Journal of Experimental Biology and Agricultural Sciences

http://www.jebas.org

ISSN No. 2320 – 8694

In silico targeting enterotoxin from *Staphylococcus aureus* with selected flavonoids: Hope for the discovery of natural anti-mastitis agents

Pawan Kumar[1], Poonam Bansal[2], Vivek Kumar Garg[3], Sonali Sangwan[2], Kuldeep Dhama[4], Deepak Chandran[5], Gurpreet Kaur Bhatia[6], Bhupesh Gupta[7], Hardeep Singh Tuli[2*]

[1]Institute of Plant Sciences, Agricultural Research Organisation (ARO), The Volcani Center, Rishon LeZion, 7505101, Israel
[2]Department of Biotechnology, Maharishi Markandeshwar Engineering College, Maharishi Markandeshwar (Deemed to be University), Mullana, 133207, India
[3]Department of Medical Laboratory Technology, University Institute of Applied Health Sciences, Chandigarh University, Gharuan, Mohali 140413, Punjab, India
[4]Division of Pathology, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly-243 122, Uttar Pradesh, India
[5]Amrita School of Agricultural Sciences, Amrita Vishwa Vidyapeetham University, Coimbatore, 642109, Tamil Nadu, India
[6]Department of Physics, Maharishi Markandeshwar Engineering College, Maharishi Markandeshwar (Deemed to be University), Mullana, 133207, India
[7]Department of Computer Science and Engineering, Maharishi Markandeshwar Engineering College, Maharishi Markandeshwar (Deemed to be University), Mullana, 133207, India

Received – October 21, 2022; Revision – February 06, 2023; Accepted – February 24, 2023
Available Online – February 28, 2023

DOI: http://dx.doi.org/10.18006/2023.11(1).132.139

KEYWORDS

Enterotoxin

S. aureus

Phytochemicals

Mastitis

Molecular docking

ABSTRACT

Staphylococcus aureus is a facultative anaerobe and catalase-positive bacterium responsible for various skin infections and life-threatening problems, including bacteremia and pneumonia. This bacterium produces a bunch of superantigens in the blood called enterotoxin. This toxin is responsible for food poisoning and toxic shock syndrome. Moreover, Bovine mastitis is also associated with *S. aureus*. Further, *S. aureus* related to drug resistance makes the infection more dreadful. Now a day, various natural compounds such as phytochemicals are gaining importance as they are effective against many diseases, including *S. aureus* infections. The present study used molecular docking of three ligands, i.e., Kaempferol, Apigenin, and Quercetin, with enterotoxin A from *S. aureus*. The docking study revealed that the binding energy of ligands with receptors was -6.6 to -6.9 Kcal/mol. Kaempferol had the highest binding affinity of -6.9 Kcal/mol, suggesting it has a potential against *S. aureus*. Therefore, in the current research, we have tried to identify occurring compounds that might be used to develop an effective anti-*S.aureus* agent. The findings are encouraging and will aid researchers in creating new mastitis-fighting medications based on natural phytochemicals.

* Corresponding author
E-mail: hardeep.biotech@gmail.com (Hardeep Singh Tuli)

Peer review under responsibility of Journal of Experimental Biology and Agricultural Sciences.

Production and Hosting by Horizon Publisher India [HPI] (http://www.horizonpublisherindia.in/).

