PSIDIUM GUAJAVA: QUERCETIN USE IN THE TREATMENT OF PERIODONTITIS

Nisha Kumari[1*], Sonia[3], Rajdeep Kaur[1], Shalini Vashisht[1], Kirti Kaushal[1], Vandana[2], Swati Thakur[2]

[1] IEC School of Pharmacy, IEC University, Baddi, Solan H.P, 174103, India
[2] Abhilashi College of Pharmacy, Nerchowk, Mandi H.P, 175008 India
[3] National Institute of Pharmaceutical Education and Research (NIPER), Mohali, Panjab, 160062, India

***Corresponding author:**
Nisha Kumari
Assistant Professor
IEC School of Pharmacy, IEC University
Baddi, Solan H.P 174103, India
E-mail: nishamnd92@gmail.com
Ph. 8988261885

Abstract:

Guava is native to the American tropical. The anme guava most is drived from the Haitian name Guajaba. Plant for hundreds of years has been used to decorate health and for medicinal purposes. Psidium guajava (Family Myrtaceae) has an extensive wealth of medicinal value. Guava due to its anti-inflammatory action can inhibit iNOS, COX-2, NF-kβ it could be a valuable agent in treating periodontal disease. Quercetin is the main constituent present in guava and has shown excellent against some periodontal pathogens. This review paper explains the pharmacological use of guava leaves in the treatment of Periodontitis.

Keywords: *Psidium guajava, Periodontitis, Quercetin, Antibacterial, Pharmacological use.*

INTRODUCTION

Periodontal is a common but fairly preventable ailment. Periodontal disease is a serious infection caused by poor oral hygiene. Microorganisms present in dental plaque trigger periodontitis. A direct relationship exists between dental plaque and the development of periodontitis. (1)

According to the Global Burden of Disease study (2016), severe periodontal disease was the 11th most prevalent disease. Periodontal disease is stated to range from 20% to 50% around the world. It is one of the primary causes of enamel loss which can compromise mastication, esthetic & self confidence. Globally periodontal diseases accounted for 3.5 million years lived with incapacity in 2016. During the length of 1990 to 2010, there was a 57.3% expansion in the international burden of periodontal disease. In 2010 international loss of productiveness due to severe periodontitis is used to be estimated to US$54 billion per year. The world prevalence of periodontal disorder is expected to enlarge in the coming years due to the growth in the aging populace. (2)

India represents 17.31% of the World's Population which means that out of six people on this planet lives in India. There are lots of disparities in India in terms of ratios, one of which is the area of oral health. The dentist-to-population ratio in the Rural Areas is dismally low with less than 2% dentists being available for 72% of the rural population. Statistics present the grim reality that 95% old of the population in India goes through periodontal disease. Solely 50% use a toothbrush and just 2% go to the dentist. 23,690 undergraduate and 1,138 postgraduate college students are skilled in 291 dental colleges in India. (3)

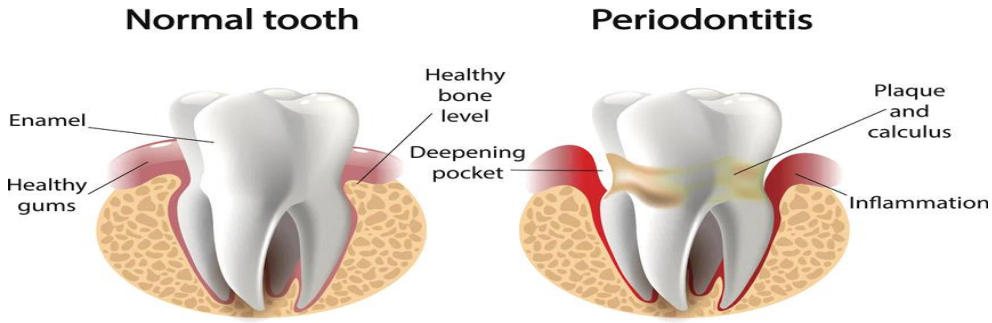


Figure 1: Comparision between Normal tooth and periodontitis

PATHOGENESIS

Periodontium is a complex of tissues with blood vessels, nerves, and bundles of fibers. It has the potential to regenerate and remodel throughout life. The proper functioning of the periodontium is only through the structural integrity and interaction between its components. The main function of the periodontium is to join the tooth to the bone tissue and maintain integrity on the surface of the masticatory mucosa of the oral cavity. [22] Presence of Homeostasis is indicated between periodontal host and microbe. Studies uncovered the novel mechanisms underlying the breakdown of periodontal host-microbe homeostasis, which can precipitate dysbiosis and periodontitis in susceptible hosts. [24]

