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Review Article

Dentistry Section

Rethinking Therapeutics: Drug Repurposing in Periodontal Therapy: A Narrative Review

GAURI JAYACHANDRAN[1], BIJU THOMAS[2], G KARTHIKA[3]

ABSTRACT

Drug repositioning investigates new uses for existing drugs, including both approved and discontinued medications. This strategy offers lower failure risks, faster development times and higher success rates while reducing reliance on antibiotics. Current treatments for periodontitis focus on modulating the immune response to combat pathogens. A promising approach involves using pharmaceuticals to reduce inflammation, which is the main cause of bone resorption, and to promote regeneration. Metformin, an antidiabetic drug, can enhance alveolar bone formation. Statins, known for lowering cholesterol levels, possess antimicrobial and anti-infective properties. Bisphosphonates, used to improve bone density, can affect osteoblast and osteoclast morphology and have antibacterial properties. Melatonin, typically used for sleep disorders, is an antioxidant that reduces the expression of proinflammatory cytokines. The present review explores the multifaceted benefits of repurposing these drugs for the management of periodontal disease.

Keywords: Drug repositioning, Drug resistance, Hydroxymethylglutaryl-coenzyme A reductase inhibitors, Melatonin, Metformin, Periodontitis

INTRODUCTION

Drug repurposing, also known as repositioning or drug reprofiling, involves identifying new applications for existing drugs, including those in early developmental stages or those that have been discontinued [1]. It is based on two fundamental insights. Firstly, many drugs have the ability to interact with multiple protein targets. Secondly, various diseases may share common genetic factors, molecular pathways, or clinical features [2].

Drug repurposing utilises two key methods: experimental approaches, which directly test existing drugs, and computational methods, which employ virtual tools like bioinformatics and network analysis to predict drug-target interactions based on public databases and molecular data [1].

Repurposing a drug has several key advantages. It is safer because these drugs already have known safety profiles. It is cost-effective, as it reduces the time and money required for development. It also taps into market potential more quickly, providing a competitive edge. Additionally, it offers a faster return on investment, which is appealing to both pharmaceutical companies and investors [3].

Periodontitis represents a progressive inflammatory disease initiated by specific bacterial pathogens, modulated by the host's immune response, and influenced by genetic and environmental factors, ultimately leading to the destruction of the supporting structures of the teeth [4]. Lipopolysaccharides (LPS), along with other virulence factors produced by periodontal pathogens, activate host macrophages and other cells, such as fibroblasts, to release proinflammatory cytokines, including Tumour Necrosis Factor (TNF)-α, Interleukin (IL)-1β, and Prostaglandin E2 (PGE2) [5]. These cytokines trigger the production of Matrix Metalloproteinases (MMPs) by these cells, leading to the breakdown of collagen fibres in periodontal tissues [5,6]. Moreover, the proinflammatory cytokines stimulate the production of Receptor Activators of Nuclear Factor κB Ligand (RANK-L) on osteoblasts and T helper cells. RANK-L then binds to the RANK on osteoclast precursors, leading to the formation and maturation of osteoclasts. Fully developed osteoclasts are crucial for the degradation of alveolar bone in the context of periodontal disease [7].

Contemporary periodontal therapy adopts a multimodal strategy to manage periodontal disease. This approach integrates mechanical debridement for plaque and calculus removal, with the adjunctive use of antiseptics for bacterial control. In severe cases, surgical intervention may be necessary to enhance periodontal health [8].

In the field of periodontology, the scope of drug repurposing can be quite promising. The potential benefits in terms of cost, safety, and efficacy make this approach an exciting avenue for developing novel treatments for periodontal diseases and conditions. Investigating the repurposing of drugs for periodontal application adds an intriguing dimension to this field of research. Therefore, the present review aimed to explore the advantages of various drugs that have been repurposed for the treatment of periodontal conditions.

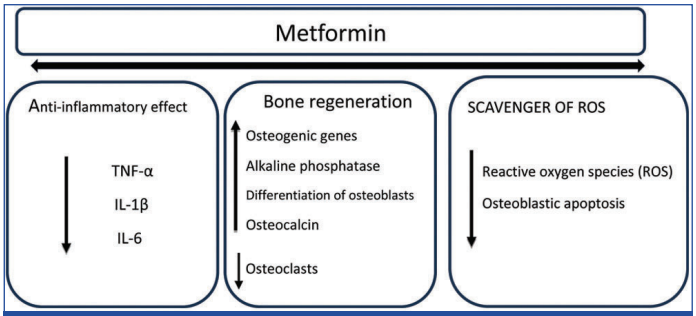
Metformin

Metformin is a second-generation biguanide with insulin-sensitising properties that is derived from the plant Galega officinalis. It has been used for the treatment of type 2 diabetes and as an adjunct to insulin therapy in type 1 diabetes since 1957 [9]. Metformin works by lowering blood glucose concentration through several mechanisms: increasing glucose uptake by the muscles, decreasing hepatic gluconeogenesis, and reducing glucose absorption in the intestine [10].

