ADMINISTRATION OF SYSTEMIC PROPOLIS VERSUS MOXIFLOXACIN AS ADJUNCTIVE TREATMENT OF SEVERE GENERALIZED PERIODONTITIS

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ABSTRACT

To-date, emerging bacterial resistance to the commonly prescribed antibiotics in the management of periodontitis has become a challenging problem making scientists continually seek for new agents. In the present study, propolis (PRO) (natural bee glue) and moxifloxacin (MXF) (new quinolone antibiotic) were evaluated in the treatment of severe generalized periodontitis (gP) as adjuncts to scaling and root planing (SRP). Fifty four subjects with severe gP were randomly assigned into three groups (3 subjects did not complete the study after participation). Group I in which SRP alone was performed to gP patients (SRP group; n=17); group II in which SRP was done to gP patients combined with orally administered propolis 400 mg once daily for 7 days (PRO group; n=16); and group III in which SRP was performed to gP patients combined with oral moxifloxacin 400 mg once daily for 7 days (MXF group; n=18). Pocket depth (PD), clinical attachment level (CAL), bleeding on probing (BOP), plaque (PI) and gingival (GI) indices were recorded at baseline, after 6 and 12 weeks of SRP. Salivary interleukin-1 beta (IL-1β) was evaluated at the same time points for all groups. All three procedures led to significant reductions in PD, CAL, BOP, PI and GI after 6 and 12 weeks. PD reduction and CAL gain were significantly greater in the PRO and MXF groups compared to SRP group at 6 and 12 weeks after therapy (p < 0.01). Importantly, there was no significant variation between PRO group and MXF group after treatment (p > 0.05). Likewise, in PRO and MXF groups, the salivary inflammatory marker (IL-1β) was significantly reduced in comparison to SRP group (p < 0.01). In all groups, salivary IL-1β levels were decreased at 6 and 12 weeks compared to baseline values. It was concluded that the adjunctive use of PRO and MXF to SRP had significantly improved the treatment outcomes in subjects with severe gP comparable to SRP alone. Thus, PRO and MXF showed promising results in the treatment of periodontal disease.

KEYWORDS Propolis, Moxifloxacin, Adjunctive treatment, Periodontitis.
INTRODUCTION

Periodontitis is a chronic inflammatory disease which results from an imbalance between periodontopathogenic microorganisms and the host immune defense and is characterized by an irreversible progressive damage of the periodontal tissues.\(^1\) It has been previously exhibited that most of the periodontal tissue destruction is caused by the host response to infection and not directly by the infectious agents.\(^2\) In 2012, a newly established paradigm of periodontal disease etiopathogenesis stated that periodontitis is initiated by a synergistic and dysbiotic variety of microbial pathogens rather than by specific microorganisms, such as the ‘red complex’.\(^3\) In the polymicrobial synergy and dysbiotic model, certain microbes; known as keystone pathogens, have the potential to modulate the host response via the impairment of immune surveillance and tipping the ecological balance from homeostasis to dysbiosis. Moreover, keystone periopathogens enhance the virulence of the whole existing microorganisms via interspecies communication with other accessory pathogens.\(^3\)

Efficient host response to the bacterial challenge is mainly mediated by polymorphonuclear leukocytes (PMNs) and characterized by an influx of PMNs into the gingival sulci. The PMNs recruitment and their influx in the vicinity of gingival crevices and periodontal pockets depend on a variety of chemotactic molecules, such as TNF-α, IL-1, IL-6 as well as matrix metalloproteinases (MMPs) which are synthesized and released into the area of inflammation.\(^4\) The primary goal for periodontal therapy is to reduce infection, resolve inflammation, and prevent any further periodontal tissue destruction. The effectiveness of scaling and root planing (SRP) as an essential arm of nonsurgical treatment of periodontitis patients has been evidenced through various investigations.\(^5-7\) Thus, meticulous mechanical root debridement has been proved as a key determinant of periodontal therapy success. Nevertheless, various anatomical factors, such as narrow inaccessible furcation areas and deep pockets, have been suggested to reduce the efficacy of non-surgical periodontal therapy.\(^8\) Furthermore, bacterial penetration deeper inside the periodontal tissues or yet in the dentinal tubules impairs the final outcomes of conventional periodontal therapy.\(^9\) Therefore, adjunctive antibiotics can be used to improve the treatment outcomes in chronic periodontal disease.\(^10\) Several antibiotics including amoxicillin, tetracyclines, clindamycin and metronidazole have been studied solely or in combination in periodontal therapy, however, problems of bacterial resistance suggest that alternatives for the currently used antibiotics may be needed.\(^11-13\) Few years ago, moxifloxacin (MXF); which is a new fourth-generation fluoroquinolone antibiotic, has been found to exert excellent antibacterial activity against a wide variety of putative periopathogens, such as Porphyromonas gingivalis, Tannerella forsythia, Aggregatibacter actinomycetemcomitans and Actinomyces species.\(^14\) Its bactericidal activity against biofilm-embedded P. gingivalis, A. actinomycetemcomitans, and Streptococcus constellatus was found to be more potent than clindamycin, metronidazole, and doxycycline.\(^15\) MXF was found to have greater penetratability inside the soft tissues and potent bactericidal activity against intracellular periodontopathogens.\(^16\) Hence, systemic MXF when used as adjuvant to scaling and root planing (SRP) in periodontitis therapy, yielded significant outcomes in comparison to doxycycline or SRP alone.\(^14\)

