Virtual Screening for Molecular Targets of Emodin Against Red Complex Pathogens

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ABSTRACT

Objective: Periodontitis is a chronic inflammatory disease affecting teeth' supporting tissues. It is caused by specific bacterial species, including *Porphyromonas gingivalis (Pg), Tannerella forsythia (Tf),* and *Treponema denticola,* known as the "red complex" group. These bacteria manipulate the immune response and promote tissue destruction, making them key players in periodontal pathogenesis. The present study aims to identify the potential molecular targets of Emodin against the red complex pathogens.

Method: The interaction between the phytocompound Emodin and red complex pathogens was identified using the STITCH tool. The proteins identified were then classified into functional categories using the VICMPred. The virulent proteins identified were then subjected to Bepired prediction, which provided information about the epitopes in the virulent proteins. Finally, the subcellular location of the proteins was demonstrated with the pSORTb tool.

Results: Carbamoyl-phosphate synthase is a large subunit identified as a virulence protein in *Pg* and *Tf*. DNA topoisomerase IV subunit A was found to be the common virulence protein for *Pg* and *Td.* The DNA gyrase subunit A and ATPase/histidine kinase/DNA gyrase B/HSP90 domain-containing protein were found to be identified in *Td* and *Tf.* It was the only protein predicted to be in the cytoplasmic membrane, while others were found in the cytoplasm. The four virulent proteins targeted by Emodin were found to harbor multiple epitopes.

Conclusion: Emodin was found to interact with all three pathogens of the red complex group. However, further experimental validation is warranted to prove the antimicrobial effect of Emodin against periodontal pathogens.

Keywords: Emodin, Red complex pathogens, Epitopes, computational tools, virulent protein.

1. INTRODUCTION

Periodontitis is a disease caused by a specific microbial composition found on the surface of teeth and tooth roots. Still, bacteria's exact contribution to the disease's progression is not yet fully understood. Commensal bacteria are believed to be protective in preventing disease development. However, some bacterial species, including *Porphyromonas gingivalis, Tannerella forsythia,* and *Treponema denticola,* found in plaque, use various mechanisms to interfere with host defense mechanisms, leading to disease progression [1]. *Porphyromonas gingivalis (Pg),* a Gram-negative oral anaerobe, is a pivotal player in periodontitis pathogenesis among over 500 oral bacterial species. While a natural member of the oral microbiome, its specialized virulence factors enable destructive proliferation in periodontal lesions, marking it as a pathobiont. Certain spiral-shaped bacteria species, particularly *Treponema denticola (Td),* are considered significant players in the development and progression of

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Received: 06/02/2024 Accepted: 14/06/2024.
DOI: https://doi.org/10.35516/jjps.v17i4.2347

periodontal disease [3]. *Tannerella forsythia (Tf)* is a Gram-negative oral pathogen that targets multiple proteins associated with virulence via its O-glycosylation system [4]. The emerging phenotype of multi-drug resistance exhibited by these pathogens underscores the need for alternative therapy, emphasizing herbal medicines. Identifying potential targets of a phyto compound against oral pathogens will provide insights into the compound's mode of action and aid in predicting the application of the compound either individually or in combination with other therapeutic modalities.

Emodin is a natural anthraquinone derivative found in various plants, fungi, and lichens. It has a rich history in traditional Chinese medicine and has been found to exhibit a range of biological activities. These include antibacterial, anti-inflammatory, and anticancer properties. It was found to show promising effects in reversing chemotherapy resistance and has antimalarial and antiallergic effects [5]. A recent study examined the photodynamic effects of aloe-emodin (AE) on *Candida albicans*, a common fungus that can be resistant to some medications. The researchers used antimicrobial photodynamic therapy (PDT) to test the effectiveness of AE, a natural compound found in *Aloe vera* and *Rheum palmatum*. The results showed that AE had no negative effects in the absence of light but effectively eliminated *C. albicans* cells *in vitro* when exposed to light. Confocal microscopy also revealed that fungal cells took up AE more easily when exposed to light. Finally, transmission and scanning electron microscopy showed that AE-mediated aPDT caused damage to the cell structures of *C. albicans*, suggesting that AE could potentially be used as a photosensitizer to combat drug-resistant strains of the fungus [6]. Although, several plant compounds have been assessed using *in vitro* approaches to deduce their biological activities [7], it has been a time-consuming and expensive process demanding labor and expertise in the field. Alternatively, computational methods have been considered to be a boon to researchers, wherein the initial screening of multiple bioactive compounds can be done within less time duration and an inexpensive manner [8]. In line with this, the phytocompound emodin was assessed for its interaction with a red complex pathogen to develop therapeutic strategies employing Emodin empoying computational tools to elucidate their activities against periodontal pathogens.

