Current Botany 2023, 14: 17-23
doi: 10.25081/cb.2023.v14.8002
https://updatepublishing.com/journal/index.php/cb

Research Article

ISSN: 2220-4822

In silico molecular docking and *in vitro* antimicrobial efficacy of phytochemical compounds of *Lantana camara* Linn.

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ABSTRACT

The rise of multi-drug resistant bacteria and the extensive use of antibiotics has become a serious threat worldwide. The side effect of antibiotics swirled the researchers towards traditional medicine to find a therapeutic agent with antibacterial activity. The phytochemical compound from medicinal plants paves a way for the novel antibacterial agent. In the present study, *in silico* molecular docking of phytochemical compounds identified through GC-MS analysis and *in vitro* antibacterial efficacy of ethanolic leaf extract of *Lantana camara* were evaluated. *In silico* docking studies of 11 Phyto-ligands were carried out against 4 motifs- 1PHO, 5I5H, 5UW2 and 6NTW of *Escherichia coli* to estimate the binding energy and to know the protein-ligand interaction. Amongst all the phyto-ligands studied, 4,8,13-Cyclotetradecatriene-1,3-diol,1,5,9-trimethyl-12-(1-methylethyl) showed good affinity towards 1PHO, 4a(2H)-Phenanthrenecarboxaldehyde,1,3,4,9,10,10a-hexahydro-6-methoxy-1,1-dimethyl-7-(1-methylethyl) exhibited highest affinity with 5I5H motifs of *E. coli*, 4,8,13-Cyclotetradecatriene-1,3-diol, 1,5,9-trimethyl-12-(1-methylethyl) showed better affinity towards motif 5UW2 of *E. coli* and (Z)-4-Nitro-alpha-(p-nitrophenyl)cinnamic acid showed good affinity towards 6NTW motif of *E. coli*. The ethanolic leaf extract of *L. camara* L. showed concentration dependent activity against *E. coli*.

Received: September 26, 2022
Revised: February 16, 2023
Accepted: February 17, 2023
Published: February 27, 2023

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KEYWORDS: *Lantana camara*, molecular docking, antimicrobial activity, phytochemical compounds, *Escherichia coli*, GC-MS analysis

INTRODUCTION

Antibiotic resistance to pathogenic bacteria has become a threat to public health, leading to the research of novel drugs for treating pathogenic bacteria (Aslam *et al.*, 2018). The war between the multidrug resistant bacteria and the side effect of antibiotics turned the researcher's focus towards traditional medicine. Since ancient times, plants have been playing a pivotal role in traditional medicine as they are the richest source of secondary metabolites with antimicrobial properties. A well-known plant in traditional medicine is *Lantana camara*, a family member of Verbenaceae (Dharmagada *et al.*, 2005). *L. camara* L., is an evergreen shrub, aromatic weed, native to tropical America (Raghu *et al.*, 2004) and grown as an ornamental plant in some countries. It is also found in tropical, subtropical and temperate regions at a high altitude of up to 2000m (Ganjewala *et al.*, 2009). The plant is commonly known as red sage (Munir, 1996). The presence of multiple phytochemical compounds in almost all parts of the plant exhibit unique and different pharmacological properties like larvicidal activity (Kumar & Maneemegalai, 2008), anti-leukemia (Badakhshan *et al.*, 2009), antioxidant (Bhakta & Ganjewala, 2009), antimutagenic activity, antihypertensive (Kaur *et al.*, 2010), antiulcerogenic (Thamotharan *et al.*, 2010), haemolytic (Kalita *et al.*, 2011), antihelmintic (Patel *et al.*, 2011), and hepatoprotective activities (El-Kassem *et al.*, 2014) as well as for antibacterial and antiproliferative (Gomes de Melo *et al.*, 2010).