1 Introduction

Gram-positive *Staphylococcus aureus* (*S. aureus*) bacteria can cause a superficial skin infection to severe illnesses like necrotizing pneumonia and bacteremia (Cheung et al. 2021). This bacterium can be detected in the normal skin microbiota of humans and animals, and healthy individuals carry it at 20-30% (Guo et al. 2020). *S. aureus*-caused bovine mastitis has cost the cattle breeding industry money due to decreased milk production and quality, higher culling and mortality rates, and other factors (Deb et al. 2013; Chakraborty et al. 2019). 30% of bovine mastitis is subclinical mastitis driven by *S. aureus* (Halasa et al. 2007; Sharun et al. 2021). According to studies, *S. aureus* infections resulted in the loss of 380 tonnes of milk annually worldwide (Loiselle et al. 2009; Zhou et al. 2018). Because of the high morbidity and antibiotic resistance prevalence, *S. aureus* infection is one of the most concerning infections for researchers and physicians. Antibiotic-resistant infections have been projected to have topped 10 million annual deaths, and by 2050, they will outnumber cancer deaths (Ahmad-Mansour et al. 2021). They showed high resistance to the majority of protein-degrading enzymes and hence continue to operate in the digestive tract after consumption. Developing an impressive list of protein toxins is crucial to *S. aureus* pathogenicity (Cassat and Thomsen 2021). These can function alone or in combination to induce various human disorders. Short-secreted proteins soluble in saline solutions and water are known as enterotoxins (Hennekinne et al. 2012). These enterotoxins share structural and biochemical characteristics and are heat resistant. Pneumonia, toxic shock syndrome, sepsis-related infections, and food poisoning are only a few of the most common disorders linked to enterotoxins (Lin and Peterson 2010). Many recent studies have suggested that staphylococcal enterotoxins (SEs) showed an important role in the presentation of other human diseases, such as respiratory tract diseases (Huvenne et al. 2013) and autoimmune disorders (Li et al. 2015). The enterotoxins of S. *aureus* are potent non-specific T-cell stimulators (superantigens) that lead to an uncontrolled immunological response (Lin et al. 2010). A large cytokine load produces toxic shock syndrome, characterized by fever, organ dysfunction, and significant mortality (Goda et al. 2021). Compared to other *S. aureus* toxins, enterotoxins require only a small amount to be dangerous to humans. As a result, this enterotoxin could be used to identify new therapeutic candidates to treat *S. aureus* infections (Goda et al. 2021). Methicillin-resistant *Staphylococcus aureus* (MRSA) strains, which have become epidemic in several countries, are representative of these challenges (Harkins et al. 2017). *S. aureus* is the most common cause of nosocomial and community-acquired bacterial infection of the blood, skin, soft tissue, and other locations in the United States, with MRSA strains accounting for the vast majority in many areas (Rose et al., 2021). Treatment includes antibiotics such as daptomycin, linezolid, nafcillin, and oxacillin. In previous literature, researchers have done insilico studies and showed that enterotoxin A, TSST-1, exfoliative toxin A, and γ-hemolysin can interact with many drugs and proved that these toxins can be drug target (Mohana and Venugopal 2017). Selvaraj (2020) showed that nafcillin analogues interact with enterotoxin I inhibits *S. aureus* growth by using docking analysis (Selvaraj 2020). As a result, molecular docking research is being used to investigate the molecular interactions of Apigenin, quercetin and kaempferolwith enterotoxin I. The study's objective is to conduct molecular docking to assess the effectiveness of natural flavonoids against the enterotoxin I receptor on *S. aureus* in mastitis.

2 Materials and Methods

2.1 Preparation of Enterotoxin 3-D structure for docking

An online resource, RCSB-PDB, was used to acquire the three-dimensional structure of the receptor protein enterotoxin A from *S. aureus* with PDB ID IESF and a resolution of 1.9 Å. Water molecules and heteroatoms from receptor proteins were disallowed during docking.

2.2 Ligand library preparation and analysis of physiochemical properties

Apigenin, quercetin, and kaempferol, three phytochemicals chosen for docking experiments, had their three-dimensional structures retrieved in sdf format from PubChem (Figure 1). An online tool examined ligand absorption, distribution, metabolism, and elimination at a pH of 7 (Jayaram et al., 2012). Lipinski's rule of five was used to determine whether a chemical compound possesses the chemical and physical properties that would make it likely to be an orally active medication in humans (Lipinski, 2004). Physiochemical properties, which include LogP (<5), molecular weight (m.w.) (<500 Da), H-bond donor (5), molar refractivity, H-bond acceptor (<10), and drug likeliness were listed in Table 1.

Table 1 Physiochemical Properties of ligands

ADME Properties	Apigenin	Quercetin	Kaempferol
Molecular weight (<500 Da)	270	302	286
LogP (<5)	2.4	2.01	2.3
H-bond donor (5)	3		4
H-bond acceptor (<10)	5	7	6
Molar Refractivity	70.8	74.0	72.3