In recent years, it has been repurposed to benefit the treatment of various diseases, including neurorestorative conditions such as Alzheimer's and Parkinson's disease [11], and it acts as an antitumour agent for the treatment of hepatocellular carcinoma [12].

Currently, metformin is being explored as an adjunct to periodontal therapy [Table/Fig-1]. The main advantage of using metformin in this context is its ability to stimulate alveolar bone formation. Metformin can directly stimulate osteoblasts, partly by enhancing the expression of Runx2 and insulin-like growth factor 1. Additionally, it can reduce intracellular Reactive Oxygen Species (ROS) and apoptosis [13].

An in-vitro study in nondiabetic rats showed that the addition of metformin to a culture of rat adipose-derived multipotent mesenchymal stromal cells resulted in the differentiation of rat adipose tissue into bone-forming cells. Additionally, it was noted that metformin activates AMP-Activated Protein Kinase (AMPK), which is a crucial regulator of osteogenic differentiation [14]. Metformin also has an anti-inflammatory effect on various LPS-induced periodontal cells by suppressing the production of IL-6, IL-1β, and TNF-α through the activation of transcription factor-3 [15].



[Table/Fig-1]: Summary of mechanism of action of metformin for periodontal application.
TNF-α: Tumour necrosis factor-α; IL: Interleukin

Several in-vivo studies on animal models with experimentally induced periodontitis have demonstrated positive effects of metformin on alveolar bone regeneration and wound healing [16,17]. A recent study that utilised a composite scaffold loaded with metformin in ligature-induced periodontitis in Sprague-Dawley male rats was analysed using Micro-Computed Tomography (CT) and histological methods, and it was shown to promote alveolar bone regeneration [16].

In humans, 1% Metformin has been successfully used as a local delivery agent as an adjunct in the treatment of chronic periodontitis [18]. It has been shown to improve clinical parameters such as Probing Depth (PD), Clinical Attachment Level (CAL), and reduction of Intrabony Defects (IBD) [19]. In the latest study, Metformin was used in combination with platelet-rich fibrin for the treatment of furcation defects. This combination therapy resulted in better clinical and radiographic outcomes, including a significant reduction in defect volume [20]. The osteogenic properties of Metformin are now being utilised due to its positive biostimulatory effect to improve osseointegration when coated on implants [21]. A systematic review on the use of Metformin as an adjunct to periodontal therapy has shown that it can improve IBD, reduce PD, and help improve CAL and peri-implant health [22].

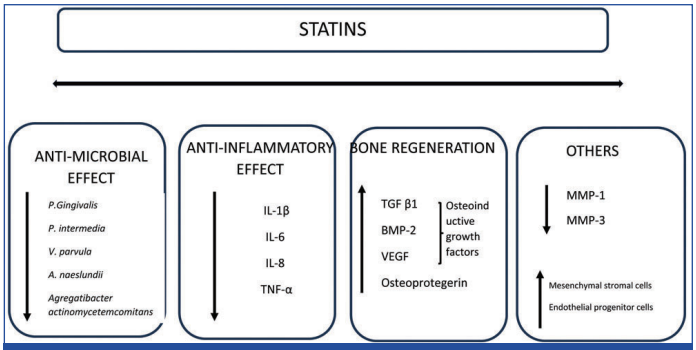
Statins

Statins are a group of drugs commonly used in the treatment of hyperlipidemia. They are the most prescribed medications for reducing plasma cholesterol levels. These drugs work by inhibiting the activity of 3-hydroxy-3-methylglutaryl-coenzyme A reductase [23]. They act by downregulating the production of mevalonate and its derivatives. In contrast to their hypolipidemic action, they stimulate nitric oxide production in endothelial cells and exhibit additional anti-inflammatory, anticoagulant, antioxidant, and antiarrhythmic activities [24]. Statins are currently being explored for repurposing in various medical contexts, including their potential use as anti-cancer agents [25], in the management of stroke [26], and even in the context of depression [27].