Long time ago, propolis (PRO) has been used in folk medicine due to its recognized anti-inflammatory properties, particularly in ancient Egypt and Europe.\(^17\) Propolis is a natural resinous mixture synthesized by honeybees from extracts collected from various plants.\(^18\) Honeybees used propolis in order to protect their hives against
winds, dust and other foreign invaders. PRO has traditionally been used as a therapeutic in several diseases, including disorders of the gastrointestinal tract and mucocutaneous ailments of viral, bacterial and fungal etiologies.\(^{(19)}\)

Noteworthy, there are several types of PRO which vary in composition depending on their plant sources based on the geographic zone. PRO contains more than 300 ingredients, such as caffeic acid phenethyl ester (CAPE), caffeic acid, flavonoids, cinnamic acids and their esters.\(^{(20)}\) Furthermore, PRO revealed a bunch of different biological activities, such as: 1) antibacterial; 2) antiviral; 3) fungicidal; 4) anti-inflammatory; 5) antioxidant; 6) immunomodulatory; 7) anti-diabetic activity and 8) hepatoprotective effects.\(^{(21)}\) A recent review has exhibited that CAPE is a crucial bioactive compound present in PRO which is responsible for the majority of its therapeutic activities.\(^{(22)}\)

Recently, an increased interest in whole mouth saliva as a diagnostic fluid has become evident. In periodontal disease, whole unstimulated saliva was reported to reflect the soluble mediator composition of the gingival and all mucosal tissues as well as gingival sulcular fluid of patients affected by periodontitis.\(^{(23)}\) Potential biomarkers of periodontal disease were previously identified in saliva and shown to be specific for the unique physiologic and pathologic aspects of periodontitis. It was shown that salivary levels of IL-1\(\beta\) appear to serve as reliable biomarker of periodontitis.\(^{(24)}\)

The purpose of the present study is to evaluate the impact of adjunctive use of systemic MXF versus systemic PRO in conjunction with scaling and root planing (SRP) compared to SRP alone in the treatment of severe generalized periodontitis. The current investigation focuses on the changes in clinical periodontal parameters and the salivary inflammatory biomarker IL-1\(\beta\) after 6 and 12 weeks of therapy.

**MATERIALS AND METHODS**

**Patient Population**

A total of fifty four systemically healthy individuals with severe generalized periodontitis selected from the outpatients coming to the Faculty of Dentistry, Mansoura University were enrolled in the study when they demonstrated interdental clinical attachment loss (CAL) \(\geq 5\) mm of more than 30% of sites and radiographic evidence of bone loss extending to or beyond the middle third of the root (stage III periodontitis) according to 2017 world workshop classification of periodontal diseases.\(^{(25)}\)

**Inclusion/Exclusion criteria**

The eligible subjects were free from any systemic conditions which could influence the outcome of the treatment and had at least 20 treatable teeth in occlusion. Subjects were excluded if they had the following: 1) allergic to quinolones; 2) had received medication (e.g., antibiotics, corticosteroids, or non-steroidal anti-inflammatory drugs) in the previous 3 months; 3) had received any periodontal therapy within the last year; 4) had any systemic disease; 5) were smokers or 6) were pregnant/lactating.

The study proposal was approved by the Ethics Committee of the Faculty of Dentistry, Mansoura University. All participants signed a written informed consent before conduction of the study.

