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Virtual Screening to Identify Protein Targets of Aggregatibacter Actinomycetemcomitans Interacting with Emodin

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Authors' contributions

This work was carried out in collaboration among all authors. Author RP designed the study, wrote the protocol, and wrote the first draft manuscript. Authors MJ and JVP managed the analyses of the study. Author SJ managed the literature searches. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Aim: The aim of the study is to identify protein targets of *aggregatibacter actinomycetemcomitans* interacting with emodin.
Introduction: *Aggregatibacter mycetemcomitans* is a gram negative bacteria that is associated with localized chronic periodontitis and other systemic diseases. The organism produces a number of virulence factors which provides some benefits to the bacterium. In this study, protein targets of *Aggregatibacter actinomycetemcomitans* interacting with emodin were identified.
Methodology: The present study follows an observational study design wherein we employed computational tools used to identify the targets, assess its functional role and virulence property.

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The protein targets in the bacteria were identified by virtual screening by using emodin as the compound.
Results: Peptide epitopes present in the virulence factors were identified using the BepiPred tool. The subcellular location of the protein targets were elucidated using emodin as the phytocompound. The 3 - Deoxy - D - manno octulosonic acid, ArcB, hypothetical protein and Arabinose - 5 - phosphate isomerase were found to be virulent.
Conclusion: Within the limits of this study, it provides substantial evidence on the protein targets acting against emodin.

Keywords: Aggregatibacter; emodin; novel method; periodontitis; protein targets.

1. INTRODUCTION

Oral cavity hosts an abundant collection of microorganisms known to be associated with diseases like periodontitis, dental caries and also deep-seated infections. It is considered to be a perplexing task to eliminate such pathogens from the site of infection, due to which antibiotics are needed. The use of antimicrobial in the clinical setting was considered a “miracle cure” for dangerous diseases [1]. Recent times, overuse of antibiotics have led to the emergence of drug resistance in microbial pathogens. This situation demands identification of novel therapeutic agents which can be used against the drug resistant species. Several bioactive compounds from plant, animal, marine sources have been extensively tested *in vitro* and *in vivo* to elucidate their potential as a antimicrobial agent.

Aggregatibacter actinomycetemcomitans is strongly known to be associated with periodontitis in young adults [2,3] and also with non oral infectious disease such as endocarditis [4]. It’s prevalence varies widely with geographic location, age, lifestyle and population [5]. There are 7 serotypes (a-g) that form genetically divergent lineages [6,7]. The mechanisms by which *A. actinomycetemcomitans* cause loss of attachment, are not entirely known. It produces a cytolethal distending toxin which kills host cells like gingival fibroblasts by blocking their proliferation [8]. Vesicles from gram negative bacteria carry out a number of functions including targeted virulence factors and tissues to manipulate host response [9,10].

Our team has extensive knowledge and research experience that has translate into high quality publications [11-30]. The aim of the study is to identify protein targets of *aggregatibacter actinomycetemcomitans* interacting with emodin.

2. MATERIALS AND METHODS

The study aims to screen protein targets in *A. actinomycetemcomitans* that could possibly interact with emodin. The interaction of those protein targets were analyzed using STITCH V.5 pipeline and the virulence properties of the interacting proteins were deduced by VICMPred and VirulentPred softwares. *A. actinomycetemcomitans* was the organism used and the compound chosen was emodin which was queried using the STITCH database.

The present study follows an observational study design which aims to screen for those proteins or virulence factors interacting with emodin. The STITCH v5.0 pipeline was primarily used for identifying protein interactions; VirulentPred and VICMPred were used for elucidating the virulence property and functional class of the proteins. The subcellular localization of virulent proteins was then assessed using PSORTb v3.0 and the epitopes were identified using BepiPred v1.0 Linear Epitope Prediction.

