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Clove oil in oral health: Therapeutic potential and applications

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Abstract
Oral infections, dental caries, periodontitis, and opportunistic oral candidiasis comprise a significant public health problem of a global scale that is further aggravated due to antimicrobial resistance and the side effects associated with conventional synthetic drugs. Clove oil, isolated from the dried flowers of *Syzygium aromaticum*, is proposed as a multi-targeted phytotherapeutic approach for preventive and remedial dental care. Its phytochemical features, powered by phenylpropenes like eugenol (50-90%) accompanied by small molecules like eugenyl acetate and β-caryophyllene, exhibit combined mechanisms of action: rapid local analgesia through voltage-gated Na^+ channel blockers and TRPV1 receptor inactivation, modulation of inflammatory cascades through inhibition of NFκB transcription and COX-2 activity, neutralizassstion of free radicals and also diminish the acid-induced decalcification of dental enamel. Its antimicrobial properties against primary oral pathogens like *Streptococcus mutans*, *Porphyromonas gingivalis* and *Candida albicans* work by permeabilizing cytoplasmic membranes of bacteria and *C. albicans*, inactivating streptococcal glucosyltransferases, degrading exopolysaccharidic matrices and blocking quorum sensing signalling molecules, although they have limitations related to volatile degradation, aqueous insolubility, unpleasant organoleptic characteristics and high-dose-mediated oral mucosal cytotoxicity. Advanced nanoemulsion-based systems and mucoadhesive nanoemulgels provide a potential remedy to address such factors, enhance dispersibility in saliva, promote delivery into biofilms and provide sustained release on the target oral niches. Standardization of bioavailable component concentrations and proper clinical investigation of these nano-delivery formulations are essential steps to their mainstream implementation in oral healthcare.

Keywords: *Syzygium aromaticum*, Eugenol, oral health, quorum sensing inhibition, nanoemulsion

Introduction
Oral infectious diseases, above all dental caries and periodontal disease, are a great public health problem worldwide. According to statistical reports from the World Health Organisation, dental caries occur in 60-80% of children around school age and nearly 100% of adults around the world [1]. Fundamentally, the pathogen of oral diseases is the dysbiotic microbial biofilms located in tooth surface and in the soft tissues of the oral cavity. Preventive and therapeutic approaches commonly are based on synthetic broad-spectrum antibiotics, like chlorhexidine gluconate, as well as traditional systemic antibiotic administration. But the long-term clinical use of synthetic antibiotics is often associated with negative side effects such as tooth staining, perturbation of the oral commensal microbial population, mucous shedding and the rapid development of multi-drug resistant bacterial [2].
As a possible measure to address the previously described disadvantages, research and development in the field of pharmacy have turned increasingly towards natural-derived bioactive complexes as alternative remedies for plant-based, multi-target treatments in the pursuit of their sustained development. Among these, clove oil, obtained from the odoriferous flower buds of *Syzygium aromaticum*, stands out as a promising candidate phytotherapeutic agent [3]. Clove oil-formerly established and used in traditional Chinese medicine, Ayurveda, and early Western medicine as an oral, clinical, and dental agent-is an exceptional topical anaesthetic, quickly analgesic, as well as an antibacterial agent with an obvious anti-inflammatory property. Modern pharmacodynamics supports that its therapeutic efficacy is the result of a complex phytochemical matrix containing eugenol as a major constituent [4].
This broad survey reviews the therapeutics of clove oil and its individual biologically active ingredients regarding their relevant application into dentistry. The botanical source and the qualitative and quantitative analysis of the chemical content of clove oil, a variety of pharmacodynamic actions in vitro and in vivo, activity against the main bacteria involved in both cariogenic and periodontal diseases and delivery by an innovative nanoemulsion-based delivery system so as to tackle its physicochemical disadvantages were elucidated with adequate research data to ascertain safe parameters for modern clinical use [5].

