ISSN 1998 – 409X

REVIEW ARTICLE

# Therapeutic Prospects of *Ageratum conyzoides* for Oral and Periodontal Health

**Dolu Degio[1], Arun Suriyan[2], Kirthanaa Elumalai[1], Abhilash Phukon[1], Praveen Irudiyaraj[1], Ganesh Kumar Anbazhagan[1]**

*[1]Department of Microbiology, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences, Chennai, Tamil Nadu, India, [2]Department of Pharmacology, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences, Chennai, Tamil Nadu, India*

## Abstract

*Ageratum conyzoides* (Asteraceae), also called goat weed, has become a focus of ethnopharmacology due to the diverse active compounds it contains and potential application in the treatment of oral and periodontal diseases. This review summarizes the morphological characteristics and phytochemical composition of Ageratum conyzoides, with particular emphasis on its potential therapeutic applications in maintaining oral and periodontal health. It was experimentally shown that it provides a powerful inhibition of pathogenic microorganisms involved in periodontitis with their membrane lysis and quorum sensing inhibition of biofilm. Ethanolic extracts of the leaves exhibited high activity with minimum inhibitory concentration of 125 µg/mL and inhibited proinflammatory cytokines (tumor necrosis factor, interleukin [IL]-1β, IL-6) and oxidative stress through nuclear factor kappa B and Mitogen-activated protein kinase pathways. Safety assessment of the herb in case of oral administration of the extract, where hepatotoxic pyrrolizidine alkaloids were absent, revealed low toxicity (no-observed-adverse-effect level of 2000 mg/kg) and the possibility of formulation of this plant in dental mouthwashes and gels. Moreover, enhanced wound healing was also confirmed by experiments with increased collagen deposition and proliferation of the epithelial layer in models, which can serve as evidence of the potential of *A. conyzoides* for regeneration of gingival tissue. Still, there are several difficulties to be overcome, such as the variability in the content of phytochemicals depending on geography and season and the lack of clinical trials.

**Key words:** *Ageratum conyzoides*, antimicrobial activity, ethnopharmacology, oral health, periodontal therapy, phytochemistry, sustainable herbal medicine

## INTRODUCTION

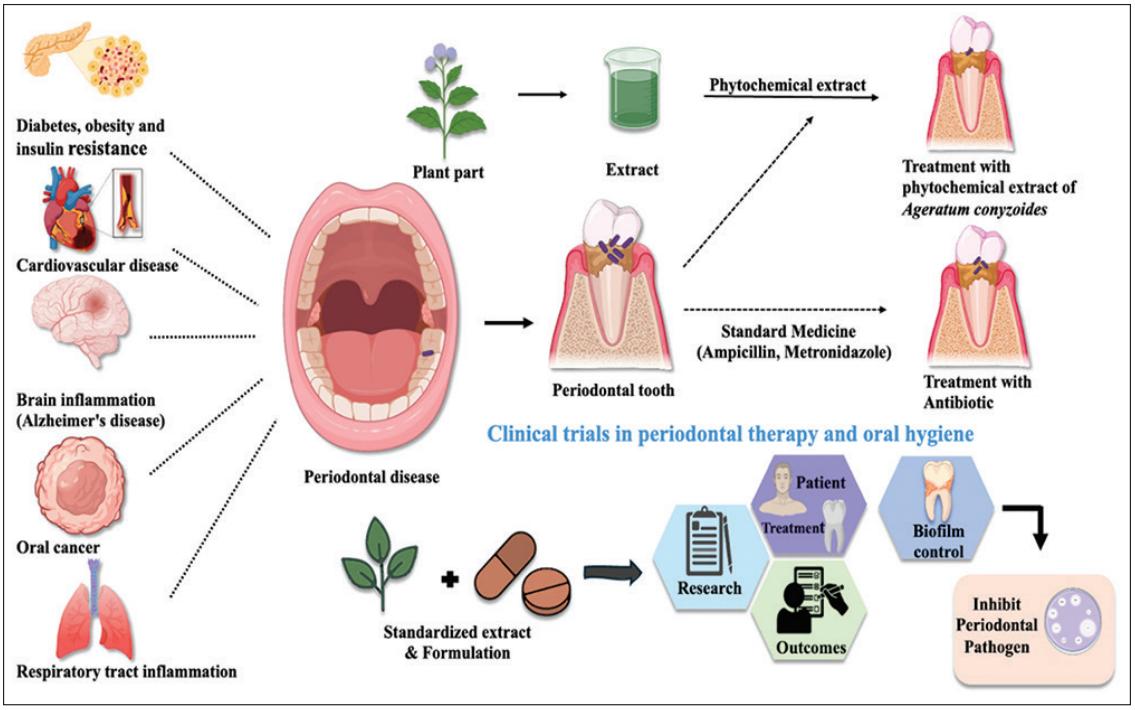
Gingivitis and periodontitis are some of the most common inflammatory diseases in the world, impacting over 50% of the world's population and contributing to tooth decay and health issues. Periodontal diseases are common in countries such as India, with >80% of individuals suffering from the condition, which is mainly attributable to low levels of knowledge about the importance of oral hygiene, reduced access to dental care, and social and economic inequalities. These disorders are predominantly instigated by microbial plaque biofilms harboring bacteria such as *Fusobacterium nucleatum*, *Aggregatibacter actinomycetemcomitans*, and *Porphyromonas gingivalis*, which elicit a dysregulated immune system reaction in the host, resulting in connective tissue degradation and alveolar bone resorption.[1,2] It is noticed that the use of traditional medicine, especially plant medicine, has surged in developed and developing countries around the world and is invariably classified together as complementary and alternative medicine. The World Health Organisation estimates that as much as 80% of the population in Africa, parts of Asia, and Latin America use herbal remedies as their first line of defence.[3] Although the traditional methods of periodontal treatment such as antibiotics and scaling work, they have their drawbacks in the form of antibiotic resistance, recurrence, and adverse effects, prompting the search for plant-derived alternatives to antibiotics.

