Tropical Journal of Pharmaceutical Research January 2018; 17 (1): 41-45
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v17i1.7

Original Research Article

Molecular docking studies on rocaglamide, a traditional Chinese medicine for periodontitis

Ya-Ping Yan[1], Xiu-Qin Zhang[1], Xiu-Kui Wang[1], Lin-Xia Li[1], Jian-jun Ma[2]*
[1]Department of Dentistry, Affiliated Hospital of Jining Medical University, Jining 272029, [2]Department of Dentistry, Jining No.1 People's Hospital, Jining 272011, China

For correspondence: **Email: majianjun617@gmail.com: **Tel:** 0086-537-2213030*

Sent for review: 16 August 2017 *Revised accepted: 27 October 2017*

Abstract

Purpose: *To undertake an in silico assessment of rocaglamide as a potential drug therapy for periodontitis (dental arthritis).*
Method: *Lamarckian algorithm-based automated docking approach using AutoDock4.2 tool was applied for calculating the best possible binding mode of rocaglamide to IL-23p19 and IL-17, the targets of anti-inflammatory drugs in periodontal disease.*
Results: *The top two interactions of rocaglamide with IL-17 (ΔG = -5.45 and -4.83 kcal/mol) were more spontaneous, and the physical interactions (two hydrogen bonds and one π-πbond) generated in the two IL-17- rocaglamide complexes were higher in number than in IL-23p14-rocaglamide complexes.*
Conclusion: *In silico analysis of rocaglamide, a known antimicrobial and anti-inflammatory agent, is a promising natural candidate for periodontitis therapy, and should be further subjected to in vitro and in vivo anti-periodontitis investigations.*

Keywords: *Periodontitis, Inflammation, Rocaglamide, Molecular docking, Lamarckian algorithm, IL-23p19, IL-17*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Periodontal disease or periodontitisis is a chronic, bacterial infection-associated auto-immune disease characterized by anomaly in the teeth-supporting structure, tissue destruction and bone loss [1]. Some of the bacterial pathogens involved in the infection leading to periodontitis are Bacteroides gingivalis, Bacteroides intermedius and Actinobacillus *actinomycete-mcomitans* [2]. The autoimmune basis of this disease was first postulated nearly fifty years ago by Brandtzaeg and Kraus [3]. The innate immune system has a general role against bacterial pathogens [4,5]. Indeed, it is the subsequent inflammatory and immune processes associated with the bacterial pathogens that are harmful to the host and contribute to the tissue injury observed in periodontitis [6]. Cell-mediated immune response plays a pathological role in many inflammatory diseases [7].

In periodontitis, the host mechanism is complex, as it involves both protective and destructive elements, which are characterized by immune-inflammatory response to the pathogen and

subsequent destruction in the teeth-supporting structure by autoimmune response [8,9]. Several studies have associated Th1 and Th2 with the etiology of periodontitis [10-14]. Th1 and Th2 are the important components of the immune response which are associated with inflammatory disease and allergic reaction, respectively. Th1 cells and its cytokines are associated with early periodontal lesions, while Th2 and its cytokines are associated with periodontitis progression [10-14].

The number of anti-cytokine drugs targeting inflammatory cytokines against IL-1b, IL-12p40, IL-6, IL-23p19 and IL-17 has increased significantly [15]. The first three cytokine targets (IL-1b, IL-12p40 and IL-60) are the most frequently drug-targeted cytokines, while IL-23p19 and IL-17 are relatively new targets. The objective of the present study was to use Computer-Aided Drug Design (CADD) to study the effectiveness of rocaglamide, a known antimicrobial and anti-inflammatory agent [16], as an anti-periodontitis agent. For this purpose, CADD, which has become a promising tool in new drug discovery [17], was used to target IL-23p19 and IL-17 with rocaglamide.

METHODS

Protein preparation

The x-ray-crystallographic structures of IL-23p19 and IL-17 proteins were retrieved from PDB (http://www.pdb.org/). The crystallographic structure of IL-23p19 protein which contains 189 amino acids bearing PDB ID: 4GRW, was retrieved and modified accordingly by removal of unwanted atoms and molecules to suit the molecular docking experiment. The IL-17 protein contains 155 amino acids and its crystallographic structure PDB ID: 2VXS [18] was downloaded for the study.

