# Virtual screening to identify protein targets of *Aggregatibacter actinomycetemcomitans* interacting with emodin


## 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. 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 (11–23),(24–28) (29) (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.

VICMpred13 and VirulentPred14 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. Figure 1 shows the protein interaction network of *A. actinomycetemcomitans* with emodin. Figure 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 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.

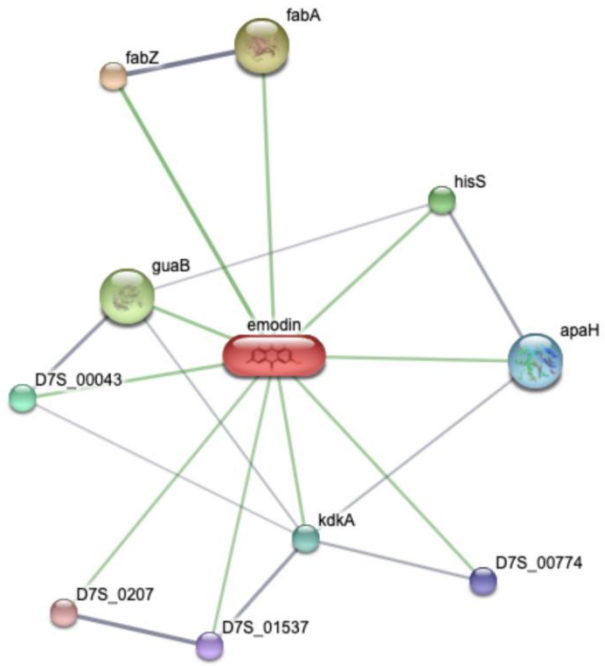
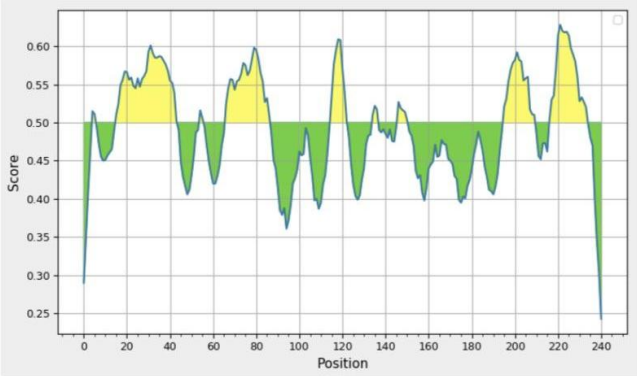


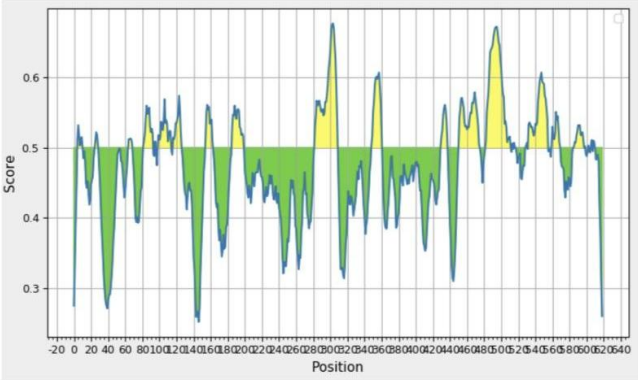

**Fig. 1. Protein interaction network of *Aggregatibacter actinomycetemcomitans* with emodin**




**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 |

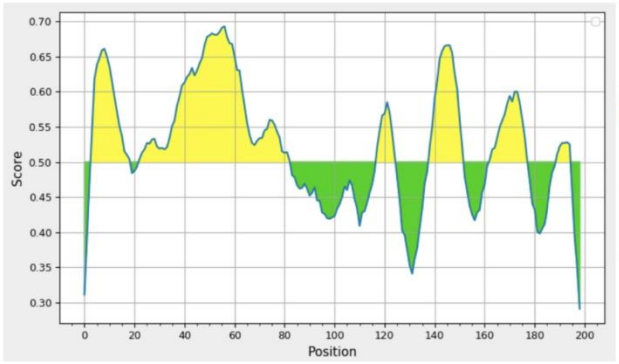
(B)




**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 | AIKPVEEDEHLPL | 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 |

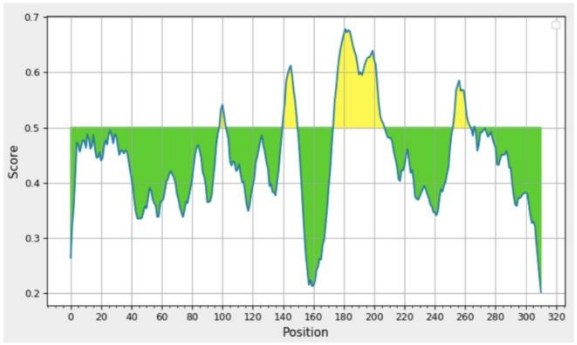
(C)




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 |

## 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.

**COMPETING INTERESTS DISCLAIMER:**

Authors have declared that no competing interests exist. 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.

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