**Study Design**

The study was designed to assess the effectiveness of the antibiotic moxifloxacin (MXF) and the natural bee-product propolis (PRO) as adjuncts to mechanical periodontal treatment compared to SRP alone. The participants were randomly assigned into three groups. Group I which includes 18 patients performing SRP alone (SRP group) which represents the control group. Group II in which SRP was performed to 18 patients combined with orally administered MXF 400 mg (Moxacin
tablets; Medical Union Pharmaceuticals, Abu-Sultan, Ismailia, Egypt) once daily for 7 days (MXF group). Group III in which SRP was done for 18 patients combined with systemically administered PRO 400 mg (BioPropolis capsule; Sigma Pharmaceutical Industries, Egypt) once daily for 7 days (PRO group). All subjects received instructions for good oral hygiene and given a medium dental brush and the same dentifrice (Colgate Total). Treatment started with chlorhexidine rinsing 0.12% (Hexitol, ADCO, Egypt) for 1 minute. The endpoint of SRP was a tactile smooth and clean root surface. The subjects began taking the antibiotics on the first day of the procedure. Individuals in the control group (SRP) received no drugs. Subjects in the MXF and PRO groups were extensively informed about the intake of the prescribed medication. Adverse effects were assessed and recorded throughout the duration of antibiotics given to the patients.

Patients in the three groups were monitored at baseline, at 6 and 12 weeks after SRP completion. At these time points, the examiner recorded the periodontal parameters and saliva samples were collected as well. All subjects received supportive periodontal treatment and reinforcement of oral hygiene procedures at 2-week intervals for a period of 12 weeks.

**Clinical Monitoring**

Pocket Depth (PD), Clinical Attachment Loss (CAL), bleeding on Probing (POB), Gingival (26) and Plaque (27) Indices were recorded at baseline, 6 and 12 weeks for all groups. Measurements were taken with a calibrated UNC-15 periodontal probe at 6 standardized sites per each tooth excluding the wisdom teeth from recording. These were the mesiofacial, midfacial, distofacial, mesiolingual, midlingual and distolingual sites. All periodontal measurements were made by the same examiner (MA).

**Saliva Sampling**

Whole mouth unstimulated saliva samples were collected at baseline and 6 and 12 weeks after therapy for all subjects. Saliva samples (2 ml) were obtained by expectoration into graduated polypropylene tubes before periodontal measurements. Salivary samples were centrifuged to remove debris, and then immediately frozen at -80 °C till their evaluation time after study completion.

**Biochemical Analysis**

At the end of the study, the frozen saliva samples of all patients were left to thaw. Each saliva sample (2 mL) was centrifuged at 10,000 x g for 5 minutes; the supernatant was transferred to clean microcap tubes and used immediately for biochemical analysis. Detection of the levels of IL-1β in saliva was determined by enzyme-linked immunosorbent assay (ELISA) (Human IL-1 β Quantikine ELISA kit, R&D Systems, Minneapolis, MN, USA).

**Data Analysis**

All data were explored firstly by Kolomogrov-Smirnov test of normality. The parametric variables were presented as mean ± SD except salivary IL-1β levels that were expressed as mean ± SE (standard error of the mean). Chi-square and t-tests were used for comparing baseline data. The analysis of variance (ANOVA) of repeated measures with Bonferroni post hoc correction was used to determine significant differences among various time intervals. The significant level of difference was determined at 5%. All analyses were carried out by using SPSS (Statistical Package for the Social Sciences v. 19, Chicago, IL).

**RESULTS**

**Clinical Outcomes**

Fifty four patients with generalized severe periodontitis (stage III) were enrolled in the present study and subdivided randomly into three groups equally (n=18); SRP, PRO and MXF groups. After study completion, one patient and two patients dropped-out from SRP and PRO
groups; respectively, because these patients did not complete the study. Thus, the finally analyzed data belonging to each group were as follows: SRP group (n=17), PRO group (n=16) and MXF group (n=18). The demographic distribution and baseline periodontal parameters in the three groups revealed no statistical differences between groups regarding age, age range, male number to female number and number of present teeth per patient (p > 0.05) (Table1).

