Research Article

An *in silico* study on the protein network interaction induced by capsaicin against dental pathogens

A. Alagu Rathi Bharathi[1], A. S. Smiline Girija[1], J. Vijayashree Priyadharsini[2]*

ABSTRACT

Introduction: The present investigation is designed to analyze the possible protein interactions of the potent phytocompound capsaicin with the common dental pathogens together with the assessments of functional class of the proteins, virulence nature, and subcellular location using *in silico* tools. **Materials and Methods:** The study follows an *in silico* design, where computational tools are used to derive the preliminary data on the molecular interactions of the drug with the protein repertoire of the pathogens. The interaction was assessed by the STITCH tool followed by the evaluation of the functional class of the protein and its virulence using VICMPred and VirulentPred. PSORTb and BepiPred were used to identify the subcellular location and epitopes on the virulent protein targeted by capsaicin. **Results:** Several virulence factors were found to be targeted by capsaicin. Molecular chaperone was found to be the common virulence factor in most of the pathogens followed by choloylglycine hydrolase of *Enterococcus faecalis*, conserved hypothetical protein of *Streptococcus mutans*, ABC transporter ATP-binding protein and superoxide dismutase of *Porphyromonas gingivalis*, and pyruvate kinase of *Treponema denticola* and *Tannerella forsythia.* **Conclusion:** Capsaicin could be used as an antimicrobial agent, especially against dental pathogens as it was found to target some of the crucial proteins such as molecular chaperones of the dental pathogens.

KEY WORDS: Capsaicin, Chaperons, Dental pathogens, *In silico*, Transporters

INTRODUCTION

Dental infections pose a significant health burden in India. Common dental diseases such as dental caries affect over 60–65% of the population, while periodontitis affects 50–90% of the general population.[1] The predominant dental pathogens associated with these diseases are *Streptococcus mutans* and *Enterococcus faecalis*, and the red complex pathogens, namely, *Porphyromonas gingivalis, Treponema denticola,* and *Tannerella forsythia.* Routine drug therapy may impose a selective pressure on the organism which transforms them into resistant forms. An alternative method to avoid synthetic or semisynthetic drug usage is to shift to phytocompounds which play an important role in arresting as well as prove to be relatively non-toxic to the host.

In addition, the emergence of drug resistance among dental pathogens has made the dental treatment procedures complex and time consuming. Furthermore, the adverse effects of drugs prescribed for combating such resistant forms are immense, leading to decline in the health of the host. The prevalence of drug-resistant species in the community is replicated in the dental settings. Several dental pathogens or even commensals have acquired genes from the organism at the vicinity to transform into a more refractory form.[2,3] Hence, there is an urgent need to identify compounds which may prove safe and efficacious against these pathogens.

Capsaicin (8-methyl-N-vanillyl-6-nonenamide) is an active pungent component of the chili pepper, *Capsicum* plants. They are grown for food and for some medicinal purpose such as pain relief, cancer

Access this article online

Website: jprsolutions.info | ISSN: 0975-7619

[1]Department of Microbiology, Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India, [2]Biomedical Research Unit and Laboratory Animal Centre-Dental Research Cell, Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India

Corresponding author: Dr. J. Vijayashree Priyadharsini, Biomedical Research Unit and Laboratory Animal Centre-Dental Research Cell, Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India. Phone: +91-9941125984. E-mail: viji26priya@gmail.com

Received on: 21-06-2019; Revised on: 28-07-2019; Accepted on: 23-08-2019

prevention, cardioprotective, and gastrointestinal effects.[4] Capsaicinoids from *Capsicum* have shown potent activity against the methicillin-resistant *Staphylococcus aureus* strains and had documented their inhibitory effect on the conjugal transfer of R-plasmids harbored in *Escherichia coli*.[5] Nanoformulations of *Capsicum* biocompounds had created interest in the drug targeting and drug delivery systems.[6] The bactericidal activity of capsaicin against erythromycin-resistant, cell-invasive pharyngeal Group A *Streptococcus* adds to the potential use of the compound in clinical settings. It was found that the sublethal concentrations inhibited cell invasion and reduced hemolytic activity, which is regarded as important virulence traits of *Streptococci*. Inhibition of intracellular invasion and hemolytic activity by capsaicin proves that it could be a promising candidate for eradication of pathogens that can cause infections of deep tissues.[7] Reports from different experiments showed that even a low capsaicin concentration was reported to reduce bacterial virulence when tested *in vitro* among both Gram positives and Gram negatives.[8,9]

The reports on antimicrobial properties have attracted attention toward using capsaicin against dental pathogens too, with only few reports. In this context, the present *in silico* study was designed to assess the possible interactions of capsaicin with the protein repertoire of common dental pathogens.