VIC Mpred13 and Virulent Pred14 pipelines were used for the identification of virulence factors. Virulence factors were screened based on amino acid composition using VirulentPred tool which classified them into two groups, virulent and avirulent. VICMpred groups proteins into four major classes such as, proteins involved in cellular process, metabolism, information storage, and virulence. The overall accuracy of VICMpred and VirulentPred servers were 70.75% and 86%, respectively. The FASTA format of the proteins retrieved from NCBI database were used as an input to run the algorithm.

3. RESULTS AND DISCUSSION

Epitopes are antigen determining sites for the confirmation of virulent properties. In this study, emodin was the drug that was used to determine its interaction with the *A. actinomycetemcomitans* which is the pathogen. Fig. 1 shows the protein interaction network of *A. actinomycetemcomitans* with emodin. Fig. 2 shows Epitope prediction (A)

3-deoxy-D-manno-octulosonic acid kinase (B) Aerobic respiration control sensor protein ArcB (C) Hypothetical protein (D) Arabinose 5-phosphate isomerase along with the predicted peptides. The graph depicts the green colour as avirulent and yellow as virulent.

Emodin is a potential compound with antibacterial property against *Aggregatibacter*. Four proteins were identified as virulent in the study, as seen in Table 1. The growth and acid production of S. mutans were significantly inhibited by emodin (0.5–2 mg/ml). Emodin also significantly suppressed the synthesis of insoluble glucans by S. These results suggest that the natural compound emodin may be a novel pharmacological agent for the prevention and treatment of dental caries.

In silico validation is inevitable while choosing a compound to be tested under in vitro and in vivo conditions. It provides clues about the pathway which can be targeted during preliminary screening [31]. The present study has been designed to identify the potential interactions with the protein targets with emodin. A study [32] reported the process of inhibition by reserpine where the phytocompound interacts with the transporters of red complex pathogens [33]. The proteins were found in the cytoplasm membrane of the bacteria [34].

ABC transporters play a major role in adherence and ATP - binding cassette [35,36]. Emodin has anti-bacterial activity which has been elucidated in several studies [38]. Most in vitro studies confirmed anti-bacterial activity and its mechanisms observed inhibition of DNA replication, cell membrane damage and biofilm formation reduction [39]. Although the in silico tools provide preliminary data on the molecular interaction between the compound and protein network of *A. actinomycetemcomitans*, there exists some limitations in the study - experimental approach, Emodin in biological system may not be same and it should target only bacterial protein not host protein so to avoid the undesirable interactions with host proteins, it is imperative to conduct in vitro and in vivo experiments, to gain some clarity on the use of phytocompounds on hosts without any adverse effects [40]. Mechanisms observed generally are inhibition of bacterial DNA replication, damage to cell membrane, activity against Plasmids, down regulation of efflux pumps, reduced biofilm formation [41]. The mechanisms which leads to the susceptibility of bacteria have to be

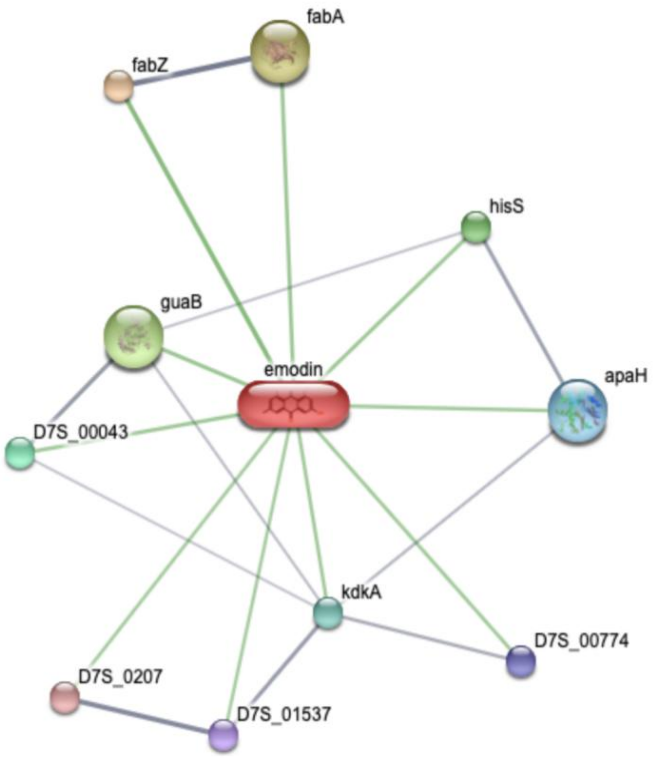
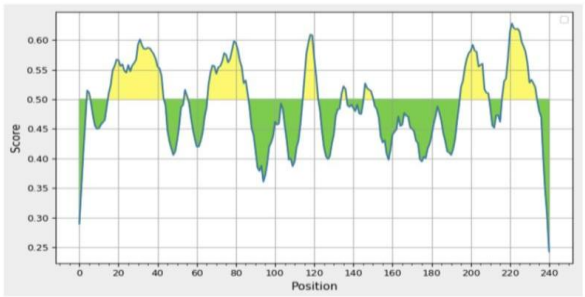


