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Review Article

Herbal and nano-based herbal medicine: New insights into their therapeutic aspects against periodontitis

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Abstract

Objective: Periodontitis is a type of prevalent chronic inflammatory disorder resulting in a failure in the function of tissues supporting the tooth, like gingiva, alveolar bone, and periodontal ligament. Although antibiotic therapy is a common therapy for periodontitis cases, this approach can cause some adverse effects in these patients. Thus, finding an effective curative option with low side effects is still a puzzle.

Materials and Methods: This narrative review was conducted on the effects of herbal and nano-based herbal medicine against periodontitis by searching different databases such as Google Scholar, PubMed, Scopus, Web of Science, Science Direct, and Scientific Information Databases.

Results: According to published studies, some popular herbal formulations, such as Aloe vera, curcumin, Melaleuca alternifolia, and Scutellaria baicalensis Georgi, can be effective in periodontitis treatment. However, these herbal products may be accompanied by some pharmacological limitations, such as poor bioavailability, instability, and weak water solubility. On the other hand, harnessing nano-based herbal formulations can elevate the bioavailability, diminish toxicity, and omit repeated administration of drugs.

Conclusion: Herbal and nano-based herbal products can create a good chance to treat periodontitis efficiently.

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Introduction

Periodontitis is categorized as one of the chronic inflammatory diseases causing the impairment of the integrity of tooth-supporting tissues, such as gingiva, alveolar bone, and periodontal ligament, collectively known as the periodontium (ArefNezhad et al., 2022; Hajishengallis, 2015). It is reported that periodontitis in severe form has a prevalence of 11.2% globally (Nilsson, 2018). This oral problem has a wide variety of manifestations, like bleeding during brushing or flossing. Also, tenderness and pain during chewing of specific substances, receding gums, sensitive teeth, the production of discoloring plaque, tooth mobility, and the loss of teeth are the more severe symptoms noted in periodontal diseases (Gasner and Schure, 2021). Many risk factors have been mentioned for disease development, especially diabetes mellitus, smoking, and poor oral hygiene (Lertpimonchai et al., 2017). Periodontitis has also been associated with some systemic conditions, such as diabetes, respiratory disorders, chronic renal disease, metabolic syndrome, and cardiovascular diseases (Craig, 2008; Irani et al., 2015; Preshaw and Bissett, 2019; Suzuki et al., 2010). Moreover, some oral anaerobic bacteria, including *Treponema denticola*, *Porphyromonas gingivalis*, and *Tannerella forsythia*, have a causative role in this disease (Socransky and Haffajee, 2005). Presently, the common therapeutic approach for periodontitis treatment is intra-pocket-targeted delivery systems of antibiotics in dental pharmacotherapy (Jain et al., 2008). However, It is associated with the risk of nephritis, allergy, gastrointestinal and hematological disorders, and nervous system impairment in cases with periodontal disorders who received this therapy (Heta and Robo, 2018). Fortunately, herbal therapy, as complementary and alternative medicine, is considered an effective remedy for improving different diseases from ancient to the present time (Samadi et al., 2022; Rezaee-Tazangi et al., 2020). In this field, some popular herbal products, like Aloe vera, curcumin, Scutellaria baicalensis Georgi, and Melaleuca alternifolia have provided a promising outlook for the amelioration of this oral condition (Akbik et al., 2014; Bhat et al., 2018; Forouzanfar, 2020; Tankeu, 2014; Yang et al., 2012; Zanuzzo et al., 2017). Furthermore, reports showed that some nanotechnology-based drug delivery systems, e.g. nanoparticles (NPs), liposomes, nanomicelles, branched dendrimers, and nanocapsules have good potential in medicine (Rezaei-Tazangi et al., 2021; Suri et al., 2007). Interestingly, it has been declared that herbal formulations formed on the basis of nanotechnology have a higher ability in treating various disorders (Barkat et al., 2020). These nano-based herbal formulations can also overcome pharmacological obstacles of herbal medicine, like weak water solubility and bioavailability, and instability (Rezaei-Tazangi et al., 2021). This is the first study in which the efficiency of some popular herbal and nano-based herbal products on periodontitis through a mechanistic insight was discussed.

Materials and Methods

In this review study, we gathered accessible data from Google Scholar, PubMed, Scopus, Web of Science, Science Direct, and Scientific Information Databases until 2022. The MeSH terms and free keywords used in this study were: periodontitis, natural products, herbal medicine, herbal extract, nano, nano-based herbal therapy, nano-based herbal medicine, nanotechnology, nano-based herbal formulations, *aloe vera*, *curcumin*, *melaleuca alternifolia*, *Scutellaria baicalensis Georgi*, *in vitro*, *in vivo*, animal model, clinical, clinical trial, and clinical study. According to the search strategy, 138 articles were found. After checking the titles and abstracts, 97 relevant papers were evaluated. The assessed papers were about herbal medicine and nano-based herbal formulations against periodontitis. The figures included in this study were created by the web-based software BioRender.

Results

Periodontitis and its pathogenesis

The adaptive and innate immune systems are involved and work together in the pathogenesis of periodontitis (Sell et al., 2017; Zacarias et al., 2019). Regarding the adaptive immune system, decreased responses of Th1 cells and increased responses of Th2 cells have been expressed (Seymour et al., 1993; Sigusch et al., 1998). In this system, interleukin (IL)-1 has a key role in the destruction of periodontal tissue and may mediate collagenolytic induction and bone-destruction factors, such as prostaglandin E2 (PGE2) and matrix metalloproteinases (MMPs) (Figure 1) (Bascones Martínez et al., 2009; Mariano et al., 2010). The innate immune reaction is performed in the disease by phagocytes (e.g. natural killer cells, neutrophils, and dendritic cells). These innate immune cells can be recruited into the infection site as a result of elevated levels of cytokines, such as interferon (IFN)-γ, IL-1β, IL-4, and IL-6 (Cairo et al., 2010; Meyle et al., 2017; Ramadan et al., 2020). Natural killer cells may participate in the resorption of alveolar bone and systemic inflammation in reaction to oral infections (Aoki-Nonaka et al., 2014). Another involved agent in the disease is neutrophils producing reactive oxygen species (ROS) (Hirschfeld, 2020; Scott and Krauss, 2012). An imbalance between the anti-oxidative protection and ROS production in periodontitis pathogenesis has been demonstrated. Increased ROS levels can trigger intracellular signals related to autophagy, which has a dual role in the disease by enhancing cell death or suppressing apoptosis in infected tissues (Liu et al., 2017). Notably, the increment of neutrophil ROS formation is linked with the increased neutrophil extracellular trap (NET) secretion leading to neutrophil recruitment and tissue damage (Kolaparthy et al., 2014; Mayadas et al., 2009). A number of Gram-negative bacteria, for instance, *Porphyromonas gingivalis* and *A ggregatibacter actinomycetemcomitans*, can also form subgingival plaques causing periodontitis progression (Gölz et al., 2014). These bacteria, through lipopolysaccharides (LPSs) present in their cell walls, trigger Toll-like receptors (TLR), which in turn activate nuclear factor κB (NF-κB). As a result, some inflammatory cytokines and chemokines are secreted, for example, IL-1, tumor necrosis factor (TNF)-α, and IL-6 (Kagiya, 2016; Venugopal et al., 2018). Recent reports revealed that *P. gingivalis* can change adaptive immune responses. Particularly, *P. gingivalis* interaction with dendritic cells provokes a cytokine pattern that has a helping role in the polarization of T helper (Th) 17 cells. Furthermore, *P. gingivalis* suppresses the formation of gingival epithelial cell-related cytokines recruiting Th1 cells (Hajishengallis, 2014; Olsen et al., 2016; Wilensky et al., 2015). Periodontal epithelium creates a physical obstacle against infection and has a fundamental role in the host innate immune system (Mariano et al., 2010). In terms of genetic aspects, it is approved that long non-coding RNAs (lncRNAs) have a substantial role in periodontitis development. Also, dysregulation of these transcripts, such as ANRIL, UCA1, FGD5-AS1, FAS-AS1, NEAT1, NKILA, Linc-RAM, and FAS-AS1, in blood samples or gingival tissues of periodontitis cases compared with normal subjects has been addressed (Sayad et al., 2020). Besides, many single nucleotide polymorphisms (SNPs) located in ANRIL, for instance, rs1333048, rs1333049, rs496892, and rs7865618, have been related to periodontitis risk in diverse populations (Motterle et al., 2012).