1. Clove Oil: Source, Composition and Bioactive Constituents
The essential oil derived from clove comes from the dried unexpanded flower bud, leaf or stem of *Syzygium aromaticum* (L.) Merr. or *Eugenia caryophyllata* Thunb., an evergreen tree belonging to the family Myrtaceae, which originated from Maluku, Indonesia [2, 6]. The range of volatile oil yield on dried whole flower bud samples is from 10 to 20% of total dry matter, whereas for industrial processes, the extraction procedure using hydrodistillation, steam distillation and organic solvent extraction has always been widely accepted. A higher percentage of active compound (up to 44%) can be extracted when using Soxhlet

extraction with ethanol or methanol and hence has a higher yield than the simple passive maceration [7].

In clove oil, the major volatile phenolic compounds and sesquiterpene derivatives comprise the overall chemical composition. As evidenced by analyses with GC-MS, eugenol ($C_{10}H_{12}O_2$; 4-allyl-2-methoxyphenol) is the principal API of clove oil essential oil (depending on plant tissue source, geographical origin and extraction procedure), accounting for typically between 50 to 90%. Other volatile elements that comprise the majority are eugenyl acetate ($C_{12}H_{14}O_3$; 5% to 19.1%) and β-caryophyllene ($C_{15}H_{24}$; 2.9% to 8.8%), with trace amounts of α-humulene, gallic acid, resins and various flavonoid glycosides, mainly quercetin and kaempferol, in minor concentrations [8, 9].

Table 1: Major bioactive constituents of clove essential oil (*Syzygium aromaticum*), detailing chemical formulas, relative abundance, chemical classes, and primary biological functions.

Bioactive Compound	Chemical Formula	Relative Abundance (%)	Class	Function
Eugenol	$C_{10}H_{12}O_2$	50.0% – 90.0%	Phenylpropanoid	Analgesic, local anesthetic, broad-spectrum antimicrobial, anti-inflammatory
Eugenyl Acetate	$C_{12}H_{14}O_3$	5.0% – 19.1%	Ester	Synergistic antioxidant, enzyme inhibition, remineralization promotion
β-Caryophyllene	$C_{15}H_{24}$	2.9% – 8.8%	Bicyclic Sesquiterpene	Anti-inflammatory via CB2 receptor binding, enhanced lipid membrane permeation
α-Humulene	$C_{15}H_{24}$	0.5% – 2.1%	Monocyclic Sesquiterpene	Complementary anti-inflammatory and antitumor properties
Gallic Acid	$C_7H_6O_5$	Trace – 1.5%	Trihydroxybenzoic Acid	Free radical scavenging, metal ion chelation, astringent effect

Pharmacological comparisons have shown that in certain cases whole clove essential oil shows higher biological activity than the extract of eugenol alone. This activity is due to further secondary synergy that occurs because other sesquiterpenes are not phenolic, as is eugenol [10]. These other compounds, like that of β-caryophyllene modify cell membrane permeability and thus permit entry of eugenol into the cell to enhance free radical scavenging and antimicrobial activity.

2. Pharmacological Properties of Clove Oil

The clinical utility of clove oil in dental medicine stems from a broad spectrum of pharmacological activities that simultaneously address pain, tissue inflammation, oxidative stress, and structural tooth degradation.

Neurosensory modulation & local anaesthetic: Clove oil, a historical dental analgesic, works through inhibition of reversible peripheral nerve conduction. Sodium channel blocker at voltage-dependent gates (Na_V), direct blockade of transmission along nociceptive A-δ fibers and C fibers within pulpal and periodontal tissue action potentials. Binding and initial activation of sensory neuron TRPV1; chronic activation results in immediate functional receptor desensitization, increased intracellular calcium levels and prolonged locally produced local analgesia [11, 12].

Control of the inflammatory cascade: Clove oil can modulate inflammatory processes via a number of transcriptional and enzymatic targets. Eugenol can inhibit COX-2 function, blocking the pathway between arachidonic acid and the inflammatory prostaglandin, PGE_2. At the molecular level, clove extracts can block the NF-κB signalling pathway. By inhibition of $I\kappa B\alpha$phosphorylation and degradation, eugenol blocks nuclear translocation of the p65/p50 NF-κB dimers, and transcriptionaly represses inflammatory cytokines, Il-IL-1β, IL-6, IL-17A, IL-36, and TNF-α [13]. It reduces the accumulation of CD11b+ granulocytes, decreases the expression of matrix metalloproteinases and offers protection of periodontal ligaments and alveolar bone against immunopathological destruction [14].

