Review Article

# A Comprehensive Review of Pazha Kirambu Pakkuva Vennai: A Siddha Topical Ocular Medicine

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**ABSTRACT**

Other than blindness and vision impairment, diseases of the conjunctiva, sclera, cornea, pupil, and eyelid such as cataracts, glaucoma, conjunctivitis, Blepharitis, keratoconjunctivitis, DED (Dry eye syndrome), Uveitis, etc. Are common eye condition in India and around the world. Siddha literature had many ophthalmic drugs and minor surgical procedures for 96 classified eye diseases. *Pazha kirambu pakkuva vennai*(PKPV) is one of the topical ophthalmic drugs, indicated for all 96 types of eye diseases like *Pillam*, *Chukkran*, *kasam*, *Emaidhosham*, *Kanmaraivu*, *Sathai vazharchi*, *Varatchi thimiram*, Etc. A scientific review of the ingredients of the *Pazha kirambu pakkuva vennai* is lemon, clove, and cow's butter have anti-inflammatory, antioxidant, anti-allergic activity, and antimicrobial activities, and copper is important in ocular physiology, proving that PKPV can be used for eye diseases.

**Keywords:** Siddha, Eye medicine, Cataract, Conjunctivitis, Dry eyes.

## INTRODUCTION

This drug review aimed to comprehensively evaluate PKPV, encompassing its pharmacological properties, efficacy, and therapeutic applications. This review critically analysed recent research findings and future directions in its use. By synthesizing available evidence, the review aims to offer valuable insights for clinicians and researchers to optimize patient care and guide future investigations.

A comprehensive literature search was conducted to identify relevant studies. Databases searched included a list of databases, e.g., PubMed, Web of Science, Scopus, Google Scholar. Also, the search was conducted to identify relevant books through the publisher's website. academic library, The search was performed using keywords and phrases relevant to the topic of interest, such as *Citrus lemon*, *syzygium aromaticum*, cow's butter, copper, and their phytochemicals. Pharmacological activities, and their role in ocular diseases

### Cataract

A cataract is an opacification or clouding of the naturally clear lens of the eye. This leads to looking blurry, hazy, or less colourful, Having trouble seeing well at night, and being extra sensitive to light Multiple factors responsible for developing cataracts such as congenital, age-related (most common), traumatic injury, systemic diseases like myotonic dystrophy, atopic dermatitis, and neurofibromatosis type 2, endocrine diseases like Diabetes mellitus, Hypoparathyroidism, secondary cataract occurs from primary ocular pathologies like Chronic anterior uveitis, Acute congestive angle closure, High myopia, Hereditary fundus dystrophies, Drugs eg. Chlorpromazine can lead to anterior star-shaped lens opacity, poor nutrition deficient in antioxidants and vitamins, Alcohol Use Disorder and Smoking. The prevalence rate in America is 17 % and in black 13 %.

### Pathophysiology

The lens is made up of fibers (modified epithelial cells) which are transparent structures and it enclosed by a membranous lens capsule. Lens had two parts superficial cortex containing young fiber and deeper nucleus containing older fibers. The degenerative processes cause lens proteins in lens fibers to denature and coagulate through various mechanisms. This subsequently leads to a loss of transparency and, ultimately, the formation of cataracts. Surgical treatment is more widely used than medicine in modern medicine. Drugs with antioxidant activity can help to slow the degenerative changes of lens fiber. [1,5]

### Dry eye disease

Dry eye is caused by Certain diseases, like rheumatoid arthritis, Sjögren's syndrome, thyroid disease, lupus, Blepharitis, Entropion, Ectropion, and environmental conditions like Being in smoke, wind, or a very dry climate, Looking at a computer screen for a long time, reading and other activities that reduce blinking, Using contact lenses for a long time.