**Address for correspondence:**
Ganesh Kumar Anbazhagan, Department of Microbiology, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences, Chennai, Tamil Nadu, India.
E-mail: drgkanbazhagan@gmail.com

**Received:** 12-08-2026
**Revised:** 16-09-2026
**Accepted:** 23-09-2026

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## GRAPHICALABSTRACT




*Ageratum conyzoides* (Asteraceae, AC), popularly known as goat or Billy goat weed, has been a subject of great scientific interest with reports of oral activity and periodontal activity. Conventionally, this plant has been used in Africa, South America, and Asia for its antibacterial, anti-inflammatory, analgesic, antioxidant, and wound-healing effects. According to indigenous sources, its medicinal applications are extensive, most notably for skin infections, gastrointestinal issues, inflammation, breathing problems, and gut ailments.[4]

The bactericidal and antibiofilm effects of *A. conyzoides* extracts (essential oils and ethanolic fractions) have also been confirmed in recent *in vitro* and *in vivo* investigations. However, these extracts had antimicrobial activity comparable to or greater than, conventional antibiotics, and less cytotoxicity to oral epithelial cells. The results are encouraging; however, the therapeutic value of this medicinal plant is restricted due to the variation in phytochemical compounds during different seasons and locations, differences in the extraction techniques employed, and a lack of toxicological data and standardized information. Moreover, the use of herb extracts in biomaterial-based hydrogel systems has been found to be very active against wound-associated infections, indicating its potential application in developed drug systems and regenerative medicine.[5]

*A. conyzoides* has considerable anti-inflammatory and wound-healing properties that may be used to treat periodontal and oral diseases. The ethanolic extract of AC, when applied topically, promotes wound healing in model animals in different ways, including wound contraction, epithelium proliferation, collagen deposition, and breaking strength of wounds. In one study, the tensile strength of wounds that were treated with the extract was approximately 40% higher than the control, and the wounds recovered considerably faster.[14] Moreover, its anti-inflammatory properties have been shown, as crude extracts suppress the activation of the NLRP3 inflammasome in immune cells, the activation of nuclear factor kappa B (NF-κB) and Mitogen-activated protein kinase (MAPK) pathways, and the production of pro-inflammatory cytokines like interleukin (IL)-6, IL-17A, and tumor necrosis factor-α (TNF-α). Periodontal disease is related to microbial insult and dysregulated host immune response, which results in progressive tissue destruction. Hence, it can control inflammatory mediators and facilitate mucosa repair.[6]

The presence of secondary metabolites such as alkaloids, flavonoids, tannins, saponins, terpenoids, coumarins, and steroids in AC makes it a popular herb for use in ethnomedicine. Pharmacognostic analysis revealed that these are present in different parts of the plant, with the highest level of flavonoids and phenols in leaves.