The medicinal value of the plant depends on the phytochemical constituents such as flavonoids, phenolics, polyphenols, tannins, terpenoids etc. (Shah *et al.*, 2011). They act as an effective inhibitory agent against all types of microbes *in vitro* (Cowan, 1999). In the present study, the phytochemical constituents were identified by GC-MS analysis and the ethanolic leaf extract of *L. camara* was investigated for antibacterial efficiency. The phyto-ligand was docked *in silico* with 1PHO, 5I5H, 5UW2 and 6NTW motifs of *E. coli* to examine the interaction of phyto-ligand with active site residues of motifs.

MATERIALS AND METHODS

Collection of Sample

Fresh and healthy leaves of *Lantana camara* L. plant was collected from Chunkankadai, Nagercoil, Kanyakumari District,

Tamil Nadu, India. Plant sample was authenticated by Dr. S. Jeeva and deposited at the herbarium (Voucher No. SCTH 3571), Department of Botany, Scott Christian College, Nagercoil. The plant was identified based on the taxonomical characteristics.

Preparation of Plant Extract

The leaves were washed with water to remove dust, then shade dried at room temperature for 14 days and powdered by an electrical blender. Twenty grams of leaf powder was used to extract with 200mL of ethanol at Soxhlet apparatus as per the standard procedure. The filtrate was evaporated by using rotary evaporator to yield residue. About 12.70 mg extract yield were obtained and stored at 4°C for further studies (Vogel, 1978).

Antibacterial Activity

Microbial strains used

Antimicrobial activity for the ethanolic leaf extracts of *L. camara* was evaluated by using the agar well diffusion method. The Gram-negative microbial strain *Escherichia coli* was obtained from Scudder lab, Nagercoil, Kanyakumari District, Tamil Nadu. The bacterial stock culture was maintained by incubating for 24 hours at 37°C on nutrient agar and stored at 4°C. For experimental purposes, the bacterial strain was grown in Muller-Hinton Agar plates at 37°C for 24 hours. Then the bacteria were cultured in the nutrient broth.

Agar well diffusion method

Antibacterial activity of the ethanolic leaf extracts of *L. camara* was carried out by the agar well diffusion method against standard test microorganisms *E. coli*. The plant extract of 2.5, 5.0 and 10.0 µg/mL was prepared for testing the antibacterial activity. Nutrient agar medium was prepared and poured into Petri plates, then cooled to solidify and the organisms maintained in the broth were swabbed in the agar plate. Wells of 5 mm were punched using a sterile gel puncher over the agar plates. The plant extract of 2.5, 5.0 and 10.0µg/mL were poured into the wells. The plates were incubated at 37°C for 24 hrs. The antimicrobial activity of the extract was determined by the diameter of the zone of inhibition produced by the sample. The diameter of the zone of inhibition (mm) was measured and compared with the positive control, Ciproflaxin.

GC-MS Analysis

Gas chromatography-Mass Spectroscopy Analysis (GC-MS)

A 100µL of the ethanolic leaves extract of *L. camara* was dissolved in 1mL of solvent, mixed and filtered, the GC-MS analysis was carried out by using Thermo GC-Trace ultra ver Thermo MsDsqII:5.0 instrument equipped with a DB 35-MS capillary standard Non-polar column (0.25 µm film thickness × 0.25 mm i.d.× 30m length). Helium was used at a flow rate of 1.0 mL/min, as the carrier gas. Samples were injected in the split mode at a ratio of 1:10-1:100. The injector of the instrument was kept at a temperature of 240 °C and the transfer line at 280 °C. In the beginning the column was maintained at 50 °C for 2 min and then increased to 260 °C at 5 °C/min and finally held for 10 min at 260 °C. The instrument was operated in the EI mode at 70 eV and m/z range 42-350. The identification of the compounds was performed with the NIST library

Molecular Docking

Ligand Selection and Drug Docking

The phytocompounds of *L. camara* from GC-MS analysis were taken as ligands. The potential ligand compounds for the docking studies were identified based on the five Index based filters that are Lipinski filter, Veber filter, Egan filter, Goose filter and Muegge filter. The chemical structure of the phytocompounds was retrieved from the PubChem-NCBI database and converted into the 3D structure using an online smiles translator.