2. MATERIALS AND METHOD

Strains and phytocompound used in the study

The phytocompound Emodin was tested against red complex pathogens, namely *Porphyromonas gingivalis, Treponema denticola, and Tannerella forsythia*. The STITCH tool [9] revealed the interaction between the compound and the pathogen's protein repertoire.

Analyzing protein Interaction Network

STITCH (Search tool for interactions of chemicals) is an exhaustive pipeline that can be used to predict the interaction between chemicals and proteins. The interaction is of two types: (a) direct or physical (b) indirect or functional association, which arises from data accumulated in the primary databases. The repertoire of proteins against red complex pathogens, namely *Porphyromonas gingivalis, Treponema denticola*, and *Tannerella forsythia* interacting with Emodin, were used for predicting virulence [9]. The FASTA format sequences were retrieved from the National Centre of Biotechnology information domain and used for predicting the functional class of proteins and their virulence properties (https://www.ncbi.nlm.nih.gov/protein/?term=).

Prediction of functional class of interacting protein

VICMpred server classifies the protein identified into four major classes: virulence factor, information and storage processing, cellular process, and metabolism. Anchorage-dependent protein effluent pumps, transporters, toxins, and hemolytic molecules are identified based on the support vector machine (SVM) algorithm, which classifies proteins based on their amino acid composition pattern [10].

Prediction of B cell Epitope in the virulence proteins

BepiPred is a software tool that predicts linear B-cell epitopes in protein sequences. It uses machine learning

algorithms that have been trained on known epitope data to identify protein regions that are probably recognized by antibodies. Researchers can apply BepiPred to facilitate the identification of possible antigenic sites on proteins, which is useful for vaccine development, immunotherapy, and understanding immune responses. This tool helps analyze antigen-antibody interactions and design experiments related to antibody production and detection. Epitopes are antigen-determining sites on the virulent proteins capable of eliciting an immune response in the host. Identifying those B cell epitopes on virulence protein adds merit to the compound. Bepred on the virulent proteins. The peptide molecules that score above a threshold >0.5 are predicted to be part of the epitope and are colored yellow in the graph [11, 12].

Prediction of subcellular localization of protein

pSORTb is a computational tool that predicts bacterial proteins' subcellular localization (SCL). Its main goal is to determine where proteins are located within bacterial cells, which helps researchers understand protein function and cellular processes better. pSORTb uses various protein features such as amino acid composition, sequence motifs, and similarity to known proteins to make accurate predictions. Using this tool, researchers can identify potential drug targets or vaccine candidates by studying bacterial proteomes. Cell surface proteins are readily targeted, while the cytoplasmic or nuclear protein needs a proper drug delivery system to target the protein of interest. Hence, pSORTb was used for the identification of sub-cellular locations of virulence protein (PSORTdb 4.0 (http://db.psort.org/)) [13].

3. RESULTS

Emodin was found to interact with the red complex pathogens *Porphyromonas gingivalis, Treponema denticola*, and *Tannerella forsythia.* Metabolism-related proteins were found to predominate in *Pg, Tf, a*nd *Td.* The DNA topoisomerase IV subunit A and carbamoyl-phosphate synthase large subunit were found to be the virulence factors in the *Pg* group (Table 1a, Figure 1a), DNA topoisomerase IV subunit B and DNA gyrase subunit A were found to be the confer virulence in *Td* (Table 1b, Figure 1b), while ATPase/histidine kinase/DNA gyrase B/HSP90 domain-containing protein and Carbamoyl-phosphate synthase large subunit were found to be the virulent proteins in *Tf* (Table 1c, Figure 1c). All the virulent proteins except for ATPase/histidine kinase/DNA gyrase B/HSP90 domain-containing protein were found to be localized in the cytoplasm. The prediction of epitopes in the virulent proteins demonstrated that these proteins were composed of multiple epitopes (Figure 2).

Table 1a: The list of proteins of *Porphyromonas gingivalis* interacting with emodin

Organism	Identifier	Protein	VICMPred
Porphyromonas gingivalis	**PGN_0472**	**DNA topoisomerase IV subunit A**	**Virulence factors**
	PGN_1594	DNA topoisomerase IV subunit B	Cellular Process
	PGN_2019	Bifunctional UDP-3-O-[3-hydroxymyristoyl] N-acetylglucosamine deacetylase/(3R)-hydroxymyristoyl-ACP dehydratase	Metabolism molecule
	PGN_1449	Inosine 5-monophosphate dehydrogenase	Metabolism molecule
	PGN_1443	**Carbamoyl-phosphate synthase large subunit**	**Virulence factors**
	gyrA	DNA gyrase A subunit	Metabolism molecule
	gyrB	DNA gyrase B subunit	Metabolism molecule
	pyrB	Aspartate carbamoyltransferase	Metabolism molecule
	carA	Carbamoyl phosphate synthase small subunit	Cellular Process
	hisS	Histidyl-tRNA synthetase	Information and Storage