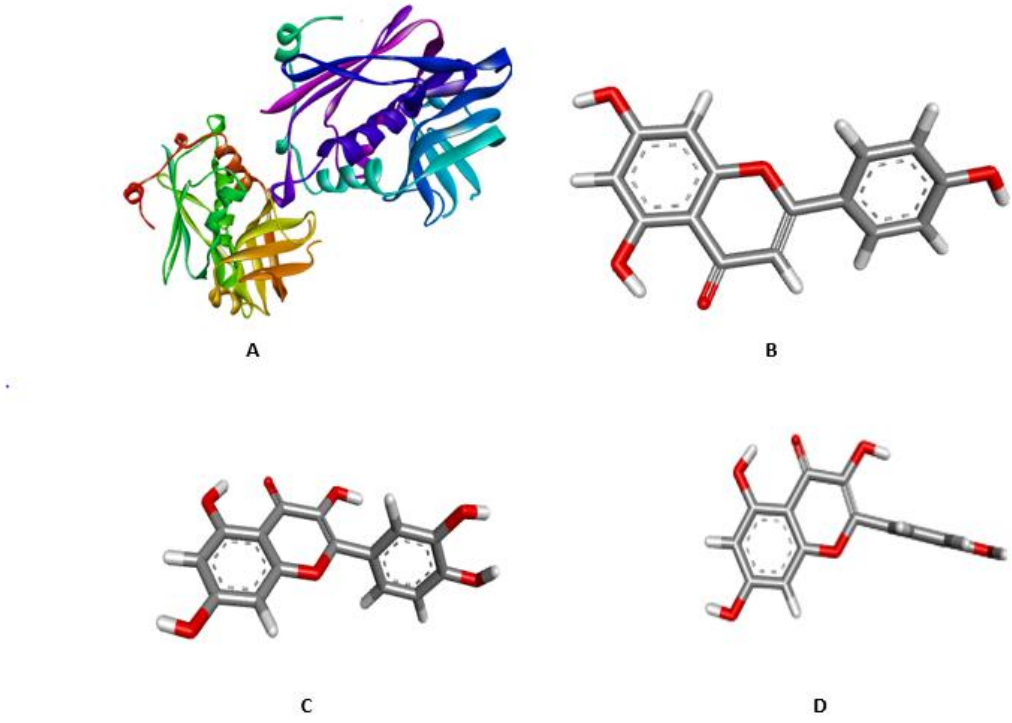


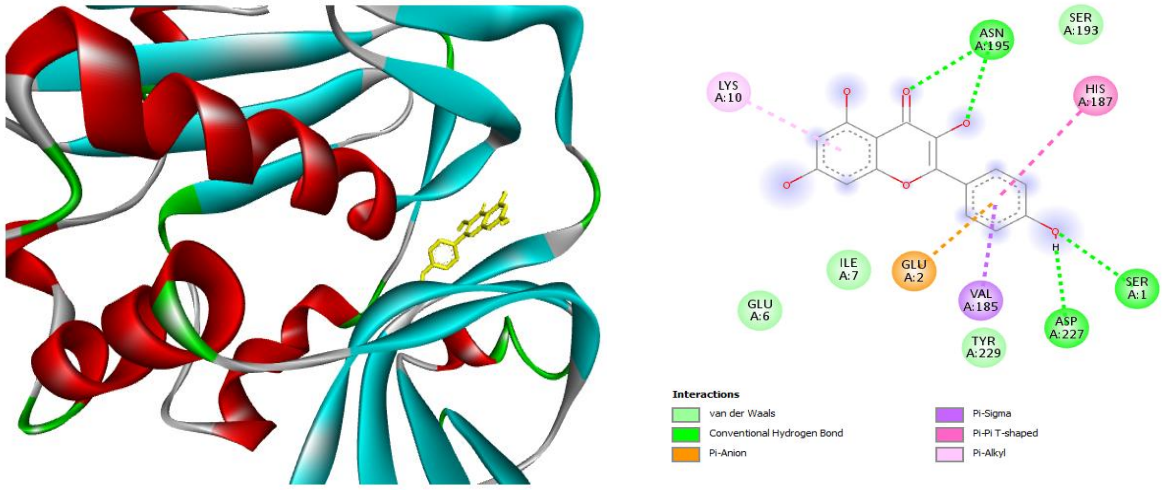
Figure 1 3-D structure of receptor and ligands; Enterotoxin A (A), Kaempferol (B), Apigenin (C) and Quercetin (D)

2.3 Computational Docking of ligands with Enterotoxin A from *Staphylococcus aureus*

PyRx v0.8 (utilizes Auto Dock vina) was used for molecular docking studies. Energy minimization of selected ligands was done by applying Universal Force Field (UFF), and ligand structure format was converted to pdbqt format via OpenBabel (O'Boyle et al., 2011). Docking studies were done as blind docking with an exhaustiveness value of 10. Discovery Studio Visualizer studied molecules that have a high binding affinity.

