Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 27s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Assessing the Antimicrobial and Neonatal Diabetes Potential of Phytol from *Scoparia dulcis*: A Combined Computational and Experimental Approach

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Cite this paper as: Arulandhu Clara Mary, Sowntharrajan Aishwariya, Murugesan Viji, Periyasamy Vijayalakshmi, Manikkam Rajalakshmi, (2025) Assessing the Antimicrobial and Neonatal Diabetes Potential of Phytol from Scoparia dulcis: A Combined Computational and Experimental Approach, *Journal of Neonatal Surgery*, 14 (27s), 1031-1040

ABSTRACT

Natural products from medicinal plants offer a safe alternative to conventional medicine for the treatment of various diseases, especially microbial infections burdened by microbial resistance, as well as metabolic disorders such as neonatal diabetes. In this study, we performed a screening study of the plant Scoparia dulcis for phytol for both anti-microbial activity and potential modulatory activity on neonatal diabetes-associated targets using in silico method. Phytol was docked in key microbial enzymes as well as neonatal diabetes targets. Phytol had the highest docking affinities with dihydrofolate reductase and lanosterol 14α-demethylase with the use of molecular docking. Additionally, phytol also had a good docking score towards KCNJ11 and ABCC8 implying it may modulate insulin secretory pathway. In vitro, Scoparia dulcis leaf water extract has also shown a inhibition of Escherichia coli in disc diffusion assay. Therefore, together these results suggest that phytol's molecular activities may be beneficial, acting as an antimicrobial agent but also potentially suggesting a therapy for neonatal diabetes.

Keywords: *Phytol, Scoparia dulcis, Antimicrobial activity, In vitro disc-diffusion assay, Computational docking, Neonatal diabetes*

1. INTRODUCTION

Humans are always at risk of acquiring infectious diseases because they are susceptible to pathological conditions caused by specific infectious agents, which can include bacteria, fungi, viruses, or protozoa. These agents affect different body parts or tissues and are characterised by a set of signs and symptoms[1]. There are various pathways of transmission and stages involved in infectious disease, and these conditions are always linked to infection, host, pathogen, and virulence[2]. Out of the total number of sick people in India, over 33 percent still have infectious diseases [3]. One of the biggest threats to global development and public health is antimicrobial resistance (AMR). Bacterial AMR is thought to have had an impact on 4.95 million deaths worldwide in 2019 and directly caused 1.27 million deaths [4]. According to a global study of AMR and its potential effects, starting in 2050, there will be 10 million yearly global AMR fatalities. One of the highest antimicrobial resistance (AMR) rates in the world is found in India. Bacterial infections were found to be responsible for 7.7 million deaths worldwide. That represents 1 in 8 or 13.6% of all deaths worldwide. Thus, bacterial infections rank as the second most common cause of death worldwide. Epidemic and pandemic disease outbreaks are known to be caused by viral pathogens. The nation's laboratory-based, IT-enabled system for monitoring diseases that are prone to epidemics is called the Integrated Disease Surveillance Programme (IDSP). The IDSP network documented 1683 cases of these diseases during the course of 2017. Data analysis revealed that viral pathogens accounted for 71% of these outbreaks, with non-viral pathogens accounting

for 29%. These outbreaks affected close to 72,000 people, and 60% of those cases had a viral cause (IDSP 2018). Over a billion people are impacted and over 1.5 million people die from fungal diseases. A number of medical conditions, such as asthma, AIDS, cancer, organ transplantation, and corticosteroid therapy, can lead to serious fungal infections [7].

New safe and effective antimicrobial agents are desperately needed due to the rising number of drug-resistant cases, the unfavourable side effects of current antibiotics, and the resurgence of previously identified infections [6]. Plants with medicinal properties are a valuable resource for developing new bioactive compounds for drug discovery and development [8].

It seems that traditional medicine is the origin of healthcare, especially because of its inherent characteristics, distinctive and all-encompassing methods, accessibility, and affordability [9]. On the basis, *Scoparia dulcis* Linn, grown all over India is popularly called "Ghoda Tulsi". This common weed with glabrous branches that grows widely in open spaces has long been used as a medicinal herb in tropical and subtropical regions [10].

