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Inhibitory Activities of Phytoconstituents from *Azadirachta indica* and *Murraya koenigii* as Potential Drugs for Secondary Infection of Atopic Eczema Disease - In silico study

Mikidadi S. Gurisha, Pulapa V. Kanaka Rao and Laxmikanth Cherupally
Department of Physics, College of Natural and Mathematical Sciences, University of Dodoma
P. O. Box 338 Dodoma, Tanzania.
Correspondence Author: salehegs@gmail.com
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Abstract

Atopic Eczema (AE) disease is a chronic inflammatory skin condition that is caused by a person's inability to repair damage to the skin barrier. *Staphylococcus aureus* (SA*)* is a virulent pathogen that plays an important role in the progression of secondary infection in AE patients, thus intensifying the disease's virulence. In this study, the inhibitory activities of phytoconstituents from *Azadirachta indica* and *Murraya koenigii* against the SA (Protein Data Bank ID: 7TIO) using an *in silico* approach are presented. Site-specific docking analysis was carried out on the virulent pathogen with the docking center at X: 1.65044, Y: 1.7980, Z: 3.1878, for a box of dimension X: 64.2332, Y: 40.2828, Z: 41.8202. The natural compounds were chosen based on their absorption, distribution, metabolism, excretion, and toxicity characteristics, as well as other drug-like characteristics computed in Swiss ADME and pkCSM software. Four compounds, Gedunin (-7.2 kCal/mol), Curryanine (-7.1 kCal/mol), Mahanimbinine (-6.6 kCal/mol) and Mahanine (-6.5 kCal/mol) with good inhibition for the *S. aureus* pathogen were discovered to exhibit better docking scores compared to Prednisone (-6.1 kcal/mol) (control drug). The studied Phytoconstituents of *A. indica* and *M. koennigii* thus can be used as inhibitors of SA pathogen (7TIO) in the fight against AE disease.

Key Words: Phytoconstituents; Staphylococcus aureus; Atopic Eczema; *Azadirachta indica*; *Murraya koennigii*.

Introduction

Eczema is an inflammatory skin illness that causes blisters, itchy, dry, scaly skin spots, and rashes. The most prevalent sign of eczema disease is itchy skin, others are rashes, which when scratched may leak, weep clear fluid, or bleed (Chung et al. 2022). In developing nations, eczema disease affects 20% of children and about 10% of adults (Ring et al. 2019). It substantially contributes to individual disability. The most typical form of the disease is the Atopic Eczema (AE). It occurs due to an overactive immune system, which dries up and irritates the skin barrier. This illness can affect any body part and has various symptoms (Bieber 2022).

Patients are affected not only by the social stigma related with having visible recurrently caused skin injuries but also serious sleep difficulties. Genetic, immunological, and environmental factors are among the many contributing factors to AE. Its exacerbation has long been linked to *Staphylococcus aureus* (SA). SA generates various virulence factors that interact with the immune system and skin of humans. It has been demonstrated that these superantigens and toxins play an important role in adhesion, inflammation, and skin barrier breakdown (Hwang et al. 2021). The bacterium SA has a direct impact on pathogenesis and various substances it produces such as the staphylococcal

superantigen B and the delta-toxin, worsen atopic eczema (AE) symptoms by promoting inflammation (Iwamoto et al. 2019).

Prednisone, flucloxacillin, cloxacillin, and cephalexin are among the antibiotics that are frequently used to treat AE in many developing nations. Even though some of these medications have been demonstrated to help reduce the clinical symptoms of AE, many individuals still experience recurrent and chronic infections because of drug resistance (Ngoc et al. 2019).

Phytochemicals resulting from natural products have been employed in drug synthesis; these products have been considered during searching for a novel medication (Gurisha et al. 2024). *Azadirachta indica* elaborated an enormous variety of chemically and structurally complex biologically active compounds extracted from various parts of this plants, over 140 compounds have been identified. These compounds possess multiple properties such as antioxidant, anti-inflammatory, anti-viral, antibacterial, anti-fungal, anti-parasitic, antimicrobial anti-cancer, antidiarrheal and anti-diabetic (Shakib 2020). Similar cases are reported for *Murraya koenigii* plant's bark, roots, and leaves which are widely used in the Ayurvedic medical system, and are abundant in carbazole and alkaloids that have strong pharmacological and biological effects. They consist of neuroprotective, antitumor, antidiabetic, woud healing, anti-inflammatory, and antioxidant properties (Balakrishnan et al. 2020). Previous studies reported that *A. indica* and *M. koenigii* have antimicrobial activities against common endodontic pathogens such as *Staphylococcus aureus, Streptococcus mutants,* and *Candida albicans (*Vats et al. 2011, Wylie and Merrell 2022).