Protein sequence retrieval system

In order to perform protein modelling studies, the gene-encoded protein sequence of *E. coli* – a crystal structure of two *E. coli* porins (PDB-1PHO), the structure that transfers cardiolipin from the inner membrane to the outer membrane by PbgA in Gram-negative bacteria (PDB-5I5H), structure of *E. coli* mammalian cell entry protein MIaD, periplasmic domain (PDB-5UW2) and YcbB-mediated beta-lactam resistance protein in *E. coli* (PDB-6NTW) were selected for their interaction with phytocompounds of *L. camara*. The 3D structure of the protein was retrieved from Protein Data Bank and viewed through Discovery Studio software. Finally docking studies were analyzed using Auto Dock Vina (version 4).

RESULTS AND DISCUSSION

The rise of antibiotic-resistant of Gram-negative bacteria is due to the envelope of Gram-negative bacteria, composed of an asymmetrical composition of lipids in a cytoplasmic membrane, peptidoglycan layer and an outer membrane (Lugtenberg & Alphen, 1983). The outer membrane of the Gram-negative bacteria plays a vital role in protecting the cell from harmful agents like antibiotics, detergents and toxins, also from changes in osmotic pressure. Transmembrane proteins, the porins assembled in the outer membrane, allow only the uptake and discharge of small hydrophilic compounds like nutrients and waste products (Nikaido & Vaara, 1985). One of the antibiotic-resistant, Gram-negative bacteria is *E. coli*, a food-borne pathogen, which causes diarrhoea, gastroenteritis, and a series of other complications (Miri *et al.*, 2017). When compared to Gram-positive bacteria, Gram-negative bacteria are known to exhibit high resistance against synthetic antibiotics and chemical agents, and are the major causes of a large number of deaths (Villegas & Quinn, 2004; Canli *et al.*, 2015). The search for an alternative drug gave insight into traditional methods of curing illness with plant compounds. The phytoconstituents have been reported to possess a wide spectrum of antibacterial activities against pathogenic microbes (Prasad *et al.*, 2019). Hence in the present study, the ethanolic leaf extract of *L.*

camara was screened for *in vitro* antibacterial activity against a Gram-negative bacteria, *E. coli* at different concentrations of 2.5, 5.0 and 10.0µg/mL and the diameter of zone of inhibition is listed in Table 1. The negative control was ethanol and the positive control was Ciproflaxin. Among the tested ethanolic leaf extract, the concentration of 10.0µg/mL exhibited the highest activity (23.00 mm) against *E. coli* followed by the concentration of 5.0µg/mL (17.63 mm) and 2.5µg/mL (14.73 mm). With the increase in the concentration of the plant extract, there was an increase in the zone of inhibition. The result of the present study substantiates the finding of Swamy *et al.* (2015). Previously, researchers have reported that Gram-negative bacteria seem to be more influenced by the *L. camara* extract than the Gram-positive bacteria (Swamy *et al.*, 2015).

Table 1: *In vitro* antibacterial activity of ethanolic leaf extract of *L. camara* against a Gram-negative bacteria *E. coli*

Concentration (µg/mL)	Zone of inhibition (mm)		
	Plant extract	Positive control	Negative control
2.5	14.73±0.31	17.00±0.20	15.07±0.31
5.0	17.63±0.32	20.00±0.20	17.00±0.35
10.0	23.00±0.20	22.53±0.42	17.87±0.42

