WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 12, 582-593. Research Article ISSN 2277–7105

ESTABLISHED PHYTOLIGANDS FROM *TRIDAX PROCUMBENS* LINN. AGAINST BACTERIAL DNA-GYRASE B RECEPTOR: MOLECULAR DOCKING APPROACH

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Article Received on
26 April 2018,
Revised on 16 May 2018,
Accepted on 06 June 2018
DOI: 10.20959/wjpr201812-12576

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ABSTRACT

The medicinal plant, *Tridax procumbens* Linn. is a common weed and in the different parts of this plant are containing phytochemicals that inhibit the growth of bacteria and known natural antibacterial agents. The objective of the present study was to detect receptor-ligand binding energy and interaction through molecular docking for phytocompounds established in *T. procumbens* against bacterial DNA gyrase B protein (PDB ID: 3G7B). Molecular docking was performed by using PyRx (Version 0.8) for the structure-based virtual screening and visualized the interaction in the MGL tool (Version 1.5.6). Among 16 phytochemicals and 1 antibiotic (Ciprofloxacin), highest binding energy value was obtained in Epigallocatechin-3-gallate (-7.8 Kcal/mol) in comparison with Ciprofloxacin (-6.4 Kcal/mol). The binding interaction of target protein with this phytocompound found binding at opposite to the active site may be treated as non-competitive inhibitor. In conclusion, phytocompound Epigallocatechin-3-gallate can be alternative of synthetic antibacterial drug as per binding energy value and interaction. It is suggesting further pharmacological and toxicological assay with this phytocompound after isolation from medicinal plant (*T. procumbens*).

KEYWORDS: *Tridax procumbens*; Phytoligands; Bacterial DNA gyrase B; Molecular docking; Receptor-ligand binding; Computational prediction.

INTRODUCTION

Among various medicinal plants, *Tridax procumbens* Linn. is a common weed found in the tropics. From past to recent study, it was reported that the phytochemicals in the parts of this plant are antibacterial, antimicrobial, antiseptic, etc. in nature.[1-7]

Although, researchers have studied antimicrobial effect on *Escherichia coli*, *Staphylococcus aureus* and *Klebsielle pneumoniae* by crude extract of different parts of *Tridax procumbens* weed,[7] which is still unclear that single or combination of phytochemicals is acting as lead compound(s). Also, it is not possible to isolate each phytocompound and conduct experiment to detect antimicrobial activity that may require laboratory expanses, long duration and many animal harm, etc.

In this regard, computer-based receptor-ligand binding as a suitable approach for structure-based drug screening and exact phytocompound or combinations of few phytochemicals can be predicted within a few hours by using molecular docking and interaction.[8] On the other hand, the molecular docking tool is used to predict the interaction between a small molecule (ligand) and a macromolecule (protein) that describes the behavioural characterization of small molecules in the binding site of target receptor.[8-21]

Now-a-days plant derived compounds are potential in new drug discovery for pharmaceutical research. Antibiotic is an important drug to prevent various bacterial infection in which researchers are showing interest to inhibit the multiplication of bacteria. Among several enzymes in bacteria, DNA gyrase enzyme is most effective for metabolic regulation in bacteria and help in the process of DNA replication, and also known as type II topoisomerase.[22-25] Moreover, bacterial resistance to existing antibiotic pose serious threat to prevent infection[26-29] but plant-based phytomedicine may be suitable antibacterial drug and prevent bacterial resistance.

The aim of the present study was to detect suitable receptor-ligand binding energy and molecular interaction through molecular docking approach for phytocompounds established in *T. procumbens* against bacterial DNA gyrase B protein (PDB ID: 3G7B).

MATERIALS AND METHODS

Selection of protein (receptor)

The crystal three-dimensional structure of protein of bacterial DNA gyrase B (PDB ID: 3G7B) was retrieved from the website of protein data bank (http:www.rcsb.org/). Ronkin[23] have experimented and deposited the X-ray diffraction crystallographic structure of the bacterial DNA gyrase B (*Staphylococcus aureus* gyrase B co-complex with methyl ({5-[4-(4-hydroxypiperidin-1-Yl)-2-phenyl-1,3-thiazol-5-Yl]-1H-pyrazol-3-Yl}methyl)carbamate inhibitor) at 2.30Å resolution. The 3-D ribbon structure is exhibited in Fig 1 after visualizing in MGL Tool developed by The Scripps Research Institute.[30] The pictorial (2-D) representation of ligand attachment with DNA gyrase B protein in chain A and B are exhibited in Fig 2–3 after obtaining two-dimensional view in Ligand Environment Viewer (LeView version 1.0) tool developed by Caboche.[31]

