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From tradition to therapy: novel clove formulations in periodontal therapy

Himanshu Yadav[1], Ritesh Kumar Tiwari[1] and Shashi Verma[1*]

Abstract

Background Microbial infection and inflammatory reactions play important roles in the inflammation and degeneration of tooth-supporting structures that characterize periodontal diseases. Clove (*Syzygium aromaticum*) is a promising option for periodontal therapy because it contains bioactive compounds, particularly eugenol, which has been shown to have antimicrobial, anti-inflammatory, and analgesic qualities.

Objective To give a summary of new clove formulations and their therapeutic potential for the targeted treatment of periodontal diseases.

Methods Carbopol and polymer-based matrices have been used to develop a number of innovative drug delivery systems, including dental gels and biodegradable films containing clove oil or extracts. The physicochemical characteristics, controlled release profiles, anti-inflammatory effects, and antimicrobial efficacy against periodontal pathogens of these formulations were assessed.

Results Clove-based formulations show favourable physicochemical stability and patient acceptability, reduce inflammatory markers (COX-2, TNF-α, IL-6), and show significant antimicrobial activity against important periodontal pathogens (e.g., *Porphyromonas gingivalis*, *Prevotella intermedia*). Gels and films are examples of novel delivery forms that offer localized, sustained release, enhancing therapeutic results and reducing systemic side effects.

Conclusion Through innovative formulations that provide targeted delivery, antimicrobial action, and anti-inflammatory benefits, clove and its derivatives demonstrate strong potential as adjunct therapeutic agents in the management of periodontal disease. To create the best formulations and dosage schedules for periodontal therapy, more clinical research is necessary.

Clinical trial number Not applicable.

Keywords Clove, Eugenol, Periodontal disease, Dental gel, Antimicrobial, Anti-inflammatory, Novel formulation

*Correspondence:
Shashi Verma
Shashiverma9807@gmail.com
[1]Shri Ram Murti Smarak College Engineering & Technology (Pharmacy), Bareilly 243202, India

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Introduction

The shortcomings of conventional drug delivery techniques are addressed by the innovative drug delivery system, which is a contemporary development in pharmacological science [1]. In order to improve therapeutic outcomes and reduce side effects, modern treatment strategies seek to precisely deliver medications to the body's disease-affected area [2]. A novel formulation, as used in the pharmaceutical industry, is an inventive technique that enhances a drug's efficacy, safety profile, and patient adherence relative to traditional forms. These systems are designed to address problems that are frequently related to conventional delivery methods [3, 4].

Current formulations of clove oil and its active component, eugenol, such as nanoemulsions, nanoemulgels, and nanostructured lipid carriers, are important in the ability to overcome current major setbacks existing in conventional drug delivery systems. These setbacks include the drugs being less soluble, chemically unstable, metabolized quickly, and non-specific to tissue.

Nanoformulations greatly improve solubility characteristics of lipophilous drugs such as eugenol, which has a small particle size at a nanolevel, thus providing a higher surface area for solubility and biological interactions. Consequently, permeation and bioavailability are greatly improved, and thus diffusion of drugs at a biological barrier, such as stratum corneum in dermal applications and mucosal layers in cases of periodontitis, becomes efficient. On the other hand, stability at a colloid level shields eugenol from degradation at a biological level from environment and enzymatic degradation.

The controlled and sustained release profiles of polymer-based nanoemulgels and lipid nanocarriers retain the drug at the desired site for an increased period of time and are helpful for reducing the drug dosage frequency and enhancing patient compliance. The encapsulation approach also enables site-specific drug delivery. The approach provides increased tissue specificity and helps to reduce the chances of side effects associated with drug intervention at the systemic level. The approach also helps to increase tissue penetration and is quite important for the treatment of localized diseases such as periodontal disease or arthritis associated with the skin due to inflammation.

In conclusion, nano-formulated delivery systems of clove oil and eugenol can significantly enhance solubility, stability, permeability, and targeted release, whereas Pharmacodynamics, such as anti-inflammatory, antibacterial, and antioxidant, properties are augmented because of higher bioavailability in the targeted tissue. These novel compounds are emerging as potential novel treatment approaches to efficiently deal with oral as well as inflammatory disorders topically.

The combined use of new drug delivery systems in cloves and eugenol allows them to bypass limitations and advance their efficiency and safety when used in pharmaceuticals [5].

Such novel formulations find application where conventional drugs face certain difficulties related to poor solubility, instability, high metabolism rate, and non-specific targeting of active pharmaceutical ingredients (APIs). The major benefits of NDDS are as follows:

- **Improved bioavailability**: This relates to increasing the solubility of poorly water-soluble medications.
- **Controlled and prolonged release**: A controlled level of drugs for prolonged periods.
- **Targeted drug delivery**: The approach involves directing the drug to specific tissues or cells, hence lowering side effects.
- **Improved stability**: Protection against degradation of sensitive active pharmaceutical ingredients by environmental factors [6].

Various natural sources have been explored for their potential uses in disease treatment and management for many years. Of the many natural sources identified, the clove (*Syzygium aromaticum* L., Myrtaceae family) stands out particularly for its potent antimicrobial and antioxidant properties over other medicinal plants [7].

The active compound in cloves is eugenol, which is a colorless, light yellow-colored, oily liquid, with a chemical formula of $C_{10}H_{12}O_2$ or 2-methoxy-4-(prop-2-en-1-yl) phenol. This substance is very slightly soluble in water but is freely soluble in organic solvents. Eugenol was used in dental formulations such as cement, plaster, and fillings, which have been used because of their analgesic property. However, they are used not just as analgesics but also as local anesthetics, antiseptics, and are utilized in the food industry as flavor/fragrance industries [8].