MATERIALS AND METHODS

Strains Used in the Study

Using the STITCH database, the following dental strains available were selected for the present study, namely, *S. mutans* UA159, *Enterococcus faecalis* V583, *Porphyromonas gingivalis* ATCC 33277, *Treponema denticola* ATCC 35405, and *Tannerella forsythia* ATCC 43037.[10]

Analyzing Protein Interaction Network

The repertoire of the proteins from *S. mutans*, *Enterococcus faecalis*, *Porphyromonas gingivalis, Treponema denticola,* and *Tannerella forsythia* was evaluated using an exhaustive pipeline named STITCH tool[10] and further assessed for their interactions with capsaicin. The prediction of functional class and virulence properties of proteins were done after retrieving the sequences in FASTA format from the National Center for Biotechnology Information domain.[11]

Prediction of Functional Class of Interacting Proteins

The predicted proteins were classified into four major classes, namely, virulence factors, information and storage processing, cellular process, and metabolism using VICMpred server which aid in the classification of pathogenic microbial proteins. Virulence factors were designated based on the support vector machine (SVM) algorithm which classifies protein based on their amino acid composition and sequence pattern.[12]

Prediction of Virulence Properties of Interacting Protein

To substantiate the antimicrobial activity of the phytocompound capsaicin and to be targeted, the virulent proteins were predicted using VirulentPred tool, which is yet another SVM-based method, used for automated prediction of virulent proteins based on the sequences.[13] The scores with positive predicted values are more often categorized into virulent protein and those with negative predicted values are categorized as avirulent proteins.[14]

Prediction of B-cell Epitopes in the Virulence Proteins

Epitopes being the specific small regions on the antigens and to be recognized by antibodies, prediction of B-cell epitopes on the virulence proteins identified from the dental pathogens using BepiPred 2.0 server. The yellow peaks in the graph represent the peptide epitopes present in the virulent protein.[15,16]

Prediction of Subcellular Localization of Proteins

The identification of the subcellular localization of virulence proteins is of prime importance as the efficiency of the compound lies in target identification. Cell surface proteins are readily targeted, while the cytoplasmic or nuclear proteins need proper drug delivery systems to target the protein of interest. Hence, PSORTb V.3.0 was used for the identification of subcellular location of virulence proteins.[17]

RESULTS

Capsaicin showed promising interactions with multiple proteins predicted from the dental pathogens understudy [Figure 1]. Among the entire protein pool, molecular chaperone encoded by the gene dnaK in *S. mutans, E. faecalis, P. gingivalis,* and *T. denticola* was found to be the virulence factor. Apart from them, other proteins such as Trp-synth-beta_II of *E. faecalis* conserved hypothetical protein PksD of *S. mutans* and ABC transporter ATP-binding protein of *T. forsythia* were also found to possess the virulence nature as predicted by VICMPred. Certain other proteins such as choloylglycine hydrolase family protein of *E. faecalis*, ABC transporter ATP-binding protein MsbA family of *P. gingivalis*, pyruvate kinase, and superoxide dismutase of *T. forsythia* were also found to be virulent in nature, as predicted by VirulentPred software [Table 1]. All the proteins identified belong to either of the functional class, namely, cellular process, metabolism, and virulence factor. The virulent proteins were located in the cytoplasm, cytoplasmic membrane,