The active components present in the plants are called phytochemicals, they are rich in medicinal qualities, and they are regarded as drugs or medicines. Phytol, a unsaturated alcohol with a branched chain is a bioactive phytochemical present in all plants in the form chlorophyll [11]. It has various pharmacological activities which include anti-diabetic, anti-radial, anti-schistosomiasis, anti-inflammation, anti –anxiety and it has the capacity of lowering the cholesterol level [12].

The initial stage in the process of finding and developing new medications is the synthesis of chemical structures. The activity, geometry, and reactivity of the compounds should be enhanced before being synthesized experimentally, with the use advance of computational technologies [13]. A "molecular docking" simulation uses computer techniques to forecast or characterize the interaction between a ligand and a target protein or receptor [14]. The compound phytol is thought to possess antimicrobial qualities. Phytol is docked with different anti-microbial targets in order to determine its potential. Dihydrofolate reductase, Penicillin-binding protein A, DNA topoisomerase, DNA Gyrase, beta-lactamase, and Alanine racemase were utilised as bacterial targets; herpes simplex virus, spike glycoprotein, and lanosterol 14alpha-demethylase were utilised as viral and fungal targets. This study focus on the identification of the efficacy of the compound phytol from *Scoparia dulcis* for antimicrobial activity through computational approach and agar well diffusion method [15].

Furthermore, neonatal diabetes mellitus (NDM) offers a special field of research when examining other important health issues where natural substances may have a therapeutic effect. Neonatal diabetes mellitus (NDM), a rare form of diabetes that appears within the first six months of life, affects roughly 1 in 90,000 to 160,000 live infants. About 1 in 90,000 to 160,000 live infants have neonatal diabetes mellitus (NDM), an uncommon type of diabetes that develops during the first six months of life. Neonatal diabetes is typically brought on by genetic abnormalities that affect insulin production, as opposed to type 1 diabetes, which is autoimmune in nature. There are two types: permanent newborn diabetes mellitus (PNDM), which needs lifelong care, and transient neonatal diabetic mellitus (TNDM), which goes away in infancy but may recur later. KCNJ11, ABCC8, and INS are the genes most frequently implicated (Hattersley & Ashcroft, 2005). Because some types react strongly to oral sulfonylureas rather than insulin therapy, which greatly improves outcomes and quality of life, early diagnosis is essential (Gloyn et al., 2004).

2. METHODOLGY

Target preparation

The targets were downloaded from Protein Data Bank (PDB) database in PDB format. The targets used are Dihydrofolate reductase (PDB ID:3FYV), penicillin Binding protein A(PDB ID :3UPP), DNA topoisomerase IV(PDB ID:3FV5), DNA gyrase (PDB ID:1AB4), Beta lactamase (PDB ID:1ALQ), alanine racemase (PDB ID :3E5P), Spike glycoprotein (PDB ID 6XLU), Inner tegument protein(PDB ID 5VYL) and Lanoestrol 14-α demethylase (PDB ID 4WMZ), ATP-binding cassette sub-family C member 8(PDB ID:6BAA) (PDB ID 6C3O),insulin (PDB ID :2KQP) (PDB ID 4INS),glucokinase (PDB ID 1V4S),(PDB ID 1V4T).Thus, obtained targets were prepared by removing any hetero-atoms, water molecules chains, and other associated ligand groups by using Discovery Studio Bio via visualizer client.

Ligand preparation

It is necessary to compile the chemical structures for a given pharmacological target before beginning a virtual screening. Compound databases have been developed recently, storing not only the structure of the compound molecules but also a multitude of chemical and biological data. One such database is Pub chem; using the canonical smiles and ACD/labs Chemskectch the 2D structures of the phytol (ligand) were generated.

Pharmacokinetics properties

The pharmacokinetics properties like Lipinski rule of five and ADMET were obtained through pkCSM online server.

Docking

Molecular docking is a useful tool for studying the interactions between ligands and biological macromolecules. PyRx

(version 0.8) and Discovery studio 2017 R2 client software were used to assess the strength and visualise the interaction between ligand and target. Every ligand was uploaded using the Open Babel plug-in tool by PyRx (version 0.8), a digital screening molecular docking program. In order to get them ready for molecular docking, the reference drugs and natural substances' 3D structures were changed from the SDF format to the "PDB, Partial Charge & Atom Type (PDBQT) format." Conjugate gradient descent was employed in the optimisation algorithm, and the Universal Force Field (UFF) was the energy reduction parameter. Therefore, the lower binding energy indicates the stronger binding capacity. The Discovery Studio 2021 R2 client software suite was utilised to investigate the complexes that were produced by the binding sites of ligands and the target protein. Hydrophobic and hydrogen bond interactions, among other intermolecular interactions, are analysed. The ability of targets for microbial disease to bind with phytol assessed in this work.