Lipophilic statins impact a regulatory pathway in monocytes that governs cytokine production. These statins are known to trigger diverse proinflammatory responses, both invitro and in-vivo [28]. Statins also activate several downstream signalling pathways, including Mitogen-Activated Protein Kinase (MAPK), p38, ERK1/2, and Nuclear Factor (NF) κB. This activation leads to increased production and release of both proinflammatory and anti-inflammatory cytokines, such as TNF-α, IL-1β, IL-6, IL-10, and IL-12p20 [29].

The use of statins in periodontal therapy is supported by their versatile properties, which encompass antimicrobial [30], anti-inflammatory [31], and bone-enhancing effects by enhancing the expression of three osteoinductive growth factors, namely Transforming Growth Factor beta 1 (TGF-beta 1), Bone Morphogenetic Protein-2 (BMP-2), and Vascular Endothelial Growth Factor (VEGF) [32] [Table/Fig-2].

Additionally, statins are known to inhibit enzymes responsible for tissue breakdown, such as MMP [33]. They also promote the proliferation of mesenchymal stromal cells and endothelial progenitor cells [34]. Given these diverse therapeutic effects that go



[Table/Fig-2]: Summary of mechanism of action of statins for periodontal application.
TNF-α: Tumour necrosis factor-α; IL: Interleukin; TGF-β1: Transforming growth factor beta 1; BMP-2: Bone morphogenetic protein-2; VEGF: Vascular endothelial growth factor; MMP: Matrix metalloproteinases

beyond merely controlling lipid levels, simvastatin, atorvastatin, and rosuvastatin are currently being repurposed for use in periodontal treatment [35-37].

Invitro experiments have shown that simvastatin and atorvastatin possess antimicrobial properties, effectively reducing Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans [38,39]. A study by Liu S et al., has shown that simvastatin can have a mild impact on cell metabolism and can enhance the expression of genes related to differentiation and osteogenesis in alveolar osteoblasts and periodontal ligament cells. These findings suggest that simvastatin may play a role in promoting the formation of alveolar bone and periodontal regeneration [40].

An in-vivo study involving experimentally induced periodontitis in rats demonstrated that the local administration of simvastatin could uphold heightened alkaline phosphatase activity and maintain a high level of osteoblastic function [41]. A systematic review of the effect of statins in experimentally induced periodontitis in animal models has shown that the utilisation of statins for periodontal purposes has a beneficial impact on various periodontal tissue parameters. These results substantiate the favourable clinical outcomes observed when statins are applied locally as an adjunct to both non surgical and surgical periodontal interventions [42].

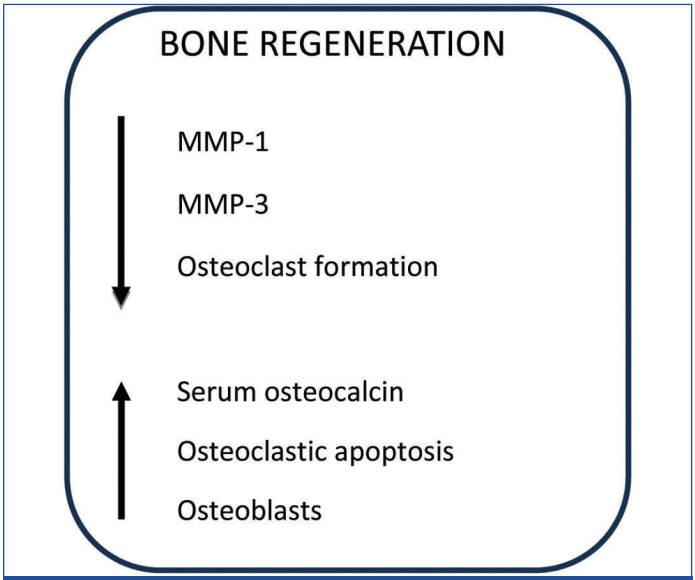
In patients with chronic periodontitis, the combination of scaling and root planing along with the local application of simvastatin resulted in a more substantial reduction in PD, gain in CAL, and improved IBD fill [35]. In a comparative study, atorvastatin demonstrated a more significant enhancement in clinical parameters, including a higher percentage reduction in radiographic defect depth compared to simvastatin [36]. Rosuvastatin has also been shown to enhance bone formation at IBD, decreasing PD and increasing CAL [37]. Statins are becoming increasingly popular in the field of implant treatment. A systematic review has indicated that statins have a positive impact on enhancing new bone formation around implants and/or increasing bone-to-implant contact. Both local and systemic administration of statins appears to bolster osseointegration [43].