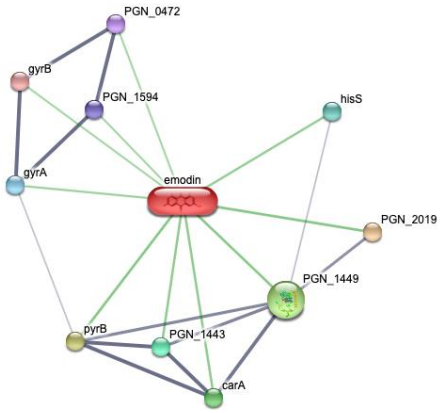

Figure 1a: The protein interaction network of *Porphyromonas gingivalis* with emodin

Table 1b: The list of proteins of *Treponema denticola* interacting with emodin

Organism	Identifier	Protein	VICMPred
Treponema denticola	**TDE_2245**	**DNA topoisomerase IV subunit B**	**Virulence Factors**
	TDE_0492	Sensor histidine kinase/response regulator	Metabolism Molecule
	TDE_2693	Ankyrin repeat-containing protein	Metabolism Molecule
	TDE_0502	Ankyrin repeat-containing protein	Metabolism Molecule
	TDE_0823	(3R)-hydroxymyristoyl-ACP dehydratase	Cellular Process
	TDE_2450	Ankyrin repeat-containing protein	Metabolism Molecule
	gyrA	**DNA gyrase subunit A**	**Virulence Factors**
	pyrBI	Bifunctional aspartate carbamoyltransferase catalytic subunit/aspartate carbamoyltransferase regulatory subunit	Cellular Process
	guaB	Inosine 5-monophosphate dehydrogenase	Cellular Process
	hisS	Histidyl-tRNA synthetase	Metabolism Molecule

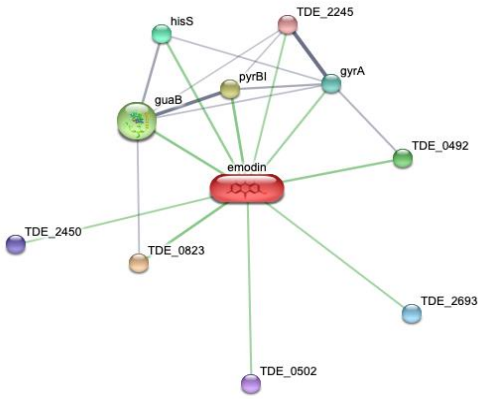

Figure 1b: The protein interaction network of *Treponema denticola* with emodin

Table 1c: The list of proteins of *Tannerella forsythia* interacting with emodin

Organism	Identifier	Protein	VICMPred
Tannerella forsythia	BFO_1082	Putative DNA gyrase, B subunit	Metabolism molecule
	BFO_2044	Putative inosine-5'-monophosphate dehydrogenase	Metabolism molecule
	BFO_2981	Kinase domain-containing protein	Metabolism molecule
	BFO_2007	**ATPase/histidine kinase/DNA gyrase B/HSP90 domain-containing protein**	**Virulence factors**
	gyrA	DNA gyrase subunit A	Cellular Process
	gyrB	DNA gyrase subunit B	Metabolism molecule
	hisS	Histidine--tRNA ligase	Metabolism molecule
	fabZ	Beta-hydroxyacyl-(acyl-carrier-protein) dehydratase FabZ	Cellular Process
	pyrB	Aspartate carbamoyltransferase	Metabolism molecule
	carB	**Carbamoyl-phosphate synthase large subunit**	**Virulence factors**

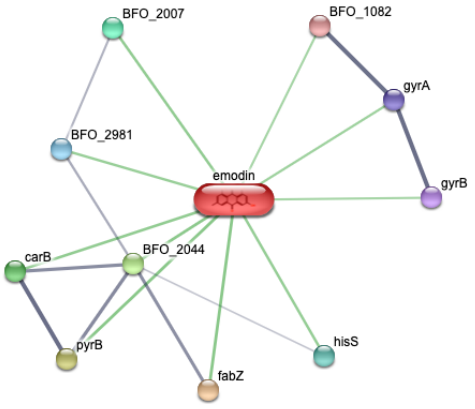

Figure 1c: The protein interaction network of *Tannerella forsythia* with emodin

Table 2: Subcellular localization of virulent proteins identified using VICMPred

Identifier	Virulent Protein	Subcellular localization	Score
PGN_0472	DNA topoisomerase IV subunit A	Cytoplasmic	9.97
PGN_1443	Carbamoyl-phosphate synthase large subunit	Cytoplasmic	9.94
TDE_2245	DNA topoisomerase IV subunit B	Cytoplasmic	9.97
gyrA	DNA gyrase subunit A	Cytoplasmic	9.97
BFO_2007	ATPase/histidine kinase/DNA gyrase B/HSP90 domain-containing protein	Cytoplasmic membrane	7.88
carB	Carbamoyl-phosphate synthase large subunit	Cytoplasmic	9.97