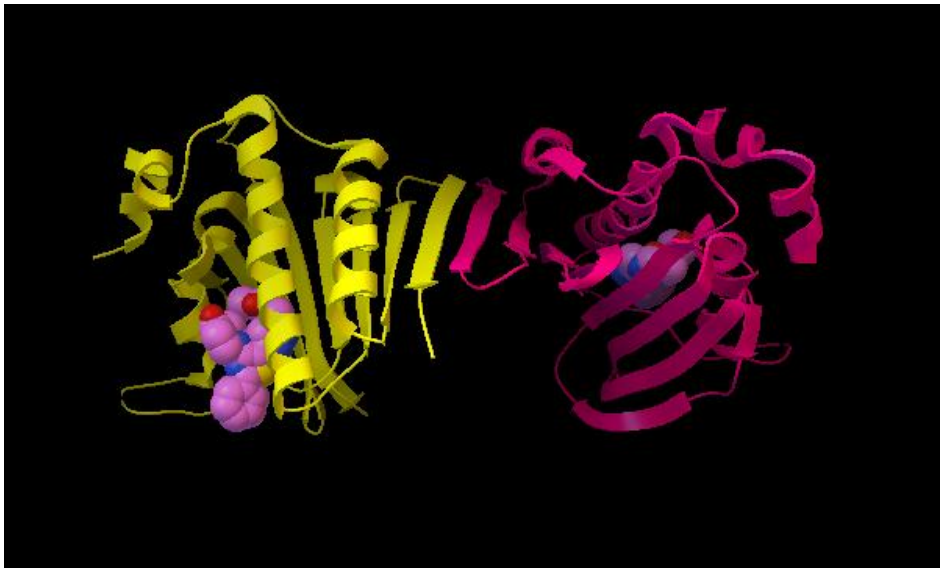


Fig 1: Three-dimensional (3D) ribbon structure of DNA gyrase B (PDB ID: 3G7B) [Chain A = yellow colour, attached with ligand (ball structure in CPK) at 471 position and Chain B = magenta colour, attached with ligand (ball structure in CPK) at 472]

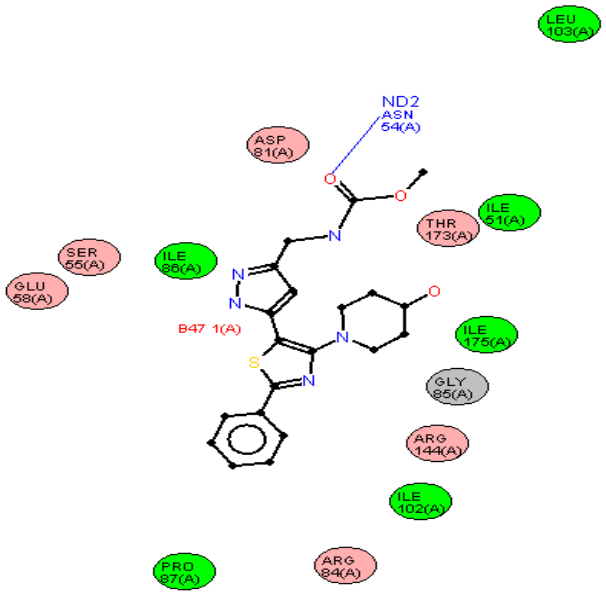


Fig 2. Attached ligand with chain A in bacterial DNA gyrase B (PDB ID: 3G7B).