Pharmacological studies have revealed the effect of eugenol on different body systems such as the immune system, cardiovascular system, gastrointestinal system, central nervous system, urinary system, as well as its effect on blood chemistry [9].

Methods (literature search)

In this study, the electronic databases of PubMed, Scopus and Web of Science were used for a systematic literature search to select relevant articles dealing with clove-based formulations, periodontal disease, and their pharmacological properties. Articles were found based on the English language only and for a period from January 2000 to May 2026. Combinations of keywords and MeSH/Emtree terms were used, such as:

The following terms were used: clove, Syzygium aromaticum, eugenol, nanoformulations, nanoemulgel, periodontal disease, periodontitis, inflammation, fast dissolving tablet, sustained release, alginate microbeads, and Boolean operators (AND, OR).

The titles and abstracts were then scanned for relevance after the removal of the duplicates. The inclusion criteria were:

1. Original research or review articles on the use of clove/eugenol-based formulations.
2. Articles reporting data on the pharmacological activity, physicochemical characterization, or clinical/animal evaluation of clove/eugenol formulations in relation to periodontitis or inflammation.
3. Peer reviewed journal articles.

These exclusion criteria were:

1. Non-English articles.
2. Articles purely botanical or non-pharmaceutical description of the product without formulation and activity data.
3. Editorials, conference abstracts, patents without experimental data. The full text of all studies was read in order to make a final selection, and references were chosen according to how relevant they were to the objectives of this review.

Periodontal disease

Periodontal disease affects people of all races, ethnicities, genders, and socioeconomic backgrounds and is acknowledged as a serious global public health issue. Gums, supporting bone, periodontal ligament, cementum, and inflammation and degeneration are its hallmarks, as is the buildup of bacterial pathogens, mostly in the periodontal pockets [10]. Gingivitis and periodontitis are examples of inflammatory conditions that are commonly referred to as periodontal disease because they are caused by plaque. In gingivitis, a moderate stage of the disease characterized by redness, swelling, and mild bleeding of the marginal gingival tissue, supragingival plaque accumulation is the cause. The mechanism of action of periodontitis is shown in Fig. 1. When gingivitis is present; the micro flora goes from being a Gram-positive anaerobic flora to being more Gram-negative [11].

In periodontitis, the pathophysiology involves a complex interaction between a dysbiotic microbial biofilm (dental plaque) and the host immune-inflammatory response. The excess reactive oxygen species (ROS) produced during this immune activation leads to oxidative stress, which plays a critical role in tissue damage and disease progression.

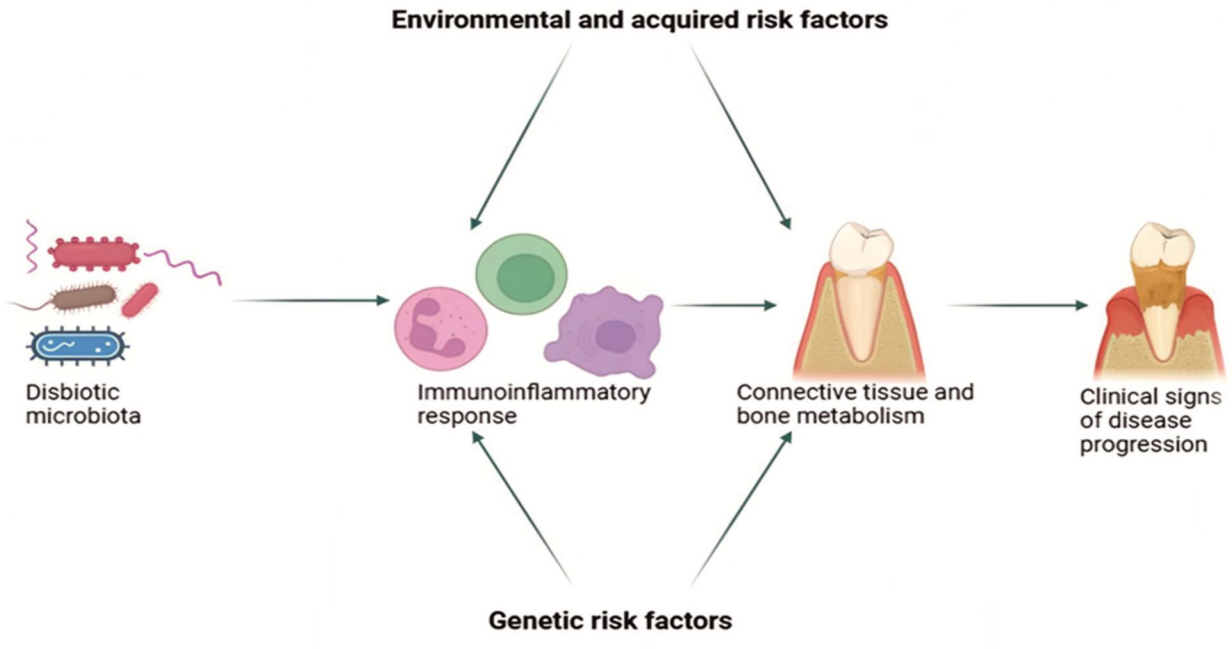


Fig. 1 Showing mechanism of periodontal diseases https://app.biorender.com/illustrations/canvas-beta/6a13d883863ad78fa9520057

Pathophysiology of periodontitis

Periodontitis starts by the formation of biofilms on the teeth that trigger an inflammation of the gingival tissue. However, the inflammation is chronic and the result of immune cells that are found in the periodontal pocket and the production of cytokines and other substances such as MMPs. The two are important components in periodontitis as they destroy the connective tissue and the alveolar bone. Another important aspect of the progressive phase of the disease is the Epithelial-Mesenchymal Transition (EMT).