*Values are means of triplicate ± Standard deviations

Further GC-MS analysis of the ethanolic leaf extract of *L. camara* led to the identification of the number of components. The 31 components present in the ethanolic leaf extract of *L. camara* that was detected by the GC-MS are shown in Table 2. 1-(3-Ethoxy-2-methyl-acryloyl)-3-(2-hydroxy-ethyl)-urea, 4a(2H)-Phenanthrenecarboxaldehyde, 1,3,4,9,10,10a-hexahydro-6-methoxy-1,1-dimethyl-7-(1-methylethyl)- and (Z)-4-Nitro-alpha-(p-nitrophenyl) cinnamic acid were the major components present in the ethanolic leaf extract of *L. camara*. Many of these identified phytoconstituents are known to have several Pharmacological activities. A phenolic compound, 1,2-Benzenediol, a major phytoconstituent of *L. camara* ethanolic leaf extract, is known to have antimicrobial activity (Kim & Lee, 2014). Another phenolic compound, 2-Methoxy-4-vinylphenol is reported with anticancer (Jeong & Jeong, 2010), antioxidant, antimicrobial, anti-inflammatory (Jeong *et al.*, 2011) and analgesic, anti-germination (Ibibia *et al.*, 2016). Octadecanoic acid, a fatty acid is also known to possess antimicrobial properties (Rahuman *et al.*, 2011). Therefore, we

Table 2: The major phytochemical compounds identified in the ethanolic leaf extract of *L. camara* fraction by GC-MS analysis

S. No.	Retention Time (min)	Compound Name	Molecular Formula	Molecular Weight (g/mol)	Percent area (%)
1	9.453	1,2-Benzenediol	$C_6H_6O_2$	110.11	2.02
2	9.764	Benzofuran, 2,3-dihydro-	C_8H_8O	120.15	3.70
3	11.120	2-Methoxy-4-vinylphenol	$C_9H_{10}O_2$	150.17	1.50
4	11.586	Phenol, 2,6-dimethoxy-	$C_8H_{10}O_3$	154.16	1.82
5	11.675	Phenol, 2-methoxy-3-(2-propenyl)-	$C_{10}H_{12}O_2$	164.2	1.30
6	12.819	2,1,3-Benzothiadiazole	$C_6H_4N_2S$	136.18	2.42
7	13.486	Naphthalene, decahydro-2,2-dimethyl-	$C_{12}H_{22}$	166.3	1.34
8	13.630	2-(1-Hydroxybut-2-enylidene) cyclohexanone	$C_{10}H_{14}O_2$	166.22	1.23
9	13.853	D-Allose	$C_6H_{12}O_6$	180.16	1.78
10	14.619	1H-Cycloprop[e] azulen-7-ol, decahydro-1,1,7-trimethyl-4-methylene-, [1ar-(1a.alpha.,4a.alpha.,7. beta.,7a.beta. 7balpha)	$C_{15}H_{24}O$	220.35	1.08
11	15.097	2,7-Octadiene-1,6-diol, 2,6-dimethyl-	$C_{10}H_{18}O_2$	170.25	1.83
12	15.563	Phenol, 2,4-bis (1-methylethyl)-	$C_{12}H_{18}O$	178.27	1.64
13	15.797	Lilac alcohol B	$C_{10}H_{18}O_2$	170.25	1.43
14	15.875	Lilac alcohol A	$C_{10}H_{18}O_2$	170.25	4.37
15	16.097	1-(3-Ethoxy-2-methyl-acryloyl)-3-(2-hydroxy-ethyl)-urea	$C_9H_{16}N_2O_4$	216.23	33.23
16	16.363	4-((1E)-3-Hydroxy-1-propenyl)-2-methoxyphenol	$C_{10}H_{12}O_3$	180.2	0.94
17	16.463	6-Bromomethyl-5-methyl-bicyclo[3.1.0]hexan-2-one	$C_8H_{11}BrO$	203.08	8.45
18	16.786	1-Methyl-3-n-propyl-2-pyrazolin-5-one	$C_7H_{12}N_2O$	140.18	1.92
19	16.941	2-Cyclohexen-1-one, 4-hydroxy-3,5,6-trimethyl-4-(3-oxo-1-butenyl)-	$C_{13}H_{18}O_3$	222.28	2.46
20	17.352	9-Octadecyne	$C_{18}H_{34}$	250.5	1.73
21	17.430	Bicyclo[5.2.0]nonane, 4-methylene-2,8,8-trimethyl-2-vinyl-	$C_{15}H_{24}$	204.35	0.96
22	17.619	Acetic acid, 10,11-dihydroxy-3,7,11-trimethyl-dodeca -2,6-dienyl ester	$C_{17}H_{30}O_4$	298.4	1.42
23	17.830	1,4-Methanoazulen-9-one, decahydro-1,5,5,8a-tetramethyl-, [1R-(1.alpha.,3a.beta.,4.alpha.,8a.beta.)]-	$C_{15}H_{24}O$	220.35	1.19
24	18.352	Cyclohexanol, 5-methyl-2-(1-methylethyl)-, (1.alpha.,2.alpha., 5.alpha.)-	$C_{10}H_{20}O$	156.26	2.01
25	18.585	Octadecanoic acid	$C_{16}H_{32}O_2$	256.42	1.24
26	19.307	3-Hexene, 1-[1-ethoxyethoxy]-, (E)-	$C_{10}H_{20}O_2$	172.26	1.06
27	20.274	Gamolenic Acid	$C_{18}H_{30}O_2$	278.4	1.17
28	21.363	Benzyl .beta.-d-glucoside	$C_{13}H_{18}O_6$	270.28	1.12
29	22.696	4,8,13-Cyclotetradecatriene-1,3-diol, 1,5,9-trimethyl-12-(1-methylethyl)-	$C_{20}H_{34}O_2$	306.5	1.11
30	27.129	4a (2H)-Phenanthrenecarboxaldehyde, 1,3,4,9,10,10a-hexahydro-6-methoxy-1,1-dimethyl-7-(1-methylethyl)-,	$C_{17}H_{14}O_6$	314.29	12.52
31	27.129	(Z)-4-Nitro-alpha-(p-nitrophenyl) cinnamic acid	$C_{15}H_{10}N_2O_6$	314.3	12.52

