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Research Article

# *IN SILICO* SCREENING AND PREDICTION OF *LYCOPODIELLA CERNUA* L. AGAINST CRYSTAL STRUCTURE OF DNA GYRASE

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**ABSTRACT**

**Objective:** The point of the review was centered around hindrance DNA Gyrase by mixtures of *Lycopodiella cernua* L., a perpetual plant through *in silico* studies.

**Methods:** The Chemical mixtures of the plant test was gathered from the *L. cernua* L. Molecules that fall inside Lipinski's standard of five such particles are frequently distinguished and finished for docking. The natural action of the mixtures was dissected utilizing the pass online device. The worth of Probability to be dynamic (Pa) and idle (Pi) are investigated. The few mixtures recovered from the plant were examined for its conceivable critical cooperation with the objective protein utilizing sub-atomic docking studies.

**Results:** The compound 2-Ethylacridine had G-Score of - 7.1 Kcal/mol and framed hydrogen bonds with the buildup GLY showing the bond length of 2.0. The future point of view of the review is to decide the strength of the protein-compound complex through elements studies. The connections were noticed utilizing Pymol.

**Conclusion:** The came about compound showed higher adequacy than controlled (anti-microbial) compound, this demonstrates the plants potential to be a successful medication compound towards the objective. The plant mixtures ought to be investigated more to be an effective and potential medication particles.

**Keywords:** *Escherichia coli*, DNA GYRASE, *Lycopodiella cernua* L, Molecular docking, 2-ethylacridine.

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## INTRODUCTION

*Lycopodiella cernua* is a plant in the family *Lycopodiaceae*, commonly known as the staghorn clubmoss. This species includes perhaps the broadest conveyance inside the family, being known from most tropical regions. *L. cernua* is an evergreen, lasting plant that is connected with the greeneries. It has a crawling principle stem of endless length, establishing at long spans. Erect shoots, to some degree looking like little pine trees, grow up to 100 cm tall. The plant is gathered from the wild for a scope of conventional therapeutic employments. Bacterial DNA gyrase is an appealing objective for the examination of new antibacterial specialists. Inhibitors of the GyrB subunit, which contains the ATP-restricting site, are portrayed in this correspondence. A novel subbed 5-(1H-pyrazole-3-yl) thiazole compounds were distinguished as inhibitors of bacterial gyrase. Structure-directed improvement prompted more prominent enzymatic power and moderate antibacterial strength. Information is introduced for the exhibition of specific protein restraint of *Escherichia coli* GyrB over *Staphylococcus aureus* GyrB [1].

A wide scope of normal items and protein-based mixtures have been recognized and considered as DNA gyrase inhibitors and this adds a gigantic measure of primary variety that can be taken advantage of an outfit in the revelation of new antibacterial specialists. The advancement of new substance compounds with DNA gyrase inhibitory action (from normal sources, irregular screens, or level headed plan) will additionally approve/prove the capability of this catalyst as a helpful objective [2]. The fluoroquinolone class of antibacterials acts through restraint of the DNA gyrase chemical. In any case, their viability is thwarted by the expanding frequency of antimicrobial opposition. Consequently, in this audit, we give a record concerning the design of DNA gyrase and quinoline [3]. Further, we additionally examine atomic communications and construction movement relationship investigations of the distributed inhibitors [4]. New antibacterial medications are desperately expected to handle the fast ascent in multi-drug-safe microscopic organisms. DNA gyrase is an approved objective for the advancement of new antibacterial medications [5].

The utilization of plants in the arrangement of medication and ethnobotanical studies is being rehearsed since the days of yore. The term restorative plants have been in power since antiquated occasions and these therapeutic plants are utilized in the readiness of customary prescriptions. In India, the utilization of spices is referenced in Vedic sacred texts. Restorative plants were made use of standard medicine practices since antiquated events. Plants consolidate many mixtures for size contains guard against parasites, diseases, and herbivorous warm-blooded animals. Different photochemical with potential or set up natural activity had been perceived. Helpful plants are the "spine" of standard prescription, which suggests more than 3.3 billion people in less developed countries utilize remedial plants constantly [6]. The point of this review is to anticipate the endeavor of the mixtures from the Plant by playing out the Molecular docking studies against the Crystal Structure of DNA Gyrase.

