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Persimmon (*Diospyros Kaki*) Leaves Extract (PLE): A Potential Drug for Eye-Related Diseases

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Abstract

Persimmon (*Diospyros kaki*) leaves have been used as a traditional or local medicine for multiple diseases in different eastern countries (Japan, Korea, India, and China) for centuries. In the recent past, several studies have used persimmon leaves extract (PLE) against different eye-related diseases. In this review, we discussed the ethnopharmacological use, therapeutic potentials and future opportunities for research using PLE for different ocular disorders based on the latest research. The pieces of information regarding PLE were collected using Pubmed, ACS, Elsevier, EMBASE, Web of Science, CNKI and different books. It can be concluded from this review that PLE probably have therapeutic potential against inflammation and oxidative stress induced disorders like dry eye disease (DED), corneal neurovascularization (CoNV), glaucoma, age-related macular degeneration (AMD), diabetic retinopathy (DR), and edema. However, further investigations are required to discover exact biological compounds involved in the pharmacological effects against the aforementioned diseases. Furthermore, clinical trials are needed to be performed before integrating PLE for medicinal use.

Keywords: Cell viability; Cornea; Retina; Na^+/K^+-ATPase; Glaucoma; Oxidative stress; Inflammation; *Diospyros kaki (D.Kaki*), Persimmons leaves; Dry eye disease; Corneal neurovascularization; Glaucoma; Age-related macular degeneration; Diabetic retinopathy; Edema

Abbreviations: PLE: Persimmon Leaves Extract; DED: Dry Eye Disease; CoNV: Corneal Neurovascularization; AMD: Age-Related Macular Degeneration; DR: Diabetic Retinopathy; VEGF: Vascular Endothelial Growth Factor; ROS: Reactive Oxygen Species; TBUT: Tear Breakup Time; RGC: Retinal Ganglion Cells; IOP: Increased Intraocular Pressure; BRB: Blood-Retinal Barrier

Introduction

Persimmon tree (Family: *Ebenaceae*, Genus: *Diospyros,* Specie: *kaki* or *D. Kaki*) has been cultivated throughout Asian countries (Korea, China, Japan and India) and used as sources of fruit and traditional medicine for centuries [1,2]. Because of its delicious taste and high nutritional values, Persimmon fruit is commonly used in a diet (as a fruit or in teas). Persimmon leaves extract (PLE) have been used as a traditional and/or herbal medicine against internal haemorrhage, ischemia, stroke, angina, paralysis, burns, constipation, and frostbite. PLE has largely been used in cosmetics as they contain anti-ageing compounds, and the compounds present in bark prevent melanin biosynthesis [3]. *D. Kaki* have more nutritional benefits as compared to apples [4]. PLE has anti-atherosclerotic, antidiabetic, anti-inflammatory, and anti-neurodegenerative properties [1,5-9]. Recent studies have shown that persimmons are rich in flavonoids and terpenoids [10] with other compounds like tannins, coumarins, ionones, fatty acids and naphthoquinones [11-16]. The flavonoids like quercetin and iso-quercetin in PLE are responsible for their anti-inflammatory effects [4]. These dietary flavonoids inhibit tumour necrosis factor-alpha (TNF-α) [17], vascular endothelial growth factor (VEGF) [18] interleukin-1beta (IL-1β), matrix metalloproteinase-2 (MMP-2), and matrix metalloproteinase-9 (MMP-9) [19,20] that are known to be pro-inflammatory and pro-angiogenic cytokines. *D. Kaki*'s antioxidant activity is mainly linked to the presence of high molecular weight tannins that reduce the risk of cardiovascular diseases, hypertension, diabetes,