assume that the strong antimicrobial activity exhibited by the ethanolic leaf extract of *L. camara* may be due to the occurrence of these phytocompounds with biological activities.

In vitro screening of biologically active compounds for their antimicrobial efficacy and toxic nature would consume more time. Hence, employing *in silico* computational approaches associated with molecular docking, chemoinformatics, as well as artificial intelligence, have significantly increased during the past decade in the area of designing, development, and discovery of drug (Pinzi & Rastelli, 2019; Jia *et al.*, 2020) and also enabled virtual screening of molecule interactions which would help in discovering suitable therapeutic agent in less time and cost. Several molecular docking approaches based on the structure and ligand are currently available to ease the process of drug discovery with high output (Pinzi & Rastelli, 2019; Abdullahi & Adeniji, 2020), in structural based drug design, the protein-ligand interactions play a vital role. In the present investigation, 12 phytochemicals from *L. camara* have been docked against four *E. coli* proteins and compared with the commercial antibiotic, Ciprofloxacin (control drug). All phytochemical compounds were evaluated to find out the potential phytocompounds against the targeted protein of *E. coli*. The phytochemicals of the highest binding affinity with 1PHO, 5I5H, 5UW2 and 6NTW were selected and listed in Table 3. 1PHO shows higher binding affinity with ligand 4,8,13-Cyclotetradecatriene-1,3-diol, 1,5,9-trimethyl-12-(1-methylethyl) and have docking score of -7.4 Kcal/mol, docked poses as illustrated in Figure 1. 1PHO form hydrogen bond interaction with amino acid residue Asp97 and alkyl bond interaction with residues such as Lys46 and Tyr58. The control Ciprofloxacin shows the highest binding affinity against 1PHO with a docking score of -7.6 Kcal/mol. Ciprofloxacin forms two hydrogen bonds with amino acid residues Ser95, and Arg140 and four non-bonded interactions with amino acid residues Lys46, Glu48, Tyr58, and Phe85 when interacted with 1PHO.

