

# Efficacy of Locally Administered 1.2% Rosuvastatin Gel in Patients with Periodontitis: A Randomized Placebo Controlled Clinical Trial

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## Abstract

**Objective** Periodontitis initiation and progression are a result of host immune inflammatory response to oral pathogens. Several pharmacological agents are being delivered locally, to improve periodontal health. Hence, the present randomized placebo controlled clinical trial is designed to check the clinical and antimicrobial efficacy of locally delivered 1.2% rosuvastatin (RSV) in intrabony defects (IBD) in periodontitis patients.

**Materials and Methods** One-hundred patients were randomly allotted into two treatment groups: group A received 1.2% RSV gel, scaling and root debridement and group B received placebo gel, scaling and root debridement. Clinical parameters, including modified sulcus bleeding index (mSBI), probing depth (PD), clinical attachment level (CAL), and plaque index (PI), were recorded at baseline before phase 1 and after 6 months. Radiographic assessment of IBD was done by cone beam computed tomography at baseline and after 6 months. Anaerobic colony count was done at baseline and after 180 days.

**Results** On intragroup comparison, there is a significant improvement in periodontal parameters in both the groups. On intergroup comparison, there is significant gain in CAL in group A than group B ( $p = 0.04$ ). There is significant decrease in PD in group A, compared to group B. There is significant bone fill in group A ( $p = 0.034$ ), compared to group B. With respect to mSBI, PI, and anaerobic colony count, there is no significant difference between the two groups after 6 months. No adverse effect was noticed in any subjects.

**Conclusion** The author concludes that 1.2% RSV gel when delivered locally into IBD improved periodontal clinical parameters such as PD and CAL and showed significant bone fill.

## Keywords

- ▶ bone loss
- ▶ inflammation
- ▶ periodontitis
- ▶ statins

## Introduction

Periodontitis is an infectious disease, initiated by oral microbial biofilm that results in inflammation in the supporting

tissue of teeth, leading to progressive clinical attachment and bone loss, and further creating intrabony defects (IBD).<sup>1</sup> The inflammatory condition is due to imbalance in host immune response against microbial challenge.<sup>2</sup>



Periodontitis is a site-specific disease. It is due to local bacterial infection. The microflora found in periodontitis is complex and composed of anaerobic and Gram-negative bacteria.<sup>3</sup> Progression of the disease is the net effect of immune response and inflammatory disease, rather than mere presence of microflora.<sup>4</sup>

The primary objective of treatment of periodontitis is to halt the progression of disease and resolve inflammation.<sup>5</sup> Among the various treatment modalities, scaling and root debridement remains the gold standard nonsurgical management of chronic periodontitis.<sup>6</sup> Local delivery of pharmacological agents, especially in local periodontal defect area, has gained interest due to site-specific nature of periodontal infection.<sup>7</sup> To complement mechanical debridement, local delivery of various pharmacologic agents using sustained/controlled release vehicle is directly administered into periodontal pocket, targeting specific microorganism, and even to modulate host inflammatory response.<sup>8</sup>

Statins are lipid-lowering drugs. They are competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase, which is the key enzyme in cholesterol biosynthesis. Statins are considered as main drug in treating cardiovascular diseases.<sup>9</sup> Statins exhibit broad-spectrum pleiotropic effects. The reduction in mevalonate pathway by statins is responsible for numerous pleiotropic effect of these drugs.<sup>10</sup>

The potential pleiotropic effects include cholesterol-independent anti-inflammatory, modulation, of vascular response,<sup>11</sup> microvascular reperfusion,<sup>12</sup> and antimicrobial effect.<sup>13</sup> They possess intrinsic antioxidant properties.<sup>11</sup> Both in vitro and in vivo animal models, statin stimulates bone formation, associated with increased expression of the *BMP-2* gene in bone cells. Increased *BMP-2* expression causes osteoblast differentiation. They inhibit osteoclast differentiation.<sup>14</sup>

Rosuvastatin (RSV) is synthetic sulfur containing hydrophilic statin. RSV unlike other lipophilic drug is actively transported in osteoblastic cell through solute carrier. RSV induces *BMP 2* gene expression, secretion, and increases alkaline phosphatase activity, demonstrating osteoblastic differentiation.<sup>14,15</sup>

Adult patients  $\geq 30$  years old with periodontitis showed improvement in their periodontal status on simultaneous administration of either systemic or locally delivered statins in adjunct to nonsurgical therapy.<sup>16</sup> Another systematic review with meta-analyses concluded that statin along with scaling and root debridement promotes significant periodontal parameter improvement.<sup>17</sup> Due to pleiotropic effects of statins, it can evolve as a novel economic, host modulating, and bone anabolic agent in the treatment of periodontitis. Based on the available data, the present randomized study is designed to evaluate the clinical and antimicrobial efficacy of locally administered 1.2% RSV gel adjunct to scaling and root debridement in periodontitis patients compared to placebo gel.

