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In silico investigation of various Phytoconstituents present in Mango ginger (*Curcuma amada* Roxb.) as Antibacterial agents

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ABSTRACT

Mango ginger, or *Curcuma amada* Roxb., is an uncommon spice that looks like ginger but flavors like fresh mango. Mango ginger is widely regarded in Ayurvedic and Unani medicinal systems as a digestive aid, aphrodisiac, antipyretic, emollient, diuretic, laxative, and expectorant as well as a cure for biliousness, itching, skin disorders, bronchitis, asthma, hiccups, and inflammation caused by accidents. There are number of carbohydrates, saponins, glycosides, phytosterols, resins, and flavonoids in rhizome extracts which contribute to pharmacological expressions. The main objective of this study was to explore the potential of various phytoconstituents [myrcene, (*Z*)-β-Farnesene, guaia-6,9-diene, α-longipinene, α-guaiene, epi-curzerenone, curzerenone, 1,8-cineole, isoborneol, camphor, (*E*)-hydroocimene, (*Z*)-hydroocimene, and linalool] as anti-bacterial agent by using *in-silico* approaches with the help of published literature on downregulation of enzyme expression and combining this information in order to recognize drug target [PDB ID: 3FV5; Crystal Structure of *E. coli* Topoisomerase-IV co-complexed with inhibitor; https://doi.org/10.2210/pdb3FV5/pdb]. The *in silico* studies revealed that the phytoconstituents successfully inhibited bacterial topoisomerase at varied degree which suggested plausible utilization as antimicrobial.

Keywords: Antibacterial, Phytoconstituents, Phytochemicals, Pharmacokinetics, *In silico*, *Curcuma amada*

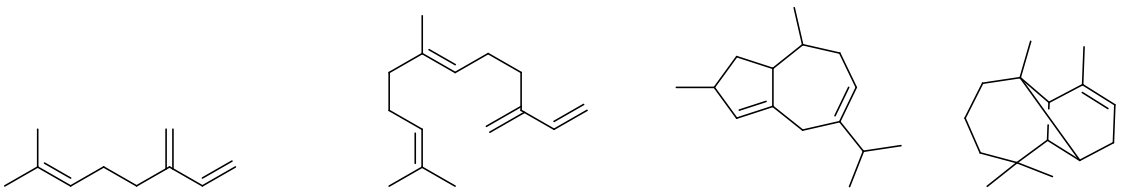
INTRODUCTION

*C. amad*a is a unique spice that tastes like fresh mango, while having a ginger-like appearance. The genus Curcuma was established by Linnaeus in his 1753 book Species Plantarum [1]. The Arabic word "kurkum," which refers to the hue yellow, is probably where the name came from. *Curcuma amada* Roxb is another name for this plant. It is a perennial herb with rhizomes that belongs to the Zingiberaceae family and has a strong taste. Seventy to eighty species of rhizomatous annual or perennial plants comprise this family [2]. The Indo-Malayan region,

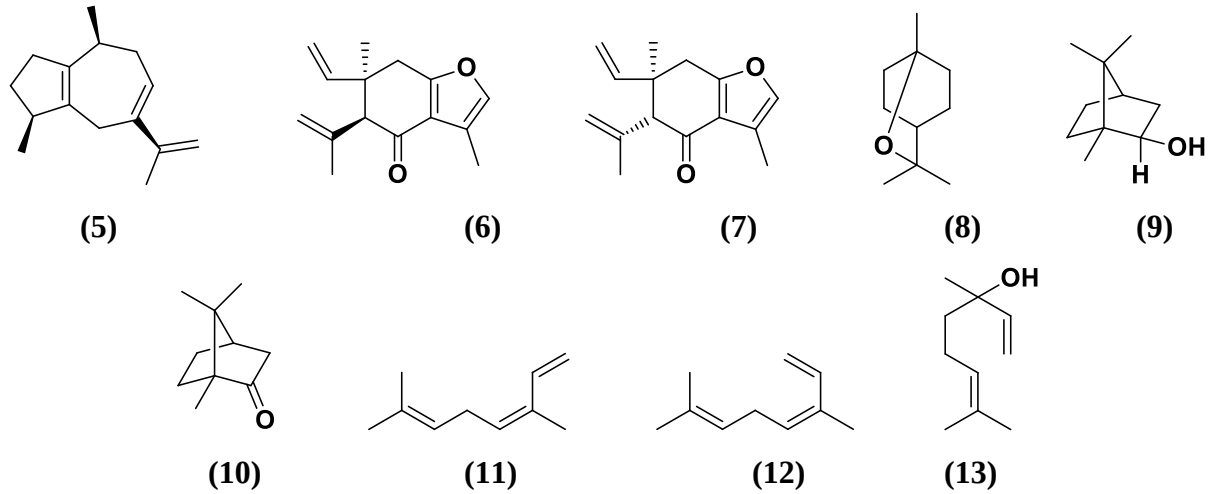
tropical Asia, Africa, and Australia are all parts of the species' wide geographic range. The plant has a one-meter height limit. The tall, oblong, lanceolate, radical, sheathed, and petiolate leaves grow in clumps. Each plant has five to six leaf pairs. Mango ginger rhizomes feature fleshy, buff-colored nodes and internodes that are 5–10 cm long and 2–5 cm in diameter. At the rhizome's nodes, scaly leaves are arranged in a circle, giving the appearance of growth rings with scars on the surface. Sympodial branches are separated into the rhizomes. The flavour of the rhizomes is strong and reminiscent of fresh mango [3].