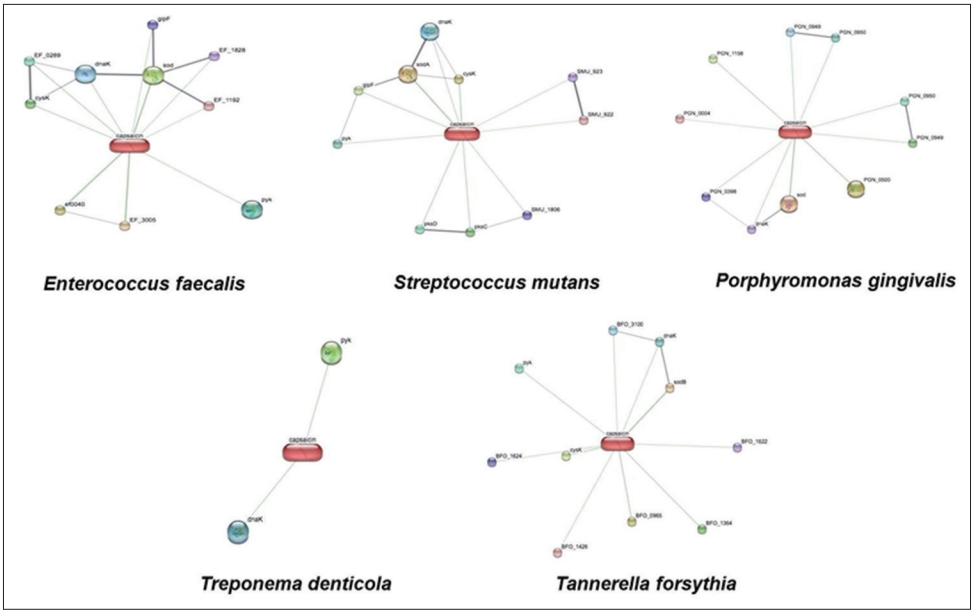

Figure 1: Interaction of capsaicin with the protein repertoire of oral pathogens

Table 1: List of proteins of oral pathogens which interacts with capsaicin

Organism	Identifier	Proteins which interacts with capsaicin	VICMPred functional class	VirulentPred	VirulentPred score
Enterococcus faecalis	EF_1828	Glycerol uptake facilitator protein	Metabolism	Avirulent	−1.004
	EF_1192	Aquaporin Z	Cellular process	Avirulent	−0.999
	EF_3005	Choloylglycine hydrolase family protein	Cellular process	Virulent	1.0418
	EF_0289	Cysteine synthase B, putative	Metabolism	Avirulent	−1.001
	ef0040	Choloylglycine hydrolase	Cellular process	Virulent	1.0489
	dnaK	Molecular chaperone DnaK	Virulence factor	Avirulent	−1.032
	cysK	Trp-synth-beta_II	Virulence factor	Avirulent	−1.048
	sodA	Superoxide dismutase	Metabolism	Avirulent	−1.024
	glpF	MIP family glycerol uptake facilitator protein GlpF	Metabolism	Avirulent	−1.004
Streptococcus mutans	SMU_923	ABC transporter ATP-binding protein	Cellular process	Avirulent	−1.056
	SMU_922	ABC transporter ATP-binding protein	Metabolism	Avirulent	−1.070
	SMU_1806	Glycosyltransferase	Cellular process	Avirulent	−0.633
	dnaK	Chaperone protein DnaK	Virulence factor	Avirulent	−0.993
	cysK	Cysteine synthaseA	Metabolism	Avirulent	−1.028
	sodA	Superoxide dismutase [Mn/Fe]	Cellular process	Avirulent	−0.996
	glpF	Glycerol uptake facilitator protein	Metabolism	Avirulent	−1.006
	pyk	Pyruvate kinase	Metabolism	Avirulent	−1.125
	pksD	Conserved hypothetical protein PksD involved in polyketide synthesis	Virulence factor	Virulent	1.0032
	pksC	Putative PKS biosynthesis protein	Metabolism	Avirulent	−1.029
	PGN_0950	ABC transporter ATP-binding protein	Metabolism	Avirulent	−1.007
	PGN_0949	ABC transporter ATP-binding protein	Metabolism	Avirulent	−0.276
		Methylmalonyl-CoA decarboxylase alpha subunit	Metabolism	Avirulent	−1.079

(Contd...)