3 Results and Discussion

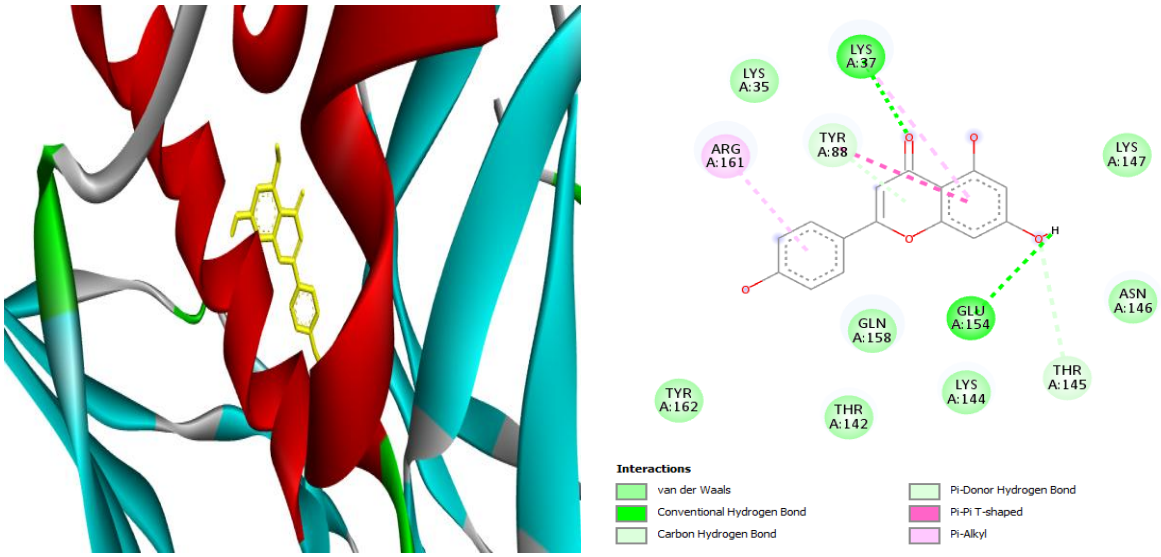
Recently, computational docking has gained popularity as a tool for drug creation (Tuli et al., 2021a; Tuli et al., 2021b; Tuli et al. 2022). *In silico* docking is cost-effective and relatively takes less



(A) **(B)**

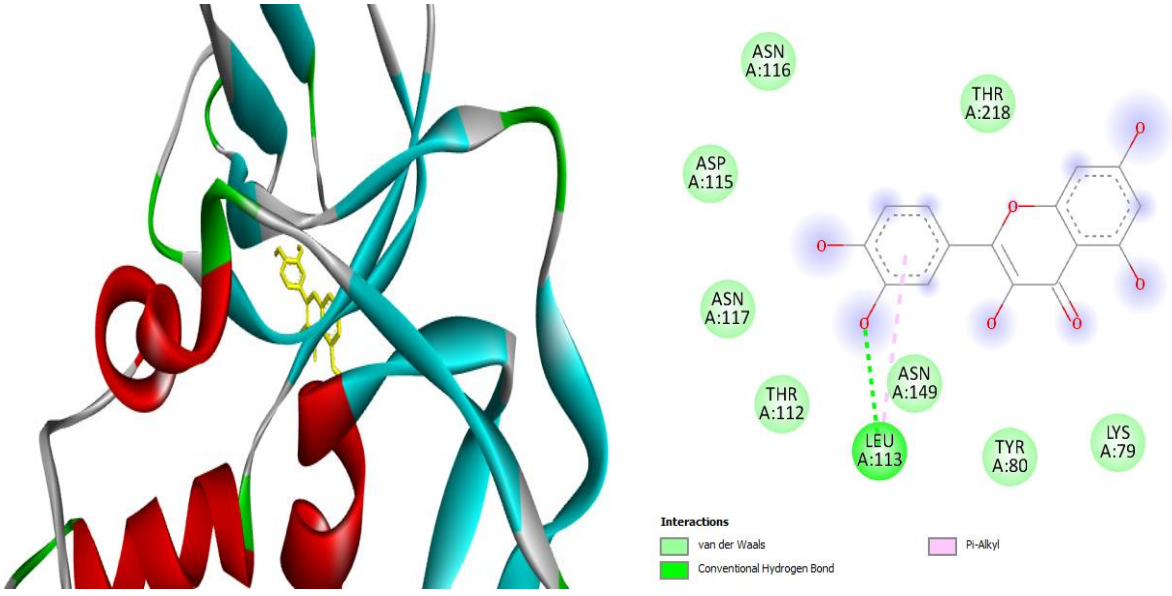
Figure 2 Binding of enterotoxin A from *S. aureus* and Kaempferol. Best interaction position in the receptor protein's pocket (A); 2-D image of interacting residues of receptor protein with ligand (B)