The review outlines the diagnostic characteristics, pre-clinical therapeutic possibilities, and bioactive molecules of *A. conyzoides* for oral and periodontal health. It evaluates the plant profile and plant mechanisms of bacterial suppression, inflammation modulation, oxidative balance, and the potential application in modern dental products such as mouthwashes and gels. Identification of knowledge gaps and future research directions should be determined to validate AC as a potential phytotherapeutic option in dentistry.

## Habitat and distribution of *A. conyzoides*

*A. conyzoides* is an annual fragrant herb native to tropical America and West Africa, and widely naturalized throughout tropical and subtropical regions of the world. It is found on disturbed sites like agricultural fields, grasslands, roadsides, and forest edges, and has clear invasive potential. It is widespread in India, from lowlands to hilly regions, and is found in the states of Tamil Nadu, Kerala, Karnataka, Maharashtra, and some of the states of Northeast India. This plant's adaptability and environmental hardiness make it a problem and a valuable source of phytochemical and medical research.[7] Spatial mapping through GIS tools shows the extensive naturalization, invasion, and spread of *A. conyzoides* throughout tropical and subtropical areas, as depicted in Figure 1.

## Biological activity of different plant extract

Oral pathogens such as *P. gingivalis* and *Streptococcus mutans* are suppressed by bioactive phytoconstituents that attenuate oxidative stress in gingival tissues, such as terpenoids, alkaloids, flavonoids, Precocene I and II, ageratochromene, and alkaloids. These bioactive compounds isolated from *A. conyzoides* possess antioxidant and antibacterial properties, and anti-inflammatory effects, and decrease inflammatory mediators associated with periodontitis.

It is common for *Streptococcus pneumoniae* to be found in the oral cavity, and for it to initiate periodontal apparatus inflammation, thereby developing cariogenic disease, particularly in people who do not practice proper dental hygiene. The bioactive potential of the botanical formulation has been tested on antibacterial activity with agar well diffusion method. Minimum inhibitory concentration (MICs) and minimum bactericidal concentration were determined using the microdilution method. The antibiofilm activity of the fractions was evaluated by a modified crystal violet test, and the optical densities (ODs) were recorded. Based on ODs measurements, the herbal extract showed significant inhibition of the formation of biofilm, with inhibition zone ranging from 9 to 23 mm. Such results indicate a potential for use along with the standard antimicrobial drugs.[8] A consolidated overview of the pharmacological activities of different *A. conyzoides* extracts is presented in Table 1.

A major proportion of studies on phytochemistry have focused on the essential oil of this plant. The oil content ranges arbitrarily from 0.11% to 0.58% for leaves and from 0.03% to 0.18% for roots, depending on the periods of the year. Hydrodistillation of the fresh plant material yielded an essential oil content of approximately 0.2% (v/w).

Among these phytochemicals, Precocene I was found at the highest level. Based on previous studies, the oil concentration of the seeds was maximum at 26%. In addition, the roots and leaves contain oil at approximately 0.11–0.58% and 0.03–0.18%, respectively. Phytoconstituents discovered in different components of *A. conyzoides*, such as flowers, stems, oil, and the entire plant, are listed in Table 2. The vital oil of *A. conyzoides* comprises various flammable and non-flammable chemicals. Monoterpenes and sesquiterpenes are flammable. Non-flammable chemicals include gallic, coumalic, benzoic, protocatechuic, p-hydroxybenzoic, sinapic, and coumaric acids, as well as flavonoids such as kaempferol, quercetin, and their glycosides.[11] The biological actions of various secondary metabolites extracted from the vital oil of *A. conyzoides* are summarized in the table.

## Antimicrobial activity

*F. nucleatum*, *A. actinomycetemcomitans,* and *P. gingivalis* are common pathogenic bacteria that cause periodontal ailments. The ethanolic leaf extract of *A. conyzoides* contains abundant