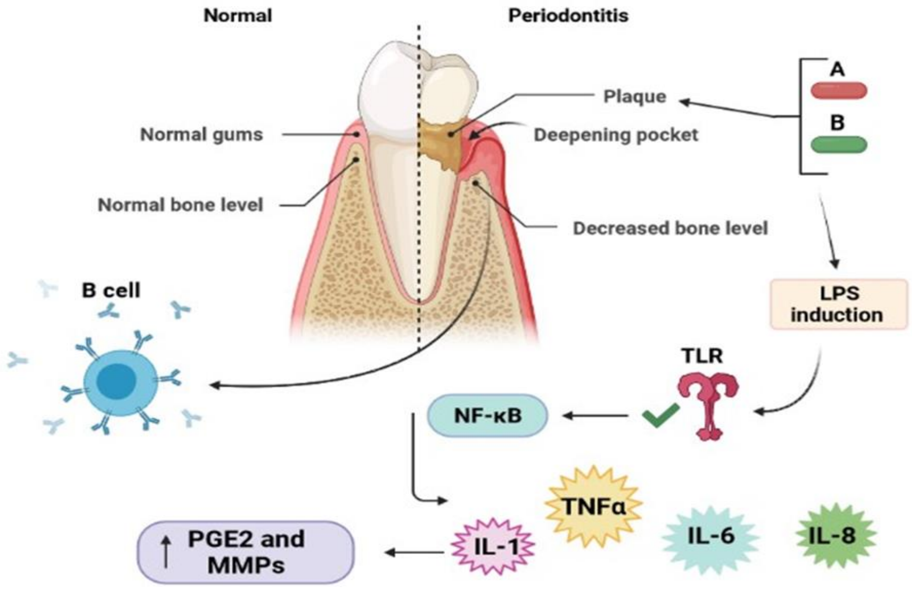

Figure1. The role of the immune system and bacterial pathogens in pathogenic mechanisms of periodontitis. A, *P. gingivalis*; B, A, *actinomycetemcomitans*; LPS, Lipopolysaccharide; TLR, Toll-like receptors; NF-kB, Nuclear factor-kappa B; TNF-α, tumors necrosis factor-α; PGE2, prostaglandin E2; MMPs, matrix metalloproteinases; interleukin 1; IL-6, interleukin 6; IL-8, interleukin 8.

Herbal and nano-based herbal therapy: An opportunity for therapeutic purposes or not?

Herbal therapy is a common and popular therapy for treating many disorders in many areas, such as India, China, and Indonesia, since the ancient era due to its advantages compared with synthetic drugs, like a lower rate of drug reactions and being safe and gentle (Ilyas, 2020; Khogta et al., 2020). On the contrary, some side effects have been reported for herbal medicine, like the possibility of overdose potential of herbal drugs. Also, the use of this remedy can cause many cutaneous reactions (Bedi and Shenefelt, 2002). On the other hand, nano-based drug delivery systems have many benefits, like biocompatibility improvement, modifiable release profiles, and nanoscale size (Majidzadeh et al., 2020). The utilization of these systems (e.g. NPs, liposomes, ethosomes, phytosomes, solid-lipid NPs, transferosomes, microsphere, and microemulsion/ nanoemulsion) for herbal products may reduce the repeated administration, overcome non-compliance, increase the therapeutic value, reduce toxicity, and increase the bioavailability (Chaudhari and Randive, 2020; Mamillapalli, 2016). Some other advantages of nano-based herbal therapy are enhancement of solubility, potentiation of pharmacological activity and stability, improvement of the distribution of tissue macrophages, sustained delivery, and protection from physical and chemical degradation (Mamillapalli, 2016). Thus, the nano-based herbal formulation may create a large chance to promote the effectiveness of herbal therapy.

Aloe vera and its nanoformulations: Their effects on periodontitis treatment

Aloe vera is a member of the Liliaceae family and is used in many countries for different therapeutic purposes, like treating diabetes, cardiovascular diseases, and metabolic syndrome (Choudhary et al., 2014; Guo and Mei, 2016; Sabbaghzadegan et al., 2021; Sahu et al., 2013; Shakib et al., 2019). This plant in light of its active components, like polysaccharides, anthraquinones, and glycoproteins, can possess many therapeutic effects, such as antiviral, anti-cancer, and anti-ulcer effects (Choi and Chung, 2003; Gao et al., 2019). *Aloe vera* can also exert ameliorative effects on supporting tissues of the tooth (e.g. periodontal ligament) and oral conditions like periodontitis. For example, an *in vitro* work revealed that exposing periodontal ligament cells to *Aloe vera* gel can give rise to the preservation of periodontal ligament cell viability (Fulzele et al., 2016). An *in vivo* study also investigated the influences of the administration of *Aloe vera* hydrogel topically (1 min) on the population of neutrophil cells in animal models of aggressive periodontitis induced by *A. actinomycetemcomitans*. Finally, they declared that using this hydrogel in the concentration of 2.5%, 5%, 10%, and 20% can significantly decrease the number of neutrophil cells, as inflammatory factors that are able to phagocyte bacteria infiltrating the tissue of gingiva (Table 1) (Prasetya et al., 2014; Susanto et al., 2021).