Biochemical Redox State Modulation: The presence of an active phenolic -OH moiety linked to an aromatic ring within eugenol makes this molecule a powerful electron/hydrogen-donating agent; thus, clove oil directly eradicates various ROS and RNS-namely, hydroxyl radicals, superoxide anions, and peroxynitrite [15]. Free radical scavenging through clove oil intervention inhibits further lipid peroxidation chain reaction within the mucosal cell membrane, protecting cell viability during severe periodontitis and chronic oxidative conditions [16].

Structural Enamel Protection and Remineralization: Besides impacting soft tissue biology, clove oil offers significant physical protection on hard tissue as well; Quantitative erosion tests proved that Clove oil, Eugenol, and Eugnyl Acetate effectively prevent enamel demineralization from ingested acids and bacterial acidogenesis by creating a hydrophobic film on the hydroxyapatite surface via surface energy modifications that result in a decreased rate of mineral leaching. The mineral-chelating strength and the enamel-protecting benefit conferred by clove oil appear comparable to low concentration of topical fluoride treatment that is aimed at tooth erosion prevention and remineralization [17, 18].

Table 2: Pharmacological modalities of clove oil, including biological targets, underlying molecular mechanisms, and resulting clinical outcomes in dental medicine.

Pharmacology	Biological Target	Mechanism	Outcome
Analgesic / Anesthetic	Voltage-gated Na^+ channels (Na_V), TRPV1 receptor	Blocks action potential conduction; induces secondary desensitization of nociceptive fibers	Immediate relief of pulpal and dental pain (anodyne effect)

Anti-Inflammatory	NF-κB signaling, COX-2, IL-17A / IL-36 axis	Inhibits p65 nuclear translocation; suppresses PGE_2 and inflammatory cytokine synthesis	Reduction of gingival edema, erythema, and periodontal tissue loss
Antioxidant	ROS, RNS, Malondialdehyde (MDA)	Hydrogen atom donation via phenolic $-OH$ group; halts lipid peroxidation	Mitigation of oxidative tissue injury in mucosal and periodontal disease
Enamel Protection	Enamel Hydroxyapatite $[Ca_{10}(PO_4)_6(OH)_2]$	Forms surface hydrophobic barrier; inhibits acidic calcium ion decalcification	Reduction of tooth erosion; enhancement of enamel remineralization

3. Clove Oil in Oral Health and Oral Infections

The complex anatomical structure of the oral cavity provides diverse microenvironments that support pathogenic bacterial and fungal colonizers. Clove oil has demonstrated therapeutic potential across several major oral pathologies.

Management of dental caries

Dental caries is a transmissible, biofilm-mediated disease that is caused by cariogenic microorganisms such as *Streptococcus mutans*, *Lactobacillus acidophilus*, and *Actinomyces* species. They metabolise carbohydrates in the diet to produce acid, which reduces plaque pH and results in enamel demineralization [19, 12]. Clove oil shows marked bactericidal activity against *S. mutans* and minimum inhibitory concentrations vary from 0.21 mg/ml to 1.0 mg/ml. Not only is bacterial growth inhibited but the formation of streptococcal glucosyltransferase (GTF) is suppressed by eugenol. Thus, streptococcal GTFs cannot synthesise insoluble extracellular glucans from sucrose that allow them to effectively attach strongly to the tooth enamel [20].

Periodontal Diseases

The primary pathogenic subgingival complex of anaerobic Gram-negative bacteria – *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, and *Fusobacterium nucleatum* – initiates a chronic inflammatory condition termed periodontitis, causing the host to mobilize defensive reactions against their expressed toxins, including lipopolysaccharides (LPs) [21]. Clove oil reaches the substructures of these complex bacterial conglomerates in a localized fashion, where they exert directly antimicrobial effects against the bacteria that cause the problem. Clove oils anti-inflammatory effect locally inhibits a key constituent (collagenase) of tooth-supporting structures and osteoclast-activating factors. In this manner, they help protect tooth supporting ligament and alveolar process [22].