Anti-microbial activity Preparation

Agars were made in compliance with the manufacturer's standard specifications. For nutrient agar 3.9 grams of Mueller Hinton agar was dissolve in 100 litre of water and sterilize at 121 °C for 15 minutes. Pour the agar liquid into the petri dish and allow it to solidify. Using a sterile gel puncture, 4 mm diameter holes was punctured on the agar medium. Different concentrations (25%, 50% and 75%) of the plant extract were added to the holes bored into the agar medium containing the cultures using a sterile micro pipette. Additionally, streptomycin discs were set as a control. Finally the plates were incubated for 37 °C for 24 hours.

3. RESULTS

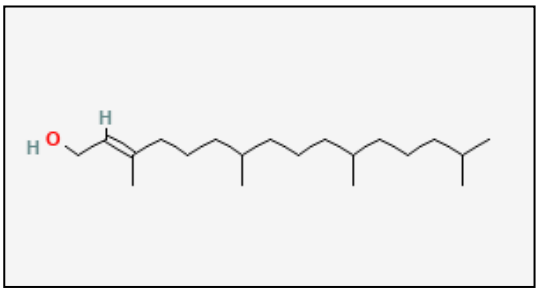

Fig: 1 2D Structure of phytol

Table: 1 Lipinski rule of five for the compound phytol

Ligand	Mol. weight	Log P	Rotatable bond	Acceptors	Donors
Phytol	296.539	6.3641	13	1	1

Table: 2 ADMET properties for the compound phytol

Property	Model name	values
Absorption parameter	Water solubility	-7.544 log mol
	Caco2 permeability	1.515 log Papp in 10^{-6} cm/s
	Intestinal absorption	90.71 %
	P-Glycoprotein substrate	No
Distribution parameter	VDss	0.468 log L/kg
	Fraction unbound	0 Fu
	BBB	0.806 log BBB
	CNS	-1.563 log PS
Metabolism parameters	CYP2D6 substrate	No
	CYP3A4 substrate	No

	CYP2D6 inhibitor	Yes
	CYP3A4 inhibitor	No
Excretion parameters	Total clearance	1.686 log ml/min/kg
	Renal OCT2 Substrate	No
	hERG inhibitor I	No
	hERG inhibitor II	Yes
	AMES toxicity	No
	Oral rat acute toxicity	1.607 mol/kg
	Oral rat chronic toxicity	1.043 log mg/kg_bw/day
	Hepatotoxicity	No

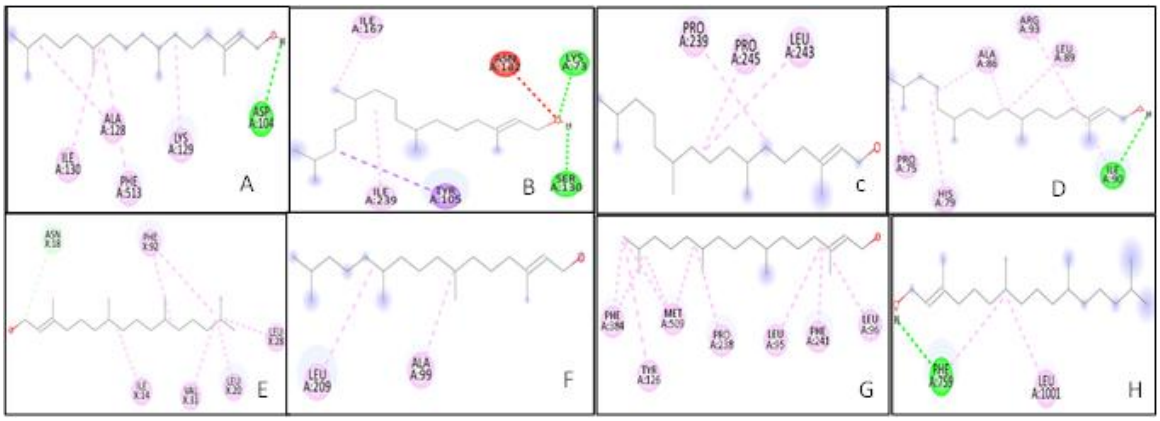

Fig :2 Molecular interaction of phytol with (A) DNA gyrase, (B) Betalactamase , (C) Alanine racemase, (D) DNA topoisomerase, (E) Dihydrofolate reductase, (F) penicillin binding protein (G) Lanoestrol 14 alpha methylase, (H) spike glycoprotein.