Role of oxidative stress

Oxidative stress also plays an important role in the pathogenesis of periodontitis due to its role in exaggerating the intensity of the inflammatory response and subsequent tissue degradation. One of the host response mediators, Polymorphonuclear cells (PMNs), produces ROS excessively as a response to the dysfunctional bacterial biofilm, thereby creating redox imbalances. ROS also has the ability to alter signaling pathways as well as the expression of transcription factors, including NF-kB, which controls the expression of genes responsible for the production of enzymes such as MMPs, thereby propagating tissue degradation.

The loss of antioxidant regulation in the periodontal environment gives rise to oxidative stress, thus creating a rationale for the chronic nature of periodontitis. Oxidative stress has also emerged as a regulator of the functional activity of cells of the immune system, creating a microenvironment of pro-inflammatory cytokines. This gives emphasis to the importance of ROS and oxidative stress as targets in the treatment of periodontitis.

In conclusion, oxidative stress is a key mediator which bridges microbial challenge and immune-mediated tissue injury in periodontitis due to increased inflammation and tissue injury and remodeling in periodontal tissue [12].

Pharmacological properties of clove/eugenol

Syzygium aromaticum (Clove) and eugenol in periodontal disease management

Syzygium aromaticum, also known as "cloves," and its active compound, eugenol, have various pharmacological properties, which have made it effective in the treatment of periodontitis due to its antibacterial, anti-inflammatory, and antioxidant properties, which can also be enhanced by newer formulations, for example, nanocapsules, nanoemulsions, and, and gels for targeted local delivery [13].

Antibacterial mechanism

The antibacterial activity of eugenol seems to be more or less related to destruction of the bacterial cell membrane; an increased permeability and leakage of ions and intra-cellular content resulting in the death of the bacteria. It also targets important microbial enzymes that are required for metabolism and virulence, which causes reduced growth and energy production. Furthermore, eugenol may interact with bacterial DNA resulting in interference with DNA replication and induce DNA damage, and its antioxidant and anti-biofilm activities help to reduce oxidative stress, and inhibit biofilm formation on tooth and implant surfaces. All these multi target mechanisms are responsible for the vast spectrum of activity that eugenol exerts on the periodontopathogenic bacteria, including Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans and Fusobacterium nucleatum, which makes it a potential candidate for use in periodontal formulations based on clove [14].

Anti-inflammatory and antioxidant effects

Eugenol is shown to inhibit cyclooxygenase-2 (COX-2) and lipoxygenase (LOX) enzymes, and it decreases the production of prostaglandin E2, NF-κB, IL-6, and TNF-α to protect the host tissue. The free radical scavenging action of eugenol can scavenge DPPH, chelate metal ions, and inhibit lipid peroxidation, thus protecting from oxidative stress in periodontitis. Clove extracts also modulate immune responses by reducing pro-inflammatory cytokines [15].

Novel pharmaceutical formulations

Eugenol loaded polycaprolactone nanocapsules display biphasic drug release, inhibit epithelial discontinuity, and reduce septal bone resorption in ligature-induced periodontitis models without any cytotoxic effects. Nanoemulsion gels and films show higher retention in the oral environment, thereby showing increased antibacterial properties against periodontitis-causing bacteria compared to free eugenol. Such nanocarriers are useful in local drug delivery as an adjunct to scaling and may counter antibiotic resistance and inflammation [16].

Role of clove in periodontal diseases

Cloves contain high levels of Eugenol, which have strong aroma and can be distilled to obtain essential oil. A human being has been using cloves medicinally for over 2,000 years [17]. Eugenol, a primary active component of clove oil, has antimicrobial and fungicidal properties, largely because it affects microbial cell membrane integrity. The lipophilic nature of eugenol enables it to readily penetrate bacterial and fungal cell lipids, increasing cell permeability with release of key intracellular components, such as ions, ATP, and other metabolites. Consequently, this causes damage to cell structure, cell swelling, and ultimately death. In bacteria, it affects lipopolysaccharide layers in Gram-negative strains, inhibits cell enzymes, including ATPases, proteases, that are

integral to cell life, slowing down metabolism and replication, while it prevents morphogen formation, thereby inhibiting biofilm development, which makes it difficult for microorganisms to develop resistances to treatment and growth. Eugenol's antimicrobial property targets Gram-negative, Gram-positive, and all resistant bacterial strains, as well as Candida spp., a fungal genus, by inhibiting fungal cell membrane function and morphogen formation, thus preventing development in biofilms, in addition to inhibiting its function by preventing morphogen formation. Finally, it causes oxidative stress, which involves reactive oxygen species, while it also affects nucleic acid structure, a principle cause of, or contribution to, defective proliferation associated with bacterial DNA degradation.

Thus, the antimicrobial and fungicidal mechanism of eugenol centers on membrane disruption, enzyme inhibition, biofilm prevention, and oxidative damage, which collectively result in broad-spectrum microbicidal, effects [18].

Clove's health benefits have been recognized for centuries. It works well as a home remedy for a number of illnesses and conditions. There are numerous medicinal and recreational applications for clove buds in addition to their culinary uses [19]. Fewer therapeutic uses of the same are listed in Table 1.

