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ANTI-*STAPHYLOCOCCUS AUREUS* ACTIVITY, ADMET PROPERTIES AND MOLECULAR DOCKING STUDY OF PHYTOCOMPOUNDS FROM *ERIANTHEMUM DREGEI*

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ABSTRACT: The constant increase in the emergence of multidrug resistance among *Staphylococcus aureus* strains threatens public health. The study aimed at evaluating the anti-*S. aureus* activity, pharmacokinetic properties and interactions of compounds from *Erianthemum dregei* with proteins in *S. aureus*. Anti-*S. aureus* activity was investigated by broth dilution method while gas chromatography-mass spectrometry (GC-MS) was used to identify the compounds. The drug-likeness, pharmacokinetic and toxicity profiles of the compounds were predicted by SwissADME and PreADMET tools. AutoDock Vina was used to assessing the binding affinities of the docked ligand-receptor complexes. The extract revealed the minimum inhibitory concentration value of 0.78 mg/mL. Phytol (93.58%) and 3-tetradecyn-1-ol (6.42%) were the revealed constituents. *In-silico* predictions suggested both compounds to have drug-like properties as they adhered to the Lipinski's rule of five. Phytol was found to have non-mutagenic effects, while 3-tetradecyn-1-ol was predicted to be mutagenic. The compounds were non-carcinogenic on mice model and carcinogenic on rat`s. Phytol has a binding affinity to DNA-gyrase and FtsZ with docking energy values of -4.1 and -5.3 kcal/mol, respectively, whereas the docking scores for 3-tetradecyn-1-ol against DNA-gyrase and FtsZ were -3.9 and -5.0 kcal/mol. The results revealed the extract to have a noteworthy activity against *S. aureus*, with its identified compounds having desirable pharma-cokinetics.

INTRODUCTION: *Staphylococcus aureus* is a member of the family Micrococcaceae that are characterized as catalase-positive and Gram-positive aerobic cocci [1]. *S. aureus* is known known to cause clinical manifestations such pneumonia, endo-carditis, toxic shock syndrome, cellulitis, abscesses and impetigo at varying severity in humans [2]. Its infections are most predominant in developing countries, especially among the elderly, young children, and immunosuppressed people [3].

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Different strains of *S. aureus* harbour a combination of different virulence genes, which express factors used for adherence, colonisation, invasion and infectiousness [1].

S. aureus infections are exacerbated by the constant increase in the emergence of multidrug resistance, which threatens global public health [4]. Generally, *S. aureus* resists the effects of anti-microbial agents through enzymatic inactivation of the anti-microbials, modification of target protein receptors, and extrusion by efflux pulp [5].

Major contributors to its resistance are; (1) the inappropriate use of anti-microbials, (2) intake of improper dosages, and (3) excessive use of anti-microbials [6]. Methicillin-resistant *S. aureus* strains have become increasingly prevalent among both

nosocomial and community-acquired infections [7]. Some strains have also shown resistance to vancomycin, one of the anti-microbials of the last resort [8]. It is, therefore, imperative to search for new compounds which are characterized by high potency.

Medicinal plants are the predominant sources of bioactive compounds used in modern-day drug discoveries and developments [9]. Over 50% of drugs on the market shelves currently have their origin in medicinal plants [10]. This is because of the high accessibility, efficacy and generally low side effects of plant-based products [11]. A high percentage of medicinal plants are reported to have anti-microbial effects. The excellent potency and pharmacotherapeutic effects are owed to their diverse bioactive compounds such as phenolics, saponins, tannin, alkaloids and steroids [12]. Nevertheless, the majority of the newly discovered compounds are rejected in the last stages of drug discovery processes due to poor pharmacokinetic profiles [13, 14].

The pharmacokinetic profiles of compounds describe their absorption, distribution, metabolism and excretion (ADME) properties [15]. The consideration of evaluating the ADME characteristics at the early stages of drug discovery can reduce the pharmacokinetics-related failures. Although the classic methods used to assess pharmacokinetics are feasible, they take a considerable length of time and are expensive [16]. Recently, computational ADME methods are becoming the methods of choice in the assessment of ADME and toxicity properties at the early stages of drug discovery.

In the last decade, many ADME prediction models have been reported and have yielded outstanding results as several drugs have been identified using these approaches [17]. The *in-silico* methods turn to offer valuable direction prior to the commencing of *in-vitro* and *in-vivo* experiments [18]. They provide advantages for practical findings and assessment of mechanisms of actions. Since there are many pharmacological targets and because most compounds demonstrate pleiotropic effects by interacting with different targets, computational models help in finding the precise targets. Thus, the most prospective compounds among an array of compounds can be easily and quickly identified and validated. In addition, they help in making cost-effective assessments prior to the costly process of drug development [19]. Although, *in-silico* methods are well established in medicinal synthetic chemistry, their application in the field of natural compounds is still underexplored [20].

Erianthemum dregei is a parasitic shrub belonging to Loranthaceae family. It is widely distributed in the northern part of KwaZulu-Natal, South Africa [21]. *E. dregei* has been used in treatments of sexually transmitted diseases, snake-bites and stomach ailments [22]. However, there are limited scientific studies confirming the medicinal properties of this plant.

The purpose of this study was to evaluate the antibacterial activity of *E. dregei `s* methanolic leaf extract against *S. aureus* and assess the chemical composition of the extract using gas chromato-graphy-mass spectrophotometer (GC-MS). Moreover, the drug-likeness of the identified compounds was assessed based on their physicochemical properties using SwissADME and PreADME online tools. The pharmacokinetic parameters, bioactive scores and ligand-protein interactions were also predicted by SwissADME, Molinspiration, and Autodock-Vina tools, respectively.

MATERIALS AND METHODS:

Plant Collection and Extraction: The leaves of *E. dregei* were sampled from Manguzi and transported to the University of Zululand, South Africa (28 °45 ′S31 °54 ′E). The plant was authenticated by Dr. Ntuli, Department of Botany, University of Zululand, at the University Herbarium. The plant was allocated specimen number NNM01. The leaves were washed with tap water, dried at room temperature and milled to a fine powder. Plant material (20 g) was extracted with 200 mL of methanol (technical grade, Merck) at room temperature at a shaking speed of 130 rpm for 48 hours. Thereafter, it was filtered using Whatman No. 1 filter paper before being transferred into a pre-weighed glass container. The methanol was removed by evaporation under a stream of air in a fume-hood.