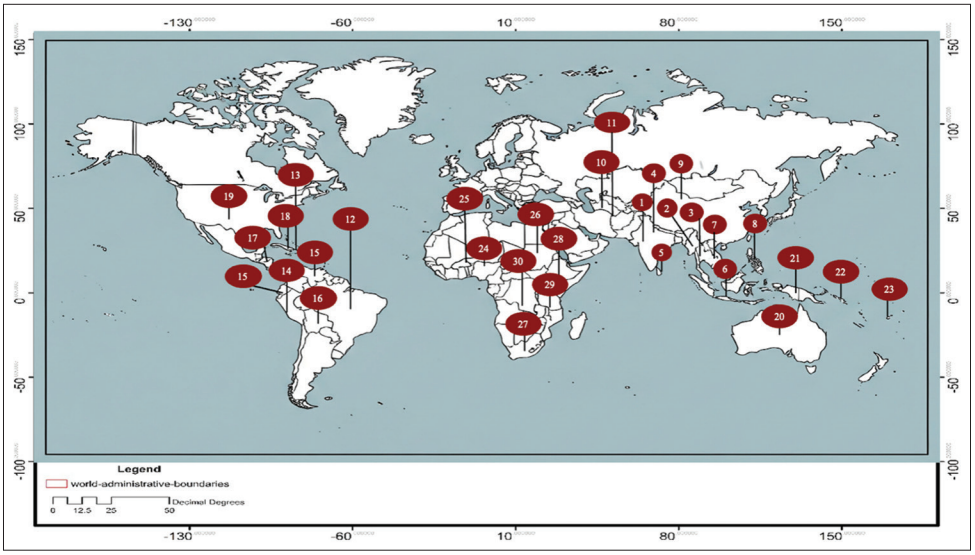



**Figure 1:** Geographical distribution of *Ageratum conyzoides* using GIS and ARGIS 10.8

**Table 1:** Pharmacological potential of *Ageratum conyzoides* extracts and their bioactivities

| Extract | Source | Bioactivity | References |
|---|---|---|---|
| Aqueous extract | Whole plant | Suppression of IL-1β and TNF-α, inflammation modulation, radical scavenging activity | [8] |
| Ethanol extract | leaves | Inhibition of *Streptococcus mutans* and *Porphyromonas gingivalis* biofilms, anti-plaque activity | |
| Methanol extract | Whole plant | Wound healing enhancement, antimicrobial activity against *Staphylococcus aureus* and *E. coli* | |
| Hydroalcoholic extract | Aerial parts | Cytoprotective and oxidative stress-modulating effects in oral epithelial cells | [9] |
| Methanol root extract | Root | Induction of apoptosis in carcinoma cell lines, cytotoxic activity | |
| Hydroalcoholic | Whole plant | Modulation of Inflammatory mediators in experimental models | |
| Ethanolic leaf extract | Leaves | COX-2 pathway inhibition, reduction of prostaglandin synthesis | |
| Aqueous extract | Whole plant | Antifungal activity against *Candida albicans* and dermatological pathogens | [10] |
| Lyophilized powder | Leaf | Neuroprotective and anxiolytic effects via GABAergic modulation | |
| Alcoholic extract | Leaves | Free radical scavenging activity | |
| Alcoholic extract | Whole plant | Radioprotective effects in experimental systems | |
| Methanol extract | leaf | Cytotoxic and antiradical activity | |
| Ethanol extract | leaf | Elevated phenolic content, antihyperglycemic activity | |

IL-1β: Interleukin-1 beta, TNF-α: Tumor necrosis factor-alpha, COX-2: Cyclooxygenase-2

**Table 2:** Major phytochemical constituents reported in *Ageratum conyzoides*

| Sl. No. | Phytochemical class | Representative constituents discussed |
|---|---|---|
| 1. | Chromenes | Precocene I, Precocene II, ageratochromene |
| 2. | Terpenoids | Monoterpenes and sesquiterpenes |
| 3. | Phenolic acids | Gallic acid, coumalic acid, benzoic acid, protocatechuic acid, p-hydroxybenzoic acid, sinapic acid, coumaric acid |
| 4. | Flavonoids | Kaempferol, quercetin and their glycosides |
| 5. | Alkaloids | Alkaloids reported in phytochemical investigations of the plant |
| 6. | Tannins and other polyphenols | Reported secondary-metabolite groups |
| 7. | Saponins | Reported secondary-metabolite group |
| 8. | Coumarins | Coumarin-related compounds |
| 9. | Steroids | Steroid-related constituents |
| 10 | Glycosides | Cardiac glycosides and other reported glycosides |

phytochemicals that demonstrate potent inhibitory effects on key pathogens implicated in periodontal diseases. The minimum inhibitory doses were 250 µg/mL for *F. nucleatum* and 125 µg/mL for *P. gingivalis*. The bioactive constituents of the extract interfere with multiple stages of biofilm development.[12] Proposed mechanisms include disruption of bacterial cell membrane integrity, inhibition of proteolytic enzymes, and attenuation of quorum sensing pathways.

