Experimental research

Newer congeners of doxycycline – do they hold promise for periodontal therapy?

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Submitted: 19 November 2021
Accepted: 14 August 2022

Arch Med Sci Civil Dis 2022; 7: e16–e23
DOI: ttps://doi.org/10.5114/amscd.2022.119600

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Abstract

Introduction: Periodontitis is a very common polymicrobial infection of the oral cavity with wide systemic implications. It is influenced by multiple aspects, such as virulence of bacteria, the host response and resistance of bacteria to antibiotics, both within and outside the biofilm. Commonly, antibiotics are employed to break this vicious activity of microbes. There is a lacuna in the literature regarding the comparative efficacy of newer congeners of doxycycline. The aim of the study was to objectively compare the binding capacity of newer congeners of doxycycline with clinically significant targets relevant to periodontitis.

Material and methods: A total of 5 drugs, viz. doxycycline, tigecycline, eravacycline, sarecycline and omadacycline, were selected, and molecular docking studies were performed with four targets: gingipain, FimA, interleukin-1β and estrogen receptor β. The studies were performed using AutoDock version 4. The results were reported based on the binding free energy, electrostatic interaction and intermolecular attraction. These values were compared and reported.

Results: The drugs selected showed good binding to all four targets but had many differences in binding efficacy. Omadacycline, tigecycline, sarecycline, and doxycycline revealed 100% binding efficacy by occupying the core amino acid residues (444 HIS, 477 CYS and 388 ASP) over the target protein.

Conclusions: Doxycycline can be replaced with omadacycline for clinical use. This result warrants future clinical investigations on omadacycline for periodontal therapy in both local and systemic administration.

Key words: molecular docking, doxycycline, tigecycline, eravacycline, sarecycline, omadacycline, gingipain, FimA.

Introduction

Periodontitis is a very common infection of the oral cavity and has profound systemic implications [1, 2]. It has been observed that approximately 47% of adults aged above 30 years harbor periodontal infection of some sort. Investigators have also related the prevalence to age and have reported that the prevalence is directly proportional to age [3]. Additionally, the incidence and prevalence of periodontitis are higher in the lower socioeconomic strata. Other risk factors, such as smoking and alcoholism, are strong contributors to periodontitis [4].

Periodontitis is a polymicrobial infection, and its pathogenesis has been studied intensively. On a clean dental surface, the formation of

a gel-like layer called the acquired pellicle marks the beginning of periodontal floral colonization on the tooth surface. The initial aerobic floral predominance is later given up to anaerobes. In this ecologic succession, every bacterium that adheres becomes a part of a biofilm, which is a well-equipped system for nutrition, signaling and resistance to antibacterial agents. Of the thousands of unculturable and culturable bacteria of the periodontal biofilm, major species implicated in the aetiology of periodontitis are *Porphyromonas gingivalis* and *Actinobacillus actinomycetemcomitans* [5, 6]. *P. gingivalis* is a major contributor to periodontal pathogenesis. It is a gram-negative and anaerobic organism called a keystone pathogen. It has developed many characteristics to evade the local immune response. Furthermore, it has certain biochemical mechanisms responsible for its virulence against the periodontium. This increase in virulence is exhibited by enzymes called gingipains, which are trypsin-like cysteine proteinases that facilitate infection by various microbes in the biofilm [7]. It is worth noting that even nonpathogenic flora can cause infection once *P. gingivalis* reduces local immunity. Hence, there is a change in the microbial population, leading to dysbiosis [8]. Here, the mechanism becomes highly complicated by the involvement of various species in the process.

Furthermore, bacteria that adhere to both biofilm and host cells have specialized structures called fimbriae. These fimbriae are shown to be important factors that facilitate bacterial interactions with host tissues, leading to invasion [9]. An increase in these fimbrial molecules, both in number and in type, therefore contributes directly to the virulence of the bacteria [10]. *P. gingivalis* is known to express two such fimbria molecules: one is long, and the other is short [11]. They are expressed on the cell surface, leading to increased host invasion and local tissue destruction.