Bisphosphonates

Bisphosphonates, which are analogues of pyrophosphate, were initially synthesised in the 1800s. Their original use was primarily as corrosion inhibitors and complexing agents in various industries, including textiles, fertilisers, and oil [44]. Pyrophosphate has a strong binding affinity for bone minerals, particularly hydroxyapatite. This binding accounts for the specific pharmacological action of bisphosphonates on mineralised tissue, especially bone [45]. Following the discovery that bisphosphonates could effectively regulate the formation and dissolution of calcium phosphate, as well as influence mineralisation and bone resorption in animal models [46], they were further developed and employed for the treatment of bone-related disorders such as osteoporosis [47], Paget's disease [48], and hypercalcaemia [49].

The primary types of adverse effects associated with some or all bisphosphonates include acute reactions, gastrointestinal disorders [50], and renal toxicity [51]. Additionally, osteonecrosis of the jaw is the most significant concern in clinical practice [52], with the mandible being the bone most affected. Patients frequently experience symptoms such as pain, halitosis, and difficulties in eating and speaking. Subtle changes in the health of periodontal tissue and unexplained infections may occur before the onset of this condition [53]. Practitioners should be mindful of this issue to avoid serious complications in patients undergoing long-term treatment with bisphosphonates.

Bisphosphonates exhibit a strong affinity for calcium ions, which results in their strong attraction to bone tissue. They employ a distinct mechanism to inhibit osteoclastic bone resorption; these compounds attach to hydroxyapatite binding sites on the bone's surface, particularly in areas undergoing active resorption. When osteoclasts initiate the resorption of bone impregnated with bisphosphonates, the released bisphosphonate interferes with the osteoclast's ability to form a ruffled border, thereby impairing bone resorption [54]. Additionally, bisphosphonates have the potential to counteract the activity of several MMP that participate in the degradation of structural elements within connective tissue [55,56]. As a result of their capacity to inhibit bone resorption and downregulate matrix metalloproteins, bisphosphonates are currently utilised as an adjunct in periodontal therapy [Table/Fig-3] [54,56].



[Table/Fig-3]: Summary of mechanism of action of bisphosphonate for periodontal application [54,56].
MMP: Matrix metalloproteinases

While bisphosphonates offer advantages when used as an adjunct to therapy, caution must be exercised regarding the dosage of the drug, as it can lead to adverse effects such as osteonecrosis [53]. Invitro investigations suggest a potential inhibitory effect of bisphosphonates on cells critical for bone homeostasis. These studies have shown a reduction in cell proliferation and collagen production among human gingival fibroblasts and osteoblasts [57,58]. However, another study suggests that as the drug concentration increases, there is a significant decrease in cell viability, rendering it cytotoxic; hence, lower concentrations of this drug should be considered to achieve therapeutic benefits [59].

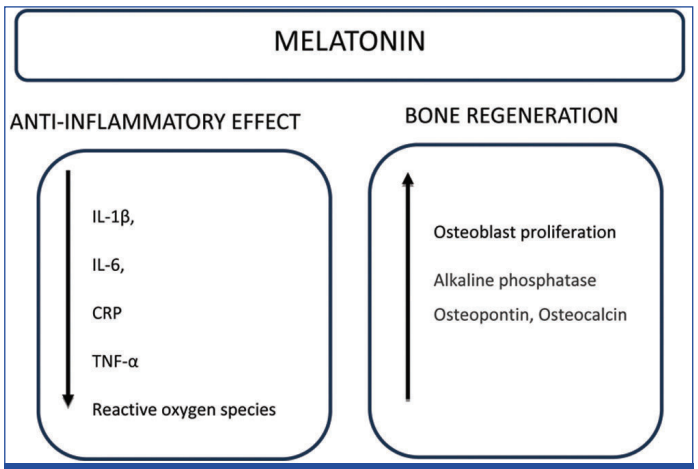
Studies involving rats with experimentally induced periodontitis revealed that treatment with systemic bisphosphonates effectively prevented bone resorption, loss of bone mineral content, and morphologic changes of the osteoclasts [60,61]. Similarly, topically applied bisphosphonates have also demonstrated the ability to inhibit intraarticular alveolar bone loss in rats [62].