Although various *in vitro* studies report significant inhibitory activity of *A. conyzoides* extracts against periodontal pathogens, most used techniques such as agar diffusion and microdilution assays without standardized extract characterization. MICs are difficult to compare between different studies due to the use of different extraction solvents, phytochemical concentrations, or plant source. Few studies have also assessed time-kill kinetics, resistance modification, and synergy with traditional antimicrobial agents in clinically relevant biofilm settings. However, these data are often not reproducible due to methodological variation and a lack of standardized bioassay methods to describe antibacterial activity; many such reports exist.

### Activity against *Gardnerella vaginalis*

In the present study, the antimicrobial activity of mentrasto (*A. conyzoides*) ethanol extract was analysed with two other herbs, gervao (*Verbena officinalis*) and malva branca (*Malva sylvestris*), against *G. vaginalis,* which has been detected in oral swabs samples and may contribute to periodontal risk. Concentration of 50,100 and 200 mg/mL demonstrated measurable antibacterial activity, with *A. conyzoides* exhibiting the greatest inhibitory effect among the tested extracts.[13]

### Activity against *Aspergillus* spp.

Phytochemical screening of AC determined the presence of alkaloids and resins. Terpenoids, cardiac glycosides, flavonoids, glucosides, and steroids. The aqueous and ethanolic extract of *A. conyzoides* L. shows inhibition of *Aspergillus fumigatus*, *Aspergillus terreus*, *Aspergillus niger*, *Aspergillus ustus,* and *Aspergillus tamari*. The extract of *A. conyzoides* (AC. E) had MIC ranging from 794 to 50 µg/mL against *Aspergillus* spp., and the ethanolic extract showed the lowest MIC (44.668 µg/mL) against *A. tamari*. In addition, the MIC against *A. fumigatus* was higher. Compared with itraconazole (3.890 µg/mL), the extract demonstrated substantially lower potency.

Laboratory studies demonstrate suppression of medically important fungal organisms, although the potency remains lower than that of established antifungal medications. This raises concerns regarding the realistic clinical doses of oral preparations. Furthermore, cytotoxicity toward human oral epithelial or fibroblast cells has not been thoroughly assessed in parallel antifungal assays, limiting the interpretation of safety and efficacy.[14]

Laboratory experiments have demonstrated the extract's antifungal activity against medically relevant fungal organisms, but the antifungal activity seems to be relatively low when compared to other widely used antifungal drugs. This poses the question of the achievable concentration via clinically relevant oral doses. Furthermore, very little has been done to investigate the effect of the extract on human oral epithelial and fibroblast cells in terms of cytotoxicity, along with the assessment of its antifungal properties. Thus, the available evidence is far from being sufficient to evaluate fully the extract's safety profile and therapeutic potential.

### Activity against *Blastomyces dermatitidis*

Although spore inhalation is the primary means by which *B. dermatitidis* infects the lungs, it may also enter the circulation and travel to the oral mucosa without first passing through the mucous. Research has shown that the extract of *A. conyzoides* may suppress *B. dermatitidis*. The study revealed that the ligands (sitosterol, catechin, stigmasterol, and 5-benzamido-4-oxo-6-phenylhexanoic acid) came into contact with and established very good binding capacity regarding the three key antifungal drug-targeting receptors (thymidylate synthase, squalene epoxidase, and lanosterol 14-alpha), which exhibited robust inhibition compared to conventional medications.[15]

### Activity against *F. nucleatum*

*F. nucleatum* is a gram-negative anaerobe. In dental plaque biofilms, it acts as a bridging organism, leading to the coaggregation of early and late colonizers and contributing to gingivitis and chronic periodontitis by promoting inflammatory cytokine production and epithelial cell invasion immunological regulation through virulence factors such as FadA adhesin. *F. nucleatum and P. gingivalis* have synergistic pathogenicity. However, there are not many direct investigations on *A. conyzoides* and *F. nucleatum.*

Previous research by Achmad *et al*. reported that *Ageratum conyzoides* leaf extract exhibited antibacterial activity against Porphyromonas gingivalis, a major periodontal pathogen associated with periodontal tissue inflammation and often detected alongside *Fusobacterium nucleatum.* The study reported a maximum inhibition zone of 16.25 ± 0.66 mm at 100% extract concentration, indicating the potential of the extract to suppress bacterial growth. However, the study did not establish the specific MIC range of 64–128 µg/mL or directly demonstrate inhibition of gingipain activity by phenolic compounds. Further investigations are required to determine the active constituents and their mechanisms of action against periodontal pathogens.[16]