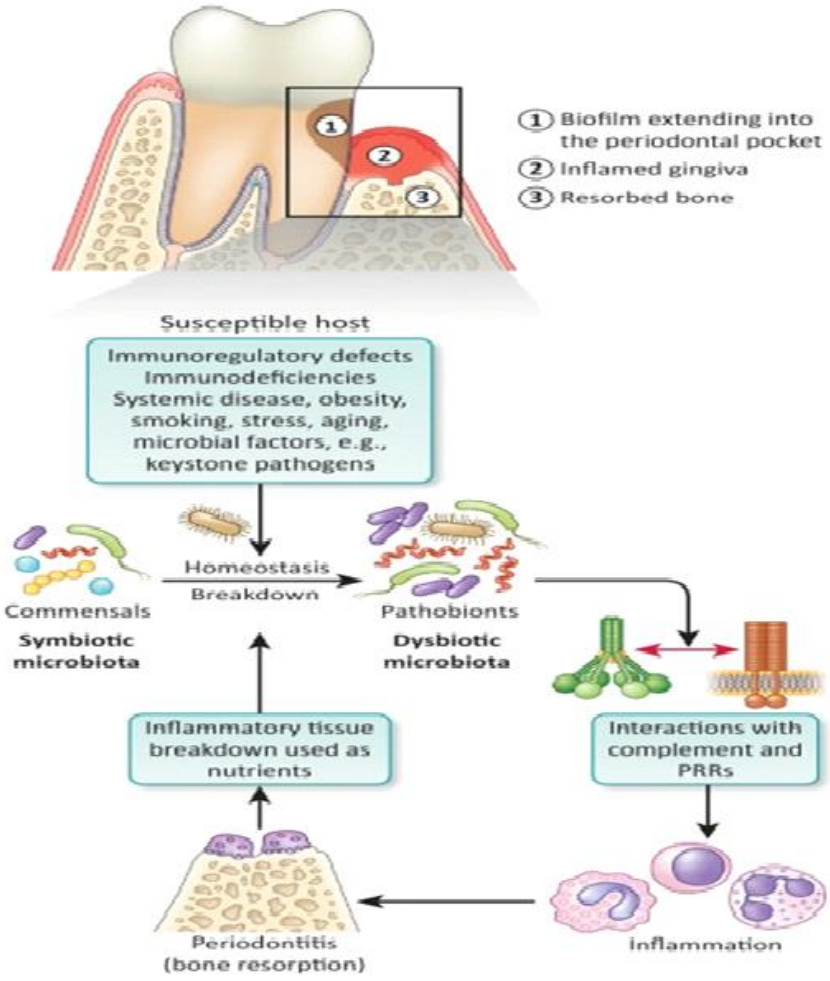


Figure 2: Pathology of Periodontitis

Lipopolysaccharides present in bacteria stimulate the production of catabolic cytokines and inflammatory mediators and also arachidonic acid metabolites which are prostaglandin E2 (PGE2), interleukin-1 (IL-1), interleukin-6 (IL-6), TNF–α (tumor necrosis factor–α)). These cytokines and inflammatory mediators in return stimulate the release of tissue-derived enzymes, such as the matrix metalloproteinases, which destroy the extracellular matrix and bone.

Reactive oxygen species are also a cause of the pathogenesis of periodontitis. Oxidative stress in tissue can directly lead to tissue damage. Oxidative stress is a major cause of hyper inflammation in periodontitis. It activates nuclear transcription factors, which can be receptor activators of nuclear factor kappa β (NF-kβ) and activated protein-1(AP-1) which can also induce gene transcription for key pro-inflammatory mediators and osteoclastogenesis stimulation. Considering all these it can be concluded that periodontitis has a multifactorial etiology. [(1)]

The intact epithelial barrier of the gingival sulcular and junctional epithelium typically prevents bacterial invasion of the periodontal tissue. The microbial biofilm colonizes the enamel surface releases large quantities of metabolites (fatty acids, peptides, and lipopolysaccharides) that may diffuse through the junctional epithelium. Microbes by releasing proteolytic and noxious waste products may damage structural factors of the periodontium. Which subsequently causes loss of tissue bones and finally, the tooth.