## METHODS

### Pdb, pubchem and pass online

The 3D protein structure for Toxic shock disorder poison 1 of *S. aureus* is recuperated from the Protein Data Bank data set (PDB ID: 2IJ0). Dynamic page locale was expected to use LigSite online mechanical assembly. The creation blends from the referred to plants are recuperated from the PubChem information base. The PASS ONLINE predicts 4130 kinds of natural exercises, for which the distinction between probabilities will be dynamic (Pa) and probabilities will be idle (Pi) was determined. The Pa-Pi esteems for exercises haphazardly chosen from the all-out rundown of anticipated natural exercises will be utilized as free relapse factors are examined [7].

**Drug ability**

Lipinski's standard of 5 aides in recognizing drug-like and non-drug-like particles. It predicts a high likelihood of progress or disappointment because of medication similarity for atoms conforming to at least 2 of the accompanying rules of 5.

- Atomic mass under 500 Dalton
- High lipophilicity (communicated as LogP under 5)
- Under 5 hydrogen bond contributors
- Under 10 hydrogen bond acceptors
- Molar refractivity must be between 40 and 130.

**Molecular docking study**

MGL instruments with AutoGrid4 is utilized to set up and to perform blind docking computations between the Ligands and Protein. A solidified 3-layered design was gotten from the PDB. Receptor (protein) and ligand (complex) documents were arranged utilizing Auto Dock Tools. The protein was encased in a crate with matrix focuses in x, y, and z bearings and a lattice dividing of 0.375 Å. The focal point of the matrix is set to -6.516, 30.278, and -1.951 Å. Lamarckian hereditary calculations, as executed in Auto Dock, were utilized to perform docking estimations. Any remaining rules are default settings. For each docking case, the most reduced energy docked affirmation, as indicated by the Auto Dock scoring capacity and the number of hydrogen bonds was chosen as the limiting mode. The result from Auto Dock was delivered with PyMol [8,9].

**PyMOL**

PyMOL is one of a couple of open-source perception apparatuses which are utilized in the underlying science. A piece of the product's name alludes to the way that it broadens and is extensible by the Python programming language. Every one of the ties is imagined by utilizing the Structure Visualizing instrument Pymol watcher, the association between the substance mixtures and target protein [10].

**RESULTS**

**PDB**

The 3D structure of protein (DNA Gyrase) was retrieved from the PDB and it was viewed using the visualization tool pymol (Tables 1 and 2).

**Table 1: Structure of protein**

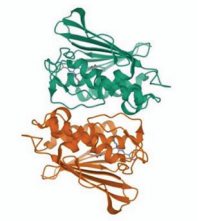
| Organism Name | Protein Name and ID | Structure | Residues count |
|---|---|---|---|
| *Escherichia coli* | Crystal structure of DNA Gyrase and 3G7E |  | 203 |

**Table 2: Molecular properties of DNA Gyrase obtained from Protein Data Bank**

| S.No | Molecular properties | DNA Gyrase |
|---|---|---|
| 1 | Protein Data Bank ID | 3G7E |
| 2 | Classification | Isomerase inhibitor |
| 3 | Structure weight | 22.72 kDa |
| 3 | Polymer | 2 |
| 4 | Length | 203 |
| 5 | Chains | A |
| 6 | Molecular function | Preventing DNA Breakage and reduces Supercoiling |

**Pubchem**

The compounds are isolated along with their molecular weight, molecular formula, and pubchemCID, where pubchem is the database for accessing small molecules (Tables 3 and 4).

**Pass online**

The biological activity of the plant molecules were analyzed using the pass online tool which predicts the pharmacological and biochemical properties. The properties predicted for each compounds were listed in the Table 5.