Compound selection

Rocaglamide, a natural compound was retrieved from PubChem compound database. The SDF format of the compound was retrieved bearing CID 331783, and it was converted to PDF prior to further studies, using Discovery Studio.

Molecular docking analysis

Molecular docking analysis of the IL-23p19 and IL-17 proteins with rocaglamide was done using Auto Dock4.2tool [19]. The Auto Dock4.2tool calculates energy values by classification of energies as internal energy and torsional free energy as in Eq 1.

$$\Delta G = \Delta G_{vdw} + \Delta G_{H\text{-}bond} + \Delta G_{elec} + \Delta G_{tor} + \Delta G_{desolv} \quad \text{…….. (1)}$$

where *ΔG* represents the overall binding energy, while $\Delta G_{H\text{-}bond}$, ΔG_{elec} and ΔG_{tor} represent hydrogen bonding, electrostatic bonding and translation/rotation energies, respectively. The term ΔG_{desolv} indicates the desolvation energy on binding and hydrophobic effect. Lamarckian genetic algorithm (GA) default parameters were used for calculating ∆G of each shortlisted compound. Grid box (60 × 60 × 60 A°) was built around the active site. Five top interactions out of ten were studied for each protein. All the visualizations were generated by Discovery studio.

RESULTS

The pathway interaction profile of IL-17A and IL-23A (IL-23p19) derived using Gene Mania database (web-based integrative software) generated the network architecture of the connections of the two cytokines and other important proteins, as shown in Figure 1. The generated protein network were proteins commonly involved in auto-immune diseases such as rheumatoid arthritis. This confirms the importance of IL-23p19 and IL1-7 as drug targets in periodontitis.

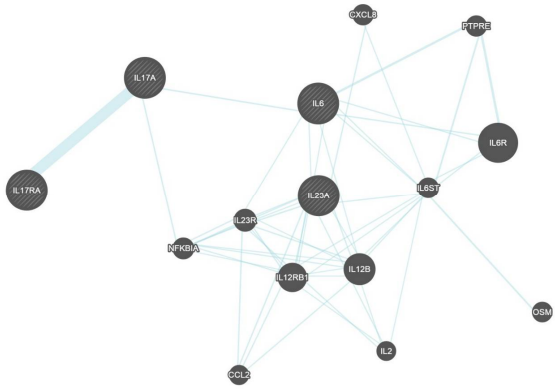

Figure 1: Protein sub-networks of IL-17A and IL-23A (queried proteins) with IL-6, NFKB1A and some important proteins involved in arthritis (only significant sub-networks are shown)

The 3D structure of the protein retrieved from protein database was trimmed to suit the experimental design using Discovery studio. The modification of both proteins are shown Figure 2a (IL-23p19) and Figure 2b (IL-17). The trimmed structures were used for molecular docking, and blind docking approach was used to look into the possibility of successful docking of rocaglamide onto the two selected cytokines. Table 1 shows the Gibbs free energy of the top two poses of each complex.

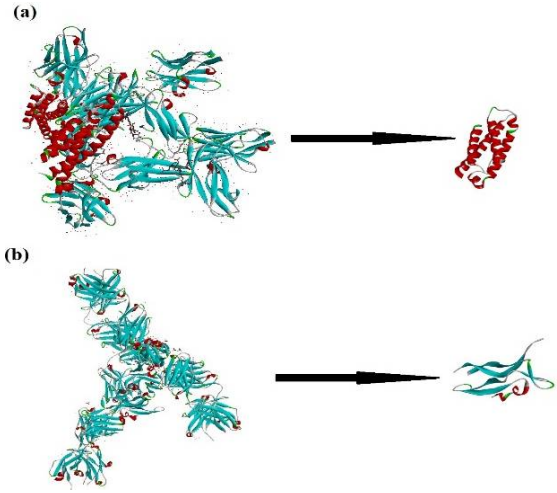

Figure 2: The original crystallographic structure of the protein available and the trimmed protein used for the study. (a) The trimmed structure represents IL-23p14 protein from amino acid 8-168 (b) The second structure represents amino acids 35- 128 of IL-17

