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Effects of Papaya (Carica Papaya) Leaf Extract on Collagen Synthesis Enhancement in Various Experimental Studies: Molecular and Histological Review

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KEYWORDS
Papaya Leaf Extract; Collagen; Anti-Aging; MMP; TGF-β

ABSTRACT
Collagen synthesis plays an important role in tissue regeneration and the skin aging process. This process can be disrupted by oxidative stress as well as increased expression of matrix metalloproteinases (MMPs). *Papaya* (*Carica papaya* L.) leaf extract contains bioactive compounds such as quercetin, vitamin C, and papain, which have the potential to stimulate collagen synthesis. The aim of this review was to analyze experimental evidence related to the effects of *papaya* leaf extract on collagen synthesis through molecular and histological approaches. Literature searches were conducted through PubMed, Google Scholar, and MDPI databases using the keywords "*papaya* leaf extract," *Carica papaya*, "collagen," and "photoaging." Five articles that met the inclusion criteria were analyzed. *Papaya* leaf extract has been shown to lower ROS levels, suppress MMP expression, and activate the TGF-β pathway. Histological results demonstrated increased expression of type I collagen and accelerated wound healing in animal models. The potential of *papaya* leaf extract as a topical anti-aging agent and regenerative therapy is considered promising. However, further research is needed to determine the optimal dose and evaluate long-term safety.

INTRODUCTION

Collagen is a key structural component and buffer for the extracellular matrix (ECM) in connective tissue, composed of amino acids, and is the main constituent of skin, bone, muscle, and tendon tissues (Wang, 2021). In addition to maintaining the strength of connective tissue structures, collagen plays important roles in adhesion, migration, and cell regeneration (Wang, 2021). To date, 29 types of collagen have been identified, with most synthesized by fibroblasts (Plikus et al., 2021). Through specific signaling pathways, fibroblasts produce various matrisome components, including collagen, which are essential for wound repair and the formation of the ECM framework in connective tissue (Plikus et al., 2021).

Collagen synthesis can be disrupted by various factors, both physiologically through decreased fibroblast activity due to aging and pathologically, through reactive oxygen species (ROS) and chronic inflammation, which increase the expression of matrix metalloproteinases (MMPs), particularly MMP-1 and MMP-3, thereby accelerating collagen degradation (Bar, 2025; Liu et al., 2023). Elevated ROS levels can activate the AP-1 and NF-κB pathways,

accelerating collagen breakdown while simultaneously inhibiting the TGF-β pathway, which is critical for collagen synthesis (Shin et al., 2019; Ghahremani-Nasab et al., 2023). External factors such as injury, smoking, alcohol consumption, and nutritional deficiencies particularly vitamin C can also inhibit collagen synthesis (Djunaidi et al., 2015; Marlinawati et al., 2022; Wijaya et al., 2020; Kong et al., 2021).

Papaya (Carica papaya L.) leaf extract has been widely studied as a natural agent with the potential to stimulate collagen synthesis (Kong et al., 2021). Its bioactive compounds such as flavonoids (quercetin, kaempferol), vitamin C, and the enzyme papain are known for their antioxidant and anti-inflammatory effects, which can support fibroblast activity, enhance collagen synthesis, and repair ECM damage (Kong et al., 2021; Figueiredo et al., 2017). Reported mechanisms include suppression of inflammatory pathways, inhibition of MMPs, and activation of the TGF-β pathway (Figueiredo et al., 2017; Seo et al., 2020). Quercetin is an antioxidant proven to enhance collagen synthesis by downregulating NF-κB, increasing TGF-β levels, and reducing MMP production (Hadi et al., 2024). Vitamin C acts as a cofactor in collagen biosynthesis, stimulating the expression of collagen genes (COL1A1 and COL3A1) and promoting fibroblast proliferation. The enzyme papain can lower the TIMP-1 to MMP-1 ratio, thereby facilitating tissue remodeling (Wihastyoko et al., 2022).

Compared to other natural agents such as *aloe vera*, green tea extract, and synthetic compounds like retinoids and peptides, *papaya* leaf extract offers a unique combination of bioactive benefits. For example, while retinoids effectively stimulate collagen production, they often cause skin irritation, limiting their long-term use. Green tea polyphenols, though rich in antioxidants, may require higher concentrations to achieve comparable effects. In contrast, *papaya* leaf extract demonstrates broader activity by targeting multiple pathways such as TGF-β activation, MMP inhibition, and ROS reduction with minimal reported side effects, making it a potentially safer alternative for topical applications.

