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Original Article

Papaya (Carica papaya) and its Cosmeceutical Applications in Hyperpigmentation: A Comprehensive Review

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ABSTRACT

Hyperpigmentation is a prevalent dermatological condition characterized by excessive melanin synthesis and uneven skin pigmentation, often resulting from ultraviolet (UV) exposure, hormonal changes, inflammation, or injury. Conventional treatments such as hydroquinone, kojic acid, and arbutin are effective but associated with adverse effects including irritation and instability, prompting a shift toward safer, plant-based alternatives. Carica papaya, a tropical fruit rich in phytochemicals, exhibits promising cosmeceutical potential due to its antioxidant, anti-inflammatory, exfoliating, and tyrosinase-inhibiting properties. Key bioactive constituents such as papain, chymopapain, vitamins A, C, and E, flavonoids, phenolic acids, and carotenoids contribute to its depigmenting and skin-renewing effects. Mechanistically, papaya reduces oxidative stress, inhibits melanogenic enzymes (tyrosinase, TRP-1, TRP-2), and promotes epidermal turnover, collectively leading to decreased melanin production and improved skin tone. Both in vitro and in vivo studies support its antioxidant, anti-inflammatory, and antifungal activities, though clinical validation remains limited. Despite its favorable safety profile, challenges persist regarding extract standardization, formulation stability, and dose optimization. Future research should focus on developing standardized, stable papaya-based formulations and conducting well-designed human clinical trials to confirm efficacy and safety. This review highlights Carica papaya as a promising natural cosmeceutical candidate for managing hyperpigmentation and promoting overall skin health.

Keywords: Papaya (Carica papaya), Cosmeceutical Applications, Hyperpigmentation

INTRODUCTION

Hyperpigmentation is a common skin condition characterized by the overproduction of melanin, leading to dark spots or patches on the skin. It affects millions of people worldwide, with a significant impact on quality of life and social stigmatization. Global Prevalence- Hyperpigmentation disorders, such as melasma, post-inflammatory hyperpigmentation (PIH), and solar lentigo, are widespread globally. According to a study published in the Journal of Clinical and Aesthetic Dermatology, the prevalence of melasma is estimated to be around 1.5% to 33% in certain populations [1].

Role of Melanin Synthesis and Melanocyte Biology

Melanin synthesis plays a crucial role in hyperpigmentation. Melanocytes produce melanin, which is then transferred to keratinocytes, resulting in skin pigmentation. Abnormalities in this process can lead to hyperpigmentation [2].

Current Synthetic Agents and Limitations

Common synthetic agents used to treat hyperpigmentation include:

- ✓ Hydroquinone: effective in reducing melanin production, but associated with side effects like skin irritation, ochronosis, and potential carcinogenic effects [3]
- ✓ Kojic Acid: a natural ingredient with skin-lightening properties, but can cause skin irritation and contact dermatitis [4]
- ✓ Arbutin: a plant-derived compound with skin-lightening properties, but its effectiveness and stability are concerns [5]

Rising Interest in Natural and Herbal Cosmeceuticals
With growing awareness of the potential side effects

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of synthetic agents, there is an increasing interest in natural and herbal cosmeceuticals for treating hyperpigmentation. Plant-based ingredients, such as those found in Carica papaya, are being explored for their potential skin-lightening and antioxidant properties [6].

Why Concentrating on Carica Papaya is Justified

Tropical fruit Carica papaya has a long history of use in treating a variety of skin disorders. Its potential as a natural skin-lightening agent is due to its antioxidant and papain content. The advantages of utilizing Carica papaya as a therapeutic option include:

✓ Carica papaya is a sustainable and natural substitute for synthetic chemicals.
✓ Antioxidant Characteristics: Carica papaya's antioxidant qualities can aid in lowering inflammation and oxidative stress in the skin.
✓ Carica papaya's papain content may aid in melanin breakdown and hyperpigmentation reduction, according to its skin-lightening effects [7].

Carica papaya's Botanical Description

The tropical plant known as papaya, or carica papaya, belongs to the family Caricaceae. Its fruit, which is high in nutrients and phytochemicals, is widely grown.