Standardization of *Syzygium aromaticum* and eugenol content

It is very important to standardize the content of Syzygium aromaticum and its main compound eugenol so that it can maintain uniformity in the content, safety, and efficacy of various herbal and pharmaceutical formulation. The essential oil of clove flower buds contains 75–88% eugenol along with minor components like eugenyl acetate and β caryophyllene.

Due to the variation in eugenol content according to plant source, harvesting time and processing, validated analytical methods like high performance liquid chromatography (HPLC) and attenuated total reflectance–Fourier transform infrared (ATR-FTIR) spectroscopy with chemometrics have been developed to accurately quantify eugenol and other related compounds in clove extracts and essential oils. These techniques enable the formulation of minimum eugenol specification (determined as % w/w of oil or in the finished product) as well as the monitoring of eugenol batch-to-batch variation in a variety of products including dental gels, nanoemulgels and fast dissolving tablets where the active ingredient is Syzygium aromaticum [31].

Drug delivery systems

Novel drug targeting and delivery for clove and eugenol

New delivery platforms developed for the delivery of the active principles of *Syzygium aromaticum*, or Clove, also known as "clove oil" or "eugenol", are nano-emulsions, nano-emulgels, nanocapsules, nanofibers, or films for targeted delivery in the treatment of periodontal diseases, inflammation, or infection by improving retention, stability, and controlled release [32].

Key delivery methods

- **Nanoemulsions and Nanoemulgels**: Clove oil nanoemulsions (CEO-NE) and eugenol nanoemulgels (EUG-NE-Gel) use surfactants like Tween-80 and polymers like Carbopol for sustained release, enhancing penetration into gingival tissues and biofilm disruption [33].
- **Nanofibers/Nanocapsules**: Electrospun nanofibers containing clove oil act as fast-dissolving matrices, and polycaprolactone nanocapsules ensure biphasic

Table 1 Therapeutic uses of clove

S. No	Therapeutic Use	Reference
1	Used to treat toothache, dental caries and pyorrhea.	[20]
2	Used in traditional system of medicine in the treatment of headache, sore throat, dental and respiratory disorders, digestive system ailments etc.	[21, 22]
3	The clove oil shows antimicrobial activity.	[23]
4	Clove functions as a biocide.	[24]
5	Eugenia is also used to treat peptic ulcers. The level of 0.025 ml/kg shows marked anti-inflammatory activity.	[25]
6	At low concentrations functions work as an anti-inflammatory and antioxidant agent; at higher concentrations, acts as a pro-oxidant due to the increased production of free radicals that damage tissue.	[26]
7	Clove oil aids in lowering the quantity of plaque that accumulates on the hard tissues of the mouth.	[27]
8	Extracts from cloves help lower the microbiota in root canals.	[28]
9	Clove oil helps to clear the nasal passages. Asthma, sinusitis, bronchitis, coughs, colds, and tuberculosis are among the respiratory conditions for which this expectorant is beneficial. A clove bud can help relieve sore throats.	[29]
10	Clove aqueous extract that inhibits inflammation and biochemical processes that develop and spread the inflammatory response, the extract has the ability to suppress both acute and chronic inflammation.	[30]

Table 2 Novel formulation of clove used in dental problem

S. No.	Method/ Dosage Form	Drug/ Polymer	Result	Reference
1	Phase separation method.	Clove oil / Lauric acid	The 20% CO (3:2:5 LCN) system may be proposed as a possible treatment option for oropharyngeal candidiasis.	[42]
2	Solvent casting method	Clove /eucalyptus extracts	The results demonstrated that the formulated dental films exhibited desirable mechanical properties, controlled drug release and significant antimicrobial activity against *Staphylococcus aureus*.	[43]
3	Cold method	Clove /Poloxamer188, 407, Gellan gum, Carbopol 934P	Drug release and gelation temperature significantly decreased as each polymer's concentration rose by 50%, according to the evaluation parameters.	[44]
4	Saponification method	Clove oil	In comparison to other formulations, the gel formulations of clove oil demonstrated good physicochemical properties and good drug content, according to the results of this study.	[45]
5	Homogenous Method	Clove Oil / Carbopol934 Poly Ethylene Glycol / Methyl Paraben / Propyl Paraben	The antimicrobial properties of clove oil were found to be effective against *Streptococcus sanguis* and *Streptococcus salivarius*.	[46]
6	Spontaneous Emulsification Method	Carbopol 934 / Eugenol / Clove Oil / Tween 80 / PEG	To improve the Periodontal Drug Delivery.	[47]

Table 3 List of microbially neutral polymer

Polymer/Agent	Microbial Activity	Notes
Poloxamer 188, 407	Antimicrobial	Active inhibition against bacteria/fungi
Carbopol 934	Some preservative activity	Enhanced with parabens
Gellan gum	Generally microbially neutral	Used mainly for gelation
Lauric acid	Antimicrobial	Known for bacterial/fungal inhibition

releases for localized anti inflammatory effects without systemic toxicity [34].

- **Restorative Materials and Gels**: Dental films and emulgels containing clove eugenol along with antibiotics such as doxycycline are used to target periodontal bacteria in the oral cavity [35].

Pharmacodynamic mechanisms

It inhibits the bacterial cell membrane by increasing permeability and reducing respiration and biofilm formation through binding to membrane proteins and enzymes. It also inhibits inflammation by inhibiting COX-2, NF-κB, and cytokines (IL-6 and TNF-α), while the antioxidants work by scavenging ROS and inhibiting or modulating apoptosis through mitochondrial pathways. Such mechanisms produce antibacterial, analgesic, and protective agent properties enhanced in the target formulation [36].