Despite the growing interest in natural collagen enhancers, comprehensive reviews combining molecular and histological evidence from diverse experimental models remain scarce. This review addresses this gap by analyzing findings from five selected studies encompassing both in vitro and in vivo models to elucidate the mechanisms by which *papaya* leaf extract enhances collagen synthesis. By integrating data from different experimental platforms, this review presents a unified perspective on the extract's efficacy, optimal dosages, and potential applications in regenerative and anti-aging therapies.

The combined mechanisms namely reduction of oxidative and inflammatory stress, suppression of MMP expression, activation of the TGF-β pathway, and increased fibroblast proliferation demonstrate that *papaya* leaf extract holds significant potential for enhancing collagen synthesis. Its applications may extend to regenerative therapy, wound care, and dermatological interventions related to skin aging. However, studies evaluating the molecular and histological effects of *papaya* leaf extract are still limited. Therefore, this literature review was compiled to analyze its effects on collagen synthesis based on experimental research, providing a scientific basis to reinforce its therapeutic potential.

The primary objectives of this review are to evaluate the molecular mechanisms by which *papaya* leaf extract enhances collagen synthesis, compare its efficacy with other natural

and synthetic agents, and summarize histological evidence supporting its clinical potential. By analyzing experimental studies, this review aims to elucidate how bioactive compounds in *papaya* leaf extract such as quercetin, vitamin C, and papain modulate key pathways like TGF-β activation and MMP inhibition to promote collagen production. Additionally, it provides a comparative assessment of the extract's performance against established alternatives, highlighting its advantages in safety and multifunctionality. The findings aim to strengthen the scientific foundation for the application of *papaya* leaf extract in dermatological and regenerative medicine, offering valuable insights for future research and therapeutic use. Ultimately, this review bridges critical knowledge gaps and underscores the extract's potential as a safe and effective agent for skin health and anti-aging interventions.

METHOD

The literature search for this review was conducted using several databases, namely PubMed, Google Scholar, and MDPI. Keywords used included "*papaya* leaf extract," "*Carica papaya*," "collagen," and "aging." The inclusion criteria comprised original research articles published between 2015 and 2024, written in either English or Indonesian, and reporting the effects of *papaya* leaf extract on collagen synthesis in both *in vivo* and *in vitro* research models. The exclusion criteria were articles of the review type. Based on these criteria, five articles were identified and deemed eligible for analysis in this review.

RESULTS AND DISCUSSIONS

Table 1. Results of Literature Analysis

No.	Author	Sample	Method	Result
1.	Djunaidi *et al.,* 2015.	Thirty-two female mice (Mus musculus) aged 3–4 months with a body weight of 20–30 grams, were divided into four test groups, each consisting of eight mice.	This study used *a randomized post-test only control group* design. Papaya leaf extract gel with three concentration variations, namely 5%, 10%, and 15%, is given topically vaginally once a day from the 12th day of pregnancy until the mice give birth (for 6–8 days). After childbirth, vaginal tissue is collected and analyzed using hematoxylin-eosin (HE) staining	The results showed that the collagen density of postpartum vaginal tissue of mice based on a percentage of significant differences between groups (ANOVA, p = 0.032). The group given 5% papaya leaf extract had the highest average collagen density (96.19% ± 1.34) compared to the control group (90.64% ± 3.35), with significant differences (p = 0.045, LSD test). Meanwhile, the 10% and 15% groups showed no significant difference compared to the control