Computational techniques such as molecular docking can be used to determine the un-accessibility preferred orientation of two molecules when they are bonded jointly to form a stable compound (Sliwoski et al. 2014, Preman et al. 2022). Numerous programs are available to conduct docking studies, but due to their precision and user-friendly features, PyRx Virtual Screening (0.9.x) SwissADME (Daina et al. 2017), pkCSM (Douglas et al. 2015) and BIOVIA Discovery Studio Visualizer (2020) are the best and were chosen in this study. Docking in glide entails a number of processes, including receptor grid generation, ligand preparation, protein preparation, docking, and binding affinity scoring (Zhang et al. 2016). Computer-aided drug design is now widely accepted by chemists and biologists as a trans-disciplinary approach towards drug discovery (Sabe et al. 2021). Therefore, computational techniques of molecular docking have been utilized to effectively identify new drug candidates from natural products.

Materials and Methods

Protein preparation

Staphylococcus aureus (7TIO) is the protein target used in this study. The protein was retrieved from the Protein Data Bank (PDB) website (Santhouse et al. 2022). The standard structure from the Protein Data Bank is not optimized for instant use, and it often includes only heavy atoms; therefore, water molecules, heteroatoms, actosite, and co-factors were deleted (Geethanjali et al. 2021).

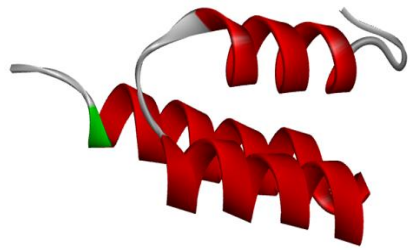


Figure 1: Protein Receptor

Since hydrogen atoms are typically absent from crystallographic structures, polar hydrogen atoms were added to the prepared protein (Jahan et al. 2021). The protein receptor was then saved in the Protein Data Bank, Partial Charge (Q), & Atom Type (T) (PDBQT) format for further analysis. The protein target was created via BIOVIA Studio visualization software (2021) (Figure 1).

Ligand preparation

A total of 32 bioactive compounds were selected (17 from *A. indica* and 15 from *M.*

koenigii) (Table 1). The native Spatial Data File (SDF) format of the bioactive compounds were downloaded from Zinc Database (Figure 2). Then, the bioactive compounds were screened using Swiss ADME and pkCSM softwares to identify the safe compounds that have drug-like properties (Daina et al. 2017).

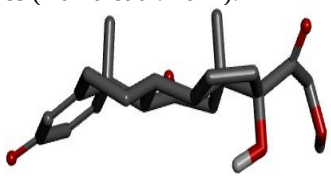


Figure 2: Prednisone Ligand (control)

The 2D and 3D structures were optimized to avoid unnatural overlapping of any two nonbonding atom in protein structure and to find the best position of the ligand against protein target, this was done using Gaussian 09 software (Saheed and Abdulaziz 2014). These natural substances were then subjected to virtual screening using PyRx software for identification of substances with high binding affinities.

Molecular Docking

According to Meng et al. (2011), Molecular Docking is a computer technique used to forecast the formation of molecular complexes. The Autodock Vina tool was used to clarify the binding conformations of the hit chemical with the protein (PDB ID: 7TIO) (Trott and Olson 2010). Energy for all ligands was minimized to allow the molecular arrangement at the favorable energetic space followed by conversion of all ligands in PDBQT format (Ferreira et al. 2015). The following values are the recorded on Vina Wizard and the Vina search: center X: 1.6504, Y: 1.7980, Z: 3.1878, for a box of dimension X: 64.2332, Y: 40.2828, Z: 41.8202, and exhaustiveness was set as eight (8). Other AutDock parameters were set to be the defaults. The binding affinities results were saved in Comma Separate Value (CSV) format after the wizard had been executed. A PDB file including the phytoconstituents with different affinities was prepared for the receptor-ligand interaction. Conformations with high affinities were taken for further study in BIOVIA Discovery Studio for examination of docking poses.

Results & Discussion

ADMET prediction

The time needed for drug development is dramatically reduced, and the success rate is much increased by applying molecular modeling approaches to find novel therapeutic candidates (He et al. 2022). Standard computational pharmacokinetics parameters and drug-likeness were developed for the initial evaluation of physicochemical, pharmacokinetic, and drug-like features during the drug development process (He et al. 2022, Madeddu et al. 2022). Using the Swiss ADME and pkCSM the physicochemical, drug-likeness, and ADMET features of the four highest-scoring natural compounds were evaluated and presented in Tables 1 and 2.