## Materials and Methods

The present study was single center, 6-month follow-up, double-blinded randomized clinical placebo-controlled trial. A total of 145 patients with periodontitis were screened at

outpatient section of the Department of Periodontics, Jaipur, Rajasthan University Health Sciences-College of Dental Science (RUHS-CODS) (► Fig. 1). One-hundred patients (47 males and 53 females, aged between 30 and 60 years) were selected based on the inclusion criteria. The study period was from February 2017 to March 2018. The study was approved by Rajasthan University Health Sciences-College of Medical Science Ethics Committee, Jaipur. The study was funded by Rajasthan University Health Sciences.

### Selection Criteria

Patients, who were systemically healthy and had periodontitis with clinical attachment level (CAL)  $\geq 3$  mm, probing depth (PD)  $\geq 4$  mm, and vertical bone loss  $\geq 3$  mm measured on cone beam computed tomography (CBCT), were included in this study. Patients with  $\geq 20$  teeth and no history of any kind of periodontal therapy and antibiotic therapy in the last 6 months were selected for the study. Patients on statin therapy or under any kind of medication, immunocompromised, use of tobacco in any form, pregnant and lactating female were excluded from the study. All volunteers signed the informed consent.

### Randomization and Clinical Procedures

On the basis of power calculation (power of study 80% and  $p \leq 0.05\%$ ), 100 patients were randomly allotted in (computer-generated randomization) into two treatment group. Group A received scaling and root debridement and 1.2% RSV gel (1.2 mg/0.1 mL) locally delivered and group B received scaling and root debridement and placebo gel. At baseline, scaling and root debridement was done by a blinded investigator. Investigator was a trained dentist. Scaling and root debridement involves the removal of supra and subgingival deposits.<sup>18</sup> Volunteers in both the groups were instructed similar oral hygiene instruction. Patients were also unaware of the allocation of RSV gel or placebo gel. Delivery of RSV gel or placebo gel into the defect site was done by another masked investigator. Allocation concealment was kept by means of coded identical container, as both examiner and dentist responsible for the periodontal therapy were not involved in that process.

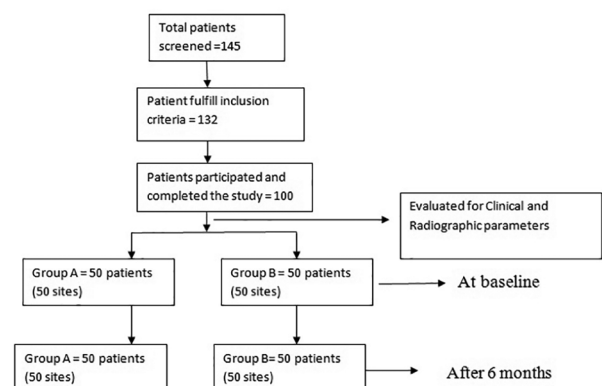


Fig. 1 Study flowchart 1.

### Clinical Parameters

Clinical parameters included site-specific-plaque index (PI),<sup>19</sup> PD, CAL, modified sulcus bleeding index (mSBI)<sup>20</sup> of the target tooth were recorded at baseline and after 6 months. For standardization, a custom-made acrylic stent and UNC-15 probe were used. CAL was measured from apical point of stent to the base of the pocket minus distance between apical point of stent to cementoenamel junction (CEJ). PD was measured from gingival margin to base of the pocket. The clinical parameter was measured by a trained and calibrated investigator.