### Pathophysiology

DED is traditionally classified into 2 types one is aqueous deficiency, Insufficient tear production defines this type of dry eye. Common causes include Sjogren Syndrome (primary or secondary), diseases, inflammation, or malfunction of the lacrimal gland, and obstruction of the lacrimal gland. and another one is evaporative dry eye which is distinguished by an increased evaporation of the

tear film and a lack of the lipid component in the tear film. In this scenario, the volume of tears produced is normal; however, the quality of the tears leads to excessive evaporation. This change is most commonly a result of dysfunction in the meibomian glands. These glands that are line the eyelid and release oils that form the lipid layer of the tear film, decreasing the evaporation of tears. Dysfunction of the Meibomian glands can result from insufficient secretion due to atrophy, gland dropout, or blockage of the gland openings. The hallmark of Dry Eye Disease (DED) is the hyperosmolarity of the tear film, which can cause direct damage to the ocular surface or indirectly lead to inflammation, instability of the tear film, epitheliopathy, and abnormalities in the neurosensory function of the ocular surface. Normal tear film osmolarity is 300 mOsm/L but in DED it becomes up to 360 mOsm/L, resulting in the release of inflammatory mediators such as tumor necrosis factor, cytokines, alarmins, interleukin 1, and interleukin 6. Consequently, it causes damage to the ocular surface, which in turn can further reduce the stability of the tear film. Modern medicine treats Topical anti-inflammatory medications, Topical ocular lubricants, Oral essential fatty acid supplements, Oral antibiotics, and Preservative-free ocular lubricants. Drugs with anti-inflammatory, antioxidant, with fatty acid substances can help this condition. [2,6]

**Conjunctivitis**

Conjunctivitis is the inflammation or infection of the conjunctiva, Conjunctivitis can be caused by a virus, bacteria that is contagious, or allergies that are noncontagious. Also known as pink eye, symptoms may include, the feeling that something is in your eye, or a gritty sensation in your eye, red eyes, burning eyes, itchy eyes, painful eyes, and watery eyes. Puffy eyelids. Blurry vision, being extra sensitive to light. Mucus or pus discharge from your eye. There can be so much that your eyelashes stick together. [3,4]

**Pathophysiology**

Conjunctivitis, or pink eye, is the inflammation of the conjunctiva due to infection or irritation. During inflammation, the blood vessels in the conjunctiva expand, leading to redness and swelling. The entire conjunctiva is affected, and discharge may be present depending on the cause. Bacterial conjunctivitis occurs when the eye's surface tissues are colonized by bacteria such as Staphylococci sp., Streptococci, and Corynebacteria. For treating bacterial conjunctivitis Liquid solutions like polymyxin B/trimethoprim, ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin, gatifloxacin, azithromycin. an ointment such as Bacitracin, erythromycin, and ciprofloxacin are administrated. Viral conjunctivitis caused by adenoviruses is typically self-limiting, and management is focused on providing symptomatic relief. The management of herpes zoster conjunctivitis involves the use of both oral antiviral medications and topical steroids. The treatment for allergic conjunctivitis involves several approaches, use of various topical agents, encompass topical antihistamines either alone or in combination with vasoconstrictors, topical mast cell inhibitors, and topical glucocorticoids, mainly on persistent symptoms.[3]

Nowadays days siddha is known globally. Even though abundant medicine formulations are available for 4448 diseases, the use of ophthalmic medicines *Kallikam*, *Anjanam*, etc. It is rare nowadays. Maybe because of unawareness and hesitation. In the 4448 disease classification, eye diseases are 96. Well-known Siddha books specially for opthalmic diseases are *Agathiyar nayana vithi* and *Nagamuni nayana vithi*. Other books like *Sarabenthirar* and *Anuboga vaithiya navaneetham* also mentioned eye diseases and their treatment. *Pazha kirambu pakkuva vennai*(PKPV) is one of the ophthalmic drugs, Indicated for all 96 types of eye diseases like *Pillam*, *Chukkran*, *kasam*, *Emaidhosham*, *Kanmaraivu*, *Sathai vazharchi*, *Varatchi thimiram*, etc.[7,8,9,10]

**PAZHA KIRAMBU PAKKUVA VENNAI**[7,8,9,10]

**Ingredient:**

Lemon fruit (*Elumichchai*) - No.1

Purified Clove (*Suththitha Lavangam*- bud removed) - Nos 108

Cow Butter(*Pasu Vennai*) - size of wood apple(*vilankaai azhavu*) (140-150 g)

Copperplate and copper cup with flat bottom

**Method of preparation**

Puncture the lime fruit with a needle make 108 holes and insert a clove in each hole. Spread butter over it, and suspend it in a pot containing water. Do not allow the fruit to rest on the bottom of the vessel, and change the water daily and keep this for forty days. Remove the butter alone leaving the cloves and the lime fruit and rub the butter on a copper plate with copper cup until it turns into a greenish color and preserve it in a copper container.