Table 1: Physicochemical and drug-like properties results

Descriptor/Properties	**Physicochemical and drug-like properties Value**				
	ZINC3978117	**ZINC1633855**	**ZINC14585298**	**ZINC45338947**	**ZINC3875357**
Molecular Weight	482.573	331.459	349.474	333.431	358.434
Rotatable Bonds	3	1	4	3	2
H.Acceptors	7	1	2	2	5
H.Donors	0	1	2	2	2
cLogP	4.561	6.24	5.735	5.856	1.766
No of aromatic heavy atoms	5	13	13	-6.29	-2.85
Fraction Csp3	0.68	0.39	0.39		
Topological Polar Surface Area	95.34	25.02	45.25	45.25	91.67
Num. of heavy atoms	35	25	26		
Molar Refractivity	126.04	106.02	110.13	105.63	96.10

Table 2: ADMET prediction of the top-scored natural compounds

Properties	**ADMET properties**	**Predicted Value**				
		ZINC3978117	**ZINC1633855**	**ZINC14585298**	**ZINC45338947**	**ZINC3875357**
Absorption	Water solubility	Soluble	Soluble	Soluble	Soluble	Soluble
	Intestinal absorption	100	94.669	89.218	High	High
	P-glycoprotein (P-gp)	No	Yes	Yes	No	Yes
	Skin permeability	-3.103	-2.774	-2.822		
	Gastrointestinal absorption	High	High	High	High	High
	$Caco_2$ permeability	0.875 cm/s	1.005 cm/s	0.97 cm/s		
Distribution	VDss (human)	0.09 L/kg	0.951 L/kg	0.594 cm/s	-4.02 cm/s	-7.45 cm/s
	Fraction unbound	0.05	0.012	0.08		
	BBB permeability	-0.665	0.418	-0.01	No	Yes
	CNS permeability	-2.841	-1.26	-1.259		

Properties	**ADMET properties**	**Predicted Value**				
		ZINC3978117	**ZINC1633855**	**ZINC14585298**	**ZINC45338947**	**ZINC3875357**
Metabolism	inhibitor CYP1A2	No	Yes	Yes	Yes	No
	CYP2C19	No	Yes	Yes	Yes	No
	CYP2C9	No	Yes	Yes	Yes	No
	CYP2D6	No	No	Yes	Yes	No
	CYP3A4	No	Yes	Yes	Yes	No
Excretion	Total clearance	**0.072**mL/min/kg	0.431mL/min /kg	0.29mL/min/kg	0.19 mL/min/kg	0.15 mL/min/kg
	Renal OCT2	**No**	No			
Toxicity	AMES toxicity	No	Yes	Yes		
	hERG I inhibitor	No	No	No		
	hERG II inhibitor	No	Yes	Yes	No	No
	Hepatotoxicity	No	Yes	Yes		
	Skin Sensitisation	No	No	No		
	Minnow toxicity	0.815 mM	-1.532 mM	-2.029 mM		

Out of the 32 Swiss ADMET screened phytochemicals, 15 passed (eight from *A. indica* and seven from *M. koenigii*), which were then exposed to molecular docking (Table 3).

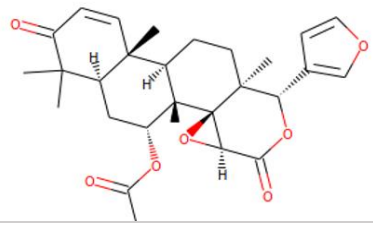
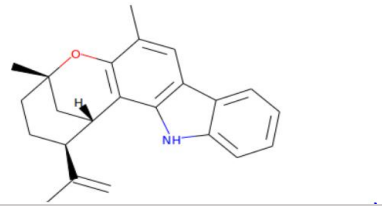
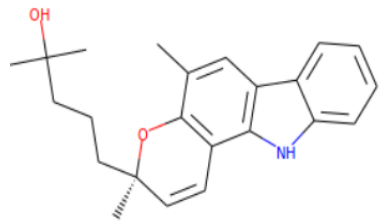
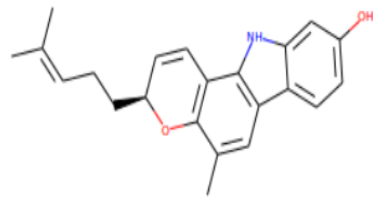
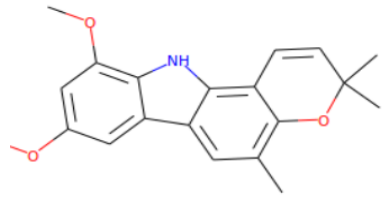
Table 3: Screened Bioactive compounds of *A. indica* and *M. koenigii* plants