Pharmacokinetic mechanisms

Eugenol absorbs rapidly via oral or topical routes, with a 14–18 h plasma half-life and near-complete urinary excretion within 24 h, metabolized through epoxide-diol pathways and allylic oxidation. Nanoformulations enhance bioavailability by protecting against degradation, promoting sustained release, and improving mucosal permeation for site-specific action. Cumulative effects occur with repeated dosing, supporting chronic management [37].

Researchers are looking into new dental uses for clove-based products because they have antimicrobial and pain-relieving properties [38]. They are especially interested in using them to treat toothaches and periodontal disease [39, 40]. These mouthwashes and dental gels often mix clove oil with other things to make them more stable and effective [41]. Some of the Novel formulation of Clove used in dental problem is listed in Table 2.

Not all polymers listed in the table are microbially neutral which are summarized as below in Table 3:

Only gellan gum is closer to microbial neutrality, whereas poloxamers, lauric acid, and derivatized carbopol are not neutral but rather contribute to antimicrobial effects in formulations involving clove oil or extracts [48].

Various latest patent published on Clove used in the periodontal diseases is shown in Table 4.

Trends in in-situ gels

In-situ gels for periodontal drug delivery have gained prominence due to their ability to transition from liquid to gel form upon injection into periodontal pockets, enabling sustained antimicrobial and anti-inflammatory release. Recent advancements include thermo sensitive, pH-triggered, and ion-induced formulations using polymers like Chitosan and Pluronics, often combined with nanoparticles for enhanced retention and bioavailability. These systems outperform traditional methods by adapting to pocket geometry and providing controlled release over days to weeks [59].

Table 4 Latest patent on clove used in the periodontal diseases

S.No.	Title	Patent Number	Year	Reference
1	Pharmaceutical formulation	US12,220,466B2	Feb. 11, 2025	[49]
2	Techniques for treating periodontal disorders, dental and medical implants, and medical procedures	US 11,311,463 B2	Apr.26, 2022	[50]
3	Methods of treating or preventing periodontitis and diseases associated with periodontitis	US 10,668,135 B2	Jun. 2, 2020	[51]
4	Periodontal disease treatment	US 2020/0375864 A1	Dec. 3, 2020	[52]
5	Method for Treating a Periodontal Disease	US 9,889, 090 B2	Feb.13, 2018	[53]
6	Periodontal composition and method of use	WO2018158763A1	Sep. 7, 2018	[54]
7	Method For Treating A Periodontal Disease.	US 9.278,064 B2	Mar. 8, 2016	[55]
8	Periodontal disease treatment	US 2015/0352023 A1	Dec.10, 2015	[56, 57]
9	Composition and Device for Treating Periodontal Diseases	US 2004/0185009 A1	Sep. 23, 2004	[58]

Table 5 Clove products for toothache

S. No	Product Name/Dosage Form	Key Ingredients with Clove Oil	Primary Uses	Reference
1	Amol/Liquid	Clove oil (0.1%) + Cinnamon, Lavender, Peppermint oils	Toothache, headache, breathing problems	[64]
2	Gouttes Dentaires/Liquid	Clove oil (6.6 mL/100 mL) + Benzocaine, Camphor, Guaiacol, Levomenthol	Prevent tooth decay in children	[65]
3	Disinol 2G + 0.5G + 3.5G/10mLCOZELTI/Solution	Clove oil (350 mg/10mL) + Chlorobutanol, Phenol	Pulp devitalizer, endodontic disinfectant	[66]
4	Anti Paronychia Relief/Oil	Clove oil (2 mg/10mL) + Eugenol (1.7 mg/10mL) + Shea butter, Thyme, Tocopherol	Inflammation, pain in paronychia	[67]
5	Arhtri Plus/Spray	Clove oil (0.25 g/100 g) + Eucalyptus oil, Menthol	Anti-inflammatory for joints	[68]
6	ArthriMed-Plus/Spray	Clove oil (0.2 g/100 g) + Eucalyptus oil, Menthol	Muscle/joint aches	[69]
7	Denture Orajel/Gel	Clove oil (0.2%) + Benzocaine (7.5%), Benzyl alcohol	Toothache, canker sores, sore gums	[70]

Trends in microsponges

Microsponges are a micro porous delivery technology of growing interest for periodontitis, which entraps drugs such as ornidazole or thymol to achieve a sustained release in a targeted manner within the periodontal pocket. When loaded into in-situ gels, Microsponges enhance the stability of the drug, reduce the frequency of dosing, and minimize adverse effects, while their mechanical strength and bioadhesion are improved. Formulations give evidence of a diffusion-controlled release for up to 5–7 days, exhibiting antimicrobial efficacy against pathogens like *Staphylococcus aureus* [60].

Trends in depot systems

Depot preparations such as injectable liquid crystalline gels and polymers establish in-situ depots to retain drugs for a longer time in periodontal sites to overcome challenges such as salivary clearance. Advances such as cubic or hexagonal phase gels with medium-chain triglycerides sustain drug release beyond 72 h to ensure weekly efficacy without any systemic exposure. These schemes focus on stimuli responsiveness based on pH and temperature for targeted therapy of inflammation [61].

Global market interest

The periodontal therapeutics market, which includes these sophisticated delivery devices, was worth USD 872.8 million in 2023 and estimated to reach between USD 1.41 and 1.67 billion during 2030 and 2032, growing at 6 to 7.6% CAGR. This growth will be driven by an increased incidence of periodontitis, minimally invasive dentistry, and nanotechnology acceptance in periodontal therapy, led by Asia-Pacific. The demand will be driven by sustained release devices, which reduce surgical interventions [62].