**Molecular docking analysis**

Computer docking techniques play an important role in drug design and elucidation of mechanism. The flexible docking programs, Auto Dock and molecular operating environment help in predicting favorable protein–ligand complex structures with a reasonable accuracy and speed. These docking programs, when used prior to experimental screening, can be considered as powerful computational filters to reduce labor and cost needed for the development of effective medicinal compounds. When used after experimental screening, they can help in better understanding of bioactivity mechanisms. Molecular models were built to discuss the binding modes by docking using Auto Dock program for the interactions of Diethyl phthalate, 1-beta-d-Ribofuranosyl-4-imidazoline-2(3H)-one, Methyl Lathodoratin, 1,2-Cyclohexane dimethanol, 2-Ethylacridine and Nalidixic acid (Control) molecule with multiple DNA Gyrase Protein. The structure of each drug was drawn and subjected to energy optimization. These were then imported to pdb file for docking purpose. Final analysis of docking resulted that the compound 2-Ethylacridine was binded to 1 amino acids such as GLYwith binding energy of -7.74. The compound used as control Nalidixic acid was bindedto 1 amino acids such as GLY with binding energy of -4.03.The resulted compound showed higher efficacy than controlled (antibiotic) compound, this indicates the plants potential to be an effective drug compound towards the target (Table 6). All the bindings are visualized by using the Structure Visualization tool Pymol viewer, the interaction between the chemical compounds and target protein was observed, and further were shown in the Figs. 1-6.

Intermolecular interactions between compounds derived from *Lycopodiella cernua* L. and the binding site of the DNA Gyrase protein (3G7E).

Ligands are shown in red colour and the binding active site was showen in Green.

**DISCUSSION**

The point of this review was to explore structures and acetylcholinesterase inhibitory exercises of lycopods-type alkaloids

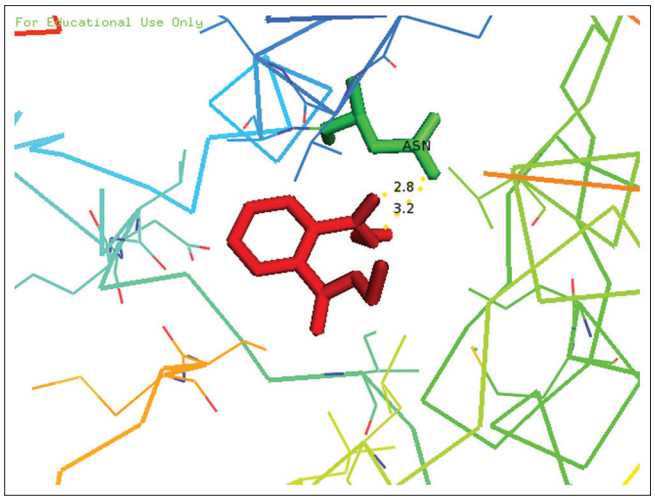



**Fig. 1: Interactions of Diethyl phthalate (6781) and its binding site on the DNA Gyrase protein (3G7E)**

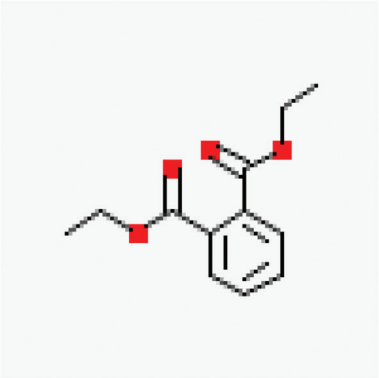
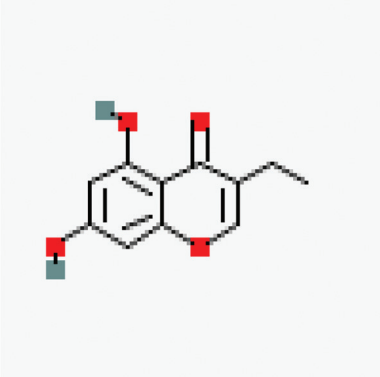
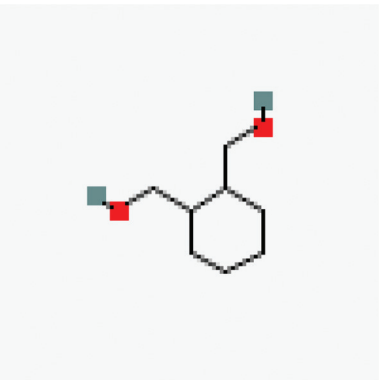
**Table 3: Information of plant compounds**