As the disease progresses, there is a clear increase in inflammation mediated by various biochemical factors, such as interleukins and tumor necrosis factor α (TNF-α). Interleukin 1β (IL-1β) is a proinflammatory cytokine and is involved in inflammation and bone resorption. Various studies provide great evidence about its role in this process. It is initially synthesized as pro-IL-1 β and must be proteolytically cleaved by caspase 1 to attain the active form [12]. Additionally, periodontal pathogens upregulate the synthesis of IL-1β. The inflammatory effect is dependent upon the local concentration, and its increase leads to an upward shift in the inflammatory process. After it assumes the functional form, it triggers a cascade of inflammatory reactions leading to raised local blood flow, increased leucocyte recruitment and enhanced neutrophil infiltration. Most importantly, IL-1β is a strong stimulator of bone resorption, which worsens periodontitis. Hence, therapeutic modalities to block IL-1β are constantly being searched for [13].

As a result of periodontal inflammation, there is increased bone resorption due to the shift of bone homeostasis to the negative side. It has been reported that a wide range of host factors (inflammatory mediators, genetic factors, etc.), as well as microbial factors (virulence factors, enzymes, lipopolysaccharides, etc.) contribute strongly to alveolar bone loss in periodontitis [14]. It is hence understood that upregulation of osteoblasts will lead to a shift of this homeostasis to the anabolic or positive side.

Hence, periodontitis must be addressed from four perspectives: gingipain control, inhibition of fimbrial proteins (FimA), inhibition of interleukin 1, and promotion of osteoblast differentiation and subsequent osteogenesis [15–17] In the literature, various drugs have been reported to have inhibitory action on the bacterial population, and the spectrum of activity varies widely among antibacterial drugs. Commonly, tetracyclines are used to kill or inhibit periodontal pathogens. In this regard, there is a lacuna in the literature regarding the binding of various congeners of tetracycline with various parts of gingipain, IL-1β, FimA protein and estrogen receptor β. The molecular interaction of residual amino acids with the core functional groups determines the efficacy of the drug molecules. In this study, molecular docking methods were applied to determine the binding efficacy of various commonly used drugs to these targets, resulting in the control and eradication of periodontal pathology.

Molecular docking is a powerful and capable tool for in silico screening. It is becoming increasingly important in rational drug design. Docking is a computational procedure for finding a suitable ligand that fits the protein's binding site both energetically and geometrically. In other words, it is the study of how two or more molecules, such as a ligand and a protein, interact with one another. The problem is similar to putting together a 3D puzzle. The application of computational methods in this field has been subjected to intensive research over the last decade to understand the formation of intermolecular complexes [18].

It is well understood that accurate drug activity is caused by the molecular binding of one molecule (the ligand) with the pocket of another molecule (the receptor), which is typically a protein. Molecular docking has proven to be an extremely effective tool for discovering new drugs that target proteins. Because of its application in the pharmaceutical industry, protein-ligand docking is of par-

Table I. Details of the targets used for docking

PDB Number	Name of the target
6I9A	Gingipain K – *Porphyromonas gingivalis* (Abrão *et al.*, 2021; Guevara *et al.*, 2019)
4Q98	FimA of *Porphyromonas gingivalis* (Qingping *et al.*, 2016; Shibata *et al.*, 2020)
1ITB	IL-1β (Halim & Jawad, 2015)
1QKM	Estrogen receptor β (Balaji *et al.*, 2012, Grande *et al.*, 2018)

ticular interest among the various types of docking [19]. When the structure of a protein is known, protein-ligand docking refers to the search for accurate ligand conformations within that protein [20].

Docking procedures are essentially an integration of search algorithms and a scoring function. Search algorithms predict the ligand binding orientation and conformations known as posing. The scoring functions, which predict the binding free energies, are used to distinguish between active and random compounds [21–27].

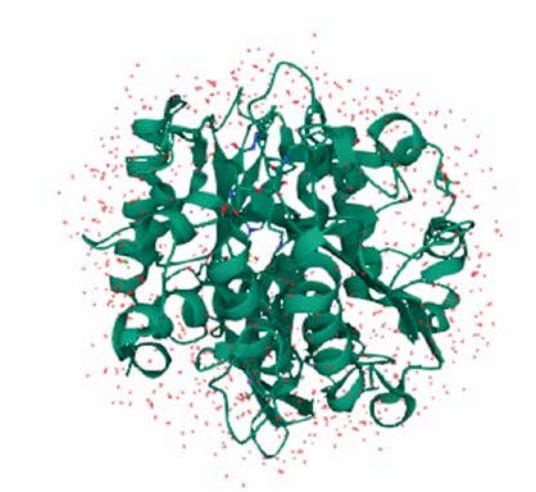


Figure 1. 3D crystalline structure of the target protein gingipain K – *Porphyromonas gingivalis* – PDB 6I9A