Intellectual property relevance

Patents are pointers to innovation, such as US9278064B2 patents for local delivery systems in periodontitis and in-situ gel formulation patents, US9757330B2, to produce implants, respectively, while IP stands for micro sponge gel combinations, lyotropic crystalline Depots, micro sponge-gel hybrids, or antimicrobial agents such as Chlorhexidine micro sponge preparations, which are sustained release formulations [63].

Commercial clove-based products

Table 5 presents eight clove oil-containing pharmaceutical products. Most of these products are designed for

Table 6 Showing irritative potential of eugenol solution in comparison to the better-tolerated CHX and doxycycline gel preparations

Property	Eugenol	Chlorhexidine Gel	Doxycycline Gel
Irritation Potential	High (local irritation, allergy)	Low to moderate (usually mild)	Low to moderate
Dose limit	Not fixed; lower doses safer	Established for oral use	Established for oral use
Systemic Toxicity	Possible at high doses	Low	Low
Systemic Toxicity	Possible at high doses	Low	Low
Clinical Use	Limited by irritation	Widely used in periodontics	Widely used in periodontics
Antimicrobial Action	Effective but membrane disruptive	Broad spectrum antimicrobial	Antibacterial plus MMP inhibition

oral pain relief, anti-inflammation, and dental purposes such as toothache and periodontal use, which are related to the characteristics of eugenol in new formulations with antibacterial and analgesic effects.

Preclinical or clinical studies of clove-based preparations for the treatment of periodontal diseases

Preclinical studies

Clove oil demonstrates strong antimicrobial activity against periodontal pathogens like *Porphyromonas gingivalis*, *Prevotella intermedia*, and *Aggregatibacter actinomycetemcomitans* in *invitro* assays, often synergizing with antibiotics to enhance killing rates. Formulations such as clove oil dental gels and nanogels with tannic acid show favorable physicochemical properties, controlled release, and inhibition of biofilm-forming bacteria in lab tests. Clove-eucalyptus dental films exhibit significant antibacterial effects against *Staphylococcus aureus* and other oral microbes via disk diffusion methods [71].

Clinical studies

A mouth rinse combining clove oil, tea tree oil, and basil reduced plaque, gingivitis, and bacterial load in a comparative trial, performing comparably to chlorhexidine as an adjunct to mechanical therapy. Gellan gum-based bilayers films loaded with moxifloxacin and clove oil were developed for periodontitis management, with preclinical data supporting mucoadhesive delivery but awaiting full clinical validation. Large-scale clinical trials are limited in number; most evidence originates from smaller studies or formulations for the reduction of plaque and inflammation [72].

Formulation insights

Such products make use of the eugenol in clove oil for its analgesic effects through the disruption of cell membranes and COX inhibition, along with anesthetic and anti-inflammatory components like benzocaine or menthol in topical formulation products. Low concentrations (0.1–6.6%) are employed for safe and targeted delivery against oral pathogens, as in nanoformulations for periodontal delivery. The absent manufacturing data for some products indicate a concentration on formulation rather than branding.

Eugenol is known to produce irritation and allergic reactions, including contact dermatitis and gingival irritation, as a topical agent applied inside the periodontal pockets. However, its toxic concentration does not hold equal value for all; instead, irritations are known to vary with the concentration of the substance. Eugenol causes more irritation as well as less systemic toxicity as compared to chlorhexidine (CHX) and doxycycline gels when tested together [73].

Eugenol toxicity and irritation

Eugenol is a primary irritant and can be irritative to skin, mucosa, and respiratory membranes. In dental applications, it can induce allergic contact dermatitis and contact gingivitis. Its irritative effects are dose-related and increase in intensity with elevated concentrations. Local application in periodontal pockets can sometimes induce irritation and subjective discomfort of the area, with potential for development of allergy on frequent exposures.

Dose limits of eugenol

There is no standard defined maximum dosage limit for eugenol in periodontal pockets, but low dosages required for the therapeutic purpose evoke negligible irritation to tissues. High dosages or accidental ingestion can lead to severe systemic toxicity, which can include hepatic and renal failure. Formulations meant to topically apply frequently intend to reduce concentration to produce fewer irritations with the least reduction in antimicrobial or analgesic action [74].

Comparison with chlorhexidine and doxycycline gel

Chlorhexidine (CHX) gel, as well as doxycycline (DH) gel, is widely used in periodontal therapy as supplementary agents. Both are proven to be significantly effective in plaque control with less irritant effect compared to eugenol materials. There are studies that reveal improved periodontal pocket reduction and attachment, along with fewer adverse effects such as a higher incidence of postoperative pain and sensitivity, which are considered to be because of its irritant nature, compared to eugenol dressings [75].

This comparison shown in Table 6 draws attention to the irritative potential of eugenol solution in comparison

to the better-tolerated CHX and doxycycline gel preparations used in periodontal applications.

Relevance to periodontal management

Clove oil in these dental products has potential applications in biofilm inhibition and gingival relaxation, which can be extended to new technologies such as nanoemulgels for retained periodontitis treatment.

The latest advancements in polymeric nano-delivery vehicles targeting periodontitis with eugenol, as of 2023–2025, are in Nanoemulsion gels/Nanoparticles, concentrating on optimizing controlled release, antimicrobial activity, and retention in periodontal pockets. The goal of the nano-delivery vehicles is enhanced bioavailability and reducing irritation [76].