| Plant Name | Pubchem Compound | Pubchem CID | Molecular Formula | Molecular Weight |
|---|---|---|---|---|
| *Lycopodiella cernua* L. | Diethyl phthalate | 6781 | $C_{12}H_{14}O_4$ | 222.24 g/mol |
| | Cytidine | 6175 | $C_9H_{13}N_3O_5$ | 243.22 g/mol |
| | Methyl Lathodoratin | 5281344 | $C_{11}H_{10}O_4$ | 206.19 g/mol |
| | 1,2-Cyclohexanedimethanol | 85902 | $C_8H_{16}O_2$ | 144.21 g/mol |
| | 2-Ethylacridine | 610161 | $C_{15}H_{13}N$ | 207.27 g/mol |
| | Nalidixic acid (Control) | 4421 | $C_{12}H_{12}N_2O_3$ | 232.23 g/mol |

**Table 4: ADMET properties of the ligands present in methanol extract of *Lycopodiella cernua* L.**

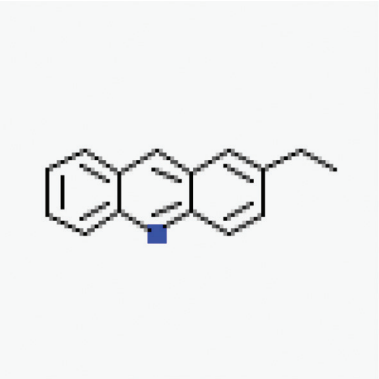
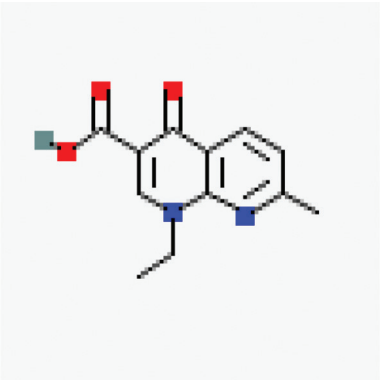
| Name of the ligand | Molecular mass<500 Dalton | High lipophilicity (expressed as LogP<5) | <5 hydrogen bond donors | <10 hydrogen bond acceptors | Molar refractivity should be between 40 and 130 |
|---|---|---|---|---|---|
| Diethyl phthalate | 222.000 | 2.04 | 0 | 4 | 58.35 |
| Cytidine | 243.00 | -2.26 | 5 | 8 | 55.75 |
| Methyl Lathodoratin | 206.00 | -1.96 | 2 | 4 | 53.104 |
| 1,2-Cyclo hexane dimethanol | 144.00 | 0.77 | 2 | 2 | 40.61 |
| 2-Ethylacridine | 207.00 | 3.905 | 0 | 1 | 68.62 |