Table 1: ***(Continued)***

Organism	Identifier	Proteins which interacts with capsaicin	VICMPred functional class	VirulentPred	VirulentPred score
	PGN_0398	ABC transporter ATP-binding protein MsbA family	Cellular process	Virulent	1.001
	PGN_0004	Putative nicotinate mononucleotide: 5,6-dimethylbenzimidazole phosphoribosyltransferase	Cellular process	Avirulent	−1.001
	PGN_1158	Putative purine nucleoside phosphorylase	Metabolism	Avirulent	−1
	dnaK	Molecular chaperone DnaK	Virulence factor	Avirulent	−0.992
	sod	Superoxide dismutase	Metabolism	Virulent	0.9851
Treponema denticola	*pyk*	Pyruvate kinase	Metabolism	Virulent	0.897
	dnaK	Molecular chaperone DnaK	Virulence factor	Avirulent	−0.963
Tannerella forsythia	BFO_3100	Antibiotic ABC transporter ATP-binding protein	Metabolism	Avirulent	−1.035
	BFO_1622	ABC transporter ATP-binding protein	Metabolism	Avirulent	−0.923
	BFO_1364	Phosphorylase	Cellular process	Avirulent	−0.808
	BFO_0965	Methylmalonyl-CoA carboxyltransferase	Metabolism	Avirulent	−1.012
	BFO_1426	Conserved hypothetical protein PksD, ABC transporter ATP-binding protein	Virulence factor	Avirulent	−1.012
	BFO_1624	ABC transporter ATP-binding protein	Metabolism	Avirulent	−1.023
	pyk	Pyruvate kinase	Cellular process	Virulent	0.8206
	cysK	Cysteine synthase	Metabolism	Avirulent	−1.005
	dnaK	Chaperone protein DnaK	Metabolism	Avirulent	−0.954
	sodB	Superoxide dismutase [Mn/Fe]	Cellular process	Virulent	0.8912

while proteins such as superoxide dismutase were found to secrete extracellularly [Table 2]. Peptide epitopes were also identified in the virulent proteins which confirm the antigenic potential of these proteins [Figure 2]. It is quite evident from the results that capsaicin has the potential to target crucial proteins of the dental pathogens.

DISCUSSION

In the present study, we successfully predicted the potent target proteins using computational tools among the most common dental pathogens that induce serious complications in the dental patients if untreated. Amid many potent phytocompounds, capsaicin had spurred renewed interest in recent years for its promising pharmacological activities. In South India, it has been used in various culinary preparations. Several researchers have demonstrated the bactericidal effect of capsaicin against food-borne pathogens such as *Helicobacter pylori*, *Bacillus cereus, Bacillus subtilis, Enterobacter aerogenes,* and *Pseudomonas aeruginosa*.[18,19] In view with this, the present study has documented the possible interactions with potent proteins from the dental pathogens *E. faecalis, S. mutans, P. gingivalis, T. denticola,* and *T. forsythia* with capsaicin. Maximum protein interactions were observed against *S. mutans* and *T. forsythia* (n = 10) followed by *E. faecalis* and *P. gingivalis* (n = 8). Minimum interactions (n = 2) were observed with *T. denticola*.

VICMPred for the functional classes of the putative proteins from the dental pathogens showed capsaicin interactions with the proteins involved with metabolic processes. Cysteine synthases of *S. mutans*, *E. faecalis,* and *T. forsythia* were the main metabolic proteins targeted by capsaicin. Cysteine is an essential amino acid playing a key role in the catalytic activity of many structural proteins and their residues are vital in the synthesis of ubiquitous proteins such as cytochromes. In addition, they also have role in maintaining the intracellular oxidative stress mechanisms.[20] Cysteine residues also play a key role in the formation of disulfide bonds in the activation of the transcription regulators and the molecular chaperones in bacterial cells.[21] *In silico* assessments of capsaicin with the cysteine synthase in the potent dental pathogens suggest that it could be an effective drug of choice with further experimental evaluations.

Table 2: Subcellular localization of virulence proteins targeted by capsaicin

Organism	Protein	Subcellular location
Enterococcus faecalis	Choloylglycine hydrolase family protein	Unknown
	Choloylglycine hydrolase	Unknown
Streptococcus mutans	Conserved hypothetical protein	Unknown
Porphyromonas gingivalis	ABC transporter ATP-binding protein MsbA family	Cytoplasmic membrane
	Superoxide dismutase	Extracellular
Treponema denticola	Pyruvate kinase	Cytoplasm
Tannerella forsythia	Pyruvate kinase	Cytoplasm
	Superoxide dismutase	Extracellular