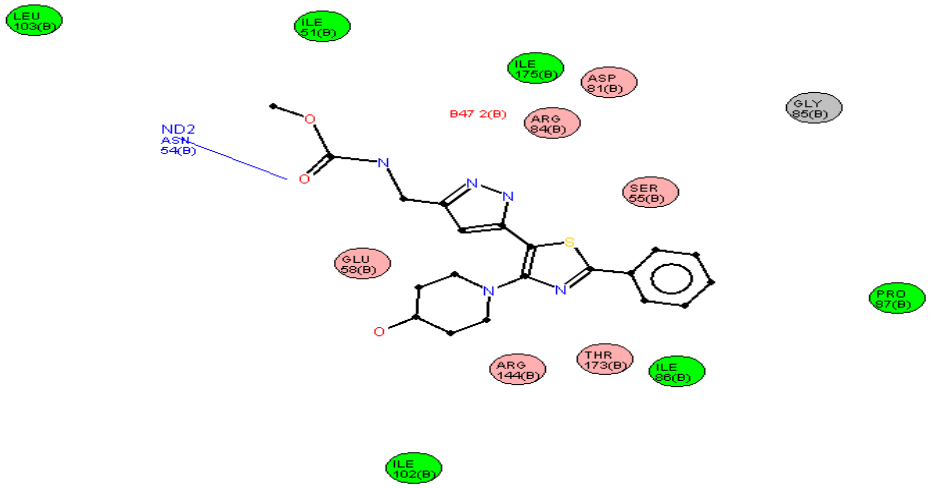


Fig 3: Attached ligand with chain B in bacterial DNA gyrase B (PDB ID: 3G7B)

Selection of phytochemicals (ligands)

The selection of phytochemicals (ligands) were done from the literatures as per antibacterial properties.[6-7] In the present study, established 16 phytochemicals of *T. procumbens* reported as antibacterial agents and one synthetic compound as known antibiotic (ciprofloxacin) were taken**.** The Canonical SMILES of these compounds were retrieved from the PubChem database (www.ncbi.nlm.nih.gov/pubchem) and .pdb file of each phytochemical was obtained from CORINA online server after inserting SMILES string in appropriate place. The plant is depicted in Fig 4.

Fig 4: Medicinal weed (*T. procumbens* Linn.).

Study of molecular docking and interaction

The docking was carried out by a virtual screening method through PyRx software (Virtual Screening Tool, Ver 0.8) developed by Trott and Olson.[32] The molecular docking was visualized the output .pdbqt file by using MGL tool, developed by The Scripps Research Institute (Morris et al., 1998) and the results of three-dimensional structure were rendered by using MGL Tools. Docking of 16 phytochemicals and ciprofloxacin (ligands) with bacterial DNA gyrase B protein (PDB ID: 3G7B) were analysed to detect suitable binding energy value. The phytoconstituents and synthetic drug (ligands) with the DNA gyrase B protein (receptor) to identify the residues involved in each case of receptor-ligand interactions. The docking site on this target protein was expressed by forming a grid box with the dimensions of X: 69.0824, Y: 46.5718 Z: 71.4695 Å, with a grid spacing of 0.375 Å, centered on X: 27.0389, Y: 0.0933 Z: 8.8102 Å. The present tool predicts docking result by obtaining energy value for each ligand. Finally, all the 17 ligands were analysed to detect binding position and energy value. The resultant structural complexes of the individual ligand/receptor binding were finally observed in AutoDoc Vina software (Morris et al., 1998), to determine some specific contacts between the atoms of the test compounds and amino acids of the DNA gyrase B protein.