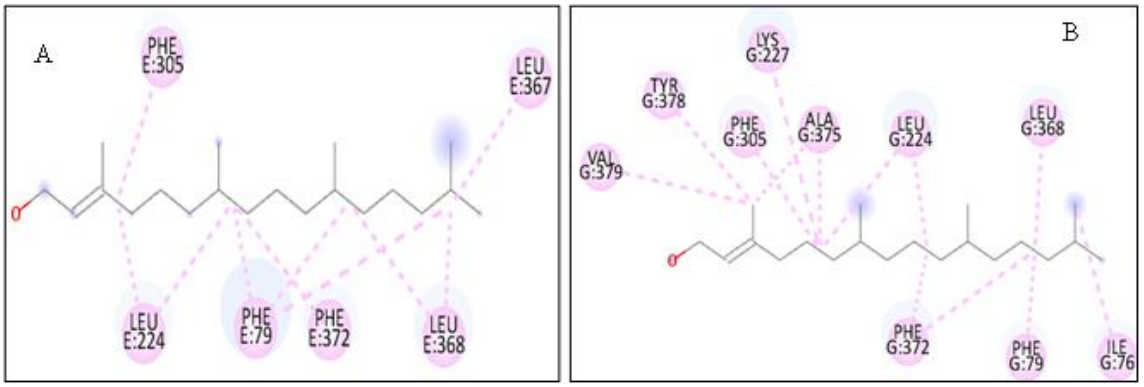

Fig:3 Molecular Interaction on (A) ATP-binding cassette sub-family C member (86baa E chain) with phytol , (B) ATP-binding cassette sub-family C member 8 (6baa G chain) with phytol

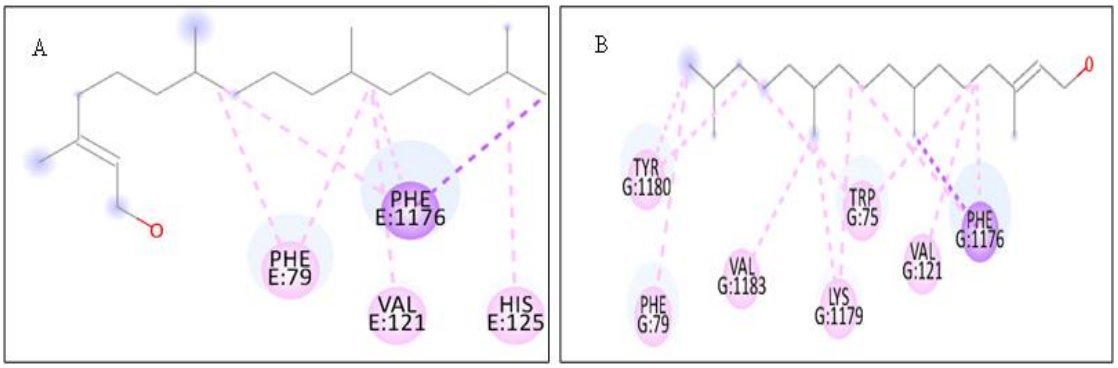

Fig :4 Molecular Interaction (A) ATP-binding cassette sub-family C member 8(6C3O E chain) with phytol , (B) ATP-binding cassette sub-family C member 8 (6C3O G chain) with phytol