Table 1: Gibbs free energy of top two poses of rocaglamide with IL-23p14 and IL-17

Rank	ΔG(kcal/mol) *IL-23p14*	ΔG(kcal/mol) *IL-17*
1	-1.54	-5.45
2	-0.64	-4.83

The best poses of both protein-drug complexes are shown in Figure 3. Table 2 shows the top two interactions of the drug with each protein. The protein-drug interaction (covalent or non-covalent), and the number of hydrogen bonds formed by both proteins with the drug are displayed in Figure 4, where 4(a) represents IL-23p14, and 4(b) represents IL-17.

The only interaction formed by rocaglamide and IL-23p14 was the *pi-pi* interaction as shown in Figure 5 (a), the binding pocket in this pose was TRP26, LEU31, ARG148, GLN151, ALA152, ALA155, VAL156 and ARG159. Figure 5 (b) represents the second best pose of IL23p14-rocaglamide docking.

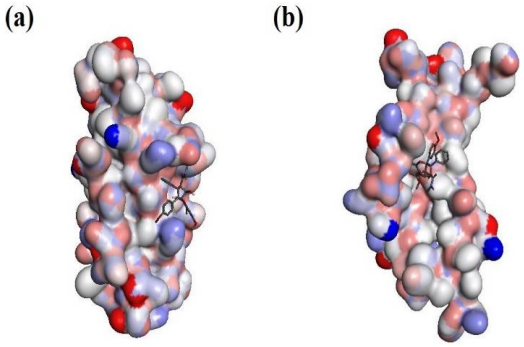

Figure 3: The two best poses of rocaglamide with (a) IL-23p14 and (b) IL-17

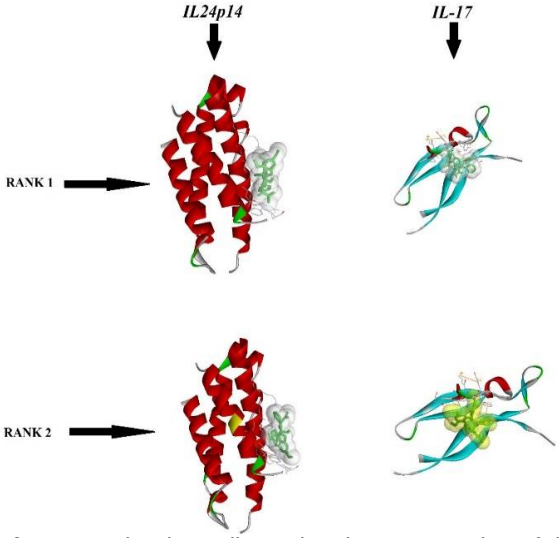

Figure 4: The three dimensional representation of the top two poses of rocaglamide. The top two interactions of IL-23p14 and rocaglamide had ΔG values of -1.54 and -0.63 kcal/mol

DISCUSSION

Rocaglamide formed better interactions with IL-17. The top pose had a ΔG of -5.45 kcal/mol, and exhibited two hydrogen bond interactions with TYR-44 andVAL-119 in the binding pocket. The binding pocket of IL-17 for rocaglamide contained the following amino acids: PRO-37,

Table 2: Auto dock analysis of the top two poses of protein-rocaglamide complexes.

Cytokine	Rank	Ligand binding pocket	H-bond
IL-23p14	1	TRP26, LEU31, ARG148, GLN151, ALA152, ALA155, VAL156, ARG159	*pi-pi* interaction with***ARG159***
	2	CYS22, TRP26, LEU31, ARG148, GLN151, ALA152, ALA155, ARG159	Two *pi-pi* interactions with***TRP51***
IL-17	1	PRO37, LYS38, SER41, TYR43, TYR44, SER47, TRP51, LEU53, ILE92, VAL119, GLY120, CYS121	One Hydrogen bond with **VAL119** One Hydrogen bond with **TYR44**
	2	THR35, PRO37, LYS38, SER40, SER41, TYR44, TRP51, VAL119,GLY120	*pi-pi* interaction with***TRP51*** One Hydrogen bond with **TRP51** One Hydrogen bond with **SER40**