### Subgingival Plaque Sampling and Microbial Culture

Subgingival plaque samples were randomly collected from 32 patients (32 sites) from each group (► Fig. 2). Subgingival microbial plaque sample was collected from the same site as of local drug delivery area at baseline and after 180 days with the help of sterile Gracey curette. *The site of collection was isolated with cotton roll and supragingival plaque was gently removed.* The curette was inserted deep into the pocket without applying any pressure on the tooth surface, to avoid dislocation of subgingival plaque. As soon as the curette reached the apical part of the pocket, subgingival sample was collected with single vertical stroke. For transport of the sample, the working end of the curette was swiped with sterile swab stick. The swab stick was immediately transferred to thioglycolate broth (anaerobic transport media). The samples were processed for anaerobic growth within 4 hours. Measurement was done in colony-forming unit/mL (CFU/mL).

### Radiographic Evaluation of Intrabony Defects

IBD was measured using CBCT. The patients who fulfilled the inclusion criteria underwent CBCT examination with a field of volume 10 cm × 10 cm. CBCT analysis was done by a blinded trained investigator, who was not involved in another evaluation or clinical procedure. The vertical defect was measured in sagittal section from a reference point, that is, CEJ to base of the defect. The analysis was done at baseline and after 6 months (► Figs. 3 and 4).

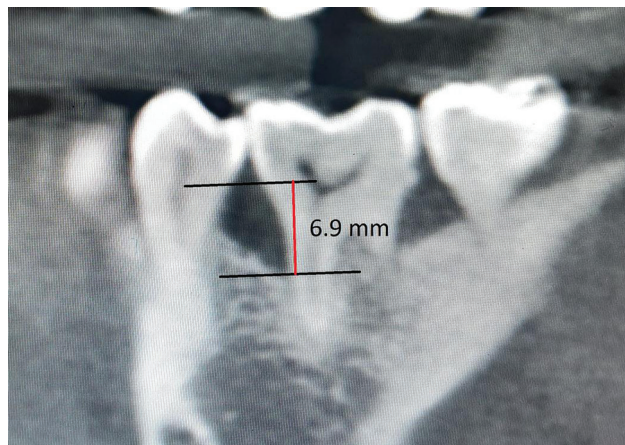


Fig. 3 Sagittal section preoperative image of angular defect, measured from cemento-enamel junction to base of defect.



Fig. 4 Sagittal section postoperative image of the angular defect, measured from cemento-enamel to the base of defect.

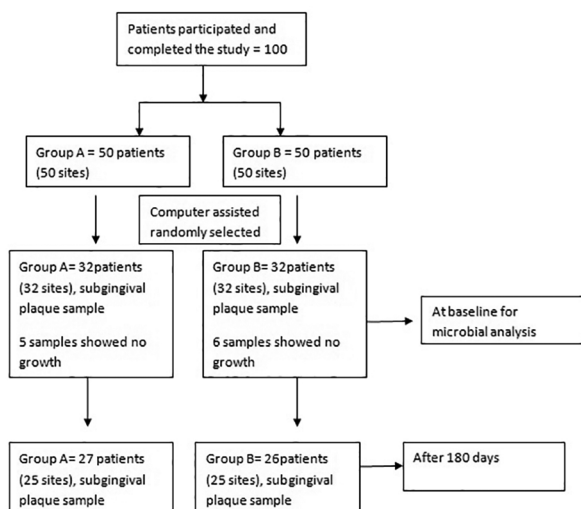


Fig. 2 Study flowchart 2.

### Formulation and Delivery of 1.2% Rosuvastatin and Placebo Gel

Methylcellulose was used as vehicle for sustained release of drug.<sup>21</sup> 2.0%w/v methylcellulose was dissolved in triple-distilled water to produce methylcellulose gel, which was used as the RSV carrier after it cooled down. Sodium methylparaben and sodium propylparaben were added to methylcellulose gel in the concentration of 0.1 and 0.02%, respectively, as preservative. RSV was then added to the methylcellulose gel to generate suspension of the desired concentration, 1.2 mg/0.1 mL. The suspension was sonicated and stored at 4°C for future use. Placebo gel was methylcellulose without any active ingredient.

A volume of 0.1 mL RSV gel (1.2 mg/0.1 mL) was injected into the periodontal pocket through a syringe. After placement of gel in both the groups, patients were instructed not to chew and to gently clean the treated area. Patients in both groups were given same oral hygiene instructions and were made to recall after 6 months. There was no adverse effect reported to RSV gel.