Physiological, molecular and nutrient analyses are crucial for assessing the nutritional value and nutraceutical content of edible rhizomes. Mango ginger rhizome was shown to be a significant source of carbohydrates and fibre. The well-known curcumins curcumin, bis-demethoxycurcumin, and demethoxycurcumin are the primary ingredients in acetone extract [4]. Ferulic acid, caffeic acid, syringic acid, gentisic acid, gallic acid, cinnamic acid, protocatechuic acid, p-coumaric acid, syringic acid, etc. are the free phenolic acids found in mango ginger. Three terpenoid bioactive compounds, namely adannulen, adanaldehyde, and difurocumenonol, were successfully isolated and characterised from the chloroform extract of the *C. amada* rhizome [5]. Cis-ocimene and car-3-ene are primarily responsible for the flavour of the mango among the >60 volatile aroma elements in the essential oil of mango ginger rhizome. Trans-hydroocimene, cis-hydroocimene, myrcene, and ocimene were found to be the main substances in the volatile oils. The mango ginger acetone extract is made of the colourless oil made of phytosterol and curcumin and the azulenogenic oil made of camphor, pinene, ar-turmerone, and curcumene [6].

The current research emphasized on exploring the inhibitory perspectives of phytochemicals such as myrcene **(1)**, (*Z*)-β-Farnesene **(2)**, guaia-6,9-diene **(3)**, α-longipinene **(4)**, α-guaiene **(5)**, epi-curzerenone **(6)**, curzerenone **(7)**, 1,8-cineole **(8)**, isoborneol **(9)**, camphor **(10)**, (*E*)-hydroocimene **(11)**, (*Z*)-hydroocimene **(12)**, and linalool **(13)** **(Figure 1)** against *E. coli* Topoisomerase-IV co-complexed with inhibitor (PDB ID: 3FV5) by molecular docking approach using the iGEMDOCK (Genetic Evolutionary Method for Molecular Docking) software.



(1) **(2)** **(3)** **(4)**



(5) **(6)** **(7)** **(8)** **(9)**

(10) **(11)** **(12)** **(13)**

Figure 1. Structure of phytoconstituents.

MATERIALS AND METHODS

Preparation of Ligand

The phytochemicals were sketched out in the Cambridge Soft ChemDraw Ultra v.8.0 software. The produced .cdx files were converted into .mol2 files by using the Open Babel Software. The optimization and energy minimization of the sketched compounds was performed by the application of molecular mechanics as a force field (MM2), keeping the RMS cut-off at 0.100 [7,8].

Preparation of Protein

Crystal Structure of *E. coli* Topoisomerase-IV co-complexed with inhibitor; https://doi.org/10.2210/pdb3FV5/pdb (PDB ID: 3FV5) was downloaded from the Protein Data Bank (PDB) (http://www.rcsb.org/pdb) and optimized later by assigning the bond orders, removing the crystal water molecules beyond 5 Å distance from any heterogroup, addition of hydrogen atoms, assigning the tautomeric states, heterogroup ionization, and application of Kollman charges [9,10].