**Table 5: Prediction of pharmacological activity for plant compounds**

| Compound Name and Id | Compound structure | Compound Activity | |
|---|---|---|---|
| Diethyl phthalate 6781 |  | 0,337 | 0,058 P-benzoquinone reductase (NADPH) inhibitor |
| | | 0,284 | 0,005 Protocatechuate 3,4-dioxygenase inhibitor |
| | | 0,357 | 0,080 Spermidine dehydrogenase inhibitor |
| | | 0,381 | 0,106 1,4-Lactonase inhibitor |
| | | 0,280 | 0,005 Imidazoleacetate 4-monooxygenase inhibitor |
| | | 0,325 | 0,051 Antibacterial ★ |
| | | 0,352 | 0,078 CYP2A4 substrate |
| | | 0,293 | 0,019 3,4-Dihydroxy-9,10-secoandrosta-1,3,5(10)-triene-9,17-dione 4,5-dioxygenase inhibitor |
| | | 0,316 | 0,043 Hepatic disorders treatment |
| | | 0,360 | 0,088 Acetylgalactosaminyl-O-glycosyl-glycoprotein beta-1,3-N-acetylglucosaminyltransferase inhibitor |
| Lathodoratin 5281344 |  | 0,937 | 0,001 Penicillin amidase inhibitor |
| | | 0,927 | 0,002 Acylaminoacyl-peptidase inhibitor |
| | | 0,875 | 0,001 Deacetoxycephalosporin-C synthase inhibitor |
| | | 0,862 | 0,002 Cytosol alanyl aminopeptidase inhibitor |
| | | 0,803 | 0,001 Beta lactamase inhibitor |
| | | 0,791 | 0,001 Antispirochetal |
| | | 0,775 | 0,003 CYP2C9 inducer |
| | | 0,767 | 0,000 D-stereospecific aminopeptidase inhibitor |
| | | 0,674 | 0,005 Antibacterial ★ |
| | | 0,706 | 0,044 Antieczematic |
| 1,2-Cyclo hexanedimethanol 85902 |  | 0,991 | 0,000 Muramoyltetrapeptide carboxypeptidase inhibitor |
| | | 0,627 | 0,007 Antibacterial ★ |
| | | 0,638 | 0,025 Proteasome ATPase inhibitor |
| | | 0,567 | 0,001 Membrane dipeptidase inhibitor |
| | | 0,551 | 0,002 Beta lactamase inhibitor |
| | | 0,534 | 0,000 Antibiotic Carbapenem-like |
| | | 0,459 | 0,001 Cell wall synthesis inhibitor |
| | | 0,521 | 0,070 Nicotinic alpha4beta4 receptor agonist |
| | | 0,421 | 0,007 Antibiotic |
| | | 0,379 | 0,001 Antibiotic beta Lactam-like |

*(Contd...)*

**Table 5: (*Continued*)**

| Compound Name and Id | Compound structure | Compound Activity | | |
|---|---|---|---|---|
| 2-Ethylacridine 610161 |  | 0,991 | 0,000 | Muramoyltetrapeptide carboxypeptidase inhibitor |
| | | 0,627 | 0,007 | Antibacterial ★ |
| | | 0,638 | 0,025 | Proteasome ATPase inhibitor |
| | | 0,567 | 0,001 | Membrane dipeptidase inhibitor |
| | | 0,551 | 0,002 | Beta lactamase inhibitor |
| | | 0,534 | 0,000 | Antibiotic Carbapenem-like |
| | | 0,459 | 0,001 | Cell wall synthesis inhibitor |
| | | 0,521 | 0,070 | Nicotinic alpha4beta4 receptor agonist |
| | | 0,421 | 0,007 | Antibiotic |
| | | 0,379 | 0,001 | Antibiotic beta Lactam-like |
| Nalidixic acid (Control) 4421 |  | 0,427 | 0,010 | Hydroxymethylbilane synthase inhibitor |
| | | 0,437 | 0,021 | Hydroxylamine reductase (NADH) inhibitor |
| | | 0,489 | 0,074 | Gastrin inhibitor |
| | | 0,492 | 0,076 | Phthalate 4,5-dioxygenase inhibitor |
| | | 0,437 | 0,023 | Antibacterial ★ |
| | | 0,462 | 0,054 | Erythropoiesis stimulant |
| | | 0,417 | 0,008 | Trimethylamine-N-oxide reductase inhibitor |
| | | 0,447 | 0,043 | Centromere associated protein inhibitor |
| | | 0,411 | 0,006 | Phosphoglycerate mutase inhibitor |
| | | 0,431 | 0,029 | Adenylyl-sulfate reductase inhibitor |

This symbol indicates the main activity of the compound

**Table 6: Interaction of compounds with DNA Gyrase protein (3G7E)**

| S.No | Name of the ligand/PubChem ID | Binding energy | Interacting amino acids | Bond Length | No of H-Bonds |
|---|---|---|---|---|---|
| 1. | Diethyl phthalate 6781 | -5.64 | ASN | 2.8<br>3.2 | 2 |
| 2. | 1-beta-d-Ribofuranosyl-4-imidazoline-2 (3H)-one 6175 | -5.08 | ASP<br>GLY<br>ASN | 1.8<br>2.8 | 3 |
| 3. | Methyl Lathodoratin 5281344 | -5.85 | ASN<br>ASP<br>GLY | 2.2<br>1.8<br>2.8 | 3 |
| 4. | 1,2-Cyclohexanedimethanol 85902 | -4.64 | ASP<br><br><br>GLY | 2.1<br>1.9<br>1.9<br>2.9 | 3 |
| 5. | 2-Ethylacridine 610161 | -7.1 | GLY | 2.0 | 1 |
| 6. | Nalidixic acid (Control) 4421 | -4.03 | GLY | 2.0 | 1 |