Table 1. List of studies in which the effect of Aloe vera formulations on periodontitis has been investigated

Author/ year	*In vivo*/*in vitro*/ human	Herbal / others	Effect/mechanism
Bhat et al. 2011	Human	*Aloe vera* gel	Decrease of plaque, pocket depth, and gingival indices
Ashouri Moghaddam et al. 2017	Human	*Aloe vera* gel	Decrease of plaque index
Abdelmonem et al. 2014	Human	*Aloe vera* gel	Decrease of the activity of *P. intermedia* and *P. gingivalis* bacteria
Mokhtar et al. 2016	*In vivo*	*Aloe vera* gel	Reduction of inflammatory reactions and caspase-3 area
Deepu et al. 2018	Human	*Aloe vera* gel	Decrease of pocket depth index and gingival inflammation
Hudwekar et al. 2019	Human	*Aloe vera* extract	Wound healing effects following periodontal flap surgery
Shamim et al. 2016	Human	*Aloe vera* extract	Wound healing effects following periodontal flap surgery
Vangipuram et al. 2016	Human	*Aloe vera* extract	Reduction of plaque and gingival indices
Pradeep et al. 2016	Human	*Aloe vera* gel	Reduction of plaque, bleeding, and pocket depth indices
Kurian et al. 2017	Human	*Aloe vera* gel	Decrease of pocket depth, gingival, and bleeding indices
Penmetsa et al. 2019	Human	*Aloe vera* gel	Decrease of plaque, gingival, bleeding, and pocket depth indices
Susanto et al. 2021	*In vivo*	*Aloe vera* hydrogel	Reduction of the number of neutrophil cells

Hydrogels are biomaterials like extracellular matrix (ECM) in terms of porous structures and have high biocompatibility; therefore, they can be useful for carrying drugs to cells (Buwalda et al., 2017). Other therapeutic influences of *Aloe vera* comprise anti-bacterial, anti-oxidative, and anti-inflammatory impacts (Langmead et al., 2004; Nejatzadeh-Barandozi, 2013). *Aloe vera* consumption exerts its anti-bacterial effect on *Staphylococcus aureus*, *Streptococcus pyogenes*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Propionibacterium acne*, *Escherichia coli*, *Salmonella typhi*, *Helicobacter pylori*, Streptococcus *mutans*, and Streptococcus *sanguis*. Among these bacteria, *E. coli*, *K. pneumoniae*, *P. aeruginosa, and S. aureus* are found in periodontitis patients; thus, they can be affected by the anti-bacterial effect of *Aloe vera* causing reduction of plaque and improving the periodontal health (Lawrence et al., 2009; Penmetsa et al., 2019; Souto et al., 2006). Also, the antioxidant properties of *Aloe vera* have been reported by Aggarwal et al. by suppressing the formation of free oxygen radicals through the activated polymorphonuclear leukocytes (Aggarwal et al., 2011). One of the antioxidant agents present in *Aloe vera* is vitamin C, which has a role in collagen synthesis and increases oxygen levels in the wound region through blood vessel dilation (Figure 3) (Hudwekar et al., 2019; Wang et al., 2017). Another possible mechanism of this herb in periodontitis therapy is the inhibition of stimulated granulocyte MMPs, which gives rise to the inhibition of cyclooxygenase (COX) and lipoxygenase (LOX) pathways (Bhat et al., 2011). The suppression of the COX pathway and reduction of prostaglandin synthesis are among the mechanisms of *Aloe vera* to inhibit inflammation (Vangipuram et al., 2016). Also, some clinical evaluations indicated the positive effects of this plant against periodontitis cases (Adam et al., 2018; Hudwekar et al., 2019; Karim et al., 2014). In a randomized controlled trial, the effectiveness of mouthwash with *Aloe vera* juice (0.001% Spearmint flavor, 0.2% preservative, 99% aloe juice, and sorbitol for sweetening) on gingival inflammation and plaque accumulation was assessed, and it was shown that it can be an alternative way to treat and prevent gingivitis by reducing plaque and gingival indices (Vangipuram et al., 2016). Moreover, subgingival administration of the gel form of *Aloe vera* in periodontal pockets of periodontitis subjects ameliorated periodontal disorder by improving clinical parameters, like gingival, plaque, and pocket depth indices (Bhat et al., 2011). However, the toxic and carcinogenic impacts of this plant have been stated in some papers (Guo and Mei, 2016). Some evidence addressed the possible therapeutic capacity of nano-based formulations of this herb against the disease. In this direction, Subramani et al. explored the anti-bacterial features of herbal NPs obtained from the shade-dried gel of *Aloe vera* (Subramani et al., 2018). In this experiment, The NPs were combined with chitosan polymer and subsequently were coated on cotton fabrics. At the end of the study, they concluded that these chitosan nanocomposites have anti-bacterial effects against *E. coli* and *S. aureus*, which are related to the disease induction and progression, respectively (Gürkan et al., 2009; Passariello et al., 2012; Subramani et al., 2018). Chitosan biomaterials have special characteristics, such as biodegradability, biocompatibility, muco-adhesion, and non-toxicity. Plus, chitosan is the sole cationic polysaccharide in the world with the ability of modification to its derivatives chemically (Fakhri et al., 2020). In another work, the possible bactericidal effects of silver NPs synthesized by *Aloe vera* and neem on dental pathogens resulting in dental caries and periodontitis, comprising *Enterococcus faecalis*, *S. aureus*, *S. mutans*, and *Pseudomonas* species, were studied using the agar well diffusion method (Rajeshkumar et al., 2019). At the end of the research, they demonstrated the anti-bacterial effects of these silver NPs against *Pseudomonas* species and *S. mutans* (Rajeshkumar et al., 2019). Silver NPs incorporated into biomaterials have the capability to diminish or prevent biofilm creation, and they have a considerable antimicrobial function due to their small particle size and large surface-to-volume ratio (Bapat et al., 2018). Therefore, it seems that these nano-based drug delivery systems, like NPs combined with chitosan polymer and silver NPs, may promote the curative and pharmacological effects of *Aloe vera* on periodontitis mainly through inhibitory influences on dental biofilm and dental pathogens.