Table 3: The Binding affinity of tested *L. camara* plant phytochemicals against *E. coli* protein

S.No	*E. coli* motifs	Ligand	PubChem ID	No. of Hydrogen bond	No. of alkyl bond	Residues involved in Bonded Interactions	Residues involved in Non-Bonded Interactions	Docking Score (-Kcal/mol)
1	1PHO	4,8,13-Cyclotetradecatriene-1,3-diol, 1,5,9-trimethyl-12-(1-methylethyl)-	5367548	1	2	Asp97	Lys46, Tyr58	-7.4
2	5I5H	4a (2H)-Phenanthrenecarboxaldehyde, 1,3,4,9,10,10a-hexahydro-6-methoxy-1,1-dimethyl-7-(1-methylethyl)-,	628740	1	4	Arg451	Phe412, Pro454, Gly452, His468	-8.2
3	5UW2	4,8,13-Cyclotetradecatriene-1,3-diol, 1,5,9-trimethyl-12-(1-methylethyl)-	5367548	-	4	-	Ile60, Val63, Val65, Tyr90	-6.6
4	6NTW	(Z)-4-Nitro-alpha-(p-nitrophenyl) cinnamic acid	1550723	1	1	Arg407	Leu431	-7.5
Standard drug								
5	1PHO	Ciprofloxacin	2764	2	4	Ser95, Arg140	Lys46, Glu48, Tyr58, Phe85	-7.6
6	5I5H	Ciprofloxacin	2764	2	3	Ser407, Arg451	Asp406, Phe412, Pro454	-7.2
7	5UW2	Ciprofloxacin	2764	3	-	Gly51, Gln110, Met141	-	-6.1
8	6NTW	Ciprofloxacin	2764	2	2	Tyr446, Arg490	Asp435, Pro512	-7.5

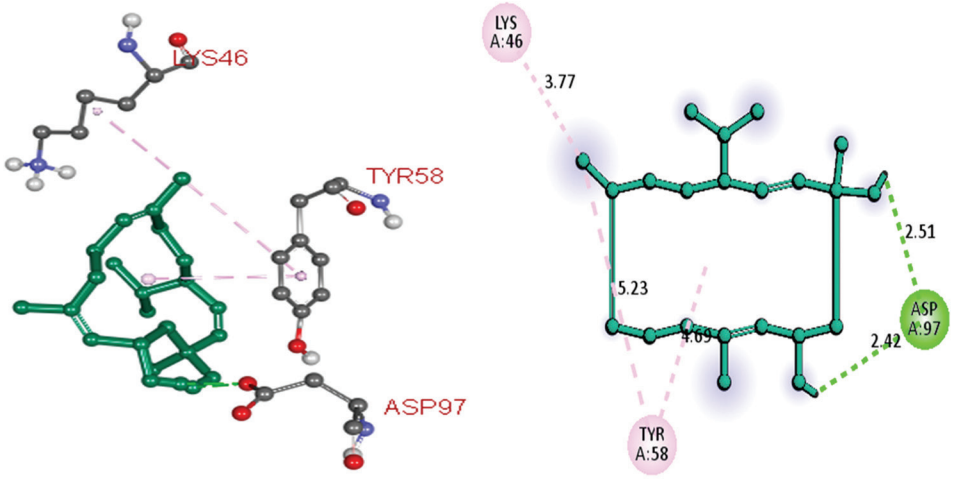

Figure 1: 3D Pose and 2D Interaction Plot of plant compound 4,8,13-Cyclotetradecatriene-1,3-diol, 1,5,9-trimethyl-12-(1-methylethyl) with *E. coli* motifs, 1PHO (- 7.4 Kcal/mol)