Endodontic Therapeutics and Direct Pulp Capping

In restorative dentistry, eugenol is conventionally employed in a mixture of powder that it has had blended with it and a cement-making (liquid) component by the name of zinc oxide and these are commonly referred to as a "Zinc Oxide-Eugenol (ZOE) and these materials may be utilized as the final sealer in the space created around the restorative material, as root canal fillers, a temporary restorative covering and or temporary filling. In "vital" therapy with some direct capping, if the exposed tissue on the floor of the cavity is exposed pulp will respond because it requires protecting it from invading microorganisms so, eugenol at a very low rate, being delivered to that exposed pulp, gives to it an antiseptic and anodyne action and helps create a more favourable condition. A recent alternative being introduced to dentistry will provide a biologic alternative. Some bio-ceramics have similar effects [23, 24, 25].

Oral Mycoses and Opportunistic Infections

Generally, immunocompromised and aged patients, as well as individuals wearing removable prostheses for prolonged periods, are commonly subjected to oral candidiasis, most of which is due to *C. albicans*. Clove oil showed a potent fungistatic effect against *C. albicans*, which both sensitive and resistant to azoles. Eugenol targets ergosterol biosynthesis of the fungal membrane and disrupts the function of the fungal membrane. Additionally, it affects the development of the dimorphic characteristic of *C. albicans* to invade from the unicellular form into the hyphal form, thereby largely compromising its potential to invade the oral mucosal tissue as well as form durable biofilms on acrylic denture surfaces [26].

4. Antimicrobial Mechanisms of Clove Oil

The broad-spectrum antimicrobial activity of clove oil against Gram-positive, Gram-negative, and fungal organisms involves multiple distinct cellular targets, reducing the likelihood of single-gene mutation resistance.

Bacterial Cell Membrane Permeabilization: Lipophilicity and easy penetration into the lipid bilayer, which allows eugenol and sesquiterpenes co-present within the membrane, enables rapid entrance to the lipophilic core in bacterial cell membrane. In Gram-negative cells, eugenol can go through outer membrane LPS layers and enter the inner cytoplasmic membrane. It increases membrane fluidity, changes fatty acid composition and protein conformations inside the cell membrane [27]. Electron micrograph examination that, when treated with clove oil cell wall deformities, formation of pore structures in the cell membrane, and irreversible cell membrane disruption is produced. Therefore, some essential inner cell components are released into the exterior, such as K^+ ions, inorganic phosphate, ATP, and nucleic acids, which result in the loss of proton motive force quickly cell lysis [28].

Disruption of biofilm architecture: Pathogenic oral bacteria typically reside in organized biofilm colonies that are surrounded by matrix-producing extracellular polymeric substances (EPS). Biofilm-encapsulated micro-colonies demonstrated a 1,000-fold greater resistance to standard antibiotics than planktonic cells. Clove oil effectively penetrates mature biofilm matrices. Below the MIC dose, eugenol disrupts initial adhesion of the bacterium to the enamel pellicle, leads to decreased amounts of surface cell-bound adhesins and decreases the production of exopolysaccharides that maintain matrix integrity and expose the contained bacteria to the host immunity and the secondary mechanisms of clearance [29].