Minimum Inhibitory Concentration (MIC): The extract was evaluated for its antibacterial activity against *Staphylococcus aureus* (ATCC 25923).

Prior to the antibacterial activity test, the bacterium was resuscitated on nutrient broth and incubated at 37 °C. After overnight incubation, McFarland standard was used to standardize the inoculum density of the bacterium (1×10^6 CFU/mL) using a spectrophotometer (Spectroquant-Pharo 100). The MIC of the extract was assessed using the broth dilution method in a sterile 96-well plate. Mueller-Hinton broth (50 µL) was added into the wells and 50 µL of 100 mg/mL of the extract was added to the first row. Serial dilution was performed to vary the concentrations (50 - 0.3 mg/mL). About 50 µL of the bacterial suspension was separately pipetted into the wells and the plate was incubated at 37 °C. After overnight incubation, 40 µL of p-iodo-nitrotetrazolium violet (0.2 mg/mL) was added into each well and incubated at 37°C for 15 minutes. The lowest concentration that inhibited the growth of *S. aureus* (ATCC 25923) was considered as the MIC [23].

Minimum Bactericidal Concentration (MBC): Bactericidal effect of the extract was investigated on nutrient agar. Briefly, each well that demonstrated no visible bacterial growth during MIC evaluation was streaked on nutrient agar plates. Thereafter, the agar plates were incubated at 37°C for 24 h. The lowest concentration to induce a bactericidal effect on *S. aureus* (ATCC 25923) was considered as MBC [12].

Phytochemical Analysis: A phytochemistry test of the methanolic extract was done using GC-MS. The GC oven temperature was initially adjusted to 40 °C for 3 minutes and subsequently raised by 5°C per minute to 220°C. The injector temperature was set at 250°C and the flow rate of helium gas was 1.0 mL per minute, with a 10:1 split ratio. The MS system had an ion source temperature of 250°C and voltage of 70 eV [24].

Physicochemical and Pharmacokinetic Properties: SwissADME online tool was utilized to determine the physicochemical and pharmacokinetic properties of the identified compounds. The simplified molecular-input line-entry system (SMILES) for each compound was produced by the structure file generator, available at the SwissADME tool, after drawing their 2-dimensional structures. Thereafter, the physicochemical descriptors such as the molecular weight (MW), number of hydrogen bond acceptors (nHBA), number of hydrogen bond donors (nHBD) and number of rotatable bonds (nRB) were computed. The lipophilicity was evaluated using a consensus logP (cLog*P*) estimation [25, 26]. The aqueous solubility (Log*S*) was assessed using the three predictive models namely ESOL, Ali, and SILICOS-IT. The pharmacokinetic properties such as human intestinal absorption (HIA), penetration of the blood-brain barrier (BBB), the interaction of compounds with P-glyco-protein (P-gp), metabolism and skin permeability (Log*Kp*) were predicted [26].

Drug-likeness Prediction: The drug-likeness assessment was carried out using the validated rules used as filters in many pharmaceutical companies, as follows: Lipinski, Ghose, Veber, and Egan. Moreover, the bioavailability scores of the compounds were computed based on their molecular weight, cLog*P*, number of hydrogen bond acceptors and hydrogen bond donor [26, 27].

Bioactivity Scores: Bioactivity scores of the compounds were predicted using software Molin-spiration score online. The scores were evaluated against G protein-coupled receptors (GPCR ligand), ion channel modulator, a kinase inhibitor, nuclear receptor ligand, protease inhibitor and enzyme inhibitor [28].

Toxicological Study: The toxicological properties of the compounds were computed using the online server PreADMET. The 2D structural models of the compounds were drawn and each compound was screened to determine its mutagenicity, carcinogenicity and their ability to inhibit the human ether-a-go-go-related (hERG) gene [29].

Molecular Docking Study:

Retrieval and Preparation of the Receptors: The three-dimensional structures of the two target receptor proteins were retrieved from the Protein Data Bank (PDB). The receptor proteins were DNA-gyrase (PDB: ID5z9n) and FtsZ (PDB ID: 3v08). DNA-gyrase is responsible for DNA replication, while the FtsZ enzyme plays an important role in cell division [30]. The structures were loaded into the Biovia Discovery Studio 4.1 Visualizer. The water molecules, heteroatoms and ligands were deleted. Thereafter, polar hydrogen was added to the proteins.

Ligand Preparation: The structures of the identified compounds and ciprofloxacin (control) were procured from the National Centre for Biotechnology Information (NCBI) PubChem compound database. The compounds were downloaded in Structure-Data File (SDF) format and converted to PDB coordinates using Biovia Discovery Studio 4.1 visualizer and energy minimised.

Docking and Visualisation of the Complexes: The docking of the target proteins with the ligands was done using AutoDock Vina [31]. Docking was performed to get a set of possible conformations and orientations for the ligand at the binding site. The ligand displaying the lowest binding affinity was chosen as the best conformation. The docked protein-ligand complexes were visualized using Biovia Discovery Studio 4.1 Visualiser to analyze the formed interactions.

RESULTS AND DISCUSSION:

Antibacterial Activity: The extract was tested for its *in-vitro* antibacterial activity against *S. aureus* ATCC 25922. *S. aureus* (ATCC 25923) was susceptible against the extract with the MIC value of 0.78 mg/mL **Table 1**. The extract was more effective than the positive control-ciprofloxacin, which gave the MIC value of 3.13 mg/mL. Gram-positive strains are often susceptible to most anti-microbial agents due to their outer membrane, which tends to allow some anti-microbials to penetrate the bacterial cells and inhibit the bacterial growth through different mechanisms [32]. The extract demonstrated an MBC value greater than 50 mg/mL against *S. aureus* ATCC 25922 **Table 1**. This implied that the extract has only bacteriostatic effect at the utilized concentrations. Nevertheless, the results do not nullify the potential of the extract as a source of therapeutic antibacterial compounds.