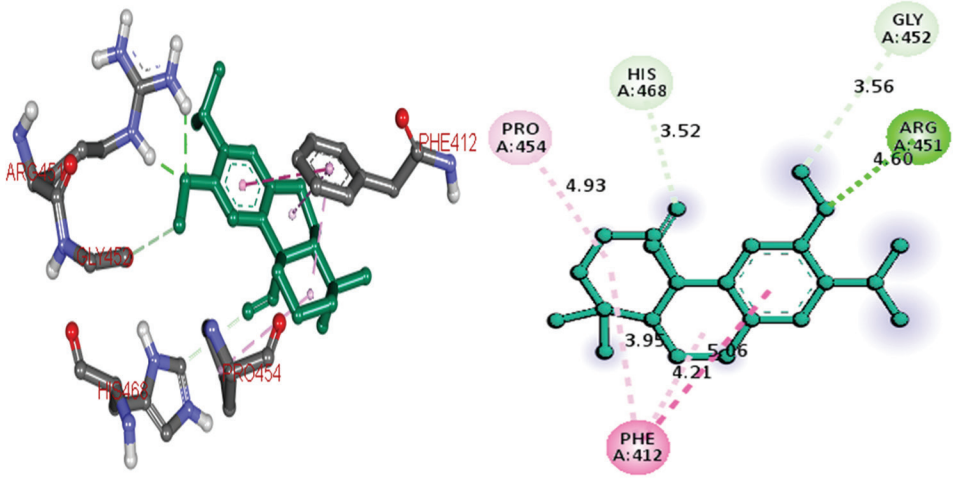

Figure 2: 3D Pose and 2D Interaction Plot of plant compound 4a(2H)-Phenanthrenecarboxaldehyde, 1,3,4,9,10,10a-hexahydro-6-methoxy-1,1-dimethyl-7-(1-methylethyl)- with *E. coli* motifs, 5I5H (- 8.2 Kcal/mol)

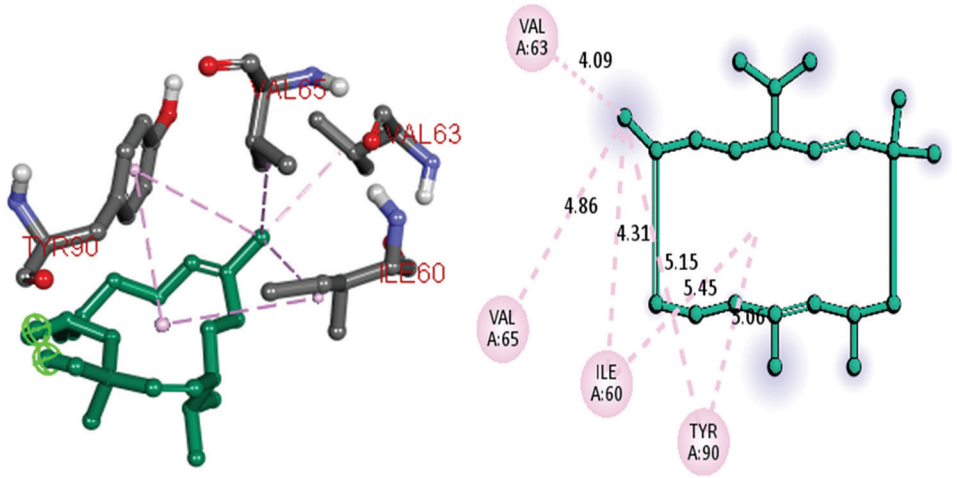

Figure 3: 3D Pose and 2D Interaction Plot of plant compound 4,8,13-Cyclotetradecatriene-1,3-diol, 1,5,9-trimethyl-12-(1-methylethyl)- with *E. coli* motifs, 5UW2 (- 6.6 Kcal/mol)