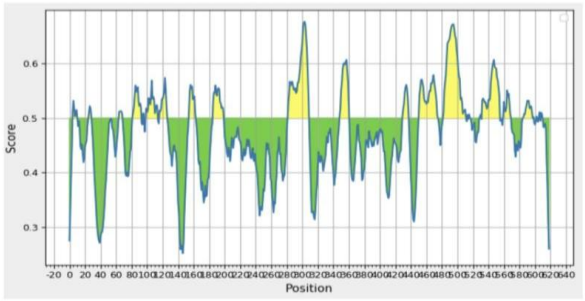
Fig. 1. Protein interaction network of *Aggregatibacter actinomycetemcomitans* with emodin



Predicted peptides:

No.	Start	End	Peptide	Length
1	5	6	QL	2
2	16	44	DQPLANQTQFFEAAFWQQQNRVIGAAKGR	29
3	55	56	LF	2
4	67	87	RGGLWGKINKDRYHFSELKNT	21
5	116	123	KGNLGMCY	8
6	135	137	ARD	3
7	147	151	LESTQ	5
8	196	210	CGEKSGRFWKEANLQ	15
9	217	234	NKEAARMHIHFTEQNWQD	18

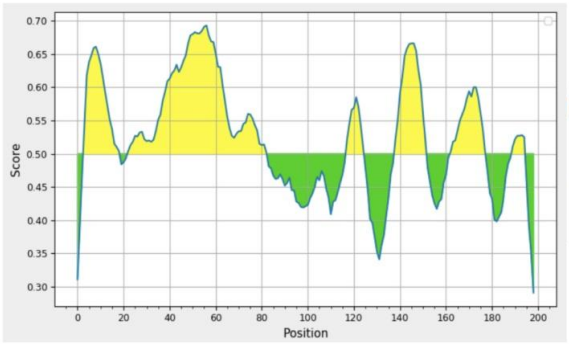
(B)



Predicted peptides:

No.	Start	End	Peptide	Length
1	5	11	KDFVRDF	7
2	26	29	RFSL	4
3	65	69	FGLIS	5
4	82	93	EKLEHSRQALSC	12
5	96	96	E	1
6	99	114	RREVQERVSAEKKLSE	16
7	117	127	DNLEKINRDKT	11
8	155	163	NPSERQQNY	9
9	186	199	KIDAKRIELNRKAT	14
10	283	309	IGIVEQDLQKIFELYYQAGSDANKSLG	27
11	349	361	AIKFVEEDEHLFL	13
12	430	438	QNYENGVYD	9
13	451	475	VQKKQEYLAQGMDDVIHKPLSLEEL	25
14	483	512	FGEELTQFNLPSNKPQAESVELDTKMLTEL	30
15	514	514	E	1
16	516	517	LG	2
17	530	531	QT	2
18	533	555	QDYVAELQQAYQAYLNDPHTQPE	23
19	560	569	VHKIKGALAS	10
20	586	599	DTADWQGNIAHWVN	14
21	603	603	K	1
22	606	607	QT	2
23	609	610	VA	2