Curcumin and its nanoformulations: Their effects on periodontitis treatment

Curcumin is derived from the underground stem or the rhizome of a ginger-like plant from the *Zingiberaceae* (ginger) family and contains several active components, including curcuminoids, triterpenoids, diterpenes, and sesquiterpenes (Catanzaro et al., 2018; Lal, 2012). This polyphenol possesses many pharmacological influences, like anti-inflammatory, anti-oxidative, and anti-cancer properties (Damiano et al., 2021;

Sharma et al., 2005). Curcumin consumption can contribute to the management of many complicated conditions, for instance, cardiovascular disorders, metabolic syndrome, arthritis, and anxiety (Hewlings and Kalman, 2017; Pourbagher-Shahri et al., 2021). Reports have also approved the therapeutic potential of curcumin against some oral problems, such as periodontitis (Al-Maweri et al., 2022; Iova et al., 2021; Li et al., 2021). In this regard, documents indicate that curcumin improves osteogenic differentiation, elevates cell proliferation, and decreases the apoptosis and ROS levels of periodontal ligament stem cells by different mechanisms, like affecting the PI3K/AKT/Nrf2 signaling pathway and early growth response gene 1 (EGR1) expression (Figure 3) (Shi et al., 2021; Tan et al., 2021; Xiong et al., 2020). Bhatia and co-workers addressed the anti-bacterial effects of this plant-derived agent on *P. gingivalis*, *Fusobacterium nucleatum*, *Capnocytophaga*, and Prevotella *intermedia* and its therapeutic activities in chronic periodontitis patients by promoting clinical parameters, for example, plaque, bleeding, and clinical attachment indices (Table 2) (Bhatia et al., 2014). Indeed, they inserted 1% curcumin gel locally into periodontal pockets, and pluronic 407 (PF-127) hydrogel was utilized as a local drug delivery system in this work (Bhatia et al., 2014). The hydrogel of Pluronic F-127, a nonionic surfactant, has several advantages, such as non- immunogenicity, non-toxicity, prolonged drug release, and thermo reversibility (Álvarez et al., 2011).

Table 2. Curcumin in different formulations can target periodontitis efficiently

Author/ year	***In vivo*/*in vitro*/ human**	**Herbal/nano-based herbal/ others**	**Effect/mechanism**
Guimarães et al. 2011	*In vivo*	Curcumin	Suppression of cytokine gene expression, elevation of fibroblastic cell number and collagen content, and decrease of infiltration of inflammatory cells
Xiao et al. 2018	*In vivo*/*in vitro*	Curcumin	Decrease of gingival inflammation, alveolar bone loss, and TNF-α and IL-1β formation, regulation of collagen fibers, and suppression of NF-κB activation
Curylofo-Zotti et al. 2018	*In vivo*	Curcumin	Decrease of inflammatory cell infiltration and numbers of osteoclasts, apoptotic cells, and osteocytes
Corrêa et al. 2017	*In vivo*	Curcumin	Reduction of alveolar bone loss and IL-1β and INF-γ levels
Guimaraes-Stabili et al. 2018	*In vivo*	Curcumin	Reduction of NF-κB triggering and promotion of collagen repair and TGF-β level
Lova et al. 2021	*In vivo*	Curcumin	Reduction of oxidative stress
Pimentel et al. 2020	*In vivo*	Curcumin	Reduction of alveolar bone loss and TNF-α, INF-γ, IL-1β, and IL-6 levels
Guimaraes et al. 2012	*In vivo*	Curcumin	Suppression of cytokine gene expression and NF-κB activation, decrease of inflammatory cell infiltration, and elevation of collagen content and the number of fibroblastic cells
Zhou et al. 2013	*In vivo*	Curcumin	Reduction of alveolar bone loss, receptor activator of nuclear factor-κB ligand (RANKL), osteoprotegerin (OPG), and IL-6 and TNF-α expression
Mau et al. 2016	*In vivo*/*in vitro*	Curcumin	Suppression of osteoclast differentiation, MMP-9 expression, myeloperoxidase function, and reduction of alveolar bone loss
Akpinar et al. 2018	*In vivo*	Curcumin	Reduction of alveolar bone loss and IL-1β level, and elevation of osteoblast number
Nasra et al. 2017	*In vitro*	Curcumin gel	Decrease of plaque formation, pocket depth, and bleeding indices
Bhatia et al. 2014	Human	Curcumin gel	Decrease of the count of *Capnocytophaga*, *F. nucleatum*, *P. intermedia*, and *P. gingivalis* bacteria and reduction of bleeding index
Mohammad et al. 2020	Human	Curcumin gel	Decrease of TNF-α, IL-1β and copper levels and plaque, bleeding, gingival, clinical attachment, and pocket depth indices, and elevation of magnesium and zinc levels
Sha et al. 2021	*In vivo*	Curcumin gel	Reduction of inflammatory infiltration and IL-1β and RANKL levels, and osteoclast number
Kaur et al. 2019	Human	Curcumin gel	Decrease of gingival inflammation
Dave et al. 2018	Human	Curcumin gel	Reduction of plaque, gingival, and pocket depth indices

Table 2. Continue

Nagasri et al. 2015	*In vitro*/human	Curcumin gel	Decrease of the activity of *T. denticola*, *T. forsythia*, and *P. gingivalis* bacteria and gingival, plaque, and pocket depth indices
Sreedhar et al. 2015	*In vitro*/human	Curcumin gel	Reduction of bleeding, pocket depth, clinical attachment, and plaque indices and the activity of *A. actinomycetemcomitans*, *P. intermedia*, and *P. gingivalis*
Hosadurga et al. 2014	*In vivo*	Curcumin gel	Reduction of pocket depth and gingival indices
Ravishankar et al. 2017	Human	Curcumin gel	Reduction of plaque, pocket depth, and clinical attachment indices
Elburki et al. 2014	*In vivo*	Triketonic phenylamino carbonyl curcumin	Reduction of alveolar bone loss and IL-1β level
Curylofo-Zotti et al. 2018	*In vivo*	Chemically modified curcumin	Decrease of inflammatory cell infiltrate, bone resorption, and osteoclast number
Deng et al. 2020	*In vivo*	Chemically modified curcumin	Decrease of gingival and pocket depth indices and IL-1β, MMP-2, and MMP-9 levels, and alveolar bone loss
Wang et al. 2019	*In vivo*/*in vitro*	Chemically modified curcumin	Inhibition of TNF-α and IL-1β release and reduction of MMP-9 release and alveolar bone loss
Theodoro et al. 2017	*In vivo*	Curcumin solution	Diminution of osteoclastic function and inflammatory infiltration
Zambrano et al. 2018	*In vivo*	Nanocurcumin	Reduction of the number of fibroblastic cells, bone resorption, osteoclast level, inflammatory infiltration, and NF-kB and p38 MAPK triggering
Malekzadeh et al. 2021	Human	Nanocurcumin	Decrease of gingival and bleeding indices
Pérez-Pacheco et al. 2021	Human	Curcumin-loaded polyglycolic and poly-lactic acids (PGLA/PLA) nanoparticles	Reduction of IL-6 level
Singh et al. 2018	*In vitro*	Quantum curcumin	Suppression of growth and biofilm formation of *P. gingivalis*, *S. mutans*, and *A. viscosus*