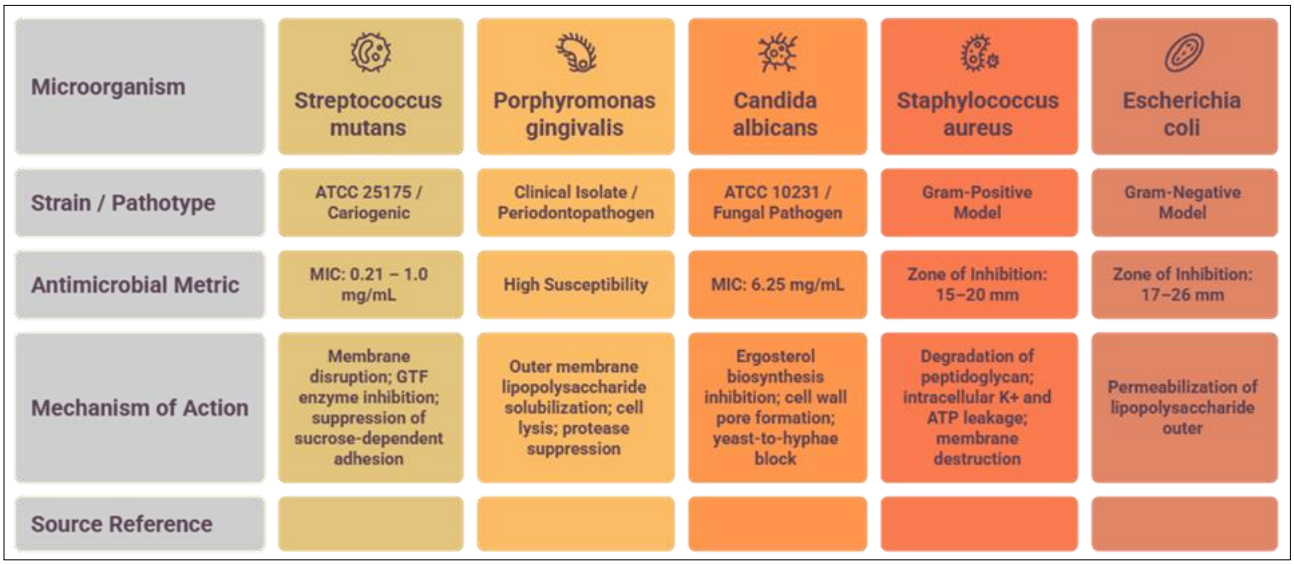


Fig 1: Antimicrobial spectrum, quantitative efficacy metrics, and key cellular mechanisms of action of clove oil and eugenol against major oral and model pathogens.

Reduction in virulence by Inhibition of Quorum Sensing: Bacteria use quorum sensing for communicating with each other so they can coordinate virulence factor expression, swarming mobility and biofilm formation. Clove oil serves as a natural quencher. Below the MIC, eugenol reduces the expression of autoinducer signals [30] (N-acylhomoserine lactones for Gram-negatives, oligopeptides for Gram-positives), which has been shown to reduce swarming motility, reduce pyocyanin production, and block hemolytic toxin export from such opportunistic pathogens as Pseudomonas aeruginosa and Staphylococcus aureus below the MBC dose, and does not impose selection on antibiotic resistance [31].

5. Clove Oil Delivery Using a Nanomulsion

A range of pharmaceutical issues hinder its application to the oral health area, while an unformulated bulk clove oil. Its high volatility, poor solubility in aqueous saliva; possibility of undergoing oxidative degradation in the presence of light and air and unpleasing smell and taste cause problems. Moreover, high eugenol content causes undesirable localized mucosal irritation and toxicity. Nanomulsions in particular nanotechnology delivery system, address the problems [32].

Formulative Engineering of Clove Oil Nanoemulsions

A nanoemulsion is a thermodynamically or kinetically stable isotropic system that contains oil, water and a combination of surfactant and co-surfactant (S_{mix}) with droplet size usually between 20 and 200 nm. The formulation procedures are either low-energy emulsification methods, like phase inversion temperature (PIT) or phase inversion titration (PIT) or high-energy mechanical homogenization (e.g., high-pressure homogenization (HPH) or sonication) [33]. The internal hydrophobic phase contains oil phase (clove oil), which is stabilized in the external continuous aqueous phase by biodegradable surfactants such as Polysorbate 80 (Tween 80) along with co-surfactants like Polyethylene glycol 400 (PEG 400). In order to prolong residence time at oral sites, nanoemulsions can be loaded into a hydrogel matrix e.g. Carbopol 980, gelatine or chitosan, to formulate nanoemulgels. The hydrogel network formed here can be mucoshesive, facilitating controlled release of the entrapped essential oil at periodontal pocket or across mucosal surfaces [34, 35].

Physicochemical Characterization and Stability

For effective development of clove oil nanoemulsion, the systematic analytical characteristics are needed:

Droplet Size Distribution and Zeta Potential: The measurements by DLS ensure that the size of dispersed nano-droplets was less than 100 nm and PDI was less than 0.2 so as to get good homogeneity of droplet sizes. Moreover, the values of the zeta potential (ζ) of the formulation are higher than -20 mV which could prevent droplets coagulate by electrostatic repulsion, which lead to the physical instability of the formulations like phase separation and coalescence [36]. Morphological Evaluation: TEM shows individual spherical nanodroplets and that they are uniformly dispersed into the gel matrix [37].