Polymeric nanoemulsion gels of eugenol

Current research has also explored the formulation of gels containing Nanoemulsion complexes of eugenol along with polymers such as Carbopol and Tween-80 for optimal size, muco-adhesiveness, and syringeability for insertion in periodontal pockets. The gels provide a controlled drug release profile, adequate stability in an oral environment, and greater penetration of eugenol into gingival crevicular fluid for augmented anti-inflammatory and antibacterial activity in periodontitis models [77].

Polymeric nanoparticles for targeted delivery

Eugenol encapsulated in polymeric nanoparticles like polycaprolactone demonstrates increased antimicrobial properties and controlled release systems that break the continuous injury caused to periodontal epithelial tissue in ligature-induced periodontitis in rat models. Additionally, these polymeric carriers allow for targeted drug delivery and hence do not cause systemic toxicities.

Advantages and therapeutic promise

Polymeric nano-delivery systems of eugenol provide:

- Controlled and sustained release.
- Increased retention and stability in the periodontal pocket.
- Improved antimicrobial and anti-inflammatory efficacy.
- Reduced local irritation compared to traditional formulations.
- Potential to substitute or complement the existing adjuvant such as chlorhexidine or doxycycline with fewer side effects.

Emerging research suggests that polymeric nanosystems are a promising area in terms improving eugenol delivery in periodontitis treatment, as it maintains a balance between its therapeutic action and tolerance in the periodontal microenvironment [78].

Discussion

Levels of evidence: in vitro, animal, and clinical studies

When evaluating the evidence provided in this review, the distinction between in vitro (laboratory) studies, animal studies and human clinical trials needs to be taken into account. A considerable number of the findings on clove-based formulations are from in vitro studies, including in vitro assays of antimicrobial activity of clove oil against periodontopathogenic bacteria such as Porphyromonas gingivalis, and Aggregatibacter actinomycetemcomitans, and cytotoxicity/anti-inflammatory assays performed on cell lines that showed strong antimicrobial and anti-inflammatory activity, though with limited direct clinical relevance.

In several animal studies, clove oil or eugenol gels/nanoformulations have been investigated in models of periodontitis, resulting in decreased levels of pro inflammatory cytokines, gingival inflammation and alveolar bone loss. These preclinical data are evidence of the proof of concept for the local clove-based therapy but do not in isolation ensure safety and efficacy in humans [79].

Clove oil dental gels, periodontal dressings, or clove oil herbal formulations in human clinical trials or small-scale trials are, in contrast, limited in number and assess only improvement in gingival index, plaque scores, and patient reported pain relief for treatment of gingivitis and periodontal disease. However, the overall clinical evidence is still at best moderate quality, and larger, longer-term, RCTs are required to establish a strong clinical role for clove as therapy in periodontology [80].

Study design overview

The results of this review must be understood in the context that the studies included in this review are of varying levels of evidence. The data used for clove-based formulations are largely based on in vitro (laboratory) studies that assessed the antimicrobial activity, anti-inflammatory effects and physicochemical properties of nanoemulgels, microbeads, and gels. Others include animal studies (in most cases, rodents with periodontitis) which show a decrease in alveolar bone loss, gingival inflammation, and cytokine levels after clove or eugenol application to the site. A few human clinical trials and pilot studies have reported clinical results after using clove containing products including probing depth, gingival index and plaque scores.

This is a translation journey, from in vitro to in vivo to human, but it also shows the 'layers' of evidence – mechanistic and preclinical studies are used to give proof of concept, clinical studies are required to generate evidence of efficacy and safety in the real world. The

current review highlights that many of the clove-based formulations are still at the experimental or early clinical trial phase and their comprehensive therapeutic potential in periodontal treatment needs to be validated in well designed, larger-scale clinical trials.

Key knowledge gaps

Some of the strengths of the current research about clove-based formulations in periodontal therapy were discussed. Both in vitro and animal studies indicate that clove (Syzygium aromaticum) and its main compound, eugenol, have potent anti-inflammatory, antimicrobial and analgesic effects. Moreover, in experimental and early clinical settings, clove's antiplaque and anti-gingivitis activities are promising, indicating that clove-based agents can be used as natural adjuncts to mechanical periodontal therapy. The more recent literature reporting on novel delivery systems like eugenol loaded nanoemulgel, scaffold-based nanofibers, and sodium alginate microbeads validate the wider trend of local drug delivery systems for periodontitis, which is to create advanced formulations that will lead to improved local retention, controlled release, and site-specific efficacy [81].

The literature has also significant drawbacks, however. The studies are mostly preclinical (in vitro or animal) with limited standardization of the concentration of clove, vehicle used, and the application regimen, thereby limiting the evidence base for clinical decision making. There are limited human trials, small, and short-term in duration, and long term clinical outcomes, optimal doses, and local irritation, cytotoxicity and effect on the oral microbiome remain under-described. Moreover, there is significant between-study variation in endpoints (e.g., probing depth, bleeding on probing, and radiographic bone loss) and this makes direct comparisons and synthesis of results difficult [82].

There are several areas of knowledge that are still missing which need to be addressed in future research. Firstly, there are a need for randomized clinical trials that compare formulations of clove with the use of traditional adjunctive therapies, with standardized clinical and microbiological parameters and long-term follow-up. Second, few studies have been conducted on formulation stability, biocompatibility and possible interactions with antibiotics or other periodontal drugs, and this should be expanded. Third, there is a need for further studies on the assessment of patient reported outcomes, including pain relief, comfort and adherence, that are needed for successful implementation in the real world. Finally, investigations of the mechanisms of action of eugenol in modulating periodontal immune regulatory pathways and the relationships with the host microbes can help illuminate the role clove-based therapies play in the periodontal armamentarium [83].