TABLE (1) Demographics of Patient Population and Baseline Periodontal Parameters (mean ± SD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SRP (n=17)</th>
<th>PRO (n=16)</th>
<th>MXF (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>47.3 ± 5.6</td>
<td>44.5 ± 7.3</td>
<td>45.8 ± 6.1</td>
</tr>
<tr>
<td>Age range (years) (min-max)</td>
<td>37-58</td>
<td>39-61</td>
<td>41-59</td>
</tr>
<tr>
<td>Male/Female (n)</td>
<td>11/6</td>
<td>9/7</td>
<td>13/5</td>
</tr>
<tr>
<td>Teeth (n)</td>
<td>22.4 ± 2.2</td>
<td>23.1 ± 1.9</td>
<td>21.8 ± 2.4</td>
</tr>
<tr>
<td>PI</td>
<td>2.2 ± 0.3</td>
<td>2.3 ± 0.2</td>
<td>2.4 ± 0.3</td>
</tr>
<tr>
<td>GI</td>
<td>1.7 ± 0.1</td>
<td>1.6 ± 0.3</td>
<td>1.8 ± 0.2</td>
</tr>
<tr>
<td>BOP (%)</td>
<td>62 ± 19</td>
<td>64 ± 21</td>
<td>60 ± 17</td>
</tr>
<tr>
<td>PD (mm)</td>
<td>4.8 ± 0.9</td>
<td>4.6 ± 0.8</td>
<td>4.7 ± 0.6</td>
</tr>
<tr>
<td>CAL (mm)</td>
<td>5.7 ± 0.7</td>
<td>5.8 ± 0.9</td>
<td>5.6 ± 0.8</td>
</tr>
</tbody>
</table>

*There were no significant difference between groups (p > 0.05).*

Table 2 summarizes the full mouth mean (±SD) of Plaque Index (PI), Gingival Index (GI) and Bleeding on Probing (POB) index of all groups at baseline and after 6 and 12 weeks of therapy. The PI showed significant reduction in SRP, PRO and MXF groups at 6 and 12 weeks compared to baseline data. Notably, there was no statistically significant difference among groups at 6 and 12 weeks after treatment (p > 0.05).

<table>
<thead>
<tr>
<th>Index</th>
<th>SRP (n=17)</th>
<th>PRO (n=16)</th>
<th>MXF (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>baseline</td>
<td>2.2 ± 0.3</td>
<td>2.3 ± 0.2</td>
<td>2.4 ± 0.3</td>
</tr>
<tr>
<td>6 W</td>
<td>0.9 ± 0.3*</td>
<td>1.0 ± 0.2*</td>
<td>1.1 ± 0.4*</td>
</tr>
<tr>
<td>12 W</td>
<td>0.7 ± 0.2*</td>
<td>0.9 ± 0.3*</td>
<td>0.8 ± 0.3*</td>
</tr>
<tr>
<td>baseline</td>
<td>1.7 ± 0.1</td>
<td>1.6 ± 0.3</td>
<td>1.8 ± 0.2</td>
</tr>
<tr>
<td>6 W</td>
<td>0.8 ± 0.2*</td>
<td>0.6 ± 0.2*</td>
<td>0.7 ± 0.3*</td>
</tr>
<tr>
<td>12 W</td>
<td>0.7 ± 0.1*</td>
<td>0.5 ± 0.1*</td>
<td>0.6 ± 0.2*</td>
</tr>
<tr>
<td>baseline</td>
<td>62 ± 19</td>
<td>64 ± 21</td>
<td>60 ± 17</td>
</tr>
<tr>
<td>6 W</td>
<td>38 ± 15*</td>
<td>33 ± 14*</td>
<td>39 ± 16*</td>
</tr>
<tr>
<td>12 W</td>
<td>38 ± 14*</td>
<td>31 ± 11*</td>
<td>37 ± 13*</td>
</tr>
</tbody>
</table>

*p < 0.05 compared to baseline (repeated ANOVA with the Holm-Sidak post hoc test between time points).*

The GI records tended to be lower in all groups at 6 and 12 weeks compared to baseline scores. There was also no significant variation among the three groups at 6 and 12 weeks after treatment (p > 0.05). BOP scores followed similar pattern with significant differences from baseline compared to 6 and 12- week scores. No statistically significant difference between groups at 6 and 12 weeks after therapy was noted (p > 0.05).

Table 3 shows that there was no statistical difference between groups for PD and CAL at baseline (p > 0.05). However, at 6 and 12 weeks, the three groups showed significant improvements in PD and CAL over baseline measurements. Importantly, there was no statistical difference between PRO and MXF groups at 6 and 12 weeks (p > 0.05). More interestingly, there were significant variations in MXF and PRO groups at 6 and 12 weeks compared to SRP group (p < 0.01).
It was important to record any adverse effects of both propolis and moxifloxacin when given to the patients included in both PRO and MXF groups during the first week of the study. It was observed that there were no major deviations in using the drugs by the patients and there was no significant difference between the two groups regarding the recorded adverse events (Table 4).