Thermodynamic Stability: Formulas were subjected to forced ageing processes including heating-cooling cycles 4°C and 45°C, centrifugation at 3500rpm at a temperature, freeze thaw cycles between -20°C and 25°C to make sure the formulas being stability without drug precipitation or phase inversion [38] .

Encapsulation Efficiency: Using a high-performance hydrogel to entrap, the encapsulation efficiency of eugenol were calculated as 84.65% ± 0.12%, which ensures reduction of early loss [37].

Pharmacokinetic and pharmacodynamic benefits

The effectiveness of therapeutic application of clove oil is tremendously improved when it is encapsulated at the nanoscale. The large interfacial surface area owing to smaller droplet size ensures much better diffusion through mucosa into a much more intricate subgingival biofilm. Controlled release kinetics allow avoiding the spike in concentration, thus maintaining an optimal topical level of eugenol, thus ensuring epithelial toxicity minimization. Nanoencapsulation further protects the volatile constituents from being wasted as well as masks the unpleasant smell and taste [39, 40].

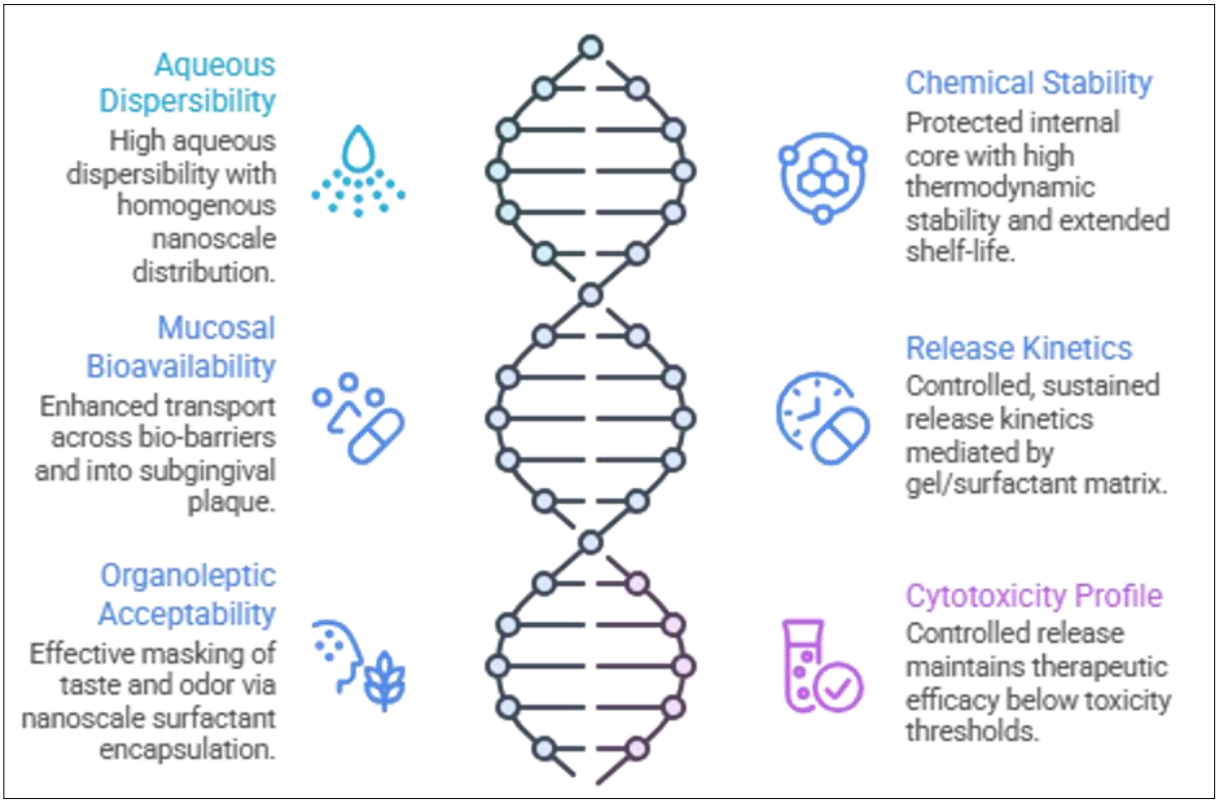


Fig 2: Comparative evaluation of the physicochemical, pharmacokinetic, organoleptic, and toxicity profiles of unformulated bulk clove oil versus nanoemulsion delivery systems.