TABLE 1: MINIMUM INHIBITORY CONCENTRATION AND MINIMUM BACTERICIDAL CONCENTRATION OF THE EXTRACT

Bacterium	Extract		Ciprofloxacin	
	MIC (mg/mL)	MBC (mg/mL)	MIC (mg/mL)	MBC (mg/mL)
S. aureus (ATCC 25923)	0.78±0	> 50±0	3.13±0	6.25±0

Chemical Composition: The GC-MS chromatogram profile revealed the presence of 3, 7, 11, 15-tetramethyl-hexadecen-1-ol also known as phytol (93.58%) and 3-tetradecyn-1-ol (6.42%) **Table 2** and **Fig. 1**. Phytol is a diterpene used as precursor for vitamin K and is recognised for its anti-microbial, anticancer, ant-inflammatory, anti-diuretic, hypocholesterolemic and antioxidant activities [33]. 3-Tetradecyn-1-ol is an alcoholic compound that has antibacterial effect [34]. Thus, the compounds were assumed to have contributed to the antibacterial activity of the extract against *S. aureus* (ATCC 25923).

TABLE 2: PHYTOCOMPOUNDS IDENTIFIED BY GC-MS

Number of compounds	Compounds	Area (%)
1	Phytol	93.58
2	3-Tetradecyn-1-ol	6.42

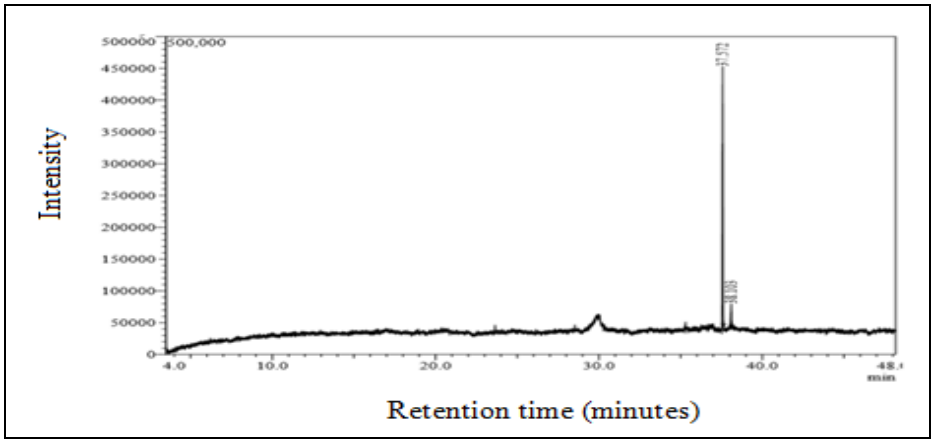

FIG. 1: A GC-MS CHROMATOGRAM PEAK PROFILE OF METHANOLIC *ENCEPHALARTOS FEROX* FRUIT EXTRACT

MW, nHBA and nHBA: The molecular weight (MW) plays a pivotal role in the drug action: the higher the MW (500 g/mol ≤ MW), the poorer the absorption and bioavailability [35]. The MW of

phytol and 3-tetradecyn-1-ol were calculated and the results are shown in **Table 3**. Phytol and 3-tetradecyn-1-ol were found to be 296.5 g/mol and 210.36 g/mol, respectively. This implied that both compounds have potential to be easily absorbed and transported as they comply with the Lipinski's rule of five concerning MW. The number of hydrogen bond acceptor (nHBA) and bond acceptors (nHBA) and were calculated and the results are illustrated in **Table 3**. The results indicated that both phytol and 3-tetradecyn-1-ol have one hydrogen bond acceptor and one hydrogen donor. Lipinski's rule of five states that the drug-like compounds ought to have less than or equal to ten hydrogen bond acceptors (nHBA ≤ 10) and less than or equal to five hydrogen bond donors (nHBA ≤ 5). Based on the obtained results, both compounds have potential to be used as oral drug candidates.

TABLE 3: THE PHYSICOCHEMICAL PROPERTIES AND LIPOPHILICITY OF THE IDENTIFIED COMPOUNDS

Compounds	Properties				
	MW (g/mol)	nHBD	nHBA	nRB	CLog*P*
Phytol	296.5	1	1	13	6.22
3-Tetradecyn-1-ol	210.36	1	1	9	4.27

nRB and cLog*P*: The number of rotatable bonds (nRB) is a measure of molecular flexibility and is one of the widely used filters during drug discovery process [36]. **Table 3** displays the nRB of the two identified compounds. 3-Tetradecyn-1-ol has nine rotatable bonds, while phytol possesses 13 rotatable bonds. Therefore, only 3-tetradecyn-1-ol adhere to the filter which states that the number of rotatable bonds ought to be ≤ 10 [37]. This means that phytol exhibits low conformational flexibility in comparison to 3-tetradecyn-1, hence it has a high probability of being bioavailable. The lipophilicity (cLog*P*) of the compounds is a quality that is used to calculate their hydrophilicity. The cLog*P* plays a major role in ADME processes of drug-like compounds, consequently influencing their therapeutic potential and adverse effects [38]. The cLog*P* values of phytol and 3-tetradecyn-1-ol were calculated and the results are displayed in **Table 3.** Phytol was estimated to have cLog*P* value of 6.22 whereas 3-tetradecyn-1-ol has cLog*P* value of 4.27. Low cLog*P* values (cLog*P*≤5) translate better absorption and bioavailability and vice versa. On this basis, only 3-tetradecyn-1-ol has a reasonable probability of being bioavailable.

Solubility Properties: The aqueous solubility of a compound is a significant parameter that greatly affects its absorption and distribution characteristics [39]. Typically, low solubility goes along with a poor absorption and therefore the general aim is to avoid poorly soluble compounds. The solubility of the identified compounds is demonstrated in **Table 4**. The results revealed that phytol is moderately soluble to poorly soluble while 3-tetradecyn-1-ol is soluble to moderately soluble, depending on the Log*S* prediction model. Thus, it was concluded that both compounds have the potential to be absorbed and available in biological systems [40].