**Indication**

All 96 eye diseases such as

*Kasam* – Cataract, corneal, iris, lens(*Karu vizhi*) diseases

*Varatchi thimiram* kind of eye disease marked by irritation, growing pain, and itching on the head and the face associated with mucopurulent discharge resulting in varied vision

*Chukkran* - is an eye disease characterized by the following symptoms - inflammation of the sclerotic coat (white of the eye) swelling morbid growth of flesh on the choroid including the iris, piercing acute pain, headache, lesions on both inner and outer corners of the eye sleeplessness- may compared with conjunctivitis

*Pillam* – a disease of the eyelid, an eye disease caused by Phlegmatic and bilious disorders in the system.

*Emaidhosham* - a disease of the eyelid

*Sathai vazharchi* - Pterygium, episcleritis[15]

**1. Lemon fruit (*Citrus lemon* - *Elumichchai*)**

Domain: Eukarya

Kingdom: Plantae

Phylum: Magnoliophyta

Class: Magnolicpsida

Order: Sapindales

Family: Rutaceae

Genus: *Citrus*

Species: *Citrus limon*

Part used: Fruit

Taste: Sour

Potency: Heat

Characteristics: It cures giddiness, nausea, vomiting, aggressiveness, thirst, earache, nail infection and cures eye diseases. It also has rejenuvating (*kaya karpam*) action.[11,13]

**Chemical constituents**

Flavonoids such as flavanones (eriodictyol, hesperidin, hesperetin, naringin), flavones (apigenin, diosmin), and flavonols (quercetin; and their derivatives) D-limonene, γ-terpinene, p-cymene,β-phellandrene, β -pinene,δ-3-carene, myrcene), terpene alcohol (e.g., linalool, (E)-carveol, (E)-verbenol, geraniol, and α-terpineol) are the major chemical constituents of the volatile fractions of citrus essential oil are the important biologically active compounds in C. Limon fruit. In the complete fruit, there are also other flavonoids present: flavonols such as limocitrin and spinacetin, and flavones such as orientin and vitexin. Some flavonoids, such as neohesperidin, naringinand hesperidin, are characteristic of C. Limon fruit. In both the juice and the fruit, there are crucial compounds known as phenolic acids. Ferulic acid and synapic acid, along with their derivatives, are mainly found in the juice. Additionally, the fruit has been confirmed to contain p-hydroxybenzoic acid. In the fruit, coumarin compounds, carboxylic acids, carbohydrates, amino acids, a complex of B vitamins, and, importantly, vitamin C (ascorbic acid) have been confirmed. Another interesting group of compounds is limonoids (highly oxidized secondary metabolites with polycyclic triterpenoid backbones), which are found mainly in the seeds, pulp, and peel. Macroelements in C. Limon fruit pulp and peel are calcium (Ca), magnesium (Mg), phosphorus (P), potassium (K), and sodium (Na). Fatty acids such as behenic acid, erucic acid, gondoic acid, lauric acid, margaric acid, linoleic acid, α-linolenic acid, palmitic acid, palmitoleic acid, pentadecanoic acid, and stearic acid have been identified in C. Limon pulp oil. [15,16]

**Pharmacological activity**

***Antioxidant Activity***

A study for the antioxidant activity of the flavonoid hesperidin and hesperetin from C. Limon—has been proven for their radical scavenging activity and also augmented the antioxidant cellular defenses via the ERK/Nrf2 signaling pathway. [17] Tsou et al. study showed that LUWE(lemon peel ultrasonic assisted water extract), prevented retinal distortion and thinning on the inner and outer nuclei layers of NaIO3-induced retinal degeneration in RPE(retinal pigment epithelium) cells of mice. LUWE suppressed apoptosis associated with proteins like cleaved PARP and cleaved caspase-3 also suppressed the expression of p-MEK-1/2 and p-ERK 1/2 in NaIO3-induced ARPE-19 cell models. Results indicated that via the MEK/ERK pathway, LUWE prevents mitochondrial oxidative stress-mediated RPE damage. [18]

***Anti-Inflammatory Activity***

Multiple in vitro and in vivo investigations have been carried out to assess the efficacy of hesperidin metabolites and their synthetic derivatives in targeting inflammatory markers such as NF-κb, inos, and COX-2, as well as indicators of chronic inflammation. [19] The essential oil from C. Limon (30 or 10 mg/kg p.o.) Exhibited anti-inflammatory effects in mice under formalin test by reducing cell migration, cytokine production, and protein extravasation induced by carrageenan. These effects were also obtained with similar amounts of pure D-limonene, The high concentration of D-limonene in C. Limon essential oil is likely responsible for its anti-inflammatory effect. [20]