### Primary and Secondary Outcome

The primary outcome of the study was bone fill. The secondary outcome was improvement in the clinical parameters such as mSBI, PI, PD, CAL, and reduction in anaerobic CFU.

### Statistics

Data obtained was compiled on an MS Office Excel Sheet (v 2010, Redmond, Washington, United States) and was subjected to statistical analysis using Statistical package for social sciences (SPSS v 21.0, IBM, Armonk, New York, United States). Normality of data was checked using Kolmogorov–Smirnov test and was found that data followed a normal distribution. Intergroup comparison of numerical variables was done using *t*-test. In addition, intragroup comparison was done using paired *t*-test. Comparison of frequencies of colony patterns in both the groups and intragroup has been done using chi-squared test.  $p < 0.05$  was considered to be statistically significant, keeping  $\alpha$  error at 5%, and  $\beta$  error at 20%, thus giving a power to the study as 80%.

### Results

A total of 145 patients were screened, out of which 100 patients fulfilled the inclusion criteria and completed the study. There were 50 participants in each group.

On intergroup comparison at baseline, there was no statistically significant difference between clinical periodontal, radiographic, and anaerobic colony count parameter. CAL parameter at baseline of both the groups was similar ( $p = 0.454$ ). There was statistically significant gain in CAL in group A compared to group B after 6 months ( $p = 0.044$ ). The mean PD of both the groups was similar at baseline ( $p = 0.888$ ). There was statistically significant decrease in mean PD in group A compared to group B after 6 months ( $p = 0.00$ ). IBD was similar in both the groups at baseline ( $p = 0.394$ ). On intergroup comparison, there was statistically significant decrease in mean IBD in group A ( $6.5 \pm 1.71$ – $5.23 \pm 1.46$ ), compared to group B ( $6.22 \pm 1.50$ – $6.02 \pm 0.299$ ) from baseline to 6 months ( $p = 0.034$ ; ► **Tables 1 and 2**). On intragroup comparison in group A, all the periodontal clinical parameter and radiographic parameters showed significant improvement after 6 months. Within group B, except for radiographic parameter, all clinical parameters showed significant improvement after 6 months (► **Tables 3 and 4**).

At baseline, mSBI scores were similar in both the groups, with  $p = 0.968$ . There was statistically no significant difference in mSBI scores in both the groups after 6 months, with  $p = 0.692$ . The mean PI also showed no significant difference after 6 months. The mean values of anaerobes CFU/mL of the two groups were similar at baseline, and there was no significant difference after 180 days in the mean value of anaerobes CFU/mL between two groups (► **Table 5**). None of the patients showed any kind of side effect to RSV and placebo gel.

### Discussion

The present study evaluates the clinical and antimicrobial efficacy of RSV. In periodontitis, the balance between periodontal

**Table 1** Intergroup probing depth, clinical attachment level, intrabony defect, plaque index, modified sulcus bleeding index (mean  $\pm$  6 standard deviation) at baseline

Parameters (at baseline)	<i>n</i>	Mean	<i>p</i> -Value
CAL			
Group A	50	7.32 $\pm$ 1.51	0.454
Group B	50	7.10 $\pm$ 1.40	
PD			
Group A	50	6.29 $\pm$ 1.17	0.88
Group B	50	6.25 $\pm$ 1.59	
mSBI			
Group A	50	3.83 $\pm$ 0.73	0.968
Group B	50	3.82 $\pm$ 0.75	
PI			
Group A	50	1.83 $\pm$ 0.58	0.213
Group B	50	1.96 $\pm$ 0.47	
IBD			
Group A	50	6.50 $\pm$ 1.71	0.394
Group B	50	6.22 $\pm$ 1.50	

Abbreviations: CAL, clinical attachment level; IBD, intrabony defect; mSBI, modified sulcus bleeding index; PD, probing depth; PI, plaque index.