GUAVA (*Psidium cujavillus* , *Psidium pomi ferum L.* , *Psidium pumilum Vahl* , *Psidium pyriferum Linn.***)**

Common Name: Guava, lemon guava, mpera, mubera, mupeera [(1)]

Psidium guajava is the common Guava, which is yellow in color or additionally called lemon guava. It is called Goiaba in Portuguese and Guayaba in Spanish. Guava is an evergreen bush or little tree which is local to the Caribbean, Central America, and South America. Its flowers can be effectively pollinated predominantly by regular bumblebee *Apis mellifera*. The genus Psidium (Myrtaceae) comprises around 150 genera and around 5000 species which are widely distributed in the American, Asian and African tropicals. [(17)]

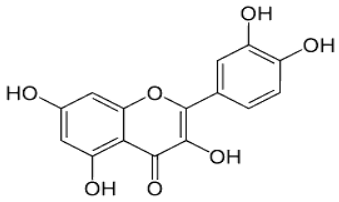
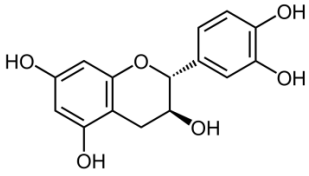
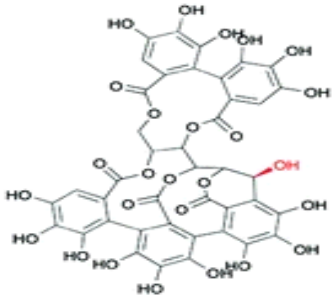
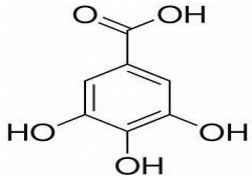
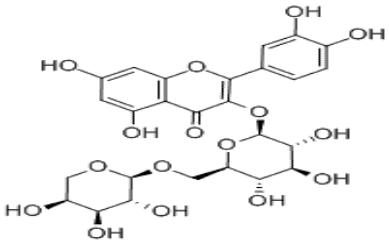
Figure 3: *Psidium guajava tree*

1.1 Classification [1]

Kingdom	Plantae
Division	Mangoliophyta
Class	Mangoliophyta
Order	Myrtaceae
Genus	*Psidium L.*
Species	Guajava
Family	Myrtaceae

CHEMICAL CONSTITUENTS

Table 1: Bioactive constituents (along with their chemical structure) present in *Psidium guajava* Leaves.

Sr. No.	Bioactive compounds	Structure
1.	Quercetin	
2.	Catechin	
3.	Vescalagin	
4.	gallic acid	
5.	Peltatoside	

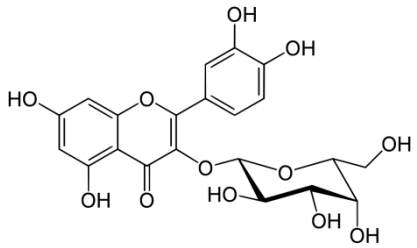
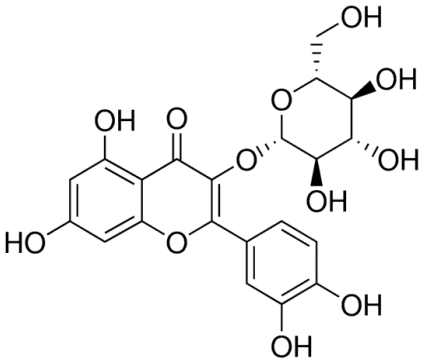
6.	Hyperoside	
7.	Isoquercitrin	

Table 2: Pharmacological activity of different parts of in *Psidium guajava* plant.