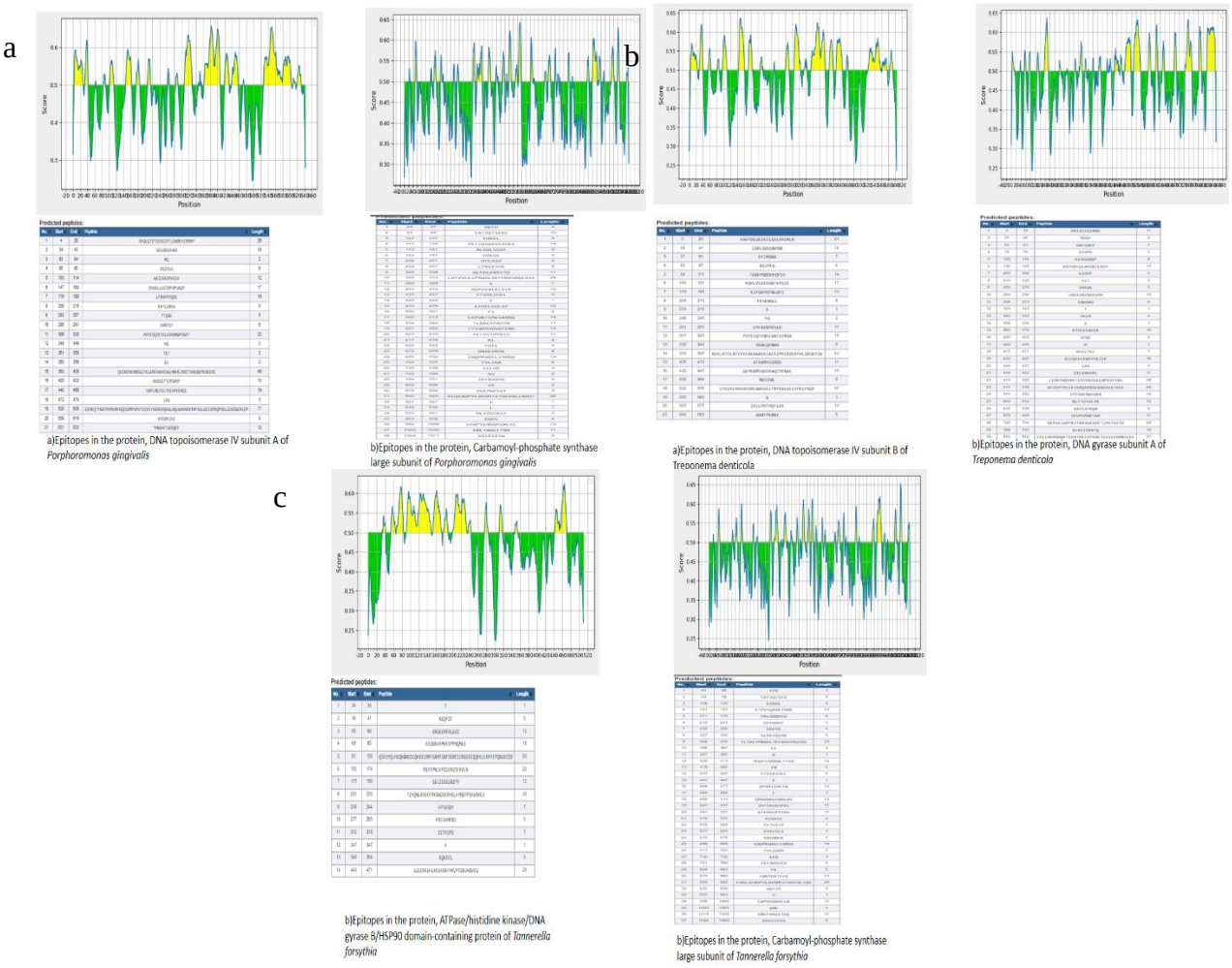

Figure 2: Epitopes in the virulent proteins of red complex pathogen a) *Porphoromonas gingivalis* b) *Treponema denticola* c) *Tannerella forsythia* targeted by Emodin