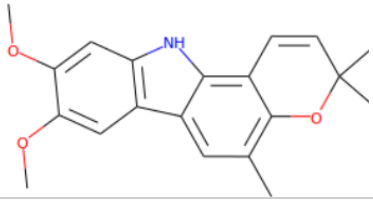
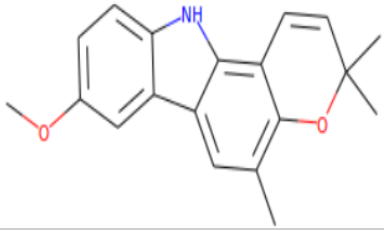
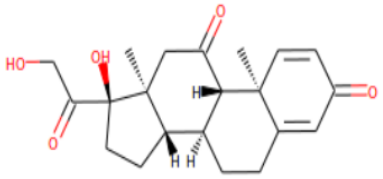
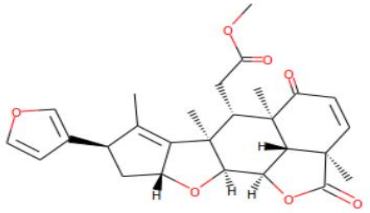
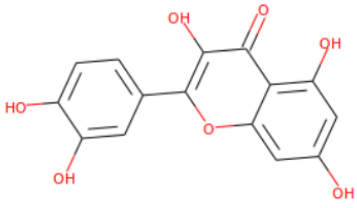
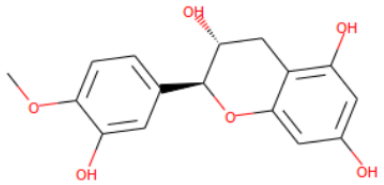
Natural Plant	ZINC ID	Bioactive compounds	Chemical formulae
Azadirachta indica L	ZINC3978117	Gedunin	$C_{28}H_{34}O_7$
Azadirachta indica *L*	ZINC3869685	Meletin	$C_{15}H_{10}O_7$
Azadirachta indica *L*	ZINC517261	Isorhamnetin	$C_{19}H_{20}O_7$
Azadirachta indica L	ZINC6484712	Quercetin Pentamethyl Ether	$C_{19}H_{20}O_7$
Azadirachta indica L	ZINC119978	Catechin	$C_{15}H_{14}O_6$
Azadirachta indica L	ZINC2170446	Catechin Tetramethylether	$C_{19}H_{22}O_6$
Azadirachta indica L	ZINC2525300	4'-O-Methylcatechin	$C_{16}H_{16}O_6$
Azadirachta indica L	ZINC1504	Galop	$C_7H_6O_5$
Azadirachta indica L	ZINC347833	Eudesmic Acid	$C_{10}H_{12}O_5$
Azadirachta indica L	ZINC39205816	Nimbolide	$C_{27}H_{30}O_7$
Azadirachta indica L	ZINC103199484	Nimbinolide	$C_{30}H_{36}O_{11}$
Azadirachta indica L	ZINC3869685	Meletin	$C_{15}H_{10}O_7$
Azadirachta indica L	ZINC8382508	Nimbin	$C_{30}H_{36}O_9$
Azadirachta indica L	ZINC103177092	Desacetylnimbin	$C_{28}H_{34}O_9$
Azadirachta indica L	ZINC31495483	Azadiradione	$C_{28}H_{34}O_5$
Azadirachta indica L	ZINC72132847	Salannin	$C_{34}H_{44}O_9$
Azadirachta indica L	ZINC100053758	Ascorbic Acid-2-Sulfate	$C_6H_8O_6$
Murraya koenigii	ZINC1633855	Curryanine	$C_{23}H_{25}NO$
Murraya koenigii	ZINC14585298	Mahanimbinine	$C_{23}H_{27}NO_2$
Murraya koenigii	ZINC45338947	Mahanine	$C_{22}H_{23}NO_2$
Murraya koenigii	ZINC15257211	Mukonicine	$C_{20}H_{21}NO_3$
Murraya koenigii	ZINC1715689	Kenidine	$C_{20}H_{21}NO_3$
Murraya koenigii	ZINC1715690	Kenimbine	$C_{19}H_{19}NO_2$
Murraya koenigii	ZINC6787	Resveratrol	$C_{14}H_{12}O_3$
Murraya koenigii	ZINC15257207	Kenigine	$C_{19}H_{19}NO_3$
Murraya koenigii	ZINC14585296	Afc	$C_{23}H_{23}NO_2$
Murraya koenigii	ZINC5845755	Isomahanine	$C_{23}H_{25}NO_2$
Murraya koenigii	ZINC15206004	Murrayanol	$C_{24}H_{29}NO_2$
Murraya koenigii	ZINC1715690	Kenimbine	$C_{19}H_{19}NO_2$
Murraya koenigii	ZINC1615142	Girinimbine	$C_{18}H_{17}NO$
Murraya koenigii	ZINC5158373	Phebalosin	$C_{15}H_{14}O_4$
Murraya koenigii	ZINC85853395	Bismurrayafoline E	$C_{48}H_{56}N_2O_4$