Furthermore, systematic administration of curcumin (30 and 100 mg/kg) can result in the suppression of gene expression of PGE2, IL-6, and TNF-α and significant and dose-dependent inhibition of NF-kB activation in periodontitis *in vivo* (Guimarães et al., 2011). A research also proposed a crosslinked gelatin film, which is a biodegradable, mucoadhesive, and nontoxic material acquired by hydrolysis of animal connective tissues, bones, and skin, for loading curcumin to enhance periodontitis treatment (Chauhan et al., 2018; Perioli et al., 2004). This work implicated that this optimized film entraps curcumin without chemical and physical interactions. Plus, this formulation has suitable resistance and strength to forces and possesses enough flexibility to prevent an uncomfortable feel following its insertion into the periodontal pockets (Chauhan et al., 2018). Interestingly, it has been shown that curcumin gel injection (10 mg) into the periodontal pocket can increase magnesium and zinc levels in individuals with chronic periodontitis (Mohammad, 2020). These elements are crucial for the normal metabolism of lipids, carbohydrates, and proteins and act as antioxidant factors (Yamaguchi and Weitzmann, 2011). Curcumin can also exert its anti-inflammatory effect through the upregulation of peroxisome proliferator-activated receptor-*γ* (PPAR-*γ*) activation (Figure 2) (Jacob et al., 2007). PPAR-γ may curb bone resorption in periodontitis through the suppression of osteoclastogenesis induced by RANKL (Hassumi et al., 2009). Recently, the anti-inflammatory impacts of curcumin on the disease have been demonstrated by Justo et al. They revealed these effects through curcumin administration (once a day for 15 days, orally) in an animal model of apical periodontitis by reducing the levels of pro-inflammatory agents including IL-1β, TNF-α, and IL-6 (Justo et al., 2022). Moreover, a clinical study pointed out the mild benefits of subgingival use of curcumin gel in the decrement of gingival inflammation in chronic periodontitis patients (Kaur et al., 2019). Another clinical investigation highlighted the potential role of local curcumin gel in the reduction of sulcular bleeding, pocket depth, and plaque indices in patients with mild chronic periodontitis (Dave et al., 2018). However, one of the problems of curcumin is its low aqueous solubility and poor bioavailability. This problem can be solved through the preparation of curcumin-loaded NPs (Bhawana et al., 2011). In this line, Zambrano et al. investigated the effects of local utilization of curcumin-loaded NPs (0.05 mg/ml curcumin) in an animal model of periodontal disease induced by injecting LPS solution into the gingival tissue. They demonstrated that these NPs suppress inflammatory bone resorption and attenuate osteoclast levels and NF-kB (p65) and p38 MAPK function (Zambrano et al., 2018). In addition, an *in vitro* study addressed the possibility of the effectiveness of curcumin quantum dots (mean particle size 3.5 nm) on the suppression of growth and biofilm formation of periodontitis-related pathogens, such as *P. gingivalis*, *S. mutans*, and *Actinomyces viscosus* (Singh et al., 2018). Quantum dots are one of the nano-carriers for herbal products by coupling, dispersing, dissolving, and adsorption, etc. and can potentiate the bioavailability of drugs (Zhao et al., 2016). These nano-carriers enhance the penetration and interplay with the biofilm matrix and absorption by the bacterial cells (Singh et al., 2018). A double-blind randomized clinical trial also showed that the oral administration of nano-curcumin capsules (80 mg daily for 4 weeks) has favorable effects on gingival bleeding and the reduction of inflammation in subjects with mild periodontitis and gingivitis (Malekzadeh et al., 2021). In these capsules, spherical hydrophobic nanomicelles (~10 nm size) encompassed all curcumin and could subsequently elevate the water solubility of curcumin (Malekzadeh et al., 2021). Taken together, nano-based formulations of curcumin, such as curcumin-loaded NPs and curcumin quantum dots, can elevate the effectiveness of this polyphenol against periodontitis by some mechanisms, like inhibiting bone resorption, inflammatory events, growth, and biofilm formation of disease-associated pathogens.

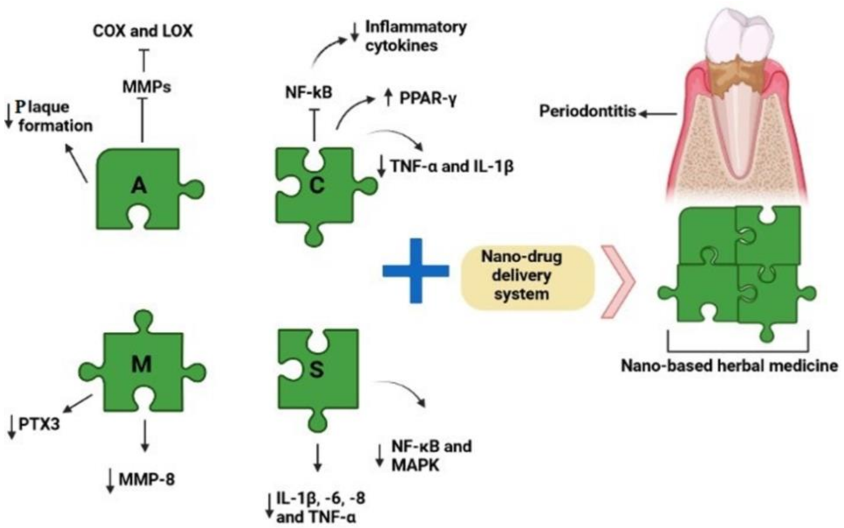

Figure 2. Nano-based herbal medicine using Aloe vera, curcumin, Melaleuca alternifolia, and Scutellaria baicalensis Georgi can significantly solve the pharmacological problems of herbal therapy and can ameliorate periodontitis through different mechanisms. COX, cyclooxygenase; LOX, lipoxygenase; NF-kB, Nuclear factor-kappa B; PPAR-γ, Peroxisome proliferator-activated receptor-γ; MMPs, Matrix metalloproteinases; MMP-8, Matrix metalloproteinase-8; TNF-α, Tumour necrosis factor-α; PTX3, Pentraxin 3; IL-1β, Interleukin 1β; IL-6, Interleukin 6; IL-8, Interleukin 8; The letters of A, C, M and B are the abbreviations of following plant names Respectively: Aloe vera, curcumin, Melaleuca alternifolia and Scutellaria baicalensis

