ORIGINAL RESEARCH

Formulation and Evaluation of Antimicrobial Activity of *Boswellia serrata* Roxb. Gel against Periodontal Pathogens: An *In Vitro* Study

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Abstract

Aim: To assess the antimicrobial activity of *Boswellia serrata* Roxb. in the form of gel against *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Fusobacterium nucleatum*, and *Tannerella forsythia*.

Materials and methods: The bacterial strains of selected periopathogens were cultured in thioglycolate broth. The serial dilution method was used to evaluate Minimum Inhibitory Concentration (MIC). The tubes which were sensitive to MIC were plated and incubated for 24 hours. The colony count was done to determine the Minimum Bactericidal Concentration (MBC). Depending on the obtained concentrations, *Boswellia serrata* Roxb. gel was formulated in five concentrations and the physicochemical properties were evaluated. The periopathogens were cultured in brain–heart infusion agar plates. A disk diffusion test was performed to determine the zone of inhibition.

Results: *Boswellia serrata* Roxb. impeded the growth of the selected periopathogens in a dose-dependent manner. *F. nucleatum* showed the maximum zone of inhibition at 3 µg/mL concentration.

Conclusion: The physicochemical and antimicrobial properties of our study reveal that *Boswellia serrata* Roxb. gel can be used as an adjunct to non-surgical periodontal therapy (NSPT) as a topical gel or as a local drug delivery agent.

Clinical significance: Periodontal diseases are primarily caused by plaque biofilm which commences with inflammation of the investing tissues of the tooth which, if left untreated, leads to progressive attachment loss. NSPT is the gold standard and indispensable phase of periodontal therapy. The insufficiency of NSPT in obliterating microbial growth in deep periodontal pockets and spurting microbial resistance to antibiotic drugs widened the array of research on botanical therapeutics. *Boswellia serrata* Roxb. is widely gaining popularity because of its antimicrobial properties and nary a side effect.

Keywords: Disk diffusion test, Gingivitis, Local drug delivery, Minimum inhibitory concentration, Periopathogens.

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Introduction

With the breakthrough of antibiotics, the healthcare community believed that the battle with contagious diseases was victorious. However, it was soon understood that the microorganisms were capable of developing resistance against any kind of antimicrobial drugs in use.[1] Herbal plants have been used since time immemorial for the management of systemic diseases. They are specifically favored on account of their minimal side effects.[2] In the last few decades, researchers have turned their attention to investigating the potential of traditional medicinal plants for their remedial properties.[3]

Boswellia serrata Roxb., which is most commonly known as Frankincense, has distinct names in numerous languages. It is called as Indian olibanum, Salai guggul, and Sallaki in Sanskrit. Commonly found in dry mountainous regions of India, Northern Africa, and the Middle East, *Boswellia serrata* Roxb. is indigenous to Iran.[4] Since time immemorial, the gum resin of *Boswellia serrata* Roxb. has been used as incense in religious ceremonies.[5]

Traditionally, the resin extract obtained from the gum of *Boswellia serrata* Roxb. has been used for an era for therapy of various inflammatory diseases like arthritis, diabetes, asthma, inflammatory bowel disease, and cancer.[6] The promising results of *Boswellia serrata* Roxb. can be attributed to the anti-inflammatory, antioxidant, antiplatelet aggregation, immunomodulatory, antibacterial, antifungal, and broad antiviral activity.[7]

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Around 12 distinct Boswellic acids have been recognized. Out of these, only AKBA (3–0–acetyl–11–keto–β–boswellic acid) and KBA (11–keto–β–boswellic acid) have received pronounced pharmacological heed.[8] These acids show comprehensive anti-inflammatory action by inhibiting 5-lipo-oxygenase and cyclo-oxygenase enzymes. AKBA and 11-keto-β-Boswellic acids inhibit nuclear factor kappa B (NF-κB), a nuclear factor that regulates the proinflammatory cytokine cascade comprising Tumor Necrosis Factor-α (TNF-α) and Interleukin-1β (IL-1β).[9]

Periodontal disease is a polymicrobial infection resulting from the concomitant interaction of different bacterial species. Scaling and root planing is the first recommended step in the management of plaque-induced periodontal diseases and is an

indispensable phase of periodontal therapy, but there are factors such as accessibility or presence of plaque in retentive areas that can limit instrumentation.[10] Local drug delivery has been advocated to complement the NSPT. Numerous antimicrobials such as metronidazole, chlorhexidine, tetracycline, minocycline, and doxycycline are being used to eliminate periodontopathogens. On the contrary, the major disadvantage is the emergence of antimicrobial-resistant pathogens resulting from the extensive utilization of antibiotics in medical science.[11]

However, there are insufficient studies for evaluating the effects of *Boswellia serrata* Roxb. extract in the management of periodontal diseases. For topical application, gel offers faster drug release when compared to ointments or creams.[12] To date, there are no studies evaluating the efficacy of antimicrobial activity of *Boswellia serrata* Roxb. gel against periodontal pathogens.