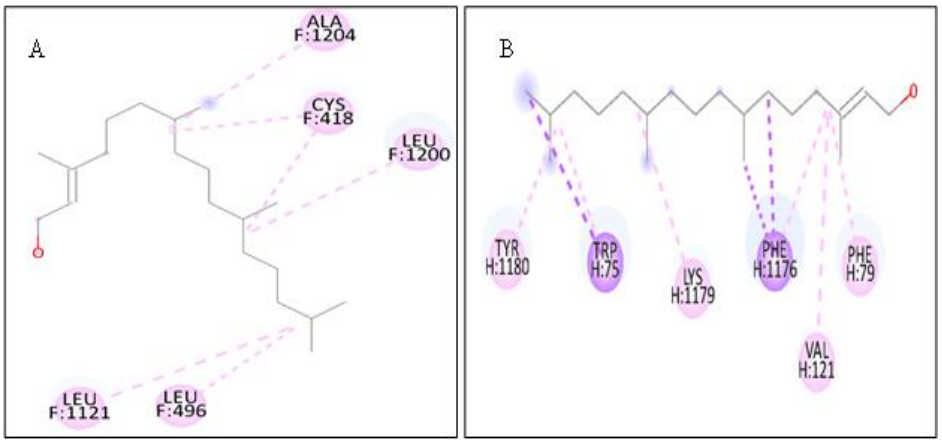

Fig: 6 Molecular Docking (A) Insulin (2KQP) with phytol (B) Glucokinase (1V4S) with phytol

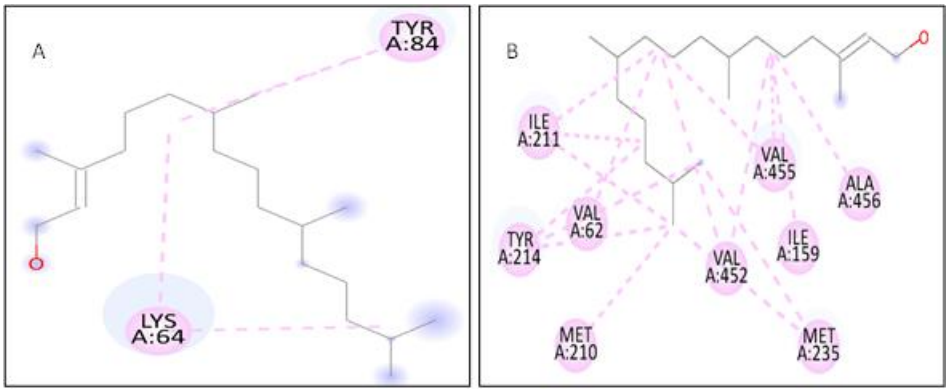

Fig: 5 Molecular docking on (A) ATP-binding cassette sub-family C member 8 (6C3O F chain) with phytol , (B) ATP-binding cassette sub-family C member 8 (6C3O H chain) with phytol

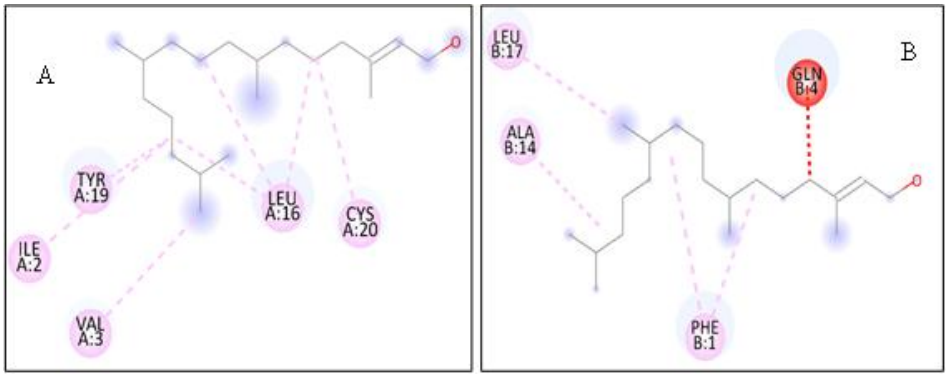

Fig: 7 Molecular Docking (A) Insulin (4INS A chain) with phytol (B) Insulin (4INS B Chain) with phytol

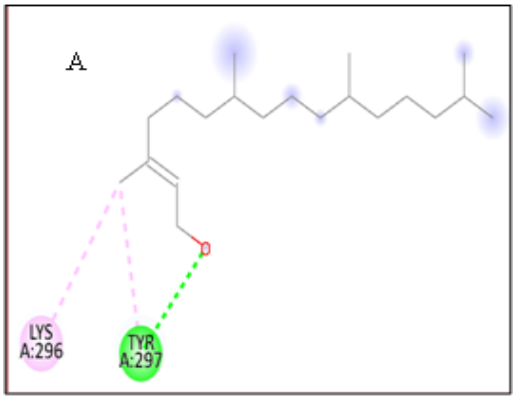

Fig: 8 Molecular Docking (A) Glucokinase (1V4T A chain) with phytol

Table: 3 Binding scores and Hydrogen bond interaction between phytol and microbial targets.