time for drug designing. In virtual screening by PyRx, the binding affinity score of the receptor-ligand complex was calculated, and it was reported that the higher the binding affinity of a molecule, have higher the stability of the molecule. In the present study, docking of enterotoxin and ligands (Kaempferol, Apigenin, and Quercetin) was done. According to docking research, the binding affinities of kaempferol, apigenin, and quercetin to the receptor molecule were between -6.9 and -6.6 Kcal/mol. With enterotoxin, kaempferol had the most binding affinity, measuring -6.9 Kcal/mol. Kaempferol forms hydrogen bonds via Asn195 (two H-bonds), ser1, and Asp227 residues with receptor molecules (Figure 2).Further, enterotoxin interacts with apigenin with a binding affinity of -6.7 Kcal/mol via two hydrogen bonds with Lys37 and Tyr88 residues (Figure 3). In silico studies revealed that Quercetin forms one hydrogen bond via Leu113 with receptor molecule having a binding affinity of -6.6 Kcal/mol. Binding affinity with different RMSD value are mentioned in Table 2 and figure 4.



(A) **(B)**

Figure 3 Binding of enterotoxin A from *S. aureus* and Apigenin. Best interaction position in the receptor protein's pocket (A); 2-D image of interacting residues of receptor protein with ligand (B).



(A) **(B)**

Figure 4 Binding of enterotoxin A from *S. aureus* and Quercetin. Best interaction position in the receptor protein's pocket (A); 2-D image of interacting residues of receptor protein with ligand (B).

Table 2 Binding affinity of Kaempferol, Apigenin, Quercetin, and RMSD value in 10 different modes

Ligand	Binding Affinity (ΔG Kcal/mol)	rmsd/ub	rmsd/lb
Kaempferol			
Kaempferol_5280863_uff_E=362.50	-6.9	0	0
Kaempferol_5280863_uff_E=362.51	-6.6	23.183	21.137
Kaempferol_5280863_uff_E=362.52	-6.5	27.186	24.641
Kaempferol_5280863_uff_E=362.53	-6.3	32.493	31.336
Kaempferol_5280863_uff_E=362.54	-6.3	36.575	34.532
Kaempferol_5280863_uff_E=362.55	-6.3	33.563	31.742
Kaempferol_5280863_uff_E=362.56	-6.3	26.532	24.765
Kaempferol_5280863_uff_E=362.57	-6.2	32.737	30.996
Kaempferol_5280863_uff_E=362.58	-6.2	23.749	21.029
Apigenin			
Apigenin_5280443_uff_E=233.26	-6.7	0	0
Apigenin_5280443_uff_E=233.27	-6.6	20.623	18.599
Apigenin_5280443_uff_E=233.28	-6.5	21.293	17.805
Apigenin_5280443_uff_E=233.29	-6.4	27.244	24.783
Apigenin_5280443_uff_E=233.30	-6.2	15.229	13.34
Apigenin_5280443_uff_E=233.31	-6.2	19.845	18.173
Apigenin_5280443_uff_E=233.32	-6.2	25.921	23.913
Apigenin_5280443_uff_E=233.33	-6.1	20.391	17.962
Apigenin_5280443_uff_E=233.34	-6	6.63	1.642
Quercetin			
Quercetin_5280343_uff_E=380.43	-6.6	0	0
Quercetin_5280343_uff_E=380.44	-6.6	21.064	18.067
Quercetin_5280343_uff_E=380.45	-6.5	7.014	2.239
Quercetin_5280343_uff_E=380.46	-6.5	29.101	27.426
Quercetin_5280343_uff_E=380.47	-6.4	28.757	28.019
Quercetin_5280343_uff_E=380.48	-6.3	7.126	2.313
Quercetin_5280343_uff_E=380.49	-6.3	20.823	18.296
Quercetin_5280343_uff_E=380.50	-6.3	28.672	27.76
Quercetin_5280343_uff_E=380.51	-6.1	26.008	23.263