***Anti-nociceptive and anti-inflammatory***

Erik et al evaluated the anti-nociceptive and anti-inflammatory effects of d-limonene (LIM - a common monoterpene found in citrus fruits) alone and complexed with hydroxypropyl-β-cyclodextrin (LIM/HPβCD) by the administration of hypertonic saline on the corneal surface, the injection of formalin into the temporomandibular joint (TMJ), or chronic constriction injury of the infraorbital nerve (CCI-IoN) in male Wistar rats and Swiss mice assed by eyes wiping, face rubbing or mechanical hyperalgesia respectively. The results showed a significant reduction in corneal nociception and formalin-induced TMJ nociception, attenuated mechanical hyperalgesia ($p < 0.001$). The study found that there was a decrease in TNF-α levels, along with the downregulation of the NFκB and p38MAPK signaling pathways. There was also a reduction in PKC substrate phosphorylation and PKA immunocontent. [21]

***Anti cataract activity***

D limonene the active compound of C. limon, Praveen Kumar et al investigated the effect of D limonene to inhibit aldose reductase hypoglycemic activity in lens organ culture and its anti-glycating properties in STZ-induced cataracts of rats with diabetes. D-limonene repressed aldose reductase in vitro with IC50 ranges of ~13.9 ± 0.31

mg/mL, also prevented hyperglycemic induced increases in aldose reductase activity, accumulation of sorbitol, altered crystalline proteins (a, b, and c), and opacification of the rat lens in ex-vivo lens organ culture. Supplementation of D limonene in STZ-induced diabetic rats restored these changes and delayed the progression of cataracts. [22]

***Antimicrobial Activity***

Sivamani studied the antibacterial activity of various essential oils in bacterial isolates from conjunctival swabs(Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes, Escherichia coli, Pseudomonas aeruginosa, Micrococcus luteus, Proteus mirabilis) of patients by agar well diffusion method. The chosen essential oils displayed activity against both gram-positive and gram-negative bacterial isolates from ocular infection cases. Active compounds of these oils are principally carvacrol, thymol, citral, eugenol, 1 8 cineole, limonene, pinene, linalool. There, limonene and pinene are the main compound of citrus limon. Eugenol and thymol are the main components of *Syzygium aromaticum*. [23] Additionally, in a separate study, C. Limon essential oil exhibited antibacterial activity against a range of bacteria. This activity was observed against Gram-positive bacteria such as Bacillus subtilis (MIC 2 mg/ml), Staphylococcus capitis (MIC 4 mg/ml), and Micrococcus luteus (MIC 4 mg/ml). Furthermore, the essential oil showed activity against Gram-negative bacteria including Pseudomonas fluorescens (MIC 4 mg/ml) and Escherichia coli (100% inhibition). [24] The C. Limon essential oil exhibits inhibitory activity against Staphylococcus mutans (MIC 4.5 mg/ml) and effectively reduced the adherence of S. Mutans on a glass surface, with adherence inhibition rates (AIR) from 98.3% to 100%, and on a saliva-coated enamel surface, for which the airs were from 54.8% to 79.2%.[25] Mehanna study aimed to develop a new antimicrobial agents ocular limonene-based nanoemulgel to improve the efficacy of fluoroquinolones against *Methicillin-resistant Staphylococcus Aureus* (MRSA) strains which is leading cause of ocular keratitis, through the *in-vitro* antimicrobial susceptibility on biofilm-forming MRSA strain assed by kinetics of killing and biofilm assay and *in-situ* nanoemulgel ocular irritation assessed by HET-CAM test. The results showed that levofloxacin-loaded limonene-based nanoemulsion improved the eradicating efficacy of MRSA biofilm more than the MIC of the loaded nanoemulgel. Its irritation score was zero. [26] Another study confirmed that C. Limon essential oil promoted a 100% reduction in the growth of C.albicans.[27] Moreover, other studies have shown that C. Limon essential oil at a concentration of 0.05% inhibits Herpes simplex replication to the extent of 33.3%. [28]