Sr. No.	Part of Plant	Pharmacological / Biological Activity	References
1.	Fruits	used as astringent, anti-diarrhoeic, used for the treatment of diabetes.	(Rishika et al.2012, Mittal *et al 2010)*
2.	Leaves	diarrhea, wounds, ulcer, toothache, stomachache, and diabetes. leaves are used as gargles or sore throats, swelling of the mouth, laryngitis, external ulcer on the skin, and vaginal irritations. used as an antimicrobial agent.	(Rishika et al.2012, Kenneth E. et al.2017)
3.	Bark	astringent, febrifuge, antiseptic.	(Rishika et al.2012,)
4.	Roots	Diarrhea, coughs, stomach-ache, dysentery, toothaches, indigestion, constipation	(Rishika et al.2012, Mittal *et al 2010)*

PHARMACOLOGICAL USES IN THE TREATMENT OF PERIODONTITIS

Oral wellbeing is a critical pointer of health, prosperity, and personal satisfaction. WHO characterizes oral health as "a state of being free from chronic mouth and facial pain, oral and throat cancer, oral infection and sores, periodontal (gum) disease, tooth loss, and other disease and disorder that limits an individuals capacity in biting, chewing, smiling, speaking and psychosocial wellbeing". [(11)] Dental plaque is one of the principal etiologic factors in the development of periodontal disease. [(12)]

Shetty S. Et. Al. (2018) studied the inhibitory effect of the guava extracts on *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* by there study they concluded that the minium inhibitory concentration determined for aqueous guava extract (AGE) and ethanolic guava extract (EGE) was at 75 µL/mL concentration for *P. gingivalis,* although EGE of guava exhibited this activity at 75 µL/mL on *P. gingivalis*. The MIC determined for AGE was at 50 µL/mL for *A. actinomycetemcomitans,* although MIC determined for EGE extract was at 3.12 µL/mL for bacteria *A.actinomycetemcomitans*. From this, it can be concluded that *Porphyromonas gingivalis* was susceptible to EGE compared with AGE**.** [(12)]

Das M. Et. Al. (2019) concluded from their study that Gram-negative bacteria (Escherichia coli) are less sensitive compared to Gram-positive bacteria (Bacillus subtilis) towards the antimicrobial property of Guava leaves, whereas the fungal strains are strongly sensitivity towards the antimicrobial property of guava leaves. The reason behind this may the difference in their respective cell wall structures. [(7)]

Abdullah S. Et. Al. (2019) justified the antibacterial action of leaf and stem bark extract of *P. guajava.* [(8)] *P. guajava* leaves show its action by reacting phenolic antioxidants with the cellular membrane, impairing both its functions and integrity The loss of cell viability may not be attributed to a single particulate event, but multitarget inactivation, resulting in several lesions that together cause death. The key target may also be affected when a secondary structure is previously damaged. The presence of flavonoids and terpenes and a certain degree of lipophilicity might determine toxicity by the interactions with the membrane constituents and their arrangement. [(13)] Conventionally, tender leaves of guava are used to make a paste and used to maintain oral hygiene. It also acts as an antibacterial agent against both Gram-positive and

Gram-negative bacteria. [31] *P. guajava leaves* can be used in the prevention of disorders due to the presence of some useful phytochemicals and in the treatment of diseases caused by some bacterial pathogens such as *P. aeruginosa, E. coli, S. aureus, S. pneumoniae and K. pneumoniae.* [16]

Philip D. Et. Al. (2015) reported that *Psidium guajava Linn* leaf exhibits better phytochemical, antioxidant, and antibacterial activity than other extracts along with other properties such as antispasmodic, antidiarrhoeal, antidepressant, anti-inflammatory, anticough, and sedative agent. [14]

Kumar R. Et. Al. synthesized nanoparticles of silver nitrate using *P. guajava* leaf extract. The plant phytochemicals molecules are responsible for the reduction of AgNPs and enhanced antibacterial activity. [15] The main cause of periodontitis is dental plaque when plaque is left unattained without any care it ultimately leads to gingivitis which if not gets treated on time turns into Periodontitis. [19] In Andhra Pradesh (India) guava leaves are used in mouth ulcers. People of North Sikkim (India) use raw young leaves and tender shoots of guava for toothache and mouth ulcers. [17] In the USA guava leaves are used as an antibiotic in the form of poultice or decoction for wounds, people also used it to treat ulcers and toothache. [21] Southern Nigerians used the twigs as chew sticks and the bioactive compounds present in chewing sticks comprised of saponins, tannins, flavonoids, alkaloids which are responsible for their effectiveness. Chewing sticks are more efficient when used without toothpaste and also reliable for cleaning teeth. It is observed that the teeth of chewing stick users are usually strong, clean, fresh, and devoid of dental plaque carries. [28]