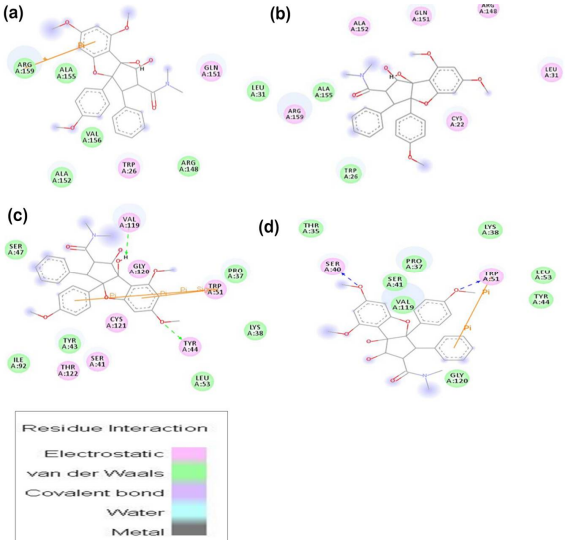

Figure 5: Two dimensional representations of the top four poses. (a) and (b) show the top two poses of IL-23p14, while (c) and (d) show IL-17 interactions with rocaglamide

LYS-38, SER-41, TYR-43, TYR-44, SER-47, TRP-51, LEU-53, ILE-92, VAL-119, GLY-120, and CYS-121. Two rocaglamide atoms, O-6 and H-41formed bond with TYR-44 andVAL-119, respectively with bond lengths of 3.16 and 2.29 Å, respectively. Rather than forming two hydrogen bond interactions, the complex rocaglamide-IL-17 complex exhibited two *pi-pi* interactions, as shown in Figure 5 (c). The second best pose of IL-17 in the rocaglamide-IL-17 complex had a ΔG of -4.83 kcal/mol. It also exhibited two hydrogen bond interactions in the binding pocket. The binding pocket in this case contained the following amino acids: THR-35, PRO-37, LYS-38, SER-40, SER-41, TYR-44, TRP-51, VAL-119 and GLY-120.The O-6and O-7atoms of rocaglamide interacted with SER-40 and TRP-51, with bond lengths of 2.7 and 2.8 Å, respectively. Based on binding energies, rocaglamide showed the least binding energy of -0.63kcal/mole with IL-23p14.

Various conceptual models spanning over five decades have been proposed to describe the etiology of periodontitis. Two factors, microbial infection and inflammation, are thought to play pivotal roles in the shift from the healthy state to periodontitis. Thus, the development of strategies is based on these two factors. Compounds of natural origin are invaluable in novel drug discovery, and many natural compounds have been reported to have dual functions [17,20]. The present study was focused on a compound with antimicrobial and anti-inflammatory properties. This was based on knowledge from Traditional Chinese Medicine. Rocaglamide, a flavagline of natural origin, is a known traditional Chinese medicinal compound with antimicrobial and anti-inflammatory activities. However, the mechanism of action of rocaglamide is yet to be ascertained. It is well established that CADD is an important route for investigating the possible mode of action of drugs. The present study has explored possible targets in the inflammatory pathway that rocaglamide can act on. The data generated here will be useful in developing more robust methods for targeting the pathogenesis of periodontal disease.

CONCLUSION

The results obtained in this study suggest that rocaglamide may have potent anti-periodontitis effects. Being an anti-inflammatory drug with known anti-microbial activity, these findings make it potentially suitable for the development of a new drug for treating periodontitis, a disease in which microbial infection and inflammation are common challenges.

DECLARATIONS

Acknowledgement

The authors would like to thank the management of Jining No.1 People's Hospital for providing the infrastructure for this research work.

Conflict of interest

There are no competing interests with regard to this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. YPY and XQZ carried out the study; XKW analyzed the results, while LXL and JJM Developed the concept and wrote up the manuscript. JJM reviewed the manuscript.