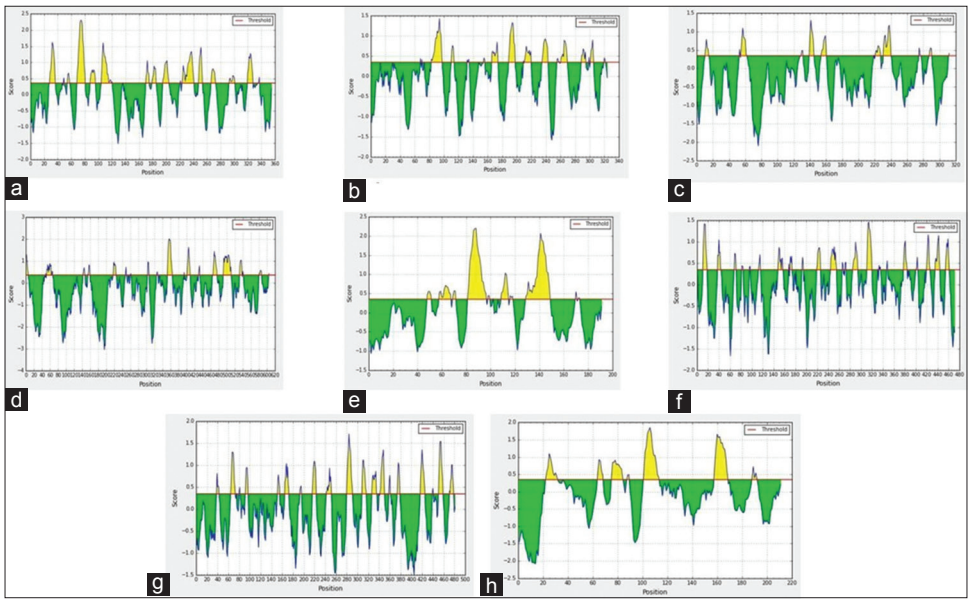

Figure 2: Peptide epitopes identified in (a) choloylglycine hydrolase family protein, (b) choloylglycine hydrolase of *Enterococcus faecalis,* (c) conserved hypothetical protein PksD, involved in polyketide synthesis of *Streptococcus mutans*, (d) ABC transporter ATP-binding protein MsbA family, (e) superoxide dismutase of *Porphyromonas gingivalis,* (f) molecular chaperone DnaK of *Treponema denticola,* (g) conserved hypothetical protein PksD, ABC transporter ATP-binding protein, and (h) superoxide dismutase of *Tannerella forsythia*

Functional class protein analysis among the dental pathogens understudy also predicted few proteins that were highly involved with cellular processes. These include choloylglycine hydrolase family protein, ABC transporter ATP-binding protein, glycosyltransferases, superoxide dismutase [Mn/Fe], and phosphorylase pyruvate kinase. Choloylglycine hydrolase has its role to form the bile salt hydrolase derivatives that help the dental pathogens and other clinical pathogens in establishing virulence in the host tissues.[22] Similarly, ABC transporters along with ATP-binding protein have its role in the primary and secondary membrane transport channel in the cell membrane of various bacterial pathogens.[23] In the present study, we observed that capsaicin interacted with this channel protein from *S. mutans*, *P. gingivalis,* and *T. forsythia*. Glycosyltransferases SMU_1806 from *S. mutans* was yet another functional protein targeted by capsaicin. This yields a preliminary clue about capsaicin inhibiting the glucose synthesis pathway in bacteria as glucosyltransferases are involved in the active breakdown of sugar moieties and leading to the plaque formation in dental biofilms.[24]

Superoxide dismutase is yet another cellular process protein targeted by capsaicin in *S. mutans* (*SodA*) and *P. gingivalis* (*SodB*). Superoxide dismutases are enzymes present in most of the dental pathogens and are involved in the vital oxidation-reduction mechanism resulting in oxygen tolerance or antioxidative reactions in the host tissues.[25] Capsaicin targeting the same is a good indication toward its novel candidature in drug designing against the dental pathogens. A minimum inhibitory concentration (MIC) and a minimum bactericidal concentration (MBC) of 16 and 64 mg/l, respectively, of capsaicin have been shown to inhibit *P. gingivalis* and the biofilm formation was arrested at minimum biofilm inhibition concentrations $MBIC_{50}$ and $MBIC_{90}$ of 16 and 32 mg/l, respectively.[26] In view with this, pyruvate kinases, namely, *pksC in S. mutans* and *pyk* in *T. forsythia* and *T. denticola* predicted in the present study were efficiently targeted by capsaicin proving its role in the inhibition of glucose

metabolism pathways and also aid in acid tolerance[27] documenting its role in biofilm inhibition on the tooth surfaces during colonization. Anti-virulence