Previous studies reported docking of nafcillin analogues with enterotoxin I from *S. aureus*. It was shown that Thr74 and Asn15 residues of enterotoxin interacted to form hydrogen bonding (Selvaraj 2020). Kurjog et al. (2018) reported that natural antitoxin compounds such as 28-Norolean-12-en-3-one and Betulin might give an effective treatment against *S.aureus* (Kurjogi et al. 2018). Moreover, phytochemicals extracted from medicinal plants might act as potential drugs against diseases like Covid-19 and typhoid (Bansal et al. 2022; Tuli et al. 2022). Somehow, our results agree with the previous study of Emran et al. (2015) those who reported luteolin from *Bacopa monnier* had the highest binding score for penicillin-binding protein from *S.aureus* (Emran et al. 2015). Protohypericin, Berbamine, Hypericin, Galangin, and Berberine were the best active compounds against *S. aureus* (Dorcheh et al.

2022). Shidiki and Vyas (2022) reported that taxifolin compounds and diferulic acid were potential inhibitors against *S. aureus* (Shidiki and Vyas 2022). It has been in silico proven that chrysin and luteolin have the highest efficiency for receptors of enterotoxin A of *S. aureus* (Kumar et al. 2022).

Conclusion

Staphylococcus aureus is a facultative anaerobe causing pus-foaming skin infections in humans. In the current study, natural phytochemicals were docked in-silico with enterotoxin A *S. aureus*. The binding affinity of studied ligands, i.e., Kaempferol, Apigenin, and Quercetin were found to be in the -6.6 to -6.9 Kcal/mol range. Ligands used in the current study follow Lipinsik's rule of five and may be used as *anti-staphylococcus aureus* agents. Before using these drugs as anti-*Staphylococcus aureus* agents, *in-vitro* and *in-vivo* studies are suggested to carry out against *S.aureus* infection. If it is proven that the phytochemicals mentioned above can be effective against *S. aureus*, they can be used to treat diseases caused by *S. aureus*.

Conflict of Interest

There are no conflicts of interest among the authors.

Acknowledgment

The authors want to acknowledge MMEC, Maharishi Markandeshwar College, for providing the requisite facility to complete the work.

References

Ahmad-Mansour, N., Loubet, P., Pouget, C., Dunyach-Remy, C., Sotto, A., Lavigne, J. P., & Molle, V. (2021). Staphylococcus aureus Toxins: An Update on Their Pathogenic Properties and Potential Treatments. *Toxins*, *13*(10), 677. https://doi.org/10.3390/TOXINS13100677

Bansal, P., Tuli, H. S., Sharma, V., Mohapatra, R. K., Dhama, K., Priti, & Sharma, A. K. (2022). Targeting Omicron (B.1.1.529) SARS CoV-2 spike protein with selected phytochemicals: an in-silico approach for identification of potential drug. *Journal of Experimental Biology and Agricultural Sciences*, *10*(2), 396–404. https://doi.org/10.18006/2022.10(2).396.404

Cassat, J. E., & Thomsen, I. (2021). Staphylococcus aureus infections in children. *Current Opinion in Infectious Diseases*, *34*(5), 510–518. https://doi.org/10.1097/QCO.0000000000000752

Chakraborty, S., Dhama, K., Tiwari, R., Iqbal Yatoo, M., Khurana, S. K., Khandia, R., Munjal, A., Munuswamy, P., Kumar, M. A., Singh, M., Singh, R., Gupta, V. K., & Chaicumpa, W. (2019). Technological interventions and advances in the diagnosis of intramammary infections in animals with emphasis on bovine population-a review. *The Veterinary Quarterly*, *39*(1), 76–94. https://doi.org/10.1080/01652176.2019.1642546

Cheung, G. Y. C., Bae, J. S., & Otto, M. (2021). Pathogenicity and virulence of *Staphylococcus aureus*. *Virulence*, *12*(1), 547–569. https://doi.org/10.1080/21505594.2021.1878688

Deb, R., Kumar, A., Chakraborty, S., Verma, A. K., Tiwari, R., Dhama, K., Singh, U., & Kumar, S. (2013). Trends in diagnosis and control of bovine mastitis: A review. *Pakistan Journal of Biological Sciences*, *16*(23), 1653–1661. https://doi.org/10.3923/pjbs.2013.1653.1661