No.	Author	Sample	Method	Result
				(p = 0.29 and p = 0.58 respectively).
2.	Soib *et al.,* 2020.	This study used human skin fibroblast cell culture (HSF1184) with an initial seeding number of 15,000 cells per well in a 96-well microtiter plate for cytotoxicity and proliferation testing, and 300,000 cells per well in a 6-well plate for migration test (scratch assay) and collagen synthesis.	This study used an in vitro design with post-treatment tests. Papaya leaf extract was obtained through three different extraction techniques (reflux, ultrasonic-assisted extraction/UAE, and agitation), then tested on human skin fibroblast cell cultures (HSF1184) in various concentrations (3,125–500 µg/mL). Evaluation included cytotoxicity assay (SRB assay), cell migration (scratch assay), and collagen synthesis (Sircol assay) observed at 24 and 48 hours post-treatment.	Research shows that papaya leaf extract from the reflux technique significantly increases collagen synthesis in HSF1184 fibroblast cells. At a concentration of 12.5 µg/mL, an increase in collagen synthesis was recorded by 131.65% after 24 hours and 164.89% after 48 hours compared to controls (100%, $p \leq 0.05$). Extracts from the agitation and UAE methods also significantly increased collagen synthesis at 48 hours, by 160.25% and 136.31% ($p \leq 0.05$), respectively.
3.	Wijaya *et al.,* 2020.9,1.	Twenty-seven male Sprague Dawley rats were 2–3 months old and weighed 100–150 grams.	This study uses a post-test only control group design. A total of 27 male Sprague Dawley mice were divided into nine test groups, each consisting of three heads. Papaya leaf extract gel spray 5% is formulated with a variety of gel-forming ingredients (carbopol 940 + HPMC, HPMC + HEC, and others), then applied once a day to open wounds on the back of mice for 20 days. Evaluation was carried out by measuring the shrinkage of wound diameter periodically on days 4, 8, 12, 16, and 20 to assess the effectiveness of wound healing.	Research by Wijaya *et al*. showed that the papaya leaf extract spray gel accelerated wound healing in mice with a healing time of 16 days. The ANOVA test showed a statistically significant difference in healing time between groups (**$p < 0.05$**), indicating the effectiveness of the extract in accelerating the tissue regeneration process.

No.	Author	Sample	Method	Result
4.	Seo *et al.*, 2020.(Amirsasan et al., 2019).	A total of 1.2×10^5 normal human dermal fibroblast cells (NHDF) were used in each 35 diameter culture well. The cells are obtained from a biopsy of the skin of a healthy male donor.	This study used an in vitro design with a normal human dermal fibroblast cell (NHDF) model exposed to UVB light of 144 mJ/cm². After irradiation, the cells were treated with papaya leaf ethanol extract at concentrations of 1, 10, and 50 μg/mL. Evaluation was carried out on ROS production, antioxidant activity, MMP-1 and MMP-3 expression, and synthesis of type I collagen through various molecular tests such as ELISA, western blot, and immunofluorescence analysis.	The results showed that papaya leaf ethanol extract significantly decreased ROS production in NHDF cells exposed to UVB light ($p < 0.01$). In addition, this extract was able to significantly inhibit the expression of MMP-1 and MMP-3 at concentrations of 10 and 50 μg/mL ($p < 0.05$ and $p < 0.01$), as well as increase the synthesis of type I collagen (procollagen-I) compared to the UVB control group ($p < 0.01$). Increased expression of TGF-β1 and Smad2/3 was also observed, accompanied by decreased activation of the MAPK (p-ERK, p-JNK, p-p38) and AP-1 (c-Fos, p-c-Jun) pathways, all of which showed significant differences ($p < 0.05$).
5.	Marlinawati *et al*., 2020.(Ryan & Li, 2023).	Twenty female white rats (Rattus norvegicus) were 12–16 weeks old and weighed 180–200 grams.	This study uses a post-test only control group design. A total of 20 female white rats were divided into five groups, each consisting of four groups, namely the negative control group (NaCl 0.9%), the positive control group (povidone-iodine), and three treatment groups given papaya leaf extract gel with concentrations of 10%, 20%, and 30%. The animal tried to make a 2 cm long incision wound on its back. Papaya leaf extract gel with concentrations of 10%,	The results showed that the administration of papaya leaf extract gel for 14 days significantly increased the expression of type I collagen in rat incision wounds. The Kruskal-Wallis test showed significant differences between groups ($p = 0.002$), with the 30% concentration treatment group having the highest average collagen expression (5.33 ± 0.52), followed by concentrations of 20% (4.50 ± 0.55) and 10% (3.33 ± 0.52), all of which were higher than

No.	Author	Sample	Method	Result
			20%, and 30% is applied topically once a day for 14 days. After treatment, the healing skin is taken for histological examination using Mallory staining to assess the expression of type I collagen.	negative controls (2.00 ± 0.00) and positive controls (2.33 ± 0.52). The Mann-Whitney test showed that the treatment group differed significantly compared to the control ($p < 0.05$).