6. Safety, Challenges and Future Perspectives

Evaluating the therapeutic potential of clove oil requires a clear understanding of its toxicological profile, formulation constraints, and requirements for clinical translation.

Toxicology and Cytotoxicity Profiles

The dose-response in biological activities appears to involve a sharp curve with regard to eugenol: low doses (0.1%-1.0%v/v) are, for all intents and purposes, safe and exert protective activity through anti-inflammatory, antioxidant and anti-cariogenic actions with minimal effects on cell toxicity; high systemic or direct administration produces the opposite effects. In fact, in an in vitro assay for cell viability, higher concentrations of eugenol lead to cytotoxic effects in human oral keratinocyte cells, gingival fibroblast cells, macrophages, and osteoblast cells in a concentration-dependent manner [41]. Direct mucosal administration of the concentrated form of eugenol has been shown to induce contact stomatitis, discrete desquamation, discrete localized tissue necrosis, and allergic contact dermatitis while ingestion (accidental or high dose over-administration) of the high systemic concentration leads to marked, debilitating clinic presentation: hepatocellular necrosis, pronounced elevation of the liver enzymes profile, acute renal insufficiency, acid-base disorder and coma with convulsing activity as well as centralized nervous system depression [42] .

Standardization and Regulatory issues

The most significant hurdle in converting raw clove oil into standardized, reproducible clinical preparations lies in the inherent variability of botanical extracts. The actual phytochemical components of *S. aromaticum* essential oil differ depending on: geographical location, soil composition, season of the harvest, maturity of the plant, and method of extraction used to collect [43] the oil. All these factors make it difficult to have batch-to-batch reproducible identical quality. Secondly, whereas clove oil as a botanical extract is GRAS as a food additive and a flavouring agent; the drug, pure eugenol, has not received FDA approval as systemic monotherapy for any specified diseases. Bridging this regulatory gulf necessitates standardizing levels of the bioactive markers to a standardized marker concentration ($\geq 80\%$ eugenol content) along with batch testing to validate the standardization [44, 45].

7. Future Directions and Translational Implications

To capitalize the clinical prospects of Clove oil in current-day dentistry, it is necessary to conduct studies focusing on various aspects:

Smart Stimuli-Responsive Carriers- These smart nano-carriers could be made to release the eugenol when the pH becomes low due to acidic environments generated by caries or it can be designed in such a way that bacterial lipase would be responsible for eugenol release[46] .

Hybrid Restorative Materials- Eugenol will be encapsulated in the nano- carriers and incorporated to smart bioceramic sealers, GICs, and restorative resins. Long-term intrinsic antibacterial properties would be maintained and would not affect the material properties at all [47].

Subgingival Nanoemulgels- Rigorous planned Clinical Trials for the effective utility of subgingival nanoemulgels on adjunctive therapy to scaling and root planing for periodontal patients are required [48].

Daily hygiene formulations- Nanostructured Eugenol will be loaded in various dental care formulations for its daily use, which could include non-irritant alcohol-based mouthwash, toothpaste, or irrigation liquid for long-term biofilm maintenance in mouth rinse or a specialised toothpaste [49, 50].

Conclusion

Clove oil and its active component eugenol constitute a clinically evidence-based phytotherapeutic platform for dentistry, working in synergy through a multi-target approach, with localized anesthetic and anti-inflammatory and broad-spectrum antimicrobial activities as well as antioxidant effects, able to destabilize bacteria, inhibit glucan formation and adhesion into biofilms, impair quorum sensing and block the initial tooth demineralization with no antibiotic-resistance promotion. As raw essential oils are volatile, prone to oxidize and locally toxic at high doses, nanoemulsions may represent a real opportunity to circumvent this major limitation by increasing oil solubility, enhancing penetration into biofilms and providing controlled release with lower tissue toxicity. Further efforts directed at standardization of bioactive components and further clinical studies will allow the formulation of clove-oil-nano-based treatments suitable for routine preventive and restaurative dentistry.

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