activity of capsaicin was demonstrated against *Vibrio cholerae*,[9] *Staphylococcus aureus,* and *Porphyromonas gingivalis,*[28] and the analysis of the capsaicin interactions with the virulent protein was assessed for the same. We evaluated nearly eight virulent proteins using ViruPred tool interacting with capsaicin. Molecular chaperones are vital virulent proteins targeted by capsaicin from four dental pathogens understudy. Molecular chaperones help the prokaryotic bacteria during protein folding and help to avoid repairs in various vital structures.[29] In addition, four of the functional class proteins involved in the metabolism and cellular processes, namely, choloylglycine hydrolase, ABC transporter ATP-binding protein, superoxide dismutase [Mn/Fe], and phosphorylase pyruvate kinase were also predicted to be virulent proteins targeted by capsaicin. Subcellular location analysis showed pyruvate kinases from *T. forsythia* and *T. denticola* in cytoplasm. Superoxide dismutases from *P. gingivalis* and *T. forsythia* were assessed as extracellularly secreted and the choloylglycine hydrolase from *E. faecalis* and *S. mutans* was unable to predict their location.

We also assessed the possible epitome peptides on the virulent proteins among the dental pathogens that had yielded >15 epitopes in choloylglycine hydrolase family protein of *E. faecalis* and pyruvate kinase from *T. denticola* and *T. forsythia*. BepiPred server holds good in determining the antigenic peptides from the virulent proteins predicted by analyzing the threshold value each protein. In addition, PSORTb tool predicted the location of each virulent protein which could easily give us a preliminary clue in the drug delivery system. There is a good indication from the present study that the functional class of proteins predicted by the *in silico* tools had possible target structural proteins to be interacted with novel drug candidates such as capsaicin. Novel methodology using the computational tool in the present study aids in the promising candidature of potent compound like capsaicin as future drug of choice in treating dental infections or in the process of vaccine development.

The present study is the first of its kind throws light on the molecular targets of capsaicin in common dental pathogens. Although the study reveals the targets of capsaicin, there exist some limitations which should be addressed. First, the interaction between capsaicin and the proteins of dental pathogens may purely be physical rather than being functional. Second, the protein interactions observed *in silico* may not always occur in a complex biological environment. Third, the similarity between host and microbial proteins should also be investigated to avoid any adverse reaction toward host system. With all the factors revealed, capsaicin could be a promising drug in treating dental illness, provided, their role in *in vivo* conditions is properly examined and proved.

CONCLUSION

The present study gives a vivid picture on the molecular targets of capsaicin in dental pathogens. Further, *in vitro* and *in vivo* analyses are warranted to substantiate the role of capsaicin against dental pathogens. Since the oral cavity harbors a polymicrobial community, the study can be extended toward obligate anaerobes and other rare pathogens causing dental problems.

Compliance with Ethical Standards

This article does not contain any studies with human participants or animals performed by any of the authors.

REFERENCES

1. Lin S, Mauk A. Oral health: Addressing dental diseases in rural India. In: Raghavan R, Johar Z, editors. Implementing Public Health Interventions in Developing Countries. Thanjavur: ICTPH; 2012. p. 105-65.
2. Priyadharsini JV, Girija AS, Paramasivam A. Enterococcus faecalis an emerging microbial menace in dentistry-an insight into the in-silico detection of drug resistant genes and its protein diversity. J Clin Diagn Res 2018a;12:GC06-10.
3. Vijayashree Priyadharsini J, Smiline Girija AS, Paramasivam A. In silico analysis of virulence genes in an emerging dental pathogen A. baumannii and related species. Arch Oral Biol 2018;94:93-8.
4. Luo XJ, Peng J, Li YJ. Recent advances in the study on capsaicinoids and capsinoids. Eur J Pharmacol 2011;650:1-7.
5. Oyedemi BO, Kotsia EM, Stapleton PD, Gibbons S. Capsaicin and gingerol analogues inhibit the growth of efflux-multidrug resistant bacteria and R-plasmids conjugal transfer. J Ethnopharmacol 2019;245:111871.
6. Dima C, Coman G, Cotarlet M, Alexe P, Dima Ş. Antioxidant and Antibacterial Properties of Capsaicine Microemulsions. Ann Univ Dunarea Galati 2013;37:39-49.
7. Marini E, Magi G, Mingoia M, Pugnaloni A, Facinelli B. Antimicrobial and anti-virulence activity of capsaicin against erythromycin-resistant, cell-invasive group A streptococci. Front Microbiol 2015;6:1281.
8. Xu Q, Barrios CA, Cutright T, Zhang Newby BM. Evaluation of toxicity of capsaicin and zosteric acid and their potential application as antifoulants. Environ Toxicol 2005;20:467-74.
9. Chatterjee S, Asakura M, Chowdhury N, Neogi SB, Sugimoto N, Haldar S, *et al*. Capsaicin, a potential inhibitor of cholera toxin production in Vibrio cholerae. FEMS Microbiol Lett 2010;306:54-60.
10. Szklarczyk D, Santos A, von Mering C, Jensen LJ, Bork P, Kuhn M, *et al*. STITCH 5: Augmenting protein-chemical interaction networks with tissue and affinity data. Nucleic Acids Res 2016;44:D380-4.
11. Available from: https://www.ncbi.nlm.nih.gov/protein/?term=.
12. Saha S, Raghava GP. 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;4:42-7.
13. Available from: http://www.bioinfo.icgeb.res.in/virulent. [Last accessed on 2019 Jun 03].
14. Garg A, Gupta D. VirulentPred: A SVM based prediction method for virulent proteins in bacterial pathogens. BMC Bioinformatics 2008;9:62.
15. Larsen JE, Lund O, Nielsen M. Improved method for predicting