**TABLE (4) Adverse Events of the Drugs Used After 1st Week of the Study**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>PRO (n=16)</th>
<th>MXF (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Skin rash</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

There is no significant difference between the two groups; p > 0.05.

**TABLE (3) Full Mouth PD and CAL (mean ± SD) at different time points**

<table>
<thead>
<tr>
<th></th>
<th>PD (mm)</th>
<th>CAL (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>baseline</td>
<td>6 W</td>
</tr>
<tr>
<td>SRP</td>
<td>4.8 ± 0.9</td>
<td>3.8 ± 0.6*</td>
</tr>
<tr>
<td>PRO</td>
<td>4.6 ± 0.8</td>
<td>3.1 ± 0.5*</td>
</tr>
<tr>
<td>MXF</td>
<td>4.7 ± 0.6</td>
<td>3.4 ± 0.3*</td>
</tr>
</tbody>
</table>

* Significant difference when compared to their baseline values; p < 0.01.

Figure 1 showed the mean values of pocket depth reduction (PDR) in the three groups at 6 and 12 weeks of therapy. The PDR value in the SRP, PRO and MXF groups were 1 ± 0.13 mm, 1.3 ± 0.14 mm and 1.5 ± 0.1 mm, respectively after 6 weeks of treatment. At 12 weeks, the PDR values for SRP, PRO and MXF were 1.1 ± 0.12 mm, 1.4 ± 0.12 mm and 1.6 ± 0.11 mm, respectively. There was a modest reduction in pocket depth of PRO group compared to MXF group at 6 and 12 weeks, however, it is not statistically significant. The PRO and MXF values of PDR at 6 and 12 weeks showed significant differences when compared to the corresponding values in SRP group (p < 0.01).

Figure 2 showed the mean values of clinical attachment (CAL) gain in the three groups at 6 and 12 weeks after therapy. The CAL gain value in the SRP, PRO and MXF groups were 0.09 ± 0.11 mm, 1.7 ± 0.15 mm and 1.6 ± 0.12 mm, respectively at 6 weeks of treatment. At 12 weeks, the CAL gain values for SRP, PRO and MXF were 1 ± 0.14 mm, 1.8 ± 0.14 mm and 1.6 ± 0.13 mm, respectively. There was also no statistically significant difference between PRO and MXF values at 6 and 12 weeks. Both PRO and MXF values of CAL gain at 6 and 12 weeks exhibited significant improvement compared to the corresponding values in SRP group (p < 0.01).
Biochemical Outcomes

The salivary IL-1β levels (picograms per milliliter) (mean ± standard error of the mean) of SRP, PRO and MXF groups at various time points are summarized in Figure 3. No significant difference of all groups at baseline was observed. It was statistically noted that significant reductions of salivary IL-1β are present in all groups at 6 and 12 weeks when compared to their baseline levels (p< 0.01). More importantly, there was significant decrease of salivary IL-1β levels of PRO and MXF groups at 6 and 12 weeks when compared to their corresponding values of SRP group (p< 0.01).

Discussion

The present comparative clinical study assessed the effectiveness of the use of moxifloxacin (MXF) and propolis (PRO) as new adjunctive therapeutics to the conventional non-surgical periodontal therapy represented by scaling and root planing (SRP) in generalized severe periodontitis. In general, antibiotics have been used as adjunctive therapy in chronic and aggressive periodontitis patients with inconsistent outcomes. It was reported that increasing rates of bacterial resistance to some antibiotics became evident, hence, several warnings regarding their profligate prescription in all cases of periodontal disease were addressed. For decades, the most extensively investigated periodontal antibiotic regimen is the combination of amoxicillin and metronidazole which is prescribed three times for one week, in conjunction with mechanical periodontal therapy. However, another investigation demonstrated that mechanical debridement in addition to topical chlorhexidine exhibited the same efficacy as adjunctive amoxicillin/metronidazole after 6 months and also indicated that the early ameliorative effects were short lived. Thus, pharmacologists are still searching...
for new promising antimicrobials with least incidence of bacterial resistance and have potent bactericidal effect against most oral pathogens.