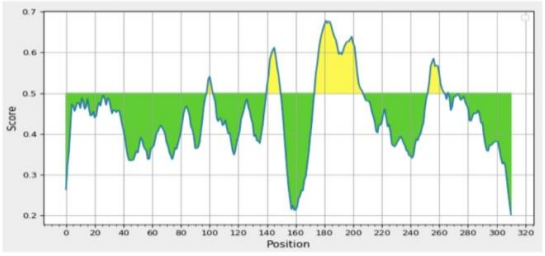
(C)



Predicted peptides:

No.	Start	End	Peptide	Length
1	4	19	SDDKQANLTGLHVLNP	16
2	23	83	LEHQHSSPSSALTDNNRSTHAQSAVNANSTQSAVNSHRVSSRYEKYDYPGRYQRDEQGKQC	61
3	118	125	HINPAFNQ	8
4	139	152	TGVLEEEAGESGNY	14
5	163	178	HTLWRSPQKPRPIIRG	16
6	190	195	KKSIVI	6

(D)



Predicted peptides:

No.	Start	End	Peptide	Length
1	99	103	ETDDV	5
2	141	150	EREVCPNNLA	10
3	174	207	DFQPEDFAKFHPGGSLGRRLLCRVKDQMQTHLPI	34
4	253	264	NGAETLNKTAQE	12
5	267	267	T	1

Fig. 2. Epitope prediction (A) 3-deoxy-D-manno-octulosonic acid kinase (B) Aerobic respiration control sensor protein ArcB (C) Hypothetical protein (D) Arabinose 5-phosphate isomerase

Table 1. Proteins of aggregatibacter actinomycetemcomitans interacting with emodin

Organism	Identifier	Proteins which interacts with emodin	VICMPred Functional Class	Virulent Pred	Virulent Pred Score
Aggregatibacter actinomycetemcomitans	D7S_0123	Beta-hydroxydecanoyl thioester dehydrase	Cellular Process	Avirulent	-1.024
	D7S_0947	FabA protein	Metabolism	Avirulent	-1.010
	D7S_1931	Histidyl-tRNA synthetase	Cellular Process	Avirulent	-1.055
	D7S_1159	Diadenosine tetraphosphatase	Metabolism	Avirulent	-0.788
	D7S_0791	Murein transglycosyllase C	Metabolism	Avirulent	-0.339
	D7S_0879	3-deoxy-D-manno-octulosonic-acid kinase	Metabolism	Virulent	0.5992
	D7S_1569	Aerobic respiration control sensor protein ArcB	Cellular Process	Virulent	1.0580
	D7S_0207	Hypothetical protein	Cellular Process	Virulent	0.9795
	D7S_0043	Arabinose 5-phosphate isomerase	Cellular Process	Virulent	1.0306
	D7S_2311	Inosine-5'-monophosphate dehydrogenase	Metabolism	Avirulent	-1.079

addressed by performing in vitro experiments to expand the use of such drugs and justify their entry as bactericidal agents. A few limitations of the study are as follows: 1) the drug-protein interactions may be purely physical, that may or may not lead to functional consequences, 2) certain proteins of host may share homology with the bacterial proteins, so the targets should be carefully chosen to avoid adverse effects in the host and 3) the protein interactions evidenced by in silico method may not mimic the type of interactions happening in vivo, as other complex proteins in the vicinity might interfere with the functional pathway confirmed [42].

Further research in this area may also aid in identifying the synergistic and antagonistic effect of these drugs in combination with routine antibiotics, which might open new avenues for handling deadly pathogens in the antibiotic resistant era.

4. CONCLUSION

The study identified the protein targets in A. actinomycetemcomitans interacting with emodin through virtual screening, which has to be further validated. This study is the first of its kind which aims in understanding the protein targets against the specific phytocompound.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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