Ligand	Targets	Binding affinity	H-bond interaction	Distance
	DNA gyrase	-4.9	ASP-104	2.10 Å
	Beta lactamase	-5.0	LYS-73, SER-130	2.47 Å. 2.60 Å
	Alanine racemase	-4.3	-	-
	DNA topoisomerase	-4.4	ILE- 90	2.49 Å
	Dihydrofolate reductase	-6.6	-	-
	Penicillin binding protein	-5.0	-	-
	Lanoestrol 14 alpha methylase	-6.3	-	-
	Spike glycoprotein	-4.9	PHE- 759	2.21 Å
	ATP-binding cassette sub-family C member 8 (6BAA E Chain)	-6.5	No interaction	

Phytol	ATP-binding cassette sub-family C member 8(6BAA G chain)	-6.2	No interaction	
	ATP-binding cassette sub-family C member 8(6C3O E chain)	-5.9	No interaction	
	ATP-binding cassette sub-family C member 8(6C3O G chain)	-6.2	No interaction	
	ATP-binding cassette sub-family C member 8(6C3O F chain)	-5.2	No interaction	
	ATP-binding cassette sub-family C member 8(6C3O H chain)	-6.0	No interaction	
	Insulin (2KQP A chain)	-4.0	No interaction	
	Glucokinase (1V4S A chain)	-6.8	No interaction	
	Insulin (4INS A chain)	-3.7	No interaction	
	Insulin (4INS B Chain)	-4.2	No interaction	
	Glucokinase (1V4T A chain)	-4.7	TYR: 297	

Fig: 9 Anti-bacterial activity of Phytol.

Anti-bacterial activity of phytol against gram negative bacteria E.coli

4. DISCUSSION

Since conventional antibiotics have considerably lost their effectiveness due to rising antimicrobial resistance rates, new medications must be developed. According to research by (Sampaio *et al.*,2022) many phytochemicals have the potential to

be used in the treatment of illnesses brought on by multidrug-resistant (MDR). This work focuses on an agar well diffusion method and a computational approach to determine the antimicrobial activity of the compound phytol from *Scoparia dulcis.* Sweet broomweed, or *Scoparia dulcis,* is a common herb in Indian traditional medicine used to treat a variety of conditions including diabetes mellitus, bronchitis, stomach problems, insect bites, wounds on the skin, and hypertension [16]. *Scrophulariaceae* is the family to which *Scoparia dulcis* belongs. This healing herb is home to the tropical and subtropical regions of India, America, Brazil, the West Indies, and Myanmar [17]. A one constituent bioactive compound present in the plant extract was phytol, which is an organic substance utilised to make synthetic vitamins K1 and E. Phytol was initially produced in 1909 by the German chemist Richard Wilstätter through the process of hydrolysis, or the breakdown of chlorophyll. F.G. Fischer, a German chemist, determined its structural composition in 1928. Rats' reproduction requires the most potent E vitamin, α-tocopherol, produced when phytol is converted to it [18].

Phytol promotes autophagy and apoptosis in AGS cells from human gastric adenocarcinoma [19]. It can replace the metabolic processes involved in type 2 diabetes and is also useful in controlling blood glucose [20]. This bioactive compound dramatically lowers the parasite burden caused by the chlorophyll molecule and may offer a novel approach to treating human schistosomiasis [21]. Phytol reduce the severity of arthritis during the chronic phase of the disease, along with having protective effects on both macroscopic and microscopic inflammatory processes and provide a quick inhibitory effect on arthritogenic T cells [22]. Phytol from betel leaves have anti-tuberculosis properties through the dihydrofolate reductase pathway [23]. Phytol from *Premna serratifolia* shows anti-viral activity for Herpes Simplex Virus (HSV) [24].