***Anti-Allergic Effect***

A research experiment was carried out utilizing aqueous extracts from the peel of C. Limon fruits to examine their influence on the histamine release from rat peritoneal exudate cells (pecs). The findings revealed that the extracts effectively inhibited the release of histamine from rat pecs induced by the calcium ionophore A23187. Furthermore, the extracts demonstrated potential in suppressing inflammation in the mice cavity, similar to the effects of the well-known anti-inflammatory drug indomethacin. [29]

**2. Clove (*Syzygium aromaticum, Eugenia caryophyllata, Eugenia aromaticum – Kirambu*)**

Kingdom: Plantae

Phylum: Magnoliophyta

Class: Angiospermae

Category: Malvids

Order: Myrtales

Family: Myrtaceae

Subfamily: Myrtoideae

Genus: Syzygium

Species: aromaticum

Part used: Bud

Taste: Pungent

Potency: Heat

Characteristics: It cures dizziness, vomiting, diarrhea, chronic diarrhea, blood-stained diarrhea, ear diseases, eye diseases like conjunctivitis, cataract (*kan poo*)

**Chemical constituents**

Alma et al. Reported that the clove bud essential oil has 18 components. The main components characterized were eugenol (I, 87%), chavibetal (II, 19.7%), β-caryophyllene (III, 13%), eugenol acetate (IV, 8.01%), trisiloxane1, 1, 1, 5, 5, 5-hexa-methyl-3, 3-bis [(trimethylsilyl) oxy] (V, 1.7%) etc[30]. Fankem et al. Showed the presence of oxygenated monoterpenes (89.06%), monoterpenes (0.04%), sesquiterpenes (10.6%), and linear components (0.03%) in clove bud essential oil and eugenol (I, 87.62%) as major compound.[31] Recent study by Mohamed et al. Reported that monoterpenes were dominant components of clove bud essential oil and the major compound was found to be eugenol (I, 76%). [32] Ereifej et al. also showed the presence of (%) dry matter (83.6), ash (7.8), crude fat (4.3), crude protein (9.3), crude fiber (31.2) and carbohydrate (31) content and presence(mg/100g) of 9 minerals namely magnesium (196.8), calcium (117.5), potassium (111.6), sodium (61.6), manganese (20.9), iron (8.3), phosphorus (1.6), zinc (1.4) and copper (0.4) in cloves. [33]

**Pharmacological activity**

***Antibacterial activity of clove***

Mahmoud et al study showed that Out of the 200 patients with corneal ulcers, The primary predisposing factor for bacterial corneal ulcer was trauma (26.5%), with 96.7% of isolates being multidrug-resistant. S. aureus was the predominant isolate with 33 cases. Analysis of antibiotic susceptibility in bacterial isolates revealed that the fourth-

generation fluoroquinolone, gatifloxacin, exhibited the highest effectiveness, with a sensitivity rate of 81.3%. from seven selected essential oils, Syzygium aromaticum oil(The main constituent was eugenol) exhibited significant activity against all examined bacterial species, displaying the highest sensitivity rate of 97.5% and low MIC values against S. aureus (0.10 µl/ml). [34] Rasha et al. Evaluated in-vitro antimicrobial effects of some essential oils against multidrug-resistant isolates from patients undergoing cataract surgery, In gram-positive coagulase-negative Staphylococci (CoNS) the most common isolate followed by S.aureus, Moraxella spp. the most frequent Gram-negative isolates. Fifteen essential oils showed antibacterial effects against one or more bacterial strains, highest was cinnamon oil, Good antibacterial activity was shown by eugenol oil(*syzygiyum aromaticum*) by disc diffusion method.[35] Zengin and Baysal reported the antimicrobial activity of clove oil against three gram-positive bacteria (Listeria innocua, Carnobacterium divergens, and Staphylococcus aureus) and four gram-negative bacteria (Salmonella typhimurium, Escherichia coli, Serratia liquefaciens, and Shewanella putrefacians) by broth microdilution method. The result showed that clove essential oil inhibited the growth of all bacteria while Shewanella and Listeria were found to be resistant to oil. [36] Hassan et al. tested the antifungal activity of eugenol(active principle of *Syzygium aromaticum*) against C. albicans strains via an experimental model of Candida albicans keratitis in rabbits results showed that 75% of all eugenol-treated eyes recovered from keratitis.[37] Warnke et al, reported the antimicrobial activity of different essential oils including clove bud oil against six Staphylococcus strains including methicillin-resistant Staphylococcus aureus(MRSA), three Candida strains, and four Streptococcus strains by using agar diffusion test. The clove oil showed considerable antimicrobial activity with a diameter of inhibition zone of 12 to 20 mm. [38]