confined from an Icelandic assortment of Lycopodium annotinum ssp. alpestre. Ten alkaloids were disengaged, including annotinine, annotine, lycodoline, lycoposerramine M, anhydrolycodoline, gnidioidine, lycofoline, lannotinidine D, and acrifoline, just as a formerly obscure N-oxide of annotine. 1H and 13C NMR information of a few of the alkaloids were accommodated the initial time. Dissolvable dependent equilibrium constants among ketone and hemiketal type of still up in the air. Conformation of acrifoline was described utilizing NOESY spectroscopy and sub-atomic displaying. The isolated alkaloids were considered for their in vitro inhibitory movement in contrast to acetyl cholinesterase and butyryl cholinesterase. Ligand docking concentrates on because of transformed 3D construction of Torpedo California acetyl cholin esterase provided reasoning for low inhibitory movement of the detached alkaloids as looked at to huperzine An or B, which are powerful acetylcholinesterase inhibitors having a place with the lycodine class. Based on the displaying studies the lycopods-type alkaloids appear to squeeze into the dynamic site canyon of the enzyme yet the place of their utilitarian gatherings isn't viable with setting up solid hydrogen bonding connections with the amino corrosive buildups that line the limiting site. The docking concentrates on indicating possibilities of extra functionalization of the lycopods skeleton to deliver possibly more active analogs [11].

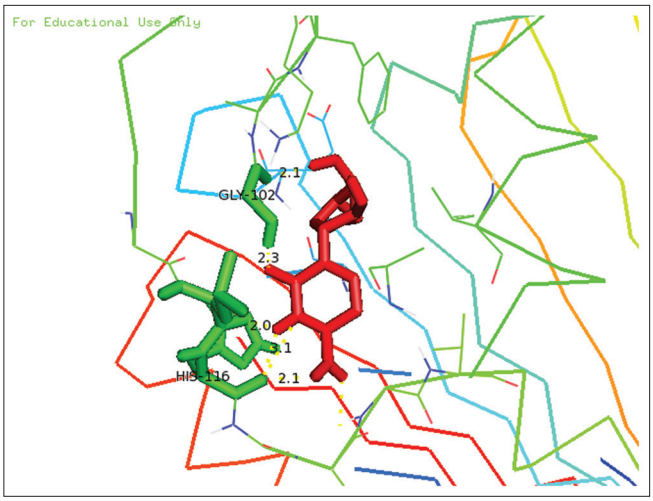



**Fig. 2: Interactions of 1-beta-d-Ribofuranosyl-4-imidazoline-2(3H)-one (6175) and it's binding site on the DNA Gyrase protein (3G7E)**