RESULTS AND DISCUSSION

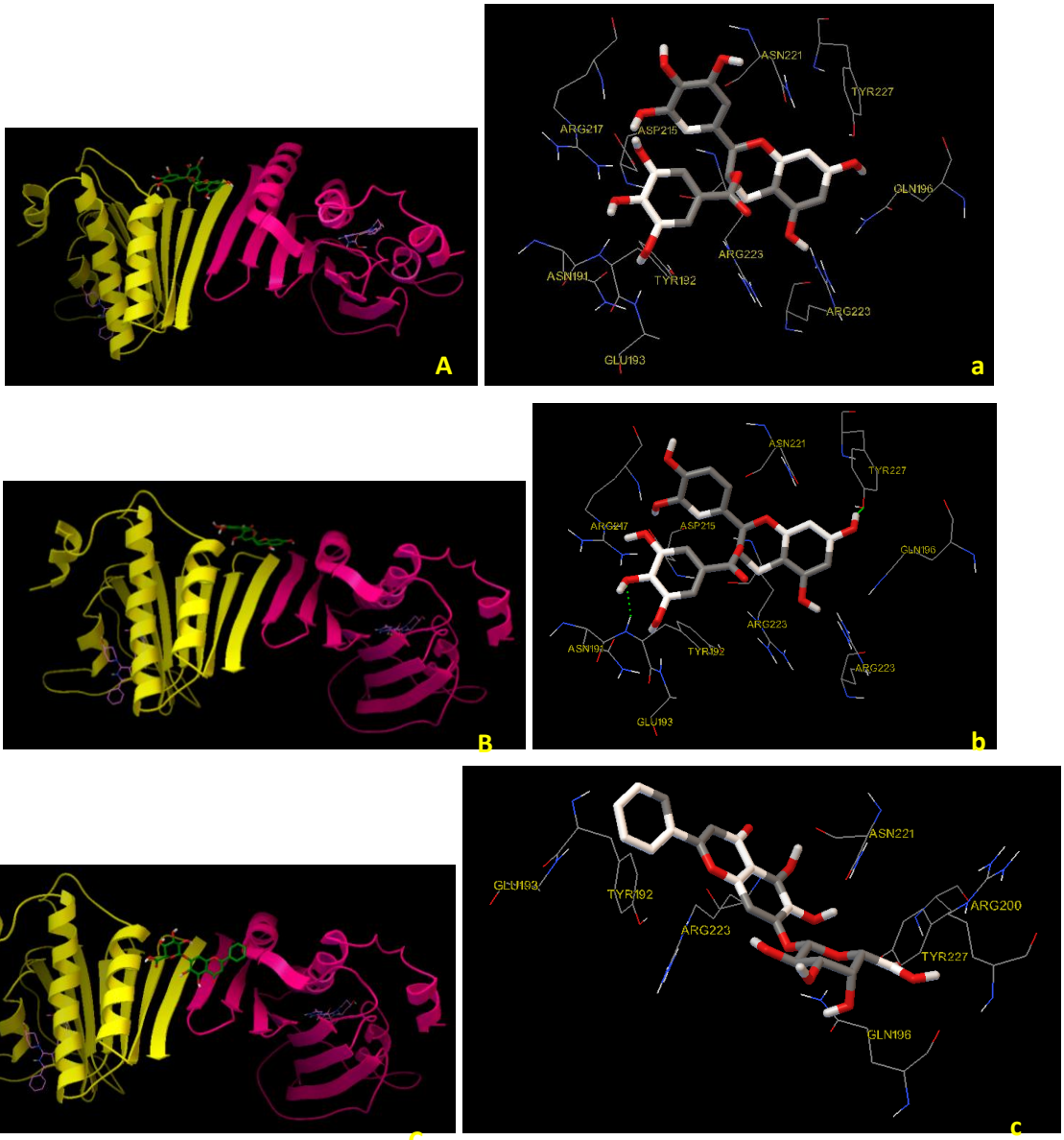
Present computational screening (molecular docking) indicates that favourable binding energy was observed, and highest binding energy value was observed in Epigallocatechin-3-gallate (-7.8 Kcal/mol), followed by Epicatechin-3-gallate (-7.7 Kcal/mol) and Baicalin (-7.7 Kcal/mol) and lowest value was obtained in Kaempferol and Akuammidine (-6.5 Kcal/mol) among other secondary metabolites of *T. procumbens* in comparison with Ciprofloxacin, a synthetic compound, obtained (-6.4 Kcal/mol) binding energy value (Table 1).

Figs 5A-D and a-d exhibited binding pose and interaction, where all four compounds (three phtyoligands and one synthetic ligand) found opposite to the active site of target receptor (PDB ID: 3G7B). The binding of Epigallocatechin-3-gallate was observed at chain A of receptor without hydrogen bonding and the attached amino acid residues were observed ASN221, TYR227, ASP215, ARG217, ASN191, TYR192, ARG223, GLU193, GLN196 and ARG223 respectively. Other two phytoligands such as Epicatechin-3-gallate and Baicalin were obtained same binding energy value but former ligand attached in chain A and showed two hydrogen bonding connected with residues ASN191 and TYR227 and attached residues were ASN221, ARG247, ASP215, GLN196, ARG223, TYR192 and ARG223 while next ligand attached in the chain A and partially in chain B without any hydrogen bonding and attached residues were ASN221, ARG200, TYR227, GLN196, ARG223, TYR192 and GLU193 respectively. In case of known antibiotic, Ciprofloxacin binding was also observed in chain A with one hydrogen bonding connected to LYS170 and other attached residues were THR80, VAL174, LYS78 and HIS143 respectively.

Table 1: Selected phytochemicals of *T. procumbens* Linn. and binding energy value after docking against bacterial DNA gyrase B protein.