Taking into consideration the anti-inflammatory and antibacterial effects, low cost, availability of *Boswellia serrata* Roxb. and relatively high frequency of periodontal diseases, this study was designed for formulation of gel using *Boswellia serrata* Roxb. extract followed by evaluation of prepared gel for physicochemical properties and the antimicrobial effect of *Boswellia serrata* gel against periodontal pathogens.

Materials and Methods

Pure hydro-alcoholic extract of *Boswellia serrata* Roxb. was obtained from Himalayan Herbaria Inc., Uttar Pradesh prepared with 70% alcohol and 30% water. It was obtained from bulges of yellowish-brown latex radiated by the stems of the plant and manufactured with a resultant 30% concentration of Boswellic acids. The MIC was evaluated which was accomplished as per the guidelines of the Clinical and Laboratory Standards Institute. The bacterial cultures of periodontopathogens employed in this study, namely *A. actinomycetemcomitans, P. gingivalis, P. intermedia, F. nucleatum,* and *T. forsythia* were obtained from Maratha Mandal's Nathajirao G. Halgekar's Institute of Dental Science & Research Center, Belagavi which were purchased from LGC Promo-Chem, Bengaluru and stored at -80°C. The strains were germinated at 37°C to a stationary phase for 24 hours in an anaerobic jar at the time of reviving. The obtained growth was checked for purity by Gram staining.[13]

MIC Procedure Using Macro-broth Dilution Method

A stock solution of *Boswellia serrata* Roxb. extract (test agent) was concocted in dimethyl sulfoxide to ensure complete solubilization. For obtaining MIC, nine dilutions of each drug were done with thioglycollate broth.

In the first tube, 20 microlitres (µL) of the drug was added to 380 µL of thioglycollate broth. In order to obtain the dilutions, 200 µL of thioglycollate broth was added to the next nine tubes separately. From the initial tube containing the drug, 200 µL was transferred to the first of nine tubes accommodating 200 µL of thioglycollate broth. The resulting dilution was considered as 10^{-1} dilution. An amount of 200 µL from this tube was transferred to the second tube to make 10^{-2} dilution. This procedure was replicated until 10^{-9} dilution was obtained for each drug. A culture suspension was prepared by adding 5 µL from the maintained stock cultures of required organisms (*A. actinomycetemcomitans*, *P. gingivalis*, *P. intermedia*, *F. nucleatum*, and *T. forsythia*) into 2 mL of thioglycollate broth. An amount of 200 µL of prepared culture suspension was added to each serially diluted tube. The tubes were incubated for 48–72 hours in anaerobic jar at 37°C and observed for turbidity. The minimum concentration of the extract showing no turbidity was recorded as MIC. This test was triplicated and average values were taken for accuracy. Ciprofloxacin was used as a control.

MBC Procedure

The first three dilution tubes which were sensitive to MIC, 1.6 µg/mL, 3.12 µg/mL, and 6.25 µg/mL were plated on three plates and incubated for 24 hours. Brain heart infusion agar was used as a medium. The colony count was done on the next day for each concentration and the average of three plates was recorded. The MBC was done to evaluate the bacteriostatic or bactericidal effect of the extract against the periopathogens (Fig. 1). If there is no growth of bacteria, then that concentration is said to have a bactericidal effect and if there is growth, then it is said to have a bacteriostatic effect.

Preparation of Gel

An aqueous gel was prepared in five different concentrations of extract and three different concentrations of carbopol 940 which consisted of the following constituents: *Boswellia serrata* Roxb. (0.5, 1.5, 3.0, 4.5 and 6 gm), carbopol 940 (0.4,0.6 and 0.8 gm), glycerin (wetting agent)— 0.2 mL and purified water (100 mL). The carbopol 940 was soaked in water for 24 hours. To this, *Boswellia serrata* Roxb. extract and glycerine were added. A propeller was used to homogenize the ingredients for 2 hours at 500 rpm in order to obtain the gel. A total of 15 different concentrations of gel were obtained and stored at room temperature for 24 hours to evaluate the consistency and stability of the gel.