**Table 2** Intergroup probing depth, clinical attachment level, intrabony defect, plaque index, modified sulcus bleeding index (mean  $\pm$  6 standard deviation) after 6 months

Parameters (after 6 months)	<i>n</i>	Mean	<i>p</i> -Value
CAL			
Group A	50	4.18 $\pm$ 0.96	0.044*
Group B	50	4.5 $\pm$ 0.90	
PD			
Group A	50	3.44 $\pm$ 0.73	0.000**
Group B	50	4.02 $\pm$ 0.65	
mSBI			
Group A	50	1.54 $\pm$ 0.62	0.692
Group B	50	1.59 $\pm$ 0.64	
PI			
Group A	50	0.994 $\pm$ 0.47	0.900
Group B	50	0.98 $\pm$ 0.47	
IBD			
Group A	50	5.23 $\pm$ 1.46	0.034*
Group B	50	6.02 $\pm$ 0.299	

Abbreviations: CAL, clinical attachment level; IBD, intrabony defect; mSBI, modified sulcus bleeding index; PD, probing depth; PI, plaque index.

breakdown (disease) and periodontal stability (health) is tipped toward disease by risk factors and by overactivity or underactivity of host immune inflammatory response.<sup>22</sup>



**Table 3** Intragroup comparison of PD, CAL, IBD, PI, mSBI of group A

		Mean	n	p-Value of paired t test
Pair 1	IBD B	6.50 ± 1.71	50	0.000**
	IBD 6m	5.23 ± 1.46	50	
Pair 2	CAL B	7.32 ± 1.5	50	0.000**
	CAL 6m	4.180 ± 0.96	50	
Pair 3	Probing b	6.290 ± 1.17	50	0.000**
	Probing 6m	3.44 ± 0.73	50	
Pair 4	Bleeding b	3.83 ± 0.73	50	0.000**
	Bleeding 6m	1.546 ± 0.62	50	
Pair 5	Plaque b	1.83 ± 0.58	50	0.000**
	Plaque 6m	0.99 ± 0.58	50	

Abbreviations: CAL, clinical attachment level; IBD, intrabony defect; mSBI, modified sulcus bleeding index; PD, probing depth; PI, plaque index.

**Table 4** Intragroup comparison of PD, CAL, IBD, PI, mSBI of group B

		Mean	n	p-Value of paired t test
Pair 1	IBD B	6.22 ± 1.5	50	0.341#
	IBD 6m	6.02 ± 2.11	50	
Pair 2	CAL B	7.10 ± 1.4	50	0.000**
	CAL 6m	4.0 ± 0.94	50	
Pair 3	Probing b	6.25 ± 0.59	50	0.000**
	Probing 6m	4.02 ± 0.63	50	
Pair 4	Bleeding b	3.83 ± 0.75	50	0.000**
	Bleeding 6m	1.59 ± 0.64	50	
Pair 5	Plaque b	1.96 ± 0.47	50	0.000**
	Plaque 6m	0.98 ± 0.47	50	

Abbreviations: CAL, clinical attachment level; IBD, intrabony defect; mSBI, modified sulcus bleeding index; PD, probing depth; PI, plaque index.

**Table 5** Intergroups anaerobic CFU/mL after 6 months

Frequency	6 months anaerobic CFU/mL			Total	p-Value
	No growth	10 <sup>2</sup>	10 <sup>3</sup>		
Groups A	16	6	5	27	0.628
Groups B	12	8	6	26	
Total	28	14	11	53	

Abbreviation: CFU, colony-forming unit.

Intervention in periodontal therapy nowadays includes host modulatory therapies that are being used as adjuvant conventional therapy. Researchers are continuously hunting for new host modulating agent which can be used in periodontal therapy.

RSV is potent anti-inflammatory,<sup>23</sup> stimulates osteoblastic differentiation,<sup>24</sup> and can be used as host modulating as well as bone anabolic agent in the treatment of chronic periodontitis. Author in the present study is focusing on anti-inflammatory, regenerative potential and antimicrobial efficacy of RSV.

The study showed significant reduction in mean PD in group A compared to group B and significant gain in CAL in group A compared to group B. There is a significant bone fill in group A and decrease in bone defect depth. The bone fill is due to statins act on mevalonate pathway in osteoblast and by increasing the expression of growth factor BMP-2 causes osteoblastic differentiation and bone formation.<sup>25,26</sup> In an in vivo animal study when statin was injected locally over calvaria bone of mice cause 30 to 50% increase in calvarial width. Bone formation by this drug is stimulated by inhibition of prenylation.<sup>10</sup> In addition to the above, by regulating estrogen receptors, osteoprotegerin-receptor activator of nuclear factor kappa B (NF-KB)/receptor activator of NF-KB ligand inhibits osteoclastogenesis and promotes osteoblastic differentiation and hence osteostimulative effect.<sup>27</sup> In a similar study by Pradeep et al, RSV in situ gel (1.2%), when delivered locally into IBD/pocket sites, showed a greater reduction than placebo with respect to PD and gingival index, along with increased gain in CAL.<sup>28</sup> The bone fill is due to RSV which possesses osteoblast differentiation. The limitation of above study is that it employs conventional intraoral periapical radiograph for radiographic analysis. The two-dimensional (2D) IBD analyses are limited to projection geometry.