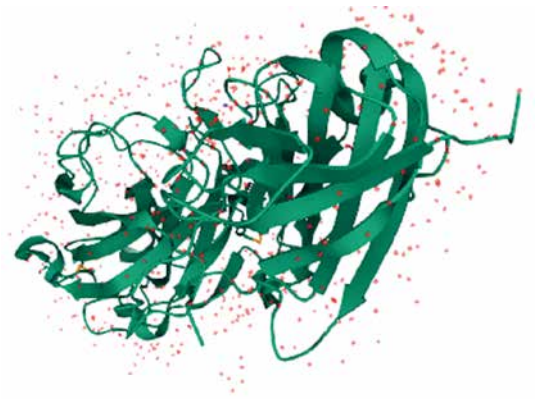


Figure 2. 3D crystalline structure of the target protein FimA with PDB 4Q98

In the current scenario, systemic drug administration is also used as an adjunct to local therapy. Doxycycline is observed to have a good impact on clearing the pathogenic flora of periodontitis, as it is well secreted through the gingival crevicular fluid. However, there is a lacuna in the literature regarding the comparative efficacy of newer congeners of doxycycline, such as tigecycline, eravacycline and sarecycline. Hence, this study was performed to objectively compare the binding capacity of these drugs with clinically significant targets relevant to periodontitis.

Material and methods

Details of lead compounds

A total of 5 drugs were selected, of which doxycycline was used as a control. The chemical structures of drugs used were retrieved from PubChem, and the development of 2d and 3d structures was performed using chem draw software.

Protein preparation

The crystal structure of the targets shown in Table I was downloaded from the RCSB Protein Data Bank (PDB) using AutoDock version 4 software, and a protein clean-up process was performed. The protein structures used for docking are shown in Figures 1–4.

Molecular docking analysis

In silico docking simulations were also performed using Auto Dock version 4. Three-dimensional pharmacophores of these lead molecules (Table II) were subjected to virtual screening against the selected protein targets mentioned in Table I. Docking grids were set with pocket size measuring maps of 70 × 70 × 70 Å grid points and with 0.375 Å. Each docking calculation was set to run with 10 different cycles after a maximum of 250 000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å and quaternion and torsion steps of 5 were applied [28, 29]. Different orientations of the lead molecules with regard to the target proteins were evaluated, and the best dock pose was selected based on the interaction study analysis. The docking tool provides binding free energy, inhibition constant, electrostatic energy, intermolecular energy and total interaction surface. The best pose of docking for each target is selected and displayed in this paper.

Results

A total of 5 lead compounds were investigated. Of them, omadacycline, tigecycline, sarecycline, and doxycycline revealed 100% binding efficacy

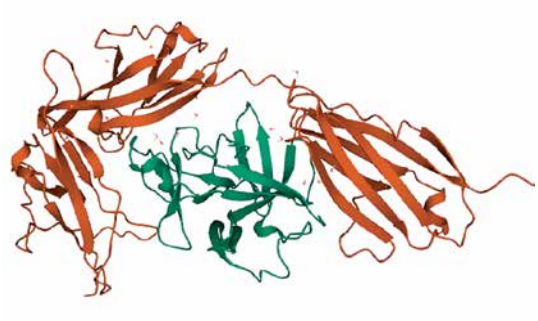


Figure 3. 3D crystalline structure of the target protein IL-1β – PDB 1ITB

by occupying the core amino acid residues (444 HIS, 477 CYS and 388 ASP) over the target protein. However, eravacycline ranked second with the maximum of 3 interactions with the active site of the target enzyme gingipain K. Based on the results of the computational analysis, there was significant binding affinity with the amino acids present on the active site of the target protein gingipain K; therefore it was concluded that these compounds may exert promising inhibition against gingipain K and thus may be expected to halt the progression of periodontitis.

A total of 5 lead compounds were investigated with the FimA protein. Nearly 24 amino acids are present in sequences 339–363 present in the active site of FimA of *Porphyromonas gingivalis*. In our present investigation, it was observed that out of 5 compounds, tigecycline and eravacycline revealed 12–16% binding efficacy by occupying some of the active amino acid residues with the sequence 339–363 present on the target protein. The binding efficacy was lower in omadacycline, sarecycline and doxycycline, with a maximum of 1 or 2 interactions that accumulated 4–8% affinity with the active site of the target protein FimA. Based on the results of the computational analysis, it was concluded that these compounds may exert some productive efficacy in hindering biofilm formation by the organism *Porphyromonas gingivalis*.