### Activity against *Candida* spp. and *Staphylococcus aureus*

Contaminants in the oral cavity, such as *Candida* spp., are opportunistic fungi that can cause oral candidiasis in immunocompromised patients. They adhere to the epithelial surface, create biofilms, and release phospholipases and proteases that can harm host tissues. When *Candida* and *S. aureus* coexist in biofilms, they may result in synergistic pathogenicity. The ethanolic extract and ether showed significant antibacterial action against *S. aureus* and *Candida albicans*.[10] The investigation showed that the methanolic extract showed a good zone of inhibition against *S. aureus* and *C. albicans* and had a higher value than the ether extract. Terpenoids, coumarins, flavonoids, and alkaloids exert antibacterial effects by interfering with enzymatic activities. Although this study did not specifically focus on oral isolates, the known suppression of pathogens may show potential in the treatment of dental infections [Figure 2].[8] summarizes the antimicrobial activity of the extract against fungal and bacterial pathogens associated with oral health.

Preclinical studies support the antihyperglycemic potential of *A. conyzoides*, demonstrating notable reductions in blood glucose levels along with modulation of oxidative stress pathways. The water-based and methanolic components of the herb markedly reduced blood glucose levels, especially in diabetic mice. This suggests insulin-sensitizing or insulin-mimetic properties. At higher doses, the hypoglycemic action was more clinically relevant, indicating a dose-dependent mechanism. The plant contains high concentrations of phenolic and flavonoid compounds that may influence glucose metabolism and improve the activity of pancreatic β-cells. The proposed mechanism linking phytochemical-mediated glycemic control with oxidative stress reduction in oral tissues is summarized in Figure 3.

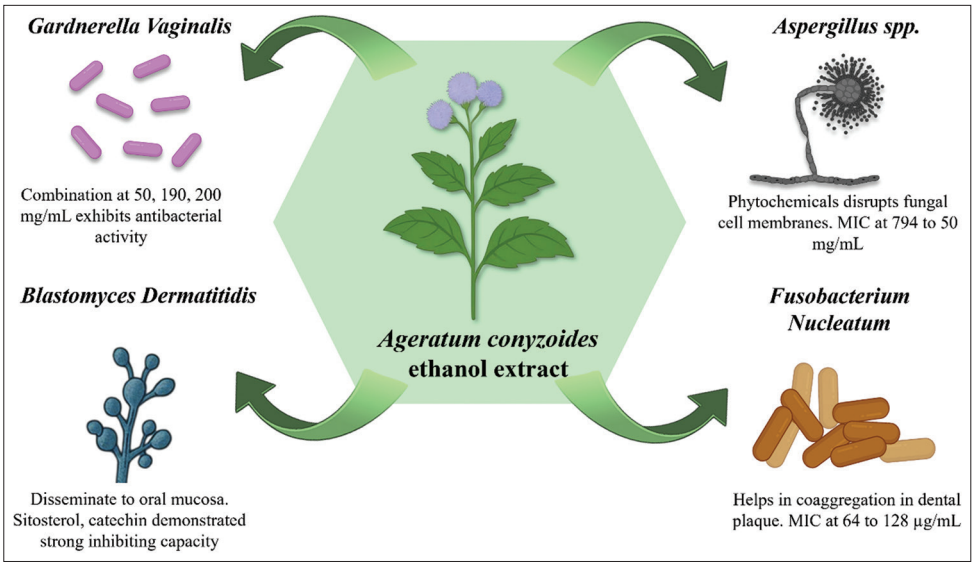



**Figure 2:** Hypoglycemic effects on oral health and its molecular mechanisms on *in vivo* model

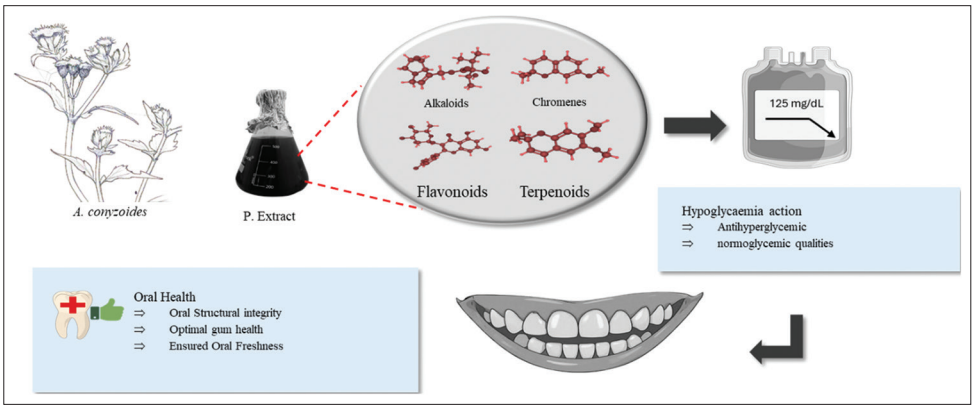



**Figure 3:** This figure illustrates glycemic regulation by plant phytochemicals that reduce oxidative stress across the mouth's soft-hard tissue zones