Molecular interaction

Virtual screening techniques, such as drug-likeness, ADMET, are computational methods used in drug development to quickly and affordably identify compounds with a high probability of exhibiting physiological activity through various *in silico* simulation techniques [27]. The compound phytol following the Lipinski rule of five. In absorption parameter, Intestinal Absorption is used to see the primary absorption of the drug administered orally. The compound phytol that have an absorption value of 90% are regarded it forecasts that the compound will be consumed into portal blood via the human intestine. The compound is not a substrate for p-glycogen substrate. In distribution, VDss is used to see whether the drug is uniformly distributed in plasma, the compound have VDss value of 0.468L/kg which is lower than 0.71L/Kg, thus it can evenly distributed in plasma rather in tissue which does not cause renal failure. In order to prevent any potential psychotropic side effects, medications that target different parts of the body should ideally not cross the Blood Brain Barrier (BBB). Here the compound have the BBB value 0.806 is greater than the normal value, but the value of CNS permeability should be less than -2 log PS, where the value of phytol for CNS permeability was -1.563 were it couldn't penetrate CNS. The fractional unbound value for the compound was zero. In metabolism parameter, the body's major detoxifying enzyme class, cytochrome P450s, is primarily located in the liver. They are in charge of breaking down foreign substances so that the urine can more easily eliminate them. Drug metabolism can be altering if the compound is subjected as cytochrome inhibitors; phytol is not an inhibitor for CYP2D6 and CYP3A4.In excretion parameter the compound is not a substrate for renal OCT2 so, phytol have the greatest metabolic value, which the body excretes them quickly and the value for total clearance is 1.6856 ml/min/kg. In toxicity, AMES toxicity is measured to know the mutagenic effect of the compound, the negative result of AMES indicates that phytol does not act as carcinogen. The hepatotoxicity and hERG values depicted that phytol does not cause liver injury and ventricular arrhythmia.

The targets β- lactamase will inactivate the beta lactam antibiotic, will lead to poly microbial infection. Alanine racemase and penicillin binding protein A is responsible for peptidoglycan synthesis. DNA topoisomerase IV and DNA gyrase responsible for negative supercoiling of bacteria will increase the bacterial growth. Spike glycoprotein (S protein) plays a crucial role in starting host-pathogen interactions and facilitating the virus's entry into the host cell through membrane fusion [25]. All herpes viruses have a protein cluster called tegument that lies between the envelope and nucleocapsid. Proteins found in the tegument typically assist in the replication of viral DNA and immune response evasion [26]. On other hand KCNJ11, ABCC8, and INS are the genes most frequently implicated (Hattersley & Ashcroft, 2005).Thus by considering these as a targets the phytocompound phytol is docked with those eleven targets, among microbial, anti-bacterial and antifungal targets like dihydrofolate reductase and lanoestrol 14 alpha demethylase shows highest binding affinity as (-6.6 and -6.3) besides those two targets the bacterial targets Betalactamase, DNA gyrase, DNA topoisomerase and penicillin binding protein shows good binding scores as (-5.0 with double H-bond interactions LYS-73 at 2.47 Å , SER -730 at 2,60Å; -4.9 with single H-bond interaction : ASP-104 with a distance 2.10 Å and -4.4 with single H-bond interaction ILE- 90 at 2,49 Å) and for viral target phytol with spike glycoprotein shows binding score as -4.9 with single H- bond interaction PHE-759 at 2.21 Å, while the NDM targets shows good binding affinity, of them glucokinase (1V4T) shows single H- Bond interaction TYR:297 respectively.

Antibacterial activity

According to the study on greater zones of inhibition on *Staphylococcus aureus* were produced by the ethanolic extract of *scoparia dulcaris. Microsporum canis* and *Candida albicans* displayed zones of inhibition when exposed to ethanolic

extracts of *Scoparia dulcis* [28]. The study found that when the stem and root of scoparia dulcaris were extracted using chloroform, the stem had the strongest antibacterial activity against staphylococcus aureus and the root against Escherichia coli [29]. In this study, the compound phytol was tested for its antibacterial activity, and the results showed that the zone of inhibition was 15 mm for 25 µl, 16 mm for 50 µl, 18 mm for 75 µl, and 25 mm for the control disc streptomycin. Therefore, *scoparia dulcis* leaf water extract has antibacterial activity against Escherichia coli. The initial population density of the organisms, the rate at which the antimicrobial agent disperses, and the rate at which the organisms grow all affect how big the zones of inhibition are in diameter.

5. CONCLUSION

The results obtained from the study exhibited that the compound phytol has anti-bacterial , anti-viral and anti-fungal activity through the *in-vitro* and *in- silico* studies and for NDM it shows good binding affinity .This implies that the components of the plant extract may provide industrial drugs that are helpful in the chemotherapy of a certain microbiological infection and NDM theraphy

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