Evaluation of Physical Properties

Homogeneity

The homogeneity of the gel was evaluated by visual observation.

pH

An amount of 2.5 gm of each concentration of gel was mixed in 25 mL of water, the pH was recorded after 2 hours. This procedure was triplicated and the average was recorded.

Rheology and Viscosity

The rheological properties of the gel formulations were analyzed using Brookefield viscometer. The measurements were recorded at an interval of 30 seconds between speed settings of 10–100 rpm in increasing as well as decreasing order.

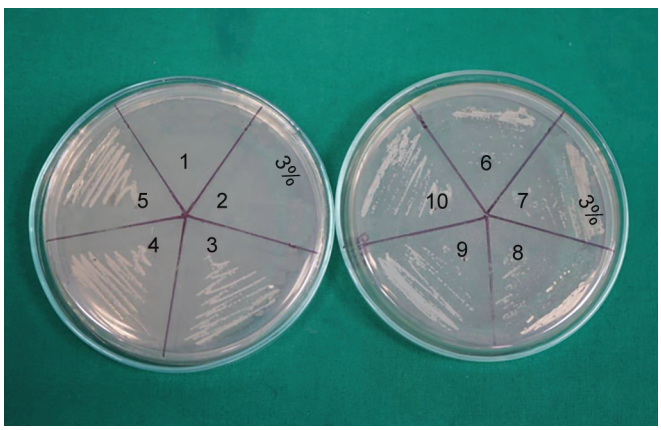

Fig. 1: MBC of *P. gingivalis* against 3% *Boswellia serrata*

Spreadability

For the topical application of gel formulation, spreadability plays a crucial role in patient compliance. A premarked glass slide was taken and 0.5 gm gel was spread within a circle of 1 cm diameter. A second glass slide was placed on it and 100 gm weight was allowed to rest on it. The increase in the diameter of the circle was recorded.

Syringeability

The syringeability of the gel was tested for its potential use as a local drug delivery agent for the treatment of deep periodontal pockets. It was evaluated by passing the gel through a 21-gauge needle.

Patch Test

The gel formulations were applied on the forearms of volunteers for a period of 48 hours. They were asked several questions based on the experience like spreadability, ease of application, immediate and long-term sense after application, odor, irritation, or any other experience.

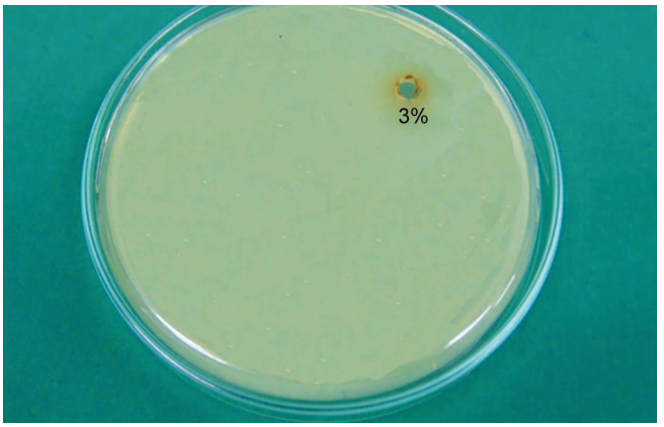

Fig. 2: Disk diffusion of *P. gingivalis* against 3% *Boswellia serrata*

Determination of Antimicrobial Activity of the Gel

The antimicrobial activity was evaluated by a disk diffusion test which was carried out at Maratha Mandal's Central Research Laboratory. Brain heart infusion agar was used as culture media. It was brought to room temperature before introducing the inoculum. The inoculation was done by transferring the colonies with a loop onto the plates. After this, the turbidity was adjusted with broth to equal that of the 0.5 McFarland turbidity standard.

Within 15 minutes, a sterile cotton swab was dipped in the inoculum in order to remove excess. For even distribution, the surface of agar plates was swabbed thrice along with approximately 60° rotations between streaking. The inoculum was allowed to stand for 3 minutes. Wells were made into inoculated agar plates with a hollow tube of 5 mm diameter. *Boswellia serrata* Roxb. gel in concentrations of 0.5%, 1.5%, 3.5, 4.5%, and 6% were placed on inoculated plates with the help of a micropipette.