Dorcheh, F. A., Balmeh, N., & Sanjari, S. (2022). In-silico investigation of antibacterial herbal compounds in order to find new antibiotic against *Staphylococcus aureus* and its resistant subtypes. *Informatics in Medicine Unlocked*, *28*, 100843. https://doi.org/10.1016/j.imu.2021.100843

Emran, T. Bin, Rahman, M. A., Uddin, M. M. N., Dash, R., Hossen, M. F., Mohiuddin, M., & Alam, M. R. (2015). Molecular docking and inhibition studies on the interactions of *Bacopa monnieri*'s potent phytochemicals against pathogenic *Staphylococcus aureus*. *DARU, Journal of Pharmaceutical Sciences*, *23*(1), 26. https://doi.org/10.1186/s40199-015-0106-9

Goda, K., Kenzaka, T., Hoshijima, M., Yachie, A., & Akita, H. (2021). Toxic shock syndrome with a cytokine storm caused by Staphylococcus simulans: a case report. *BMC Infectious Diseases*, *21*(1), 19. https://doi.org/10.1186/s12879-020-05731-y

Guo, Y., Song, G., Sun, M., Wang, J., & Wang, Y. (2020). Prevalence and Therapies of Antibiotic-Resistance in Staphylococcus aureus. *Frontiers in Cellular and Infection Microbiology*, *10*, 107. https://doi.org/10.3389/fcimb.2020.00107

Halasa, T., Huijps, K., Østerås, O., & Hogeveen, H. (2007). Economic effects of bovine mastitis and mastitis management: A review. *Veterinary Quarterly*, *29*(1), 18–31. https://doi.org/10.1080/01652176.2007.9695224

Harkins, C. P., Pichon, B., Doumith, M., Parkhill, J., Westh, H., Tomasz, A., de Lencastre, H., Bentley, S. D., Kearns, A. M., & Holden, M. T. G. (2017). Methicillin-resistant Staphylococcus aureus emerged long before the introduction of methicillin into clinical practice. *Genome Biology*, *18*(1). https://doi.org/10.1186/s13059-017-1252-9

Hennekinne, J. A., De Buyser, M. L., & Dragacci, S. (2012). Staphylococcus aureus and its food poisoning toxins: characterization and outbreak investigation. *FEMS Microbiology*

Reviews, *36*(4), 815–836. https://doi.org/10.1111/J.1574-6976.2011.00311.X

Huvenne, W., Hellings, P. W., & Bachert, C. (2013). Role of staphylococcal superantigens in airway disease. *International Archives of Allergy and Immunology*, *161*(4), 304–314. https://doi.org/10.1159/000350329

Jayaram, B., Singh, T., Mukherjee, G., Mathur, A., Shekhar, S., & Shekhar, V. (2012). Sanjeevini: a freely accessible web-server for target directed lead molecule discovery. *BMC Bioinformatics*, *13 Suppl 1*(Suppl 17). https://doi.org/10.1186/1471-2105-13-S17-S7

Kumar, A. S., Fernandes, N. J., Lobo, S. J., & Khan, N. (2022). In silico analysis of seaweed phytochemical flavonoid for the inhibition of staphylococcus enterotoxin A. *Innovare Journal of Medical Sciences*, 17–20. https://doi.org/10.22159/ijms.2022.v10i4.45116

Kurjogi, M., Satapute, P., Jogaiah, S., Abdelrahman, M., Daddam, J. R., Ramu, V., & Tran, L. S. P. (2018). Computational modeling of the staphylococcal enterotoxins and its interaction with natural antitoxin compounds. *International Journal of Molecular Sciences*, *19*(1), 133. https://doi.org/10.3390/ijms19010133

Li, J., Yang, J., Lu, Y. W., Wu, S., Wang, M. R., & Zhu, J. M. (2015). Possible role of staphylococcal enterotoxin b in the pathogenesis of autoimmune diseases. *Viral Immunology*, *28*(7), 354–359. https://doi.org/10.1089/vim.2015.0017

Lin, C. F., Chen, C. L., Huang, W. C., Cheng, Y. L., Hsieh, C. Y., Wang, C. Y., & Hong, M. Y. (2010). Different types of cell death induced by Enterotoxins. *Toxins*, *2*(8), 2158–2176. https://doi.org/10.3390/toxins2082158

