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Literature Review

Chitosan Gingival Mask Based on Guava Leaf Extract to Prevent Smoker's Melanosis

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ABSTRACT

Introduction: Smoker's melanosis is a common periodontal condition characterized by gingival hyperpigmentation due to excessive tyrosinase activity, which affects aesthetics. Guava leaves contain flavonoids, vitamin C, and coumarin, which have been shown to inhibit pigmentation in the skin and hair. Mucoadhesive films made from chitosan shrimp shell waste are biodegradable and have been proven to be effective as drug delivery systems. This literature review aims to establish a theoretical foundation for the potential combination of guava leaf extract and shrimp waste chitosan as a gingival mask for preventing smoker's melanosis. Literature was systematically compiled from Scopus, ScienceDirect, PubMed, and SAGE, from 2014 to 2024. Inclusion and exclusion criteria were used to formulate a theoretical foundation.

Review: The literature shows that flavonoids in guava leaves inhibit ORAI1 calcium channels, vitamin C blocks copper ion bonds, and coumarin prevents the formation of ROS. These mechanisms play crucial roles in inhibiting tyrosinase. Chitosan Mucoadhesive patches with vitamin C solvent enhance the biocompatibility and effectiveness of active substance delivery.

Conclusion: The chitosan–guava leaf gingival mask holds potential for preventing smoker's melanosis through targeted tyrosinase inhibition. Further research is required to optimize the potential of combining guava leaf extract and shrimp waste chitosan for use as a gingival mask.

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INTRODUCTION

The World Health Organization stated that the prevalence of smokers worldwide is 1.3 billion. This shows the possibility of a high incidence of smoker's melanosis. Dark gingiva due to smoker's melanosis leads to reduced confidence. Commonly used treatment techniques are scalpel (gingivectomy), laser, and vitamin C injection. These techniques generally cause bleeding and create wounds that require time to heal.[1]

Polyphenols in Guava leaf extract provide antioxidant biocompatible effects and antibacterial activity that promote contraction, epithelialization, angiogenesis, and fibroblast proliferation, making it effective in promoting wound healing.[2] Guava is a plant of the Myrtaceae family that is widely cultivated in tropical regions. Other guava leaf components, including vitamin C, coumarin, sesquiterpene, triterpenoids, alkaloids, and tannins, possess tyrosinase inhibitory enzyme activity. The combination of vitamin C with chitosan successfully releases active substances in a controlled manner.[3,4,5]

Chitosan is a natural polymer derived from chitin that has been deacetylated. Chitosan is derived from various sources, including shrimp shells. The use of shrimp shells for waste utilization can reduce environmental pollution. Processing shrimp shell waste into chitosan produces eco-friendly natural polymers because the molecules are similar to the environment, therefore they are easily degraded and not toxic. One of the properties of chitosan that has been widely applied in research is its mucoadhesiveness. Its ability is utilized for drug delivery in the oral mucosal area. This review aims to explore the potential of chitosan as a carrier of guava active substances in the form of a gingival mask as a method of preventing smoker's melanosis.[6,7]

REVIEW

Literature searches were conducted by searching for articles/journals in the Scopus, Science Direct, SAGE, and PubMed databases. The literature review was conducted from August to November 2024. The keywords used in the search were "Gingiva and Smoker Melanosis", "Gingiva and Guava Leaf", "Guava Leaf and Tyrosinase Inhibitor", and "Mucoadhesive Chitosan and Gingiva". The inclusion criteria for this literature review were (1) English articles/journals, (2) published between 2014 and 2024, and (3) full text. The exclusion criteria were literature that did not include review articles and books. All literature that met the selection criteria was retrieved. Articles that were irrelevant or based on opinions without evidence were excluded.

The literature search and filter descriptions are explained in detail in the flowchart (Figure 1). A literature search using the keywords "Gingiva and Smokers Melanosis", "Gingiva and Guava leaf", "Guava leaf and Tyrosinase Inhibitor", and "Mucoadhesive Chitosan and Gingiva" produced 565 articles with details of 21 from PubMed, 45 from Scopus, 96 from SAGE, and 403 from ScienceDirect. There were 362 articles that fit the inclusion criteria of full text, English, and the last 10 years of publication. After filtering out review articles, books, and other sources unrelated to research, 141 articles were obtained. Of the 141 results obtained, 50 articles were filtered by reading the entire text.