Recently, moxifloxacin (MXF) as one of the fourth generation of fluoroquinolones, showed better promising results in several in vitro and in vivo studies to be used as adjunctive antibiotic to periodontal infections.\(^\text{35, 36}\) It was previously reported that MXF is more effective than doxycycline as adjunctive antibiotic in the treatment of severe cases of periodontitis.\(^\text{14}\)

On the other hand, the promising properties of propolis, as a naturally produced substance by honeybees, especially the in vitro antimicrobial activity\(^\text{37}\) have led us to evaluate its efficacy in vivo by assessing clinical and biochemical data. Therefore, the current study was tailored to explore and assess the adjunctive effects of systemically administered propolis with those of moxifloxacin, a recently potent well-established antibacterial agent.

Several studies demonstrated that propolis is effective against Porphyromonas gingivalis, Prevotella intermedia and Aggregatibacter actinomycetemcomitans which are considered as keystone periopathogens for the etiology of periodontal diseases.\(^\text{38, 39}\) In our study, we evaluated the systemic effect of MXF and PRO as adjunctive remedies in the treatment of generalized severe periodontitis and assess their effect clinically and biochemically via one reliable salivary biomarker; IL-1β. We have proved in the present study that PRO and MXF are superior to SRP alone in reducing pocket depth and increasing clinical attachment gain. This obtained improvement was supported biochemically by the obvious reduction of salivary IL-1β after 6 and 12 weeks of therapy. The appreciated effects of both PRO and MXF as adjuvant to SRP in the treatment of generalized severe periodontitis compared to SRP alone revealed in our findings are consistent with the results of other studies.\(^\text{14, 40-42}\)

In our study, MXF showed significant changes in PD reduction and CAL gain when compared to SRP. There was an obvious reduction of salivary inflammatory biomarkers represented by IL-1β in MXF group compared to SRP group. Our findings come in agreement with a recent investigation.\(^\text{14}\) This can be explained due to the greater activity of MXF against P. gingivalis and A. actinomycetemcomitans strains and unlikelihood of MXF to the development of resistant strains of these periodontopathogens.\(^\text{43}\) In another Colombian study, superinfecting enteric were isolated in significant amounts from chronic periodontitis patients and it was found that these enteric rods and the putative periodontopathogens exhibited high susceptibility to MXF and showed variable susceptibility to amoxicillin/calvulanic acid.\(^\text{15}\)

Previous studies reported that the antibacterial effect of propolis is attributed to a synergism of several compounds rather than a single component because propolis is a natural mixture of a myriad of different molecules which possess a plethora of biologic properties.\(^\text{44}\) The antibacterial effect of propolis involves several mechanisms such as; inhibition of protein synthesis, partial bacteriolysis, and disorganization of the cytoplasm, the cytoplasmic membrane, and the cell wall.\(^\text{45}\)

In our study, it was also noticed that MXF does not show any significant variation in comparison to PRO regarding the adverse events observed in the studied populations during the period of drug intake. This shows that MXF is similar to PRO in patient tolerability.

The adopted propolis dosage prescribed in the current study (400 mg/day) seems to be safe and effective adjunctive therapeutic modality to SRP. As anticipated, our findings revealed that SRP alone was effective in reducing POB, pocket depth (PD), and clinical attachment level (CAL) gain which are in accordance with previous investigations.\(^\text{46-48}\) The PRO group showed greater PD reduction and more CAL gain when compared to the SRP group. The plausible biologic rationale for the expected anti-
inflammatory effects of propolis might result from the integration of the appreciated antibacterial, anti-inflammatory and antioxidant actions of propolis. Importantly, studies of topical propolis application as an adjunctive oral hygiene measure gave similar outcomes.\cite{49-52}

The limitations of our study included the small sample size represented by the relatively small number of patients enrolled in the study. Thus, it is recommended to conduct future large scale studies of PRO and MXF in periodontitis patients. Second, the follow-up period for 12 weeks is short to assess the long-term effects of the used drugs. Moreover, the authors did not assess the microbiological aspects of periodontitis patients and correlating them with the clinical and biochemical findings. Another limitation of the present study is the lack of confirmation of its biochemical findings by collection of GCF samples as it reflects the condition of the local periodontal environment more accurately than saliva. In total, we concluded that propolis and moxifloxacin might be used as alternative adjunctive therapeutics and showed excellent improvements in severe generalized periodontitis patients over the use of SRP alone. It is also recommended to use them in other periodontal conditions like periodontal abscesses and adjuvant to surgical periodontal treatments.

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