Classification by Taxonomy

Kingdom: Plantae
Family: Caricaceae
Carica is the genus.
Species: C. papaya [8]

Botanical Traits

The tiny, evergreen tree known as carica papaya may reach a height of ten meters. It has just one stalk with a crown of huge, palmate leaves. The plant has tiny, fragrant flowers that are dioecious, which means that it produces separate male and female blooms. The fruit is a sizable, berry-like shape with lots of seeds and a delicious, juicy pulp [9].

Geographical Distribution and Cultivation

Although it originated in Central and South America, the carica papaya is now extensively farmed in tropical and subtropical climates worldwide. India, Brazil, and Mexico are among the leading producers of papayas. Papaya thrives in a hot, humid environment and well-drained soil [10].

Items Employed

The papaya plant is utilized in many ways, such as the following:

1. Fruit pulp is high in potassium, antioxidants, and vitamins A and C.
2. Seeds: utilized for their therapeutic qualities, such as their anti-inflammatory and antiparasitic actions
3. Peel: high in fiber and antioxidants
4. Leaves: Their anti-inflammatory and wound-healing properties have made them a staple of traditional medicine.
5. Latex: includes papain, a proteolytic enzyme utilized in the food and pharmaceutical industries [11]

Abundance of phytochemicals and nutrients

Carica papaya is packed with phytochemicals and nutrients such as:

- Vitamins: A, C, E, and K
- Potassium, magnesium, and manganese are minerals.
- flavonoids, phenolic acids, and carotenoids are examples of antioxidants.
- Phytochemicals include papain, chymopapain, and other proteolytic enzymes [12].

The possible health benefits of Carica papaya, such as its antioxidant, anti-inflammatory, and antimicrobial properties, are due to these phytochemicals and nutrients.

Phytochemical Composition of Carica Papaya-Carica papaya is a great source of phytochemicals, such as carotenoids, phenolics, vitamins, flavonoids, enzymes, and other components. Papaya has the potential for health benefits, such as antioxidant, anti-inflammatory, and antibacterial properties, due to these chemicals.

Major Active Compounds

Enzymes:

1. Papain: a proteolytic enzyme found in the latex of papaya, used for its digestive and anti-inflammatory properties [13]
2. Chymopapain: another proteolytic enzyme found in papaya, used for its digestive and anti-inflammatory effects [14]

Vitamins:

1. Vitamin A: important for vision, immune function, and skin health [15]
2. Vitamin C: a potent antioxidant that supports immune function and collagen production [16]
3. Vitamin E: an antioxidant that protects against cell damage and supports skin health [17]

Phenolics and Flavonoids:

1. Quercetin: a flavonoid with antioxidant and anti-inflammatory properties [18]
2. Kaempferol: a flavonoid with antioxidant and anti-inflammatory effects [19]
3. Caffeic acid: a phenolic compound with antioxidant and anti-inflammatory properties [20]
4. Lycopene: a carotenoid with antioxidant and anti-cancer properties [9]
5. β-carotene: a carotenoid that converts to vitamin A in the body, supporting vision and immune function [10]

Other Constituents:

1. Alkaloids: a class of compounds with potential medicinal properties [11]
2. Saponins: a class of compounds with potential anti-inflammatory and antimicrobial effects [12]
3. Glycosides: a class of compounds with potential medicinal properties [13]

Compound	Source part	Activity
Papain	Latex	Digestive, anti-inflammatory
Chymopapain	Latex	Digestive, anti-inflammatory
Vitamin A	Fruit	Vision, immune function, skin health
Vitamin C	Fruit	Antioxidant, immune function, collagen production
Vitamin E	Fruit	Antioxidant, skin health
Quercetin	Fruit, leaves	Anti-inflamatory, Antioxidant
Kaempferol	Fruit, leaves	Anti-inflamatory, Antioxidant
Caffeic acid	Fruit, leaves	Anti- inflamatory, Antioxidant
Lycopene	Fruit	Antioxidant, anti-cancer
Beta – carotene	Fruit	Vision, immune function
Alkaloids	Various parts	Medicinal property
Saponins	Various parts	Anti-inflammatory, anti-microbial
Glycosides	Various parts	Medicinal property

Pathophysiology of Hyperpigmentation:

Sunlight (UV rays), hormones, stress, or skin injury
↓
Skin cells (keratinocytes) release signals
↓
These signals activate pigment cells (melanocytes)
↓
Melanocytes make more melanin (skin pigment)
└─ Enzymes involved: Tyrosinase, TRP-1, TRP-2
↓
Melanin is packed into melanosomes and sent to skin cells
↓
Too much melanin collects in one area
↓

Dark spots or patches appear → Hyperpigmentation [21]

Mechanism Of Melanin Biosynthesis:

Amino acid L-Tyrosine
↓
(Tyrosinase enzyme acts)
↓
Converted to L-DOPA (3,4-dihydroxyphenylalanine)
↓
(Tyrosinase further oxidizes)
↓
Forms Dopaquinone
↓
Pathway splits:
├── In presence of Cysteine → Forms Pheomelanin (Red-Yellow Pigment)
└── In absence of Cysteine → Forms Eumelanin (Brown-Black Pigment)
↓
Melanin Pigments stored in Melanosomes
↓
Melanosomes transferred to Keratinocytes
↓
Visible Skin Coloration [22]

Role of Tyrosinase, TRP-1, And TRP-2:

- Tyrosinase is the rate-limiting enzyme in melanogenesis. It catalyzes the key initial steps — oxidation of tyrosine to DOPA and DOPA to dopaquinone. Its activity determines the overall rate of melanin synthesis.
- TRP-1 (Tyrosinase-Related Protein-1) functions as a DHICA oxidase, helping in the conversion of 5,6-dihydroxyindole-2-carboxylic acid (DHICA) to indole-5,6-quinone carboxylic acid, contributing to eumelanin polymer formation and stabilization.
- TRP-2 (Tyrosinase-Related Protein-2 or Dopachrome Tautomerase) catalyzes the conversion of dopachrome to DHICA, preventing its spontaneous decarboxylation to DHI and influencing the melanin type and color.
- Together, these enzymes maintain the balance between melanin production and degradation. Overexpression or hyperactivity of these enzymes results in excessive melanin deposition and skin darkening. [23]

Mechanism of Action of Carica Papaya In Hyperpigmentation

1. Active Components Present in Papaya:

Papain, chymopapain, vitamin C, flavonoids, phenolic compounds, β-carotene.

2. Antioxidant Action:

↓ Neutralizes free radicals (ROS)
↓ Reduces oxidative stress that triggers melanocyte activation.

3. Anti-inflammatory Action:

↓ Decreases inflammatory mediators (cytokines, prostaglandins).
↓ Prevents post-inflammatory hyperpigmentation.

4. Tyrosinase Inhibition:

↓ Inhibits tyrosinase, TRP-1, and TRP-2 enzymes.
↓ Slows down conversion of tyrosine → melanin.

5. Exfoliating Effect (Papain Enzyme):

↓ Removes dead and pigmented skin cells.
↓ Enhances cell renewal and brightens skin.

6. Overall Effect:

↓ Decreased melanin production.
↓ Reduced dark spots and even skin tone. [24-26]

Cosmeceutical Formulations Containing Carcica Papaya:

1. Overview of Topical Formulations Containing Carica Papaya

a. Types of Formulations

Creams and Lotions: Papaya fruit extracts are incorporated into oil-in-water emulsions, enhancing skin hydration and providing antioxidant benefits.
Serums: Utilizing papaya enzymes, serums offer targeted delivery of active compounds for skin brightening and exfoliation.
Emulgels: Combining the benefits of gels and emulsions, emulgels with papaya leaf extract provide a non-greasy texture suitable for sensitive skin.

b. Preparation Methods

Extraction: Papaya extracts are obtained using methods like Soxhlet extraction with solvents such as ethanol, ensuring the preservation of bioactive compounds.
Formulation: The extracts are blended into base formulations containing emulsifiers, stabilizers, and preservatives to achieve desired consistency and efficacy.

c. Key Benefits

Antioxidant Protection: Vitamins A, C, and E in papaya combat oxidative stress, preventing premature skin aging.
Exfoliation: Papain enzyme aids in the removal of dead skin cells, promoting a smoother complexion.
Anti-inflammatory Effects: Reduces skin irritation and inflammation, beneficial for conditions like acne.

In Vitro Studies.