***Melaleuca alternifolia* and its nanoformulations: Their effects on periodontitis**

Tea tree, another name for *Melaleuca alternifolia* (MEL), is an Australian plant with three main active components consisting of terpinen-4-ol, γ-terpinen, and 1,8-cineole and is used in herbal medicine due to its anti-bacterial and antifungal characteristics (Iiyama and Cardoso, 2021; Terzi et al., 2007). One of the products of this plant is Tea tree oil (TTO), which is derived through a steam distillation from this plant. TTO has antioxidant and broad-spectrum antimicrobial activity, especially against infections of the skin and mucosa. TTO can be utilized in the treatment of acne vulgaris and seborrheic dermatitis and in the improvement of the process of wound healing (Pazyar et al., 2013). Also, documents implicated a special ability of this plant in the treatment of oral pathogens and diseases (Francisconi et al., 2020; Hammer et al., 2003; Yadav et al., 2017). In this respect, an *in vitro* investigation approved the role of TTO in the inhibition of adherence of *A. actinomycetemcomitans* and *P. gingivalis* biofilms to enamel surfaces of premolar teeth (Soulissa et al., 2020). Regarding its anti-bacterial effects, some reports manifested that TTO may attenuate plaque formation through the suppression of *P. gingivalis* and *S. mutans* adhesion (Figure 3) (Raut and Sethi, 2016). Moreover, Raut and Sethi implicated the positive action of TTO gel administration (5 ml TTO was combined with methylcellulose gel) locally on subjects with chronic periodontitis by diminishing clinical attachment and pocket probing depth indices (Raut and Sethi, 2016). Similarly, a randomized controlled clinical research indicated that local application of TTO gel (5 ml TTO was mixed into methylcellulose gel) reduced pocket probing depth index and PTX3 level in subjects with periodontitis. PTX3 has a direct relationship with the levels of TNF and IL-1 and the number of bacterial products (Elgendy et al., 2013). Another clinical study by Taalab and colleagues revealed the striking role of local use of TTO 5% gel in the enhancement of periodontitis-related clinical parameters, including pocket depth, gingival, bleeding, and clinical attachment indices, and reduction of levels of MMP-8 (Figure 2), the main cause of the destruction of type I, II and III collagen, which in turn results in the reduction of disease severity (Taalab et al., 2021). MMP-8 is considered the main enzyme in the salivary fluid and gingival tissue that plays a substantial role in the destruction of the periodontal tissues (Taalab et al., 2021). In spite of various therapeutic effects of MEL recorded in papers, this Australian plant has some pharmacological restrictions, like high oil oxidation and volatility and low solubility (Battisti et al., 2021). To overcome these restrictions and improve the curative ability of MEL, Souza et al. in an *in situ* study, evaluated the antimicrobial influences NPs of 0.3% TTO on dental biofilm (de Souza et al., 2017). In this project, the results of analyzing the biofilm structure approved the better effectiveness of TTO NPs than TTO on biofilm formation (de Souza et al., 2017). The anti-bacterial activity of MEL NPs against *P. aeruginosa* and *Candida* species has also been reported in some articles (Comin et al., 2016; de Souza et al., 2017). Plus, MEL NPs can exert an anti-inflammatory effect in mouthwash. In this regard, a clinical study addressed this result using the synthesis of nano-based lipid carriers by 7.5% weight/volume (w/v) of MEL through high-pressure homogenization (Casarin et al., 2019). So, harnessing nano-based products of this plant, for example, NPs and nano-based lipid carriers may be a good therapeutic candidate for periodontitis by exerting anti-inflammatory and anti-bacterial effects.

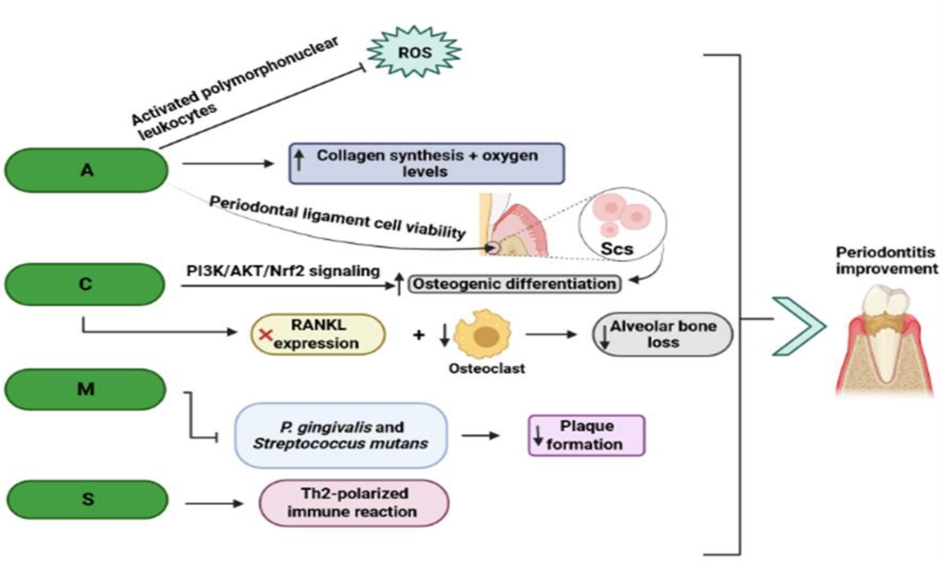

Figure 3. Aloe vera, curcumin, Melaleuca alternifolia, and Scutellaria baicalensis Georgi improve periodontitis mainly through the immune system regulation and reconstruction or viability of tissues and cells involved in the disease. The letters of A, C, M and B are the abbreviations of following plant names Respectively: Aloe vera, curcumin, Melaleuca alternifolia and Scutellaria baicalensis Georgi

Scutellaria baicalensis Georgi **and its nanoformulations: Their effects on periodontitis**