Clinical trials have investigated the effects of bisphosphonates on periodontal treatment. These studies involved either systemic administration of the drug or local delivery. The results suggested that systemic bisphosphonates, when used alongside non surgical periodontal therapy, improve clinical outcomes and bone density [63,64]. Due to concerns about potential side effects of systemically administered bisphosphonates, locally delivered bisphosphonates have been used to treat periodontitis. Local delivery of alendronate gel in patients with periodontitis has shown improvements in periodontal parameters, including bone fill and enhancements in furcation defects [65,66].

Systematic reviews have been conducted to evaluate the effectiveness of bisphosphonate therapy as an adjunct to scaling and root planing in the management of periodontitis. The results indicated that bisphosphonates are effective in managing periodontitis; however, the potential risk of osteonecrosis of the jaws and their clinical application remains a subject of debate [67,68]. Emerging research explores the application of alendronate-coated dental implants to enhance osseointegration. Preliminary findings indicate a potential increase in the rate of early bone formation around the implants [69].

Melatonin

Melatonin, initially recognised as a hormone that contracts melanophores, was first identified as a substance that lightens skin in frogs and fish. In 1917, Mccord CP and Allen FP noted that extracts from the pineal glands of cattle had a strong skin-lightening effect on frog skin [70]. This compound is synthesised by the pineal gland in the human brain and plays a role in modulating immune defense responses, regulating body weight, influencing reproductive processes, inhibiting tumour growth, and alleviating the effects of jet lag [71]. Beyond its established role in circadian rhythms, melatonin's potential as an antioxidant and its therapeutic applications in diverse conditions, such as diabetes, cardiovascular diseases, and neurodegenerative disorders, warrant further exploration, including its use in periodontal therapy [Table/Fig-4] [72,73].



[Table/Fig-4]: Summary of mechanism of action of melatonin for periodontal application [72,73].
TNF-α: Tumour necrosis factor-α; IL: Interleukin; CRP: C-reactive protein

A recent systematic review has stated that melatonin levels in Gingival Crevicular Fluid (GCF), saliva, and serum of patients suffering from chronic periodontitis are lower, suggesting that melatonin may play a role in protecting tissues from damage caused by oxidative stress [74]. Treatment with intraperitoneally administered melatonin has been shown to significantly reduce alveolar bone resorption in experimentally induced periodontitis [75]. Additionally, a reduction in proinflammatory cytokines such as IL-1β, IL-6, C-reactive proteins, and TNF-α was observed in periodontitis patients with diabetes [76]. Melatonin also downregulates the receptor activator of NF kappa-B ligand/osteoprotegerin ratios and increases the levels of salivary acid phosphatase, alkaline phosphatase, osteopontin, and osteocalcin, which are indicative of bone formation [77,78].

Clinical trials suggest that dietary melatonin supplementation can enhance periodontal health by improving clinical parameters, including

CAL and PD, with no reported adverse effects [79,80]. A recent study has shown that the application of 1% melatonin gel in IBDs results in significantly greater defect fill when used as an adjunct to non surgical periodontal therapy [73]. Additionally, a systematic review of the effect of melatonin on non surgical periodontal therapy has demonstrated that it enhances bone-to-implant contact and promotes new bone formation, potentially leading to improved success and long-term survival of implant treatments [81].

Studies evaluating the repurposed drug in periodontal therapy have been described in [Table/Fig-5] [18-21,35-37,41,60-62,64, 65,75,79,80].