4. DISCUSSION

Emodin was found to target the virulent proteins of the red complex pathogens, which is evident from the STITCH and VICMPred predictions. Furthermore, the subcellular localization demonstrated that most proteins were found in the cytoplasm. The presence of multiple epitopes in the virulent protein can facilitate further analysis of Emodin and the proteins using molecular docking studies. A study investigated the relationship between the count of red-complex bacteria in saliva, specifically *Porphyromonas gingivalis*, and the periodontal status in a Japanese population. The study utilized real-time polymerase chain reaction analysis and clinical assessments to determine that *P. gingivalis* levels strongly correlated with periodontal parameters such as probing pocket depth, bleeding on probing, and bone crest level. The detection of *P. gingivalis* and *Treponema denticola* and/or Tannerella forsythia in the saliva indicated a more severe periodontal condition, highlighting the importance of *P. gingivalis* in the progression of periodontitis [14]. A study presents novel aloe emodin-hybridized sulfonamide aminophosphates as potential antibacterial agents to combat drug-resistant bacterial infections. Among them, ethyl aminophosphate-hybridized sulfadiazine aloe emodin 7a (EASA-7a) exhibited potent antibacterial activity against drug-resistant *E. faecalis*, low hemolytic activity, and biofilm-disruptive ability. Mechanistic studies suggest its efficacy through membrane permeation, depolarization, ROS accumulation, and DNA intercalation. EASA-7a shows promise for further development in addressing life-threatening bacterial infections [15]. A study explored the possibility of using emodin, found in *Polygonum cuspidatum*, as a treatment for Glässer's disease, which affects swine and is caused by *Haemophilus parasuis*. The study found that emodin had strong inhibitory effects against *H. parasuis*, with minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) values of 32 and 64 μg/mL, respectively. Based on antibacterial kinetics, the activity of emodin was found to be concentration-dependent. Membrane integrity assays revealed that emodin can disrupt cell membranes and alter membrane protein conformation. Transmission electron microscopy showed significant cellular damage in *H. parasuis* treated with emodin, indicating its potential as a therapy for Glässer's disease [16].

A research study has identified a new class of haloemodins derived from traditional Chinese medicine that have promising potential as antibacterial agents against drug-resistant infections. These haloemodins have been found to inhibit bacterial topoisomerases while leaving human topoisomerases unaffected. They have shown remarkable efficacy against Gram-positive bacteria, including strains resistant to common antibiotics, such as vancomycin-resistant *Enterococcus faecium* and methicillin-resistant *Staphylococcus aureus*. Furthermore, the antibacterial spectrum of haloemodins against Gram-negatives was expanded using polymyxin B nonapeptide. *In vivo* studies have confirmed that haloemodins have therapeutic efficacy in treating *S. aureus*-induced keratitis in rabbits, indicating their potential use as a promising antibacterial agent against drug-resistant pathogens [17]. Li and team investigated the efficacy of antimicrobial photodynamic therapy (aPDT) that uses aloe-emodin (AE) against multidrug-resistant (MDR) *Acinetobacter baumannii* clinical isolates. The study revealed that AE did not have any dark toxicity and could effectively inactivate MDR *A. baumannii* in a concentration and light-dose-dependent manner. The study also found that AE could damage bacterial components, including genomic DNA, membrane integrity, and cellular structure. These results indicate that AE could be a potential photosensitizer for treating superficial infections caused by MDR *A. baumannii* [18]. These reports clearly agreed with the observations made in the present study.

A study presented information regarding the design, synthesis, and evaluation of twenty aloe-emodin derivatives, focusing on their biological activities. Certain derivatives, particularly those with thiosemicarbazide moieties, displayed potent tyrosinase inhibition. Structure-activity relationships were discussed, and the inhibition mechanisms of selected

compounds were investigated. Additionally, some derivatives' antibacterial and anti-inflammatory activities were screened, revealing promising candidates for further exploration in drug development [19]. In addition to exhibiting anti-bacterial activity, Emodin was found to exhibit antiviral properties, which have been elucidated by researchers worldwide. In this context, a study explored modifying emodin's structure to enhance its activity against HCoV-NL63. Halogenation improved antiviral potency, with the iodinated analog E_3I exhibiting activity comparable to remdesivir, albeit with some observed toxicity to Vero cells [20]. Aloe-emodin is a potential inducer of interferon (IFN) with low levels of toxicity. It activates the IFN-stimulated response element (ISRE) and the gamma-activated sequence (GAS)-driven cis-reporting systems, which upregulates IFN-stimulated genes. Aloe-emodin also significantly enhances nitric oxide production and has demonstrated antiviral activity against Japanese encephalitis virus (JEV) and enterovirus 71 (EV71) in a dose- and time-dependent manner. This suggests that it has potential through IFN signaling responses [21]. A recent study by Luo and the team demonstrated Aloe-emodin's (Ae) antiviral activity against the African swine fever virus (ASFV). Studies have shown that Ae can inhibit the replication of ASFV (African Swine Fever Virus) by reducing the activation of the NF-κB signaling pathway, which ASFV induces. Ae (emodin) also induced apoptosis (cell death) in infected cells by modulating the expression of apoptotic proteins. These findings offer potential therapeutic strategies for preventing and treating ASF, highlighting how Ae can help combat viral infections [22].