Lin, Y. C., & Peterson, M. L. (2010). New insights into the prevention of *Staphylococcal* infections and toxic shock syndrome. *Expert Review of Clinical Pharmacology*, *3*(6), 753. https://doi.org/10.1586/ECP.10.121

Lipinski, C. A. (2004). Lead- and drug-like compounds: the rule-of-five revolution. *Drug Discovery Today. Technologies*, *1*(4), 337–341. https://doi.org/10.1016/J.DDTEC.2004.11.007

Loiselle, M. C., Ster, C., Talbot, B. G., Zhao, X., Wagner, G. F., Boisclair, Y. R., & Lacasse, P. (2009). Impact of postpartum milking frequency on the immune system and the blood metabolite concentration of dairy cows. *Journal of Dairy Science*, *92*(5), 1900–1912. https://doi.org/10.3168/jds.2008-1399

Mohana, R., & Venugopal, S. (2017). In silico Analysis of Toxins of *Staphylococcus aureus* for Validating Putative Drug Targets. *Infectious Disorders - Drug Targets*, *17*(2), 130–142. https://doi.org/10.2174/1871526516666161230150219

O'Boyle, N. M., Banck, M., James, C. A., Morley, C., Vandermeersch, T., & Hutchison, G. R. (2011). Open Babel: An Open chemical toolbox. *Journal of Cheminformatics*, *3*(10), 33. https://doi.org/10.1186/1758-2946-3-33

Rose, W., Fantl, M., Geriak, M., Nizet, V., & Sakoulas, G. (2021). Current Paradigms of Combination Therapy in Methicillin-Resistant *Staphylococcus aureus* (MRSA) Bacteremia: Does it Work, Which Combination, and For Which Patients? *Clinical Infectious Diseases*, *73*(12), 2353–2360. https://doi.org/10.1093/cid/ciab452

Selvaraj, J. (2020). Molecular docking analysis of Enterotoxin I from *Staphylococcus aureus* with Nafcillin analogues. *Bioinformation*, *16*(10), 731–735. https://doi.org/10.6026/97320630016731

Sharun, K., Dhama, K., Tiwari, R., Gugjoo, M. B., Iqbal Yatoo, M., Patel, S. K., Pathak, M., Karthik, K., Khurana, S. K., Singh, R., Puvvala, B., Amarpal, Singh, R., Singh, K. P., & Chaicumpa, W. (2021). Advances in therapeutic and managemental approaches of bovine mastitis: a comprehensive review. *The Veterinary Quarterly*, *41*(1), 107–136. https://doi.org/10.1080/01652176.2021.1882713

Shidiki, A., & Vyas, A. (2022). Molecular docking and pharmacokinetic prediction of phytochemicals from *Syzygium cumini* in interaction with penicillin-binding protein 2a and erythromycin ribosomal methylase of *Staphylococcus aureus*. *Biotechnologia*, *103*(1), 5–18. https://doi.org/10.5114/bta.2022.113910

Tuli, H. S., Bhatia, G. K., Sood, S., Debnath, P., Aggarwal, D., & Upadhyay, S. K. (2021a). In silico analysis and molecular docking studies of plumbagin and piperine ligands as potential inhibitors of alpha-glucosidase receptor. *Biointerface Research in Applied Chemistry*, *11*(2), 9629–9637. https://doi.org/10.33263/BRIAC112.96299637

Tuli, H. S., Garg, V. K., Kapoor, D., Bansal, P., Kumar, P., Mohapatra, R. K., Dhama, K., Vashishth, A., Seth, P., & Bhatia, G. K. (2022). In silico targeting of osmoporin protein of Salmonella to identify anti-Salmonellosis phyto-compounds. *Journal of Experimental Biology and Agricultural Sciences*, *10*(2), 423–429. https://doi.org/10.18006/2022.10(2).423.429

Tuli, H. S., Sood, S., & Upadhyay, S. K. (2021b). In silico Molecular Docking of α-Glucosidase with Prangenidin and Columbin As An Anti-Hyperglycemic Strategy. *Bioscience*

Biotechnology Research Communications, *14*(3), 1191–1197. https://doi.org/10.21786/bbrc/14.3.43

Zhou, K., Li, C., Chen, D., Pan, Y., Tao, Y., Qu, W., Liu, Z., Wang, X., & Xie, S. (2018). A review on nanosystems as an effective approach against infections of *Staphylococcus aureus*. *International Journal of Nanomedicine Dovepress*, *13*, 7333–7347. https://doi.org/10.2147/IJN.S169935