1. Antioxidant Activity

Study: Formulation and in-vitro antioxidant analysis of anti-ageing cream of Carica papaya fruit extract
Findings: The 5% cream formulation exhibited significant free radical scavenging activity, suggesting its potential as an anti-ageing agent.

2. Antifungal ActivitY

Study: Antifungal activity of Carica papaya fruit extract against Microsporum canis: in vitro and in vivo study
Findings: The methanolic extract demonstrated potent antifungal activity against M. canis, with a minimum inhibitory concentration (MIC) of 1,000 µg/mL.

3. Cytotoxicity and Anticancer Potential

Study: Chemical characterization and in vitro cytotoxicity on squamous cell carcinoma cells of Carica papaya leaf extracts
Findings: Aqueous and ethanolic extracts of papaya leaves exhibited selective cytotoxicity against human oral squamous cell carcinoma cells, with high levels of phenolic and flavonoid compounds identified.

3. In Vivo Studies

1. Antioxidant activity

Study: Wound healing properties of Carica papaya latex: in vivo evaluation in mice burn model
Findings: Papaya latex formulated in Carbopol gel significantly enhanced wound healing in a burn model, with increased hydroxyproline content and accelerated epithelialization time.

2. Anti-inflammatory effect

Study: Anti-inflammatory and immunomodulatory properties of Carica papaya seeds
Findings: Methanol and aqueous extracts of papaya seeds demonstrated significant anti-inflammatory activity in vivo, supporting their traditional use in treating inflammatory conditions.

3.Anti fungal activity

study: Antifungal activity of Carica papaya fruit extract against Microsporum canis: in vitro and in vivo study
Findings: In vivo application of papaya fruit extract in rats showed improvements in tissue condition, indicating its potential as a natural antifungal agent. [30]

Safety Profile of Carica Papaya

1. General Safety

Ripe papaya is generally considered safe for consumption. Unripe (green) papaya contains the enzyme papain, which may cause esophageal irritation if consumed in large amounts.

2. Papaya Leaf Extract

Short-term use (less than five days) of papaya leaf extract is well-tolerated in adults. Minor gastrointestinal side effects, such as nausea or diarrhea, have been reported. In children (aged 1–12 years), standardized aqueous extracts have been used safely under medical supervision.

3. Papaya Seed Extract

Limited studies suggest that papaya seed extract may have antimicrobial properties. However, more research is needed to fully understand its safety profile

Toxicological Considerations

1. Acute Toxicity

Studies in rats have shown that high doses of papaya leaf extract (up to 5000 mg/kg) do not cause mortality or significant behavioral changes.

2. Chronic Toxicity

Long-term administration (up to 180 days) of papaya leaf extract at doses up to 5000 mg/kg/day did not result in significant adverse effects on body weight, organ weight, or histopathology.

3. Reproductive and Developmental Toxicity

High doses of papaya leaf extract during pregnancy in rats (120 mg/kg) led to complete resorption of fetuses. Moderate doses (60 mg/kg) resulted in fetal abnormalities. Male fertility studies indicated that papaya leaf extract can reduce sperm count and motility at certain doses.

4. Hepattooxicity

Some animal studies have reported changes in liver enzymes, suggesting potential hepatotoxicity at high doses of papaya leaf extract. [31,32]

LIMAITATION AND CHANLLEGES

Limitations and Challenges

➢ Lack of Standardization:

- Different extraction methods (ethanolic, methanolic, aqueous) lead to variable concentrations of active compounds like papain, flavonoids, and phenolics.
- This affects consistency and reproducibility of results across studies.

➢ Limited Clinical Evidence:

- Most available data are from in vitro and in vivo animal studies.
- Human clinical trials evaluating pap depigmenting efficacy and long-term safety are very limited.

➢ Formulation Stability:

- Papaya extracts, especially papain and vitamin C, are prone to oxidation and degradation.
- Maintaining formulation stability and shelf life remains a challenge.

➢ Dose and Safety Concerns:

- High doses of papaya leaf extract have shown potential hepatotoxic and reproductive effects in animal studies.
- Safe concentration ranges for topical and oral applications need further evaluation.

➢ Regulatory Challenges:

- Lack of specific guidelines for herbal cosmeceuticals makes standardization, labeling, and approval difficult.
- Quality control and purity assurance are still major concerns.
- Future Perspectives
- Development of Standardized Extracts: [33-37].

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