REFERENCES

1. *Newman, MG, Henry T, Perry RK, Fermin AC. Carranza's clinical periodontology. Elsevier Health Sciences, USA 2011.*
2. *Slots J, Listgarten MA. Bacteroides gingivalis, Bacteroides intermedius and Actinobacillus actinomycetemcomitans in human periodontal diseases. J Clin Periodontol 1988; 15(2): 85-93.*

3. *Brandtzaeg P, Kraus FW. Auto- immunity and periodontal disease. Odontol T 1965; 73: 281-393.*
4. *Boman HG. Innate immunity and the normal microfora. Immunol Rev 2000; 173: 5-16.*
5. *Ji S, Hyun J, Park E, Lee BL, Kim KK, Choi Y. Susceptibility of various oral bacteria to antimicrobial peptides and to phagocytosis by neutrophils. J Periodont Res 2007; 42(5): 410-419.*
6. *Kornman KS. Mapping the pathogenesis of periodontitis: a new look. J Periodontol 2008; 79(8): 1560-1568.*
7. *Ivanyi L, Lehner T. Stimulation of lymphocyte transformation by bacterial antigens in patients with periodontal disease. Arch Oral Biol 1970; 15: 1089-1096.*
8. *Gemmell E, Yamazaki K, Seymour G. The role of T cells in periodontal disease: homeostasis and autoimmunity. Periodonto l2000; 2007; 43: 14-40.*
9. *Kinane DF, Demuth DR, Gorr SU, Hajishengallis GN, Martin MH. Human variability in innate immunity. Periodontol 2000; 2007; 45:14-34.*
10. *Manhart SS, Reinhardt RA, Payne JB, Seymour GJ, Gemmell E, Dyer JK, Petro TM. Gingival cell IL-2 and IL-4 in early-onset periodontitis. J Periodontol 1994; 65: 807-813.*
11. *Aoyagi T, Sugawara-Aoyagi M, Yamazaki K, Hara K. Interleukin 4 (IL-4) and IL-6-producing memory T-cells in peripheral blood and gingival tissue in periodontitis patients with high serum antibody titers to Porphyromonas gingivalis. Oral Microbiol Immunol 1995; 10: 304-310.*
12. *Tokoro Y, Matsuki Y, Yamamoto T, Suzuki T, Hara K. Relevance of local Th2-type cytokine mRNA expression in immunocompetent infiltrates in inflamed gingival tissue to periodontal diseases. Clin Exp Immunol 1997; 107: 166-174.*
13. *Sigusch B, Klinger G, Glockmann E, Simon HU. Early-onset and adult periodontitis associated with abnormal cytokine production by activated T lymphocytes. J Periodontol 1998; 69: 1098-1104.*
14. *Bartova J, Kratka-Opatrna Z, Prochazkova J, Krejsa O, Duskova J, Mrklas L, Tlaskalova H and Cukrowska B. Th1 and Th2 cytokine profile in patients with early onset periodontitis and their healthy siblings. Mediators Inflamm 2000; 9:115-120*
15. *Feldmann M, Steinman L. Design of effective immunotherapy for human autoimmunity. Nature 2005; 435(7042): 612-619.*
16. *Rayavarapu S. Synthesis of Putrescine Bisamides as Antimicrobial and Anti-Inflammatory Agents. Med chem. 2014; 4: 367-372.*
17. *Zhou W, Cai JF, Yuan F, Ma M, & Yin F. In silico targeting of interleukin-6 by natural compounds. Bangladesh Journal of Pharmacology 2014; 9(3): 371-376.*
18. *Gerhardt, Abbott WM, Hargreaves D, Pauptit RA, Davies RA, Needham MRC, Langham C, Barker W, Aziz A, Snow MJ, Dawson S. Structure of IL-17A in complex with a potent, fully human neutralizing antibody. J Mol Biol 2009; 394(5): 905-921.*
19. *Morris GM, Huey R, Lindstrom W, Sanner MF, Belew RK, Goodsell DS, Olson AJ. AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. J Comput Chem 2009; 30(16): 2785-2791.*
20. *Zhou X, Lin J, Yin Y, Zhao J, Sun X, Tang K. Ganodermataceae: natural products and their related pharmacological functions. Am J Chin Med 2007; 35(04): 559-574.*