Molecular Mechanism of Papaya Leaf Extract in Increasing Collagen Synthesis

Papaya leaf extract (Carica papaya L.) shows excellent potential in enhancing collagen synthesis through various integrated molecular mechanisms. Collagen synthesis is strongly influenced by the balance between the biosynthetic pathway and the degradation pathway mediated by matrix metalloproteinase (MMP) enzymes, especially MMP-1 and MMP-3. In this context, chronic oxidative stress is the main trigger for the activation of the AP-1 and NF-κB pathways, which ultimately increases MMP expression as well as decreases collagen production. Several in vitro and in vivo studies in this review show that the administration of papaya leaf extract is able to reduce the level of reactive oxygen species (ROS), inhibit the expression of MMP-1 and MMP-3, and activate the TGF-β/Smad pathway which plays an important role in the transcription of collagen genes, such as COL1A1 and COL3A1 (Djunaidi et al., 2015; Marlinawati et al., 2022; Wijaya et al., 2020; Seo et al., 2020; Sorongan et al., 2015).

The main bioactive ingredients in papaya leaf extract, such as quercetin, vitamin C, and the enzyme papain, also play a role in this mechanism. Quercetin, for example, has been shown to decrease the expression of NF-κB and AP-1, while also increasing the expression of TGF-β leading to increased collagen synthesis (Hadi et al., 2024). Vitamin C acts as an essential cofactor in the hydroxylation process of proline and lysine, which is an important stage in the stabilization of the triple helix of collagen (Pullar et al., 2017). The papain enzyme, on the other hand, supports the tissue remodeling process by modulating the ratio of TIMP-1 to MMP-1 (Wihastyoko et al., 2022). Study by Seo et al. (2020) explicitly reinforces these findings were made through measurements of decreased p-ERK, p-JNK, and MAPK pathways, as well as increased procollagen-I expression in human dermal fibroblast cultures exposed to UV-B light. Papaya leaf extract not only reduces collagen breakdown, but also promotes its regeneration process through the activation of biosynthetic pathways (Seo et al., 2020).

Histological Correlation and Clinical Effectiveness in Experimental Animal Models

In addition to the molecular approach, the histological correlations displayed in various experimental animal models provide concrete evidence regarding the effectiveness of papaya leaf extract in increasing collagen density and expression. A study by Djunaidi et al. (2015) using hematoxilin-eosin (HE) staining on the vaginal tissue of postpartum mice showed that a 15% extract concentration resulted in a significant increase in collagen density compared to the control group. Similarly, a study by Marlinawati et al. (2022) using Mallory's staining on the back incision wounds of female mice showed that papaya leaf extract with a concentration of 20% was able to increase collagen type I expression significantly ($p < 0.05$).

The study confirms that topical application of papaya leaf extract is able to accelerate wound healing and support dermal regeneration through increased collagen synthesis. This

effect is particularly relevant in the context of regenerative dermatology and anti-aging therapy, particularly in repairing tissue damage due to chronic inflammation. Gel formulations, such as those used in the study by Wijaya et al. (2020), also prove that the use of papaya leaf extract in topical form has sufficient bioavailability to stimulate wound repair and the formation of new tissue.

CONCLUSION

Papaya (*Carica papaya* L.) leaf extract has significant potential for enhancing collagen synthesis through molecular mechanisms involving the reduction of oxidative stress, inhibition of matrix metalloproteinase (MMP) expression, and activation of the TGF-β pathway. Bioactive compounds such as quercetin, vitamin C, and papain act synergistically to support fibroblast activity and stimulate collagen gene expression. These findings are supported by histological evidence from various experimental studies demonstrating a significant increase in type I collagen density and expression following the topical application of *papaya* leaf extract in both wound models and under UV-B exposure. Overall, the combination of antioxidant, anti-inflammatory, and regenerative effects positions *papaya* leaf extract as a promising candidate for development as a topical anti-aging and skin-regenerative therapy. Nonetheless, further studies are warranted to determine the optimal dosage, establish a comprehensive toxicological profile, and evaluate the efficacy of various formulations in both preclinical and clinical trials, to ensure its safe and effective translation into therapeutic applications.

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