Plates were incubated within 15 minutes of gel application. Plates were inverted, stacked for 18–24 hours, and incubated at 37°C. If the lawn of growth was confluent or nearly confluent, plates were read. The diameter of the zone of inhibition was measured using a measuring device and rounded off in millimeters (Fig. 2). The tests were triplicated and the average was recorded.

Statistical Analysis

A statistical package for Social Sciences (v.19) was used to determine of significant difference between the values. $p < 0.05$ was considered statistically significant.

Results

The MIC of *Boswellia serrata* Roxb. extract against the tested microorganisms is shown in Table 1.

The tests were triplicated to obtain and ensure maximum accuracy. *Boswellia serrata* Roxb. extract suppressed the growth

Table 1: MIC of *Boswellia serrata* Roxb. *against* periopathogens

Sl. No.	*Samples*	*100 µg/mL*	*50 µg/mL*	*25 µg/mL*	*12.5 µg/mL*	*6.25 µg/mL*	*3.12 µg/mL*	*1.6 µg/mL*	*0.8 µg/mL*	*0.4 µg/mL*	*0.2 µg/mL*
	Boswellia serrata Roxb. extract										
01	Pg	S	S	S	S	S	S	S	R	R	R
02	Pi	S	S	S	S	S	S	S	R	R	R
03	Aa	S	S	S	S	S	S	S	R	R	R
04	Tf	S	S	S	S	S	S	S	S	R	R
05	Fn	S	S	S	S	S	S	S	S	R	R

Aa, aggregatibacter actinomycetemcomitans; Fn, fusobacterium nucleatum; Pi, prevotella intermedia; Pg, porphyromonas gingivalis; S, sensitive; R, resistant; *Tf, tannerella forsythia*

Table 2: MBC of *Boswellia serrata* Roxb. against periopathogens

Sl. No.	*Samples*	*100 µg/mL*	*50 µg/mL*	*25 µg/mL*	*12.5 µg/mL*	*6.25 µg/mL*	*3.12 µg/mL*	*1.6 µg/mL*	*0.8 µg/mL*	*0.4 µg/mL*	*0.2 µg/mL*
	Boswellia serrata Roxb. extract										
01	Pg	NG	NG	NG	NG	NG	NG	NG	16	28	146
02	Pi	NG	NG	NG	NG	NG	NG	NG	28	79	203
03	Aa	NG	NG	NG	NG	NG	NG	NG	NG	56	78
04	Tf	NG	NG	NG	NG	NG	NG	NG	NG	29	89
05	Fn	NG	NG	NG	NG	NG	NG	NG	NG	67	93

Aa, aggregatibacter actinomycetemcomitans; Fn, fusobacterium nucleatum; Pi, prevotella intermedia; Pg, porphyromonas gingivalis; S, sensitive; R, resistant; *Tf, tannerella forsythia;* NG, no growth

of *P. gingivalis*, *P. intermedia*, and *A. actinomycetemcomitans* at a low concentration of 1.6 µg/mL whereas, *Tannerella forsythia* and *F. nucleatum* were suppressed at a concentration of 0.8 µg/mL. The present test agent was found to be sensitive for all five strains at 1.6 µg/mL.

The MBC of *Boswellia* serrata against the tested microorganisms is shown in Table 2.

When tested against *P. gingivalis* and *P. intermedia*, no growth was seen at 1.6 µg/mL. No growth was seen against *A. actinomycetemcomitans*, *T. forsythia*, and *F. nucleatum* at a concentration of 0.8 µg/mL.

Evaluation of Gel

The freshly prepared gel at different concentrations was off-white to light brown in color and has a pleasant odor. A base was formulated for control which was colorless and odorless. The prepared formulations were stable in color, odor, and appearance for an observation period of 30 days.

pH

The pH of the formulations was found to be between 6.0 and 7.0 when kept under different storage conditions for a month.

Rheology and Viscosity

When kept at storage conditions for 30 days, the rheology and viscosity of the formulations and control gel were found within range.

Spreadability

The formulations prepared with 0.4 gm carbopol 940 were found to possess good spreadability within a range of 2–3 mm whereas 0.6 and 0.8 concentrations did not possess sufficient spreadability.