TABLE 4: SOLUBILITY PREDICTIONS OF THE IDENTIFIED COMPOUNDS

Properties	Compounds	
	Phytol	3-Tetradecyn-1-ol
Log*S* (ESOL)	-5.98	-3.95
Class	Moderately soluble	Soluble
Log*S* (Ali)	-8.47	-5.58
Class	Poorly soluble	Moderately soluble
Log*S* SILICOS-IT	-5.51	-4.23
Class	Moderately soluble	Moderately soluble

Pharmacokinetic Properties: The gastrointestinal absorption (GIA) of the identified compounds was evaluated and the results are presented in **Table 5.** Phytol was estimated to have low GIA, while 3-tetradecyn-1-ol demonstrated high potential to be absorbed in the gastrointestinal tract. High GIA is considered an advantage during oral administration. Thus, only 3-tetradecyn-1-ol has good probability of being absorbed in the intestinal cells and exerts its activity. The blood-brain barrier (BBB) is the endothelial cell layer of the brain that separates the brain from the blood. It regulates the exchange of drug-like compounds between blood and brain [41]. The ability of the identified compounds to permeate through BBB was predicted and the results are illustrated in **Table 5.** 3-Tetradecyn-1-ol demonstrated the potential to penetrate through the BBB, whereas phytol did not. The ability of compounds to penetrate BBB is of advantage for compounds needed in the central nervous system

(CNS) whereas BBB permeability ought to be minimised for non-CNS compounds to avoid adverse side-effects [42]. Based on the results, 3-tetradecyn-1-ol is a good candidate for treating diseases affecting CNS. The prediction of P-glycoprotein (P-gp) substrates facilitates early identification and elimination of drug candidates of low efficacy. The effects of the compounds on P-gp are illustrated in **Table 5**. Phytol showed ability to act as a substrate of P-gp, whereas 3-tetradecyn-1-ol did not. P-gp is an ATP-dependent efflux transporter which is a product of the gene that confers multidrug resistance [43]. Thus, the over-expression of P-gp may hamper the therapeutic activities of phytol and not 3-tetradecyn-1-ol.

TABLE 5: THE PHARMACOKINETIC PARAMETERS OF THE PHYTOCOMPOUNDS

Properties	Compounds	
	Phytol	3-Tetradecyn-1-ol
GIA	Low	High
BBB permeant	No	Yes
P-gp substrate	Yes	No
CYP1A2 inhibitor	No	Yes
CYP2C19 inhibitor	No	No
CYP2C9 inhibitor	Yes	No
CYP2D6 inhibitor	No	No
CYP3A4 inhibitor	No	No
Log*Kp* (cm/s)	-2.29	-3.75

Metabolism of compounds influences their absorption, distribution and excretion. Cytochrome P450 (CYP) monooxygenase is a class of enzymes that influences drug metabolism and elimination in the body [44]. The computed metabolism of the identified compounds against five isomers of CYP is displayed in **Table 5**. It was observed that phytol has the potential to only inhibit CYP2C9 while 3-tetradecyn-1-ol is an inhibitor of CYP1A2. Thus, majority of the tested CYP isomers were not inhibited by the two compounds. This means that the compounds have a high probabilities of being metabolised and exert their activities at the targeted sites, and eliminated thereafter. The skin permeability (Log*Kp*) is an important parameter for the investigation of compounds that require transdermal administration [45]. The skin permeability of the identified compounds was predicted and the results are shown in **Table 5**.

Phytol and 3-tetradecyn-1-ol had -2.29 cm/s and -3.75 cm/s, respectively. Thus, both compounds were predicted to be impermeable through the skin as they both have a negative Log*Kp*. This means that alternative routes are to be adapted when ministering this compounds. Moreover, the compounds do not present any risk upon contact with the skin [46].

Drug-likeness and Bioavailability: Lipinski rule of five is the widely used filter for drug-like properties [47]. According to Lipinski rule of five, compounds are likely to be accepted active drug-like compounds when they have: less than 5 hydrogen bond donor (nHBD ≤ 5), less than 10 hydrogen bond acceptors (nHBA ≤ 10), molecular weight ≤ 500 Da and clog*P* value≤5. Moreover, compounds that violate more than one of the rules are assumed to display difficulties in bioavailability [26]. The drug-likeness of the identified compounds is displayed in **Table 6.** Phytol and 3-tetradecyn-1-ol proved to comply with Lipinski rule. Based on the observed results, both compounds have the potential to be good drug candidates. Moreover, although phytol complied only with Lipinski rule, 3-tetradecyn-1-ol was also found in compliance with other filters such as Ghose, Veber, and Edgan. The bio-availability of phytol and 3-tetradecyn-1-ol were computed and the results are shown in **Table 6.** Both compounds were predicted to have 55% (0.5) probability of achieving the bioavailability endpoints. Normally, the amount of the compounds which reach the systemic circulation is less than the administered dose. However, compounds that display more than or equal to 50% probability of being bioavailable are generally accepted [48]. Thus, both compounds are an advantage as they displayed more than 50% probability of being bioavailable upon administration[49].

TABLE 6: DRUG-LIKENESS AND BIOAVAILABILITY SCORES OF THE COMPOUNDS

Filters	Drug-likeness	
	Phytol	3-Tetradecyn-1-ol
Lipinski	Yes	Yes
Ghose	No	Yes
Veber	No	Yes
Egan	No	Yes
Bioavailability score	0.55	0.55

Bioactive Scores: The bioactivity scores of the compounds are represented in **Table 7.** According to the bioactivity score evaluation parameters, compounds are interpreted as active (scores > 0), moderately active (scores: -5.0-0.0) and inactive (bioactivity score < -5.0) [50]. Phytol revealed to be

active against all tested parameters, except against kinase where it showed moderate activity. 3-Tetradecyn-1-ol is active as an ion channel modulator, nuclear receptor ligand and enzyme inhibitor. It also demonstrated moderate activity against other tested proteins. Thus, these compounds have the potential to treat diseases caused by hyperactive protein kinases, protease and other enzymes. Moreover, since nuclear receptors are key regulators of some metabolic disorders such as cancer, both compounds are promising therapeutic alternatives against such diseases [51]. In general, both compounds can be used as pharmacologically active agents against various diseases.

TABLE 7: BIOACTIVITY SCORES OF THE PHYTOCOMPOUNDS

Properties	Compounds	
	Phytol	3-Tetradecyn-1-ol
GPCR ligand	0.11	-0.10
Ion channel modulator	0.16	0.30
Kinase inhibitor	-0.32	- 0.21
Nuclear receptor ligand	0.35	0.06
Protease inhibitor	0.00	-0.16
Enzyme inhibitor	0.31	0.25

Toxicological Studies: The mutagenicity, carcinogenicity and capabilities of the compounds to inhibit hERG were evaluated using PreADMET and the results are displayed in **Table 8**. Ames toxicity test was employed to predict the mutagenicity of the compounds. Phytol was found to have non-mutagenic effects, while 3-tetradecyn-1-ol was predicted to be mutagenic. This means that only 3-tetradecyn-1-ol has the potential to alter the genetic makeup in biological systems, consequently causing undesirable side effects and neurodegenerative diseases [52]. Carcinogenicity is the capability of the compounds to induce modifications that can lead to cancer in the cells [53].