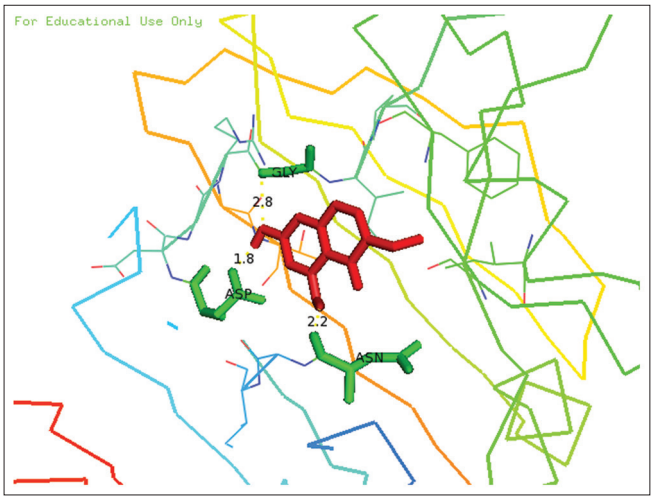



**Fig. 3: Interactions of Methyl Lathodoratin (5281344) and its binding site on the DNA Gyrase protein (3G7E)**

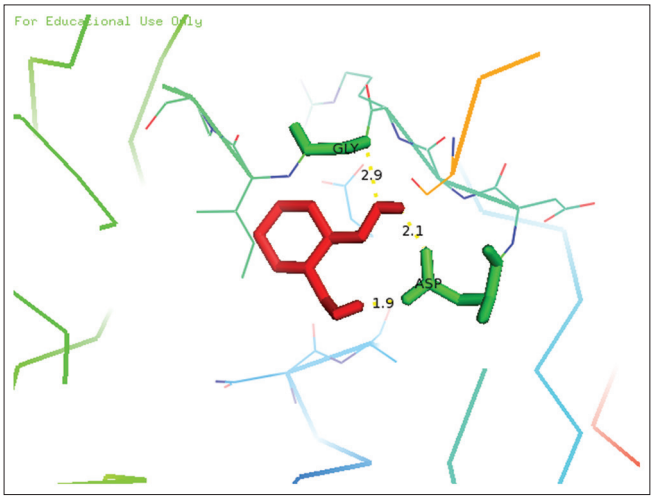



**Fig. 4: Interactions of 1,2-Cyclohexane dimethanol85902 and its binding site on theDNA Gyrase protein (3G7E)**

*E. coli* otherwise called E. coli is a Gram-negative, facultatively anaerobic, bar molded, coliform bacterium of the variety Escherichia