Antibacterial

Quercetin the chief phytoconstituent present in guava has shown excellent antibacterial actions against some periodontal pathogens which are *Aggregatibacter actinomycetemcomitans* (Aa), *Porphyromonas gingivalis* (Pg), *Prevotella intermedia* (Pi), *Fusobacterium nucleatum* (Fn). It showed inhibitory actions against *Streptococcus mutans* (S. mutans), *Streptococcus sanguinis* (S. sanguinis) and *Actinomyces species.*[1] Mechanism of action of quercetin can be cell membrane disruption and by forming irreversible complexes with the protein in susceptible microbes it can also inactivate the crucial protein. [19] Essential oils present in guava leaves may also be

effective because of their hydrophobicity. [22] Some other phytoconstituents responsible for the antimicrobial action of Guava are Guaijaverin, avicularia, caffeic acid, morin-3-0-alpha-L-arabinopyranoside. [20] It also has been found effective against E.coli which otherwise is resistant to most of the modern-day antibiotics in the market. [19] Guava leaves can be directly chewed to get some of their therapeutic effects which is cost-effective. [19] It had been observed that mouthwash which contains aqueous extract of the leaves was found highly active against periodontal bacteria such as *S. aureus* and *Escherichia coli* (E. coli). Mouth rinse which contains guava leaf extract had a deep effect on gingivitis. The aqueous extracts of *P. betle* and guava have an antiplaque activity which is observed by their effect on the ultrastructure of plaque bacteria. It shows this effect by interfering with the normal growth cycle and development of plaque bacteria. It also reduces the ability of the acquired pellicle to adhere to the tooth surface during early plaque formation. It reduces the hydrophobicity of the bacterial cell surface, which is essential for adherence. [1]

Anti-inflammatory

Guava inhibits prostaglandins, cytokinins, and histamine, making it an anti-inflammatory agent. Aggregatibacter actinomycetemcomitans is a common periodontal pathogen that is linked to advanced periodontitis. The cytolytic, pro-inflammatory response induced by Aa leukotoxin in human leukocytes was completely neutralized by Psidium guajava extract, which also prevented the release and activation of IFN-gamma.[1] Guava extract in ethanol inhibits lipopolysaccharide from releasing nitric oxide. It inhibits E2 from it being transmitted. Benzophenone and flavonoids are responsible for histamine inhibition and nitric acid production. Phenol is a vital ingredient of guava and is responsible for its anti-allergic and anti-inflammatory properties. [25] Phytoconstituents responsible for the anti-inflammatory effect of *Psidium guajava* are Ellagic acid, Asiatic acid, copaene, limonene. [20] Guava leaf and stem extracts contain anti-inflammatory properties, as they lower CRP levels, which is a modulator of the inflammatory response. Inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX2) are inhibited by fermented guava leaf extract. It also prevented NF-k beta activation caused by lipopolysaccharide. Guava due to its anti-inflammatory action can inhibit iNOS, COX-2, NF-kβ it could be a valuable agent in treating periodontal disease. [1]

Anti-oxidant

Neutrophiles generate free radicals in periodontitis, bacterias associated with periodontitis stimulate the release of free radicles from the neutrophils, which cause oxidative stress in the tissue. Due to this disequilibrium establish between oxidative stress and antioxidant activity which further leads to tissue damage. For which antioxidant micronutrients are important not only for limiting oxidative stress and not just in lowering cytokine production but also in preventing tissue injury. [(1)] Guava contains Gallic acid, protocatechuic acid, caffeic acid, ferulic acid, chlorogenic acid, guavin B, beta-carotene, asiatic acid which are responsible for the antioxidant activity of the *Psidium guajava.* [(20)] Aqueous extracts from *P. guajava* are supposed to have antioxidant or radical-scavenging activity. Most of the activity is associated with polyphenol however, the guava extracts also contain antioxidants, such as ascorbic acid and carotenoids. [(26)] Guava leaf extracts and fruits are natural antioxidants that may be a trigger. [(27)] Guava leaf extracts and essential oil from the stem and bark can neutralize free hydrogen peroxide and superoxide anion radicals while also inhibiting the development of hydroxyl radicals. As a result, guava may be used as an antioxidant-based periodontal treatment. [(1)]