According to PreADMET, the negative prediction translates clear evidence of carcinogenic activity, whereas positive means the compounds are not carcinogenic [29]. The carcinogenic profiles of the compounds revealed that both phytol and 3-tetradecyn-1-ol were non-carcinogenic on the mouse model and carcinogenic on rat`s. Moreover, both compounds are unlikely to inhibit hERG gene as they demonstrated low risks. Inhibition of the hERG gene has been strongly associated with prolonging QT syndrome, which often results in sudden heart attacks [54].

TABLE 8: TOXICOLOGICAL PROPERTIES OF THE PHYTOCOMPOUNDS

Compounds	Mutagenicity (Ames test)	Carcinogenicity		hERGinhibition
		Rat	Mouse	
Phytol	Non-mutagen	Negative	Positive	Low risk
3-Tetradecyn-1-ol	Mutagen	Negative	Positive	Low risk

Molecular Docking: Anti-microbial agents (ligands) inhibit cell wall synthesis, nucleic acid synthesis, protein synthesis and metabolic pathways by binding to the specific proteins which are responsible for biological activities [55]. To understand the mechanism of anti- *S. aureus* activity of the identified ligands, a molecular docking study was carried out. The binding energy of the selected proteins against the identified ligands is tabulated in **Table 9.** The results show that phytol has a binding affinity to DNA-gyrase and FtsZ with docking energy values of -4.1 and -5.3 kcal/mol, respectively. The docking scores for 3-tetradecyn-1-ol against DNA-gyrase and FtsZ are -3.9 and -5.0 kcal/mol. The positive control-ciprofloxacin displayed the binding energy scores of -6.9 1 kcal/mol against DNA-gyrase and -7.1 kcal/mol against FtsZ. Protein-ligand binding occurs extemporaneously when the free energy change is negative. The negative energy scores signpost the stability of the protein-ligand complexes and the lower the binding free energy, the better the binding affinity. The compounds showed binding scores that correlate to the moderate binding affinity. However, phytol revealed the lowest free binding energy against all selected receptor proteins in comparison to 3-tetradecyn-1-ol, indicative of better binding affinity than 3-tetradecyn-1-ol. Nevertheless, both compounds showed binding affinities lower than that of the standard drug-ciprofloxacin, which displayed the binding energy in the range of -6.91 kcal/mol with DNA-gyrase and -7.1 kcal/mol with FtsZ. The efficacy of weak binders like the identified compounds in comparison to the positive control-ciprofloxacin might be due to the high dissociation rates they possess and the likelihood to bind to a large number of various targets in *S. aureus* [56].

TABLE 9: MOLECULAR DOCKING ANALYSIS OF THE COMPOUNDS WITH DIFFERENT RECEPTOR PROTEINS

Compounds	Receptors	Binding scores (kcal/mol)	H-bonds interaction residues	Number of other interacting residues
Phytol	DNA-gyrase	-4.1	ILE A:94, VAL A:97, SER A:121	8
	FtsZ	-5.3	GLY A:34, GLN A:195	14
3-Tetradecyn-1-ol	DNA-gyrase	-3.9	SER A:121	8
	FtsZ	-5.0	THR A:265, ASN A:263	10
Ciprofloxacin	DNA-gyrase	-6.9	VAL A:120, SER A:121, ILE A:94	10
	FtsZ	-7.1	ASN A:299, ASN A:263	8

Hydrogen and other interactions are contributors to binding affinities and the stabilities of ligand-receptor complexes. The H-bond interactions and the number of other interactions of the selected receptors against the identified ligands are displayed in **Table 9, Fig. 2** and **Fig. 3.**

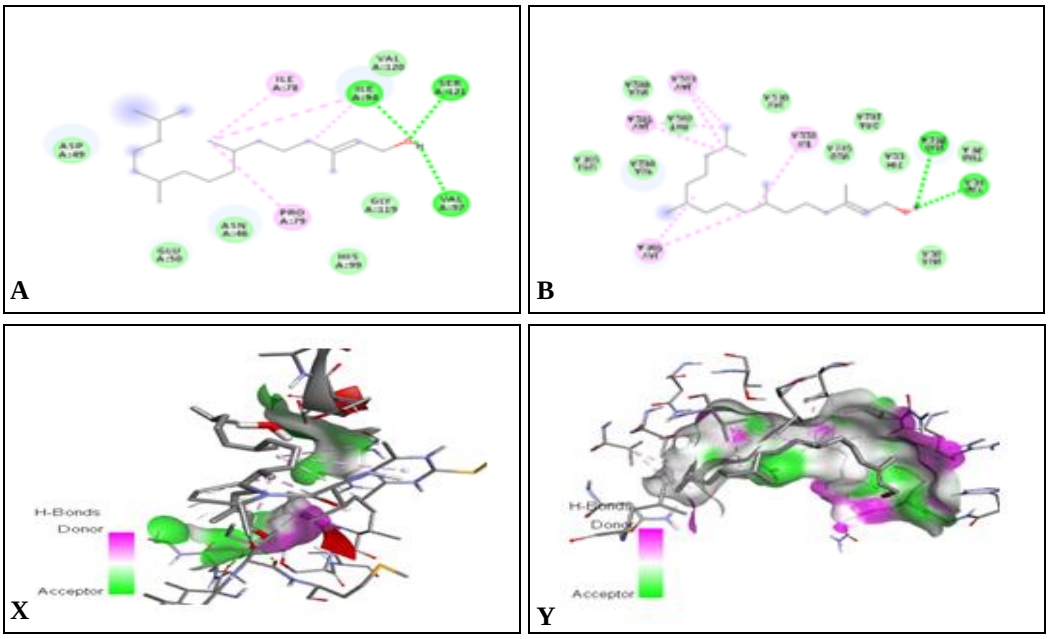

FIG. 2: 2 DIMENSIONAL (2D) AND 3 DIMENSIONAL (3D) STRUCTURES OF DOCKED COMPLEXES. A AND X ARE 2D AND 3D OF PHYTOL-DNA-GYRASE COMPLEXES. B AND Y ARE 2D AND 3D OF PHYTOL-FTSZ COMPLEXES