Scutellaria baicalensis Georgi (Lamiaceae) is a plant of the Lamiaceae family, which is used in herbal medicine and mainly found in Asian countries (Wang et al., 2018; Zhao et al., 2019). *Lamiaceae* possesses many substances, and its main active substances include baicalein, baicalin, wogonin, wogonoside, and oroxylin A (Liao et al., 2021). This herb has antiviral, anti-oxidative, anti-inflammatory, immunoregulatory, neuroprotective, anti-microbial, hepatoprotective, and antineoplastic effects (Huang et al., 2013; Wang et al., 2018; Ye et al., 2009). Also, baicalin, as a flavonoid compound in this herb, has anti-periodontitis effects by modulating the expression of some pro-inflammatory factors in the process of periodontitis (Ming et al., 2018). Baicalein reflects its ani-inflammatory and osteogenic activities by diminishing the expression of IL-1β, MMP-1, MMP-2, TNF-α, and MCP-1 and upregulating osteogenic landmarks, like collagen-I, runt-related transcription factor 2 (RUNX2), and osterix, in periodontal ligament cells *in vitro* (Ren et al., 2021). Furthermore, an *in vivo* study assessed the impacts of intragastric exploitation of baicalin in a rat model of periodontitis induced by ligating the maxillary second molars and inoculating with *P. gingivalis* (Sun et al., 2016). This research concluded that baicalin (100 and 200 mg/kg/day) remarkably decreases alveolar bone loss, myeloperoxidase expression, the levels of IL-1β, TNF-α, high mobility group box 1 protein (HMGB1), and infiltration of inflammatory agents in gingival tissue (Sun et al., 2016). Another *in vivo* project by Kim and co-workers demonstrated that oral administration of *Lamiaceae* extract (100 mg/kg) reduces alveolar bone resorption, mRNA expression of IL-6 and IL-8, and suppresses cementum mineralization in periodontitis rats induced (Kim et al., 2018). Moreover, the aqueous extract of *Lamiaceae* (50 mg/kg/day, orally) can be a good therapeutic option in mouse models with periodontitis through the stimulation of Th2-polarized immune reaction, diminution of alveolar bone loss, and accumulation of collagen fiber (Huang et al., 2013). Despite all of the benefits of *Lamiaceae*, it has some pharmacological problems, such as low solubility, poor bioavailability, and short half-life, that impairs their biomedical applications (Wang et al., 2015; Xing et al., 2005). One of the suitable choices for solving this issue can be the encapsulation of baicalin and baicalein in synthesized mesoporous silica nanoparticles (MSNs) (Figure 4) (Li et al., 2017). MSNs possess a spherical shape with ordered pore structures (the mean diameter 367±94 nm) and are among the important drug carriers because of their stability and high biocompatibility, and low cytotoxicity (Li et al., 2017; Ma et al., 2014). By harnessing this process, Li et al. expressed that nano-encapsulated baicalein can be a potential candidate against periodontitis by reducing the expression of pro-inflammatory cytokines, e.g. IL-6 and IL-8 (Li et al., 2017). It looks like the co-use of *Lamiaceae* and nano-based materials, like MSN, may have positive impacts on this oral disorder; however, this hypothesis needs more evidence.

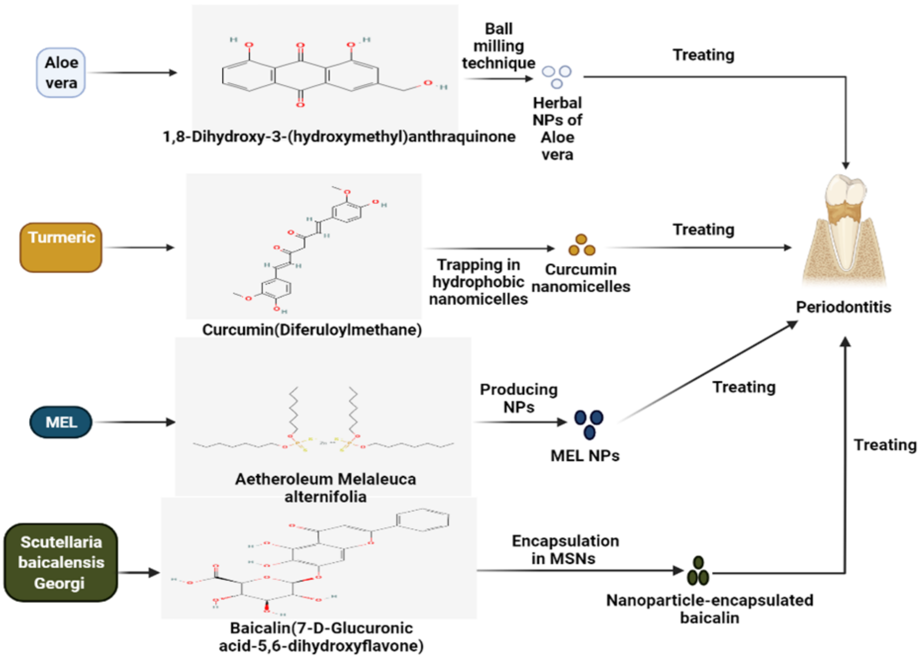

Figure 4. Different methods of preparation of nano-based herbal formulations from *Aloe vera*, curcumin, *Melaleuca alternifolia*, and *Scutellaria baicalensis Georgi* in order to treat periodontitis

Some other herbal and nano-based herbal products effective in periodontitis treatment

Some other herbal and nano-based herbal formulations have also reflected their capacity to treat periodontitis, like *Camellia sinensis*, resveratrol, and quercetin (Elagbar et al., 2020; Mallikarjun et al., 2016; Maurya et al., 1997; Mazur et al., 2021; Sezer et al., 2013; Warad et al., 2013). *Camellia sinensis* leaves, another name for green tea, can have positive effects on periodontitis treatment by reducing bleeding, gingival, plaque, clinical attachment, pocket depth indices, inflammation, alveolar bone loss, and osteoclastic function and increasing total antioxidant capacity (TAOC) and glutathione-S-transferase (GST) (de Almeida et al., 2019; Hrishi et al., 2016; Taleghani et al., 2018). Harnessing NPs of EGCG (one of the main active components of *green tea*) may also lead to the decrement of ROS levels and downregulation of expression of pro-inflammatory cytokines through the regulation of macrophages from the phenotypes of M1 to M2. Plus, this nano-based compound is capable of reducing osteoclast activity and suppressing alveolar bone loss in animal cases of chronic periodontitis (Tian et al., 2022). Resveratrol, a phenolic compound present in mulberries, peanuts, and red wines, is another plant compound effective in periodontitis therapy (Jang et al., 1997; Zhen et al., 2015). In this line, an experimental work indicated the inhibition of TNF-α, IL-8, TLR4, IL-6, and IL-1β levels in the gingival tissue of periodontitis mice receiving resveratrol (20 mg/kg, gavage administration) (Zhen et al., 2015). Shi and colleagues observed similar findings after using a liposomal system loaded with resveratrol. They reported that the utilization of this system reduced ROS levels and IL-1β, TNF-α, and IL-6 production owing to the inhibition of inflammasomes and the NF-κB signaling pathway (Shi et al., 2021). Liposomes are described as spherical vesicles comprising one or more lipid bilayer membranes that enhance the bioavailability, solubility, and function of active substances. They also curb biological and physicochemical degradation of delivered drugs, decrease toxicity and side effects of delivered drugs, and monitor their content release (Delma et al., 2021). In other attempts, the anti-periodontitis effects of quercetin, the most frequent flavonoid existent in different fruits and vegetables, have been securitized (Geoghegan et al., 2010; He et al., 2020). For instance, several *in vivo* and *in vitro* studies approved the striking role of this flavonoid in the diminution of oxidative stress level, alveolar bone absorption, L-1β, L-17, and TNF-α secretion, and suppression of growth of *P. gingivalis* and *A. actinomycetemcomitans* (Geoghegan et al., 2010; Napimoga et al., 2013; Taskan and Gevrek, 2020; Wei et al., 2021). Some researchers also utilized nano-based drug delivery methods, like nanoemulgel and ceria nanocomposite, for improving the pharmacological and therapeutic functions of quercetin against the disease (Aithal et al., 2018; Wang et al., 2021). In this line, the findings of Wang et al. revealed suppression of M1 macrophage polarization and enhancement of M2 macrophage polarization as a result of using a ceria nanocomposite loaded with quercetin in rats with periodontitis (Wang et al., 2021). Nanoceria is an appropriate nanomaterial with anti-oxidative and anti-inflammatory impacts in light of reversible transitions between ions of Ce^{3+} and Ce^{4+} in the time of redox reaction and decrease of pro-inflammatory release (Luo et al., 2020; Wang et al., 2021). Moreover, Aithal and colleagues showed that quercetin nanoemulgel developed by cinnamon oil, Carbitol® and poloxamer 407, and tween 80 have suitable physical properties, syringeability, stability, and sol-gel transition, and thus, this nanoformulation can be utilized in periodontitis profitably. On the whole, different nano-based herbal formulations have addressed their ability to overcome herbal therapy limitations and ameliorate periodontitis through various mechanisms (Tables 3 and 4). However, more investigations are thought to be needed to approve these findings.