Docking Procedure

iGEMDOCK is a multi-tasking computational software having facilities for molecular docking of the ligand against the biological target, data screening, and post-analysis. This drug design system provides binding site selection by analyzing the ligand and the surrounding amino acid residues in

the range of 8 A° from the protein–ligand complexes and facilitates the selection of 200 population size, 70 generations, and three solutions. The energy function consists of hydrogen-bonding, steric, and electrostatic potentials. By utilizing the slow docking function, the ligands were docked into the target binding active site(s) and post-analyzed by accurately determining the pharmacological interactions with the energy-based scoring function. The graphical automatic system validation was performed by docking simulation which judges the docked conformations with the co-crystallized ligands in the conformity of <2% root mean square deviation (RMSD) value. The generated data by the interaction of the ligand with the protein structure were acquired through the default energy parameters and ranked on the basis of the binding affinities where highest potent derivative was ranked first and then successive analogs [11,12].

RESULTS AND DISCUSSION

The docking study revealed that compound named Myrcene **(2)**, present in *Curcuma amada* demonstrated the highest inhibition of antibacterial *E. coli* target topoisomerase-IV with docking score of -10.889 Kcal/mol (**Table 1**) by interacting with amino acid residues HIE49 (with =O residue), GLU51 (via –OH group), and TYR92 (through =O residue) whereas the well-known compound Camphor **(12)** presented the lowest inhibition of antibacterial *E. coli* target topoisomerase-IV with docking score of -3.971 Kcal/mol by interacting with amino acid residue TYR92 (through =O residue) (**Figure 2**). 1,8-cineole (-6.725 Kcal/mol), Isoborneol (-6.251 Kcal/mol), Linalool (-7.994 Kcal/mol by forming 1 hydrogen bonding), and Curzerenone (-8.354 Kcal/mol by forming 2 hydrogen bondings) showed good inhibition of the target. However other natural compounds; showed average docking scores in the range of -4 Kcal/mol to -6 Kcal/mol.

The compounds' antibacterial action was confirmed and made more intelligible by the induced-fit molecular docking experiments. This method has been around for a while and is still used to figure out how compounds interact with their target proteins and where the ligands should be positioned to create the lowest energy complexes. The molecular docking method was used to build a binding affinity model for the inhibitors [13]. The outcomes were predicted using docking score, hydrogen bonds, Van der Waal's interactions, π-cation interaction, and π-π stacking interactions as the primary factors. Using these factors, we were able to determine the affinity of ligands for proteins. When the docking score is negative, it means that the binding affinity is good. Several important characteristics were highlighted by the docking results: The existence of more hydrogen bonding connections indicates that the inhibitor has a strong binding affinity with the

molecular target to demonstrate antagonist activity, and greater Van der Waals interactions indicate that the ligands contain a significant number of bulky groups. We can thus use the IFD module to forecast how inhibitors will bind to proteins [14].

Hydrophobic amino acid residues encircled both substances, as was readily apparent. Since neither chemical was able to evaporate into the surrounding solvent, it follows that neither were successful in penetrating the protein's active site binding cleft. The ligands may be able to reach deeper into the cavity because of their diminutive size. Applying surface representation prevented visualisation of the ligand at the cavity owing to the complete masking of the ligand by amino acid residues. Maximum stability is achieved by Van der Waals interactions, which are brought about by the stable fitting of ligands. The absence of solvent exposure indicates that the chemicals were able to reach the protein's active site. Amino acid residues form a deep bent-shaped cleft in the target's active site, which allows for strong interactions with the ligand. Better inhibition of topoisomerase-IV may be due mostly to the amino function, according to one theory [15].

The significance of the location of interacting oxygen groups was highlighted by the research. It is possible to postulate that the active site will be better interacted with if the hydroxyl group is located furthest from the scaffold and the keto group is closer to it. The drug-target interaction's stability may also be dependent on interactions of steric, hydrophobic, electrostatic, and hydrophilic origins. Their interactions were validated by molecular docking experiments, which effectively predicted the ligands' theoretical binding to the biological target [16].

Table 1. Docking scores of phytoconstituents present in *Curcuma amada*.