and leukemia [21-23]. Along with that, terpenoids present in PLE are reported to suppress stimulus-induced superoxide generation and tyrosyl phosphorylation [24]. Antioxidant and anti-inflammatory properties of PLE are crucial to maintain eye health. So, many researchers are interested in PLE to check its effects on different eye diseases. The eye is the one's window to the outside world and it is the most sensitive organ of the human body. Among two important parts of the eye, the cornea is a clear front of the eye while the retina is located at the back. The cornea controls and focuses the light that enters the eye. The retina is a nerve layer at the posterior part of the eye that detects light and generates electrical impulses that are transmitted to the brain via the optic nerve [25]. The retina is made up of millions of light-sensitive cells called rods and cones that help to convert light into signals that the brain perceives as images. Any changes or disruption in the function of the cornea or retina can cause serious damage.

In the recent past, many scientists have tried to use PLE for different eye diseases like dry eye disease (DED), corneal neurovascularization (CoNV), glaucoma, age-related macular degeneration (AMD), diabetic retinopathy (DR), and edema. So, the purpose of this review was to evaluate pharmaceutical, medicinal and ethnopharmacological applications of PLE for eye diseases. We expect that with more detailed investigations and clinical trials, the PLE can be a potential drug against different ocular abnormalities.

Factors Causing Ocular Disorders

Oxidative stress

Oxidative stress refers to cellular and molecular damage caused by reactive oxygen species (ROS). It has a major contribution in corneal as well as retinal diseases. Oxidative stress leads to ocular aging process and initiate or develop corneal injury [26]. Many corneal dystrophies are linked to oxidative stress. Oxygen is continuously required during the visual process [27]. The retina, which is made up of specialized neurons and retinal ganglion cells, is one of the body's most oxygen-consuming tissues (RGCs) [28]. High oxygen consumption causes oxidative stress-induced retinal damage and induces a high risk of ROS accumulation in the retina which in turn raise a potential risk for retinal disorders or retinal damage [29-32]. It is already reported that patients with retinal degenerations exhibit high ROS levels vs low levels of anti-oxidative proteins compared to healthy patients [33]. Antioxidants are long been used and prescribed for better eye health [34] and are associated with a reduced risk for developing retinal degeneration [35].

Inflammation

Ocular inflammation is considered one of the leading factors for visual impairment. Some corneal [36] and most of the retinal disorders are linked to inflammation [37-40]. Despite significant progress in clinical care and understanding pathophysiological mechanisms, there is still a significant unmet medical need relating to ocular disorders. Many antioxidants and anti-inflammatory drugs are being used to treat these disorders but most of them are coupled with multiple side effects. So, there is a dire need to develop some drugs that can protect the eye without any harm.

Role of PLE Against Different Eye Diseases

Recently, different groups of scientists have studied the effect of PLE on the different eye diseases. Here, we will briefly discuss the eye diseases (DED, CoNV, AMD, DR, edema and glaucoma) and the role of PLE as potential drugs.

DED

With each blink of eye, tears spread on the cornea to provide lubrication and wash off any foreign object to keep the eye clean. DED is a serious condition that develops if a person doesn't have enough quality tears to lubricate the cornea. It is an inflammatory condition with many resemblances to autoimmune diseases [41,42] that is a common problem of all ages. DED is characterized by inflammation of the ocular surface and lacrimal glands along with symptoms of discomfort, visual disruption and tear film instability [43]. Inflammatory cytokines are increased in DED conditions [44] that triggers apoptosis and apoptotic cells are found in dry eye animal models [45,46]. So, DED can be treated by inhibiting corneal inflammation [47]. Commonly used ocular drugs are unable to provide immediate and complete relief. Based on data from the National Health and Wellness Survey, 6.8 per cent of the United States adult population (approximately 16.4 million people) have been diagnosed with DED. PLE application regulated the key factors for the healthy eye like tear volume, tear breakup time (TBUT) and corneal epithelium lining in the dry eye mouse model. There were less apoptotic cells and the expression levels of apoptosis inducing inflammatory cytokines (IL-1α, IL-1β, TNF-α, MCP-1, and IL-6) were also decreased. So, PLE treatment not only helps the cornea to survive against degradation but also help cells to proliferate in a regular manner [48].