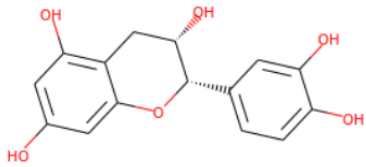
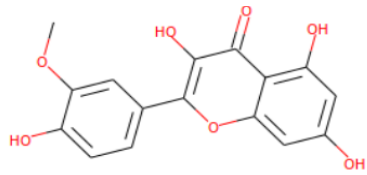
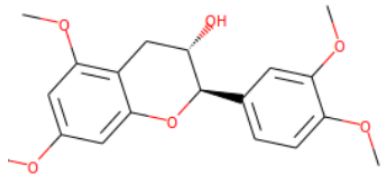
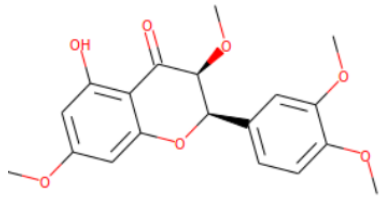
Compliance with Lipinski's Rule of Five

According to Lipinski's Rule of 5, when there are more than five H-bond donors, ten H-bond acceptors, a molecular weight larger than 500, and a computed Log P (ILog P) greater than five, poor absorption or penetration is more likely to occur during drug discovery (Benet et al. 2016). All four phytochemicals screened in the Swiss ADME tool (Gedunin, Curryanine, Mahanimbinine, Mahanine) satisfied the conditions of Lipinski's law.

Table 4: Phytochemical Docking Scores (all chemical structures were retrieved from the zinc database (Irwin et al. 2020).

Name	Chemical Structure	Binding Affinities (kcal/mol)
Gedunin		-7.2
Curryanine		-7.1
Mahanimbinine		-6.6
Mahanine		-6.5
Mukonicine		-6.4
Kenidine		-6.2

Name	Chemical Structure	Binding Affinities (kcal/mol)
		
Kenimbine		-6.2
Prednisone		-6.1
Nimbolide		-5.9
Meletin		-5.3
4'-O-Methylcatechin		-5.6
Catechin		-5.4

Name	Chemical Structure	Binding Affinities (kcal/mol)
		
Isorhamnetin		-5.5
Catechin Tetramethylether		-5.1
Quercetin Pentamethyl Ether		-5.0

Docking Score

Only four phytochemicals (Gedunin, Curryanine, Mahanimbinine, and Mahanine) out of 15 showed a greater binding affinity for the protein target following the docking analysis as presented in Table 4. It has been demonstrated that, gedunin compound which has a docking score of -7.2 kcal/mol, has antibacterial, insecticidal, antimalarial, antiallergic, anti-inflammatory, anti-cancer, and neuroprotective properties. Gedunin is a significant limonoid that is mostly found in seeds and found in various genera of the Meliaceae family. Gedunin is used as a heat shock protein (Hsp) inhibitor constituted a critical turning point in the development of the compound as a biological therapeutic agent (Braga et al. 2020). *Azadirachta indica, Cabralea, Carapa, Cedrela, Chukrasia, Entandrophragm, Guarea, Trichilia, and Xylocarpus* are among the medicinal plants that have reportedly been found to contain gedunin (Braga et al. 2020, Zhang-Jian et al. 2022). Therefore, Gedunin is a natural compound with great potential in terms of bioactivities and some of them have great value in preventing and treating a wide range of human diseases.

Compound ZINC1633855, also known as Curryanine has a docking score of (-7.1 kcal/mol) (Table 4), the Phytoconstituents is found in *Murraya koenigii* natural product. The functional group of curryanine compounds is known as carbazoles (Chakraborty et al. 1987). This compound is also referred to as cyclomahanimbine or murrayazolidine. Carbazoles are substances with a three-ring structure made up of pyrrole rings fused to benzene rings on either side. Based on its pKa, curryanineis a very weak

basic chemical that is basically neutral. More than one hundred curryanine compounds are known to have therapeutic characteristics, and has been frequently utilized to create biochemical compounds. It also has antibacterial capabilities ((Gautam et al. 2021).