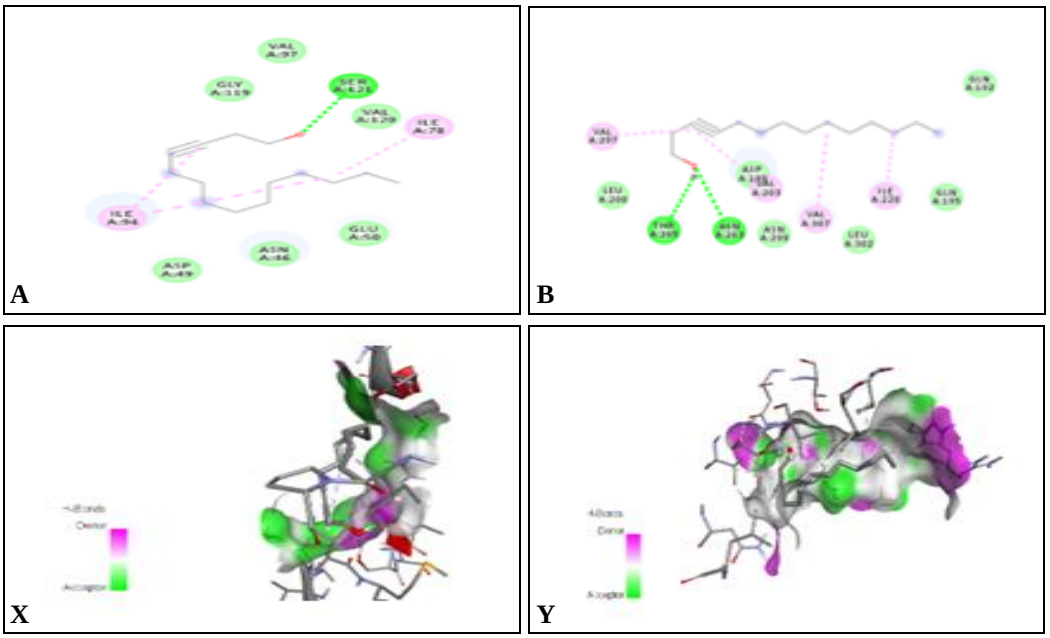

FIG. 3: 2D AND 3D STRUCTURES OF DOCKED COMPLEXES. X AND A ARE 2D AND 3D OF 3-TETRADECYN-1-OL -DNA-GYRASE COMPLEXES. Y AND B ARE 2D AND 3D OF 3-TETRADECYN-1-OL -FTSZ COMPLEXES

Although phytol manifests poor binding energy for DNA-gyrase, it showed the highest number of H-bonds. Phytol revealed three H-bonds with the amino acids ILE A:94, VAL A:97, and SER A:121. It also demonstrated alkyl interactions with ILE A:78 and PRO A:A:79 and van der Waals interactions. 3-Tetradecyn-1-ol displayed one H-bond with SER A:121, alkyl interactions with ILE A:94 and ILE A:78 and van der Waals bonds with the remaining residues. With FtsZ protein, phytol revealed H-bonds with the amino acids GLY A:34 and GLN A:195. Other interacting forces that occurred are alkyl (VAL A:307, VAL A:297, VAL A:203, and ILE A:228) and van der Waals interactions. THR A:265 and ASN A:263 of FtsZ formed H-bonds with 3-tetradecyn-1-ol. The ligand also interacted through alkyl bonds with ILE A:228, VAL A:307, VAL A:203 and VAL A:297 and van der Waals forces with the rest of the residues. The results imply that the two compounds have the potential to inhibit *S. aureus* by forming biological interactions with the target proteins, consequently resulting in the inhibition of the metabolic reactions [55].

CONCLUSION: The extract revealed noteworthy antibacterial activity against *S. aureus* (ATCC 25923). Phytol and 3-tetradecyn-1-ol were the only chemical constituents. Both compounds demonstrated to have drug-like and desirable ADME properties. The drug-like property predictions showed that both compounds comply with the Lipinski rule of five. Phytol was found to be non-mutagen but carcinogenic on rat model. Nevertheless, 3-tetradecyn-1-ol is estimated to cause mutagenic effects and carcinogenic effects in rats. Both compounds demonstrated a margin of safety as they have low probabilities of acting as hERG inhibitors. The compounds showed abilities to inhibit bacterial growth through interaction with DNA-gyrase and FtsZ proteins. Further research needs to be undertaken using *in-vitro* and *in-vivo* methods to validate the predictive results.

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REFERENCES:

1. Dunyach-Remy C, Ngba EC, Sotto A and Lavigne JP: *Staphylococcus aureus* toxins and diabetic foot ulcers: role in pathogenesis and interest in diagnosis. Toxins 2016; 8: 209.
2. Tong SY, Davis JS, Eichenberger E, Holland TL and Fowler VG: *Staphylococcus aureus* infections: epidemiology, pathophysiology, clinical manifestations, and management. Clin Microbiol Rev 2015; 28: 603-61.
3. Thorlacius-Ussing L, Sandholdt H, Larsen AR, Petersen A and Benfield T: Age-dependent increase in incidence of *Staphylococcus aureus* bacteremia, Denmark, 2008-2015. Emerg Infect Dis 2019; 25(5): 875.
4. Lin J, Xu P, Peng Y, Lin D, Ou Q, Zhang T, Bai C, Ye X, Zhou J and Yao Z: Prevalence and characteristics of *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* nasal colonization among a community-based diabetes population in Foshan, China. J Diabetes Invest 2017; 8: 383-91.
5. Reygaert WC: An overview of the anti-microbial resistance mechanisms of bacteria. AIMS Microbiology 2018; 4(3): 482.
6. George TK, Joy A, Divya K and Jisha M: *In vitro* and *in silico* docking studies of antibacterial compounds derived from endophytic *Penicillium setosum*. Microb Pathog 2019; 131: 87-97.
7. Marzec NS and Bessesen MT: Risk and outcomes of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia among patients admitted with and without MRSA nares colonization. Am J Infect Control 2016; 44: 405-08.
8. Mandal SM, Ghosh AK and Pati BR: Dissemination of antibiotic resistance in methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *S. aureus* strains isolated from hospital effluents. Am J Infect Control 2015; 43: e87-e88.
9. Newman DJ: Are Microbial endophytes the actual producers of bioactive antitumor agents? Trends Cancer 2018; 4: 662-70.
10. Gouda S, Das G, Sen SK, Shin HS and Patra JK: Endophytes: a treasure house of bioactive compounds of medicinal importance. Front Microbiol 2016; 7: 1538.
11. Mensah ML, Komlaga G, Forkuo AD, Firempong C, Anning AK and Dickson RA: Toxicity and safety implications of herbal medicines used in Africa. Herbal Medicine 2019; 63: 1992-0849.
12. Maliehe TS, Shandu JS, Basson AK, Simelane MB, Lazarus G and Singh M: Pharmacodynamic and cytotoxicity effects of *Syzygium cordatum* {S Ncik, 48 (UZ)} fruit-pulp extract in gastrointestinal tract infections. Trop J Pharm Res 2017; 16: 1349-55.
13. Ammar O: *In-silico* pharmacodynamics, toxicity profile and biological activities of the Saharan medicinal plant *Limoniastrum feei*. Braz J Pharm Sci 2017; 53: e61.
14. Fogel DB: Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: a review. Contemp Clin Trials Commun 2018: 11: 156-64.
15. Park MH, Shin SH, Byeon JJ, Lee GH, Yu BY and Shin YG: Prediction of pharmacokinetics and drug-drug interaction potential using physiologically based pharmacokinetic (PBPK) modeling approach: A case study of caffeine and ciprofloxacin. Korean J Physiol Pharmacol 2017; 21(1): 107.
16. Sreelakshmia V, Raj N and Abrahama A: Evaluation of the drug-like properties of Kaempferol, Chrysophanol and Emodin and their interactions with EGFR tyrosine kinase -

An *in-silico* approach. Nat Prod Commun 2017; 12: 1934578X1701200621.
17. Durán-Iturbide NA, Díaz-Eufracio BI and Medina-Franco JL: *In-silico* ADME/Tox profiling of natural products: A focus on biofacquim. ACS Omega 2020; 5(26): 16076-84.
18. Brogi S, Ramalho TC, Kuca K, Medina-Franco JL and Valko M: *In-silico* Methods for Drug Design and Discovery. Front Chem 2020; 8: 612.
19. Bibi S and Sakata K: Current status of computer-aided drug design for type 2 diabetes. Curr Comput-Aided Drug Des 2016; 12: 167-77.
20. Maliehe TS, Tsilo PK and Shandu JS: Computational Evaluation of ADMET properties and bioactive score of compounds from *Encephalartos ferox*. Pharmacogn J. 2020; 12(6): 1357-62.
21. Clark NF, McComb JA and Taylor-Robinson AW: Host species of mistletoes (Loranthaceae and Viscaceae) in Australia. Aust J Bot 2020; 68(1): 1-13.
22. CondeP, Figueira R, Saraiva S, Catarino L, Romeiras M and Duarte MC: The Botanic Mission to Mozambique (1942-1948): contributions to knowledge of the medicinal flora of Mozambique. Hist Cienc Saude Manguinhos 2014; 21(2): 539-85.
23. Blondeau JM and Fitch SD: Mutant prevention and minimum inhibitory concentration drug values for enrofloxacin, ceftiofur, florfenicol, tilmicosin and tulathromycin tested against swine pathogens *Actinobacillus pleuropneumoniae*, *Pasteurella multocida* and *Streptococcus suis*. PLoS One 2019; 14(1): e0210154.
24. Wibowo DP, Mariani R, Hasanah SU and Aulifa DA: Chemical constituents, antibacterial activity and mode of action of Elephant ginger (*Zingiber officinale* var. officinale) and Emprit ginger rhizome (*Zingiber officinale* var. amarum) essential oils. Pharmacog J 2020; 12: 404-09.
25. Ranjith D and Ravikumar C: SwissADME predictions of pharmacokinetics and drug-likeness properties of small molecules present in *Ipomoea mauritiana*. J Pharmacogn Phytochem 2019; 8(5): 2063-73.
26. Daina A, Michielin O and Zoete V: SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep 2017; 7: 42717.
27. Al Wasidi AS, Hassan AS and Naglah AM: *In-vitro* cytotoxicity and druglikeness of pyrazolines and pyridines bearing benzofuran moiety. J Appl Pharm Sci 2020; 10(04): 142-48.
28. Khan T, Dixit S, Ahmad R, Raza S, Azad I, Joshi S and Khan AR: Molecular docking, PASS analysis, bioactivity score prediction, synthesis, characterization and biological activity evaluation of a functionalized 2-butanone thiosemicarbazone ligand and its complexes. J Chem Biol 2017; 10(3): 91-04.
29. Cruz JV, Serafim RB, da Silva GM, Giuliatti S, Rosa JM, Neto MFA, Leite FH, Taft CA, da Silva CH and Santos CB: Computational design of new protein kinase 2 inhibitors for the treatment of inflammatory diseases using QSAR, pharmacophore-structure-based virtual screening, and molecular dynamics. J Mol Model 2018; 24(9): 1-16.
30. Acar C, Yalçın G, Ertan-Bolelli T, Onurdağ FK, Ökten S, Şener F and Yıldız İ: Synthesis and molecular docking studies of some novel anti-microbial benzamides. Bioorg Chem 2020; 94: 103368.
31. Umesh HR, Ramesh KV and Devaraju KS: Molecular docking studies of phytochemicals against trehalose–6–phosphate phosphatases of pathogenic microbes. Beni-Seuf Univ J Appl 2020; 9(1): 5.
32. Uche-Okereafor N, Sebola T, Tapfuma K, Mekuto L, Green E and Mavumengwana V: Antibacterial activities of crude secondary metabolite extracts from Pantoea species obtained from the stem of *Solanum mauritianum* and their effects on two cancer cell lines. Int J Environ Res Public Health 2019; 16: 602.
33. Islam MT, Ayatollahi SA, Zihad SNK, Sifat N, Khan MR, Paul A, Salehi B, Islam T, Mubarak MS, Martins N and Sharifi-Rad J: Phytol anti-inflammatory activity: Pre-clinical assessment and possible mechanism of action elucidation. Mol Cell Biol 2020; 66(4): 264-69.
34. Hoque MN, Mondal MF and Khan MMH: Chemical composition and anti-microbial activity of the essential oils from *Aquillaria malaccensis* in Bangladesh. Haya: Saudi J Life Sci 2018; 3: 600-08.
35. Di L, Artursson P, Avdeef A, Benet LZ, Houston JB, Kansy M, Kerns EH, Lennernäs H, Smith DA and Sugano K: The critical role of passive permeability in designing successful drugs. ChemMedChem 2020; 15(20): 1862-74.
36. Loureiro DR, Soares JX, Costa JC, Magalhães ÁF, Azevedo CM, Pinto MM and Afonso CM: Structures, activities and drug-likeness of anti-infective xanthone derivatives isolated from the marine environment: A review. Molecules 2019; 24(2): 243.
37. Zerroug A, Belaidi S, BenBrahim I, Sinha L and Chtita S: Virtual screening in drug-likeness and structure/activity relationship of pyridazine derivatives as Anti-Alzheimer drugs. J King Saud Univ Sci 2019; 31(4): 595-01.
38. Chmiel T, Mieszkowska A, Kempińska-Kupczyk D, Kot-Wasik A, Namieśnik J and Mazerska Z: The impact of lipophilicity on environmental processes, drug delivery and bioavailability of food components. Microchem J 2019; 146: 393-06.
39. Coltescu AR, Butnariu M and Sarac I: The Importance of Solubility for New Drug Molecules. Biomed Pharmacol J 2020; 13(2): 577-83.
40. Dima C, Assadpour E, Dima S and Jafari SM: Bioavailability and bioaccessibility of food bioactive compounds; overview and assessment by *in-vitro* methods. Compr Rev Food Sci Food Saf2020; 19(6): 2862-84.
41. Weber V, Olzscha H, Längrich T, Hartmann C, Jung M, Hofmann B, Horstkorte R and Bork K: Glycation Increases the Risk of Microbial Traversal through an Endothelial Model of the Human Blood-Brain Barrier after Use of Anesthetics. J Clin Med 2020; 9(11): 3672.
42. Bors LA and Erdő F: Overcoming the blood–brain barrier. Challenges and tricks for CNS drug delivery. Sci Pharm 2019; 87(1): 6.
43. Dewanjee S, Dua TK, Bhattacharjee N, Das A, Gangopadhyay M, Khanra R, Joardar S, Riaz M, Feo VD and Zia-Ul-Haq M: Natural products as alternative choices for P-glycoprotein (P-gp) inhibition. Molecules 2017; 22(6): 871.
44. Reed L, Arlt VM and Phillips DH: The role of cytochrome P450 enzymes in carcinogen activation and detoxication: an *in vivo–in vitro* paradox. Carcinogenesis 2018; 39(7): 851-59.
45. Chen CP, Chen CC, Huang CW and Chang YC: Evaluating molecular properties involved in transport of small molecules in stratum corneum: a quantitative structure-activity relationship for skin permeability. Molecules 2018; 23(4): 911.
46. Sun Y, Hewitt M, Wilkinson SC, Davey N, AdamsRG, Gullick DR and Moss GP: Development of a Gaussian Process–feature selection model to characterise (poly) dimethylsiloxane (Silastic®) membrane permeation. J Pharm Pharmacol 2020; 72(7): 873-88.