Study	Study design	Materials and methods	Conclusion
Pradeep AR et al., (2013) [18]	Human clinical trial	118 Intrabony Defects (IBD) treated with 0.5%, 1%, or 1.5% MF gel or placebo gel	MF improved IBD reduction. Maximum significance was achieved while using 1% MF
Pradeep AR et al., (2016) [19]	Human clinical trial	65 patients with IBDs; 1% MF+SRP versus SRP and placebo gel	1% MF showed significant improvement in the IBD
Swami RK et al., (2021) [20]	Split-mouth human clinical trial	21 patients with Grade II furcation defects; PRF+1% MF versus PRF alone	1% MF+PRF improved regenerative ability in Grade II furcation defects
Sharma H et al., (2021) [21]	Human clinical trial	22 patients with missing mandibular posteriors; implants coated with 1% MF versus non-coated implants	1% MF coated implant showed a bio-stimulatory effect on osseointegration
Seto H et al., (2008) [41]	Animal study on male Fischer rats	Fifteen male Fischer rats were experimentally included with periodontitis followed by a topical injection of 0.2 mg SM	SMV showed improved osteoblastic function
Pradeep AR et al., (2010) [35]	Human clinical trial	60 patients with IBD; SRP+1.2 mg SMV versus SRP alone	SRP+SMV showed significant IBD fill
Martande SS et al., (2017) [36]	Human clinical trial	96 patients; SRP+1.2% ATV, SRP+1.2% SMV and SRP plus placebo	ATV showed more significant defect depth reduction compared to SMV
Pradeep AR et al., (2015) [37]	Human clinical trial	65 patients with IBD; SRP+RSV 1.2 mg and SRP plus placebo group	A significant reduction of IBD was seen with 1.2 mg RSV
Shoji K et al., (1995) [60]	Animal study on Wistar rats	27 Wistar rats with experimentally induced periodontitis; 0.8, 1.6, or 3.2 moles/kg of Risedronate (test) and 0.9% NaCl	Doses of 1.6 and 3.2, moles/kg of Risedronate prevented alveolar bone resorption
Goes P et al., (2012) [61]	Animal study on Wistar rats	36 Wistar; Groups of six animals received 0.9% saline or ALD (0.01; 0.05; 0.25 mg kg-1)	ALD reduced the bone-specific alkaline phosphatase and inflammatory infiltrate
Goya JA et al., (2006) [62]	Animal study on Wistar rats	20 male Wistar rats; Experimental periodontitis (control group) and experimental periodontitis+topical olpadronate (test group)	Significant morphologic changes were seen in osteoclasts and the drug prevented bone loss
Tanna NK 2013 [64]	Human clinical trial	125 patients with moderate to severe periodontitis; risedronate+SRP (test), SRP alone (control	The test group showed a significant increase in bone height
Sharma A and Pradeep AR, (2012) [65]	Human clinical trial	66 patients with IBDs; 1% ALN+SRP, placebo gel+SRP	The test group showed improved bone fill
Arabacı T et al., (2015) [75]	Animal study on Sprague-Dawley rats	24 rats with experimentally induced periodontitis; control, experimental periodontitis, and experimental periodontitis treated with MEL	Osteoclast activity was significantly lower in the MEL group
El-Sharkawy H et al., (2008) [79]	Human clinical trial	74 periodontitis patients with primary insomnia; 10 mg oral MEL+SRP (test group), SRP alone	Test group showed improvements in clinical parameters and lower salivary TNF-α
Tinto M et al., (2020) [80] Human clinical trial	20 patients; SRP+1 mg MEL (test), SRP alone (control)	Improves clinical parameters were seen in the MEL group	

[Table/Fig-5]: Key studies evaluating the repurposed drug in periodontal therapy [18-21,35-37,41,60-62,64,65,75,79,80].
MF: Metformin; SRP: Scaling and root planning; SM: Simvastatin; ATV: Atorvastatin; RSV: Rosuvastatin; ALD: Alendronate; MEL: Melatonin

CONCLUSION(S)

Drug repurposing is a cost-effective and expedited approach that brings effective therapies to patients faster compared to the lengthy traditional drug discovery and development processes. This approach helps counter the rising costs associated with drug development, which, in turn, reduces the financial burden on patients and ultimately lowers the overall cost of therapy. Furthermore, drug repurposing in periodontal treatment has the potential to reduce the reliance on antibiotics, which are frequently used as an adjunct to both surgical and non surgical periodontal therapies, thereby contributing to the mitigation of issues related to antibiotic resistance. While drug repurposing offers significant promise in this field, it is important to emphasise that rigorous research, clinical trials, and safety evaluations are essential before any repurposed drug can be recommended for widespread use.

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PARTICULARS OF CONTRIBUTORS:
1. Postgraduate Student, Department of Periodontology, NITTE (Deemed to be University), A B Shetty Memorial Institute of Dental Sciences, Mangaluru, Karnataka, India.
2. Professor, Department of Periodontology, NITTE (Deemed to be University), A B Shetty Memorial Institute of Dental Sciences, Mangaluru, Karnataka, India.
3. Postgraduate Student, Department of Periodontology, NITTE (Deemed to be University), A B Shetty Memorial Institute of Dental Sciences, Mangaluru, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Biju Thomas,
Professor, Department of Periodontology, NITTE (Deemed to be University),
A B Shetty Memorial Institute of Dental Sciences,
Mangaluru-575018, Karnataka, India.
E-mail: bijunicy@yahoo.co.uk

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