Compound ZINC14585298, known as mahanimbinine has a docking score of (-6.6 kcal/mol) (Table 4), the Phytoconstituents is found in *Murraya koenigii* natural product (Suman et al. 2018). *Murraya koenigii's* leaves, stem bark, and root all contain mahanimbinine a carbazole alkaloid. The majority of the carbazole alkaloids have been found in plants belonging to the genera *Murraya*, *Glycosmic*, and *Clausena* in the family Rutaceae (Dineshkumar et al. 2010). Additionally, carbazole alkaloids have been linked to a variety of pharmacological effects, including anti-tumor, anti-viral, anti-inflammatory, anticonvulsant, diuretic, and anti-oxidant actions (Knolker and Reddy 2008).

Compound ZINC45338947 known as Mahanine has a docking score of (-6.5 kcal/mol) (Table 4), the Phytoconstituents is found in *Murraya koenigii* natural product. The carbazole alkaloid mahanine has been shown to have anticancer properties and to interfere with many oncogenic signaling events in breast, colon, and prostate cancers (Raghuram et al. 2022). The compound is usually isolated from the Indian folklore medicinal plant *Murraya koenigii*, also known as Curry Patta. Additionally, the curry plant (*Murraya koenigii*) and certain species that are similar have been shown to contain the substance (Suman et al. 2018). Mahanine has been demonstrated to have a variety of pharmacological actions, including antimutagenicity against heterocyclic amines, antibacterial activity against Gram-positive bacteria, and an anti-inflammatory impact (Roy et al. 2005). Mahanine, a carbazole alkaloid produced by curry leaves, inhibits DNA methyltransferase (DNMT). Along with improved antibacterial efficacy against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*, mahanine also increases antioxidant properties (Mishra et al. 2020).

The top four lead compounds demonstrated to have a strong affinity with *Staphylococcus aureus* protein (ZINC3978117, ZINC1633855, ZINC14585298 and ZINC45338947) (Table 4). The amino acid residues Asn A3, Gln A10, Ala A 1, and Tyr A 14 of the *S. aureus* protein were discovered to interact with ZINC3978117 (Figure 4). Two amino acid residues, Asn A3 and Gln A10, interacted via a hydrogen bond with ZINC3978117. Two residues of the *Staphylococcus aureus* protein, Tyr A14 and His A18, were found to bind with ZINC1633855 (Figure 5). While His A18 of the *S. aureus* protein created a Pi-alkyl bond relationship, Tyr A14 formed a Pi-sigma bond interaction. ZINC14585298 was found to bind with Asn A11, Tyr A14 and Leu A17 residues of *S. aureus* protein (Figure 6). Asn A11 residue was involved in hydrogen bond interaction with the targeted protein

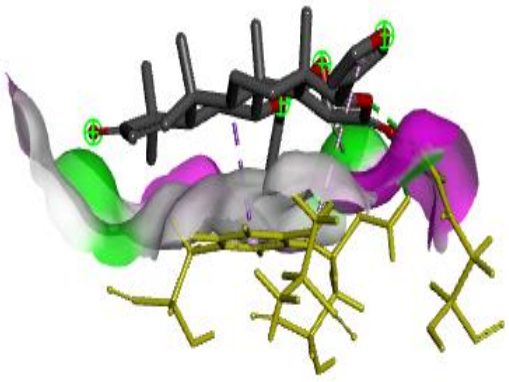
ZINC14585298, Tyr A14 was involved in the Pi-sigma bond, and Leu A17 was involved in Pi-alkyl Bond interaction. ZINC45338947 was revealed to bind with Tyr A34 and Leu A17 residues of S. aureus protein (Figure 6). Tyr A34 residue was involved in hydrogen bond interaction with ZINC45338947 while Leu A17 was involved in the Pi-alkyl bond. Prednisone (ZINC3875357) is used as the control compound in this study due to its previously reported inhibition effect on *Staphylococcus aureus*. Prednisone was observed to bind with two amino acid residues (Asn A3 and Gln A18) of the staphylococcus aureus protein (Figure 7).

Asn A3 formed a hydrogen bond interaction with Prednisone while Gln A18 formed attractive charges (Figure 8). Other compounds such as ZINC2525300 and ZINC2170446 had better binding with the, *Staphylococcus aureus* protein compared with the top four however they have lower docking scores and therefore, they were not recommended to proceed with further screening. ZINC2525300 was found to bind with Asn A11, Gln A10, His 11, Glu A15, and Tyr A14, while Asn A11, Gln A10, His

11 were involved in hydrogen bond interaction, Glu A15 was involved in Van der Waals interaction and Tyr A14 was involved in Pi-alkyl bond.