47. Loureiro DR, Soares JX, Costa JC, Magalhães ÁF, Azevedo CM, Pinto MM and Afonso CM: Structures, activities and drug-likeness of anti-infective xanthone derivatives isolated from the marine environment: A review. Molecules 2019; 24(2): 243.
48. Tripathi P, Ghosh S and Talapatra SN: Bioavailability prediction of phytochemicals present in *Calotropis procera* (Aiton) R. Br. by using Swiss-ADME tool. World Sci News 2019; 131: 147-63.
49. Ilieva Y, Kokanova-Nedialkova Z, Nedialkov P and Momekov G: *In-silico* ADME and drug-likeness evaluation of a series of cytotoxic polyprenylated acylphloroglucinols, isolated from *Hypericum annulatum* Morris subsp. annulatum. Bulg Chem Commun 2018; 193.
50. Flores-Holguín N, Frau J and Glossman-Mitnik D: Chemical-reactivity properties, drug likeness, and bioactivity scores of seragamides A–F anticancer marine peptides: conceptual density functional theory viewpoint. Computation 2019; 7(3): 52.
51. Dhiman VK, Bolt MJ and White KP: Nuclear receptors in cancer-uncovering new and evolving roles through genomic analysis. Nat Rev Genet 2018; 19(3): 160.
52. Makhafola TJ, Elgorashi EE, McGaw LJ, Awouafack DA, Verschaeve L and Eloff JN: Isolation and characterization of the compounds responsible for the antimutagenic activity of *Combretum microphyllum* (Combretaceae) leaf extracts. BMC Complement Altern Med 2017; 17: 446.
53. Calaf GM, Ponce Cusi R, Aguayo F, Muñoz JP and Bleak TC: Endocrine disruptors from the environment affecting breast cancer. Oncol Lett 2020; 20(1): 19-32.
54. Lee HM, Yu MS, Kazmi SR, Oh SY, Rhee KH, Bae MA, Lee BH, Shin DS, Oh KS, Ceong H and Lee D: Computational determination of hERG-related cardio-toxicity of drug candidates. BMC Bioinformatics 2019; 20(10): 67-73.
55. Hussain M, Qadri T, Hussain Z, Saeed A, Channar PA, Shehzadi SA, Hassan M, Larik FA, Mahmood T and Malik A: Synthesis, antibacterial activity and molecular docking study of vanillin derived 1, 4-disubstituted 1, 2, 3-triazoles as inhibitors of bacterial DNA synthesis. Heliyon 2019; 5: e02812.
56. Wang J, Guo Z, Fu Y, Wu Z, Huang C, Zheng C, Shar PA, Wang Z, Xiao W and Wang Y: Weak-binding molecules are not drugs?-toward a systematic strategy for finding effective weak-binding drugs. Brief Bioinformatics 2017; 18: 321-32.

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