***Anti-inflammatory activity***

Al-Ameedi et al. Conducted a study to assess the anti-inflammatory effects of alcoholic *Syzygium aromaticum* extract (SAE) using the formalin test. Twenty-four (24) mice were divided into four groups for the experiment. T1 and T2 groups were fed 100 and 200 mg /kg (SAE) respectively whereas the T3 group was fed with 0.3 mg/kg of meloxicam and T4 was fed with distilled water. The findings indicated a significant increase in analgesia duration ($p<0.05$) and a decrease ($p<0.05$) in licking numbers in animals exposed to various concentrations of SAE.[39]

***Corneal anesthetic and analgesic activity***

Khalilzadeh's study showed that the Topical application of essential oil of Eugenia caryophyllata (Clove) buds (EOEC), eugenol, and lidocaine significantly decreased corneal sensitivity. Systemic administration of EOEC produced analgesia in acute corneal pain through mechanisms that involved both opioidergic and cholinergic systems. Topical application of EOEC, eugenol, and lidocaine in the rat cornea produced local anesthesia.[40] Rastgarian et al. Studied the effect of eugenol administration as a topical ocular and intraperitoneal route in sodium chloride-induced acute corneal pain in male Wister rats. To measure corneal pain number of eye rubbing was counted for 30 sec after drug administration. Different concentrations showed a significant reduction of acute corneal pain, concentration of 10 in topical ocular and 30 in intraperitoneal showed the best analgesic effect. [41]

***Antioxidant activity***

The high antioxidant activity shown by clove oil was due to the presence of phenolic compounds like eugenol, thymol, and eugenol acetate. [42, 43]

**3. Cow Butter (*Pasu Vennai*)**

Category: Animal product

Characteristics (*Pothu gunam*)

It cures Eye diseases (*kannoi*), Burning sensation of eyes (*kannerichal*), and eye mucus secretion (*peelaisaral*). [12]

**Constituents of butter**

Butter is principally composed of milk fat and moisture. It also contains a small amount of fat, lactose, acids, phospholipids, air, enzymes, and vitamins

**Constituents of butter (per 100 g)**

Fat (82 g), Saturates (52.1g), Monounsaturates (20.9 g), Polyunsaturates (2.8 g), Trans fatty acids (2.9g), Protein (0.6 g), Carbohydrate (0.6 g) Thaimin (Trace), Riboflavin (0.07 mg), Niacin (Trace), Vitamin B6 (Trace) , Vitamin B12 (0.3 µg), Folate (Trace), Pantothenate (0.05 mg), Biotin (0.2 µg), Vitamin C (Trace), Retinol (958 µg), Carotene (608 µg),Vitamin D (0.9 µg), Vitamin E (1.85 mg), Sodium (9 mg) , Potassium (27 mg), Calcium (18 mg), Magnesium (2.0 mg), Phosphorus (23 mg), Iron (Trace), Copper (0.01 mg), Zinc (0.1 mg), Chloride (994 mg), Selenium (Trace), Manganese (Trace), Iodine (38 µg).[44]

**Fatty acids in butter**

The fatty acid composition of butter is important for several reasons. The body and texture of butter are largely determined by the proportion of low and high-melting triglycerides. The significant amount of short-chain fatty acids contributes to butter's quality as a softer fat with a lower melting point. [44] Lipid components of butter can act as a lubricant and help in DED.

Fatty acids composition of butter

- Monounsaturated Fatty Acids: Palmitoleic Acid, Oleic Acid

- Polyunsaturated Fatty Acids: Linoleic Acid, Linolenic Acid

- Saturated Fatty Acids: Butyric Acid, Caproic Acid, Caprylic Acid, Capric Acid, Lauric Acid, Myristic Acid, Palmitic Acid, and Stearic Acid. [44]

**Topical ocular application of butter**

In Ayurvetha Tarpana one of the ocular procedures is the topical application of clarified butter(*ghrita*) and other dosage forms of clarified butter processed with medicinal plants(*ghritakalpas*) which are lipid soluble, indicated for ophthalmic conditions like surface lesions, diseases of adnexa, intraocular and neuro-ophthalmic diseases. [45] Lipid-soluble substances have superior permeability and can easily cross ocular tissues regardless of their molecular size. As a result, they can reach therapeutic concentrations more effectively. *Ghrita kalpas* (dosage forms with clarified butter as a base), the drug is present as small particles kept suspended in a lipid medium by a dispersing agent, particles do not leave the eye as quickly as solutions that increase the tissue contact time. [46]