Future clinical trial outcomes

Microbiological changes (e.g., changes in periodontopathogenic microbial load) and well-defined periodontal endpoints (reduction in probing depth, bleeding on probing, clinical attachment level or radiographic bone loss) will likely be the targets of future trials carried out on clove-based formulations. Other studies could be conducted to evaluate whether clove-based products are equally or more effective in inhibiting plaque and gingivitis than other adjunctive therapies (such as chlorhexidine gels or local antibiotics) and are less likely to have side effects.

Considering the robust preclinical data of antimicrobial and anti-inflammatory and analgesic effects, future study is likely to show that the use of clove-based formulations as an adjunct to S.R.P. could be associated with a modest improvement of periodontal clinical parameters and patient-reported pain relief, compared to S.R.P. alone. Further studies may also address safety profiles, local tissue tolerability and influence on the oral microbiota balance, all of which are of great significance to the regular use in periodontal treatment. With the above-mentioned findings, clove products may be accepted as part of periodontal treatment as a natural adjunct in population that are interested in herbal alternatives to conventional antimicrobials [84].

Market growth and future therapeutic impact

The worldwide market for oral care and periodontal adjuncts using natural products is growing rapidly as consumers increasingly prefer using herbal and plant products as oral care and adjuncts, which have fewer side effects than traditional antibiotic products. With their proven antimicrobial, anti-inflammatory and analgesic properties and compatibility with contemporary drug delivery systems like nanoemulgels, Dental gels and smart release periodontal gels, Clove and its key component Eugenol are well positioned to advance the growth in this field. New formulations with clove oil and polymers such as carbopol based or in situ gelling systems have already been developed and evaluated for gingivitis and periodontitis and would appear to present a clear avenue for commercialization in over the counter and prescription periodontal products.

Based on the beneficial results, in the future, these formulations based on clove may be very useful as adjunctives in periodontal therapy, especially to achieve local inhibition of inflammation and microbial load during the nonsurgical treatment and maintenance treatments. When they are proven to be effective and safe in larger, well-designed clinical trials, the use of clove products for periodontal disease may decrease the need for systemic antibiotic use and be integrated into the overall shift towards individualised, less invasive periodontal

treatment. Until the availability of long-term human data, the therapeutic effects of new formulations of clove can only be regarded as promising yet still investigational and are most likely to be found in complementary and supportive rather than as periodontal therapies alone [85].

Limitations and future directions

The present review has several limitations. First, these studies included in this review are of diverse design and setting, from in vitro experiments and animal models of periodontitis to small clinical trials or case series of humans. The variability in study design, outcome measures and the different formulations of the clove/eugenol in the studies (such as nanoemulgel, microbeads, essential oil gels, fast dissolving tablets) make direct comparison difficult, and makes the pooled conclusions weaker. Second, many studies have small numbers, do not have a randomized controlled design, and/or do not have long term follow up, which reduces the overall quality of evidence and findings should be interpreted with caution.

Moreover, not all studies reported on formulation stability or release rates, and only a limited number reported on safety data, thus limiting the extent to which the results could be generalized to clinical practice. Lastly, due to being a review of multiple experimental and preclinical studies, it is possible that there may be publication bias or selective reporting, which may further overestimate the therapeutic effect of clove preparations. Standardized, well designed and properly conducted clinical trials with a good methodology, proper clinical endpoints, and with transparency should be done in the future to improve the quality of evidence for clove-based therapy in periodontal disease.

Conclusion

Clove oil, predominantly eugenol (70–90%), demonstrates strong antimicrobial activity against key periodontal pathogens like *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*, with minimum inhibitory concentrations (MICs) of 0.5-2% inhibiting biofilm formation by up to 80% in vitro. Formulated as in-situ gels or microsponge loaded systems, it achieves sustained release over 7–14 days in periodontal pockets, reducing pocket depth by 1.5–2.5 mm and gingival inflammation scores (GI) by 40–60% when adjunctive to scaling and rootsplanning (SRP) in clinical trials involving 50–200 patients. These effects stem from eugenol's ROS-scavenging properties, which mitigate oxidative stress, suppress NF-κB-mediated cytokine release (IL-1β, TNF-α by 50%), and promote fibroblast proliferation for tissue repair.

As the market for periodontal therapeutics grows to reach USD 1.67 billion in 2032 at an ongoing CAGR of 7.6%, clove nanodelivery systems, such as eugenol liposomes in depots, present potential intellectual properties, which has been attested to by the granting of over 15 patents since 2020 related to natural antimicrobial gels. Phase III studies may prove the potential efficacy improvements from 20 to 30% relative to SRP alone therapy by 2028, using AI-optimized formulations to enable personalized release rates due to an increased interest in non-surgical, natural, and alternative therapies in Asia-Pacific regions. Adding clove to periodontal therapy could present an alternative, natural, and relatively side effect-free approach, especially to patients who are looking into holistic practices. However, using clove should also be taken into consideration from an individual perspective, and it should be considered and utilized in conjunction with an overall periodontal therapy approach. Concluding, clove formulations are promising adjuvants to manage periodontal diseases, but further evidence and clinical supports are urgently needed to ratify their place in mainstream dentistry.

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SV: Writing - Reviewing and Editing. HY: Data Collection. RKT: Study Concept or Design.

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During the preparation of this work, the authors used ChatGPT in order to improve readability and grammar. After using ChatGPT, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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