With regard to interleukin 1β, out of 5 compounds, tigecycline revealed 40–50% binding efficacy by occupying the core amino acid residues (Arg11, Asp12, Ser13, Gln14, Gln15, Lys27, Gln32, Gly33, Gln34, Glu128) over the target protein. The binding efficacy was lower in omadacycline, sarecycline, eravacycline, and doxycycline, with a maximum of 2–3 interactions with the active site of the target protein IL-1β. Based on the results of the computational analysis, there was significant binding affinity with the amino acids present on the active site of the target protein IL-1β; hence it was concluded that these compounds may exert promising inhibition against IL-1β and thus may be expected to halt the progression of pain and inflammation associated with periodontitis.

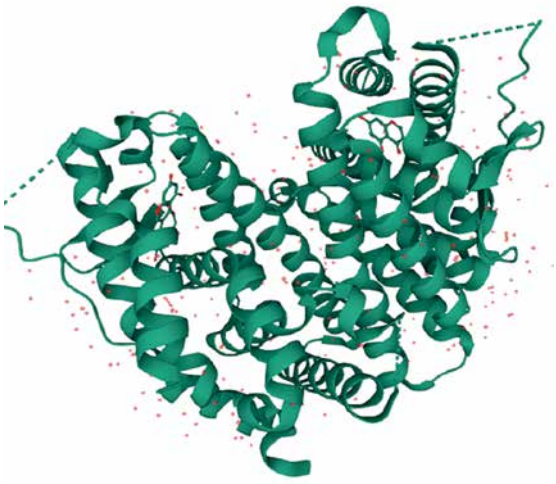


Figure 4. 3D crystalline structure of the target protein estrogen receptor β with PDB 1QKM

With regard to ERβ, omadacycline, tigecycline, sarecycline, eravacycline and doxycycline revealed 100% binding efficacy by occupying all core amino acid residues (Glu305, Arg346, His475,Met336, Ile373) over the target protein – estrogen receptor β. Based on the results of the computational analysis it was concluded that all the tested drugs revealed significant binding affinity with the amino acids present on the active site of the target protein estrogen receptor β; therefore it was concluded that these compounds may be expected to upswing the mechanism of osteoblast induction by regulating the signaling process mediated via estrogen receptor β.

The best docking poses of all five drugs with all four targets are attached in Tables IV–VI.

Discussion

Periodontitis has always been a complex puzzle to solve for clinicians due to its multiple pathways of pathogenesis. Since it is a polymicrobial infection, antibiotics are the first-line drugs to treat the infection. Usually, doxycycline is commonly used both topically and systemically to treat the infection [30]. However, in the current scenario of drug research, new congeners are being constantly developed and marketed for various uses. Therefore, there is a need to compare these new congeners with doxycycline in terms of their efficacy in reducing periodontitis.

Considering the cost of developing new drugs and testing for toxicity, designating an existing drug for new use is seen as an attractive preposition with lower risk. To make this a possibility, molecular docking has been seen as a primary tool of screening [31].

Various relevant targets are tested in this study with a specific purpose as follows. Gingipains are

