciated

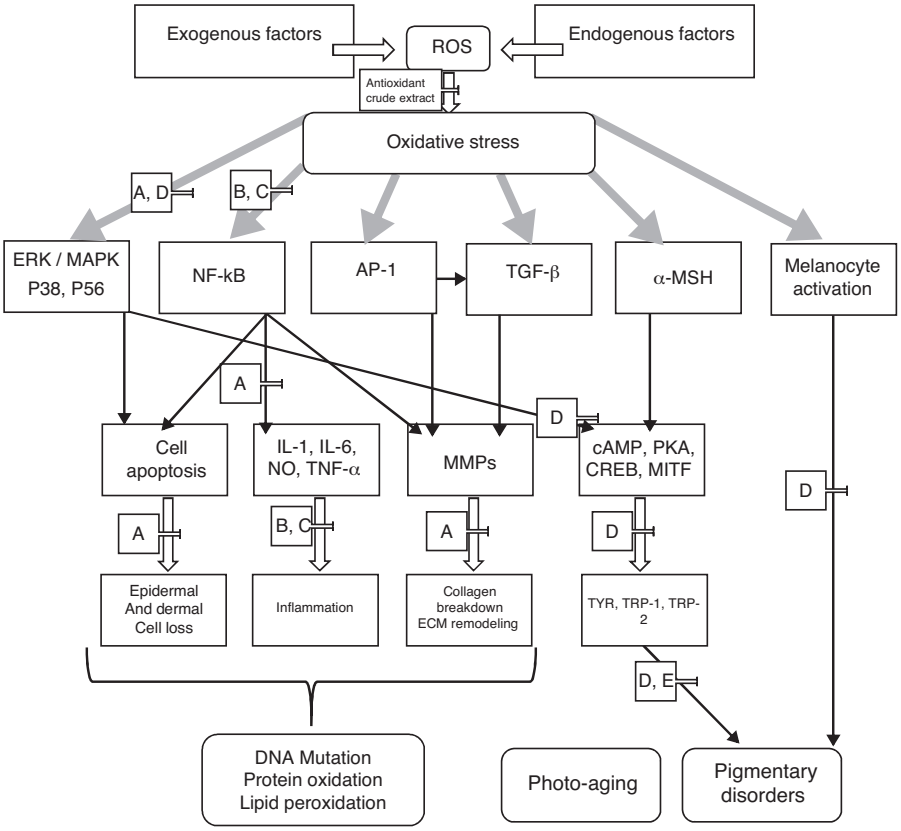

Fig. 1. Potential uses of *Diospyros kaki* crude extract and its active constituents against photoaging and pigmentary disorders. A = phenolic acid and flavonoids from persimmon, B = coussaric acid and betulinic acid, C = quercetin-3-O-β-D-(2″-galloyl)-glucopyranoside and quercetin, D = QCGG, E = isoquercitrin, hyperin, chrysontemin, gallic acid, rutogenic acid and 2-methoxy-4-vinylphenol.

momentously by cosmetic and dermatological beneficial profile of *D. kaki*.

Potent antioxidant activity

Skin aging being a dynamic process depends on both intrinsic and extrinsic factors, resulting in various skin changes at both esthetic and functional levels. Two distinct mechanism of skin aging are chronological aging (determined genetically) and photoaging due to repeated exposure to UV light resulting in microscopic changes in stratum corneum (Gao et al., 2010; Rabe et al., 2006). UV radiations results in generation of ROS leading to oxidative damage and oxidative products which are indicators of oxidative stress (Xu et al., 2012). Skin damage caused by ROS is the major factor driving toward photoaging. Skin, acting as a physical barrier between internal body and environment, is also a major target for oxidative stress. It contains numerous biochemical molecules which are prone to oxidative damage induced by ROS, including lipids, proteins, carbohydrates, and DNA. UV radiation exposure is a major contributory factor in photoaging, so preventive strategies may include avoiding sun light exposure or by maintaining cellular redox balance caused by UV radiations. In both cases, i.e. chronological aging or photoaging, utilization of different antioxidants in various skin care products has produced promising result. Fig. 1 shows potential uses and molecular mechanism of some selected valuable phytoconstituents from *D. kaki*.