Syringeability

The syringeability test of all the concentration of formulations suggests that all the concentrations prepared with 0.4 gm carbopol 940 except 6% were syringeable through a 21-gauge needle.

Patch Test

The volunteers were provided with all five concentrations prepared with 0.4 gm carbopol 940. They reported that there was no irritation and redness within 48 hours of application. They also delineated a pleasant smell and a cool sensation within five minutes of application.

The physicochemical properties rendered *Boswellia serrata* Roxb. with 0.5, 1.5, 3.0, 4.5, and 6 gm concentrations with 0.4 gm concentration of carbopol 940 suitable for topical application and local drug delivery. Therefore, these concentrations were tested for the zone of inhibition.

Disk Diffusion Test

The results of the disk diffusion test are shown in Table 3.

Boswellia serrata Roxb. gel showed the highest zone of inhibition against *Aa* (22 mm) at 4.5% concentration, followed by *Aa* (20 mm) at 4.5% concentration and the least against *Pi* (8 mm) at 3 % concentration.

Discussion

Periodontal diseases are chronic inflammatory diseases of the investing and supporting tissues of the teeth. Plaque biofilm is accountable for the gingival inflammation progressing to accelerated alveolar bone loss which leads to tooth loss in due course of time.[14] Around 700 distinct species of bacteria exist in harmony in the oral cavity. *P. gingivalis*, *P. intermedia*, *A. actinomycetemcomitans*, *T. forsythia*, and *F. nucleatum* are the principal gram-negative bacteria that exist in anaerobic environment of the deep periodontal pockets and are responsible for progressive attachment loss.[15,16] In the present study, we evaluated the MIC of *Boswellia serrata* Roxb. extract against these bacteria with the goal to utilize it as a local drug delivery agent in the forthcoming future. *P. gingivalis*, a gram-negative bacterium that is a nonmotile obligatory anaerobic rod, asaccharolytic, and colonies are black-pigmented formed on blood agar plates and require iron for its growth. *P. intermedia* is gram-negative, nonmotile, obligatory anaerobes, single cells that thrive in anaerobic growth conditions. *T. forsythia* is an anaerobic, gram-negative bacterial species in a red complex in the Cytophaga-Bacteroidetes family which has been implicated in periodontal diseases. *A. actinomycetemcomitans* is an immobile microaerophilic, facultative anaerobic, gram-negative coccoid rod, strongly associated with the pathogenesis of periodontal diseases.[17] *F. nucleatum* belonging to the Bacteroidaceae family is a gram-negative anaerobe, an intermediate colonizer bridging the interactions between gram-positive and gram-negative organisms having co-aggregation properties allowing it to transport periopathogens.[18]

Boswellia serrata Roxb. extract showed an antimicrobial effect against all five periopathogens which is in accordance with a study conducted by Raja et al. where they proved the antibacterial effect of Boswellic acids isolated from *Boswellia serrata* Roxb. gum resin against all oral cavity pathogens in a dose-dependent manner. The predominant Boswellic acids, AKBA, and 11-keto-β-Boswellic acids regulate proinflammatory cytokine cascade comprising TNF-α and IL-1β by inhibiting NF-κB. This may be attributed to the antibacterial activity of AKBA acids to disrupt the permeability barrier of the microbial membrane structure and inhibition of cell proliferation due to the inhibitory effect of lipo-oxygenases in AKBA. This may be the possible mechanism of action of *Boswellia serrata* against gingival inflammation.[19]

Table 3: Zone of inhibition at different concentrations of *Boswellia Serrata* Roxb. Gel against *Pg, Pi, Aa, Tf, and Fn*

Sl. No.	*Samples*	*0.5%*	*1.5%*	*3%*	*4.5%*	*6%*
	Boswellia serrata Roxb. gel					
01	Pg	R	9 mm	12 mm	15 mm	18 mm
02	Pi	R	R	8 mm	10 mm	13 mm
03	Aa	R	15 mm	18 mm	20 mm	22 mm
04	Tf	R	12 mm	13 mm	16 mm	17 mm
05	Fn	R	10 mm	12 mm	15 mm	15 mm

Aa, aggregatibacter actinomycetemcomitans; Fn, fusobacterium nucleatum; Pi, prevotella intermedia; Pg, porphyromonas gingivalis; Tf, tannerella forsythia