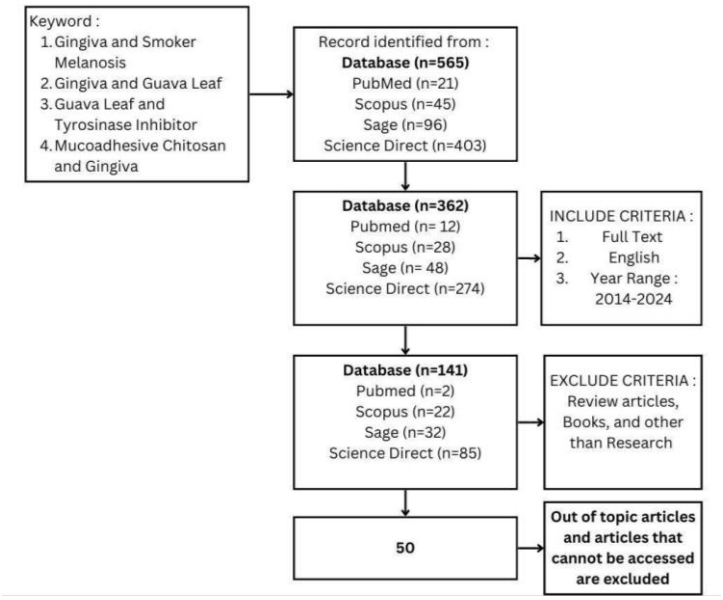

Figure 1. Flowchart of literature search in the database

Smoker's melanosis is a pigmented lesion caused by tyrosinase enzyme activity that initiates excess melanin production. Melanocyte activity protects the oral mucosa against tobacco substances in cigarettes, namely polycyclic amines (nicotine and benzopyrene). This process occurs when the enzyme tyrosinase converts the amino acid tyrosine into a molecule called dihydroxyphenylalanine (DOPA). DOPA serves as a substrate and intermediate in melanogenesis. In the melanogenic pathway, DOPA is oxidized by tyrosinase to dopaquinone, which results in the final formation of dark melanin (eumelanin). Eumelanin is transmitted through melanosomes to keratin in the epidermis. This process results in the visible melanin color on the tissur surface.

The most common impact is reduced self-confidence due to the dark gingival color. Common treatment techniques for gingival hyperpigmentation include the use of scalpels (gingivectomy), laser, and vitamin C injection. However, the currently used treatment techniques cause bleeding and pain, which affects the time required for wound healing and pain relief. On the other hand, these treatments depend on the economy of the individual.[8,9,10]

Guava (*Psidium guava*) is a tropical plant of the Myrtaceae family with the genus Psidium, order Magnoliopsida, class Streptophyta, division Viridiplantae, and kingdom Eukaryota. Guava originated in South America and migrated to other tropical and subtropical regions. Now, guava is widely cultivated throughout Indonesia.[4,11]

Ten studies have explained the potential of guava leaves in preventing pigmentation caused by the enzyme tyrosinase. Guava leaves' content, such as flavonoids, coumarins, and vitamin C, can inhibit tyrosinase enzymes.[12,13] Vitamin C, as a tyrosinase inhibitor, has been used as a treatment for reducing gingival pigmentation. Vitamin C causes a deficiency of ROS (reactive oxygen species), calcium, and copper, which inhibits melanin formation. Vitamin C has antioxidant effects and efficiently depigments skin and gingival tissue. Vitamin C injection has been administered, with the

best results obtained after four treatments, as evidenced by the improvement in tissue color.[14]

In addition to vitamin C, the high flavonoid and antioxidant content of guava leaves fights the main factor of skin damage, namely free radicals. Flavonoids have a docking mechanism with the active side of copper ions, inhibiting the enzyme tyrosinase, which is involved in pigmentation. Active compounds of guava leaf can inhibit ORAI1 Channel and tyrosinase with an activating effect on UV-induced melanogenesis through inhibition of IORAI1 in ORAI1-transfected HEK293T.[15,16,17] Coumarin inhibits cellular tyrosinase activity in B16F10 cells and zebrafish models without toxicity effects.[10]

Research has been conducted on the preparation of guava leaf extract as a tyrosinase inhibitor. Guava leaf showed the best tyrosinase inhibitor effect among bell fruits and green tea, and was 17 times better than the control, kojic acid, with an IC50 value of 205.41 µg/mL.[18] Guava leaf is able to reduce the production of H_2O_2, which induces intracellular ROS production, which plays a role in increasing the regulation of tyrosinase enzymes. This effect inhibited the formation of H2O2-induced ROS by up to 28.36 ± 3.14%. Guava leaf was extracted using a 70% ethanol solution, stirred for 4 hours, and subjected to 5800 × g centrifugation for 10 minutes.[19] N-butanol and hexane in guava leaf are potent towards tyrosinase inhibitory activity (59.8% ± 1.30% and 59.5% ± 3.84%).[17]