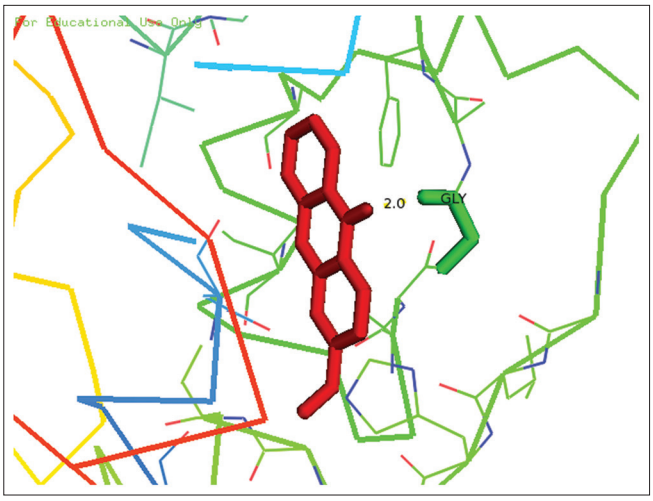



**Fig. 5: Interactions of 2-Ethylacridine (610161) and its binding site on the DNA Gyrase protein (3G7E)**

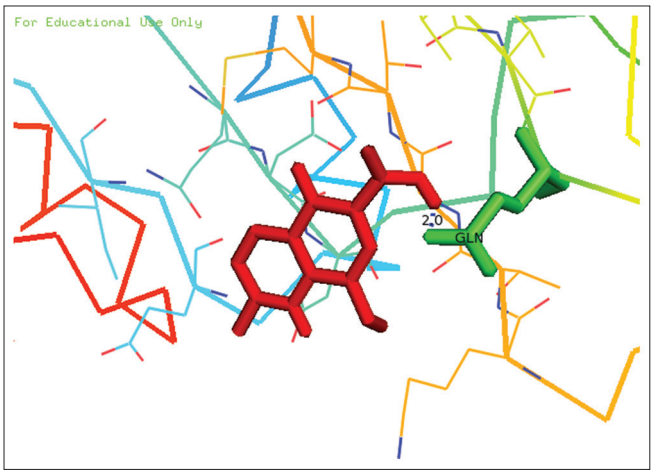



**Fig. 6: Interactions of Nalidixic acid (4421) and its binding site on the DNA Gyrase protein (3G7E)**

that is generally found in the lower digestive system of warm-blooded life forms [12]. Most E. coli strains don't cause illness, normally living in the stomach, however, destructive strains can cause gastroenteritis, urinary lot contaminations, neonatal meningitis, hemorrhagic colitis, and Crohn's infection. Normal signs and side effects incorporate extreme stomach cramps, looseness of the bowels, hemorrhagic colitis, heaving, and now and again fever [13]. Hardly any microorganisms are pretty much as adaptable as *E. coli*. A significant individual from the typical gastrointestinal microflora of people and different well evolved creatures, E. coli has additionally been generally taken advantage of as a cloning host in recombinant DNA innovation. Be that as it may, E. coli is something other than a lab workhorse or innocuous digestive occupant; it can likewise be a profoundly adaptable, and as often as possible destructive, microbe. A few diverse E. coli strains cause assorted gastrointestinal and extra digestive infections through harmfulness factors that influence a wide scope of cell processes [14].

Bacterial DNA gyrase is an alluring objective for the examination of new antibacterial specialists. Inhibitors of the GyrB subunit, which contains the ATP-restricting site, are depicted in this correspondence. A novel subbed 5-(1H-pyrazole-3-yl) thiazole compounds were recognized as inhibitors of bacterial gyrase. Structure-directed enhancement prompted more noteworthy enzymatic power and moderate antibacterial strength. Information is introduced for the showing of specific chemical restraint of *E. coli* GyrB over *Staphlococcus aureus*

GyrB.The designs of these particles were gotten from the PubChem data set. The document design change was performed utilizing OPENBABEL. The capacity of gyrase to loosen up certain super loops becomes an integral factor during DNA replication. The design of DNA gyrase which is utilized as an objective was recovered from the protein information bank. The objective and ligands were docked utilizing the sub-atomic docking programming "Hex". The E upsides of nerol, farnesol, perylene, and Ar-turmerone docked with *E. coli* DNA gyrase are −175.23, −170.13, −126.91, and 207.35 KCal mol−1 separately. The E upsides of nerol, farnesol, perylene, and Ar-turmerone docked with *S. aureus* DNA gyrase are −179.75, −176.23, −133.18, and −170.89 KCal mol−1 separately. Ar-turmerone could be a superior antimicrobial specialist for *E. coli* contaminations.

*Candida albicans*, a polymorphic contagious type of human microflora, are pathogenic and known to make monstrous harm to the host living being which incorporates biofilm arrangement, oral and skin diseases in resistant lacking people. Discharged aspartic proteinase (SAP) chemical assumes a significant part in elevating destructiveness to *C. albicans*, and consequently could be set up as a medication focus for Candida contaminations. Thus, repressing the catalyst's dynamic focus utilizing phytochemicals would decrease the seriousness of the chemical's destructiveness. The current work centers around the *in silico* examination of around 15 plant phytochemicals against the SAP compound utilizing the AutoDock 4.2.6 programming. The docking results were viewed as promising with emodin having the most elevated restricting score of −6.44 kCal/mol followed by the isoflavonoid equol with the limiting score of −6.29 kCal/mol. Consequently, these bioactive mixtures could be utilized as leads for drugs focusing on SAP compounds in treating safe *Candida* diseases [15].

## CONCLUSION

In this current review, the mixtures disconnected from the L. cernua L.was docked with the DNA Gyrase protein recovered from *E. coli*. Here, we utilized the five mixtures they are docked with the protein. Docking results were introduced as their most elevated restricting energy-7.1 and 3 hydrogen bonds at the dynamic site of GLY. The came about compound showed higher adequacy than the controlled (anti-microbial) compound, this demonstrates the plant's potential to be a powerful medication compound towards the objective. The plant mixtures ought to be investigated more to be productive and potential medication atoms.

## ACKNOWLEDGMENT

The authors are grateful to acknowledge the Department of Botany, PSG College of Arts and Science, Coimbatore, for providing the necessary facilities during the study.

## AUTHORS' CONTRIBUTIONS

T.Amudha and Dr.S. Rajeswari designed the research, performed the virtual screening, and revised the manuscript. T. Amudha carried out the bioinformatics analysis and drafted the manuscript. Dr.S. Rajeswari made the final structures and carried out the necessary corrections. Both the authors have read the final manuscript.

## CONFLICTS OF INTEREST

The authors claim no conflicts of interest in the study.

## AUTHORS' FUNDING

The project was self-funded.

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