Sl. No.	Ligands	Binding energy (Kcal/mol)
Phytochemicals		
1.	Epigallocatechin-3-gallate	-7.8
2.	Epicatechin-3-gallate	-7.7
3.	Baicalin	-7.7
4.	Tetrandrine	-7.3
5.	Luteolin	-7.2
6.	Apigenin	-7.1
7.	Stigmasterol	-7.1
8.	Catechin	-7.1
9.	Epicatechin	-7.0
10.	Quercetin	-6.9
11.	Myricetin	-6.9
12.	Gallocatechin	-6.8
13.	Epigallocatechin	-6.7
14.	Sitosterol	-6.7
15.	Akuammidine	-6.5
16.	Kaempferol	-6.5
Synthetic chemical		
17.	Ciprofloxacin	-6.4

In the present results, among other established phytochemicals of *T. procumbens*, Epigallocatechin-3-gallate showed highest binding energy (-7.8 Kcal/mol), followed by binding energy (-7.7 Kcal/mol) was obtained in two other phytoligands such as Epicatechin-3-gallate and Baicalin in comparison with Ciprofloxacin (-6.4). The binding interaction revealed no hydrogen bond contact found in Epigallocatechin-3-gallate and Baicalin but Epicatechin-3-gallate connected with two hydrogen bonds at ASN191 and TYR227 while in Ciprofloxacin, one hydrogen bond contact found but attached with LYS170. It was reported in earlier studies that active site residues are found in DNA gyrase B such as GLU50, ASN54, GLU58 and THR173 present in the ATP binding pocket, which are involved in ATPase activity.[25,33]



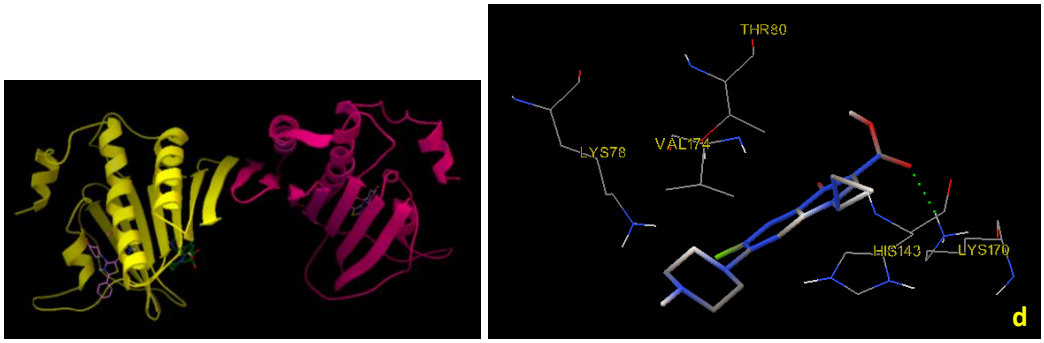


Fig 5: Docking pose (ball and stick structure) along with attached two inhibitory molecules (line structure) in chain A and B of bacterial DNA gyrase B (A = Epigallocatechin-3-gallate; B = Epicatechin-3-gallate; C = Baicalin and D = Ciprofloxacin) and ligand binding interaction with residues (a = Epigallocatechin-3-gallate; b = Epicatechin-3-gallate; c = Baicalin and d = Ciprofloxacin; green dotted line = hydrogen bonding).

But in present study the phytoligand (Epigallocatechin-3-gallate), and synthetic ligand (Ciprofloxacin) both were found binding opposite to the active site in chain A of bacterial DNA gyrase B (PDB ID: 3G7B), which may be due to non-competitive inhibition. In another research work, a similar observation is found for phytoligand Epigallocatechin-3-gallate that showed higher activity to inhibited bacterial DNA gyrase B by interaction with its ATP binding site and these catechins are containing in green tea.[34]

Although, researchers documented in experimental study that the extract of *T. procumbens* has potent antibacterial properties[6-7,35-36] but it is still unclear that which phytocompound is participating in antimicrobial activity. The selection of phytochemicals of *T. procumbens* in the present study is based on literatures where these secondary metabolites have already been investigated as antibacterial natural compound.[6]

CONCLUSION

It is concluded from the above *in silico* study, phytocompound Epigallocatechin-3-gallate can be alternative of synthetic antibacterial drug as per binding energy value and interaction of non-competitive inhibition. According Zhang et al.,[37] plant derived natural chemical can be suitable as lead compound to prevent synthetic drug resistance of bacteria. This present study is suggested further conducting functional and toxicological assay with this phytocompound after isolation from medicinal plant (*T. procumbens*) on bacterium, *Staphylococcus aureus*.

ACKNOWLEDGEMENT

The authors convey thanks to the developers of present software used in the predictive study, data bank for protein and phytochemicals.

Conflict of interest

None

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