Shieldingffect of antioxidants against different skin conditions has gained sufficient interest in cosmetics and dermatological practice (Parveen et al., 2014). Recently, many studies have been conducted utilizing different botanical extracts with proved antioxidant activities in rejuvenating skin condition, like skin mechanical characteristics, skin roughness, smoothness, scaliness, elasticity, and anti-aging effects (Mahmood and Akhtar, 2013; Khan et al., 2015; Mohsin et al., 2016). Many natural bioactive substances with proved antioxidant capacity like vitamin E, vitamin C, coenzyme Q10 (CoQ10), flavonoids, phenolic acids, carotenoids from botanical extracts and their combinations, loaded into topical formulations may reduce degenerative effects of ROS, oxidative stress and may help in treatment or prevention of clinical manifestation of aging skin. Photoaging because of oxidation may result in reduction of antioxidant enzymes and antioxidant defense mechanism which may result in significant oxidative damage, immunomodulation, activation of melanogenesis and carcinogenesis. At micro levels, UVA radiations mainly cause oxidative stress because of ROS and may alter cell's response to produce modified gene expression, DNA damage, which can stem abnormal cell morphology, cell apoptosis or necrosis and skin aging (Yue et al., 2010). To withstand the deteriorating effects after sun light exposure, nature has created different defensive mechanisms in the skin including several kinds of antioxidants such as AA, vitamin E, CoQ10, polyphenolic compounds, superoxide dismutase, glutathione-peroxidase reductase enzyme system in epidermis (Miyachi, 1995). The idea of avoiding exposure to sunlight is getting more acceptability as a practical approach to minimize skin cancer and photoaging. Research data indicates that herbal extracts enriched with antioxidant possess anti-carcinogenic, anti-proliferative, anti-inflammatory, and anti-angiogenic properties in the skin by regulating multiple signaling pathways (Humbert et al., 2010).

Food, especially fruits are a major source of antioxidants for the body. Persimmon fruits is enriched with many antioxidants including polyphenols, phenolic acids, flavonoids, carotenoids, tannins, proanthocyanidins, catechin, vitamins and others (see phytochemical section). Many reports have been published indicating potent radical scavenging activity of crude extracts and their purified fraction from different parts of *D. kaki*, and their effects on different biological functions have well been established (Han et al., 2002; Chen et al., 2008; Fukai et al., 2009; Sun et al., 2011; Lee et al., 2012). The antioxidants obtained from *D. kaki* have capability of scavenging ROS, hydroxyl ion radicals, superoxide radicals, peroxyl radicals, singlet molecular oxygen species and shows metal chelating activity (Fukai et al., 2009; Sun et al., 2011). Flavonoids from leaves can increase levels of catalase, super oxide dismutase, and glutathione peroxidase in a manner better than rutin. Total antioxidant activity and total phenolic contents in persimmon were significantly higher than that of apple, grapes and tomato (Chen et al., 2008). Some most important antioxidants that can serve as a candidate for different cosmetics and dermatologic preparations are enlisted in Box 1.

Toxicological and safety aspect

Since more than a century, no toxicity case has been reported for persimmon leaves consumed in crude form as a part of traditional medicine or botanical extract made thereof. Modern toxicological evaluation of leaves did not showed any toxic effects. Aqueous PLE was administered to both male and female mice in an acute toxicity test and LD_{50} was found to be higher than 21.5 g/kg (equal to 597.2 g/kg as crude substance), indicating non-toxic nature of extract. Micronucleus test (MNT) conducted in mouse bone marrow using aqueous PLE (10 g/kg), has revealed a normal decline in the ratio of polychromatic erythrocytes/normochromatic erythrocytes (PCE/NCE) as compared with cyclophosphamide (20 mg/kg) representing non mutagenic nature of the extract in somatic cells. The PLE at concentration of 10 g/kg did not show any sperm malformation tendency (Wu et al., 2012). In another study, ethanolic PLE was administered orally in 100 rats, at concentration of 0.5, 1.0, 3.0, and 6.4 g/kg for 90 days (Chen et al., 2005). Alterations in physiological and hematologic parameters among the control and test subject were found to be insignificant. It was concluded that ethanolic PLE at dose of 6.4 g/kg did not produce any maternal, embryonic and teratogenic toxicity in studied subjects.

Despite of the routine worldwide consumption of nutrient enriched persimmon fruits, it may sometime present a moderately complicated medical condition called diospyrobezoar which may result in small bowl and/or ileus obstruction (de Groot and Puylaert, 2008; de Toledo et al., 2012). Treatment modalities for diospyrobezoar resulted from overconsumption of persimmon fruits, may include endoscopic removal. Laser mediated pulverization, shockwave lithotripsy, or chemical dissolution by cellulose or Coca-Cola (Dolan and Thompson, 1979; Chung et al., 2006; Qin et al., 2014).