S. No.	Compound	Gscore (Kcal/mol)	Hydrogen bonding	Amino Acid residues	Other interactions
1	(*Z*)-hydroocimene	-4.079	0	-	-
2	Myrcene	-10.889	3	HIE49 (=O), GLU51 (-OH), TYR92 (=O)	-
3	*Epi*-curzerenone	-5.173	0	-	Fe502 (metal coordination), ASP262 (salt bridge)
4	α-longipinene	-4.362	1	ASN42 (-OH)	-
5	α-guaiene	-4.924	0	-	ASP262 (salt bridge)

6	(*E*)-hydroocimene	-3.994	0	-	-
7	1,8-cineole	-6.725	0	-	-
8	Isoborneol	-6.251	0	-	Fe502 (metal coordination)
9	Linalool	-7.994	1	VAL130 (-OH)	ASP262 (salt bridge)
10	Curzerenone	-8.354	2	ASN42 (-OH), TYR56 (=O)	-
11	Guaia-6,9-diene	-	0	-	Fe502 (metal coordination)
12	Camphor	-3.971	1	TYR92 (=O)	-
13	(*Z*)-β-Farnesene	-5.186	1	GLU51 (-OH)	-

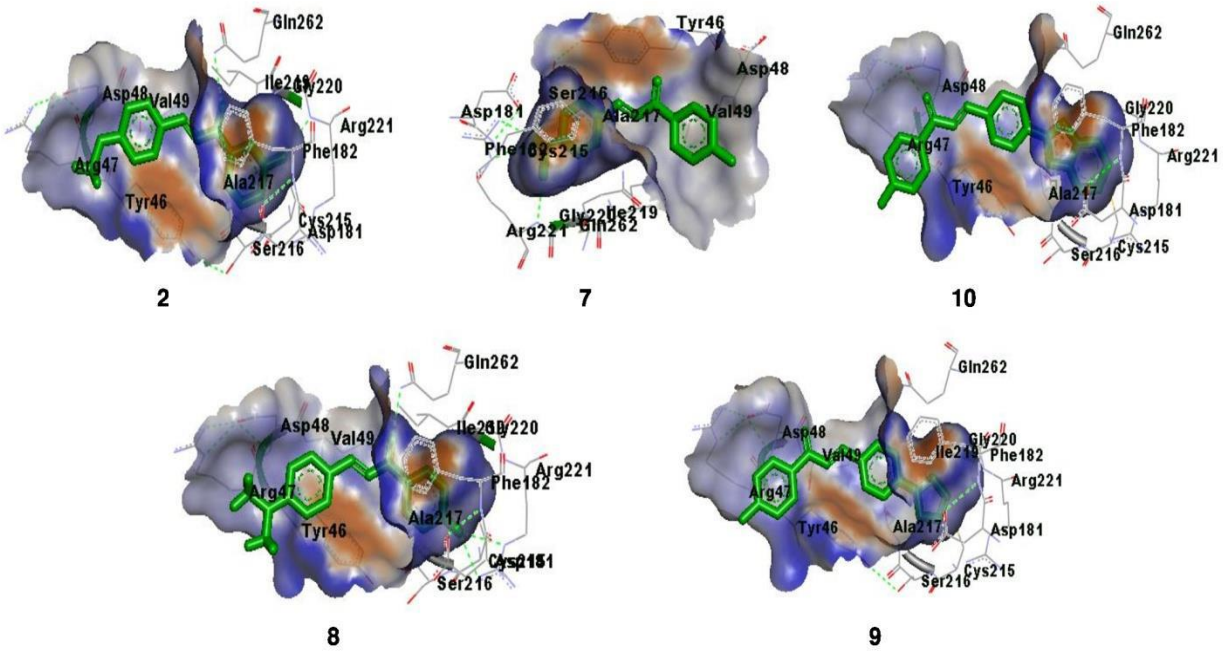


Figure 2. Docking poses of Top-5 compounds against *E. coli* Topoisomerase-IV.

CONCLUSION

The present investigation was a search for inhibitors that will help in recovering the patients suffering from bacterial infections as well as for prophylactic use. This is a nascent step towards the exploration of successful safe inhibitors for treating the complex symptoms associated with nosocomial infection or septicemia. When the whole world is running for a solution against

bacteria, probably by the discovery of natural compounds, this study will rejuvenate the minds of scientists that yet there are possibilities that low molecular weight ligands have the capability to eradicate this dangerous bacterial resistance and reduce the global impact created by this pandemic. On the other hand, it can be exclusively perceived from this interesting study that all these natural compounds showed impressive results. This eventually concludes that every nature created problem can be completely solved through inhibition of *E. coli* topoisomerase-IV, a target that will help the human mankind in combating the complex situations.

CONFLICT OF INTEREST

No conflict of interest is declared.

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ETHICAL DISCLOSURES

None required

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