In terms of solubility in 70% ethanol, guava leaf extract exhibited higher tyrosinase inhibitory activity than the control variable, kojic acid, at 12.7%. This effect is thought to be due to the presence of 1-octadecene in the extract.[20]Antioxidants contained in guava leaf extract silver nanoparticles have the potential to fight melanin-induced hyperpigmentation and decolorization of the skin. Guava leaf extract, as a potent tyrosinase inhibitor, is made into nanoparticle-encapsulated products as an anti-tyrosinase.[21] Oil microemulsion prepared from guava leaf extract potently inhibited the action of the tyrosinase enzyme.[22]

Two studies have shown the use of guava leaves in dentistry. The utilization of guava leaf extract on the oral mucosa that has been studied is an anti-plaque mouthwash, antibacterial agent, and anti-inflammatory agent against *Streptococcus mutans, Streptococcus oralis, and Lactobacillus casei*. The essential oils, pinene, avicularin, and polyphenols in guava leaves support antibacterial activity.[23,24] Guava leaf extract is an inexpensive and readily available natural resource.

Chitosan is a biopolymer derived from deacetylated chitin found in crustacean exoskeletons, insect cuticles, algae, and fungal cell walls.[25] Chitosan is degradable and non- toxic. Chitosan (C6H11NO4) is a glycosaminoglycan comprising glucosamine and N-acetylglucosamine. The presence of hydroxyl and N-acetyl groups, which easily react in chitosan, produces intra- and intermolecular hydrogen bonds, which eventually form crystalline clumps. These characteristics make chitosan a widely used material. The structure and composition of chitosan depend on the deacetylation process used.

Shrimp shell waste is the primary source of chitosan. The accumulation of this waste results in environmental damage, such as an increase in the number of mosquitoes, the production of toxic nitrogen oxides, and the spread of diseases that endanger humans. Using shrimp shell waste as a source of chitosan reduces the side effects of waste.[6]

Chitosan is biodegradable and biocompatible. Chitosan is able to adhere to the gingival mucosa and has the potential to be used in drug

delivery.[26,27] The insoluble and acid- soluble nature of chitosan has the potential to become films, gels, and nanoparticles.

Ten studies have formulated and conducted experiments with chitosan and other ingredients. In a study of a fast-disintegrating dosage form (film and tablet), chitosan mixed with thiol showed strong adhesion to the mucosa.[28,29] A chitosan-coated liposome formulation with a chitosan-maleimide mixture showed better adhesion than thiolated chitosan.[30] In addition, other studies showed that sodium alginate, hydroxyl propyl methyl cellulose, polydopamine, anionic polymer, and polyacrylic acid improved mucoadhesion.[31,32,33,34,35] The mixture of glutaraldehyde with chitosan also stabilizes the structure of the resulting film.[36] Based on all these studies, it is known that chitosan cannot stand alone to provide a strong attachment to the oral mucosa.[31,32] The viscosity of the product will increase if chitosan is the only main ingredient.[32] The strength of the product decreases if the ratio of chitosan is higher than that of other ingredients.[31] Based on these research data, the higher the concentration of chitosan, the thicker the preparation and the lower the strength.

Studies show that a chitosan mucoadhesive membrane with active substances can penetrate the sublingual mucosa.[13] In the in vivo test of rat gingiva, mucoadhesive patches made from 15% chitosan with rambutan peel extract as the active ingredient showed a reaction in the form of a decrease in neutrophils.[27] Both studies show the ability of patches or sheets made from chitosan to deliver active substances. Mucoadhesive materials, such as patches, can deliver active substances in a controlled manner for 30 minutes.[13,27] Based on its material and preparation, chitosan can serve as a carrier and conductor of active substances.