Numerous *in silico* and *in vitro* studies have been conducted with crude extracts or bioactive compounds extracted from plants. These studies reiterate using phytocompounds as potential antimicrobial leads against different classes of microorganisms [23, 24]. Molecular docking [25] and network pharmacology [26] have aided in demonstrating the mechanism of action of plant compounds and their mode of action against pathogens. Thus, the study design using computational approaches has reduced the cost and time required for analyzing bioactive compounds and paved the way for identifying novel drug targets or therapeutic leads.

Limitations: Computational methods have been utilized in the field of drug discovery and development for a long time. These in silico approaches have several advantages, such as cost-effectiveness, reduced investigation time, and real-time application of preliminary results. However, this approach has some limitations, including the need to validate data in a biological system to confirm findings. Additionally, interactions observed may be purely physical or have functional consequences that require further exploration. Furthermore, certain proteins found in bacteria may share close homology with host proteins, and in vivo experiments should be conducted to rule out any adverse side effects anticipated during the therapeutic usage of the drug.

5. CONCLUSION

In summary, this virtual investigation potentially reveals valuable insights into the molecular targets of Emodin in red complex pathogens. These findings are important for developing targeted treatments for dental caries by shedding light on the complex molecular interactions between Emodin and these microorganisms that cause periodontitis. However, further research and refinement are needed to fully utilize Emodin as a therapeutic agent against these red complex pathogens.

Declaration of competing interest: The authors have no conflicts of interest relevant to this article.

Financial & competing Interests disclosure

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

REFERENCES

1. Darveau R.P. Periodontitis: a polymicrobial disruption of host homeostasis. *Nat Rev Microbiol*. 2010; 8(7):481-90. doi: 10.1038/nrmicro2337.
2. Mysak J., Podzimek S., Sommerova P., Lyuya-Mi Y., Bartova J., Janatova T., Prochazkova J. and Duskova J. Porphyromonas gingivalis: major periodontopathic pathogen overview. *J Immunol Res.* 2014; 2014:476068. doi: 10.1155/2014/476068.
3. Zeng H., Chan Y., Gao W., Leung W.K. and Watt R.M. Diversity of Treponema denticola and Other Oral Treponeme Lineages in Subjects with Periodontitis and Gingivitis. *Microbiol Spectr*. 2021; 9(2):e0070121. doi: 10.1128/Spectrum.00701-21.
4. Veith P.D., Scott N.E. and Reynolds E.C. Characterization of the O-Glycoproteome of Tannerella forsythia. *mSphere*. 2021; 6(5):e0064921. doi: 10.1128/mSphere.00649-21.
5. Stompor-Gorący M. The Health Benefits of Emodin, a Natural Anthraquinone Derived from Rhubarb-A Summary Update. *Int J Mol Sci*. 2021; 22(17):9522. doi: 10.3390/ijms22179522.
6. Ma W., Liu C., Li J., Hao M., Ji Y. and Zeng X. The effects of aloe emodin-mediated antimicrobial photodynamic therapy on drug-sensitive and resistant Candida albicans. *Photochem Photobiol Sci*. 2020; 19(4):485-494. doi: 10.1039/c9pp00352e.
7. Abu-Darwish D., Shibli R. and Al-Abdallat A.M. Phenolic Compounds and Antioxidant Activity of *Chiliadenus montanus* (Vhal.) *Brullo* grown in vitro. *Jordan Journal of Pharmaceutical Sciences.* 2024; 17(3):611–628. doi: 10.35516/jjps.v17i3.2248.
8. Sowndhariya S.S., Ravi S., Dharani J.D. and Sripathi R.S. Chemical Constitution, In-silico Molecular Docking Studies and Antibacterial Activity of Flower Essential Oil of Artabotrys hexapetalus. *Jordan Journal of Pharmaceutical Sciences.* 2022; 15(3):341–354. doi: 10.35516/jjps.v15i3.408.
9. Szklarczyk D., Santos A., von Mering C., Jensen L.J., Bork P. and Kuhn M. STITCH 5: augmenting protein-chemical interaction networks with tissue and affinity data. *Nucleic Acids Res.* 2016; 44(D1): D380-4. doi: 10.1093/nar/gkv1277.
10. Saha S. and Raghava G.P. VICMpred: an SVM-based method for the prediction of functional proteins of Gram-negative bacteria using amino acid patterns and composition. *Genomics Proteomics Bioinformatics.* 2006; 4(1):42-7. doi: 10.1016/S1672-0229(06)60015-6.
11. Larsen J.E., Lund O. and Nielsen M. Improved method for predicting linear B-cell epitopes. *Immunome Res.* 2006; 2:2. doi: 10.1186/1745-7580-2-2.
12. Jespersen M.C., Peters B., Nielsen M. and Marcatili P. BepiPred-2.0: improving sequence-based B-cell epitope prediction using conformational epitopes. *Nucleic Acids Res.* 2017; 45(W1):W24-W29. doi: 10.1093/nar/gkx346.
13. Lau W.Y.V., Hoad G.R., Jin V., Winsor G.L., Madyan A., Gray K.L., Laird M.R., Lo R. and Brinkman F.S.L. PSORTdb 4.0: expanded and redesigned bacterial and archaeal protein subcellular localization database incorporating new secondary localizations. *Nucleic Acids Res.* 2021; 49(D1): D803-D808. doi: 10.1093/nar/gkaa1095.
14. Chigasaki O., Aoyama N., Sasaki Y., Takeuchi Y., Mizutani K., Ikeda Y., Gokyu M., Umeda M., Izumi Y., Iwata T. and Aoki A. Porphyromonas gingivalis, the most influential pathogen in red-complex bacteria: A cross-sectional study on the relationship between bacterial count and clinical periodontal status in Japan. *J Periodontol.* 2021; 92(12):1719-1729. doi: 10.1002/JPER.21-0011.
15. Deng Z., Sun H., Bheemanaboina R.R.Y., Luo Y. and Zhou C.H. Natural aloe emodin-hybridized sulfonamide aminophosphates as novel potential membrane-perturbing and DNA-intercalating agents against Enterococcus faecalis. *Bioorg Med Chem Lett.* 2022; 64:128695. doi: 10.1016/j.bmcl.2022.128695.