**Permeation enhancer**

In Ayurveda Freshly prepared butter is kept in a brass vessel and is macerated with powder of the root of Tagara [Valeriana wallichi DC.], where advised to be applied inside the palpebral aperture. The butyric acid in butter along with valeric acid in Valeriana wallichi DC., may have a sedative action on the somatosensory neurons of the eyes to soothe the foreign-body sensation and resultant watering of the eyes. [47] Nidhi Raval et al, formulated a microemulsion (ME) using chitosan (CH) and butter oil (BO) as a permeation enhancer for targeting drug (Triamcinolone acetonide (TA)) to the posterior segment of the eye, via a topical route. In ex vivo diffusion studies using goats' eyes, TA: BO ME (31.33 ± 0.46 and 33.98 ± 0.23) and TA CH ME (24.10 ± 0.41and 27.00 ± 0.18) showed higher percentage of drug diffusion in comparison to TA ME (13.29 ± 0.41and 15.56 ± 0.34) and TA solution (8.20 ± 1.04 and 10.39 ± 0.22) in presence and absence of vitreous humor. In microemulsion distribution studies in posterior segment tissue: in vivo study using Sprague-Dawley rats, results show the highest percentage of release in TA: BO at a 3:7 ratio. An in vitro corneal permeation study using SIRC rabbit corneal cell layer results indicated the significant effect induced by BO and CH in altering permeation. These results were in agreement with ex vivo permeation. This study concluded that BO rich in fatty acids was found to alter drug permeation by altering membrane fluidity. Absorption of ME after topical route was more through corneal, and non-corneal routes, whereas less through systemic routes. [48]

**4. Copper (*Semmbu*)**

**In Siddha literature**

Character (*Pothu gunam*)- It cures liver diseases (*Peeliga noi*), Kapha diseases, uterine diseases (*Soothaga noi*), respiratory diseases (*Thirithoda swasam*), infections (*Kirumi*), and eye diseases (*Kannoi*). Copper cures all 96 eye diseases, in ancient eye surgical procedure tools were made up of copper metal, they also used copper *Kalvam* for grinding eye medications and copper vessels for storing eye medicines. In five elements copper belongs to fire. In the five senses of the human body eye also belongs to the fire element. Hence any *thodam* in the eyes can be cured by fire element drugs like copper. [12]

**Copper in ocular physiology and disease**

***Functions of copper in general cell metabolism***

Cellular respiration in the form of Cytochrome C oxidase, Iron oxidation as a Ceruloplasmin and hephaestin, Melanin synthesis by Tyrosinase, Antioxidant defense through Superoxide dismutase 1, Peptide amidation as Copper amine oxidases Vascular adhesion protein 1, Connective tissue formation as a form of Lysyl oxidase. [49]

***Copper deficiency and ocular diseases***

Copper deficiency is associated with reduced visual acuity and color vision, constricted visual fields, optic atrophy, and retinal nerve fiber thinning. [49] Copper deficiency in rats fed diets with insufficient copper content results in optic nerve demyelination and damaged vacuole-containing myelin. [50]

**Blood retinal barrier**

Similar to the situation in the blood-brain barrier, copper could cross the blood-retinal barrier, as Cu(I) is released from the plasma protein albumin, by ctr1, which is expressed in the RPE, OLM, and OPL.[49] Studies in rabbits have proven that inoculation of copper particles in vitreous humor increases the copper ions of aqueous and vitreous humor. [51]

## CONCLUSION

From this review, the Siddha eye medicine *Pazha kirambu pakkuva vennai*'s ingredients have antioxidant, anti-inflammatory, antibacterial, antimicrobial activities, and anti-allergic effects which are important pharmacological activities for treating eye diseases like conjunctivitis, cataract, dry eye disease etc. This review proves that the medicine's butter-based (lipid soluble) dosage form can enhance the permeability and tissue intake. As per Siddha science and modern science, copper plays an important role in ocular physiology in the act of vision and optic nerve structure. Various study proves that copper could cross the blood-retinal layer and also make changes in aqueous and vitreous humor. So, this review concluded that PKPV can be used for eye diseases, however for more validation further scientific studies like toxicity, pre-clinical (*in vitro, in vivo*), and clinical studies should be carried out.

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