However, in the present study, CBCT was used for the analysis of IBD. CBCT displays 2D and 3D images that are required for diagnosis and treatment plan of IBD. Alamri et al confirmed that due to projection errors 2D radiographs are inadequate for detecting changes at the bone level especially in the furcation and buccal and lingual aspect. CBCT provides accurate measurements of IBD. CBCT also allows the clinician to evaluate the postsurgical follow-up results of regenerative periodontal therapy.<sup>29</sup>

In the present study, there has been no significant difference in PI and bleeding index on intergroup comparison. However, within the groups, there is a significant decrease in PI and bleeding index (→ Tables 4 and 5). Bleeding on probing is a clinical parameter with low-positive predictive value and high-negative predictive value on absent. That is absence of bleeding suggests periodontal stability.<sup>30</sup> There is no difference in bleeding index in both the groups, which suggest that the plaque control could be similar in both groups. Plaque score is an indicator of patient compliance, as patients in the study demonstrated similar daily plaque control procedures. This could be reason for similar reduction in PI and bleeding index within both groups.<sup>31</sup>

RSV has shown pleiotropic antimicrobial effect. In an in vitro study, RSV has antimicrobial shown against *Pseudomonas aeruginosa* (ATCC 9027) (Gram-negative, facultative anaerobic, *Staphylococcus aureus* (ATCC 6538).<sup>32</sup> Similarly, in another in vitro study, RSV has shown antimicrobial effect against methicillin-susceptible *S. aureus*.<sup>33</sup> Based on the above literature, antimicrobial efficacy was evaluated. To the best of

our knowledge, the present study is the first study to check the antimicrobial effect of RSV on periodontal pathogens.

Although mechanical debridement substantially reduces the number of periodontal pathogens, recolonization with pathogenic species starts immediately after mechanical therapy.<sup>13</sup> Thus, the hypothesis is locally delivered RSV could retard the recolonization. There is no significant difference in the anaerobic CFU/mL, in both the groups after 180 days (Tables 3). This could be due to the fact that the anaerobic analysis was done on smaller sample size, that is, 32 subjects per group. Further, longitudinal study with larger sample size and different concentration of RSV is required to check the antimicrobial effect of RSV.

The results of the present study confirm that when 1.2% RSV gel locally delivered into subgingival area promoted bone fill in IBD, reduction in PD, and CAL gain. The result of the study is in concordance with various studies showing improved periodontal parameters when various statins delivered locally.<sup>34</sup> In another study, RSV showed better improvement in clinical and radiographic periodontal parameters than other statin atorvastatin and simvastatin.<sup>35</sup>

RSV can evolve as new economical host modulating agent in periodontal therapy as it possesses anti-inflammatory, antioxidant, and immune modulatory properties. Studies have shown RSV reduces the expression of cytokines, such as interleukin (IL)-6, IL-1 $\alpha$ , IL-1  $\beta$ , and tumor necrosis factor in ligature-induced periodontitis in rat model.<sup>36</sup>

The local route of administration of RSV has two main advantages: first when orally administered there bioavailability is low because of their high-liver specificity<sup>37</sup> second when delivered through sustained release system, reaches the desired target area, slows the progression of disease, and shows significant bone formation, even when administered in low concentration.<sup>38</sup> Hence, locally delivered RSV can emerge as host modulating therapy adjunct to mechanical therapy.

## Conclusion

An increased knowledge of host immune inflammatory mediators in chronic periodontitis has increased the number of researches in host modulatory agents used as an adjunct therapy to periodontal therapy. The study concludes that locally administered 1.2% RSV has bone anabolic and anti-inflammatory effect and can emerge as a host modulatory agent. Further, randomized clinical controlled trials are required to evaluate the antimicrobial and clinical efficacy of RSV at different concentration to support the finding of the present study.

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Nil.

### Conflicts of Interest

None declared.

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