linear B-cell epitopes. Immunome Res 2006;2:2.
16. Jespersen MC, Peters B, Nielsen M, Marcatili P. BepiPred-2.0: Improving sequence-based B-cell epitope prediction using conformational epitopes. Nucleic Acids Res 2017;45:W24-W29.
17. Yu NY, Wagner JR, Laird MR, Melli G, Rey S, Lo R, *et al*. PSORTb 3.0: Improved protein subcellular localization prediction with refined localization subcategories and predictive capabilities for all prokaryotes. Bioinformatics 2010;26:1608-15.
18. Cowan MM. Plant products as antimicrobial agents. Clin Microbiol Rev 1999;12:564-82.
19. Omolo MA, Wong ZZ, Mergen AK, Hastings JC, Le NC, Reiland HA. Antimicrobial properties of chili peppers. J Infect Dis Ther 2014;2:1-8.
20. Lithgow JK, Hayhurst EJ, Cohen G, Aharonowitz Y, Foster SJ. Role of a cysteine synthase in Staphylococcus aureus. J Bacteriol 2004;186:1579-90.
21. Jakob U, Muse W, Eser M, Bardwell JC. Chaperone activity with a redox switch. Cell 1999;96:341-52.
22. Dean M, Cervellati C, Casanova E, Squerzanti M, Lanzara V, Medici A, *et al*. Characterization of cholylglycine hydrolase from a bile-adapted strain of Xanthomonas maltophilia and its application for quantitative hydrolysis of conjugated bile salts. Appl Environ Microbiol 2002;68:3126-8.
23. Wilkens S. Structure and mechanism of ABC transporters. F1000Prime Rep 2015;7:14.
24. Bowen WH, Koo H. Biology of Streptococcus mutans-derived glucosyltransferases: Role in extracellular matrix formation of cariogenic biofilms. Caries Res 2011;45:69-86.
25. De Vendittis A, Amato M, Mickniewicz A, Parlato G, De Angelis A, Castellano I, *et al*. Regulation of the properties of superoxide dismutase from the dental pathogenic microorganism Streptococcus mutans by iron- and manganese-bound co-factor. Mol Biosyst 2010;6:1973-82.
26. Zhou Y, Guan X, Zhu W, Liu Z, Wang X, Yu H, *et al*. Capsaicin inhibits Porphyromonas gingivalis growth, biofilm formation, gingivomucosal inflammatory cytokine secretion, and in vitro osteoclastogenesis. Eur J Clin Microbiol Infect Dis 2014;33:211-9.
27. Zhai Z, An H, Wang G, Luo Y, Hao Y. Functional role of pyruvate kinase from Lactobacillus bulgaricus in acid tolerance and identification of its transcription factor by bacterial one-hybrid. Sci Rep 2015;5:17024.
28. Qiu J, Niu X, Wang J, Xing Y, Leng B, Dong J, *et al*. Capsaicin protects mice from community-associated methicillin-resistant Staphylococcus aureus pneumonia. PLoS One 2012;7:e33032.
29. Lund PA. Microbial molecular chaperones. Adv Microb Physiol 2001;44:93-140.

Source of support: Nil; Conflict of interest: None Declared