16. Li L., Song X., Yin Z., Jia R., Li Z., Zhou X., Zou Y., Li L., Yin L., Yue G., Ye G., Lv C., Shi W. and Fu Y. The antibacterial activity and action mechanism of emodin from Polygonum cuspidatum against Haemophilus parasuis in vitro. *Microbiol Res.* 2016; 186-187:139-45. doi: 10.1016/j.micres.2016.03.008.
17. Duan F., Li X., Cai S., Xin G., Wang Y., Du D., He S., Huang B., Guo X., Zhao H., Zhang R., Ma L., Liu Y., Du Q., Wei Z., Xing Z., Liang Y., Wu X., Fan C., Ji C., Zeng D., Chen Q., He Y., Liu X. and Huang W. Haloemodin as novel antibacterial agent inhibiting DNA gyrase and bacterial topoisomerase I. *J Med Chem.* 2014; 57(9):3707-14. doi: 10.1021/jm401685f.
18. Li J., Qin M., Liu C., Ma W., Zeng X. and Ji Y. Antimicrobial photodynamic therapy against multidrug-resistant Acinetobacter baumannii clinical isolates mediated by aloe-emodin: An in vitro study. *Photodiagnosis Photodyn Ther*. 2020; 29:101632. doi: 10.1016/j.pdpdt.2019.101632.
19. Liu J., Wu F. and Chen C. Design and synthesis of aloe-emodin derivatives as potent anti-tyrosinase, antibacterial and anti-inflammatory agents. *Bioorg Med Chem Lett.* 2015; 25(22):5142-6. doi: 10.1016/j.bmcl.2015.10.004.
20. Horvat M., Avbelj M., Durán-Alonso M.B., Banjanac M., Petković H. and Iskra J. Antiviral Activities of Halogenated Emodin Derivatives against Human Coronavirus NL63. *Molecules.* 2021; 26(22):6825. doi: 10.3390/molecules26226825.
21. Lin C.W., Wu C.F., Hsiao N.W., Chang C.Y., Li S.W., Wan L., Lin Y.J. and Lin W.Y. Aloe-emodin is an interferon-inducing agent with antiviral activity against Japanese encephalitis virus and enterovirus 71. *Int J Antimicrob Agents.* 2008; 32(4):355-9. doi: 10.1016/j.ijantimicag.2008.04.018.
22. Luo Y., Yang Y., Wang W., Gao Q., Gong T., Feng Y., Wu D., Zheng X., Zhang G. and Wang H. Aloe-emodin inhibits African swine fever virus replication by promoting apoptosis via regulating NF-κB signaling pathway. *Virol J.* 2023; 20(1):158. doi: 10.1186/s12985-023-02126-8.
23. Widyananda M.H., Kurniasari C.A., Alam F.M., Rizky W.C., Dings T.G.A., Ansori A.N.M. and Antonius Y. Exploration of Potentially Bioactive Compounds from Fingerroot (*Boesenbergia rotunda* L.) as Inhibitor of Atherosclerosis-Related Proteins (CETP, ACAT1, OSC, sPLA2): An in silico Study. *Jordan Journal of Pharmaceutical Sciences.* 2023; 16(3):550–564. doi: 10.35516/jjps.v16i3.1609.
24. Girija A.S.S, Gunasekaran S., Habib S., Aljeldah M., Al Shammari B.R., Alshehri A.A., Alwashmi A.S.S., Turkistani S.A., Alawfi A., Alshengeti A., Garout M., Alwarthan S., Alsubki R.A., Moustafa N.M. and Rabaan A.A. Prediction of Putative Epitope Peptides against BaeR Associated with TCS Adaptation in Acinetobacter baumannii Using an In Silico Approach. *Medicina (Kaunas).* 2023; 59(2):343. doi: 10.3390/medicina59020343.
25. Uma Maheswari K. and Sankar S. In Silico Molecular Docking of Phytochemicals of Murraya koenigii Against Streptococcus mutans. *Cureus*. 2024; 16(2):e53679. doi:10.7759/cureus.53679
26. Suresh M., Sai K.V., Mitra K., Ravindran R. and Doble M. A network pharmacology-based approach to understanding the mechanism of action of anti-mycobacterial activity of Acacia nilotica: a modeling and experimental study. *Mol Divers*. doi:10.1007/s11030-024-10985-8