Table 3. Some other herbal and nano-based herbal products effective in periodontitis treatment

Type of plant	Effect/mechanism	In vivo/in vitro/ human	Reference
Nano-emulsion of mangosteen rind extract	Decrease of TNF-a and RANKL expression and increase of IL-10 expression	In vivo	Aljuanid et al. 2022
Propolis extract	Reducing the subgingival plaque formation and microbiota from periodontal pockets	In vivo	Seth et al. 2022
Crocus sativus L.	Anti-inflammatory effects, strong antioxidant properties and the ability to accumulate oxygen free radicals	In vivo	Maybodi et al. 2022
Eucalyptus globulus leaf, Azadirachta indica leaf	Antimicrobial activity against porphyromonas gingivalis	In vitro	Müller-Heupt et al.

Table 4. Some of clinical trials for application of herbal medicine in dentistry

Product	Number of participants	Method	Result	Ref.
Green and black tea mouth rinse	60	Comparison of *S. mutans* bacterial count found in saliva before and after *C. sinensis* mouth rinses administration	In comparison, green tea herbal mouth rinse showed higher efficacy in reducing S. mutans count than black tea mouth rinse	(Armidin and Yanti, 2019)
Herbal mouthwash	40	Quantitative microbiological laboratory cultivation assay. Comparison of S. mutans bacterial count found in saliva before and after mouth rinse administration in pre-school children	C. sinensis extract mouth rinse caused a significant decrease in S. mutans bacterial load in saliva	(Salama and Alsughier, 2019)
Tea tree oil/Aloe vera gel	40	Evaluating the anti-microbial efficacy after caries excavation and topical application of herbal medicaments on dentinal specimens by total viable count analysis	CHX as a control group exerted the strongest efficacy against cariogenic microorganisms followed by M. alternifolia	(Patri and Sahu, 2017)
mango leaf mouthwash	20	RCT/Comparison of S. mutans bacterial load detected in saliva before and after herbal mouth rinse and CHX administration by colony-forming units count	Using herbal mouthwash significantly reduced S. mutans count but not as well as CHX	(Bhat et al., 2017)
Herbal extract	45	Parallel RCT/Comparison of S. mutans bacterial load detected in saliva before and after herbal mouth rinse and CHX administration by colony-forming units count	C. Arabica showed the same efficacy as CHX in decreasing S. mutans salivary load	(Yadav et al., 2017)
Herbal aqueous extracts and Triphala	40	Linear randomized cross over study/ Comparison of S. mutans bacterial load detected in saliva before and after herbal mouth rinses individually and in combination by colony-forming units count	All groups showed significant antimicrobial efficacy but the highest results were obtained by using the combination of all herbal extracts	(Saxena et al., 2017)
Herbal mouthwash	30	Cross-sectional study/Comparison of S. mutans bacterial load detected in saliva before and after herbal mouth rinses in school children by colony-forming units count	Administration of C. sinensis mouthwash significantly reduced salivary S. mutans count	(Abdelmegid et al., 2015)
M. alternifolia nanoparticle	60	Double-blinded crossover RCT/gingival crevicular fluid volume and the Quigley & Hein plaque index comparison before and after herbal mouthwash administration	The herbal mouth rinse showed the same anti-inflammatory efficacy compared to CHX without affecting taste sensation	(Casarin et al., 2019)
Triphala mouthwash	90	Double-blinded RCT/Oral hygiene index-simplified, PI, and GI comparison before and after using an herbal mouth rinse	A significant improvement of periodontal indices was recorded in the herbal mouth rinse group	(Pradeep et al., 2016)
Curcuma longa	15	Clinical and Radiological Evaluation was conducted after using turmeric powder for primary teeth pulpotomy medicament	Pulpotomy treatment using turmeric powder in primary teeth resulted in proper clinical and radiographic success	(Purohit et al., 2017)
Aloe vera	42	Clinical, radiographic, and histologic analyses after direct pulp capping treatment with the herbal agent in primary teeth	Compared to calcium hydroxide, using acemannan as a direct pulp capping agent resulted in better histological responses and biocompatibility	(Songsiripradubboon et al., 2016)
Aloe vera	40	Cross-sectional randomized interventional method/standardized index by Landry, Turnbull, and Howley assessment after third molar surgery in patients treated with foam gel soaked in Aloe vera extract	Aloe vera extract can be used as an adjunct therapy agent for socket healing improvement after dental extraction	(Nimma et al., 2017)

Discussion

Periodontitis, as an inflammatory condition related to tooth-supporting tissues, affects a large number of subjects over the world, and unfortunately, common therapies have not reflected enough effectiveness with minimum side effects. Nowadays, popular herbal products, particularly *Aloe vera*, Curcumin, *Melaleuca alternifolia*, and *Scutellaria baicalensis Georgi*, have highlighted their abilities in the treatment of periodontitis, by improving clinical parameters, like bleeding, pocket depth, plaque, and clinical attachment indices. Also, from a mechanistic point of view, these popular herbal products target periodontitis through several mechanisms, such as suppression of COX and LOX, NF-kB signaling pathway, reduction of levels of MMP-1, MMP-2, MMP-8, MCP-1, and the expression of some inflammatory agents (e.g., IL-1β, IL-6, IL-8, and TNF-α) which all are involved in periodontitis pathogenesis directly or indirectly. However, these herbal remedies may have some pharmacological problems, such as low aqueous solubility, short half-life, and low bioavailability. On the other hand, it has been shown that the co-use of herbal medicine and nano-based formulations (like NPs, MSN, nano-based lipid carriers, and quantum dots), not only can overcome the limitation of herbal therapy but also are capable of improving periodontitis. Thus, nano-based herbal products can create a good chance to treat the disease efficiently. However, more experimental and clinical investigations are required to validate these findings.

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Conflicts of interest

The authors have declared that there is no conflict of interest.

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