Corneal neurovascularization (CoNV)

CoNV is defined as the invasion of new blood vessels into the cornea and occurs as a result of inflammation of the cornea or imbalance between angiogenic and anti-angiogenic factors [49-52]. Under inflammatory conditions, corneal cells produce angiogenic factors like VEGF [53], which upregulates the production of MMPs [54,55] and stimulates blood vessel formation. The CoNV disrupts the corneal clarity leading to vision loss in many cases. Anti-inflammatory, anti-VEGF agents and MMP inhibitors are long been used to treat CoNV. All these drugs proved beneficial for a short period and has severe side effects [56]. When PLE was applied to the injured eye representing CoNV eye model, the protein expression level of angiogenic and inflammatory proteins (VEGF, MMP, IL-6, FGF) decreased significantly [57]. It is reported that the flavonoids could be the active compounds that exert these anti-inflammatory and anti-angiogenesis effects [58].

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Glaucoma

Another lethal ocular disorder is glaucoma that affects the optic nerve [59], which is made up of a bundle of Retinal Ganglion cells (RGC) axons in the retina. The main cause of glaucoma is the flushing of aqueous humour that leads to increased intraocular pressure (IOP) [60,61]. One of the obstacles in preventing the etiology of glaucoma is protecting RGCs, and significant efforts have been made in scientific and clinical research to minimize RGC degradation [62]. PLE is shown to reduced IOP [63]. The studies show that PLE reduce glaucoma symptoms in animal models of glaucoma and play a protective role against RGCs death through its anti-oxidative and anti-inflammatory properties [64].

Age related macular degeneration (AMD)

AMD is known to be one of the leading cause of retinal degeneration and blindness [65]. It is a multifactorial disease including aging, environmental factors and genetic susceptibility [66]. Chorionic inflammation and oxidative stress are known to be the root cause of AMD and vision loss worldwide [67]. Antioxidants are long been used to treat retinal disorders [34]. *D.Kaki* fruit and leaves was proven to have antioxidant activities [21,68]. So, when PLE applied to the mouse model that represent retinal degeneration it ameliorates the symptoms [69].

Diabetic retinopathy (DR)

DR is an inflammation of macula triggered by blood-retinal barrier (BRB) breakage in diabetic patients [70]. Oxidative stress because of ROS accumulation and inflammatory cytokines plays a major role in pathogenesis of DR [71-73] The studies have demonstrated that SPARC-like protein 1 precursor (SPARCL1) is overexpressed in DR [74,75]. However, downregulation of this protein was observed in diabetic patients treated with PLE [76]. So, probably, PLE can be treated against DR disease

Edema

Corneal edema also known as the swelling of cornea it occurs because of fluid buildup in cornea. It results in loss of transparency and known to be the sign of acute corneal disorders. Damage of corneal epithelium or endothelium contributes to this. Ouabain (OU), a known Na^+ /K^+ -ATPae inhibitor, is reported to causes edema in human and rabbit eye models [77,78]. When PLE was applied to cells under the influence of OU, enzymatic activity and protein level of Na^+ /K^+ -ATPae was increased [79]. IOP also contributes to corneal edema [80,81], and a recent study showed PLE as an IOP lowering agent [63]. All these above-mentioned diseases seriously damage the eye. It is critical to diagnose the factors contributing to these conditions to treat them for the sake of healthy vision. So, the studies discusses here demonstrate that PLE can be a potential agent to prevent many corneal and retinal disorders.

Conclusions

It can be concluded from this review that PLE has the potential to be a candidate for the treatment of ocular diseases like DED, CoNV, glaucoma, AMD, DR and edema. However, further detailed studies including the identification of specific compounds responsible for these effects as well as the clinical trials on all age groups are needed before using PLE as an ocular drug.

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