Persimmon peel extracted fractions with various solvents *viz*., hexane, acetone, MeOH, and 70% ethanol were evaluated for their cytotoxic potential in two human oral tumor cell lines (HSG-2, HSG) and one human gingival fibroblast (HGF) utilizing microculture plates stained with methyltetrazolium (MTT) assay (Kawase et al., 2003). Two fractions of acetone extracts showed highest cytotoxicity in both tumor cell lines (HSG-2, HSG), and normal fibroblast (HGF) from all 23 extract and fractions. Aqueous PLE has demonstrated outstanding cytotoxic activity against brain shrimps nauplii (*Artemia salina*). This cytotoxicity activity (at 10 ppm) was comparable to that of standard drug Etoposide (Nisar et al., 2015). Ethylacetate PLE and various separated chemical compounds were evaluated for their cytotoxic activity against various cancer cell lines such as A549, HepG2 and HT29. Compound 2, 3, and 4 showed cytotoxicity against these cancerous cell lines with IC_{50} values in range of 9.3–21.1 mM (Chen et al., 2007).

The available literature did not revealed any toxic activities in PLE, which implicates a reliable safety in common use. However, a further research is obligatory to evaluate more purified fractions of various solvent extracts to strengthen the available literature. Furthermore, various crude and purified extract should be evaluated thoroughly for their suitability, safety and toxicity data before ingestion and or topical administration. For example, Butchard patch (skin irritancy) test (Mahmood and Akhtar, 2013; Mohsin et al., 2016) can be conducted for any topical formulation loaded with *D. kaki* phytoconstituents intended to be used by human volunteers.

Future perspectives

Based on literature survey it is evident that various parts of *D. kaki* are enriched with valuable phytoconstituents and has a great potential for its utilization in cosmetic industry and various skin disorders. Most of the data presented in this article is based on either *in-vitro* analysis or *in-vivo* animal model testing. There is driving thrust to evaluate this valuable plant and its active constituents in cosmetics and dermatological applications after establishing scientific validation, safety and efficacy by using different non-invasive *in-vivo* evaluation techniques. Because of lower risk profile involved in using human volunteers in dermatologic/and or cosmetic evaluation, topical formulation can be formulated and subjected to *in-vivo* studies in diseased or healthy human volunteers to establish clinical relevancy. Further purification, identification and standardization of active principles from fruits, leaves and stem can be carried out for obtaining optimum benefits from this valuable God gifted plant. Loading the active principles separated from *D. kaki* into different topical formulations viz., emulsions, gels, emulgels, creams and other beauty care products can be of value to establish relevancy between *in-vitro* data and *in-vivo* outcome for their beneficial effects on human skin and esthetic parameters. Topical formulation loaded with crude and purified extract can be subjected to *in-vivo* evaluation and their effects can be evaluated on various skin parameters such as topographic changes, wrinkle assessment, skin hydration levels, number and size of skin pores. Despite of its utilization as a valuable traditional medicines in different Asian countries for more than 100 years, it can safely be forecasted that still optimum therapeutic benefits of *D. kaki* have not fully been explored. Specifically, the active principles from root, barks, stem, flower and aerial parts of the tree are still to be evaluated for their possible involvement in cosmetic and dermatologic benefits. Cosmeceutical and commercial interest is gaining more popularity for using this plant as a source of valuable ingredients for curative and beautifying purposes in various skin disorders.

Conclusion

Crude extracts, its purified fractions and various active principles obtained from *Diospyros kaki* have a great potential for both dermatological and cosmetic application. Some of phytochemical obtained from this plant such as isoquercitrin and hyperin have better reported activities than well-known cosmetic ingredients viz., arbutin, kojic acid, hydroquinone with possibility of having no side effects. Photo protection against degenerative effects of UVA, UVB and gamma radiation can help skin to fight well against oxidative stress and ROS. This plant has a great potential as a source of natural skin whitening agent, which can further be investigated utilizing human volunteers. Thus different formulation containing crude extract from various parts of *D. kaki* may have a potential to

improve skin condition by reversing signs of photo-aged skin, producing skin lightening effects by reducing melanin levels and may help to reduce sebum production.

Authors contributions

All the authors have contributed equally toward completion and contents of this review article are well understood by them.

Conflicts of interest

This statement is to certify that all Authors have seen and approved the manuscript. We warrant that the article is the Authors' original work and declare no conflict of interest.

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