There are various side effects related to the consumption of *Boswellia serrata*, namely, nausea, diarrhea, abdominal discomfort, hyperacidity, and epigastric pain.[20]

A major disadvantage associated with this compound is low bioavailability. To overcome this, a topical gel using polymeric nanoparticles of AKBA was formulated and the results showed higher anti-inflammatory activity of AKBA nanogel compared to AKBA gel of equivalent concentration.[21]

A study conducted by Maraghehpour et al. concluded that *Boswellia serrata* Roxb. extract is effective against *A. actinomycetemcomitans* which should be taken into account for the formation of oral hygiene products. The MIC was found to be 512 µg/mL against *Aa*.[22] Recent studies reported by Alluri et al.[23] and Gomaa et al.[24] confirmed that *Boswellia serrata* Roxb. did not exhibit mortality or signs of toxicity in rats up to 2000 mg/kg. Following a single dose administration of up to 5 gm/kg in mice, no deaths were recorded.

Samani et al. proved the effects of *Boswellia serrata* Roxb. in the form of chewing gum in moderate plaque-induced gingivitis among high school students which may be attributed to an anti-inflammatory effect caused by Boswellic acids leading to inhibition of proinflammatory enzymes.[25]

Another study conducted by Khoshbakht et al. showed a significant decrease in gingival index (GI), plaque index (PI), and Gingival Bleeding Index after 21 days following intervention with mouthwash containing hydro-alcoholic extract of *Boswellia serrata* Roxb. which may be attributed to its antibacterial, antibiofilm, and anti-inflammatory properties.[26] A review by Cochrane has given a contrasting opinion about the anti-inflammatory properties of Boswellic Acids.[27]

Due to the recent discovery, *Boswellia* serrata has been proven to produce anti-inflammatory LOX-isoform-selective modulators along with the formation of classical 5-lipooxygenase products. Therefore, it has been proposed to be used as a potential therapeutic agent against COVID-19 and secondary bacterial infections caused by *P. gingivalis* and *T. forsythia*.[7]

In order to use a formulation for commercial and therapeutic purposes, tests for quality control must be performed in order to ensure safety along with efficacy. The pH of all the formulations was found to be stable for one month. The measurement of the strength of the formulations and the extent of the area to which it spreads is performed by the viscosity and spreadability test. The present study revealed that all the concentrations except 6% showed effective syringeability for considering the formulations for effective local drug delivery. No irritation or redness was reported by the volunteers during the patch test. Taking into account, the results of physicochemical parameters revealed that all the formulations are safe to use for topical application. A higher dose is recommended due to the higher concentration of active constituents available. Being an herbal product, no signs of toxicity and development of toxicity can be reported. There is no evidence of the formulation of the present research being previously studied in the literature.

The 6% concentration of the prepared formulations showed the highest antimicrobial activity against all periopathogens. However, the 4.5% concentration of the gel showed better syringeability. Therefore, within the limitations of the present study, we recommend a 6% concentration for topical application and a 4.5% concentration for local drug delivery application.

Limitations and Future Directions

This study provided reference data for future reference for drug development using *Boswellia serrata* Roxb. extract. The limitation of the study is limited analysis of the physicochemical properties. Long-term studies should be carried out in the future to look for the shelf life and sustainable antibacterial, antibiofilm, and anti-inflammatory properties.

There are limited studies conducted for the evaluation of *Boswellia* serrata against periopathogens. Further longitudinal studies can be carried out with microbial evaluation to justify the results obtained. Another shortcoming of the present study is the low absorption of gel. To overcome this, nanoemmigel formulation of *Boswellia serrata* has been proposed for topical application.

Therefore, this herbal product can be used in routine practice since no side effects or toxicity were reported.

Conclusion

Our study upholds the usage of *Boswellia serrata* Roxb. as a potential adjuvant with periodontal therapy as a topical gel and local drug delivery agent owing to its low-cost availability, low toxicity, anti-bacterial, antiplaque, antibiofilm, and anti-inflammatory properties. Although *in vitro* and *in vivo* studies have already suggested *Boswellia serrata* Roxb. to be a potential therapeutic anti-inflammatory agent. Further clinical studies are needed to realize its true potential against various periodontal diseases. Therefore, we conclude that *Boswellia serrata* Roxb. can be used as an adjuvant to standard periodontal therapy in order to overcome the side effects of anti-inflammatory agents

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