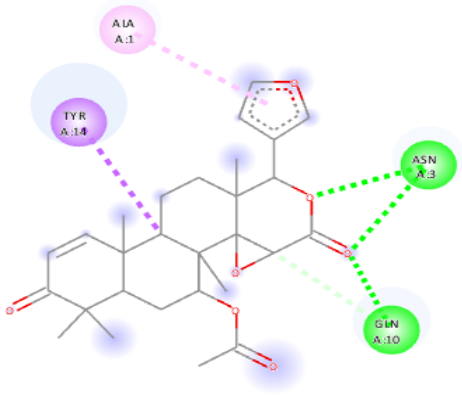
ZINC2170446 was found to bind with A28, Gln A26, Ser A33 A40, Ser A33, Phe A30, Ala A29, and Leu A59, while A28, Gln A26, Ser A33 A40, and Ser A33 were involved in hydrogen bond interaction, Phe A30 was involved in Pi-sigma bond and Ala A29, Leu A59 was involved in Pi-alkyl bond. The complexity of hydrogen bonds of ligand-protein target interaction determines the strength of molecular docking (Jaka et al. 2021).

Figure 4



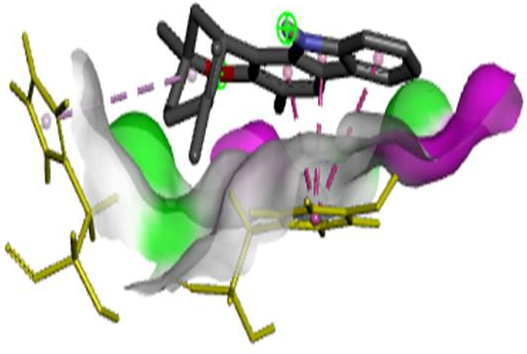
3D

Gedunin

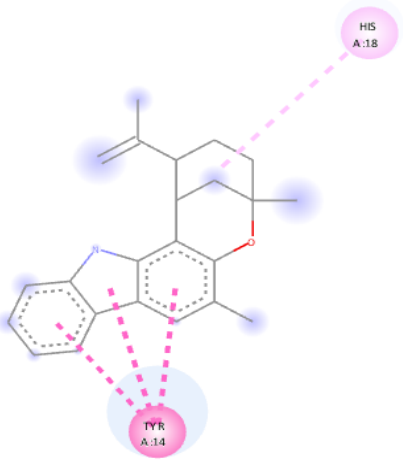


Gedunin 2D

Figure 5

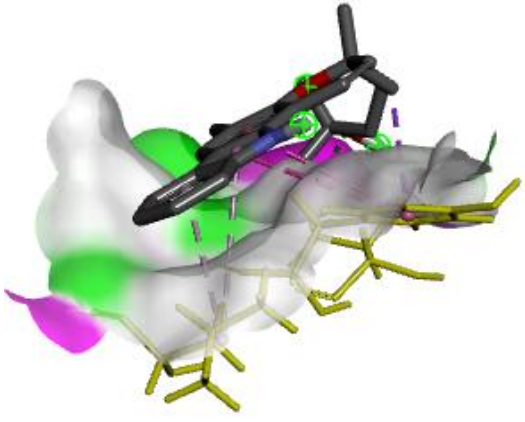


Curryanine 3D

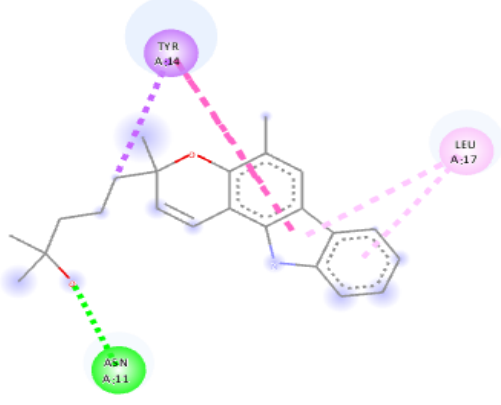


Curryanine 2D

Figure 6

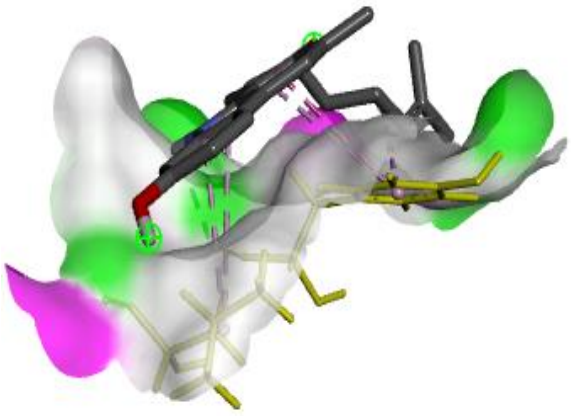


Mahanimbinine 3D

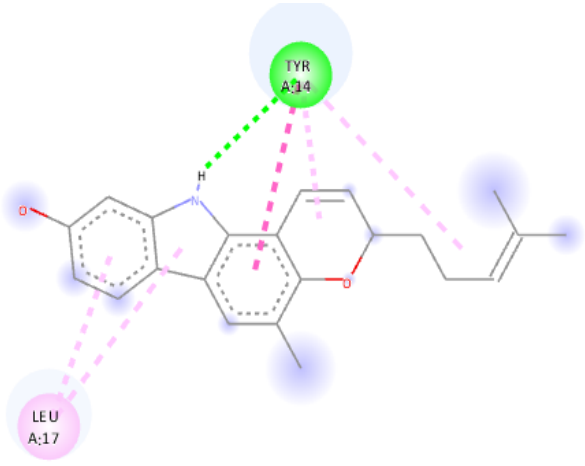


Mahanimbinine 2D

Figure 7

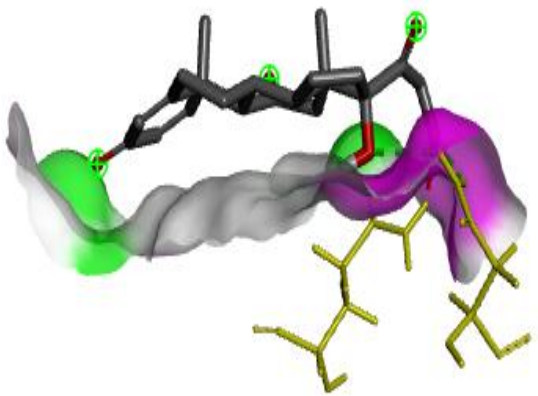


Mahanine 3D

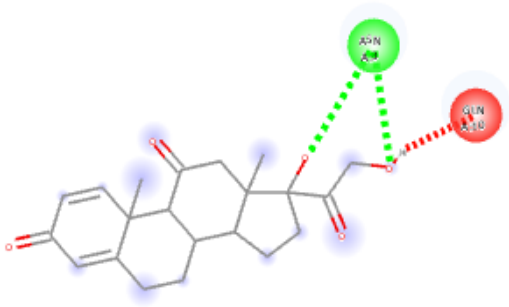


Mahanine 2D

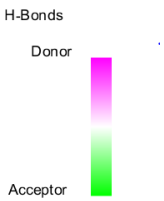
Figure 8

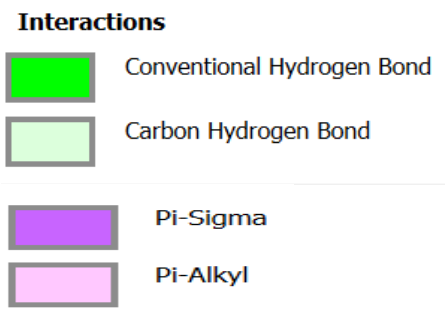


Prednisone 3D



Prednisone 2D





Conclusion

Drug development is a time-consuming and laborious procedure, but computational techniques have saved the day and unquestionably contributed to its simplification (Greethanjali et al. 2021, Preman et al. 2022,). Even if synthetic chemistry currently dominates the field of medication discovery and manufacture, the significance of chemicals derived from plants in the curative and prevention of numerous diseases cannot be understated. In the present study, 32 Phytoconstituents derived from *Azadirachta indica* and *Murraya koenigii* were screened to find lead molecules for *Staphylococcus aureus* protein (7TIO). A total of 15 Phytoconstituents qualified for SwissADME drug-likeness screening, out of which only four (4), namely Gedunin (-7.2 kCal/mol), Curryanine (-7.1 kCal/mol), Mahanimbinine (-6.6 kCal/mol) and Mahanine (-6.5 kCal/mol) exhibited significant binding with *Staphylococcus aureus* protein. These four compounds have shown better interaction with the protein target through a hydrogen bond, Van der Waals, Pi-sigma bond, Pi-alkyl bond and attractive charges. These interaction complexities determine the strength of molecular docking and therefore, these substances are potential active molecules since they could create stable complexes with target proteins. However, more research and confirmation of the actual mechanisms and results of treating the secondary infection of atopic eczema condition is recommended.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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