Although chitosan has potential as a drug delivery medium, it has some disadvantages. Salivary flow and mechanical factors can degrade it, change its strength and attachment, and affect the swelling index. The addition of other ingredients in the preparation of chitosan patches can reduce the swelling index.[30,27] In addition, chitosan is always used with acid as a solvent that produces an unpleasant taste and smell.[19]

One study conducted a clinical trial on the use of oral patches on buccal, lingual, and gingival mucosa. The oral patch exhibited the longest attachment time in the gingiva. The majority of volunteers in the clinical trial were not bothered by the oral patch on the gingiva (Figure 2).[39]

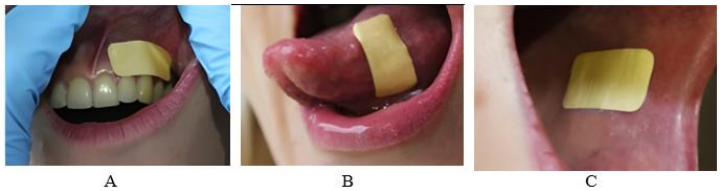

Figure 2. Oral patches applied to the gingival (A), lingual (B), and buccal (C) surfaces in the in vivo test.[39]

Guava leaf extract contains active substances, such as flavonoids, coumarins, and vitamin C, which can inhibit pigmentation. Vitamin C injections have previously been used to reduce gingival hyperpigmentation. In addition, guava leaf extract has been used in research on skin and hair pigmentation.[17] Based on this, guava leaf extract has the potential to be used as an active substance in prevention. The tyrosinase inhibitor from guava leaf extract inhibits melanin, thus preventing

pigmentation in smoker's melanosis. However, to minimize the invasiveness of the injection method, another medium is needed as a carrier for guava leaf extract on the gingiva.

Chitosan mucoadhesive patches are oral drug delivery systems that can be used on the gingiva. Chitosan polymer forms a polymer-mucin interaction and binds with the oral mucosa through ionic interaction. The naturally non-toxic chitosan, with a pH that matches the oral cavity, has the potential to serve as an oral drug delivery medium.[30]

Guava leaf's extract is mixed into mucoadhesive patches through the solving casting method. The method involves dissolving chitosan, guava leaf extract, and other supporting materials to form a solution. The solution was then heated until dry and molded to the specified size. To create a gingival mask, layers can be molded according to the size of the gingiva. The guava leaf extract gingival mask is expected to cover the gingiva so that the distribution of active substances from the extract is thorough.

The use of biodegradable chitosan can reduce environmental damage caused by shrimp shell waste. Chitosan gingival mask has biocompatibility and drug delivery capabilities. Guava leaf's extract gingival mask is expected to prevent smoker's melanosis. The potential of the gingival mask chitosan with guava leaf extract is shown in Figure 3. Further research is needed to optimize the potential of guava leaf extract and chitosan from shrimp waste as a gingival mask.

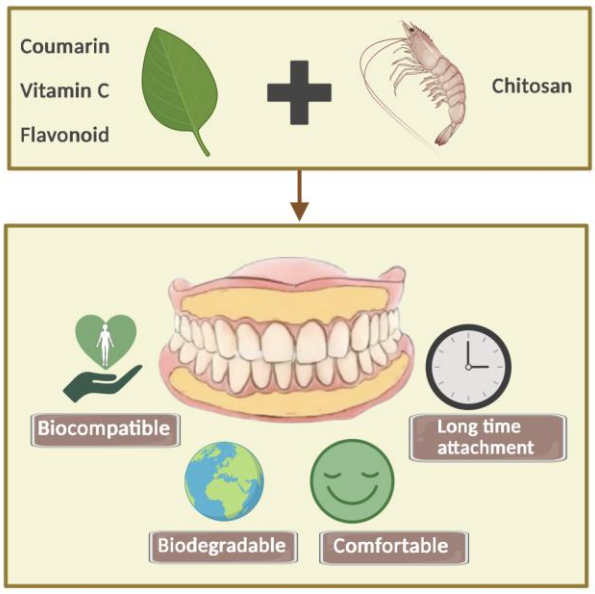

Figure 3. The potential of a chitosan gingival mucoadhesive mask with guava leaf extract

CONCLUSION

This review indicates that the integration of guava leaf extract and chitosan derived from shrimp shell waste into a mucoadhesive gingival mask contributes to oral cavity aesthetics through a promising non-invasive approach to prevent smoker's melanosis. Flavonoids, coumarins, and vitamin C in guava leaves act synergistically to inhibit tyrosinase activity, thereby reducing melanin synthesis in gingival tissue. The biodegradability, biocompatibility, and mucoadhesive properties of chitosan enable the effective delivery of active compounds. This combination also addresses ecological needs by utilizing shrimp shell and guava

leaf waste. Thus, by combining clinical aspects with environmentally friendly materials, this innovation offers a sustainable approach to enhance oral cavity aesthetics.

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