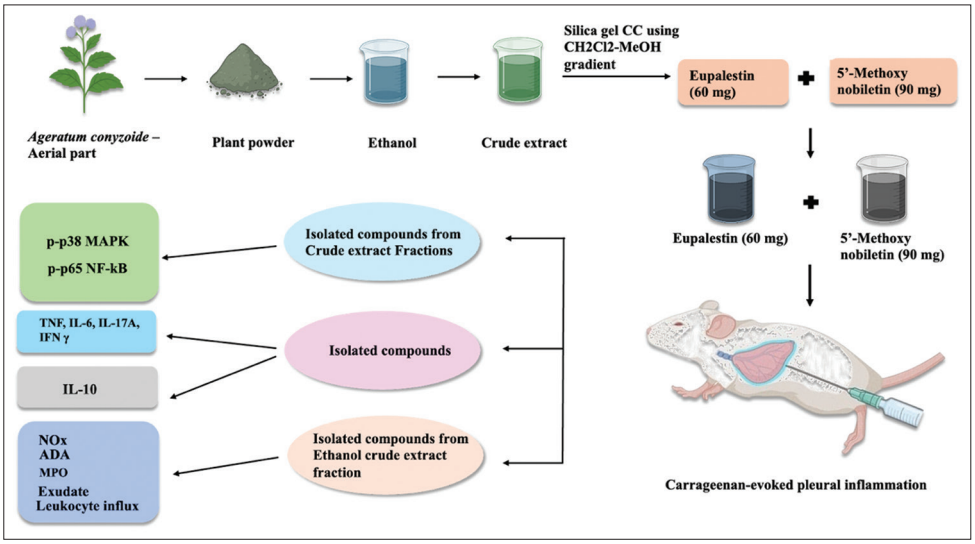



**Figure 4:** Isolation of bioactive compounds and their anti-inflammatory mechanisms from *Ageratum conyzoides* in a mouse model

Ethanolic extract of *A. conyzoides* has been shown to reduce carrageenan-induced paw swelling in rats, but no toxicity studies have been done. Moreover, anti-inflammatory activity was observed in different chronic inflammation models with

hydroalcoholic extract, such as cotton pellet granuloma and formaldehyde-induced arthritis. Both NF-κB and p38 MAPK signaling pathways were shown to be inhibited, with regulation of leukocyte infiltration. Treatment with AC significantly reduced the levels of leukocytes migration and nitric oxide production, and raised levels of proinflammatory cytokines (IL-6, IL-17A, TNF-α, and interferon- γ), and the activities of neutrophils and monocytes were also decreased. The result shows the ability of the plant to inhibit immune cell action in the inflamed area. MeONOB, eupalestin, and 1,2-benzopyrone were identified as compounds to inhibit phosphorylation of NF-κB and p38 MAPK. Inflammation-modulating activity of the pathways was revealed by the data acquired from experimental studies and is presented scheme in Figure 4. All of the above gives rise to the belief that isolated compounds can be regarded as good candidates for the agents being produced for managing inflammation.

## THERAPEUTIC IMPLICATIONS OF HERB EXTRACT IN THE MANAGEMENT OF GINGIVAL AND ORAL INFLAMMATORY CONDITIONS

In this research, the efficacy of the bandotan extract of the leaves of *A. conyzoides* into hindering the development of the bacteria that are the cause of periodontitis (*P. gingivalis*) was studied. While testing the *A. conyzoides* L. (bandotan) leaf extract, it was revealed that it exhibits dose-dependent action on bacteria. Basically, the maximum concentration of the bandotan extract (100%) causes the highest inhibition zone (16.25 ± 0.66 mm) against *P. gingivalis* compared to metronidazole. The plant has certain active components that are capable of promoting its high antibacterial effect, including flavonoids, saponins, polyphenols, and essential oils. The AC-1 compound extracted from it is effective against a number of both Gram-negative and Gram-positive bacteria.