Table II. 2D and 3D structure of ligands

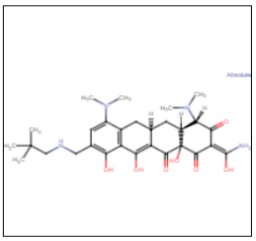
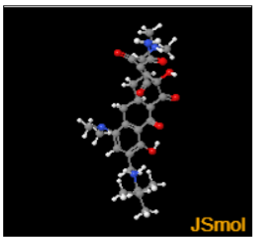
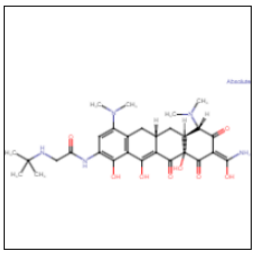
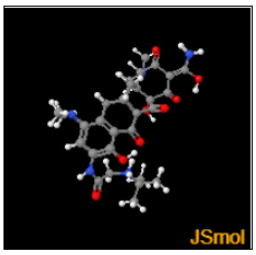
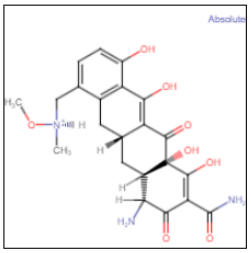
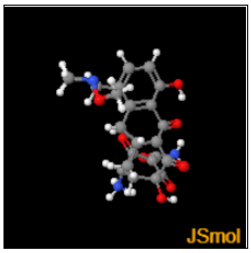
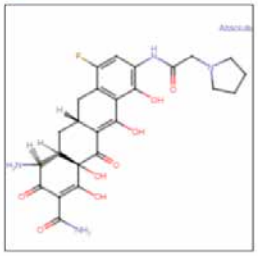
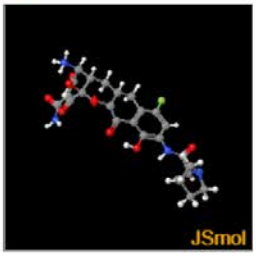
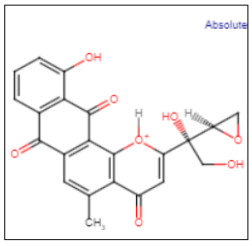
Compound	Molar weight [g/mol]	Molecular formula	H bond donor	H bond acceptor	Rotatable bonds	Structure
Omadacycline	556.6	C29H40N4O7	6	10	7	Ligand in 2D  Ligand in 3D 
Tigecycline	585.6	C29H39N5O8	7	11	7	Ligand in 2D  Ligand in 3D 
Sarecycline	487.5	C24H29N3O8	5	10	5	Ligand in 2D  Ligand in 3D 
Eravacycline	558.6	C27H31FN4O8	6	11	5	Ligand in 2D  Ligand in 3D 
Doxycycline	444.4	C22H24N2O8	6	9	2	Ligand in 2D  Ligand in 3D 

Table III. Results of docking with gingipain

Compounds	Binding free energy [kcal/mol]	Inhibition constant Ki µM (*mM) (**nM)	Electrostatic energy [kcal/mol]	Intermolecular energy [kcal/mol]	Total interaction surface	Interactions
Omadacycline	–9.57	96.78**	–1.4	–8.1	796.54	3
Tigecycline	–7.85	1.76*	–0.09	–5.89	812.23	3
Sarecycline	–8.29	844.31*	–1.05	–6.81	584.44	3
Eravacycline	–7.65	2.47*	–0.3	–6.99	686.56	2
Doxycycline	–7.31	4.38	–0.1	–6.04	578.66	3

Table IV. Results of docking with FimA

Compounds	Binding free energy [kcal/mol]	Inhibition constant Ki µM (*mM) (**nM)	Electrostatic energy [kcal/mol]	Intermolecular energy [kcal/mol]	Total interaction surface	Interactions
Omadacycline	–5.34	122.63	–0.04	–6.2	592.91	2
Tigecycline	–4.1	979.85	–0.05	–5.87	462.69	3
Sarecycline	–4.43	566.4	–0.04	–5.96	463.26	2
Eravacycline	–4.32	680.27	–0.1	–5.24	581.09	4
Doxycycline	–6.06	36.19	–0.03	–5.7	467.6	1

Table V. Results of docking with interleukin 1β

Compounds	Binding free energy [kcal/mol]	Inhibition constant Ki µM (*mM) (**nM)	Electrostatic energy [kcal/mol]	Intermolecular energy [kcal/mol]	Total interaction surface	Interactions
Omadacycline	–6.96	7.98	–0.88	–5.87	728.6	3
Tigecycline	–9.87	57.87**	–0.25	–6.87	726.86	4
Sarecycline	–7.73	2.16	–0.2	–6.48	622.27	2
Eravacycline	–6.89	8.86	–0.03	–6.73	641.12	3
Doxycycline	–6.65	13.36	–0.22	–5.83	586.63	2