Mittal Et. Al. (2010) reported that the extracts from distilled water, 65% ethanol, and 95% ethanol, respectively, had dose-dependent effects on scavenging hydroxyl radicals and inhibiting lipid peroxidation, with EC50 on scavenging hydroxyl radicals of 0.63, 0.47, and 0.58g/L, and EC50 on inhibiting lipid peroxidation of 0.20, 0.035, 0.18g/L.[(28)]

Anti Plaque

Periodontal disease is caused by dental plaque, which is the most common cause. Plaque is formed by the bacteria present in the oral cavity by breaking down the carbohydrates, fats, etc. present in the food. This plaque accumulates on the surface of the tooth. Bacteria get colonized in accumulated plaque and converted into hard callus if oral hygiene is not followed. [(1)] The current treatment for gingivitis and periodontitis is directed at the disruption of plaque maturation and reduction of the bacterial load which usually includes professional and homecare mechanical methods for the removal of plaque. [(12)] To prevent or restrict bacterial adhesion and further growth on the tooth surface, effective plaque control strategies are needed. Traditional oral hygiene has relied on a paste made from tender guava leaves. [(1)] The active flavonoid

compound quercetin-3-O-alpha-l-arabinopyranoside (guaijaverin), isolated from Psidium guajava, showed promise as an antiplaque agent by inhibiting Strep formation. Mutants are a type of mutant. [28] Guaijaverin has demonstrated its ability to act as an anti-plaque agent, making it a viable oral care option.[10] At a dosage of 1mg/m, *Psidium guajava* is effective in preventing dental caries and reducing dental plaque caused by Staphylococcus sanguinis, Staphylococcus mitis, and Actinomyces species. [27] Guava extract without disturbing the oral cavity homeostasis acts against oral plagues. It also prevents adherence of bacteria to the oral cavity thus discouraging further development of plague as well. [19] Chewing stick users teeth are typically solid, clean, fresh, and free of dental plaques. [28]

Wound Healer

Collagen fibers make up the gingival and periodontal ligaments. Fibroblasts are the most common cell type found in periodontal connective tissue. Vitamin C is essential for maintaining the periodontium's overall health. Guava has a lot of vitamin C in it. Along with its effects on the extracellular matrix, ascorbic acid can modulate the expression of the procollagen gene, resulting in collagen formation and altering fibroblast differentiation. Vitamin C helps to preserve immune function, epithelial tissue structural and functional integrity, and physiological and metabolic parameters that are essential for periodontal health. The healing process is accelerated by vitamin C and bioflavonoids. A mouthwash made from the root bark is recommended for swollen gums, and a gargle made from leaves is recommended for swollen, bleeding gums. Guava extracts can help to speed up the tissue healing process. [1] Methanolic leaf extract of *Psidium guajava* is used as a wound healer. [20] Tannins and flavonoids exhibit faster healing. [19] Tannins react with proteins to produce the typical tanning effect and this is important in the treatment of inflamed or ulcerated tissues, burns, wounds, etc. Guava has been used safely in folklore medicine for decades with no side effects. Toxicity occurs when phytochemicals are consumed in large quantities. Treatment of gingival and periodontal disease, on the other hand, does not necessitate such toxic quantities. There is a scarcity of data on the consistency, protection, and efficacy of herbal products used in dentistry. Since there is a risk of negative interactions between phytochemicals and traditional drugs, caution should be used when using them. [1]

Conclusion

The purpose of this review is to offer information on the therapeutic potential of guava leaves in the treatment of periodontal disease as an adjuvant. Various Properties of Guava such as antiplaque, antibacterial, anti-inflammatory, and antioxidant can be considered for more in future clinical trials and potential usage as a supplement too. Periodontal therapy is a type of treatment that is used to treat gum disease. Nonetheless, we must take action to emphasize the importance.

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