The quality and source of the herbs are equally important for obtaining good results. Healthcare workers must keep up with the latest information and use it responsibly. In dentistry, the extracts of this herb are used as antioxidants, antimicrobials, anti-inflammatories, and pain relievers. These natural herb extracts help people with periodontitis and gingivitis by controlling microbial plaque.[17]

The preclinical findings of *A. conyzoides* extract indicate evidence-based pharmacological effects in periodontal management, especially in the treatment of periodontal ailments and maintenance of overall oral hygiene and health care. Common pathophysiological factors of periodontal ailments include Gram-negative bacterial colonization, immunological inflammatory reactions, and progressive tissue lysis. *A. conyzoides* represents a potential botanical adjunct for avoiding and managing such ailments due to its extensive antimicrobial, antioxidant, and anti-inflammatory properties.

## RISK ASSESSMENT AND TOXICOLOGICAL INSIGHTS

With its bioactive constituents having anti-inflammatory and antimicrobial effects, *A. conyzoides* can be utilized for treating diseases of dentogingival and periodontal tissues; however, its employability requires much caution based on toxicity considerations. PAs, or pyrrolizidine alkaloids, are the toxic ones of plants, particularly necine-type PAs like lycopsamine and echinatine, known for their hepatotoxic and genotoxic activities.[6]

*In vivo* toxicity tests conducted in rodents revealed that AC extract use resulted in liver enlargement, an increase in liver enzyme activity in the serum and resulted in altered organ weight but did not cause any hepatotoxic changes as a result of its PA content. Even a dose of 2000 mg/kg of *A. conyzoides* ethanolic extract was found to have no significant toxicity in rats in a 90-day toxicity test and determined as the no-observed-adverse-effect level. The recent identification of pyrrolizidine alkaloids in AC, confirmed by liquid chromatography–mass spectrometry (LC-MS) analysis, emphasizes the importance of thorough phytochemical evaluation before its therapeutic application.[18]

## CONCLUSION

Preclinical evidence implies bactericidal and cytokine-modulating properties of *A. conyzoides,* making it a promising candidate for therapy of periodontal conditions and its use in preventive medicine. Mechanism of action of this herb makes it a valuable component for producing herbal preparations for oral use, including mouth rinses and gels. Despite the presence of promising preclinical data, there is a lack of clinical proof of its efficacy and contradictory evidence regarding the phytochemistry of various species and possible geographical variations of the herb.

This examination combines data about *A. conyzoides*' ability to protect against microbes and to heal, although the use of the plant may go beyond experimental research. Another advantage is combining historical traditional information and research in modern pharmacology. It is important to analyze ways of its application to the treatment of diseases of the gums and mouth. In this paper, the author pays attention to *A. conyzoides* while presenting information about sustainable phytopharmaceutical development as well as the potential of this agent in the modern pharmacology. To achieve this goal, bioassays of this herb and its isolation and metabolic analysis are going to be included into the plan of future experiments that will help to detect substances that influence the mediators of inflammation and biofilm pathways. Hence, various methods such as molecular docking and LC-MS/MS are necessary to understand how its bioactive compounds work with such enzymes as MAPK and NF-kB.[19]

The production of standardized extracts that do not contain any harmful substances known as pyrrolizidine alkaloids, according to the good manufacturing practices requirements, will help improve reproducibility and gain a favorable attitude of regulatory bodies. Moreover, upgrading current formulations will result in the enhancement of absorption through mucosa and prolongation of extract activity.[9] Use of green technologies like surface $CO_2$ extraction and microwave-assisted extraction will help reduce the negative ecological effects while still obtaining potent phytochemicals.[20] In the case of AC production, controlled cultivation and green extraction will be applicable. Moreover, the introduction of participation of communities into value chains will create a platform for ethical sourcing and appropriate sharing of benefits. Thus, sustainable approaches in *A. conyzoides* ethnopharmacology are helping traditional knowledge become scientifically accepted. Close cooperation of pharmacologists, ethnobotanists, and practitioners is essential for future transition of the plant from the realm of scientific potential to the practical application in traditional oral medicine.

## ACKNOWLEDGMENT

DoluDegio: Conceptualization, study idea, literature collection, and writing of the original draft, Arun Suriyan: Literature review, organization of relevant scientific information, and critical revision of the manuscript, Kirthanaa Elumalai, Abhilash Phukonand Praveen Irudiyaraj: interpretation of relevant findings, and critical revision of the manuscript, Ganesh Kumar Anbazhagan: Supervision, critical review, manuscript revision, and final approval of the manuscript.

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**Source of Support:** Nil. **Conflicts of Interest:** None declared.