Table VI. Results of docking with estrogen receptor 1β

Compounds	Binding free energy [kcal/mol]	Inhibition constant Ki µM (*mM) (**nM)	Electrostatic energy [kcal/mol]	Intermolecular energy [kcal/mol]	Total interaction surface	Interactions
Omadacycline	–8.38	35.29	–0.2	–8.59	894.5	5
Tigecycline	–6.42	64.7	–0.45	–6.98	588.24	5
Sarecycline	–2.54	55.51	–0.65	–2.6	610.37	5
Eravacycline	–4.03	23.72	–0.31	–4.71	809.41	5
Doxycycline	–2.6	640.25**	–0.1	–2.67	596.23	5

trypsin-like proteinases that cause tissue destruction and worsen periodontal integrity. Therefore, any mechanism that inhibits this enzyme can potentially slow or halt the progression of periodontal disease. Biofilm formation is facilitated by the FimA group of proteins, whose inhibition can inhibit biofilm formation, thereby reducing the pathogenesis of periodontitis. Inhibition of interleukins can lead to a reduction in inflammation, and binding to ERβ can increase bone formation. In this background, there is a lacuna in the literature regarding the capacity of the latest congeners of tetracyclines, such as omadacycline, tigecycline, sarecycline, and eravacycline, to bind to the abovementioned targets compared with doxycycline. Hence, this study was performed. The

study revealed binding free energy, inhibition constant, electrostatic energy, intermolecular energy, total interaction surface and interactions/affinity.

The binding free energy, or Gibbs free energy, is positive when there is no binding detected between the host molecule and its guest. When it is negative, it implies a spontaneous interaction within the physiological system. The inhibition constant (*Ki*) was calculated from the binding energy by the formula Ki = exp(ΔG/*RT*). (*R* is the universal gas constant, and *T* is the temperature). Hence, these two quantities are mathematically related. To completely understand the interaction, in addition to shape and structure, electrostatic interactions and the energetics of intermolecular attraction have to be discussed, in addition to exploring the affinity or the number of sites of interaction. This extensive analysis can reduce the sensitivity of the prediction procedure to structural errors. The intermolecular interaction energy is of two types: van der Waals forces and electrostatic interactions [32–34].

Comparing the binding free energies of various drugs with gingipain (Table III), doxycycline had the highest (–7.31 kcal/mol), and omadacycline had the lowest binding energy (–9.57 kcal/mol), making it the best in the category. In contrast, doxycycline had the lowest binding free energy with FimA, making it the best in the category. Other congeners had similar binding free energies ranging from –4.1 to –5.8 kcal/mol. With regard to binding free energy with IL-1β, tigecycline had exceptionally low bond energy, making it the best in the category, followed by omadacycline. Furthermore, other congeners were more or less similar. With respect to the binding free energy with ER-β, doxycycline had the highest bond energy (–2.6 kcal/mol). Omadacycline and tigecycline had the most favorable binding free energies. Therefore, while comparing the overall performance, omadacycline can be proposed as the best among the congeners. Since the inhibition constant is mathematically related to binding free energy, they are not separately discussed.

Omadacycline had the least energy of interaction with both gingipain and IL-1β. Eravacycline had the least energy of interaction with FimA, and sarecycline had the least energy of interaction with ER-. However, with FimA and ER-β, omadacycline had insignificant interactions but not repulsive interactions. With regard to intermolecular energy, omadacycline had the most favorable interaction with gingipain, FimA and ER-β. It had good interaction with IL-1β. Therefore, overall, omadacycline is the best selection with regard to electrostatic and intermolecular interactions.

With respect to the total interaction surface, omadacycline had the maximum surface area of interaction with FimA, IL-1β and ER-β. It had the second highest surface area of interaction with gingipain, next to tigecycline. With respect to affinity or sites of interaction with gingipain, all drugs were more or less similar. However, with FimA, eravacycline had maximum affinity (4), and doxycycline had the least affinity. With respect to IL-1β, all drugs had higher affinity than doxycycline. However, with regard to interaction with ER-β, all drugs were essentially similar and had a high level of affinity.

Clinical relevance

Doxycycline has been extensively used in periodontology to control the infection and, thereby, the inflammation. However, newer congeners have been compared in this study and the results show that omadacycline could potentially be a much better replacement for doxycycline. This may have far-reaching implications in clinical periodontology. The use of newer drug may modify the course of periodontitis in a highly desirable way.

In conclusion, Therefore, with respect to all four targets, omadacycline is found to have better binding capacity compared to doxycycline; hence, doxycycline can be replaced with omadacycline. However, with molecular docking studies alone, it is premature to declare the efficacy for this purpose. This result warrants future clinical investigations on omadacycline for periodontal therapy in both local and systemic administration.

Conflict of interest

The authors declare no conflict of interest.

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