الفحص الافتراضي للأهداف الجزيئية لمادة الإمودين ضد مسببات الأمراض المعقدة الحمراء

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ملخص

الهدف: التهاب دواعم السن هو مرض التهابي مزمن يصيب الأنسجة الداعمة للأسنان. يحدث بسبب أنواع بكتيرية معينة، بما في ذلك (Pg) *Porphyromonas gingivalis*، و *Tannerella forsythia* (Tf)، و *Treponema denticola*)، والمعروفة بمجموعة "المركب الأحمر ."تستغل هذه البكتيريا الاستجابة المناعية وتعزز تدمير الأنسجة، مما يجعلها عناصر أساسية في مسببات أمراض دواعم السن. تهدف الدراسة الحالية إلى تحديد الأهداف الجزيئية المحتملة لمركب الإيمودين ضد مسببات الأمراض من مجموعة المركب الأحمر.

الطريقة: تم تحديد التفاعل بين المركب النباتي إيمودين ومسببات الأمراض من مجموعة المركب الأحمر باستخدام أداة .STITCHثم تم تصنيف البروتينات التي تم تحديدها إلى فئات وظيفية باستخدام أداة .VICMPred وبعد ذلك، تم إخضاع البروتينات الفيروسية لتوقعات Bepired، التي قدمت معلومات حول الحواتم في البروتينات الفيروسية. وأخيراً، تم تحديد الموقع داخل الخلية للبروتينات باستخدام أداة .pSORTb

النتائج: تم تحديد سينثاز كارباموبل فوسفات كوحدة فرعية كبيرة كأحد البروتينات الفيروسية في Pgو.Tf كما وُجد أن وحدة DNA topoisomerase IV الفرعية A هي البروتين الفيروسي المشترك بين Pgو.Td وُجد أن وحدة DNA gyrase الفرعية A والبروتين المحتوي على نطاقات /ATPaseكيناز الهستيدين/ DNA gyrase B/HSP90 تم تحديدهما في Td و.Tf كان هذا البروتين الوحيد المتوقع أن يكون في غشاء السيتوبلازم، بينما وُجدت البروتينات الأخرى في السيتوبلازم. وُجد أن البروتينات الفيروسية الأربعة المستهدفة بواسطة إيمودين تحتوي على حواتم متعددة.

الخلاصة: وُجد أن الإيمودين يتفاعل مع جميع مسببات الأمراض الثلاثة من مجموعة المركب الأحمر. ومع ذلك، هناك حاجة لمزيد من التجارب لإثبات التأثير المضاد للميكروبات للإيمودين ضد مسببات أمراض دواعم السن.

الكلمات الدالة: الإيمودين، مسببات الأمراض المعقدة الحمراء، الحواتم، الأدوات الحسابية، البروتين الضار.

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تاريخ استلام البحث 2024/02/06 وتاريخ قبوله للنشر 2024/06/14.