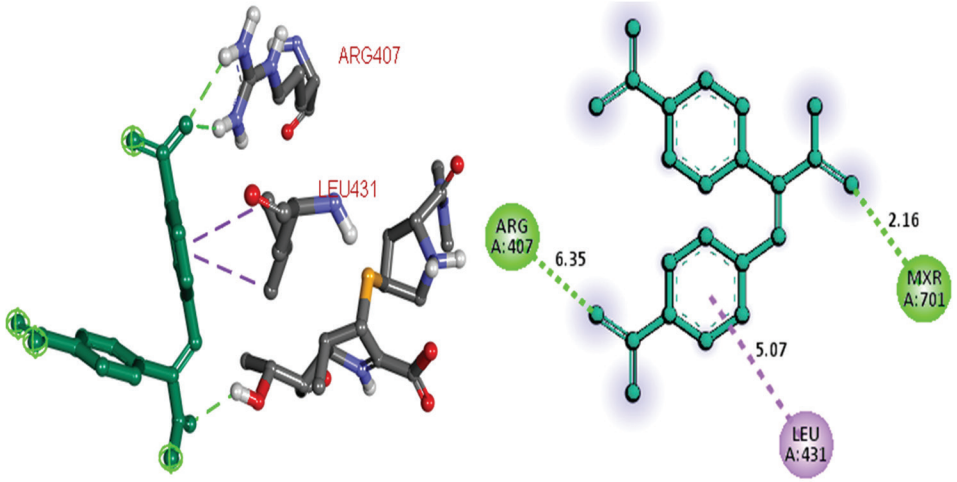

Figure 4: 3D Pose and 2D Interaction Plot of plant compound (z)-4-Nitro-alpha-(p-nitrophenyl)cinnamic acid with *E. coli* motifs, 6NTW (- 7.5 Kcal/mol)

5I5H shows higher binding affinity with ligand 4a(2H)-Phena nthrenecarboxaldehyde,1,3,4,9,10,10a-hexahydro-6-methoxy-1,1-dimethyl-7-(1-methylethyl)- (Figure 2) of docking score -8.2Kcal/mol than the control (-7.2Kcal/mol). 5I5H forms a hydrogen bond interaction with the amino acid residue Arg451 and non-bonded interaction with amino acid residues Phe412, Pro454, Gly452, His468. Ciprofloxacin when interacts with 5I5H, forms two hydrogen bonds with amino acid residues Ser95, and Arg140 and three alkyl bonds with amino acid residues such as Asp406, Phe412, and Pro454 and the docking score was -7.2kcal/mol. Four alkyl bond was formed with amino acid residues such as Ile60, Val63, Val65, and Tyr90 when 5UW2 interacted with 4,8,13-Cyclotetradecatriene-1,3-diol, 1,5,9-trimethyl-12-(1-methylethyl)- (Figure 3). The docking score was -6.6Kcal/mol. The antibiotic Ciprofloxacin interacted with amino acid residues such as Gly51, Gln110 and Met141 by forming three hydrogen bonds. The *E. coli* protein, 6NTW interacted with (Z)-4-Nitro-alpha-(p-nitrophenyl) cinnamic acid by forming one hydrogen bond and one alkyl bond with amino acid residue Arg407 and Leu431, respectively, the docking score was -7.5Kcal/mol, where the interaction of Ciprofloxacin with 6NTW also showed the same docking score (Figure 4). Ciprofloxacin shows bonded interaction with two amino acid residues (Tyr446, Arg490) and two non-bonded interactions with residues Asp435 and Pro512.

CONCLUSIONS

The present investigation clearly revealed that the phytochemical ethanolic leaf extract of *L. camara* has considerable antimicrobial activity. The molecular docking showed that the phytochemical compounds of this plant contain therapeutic properties. The phytochemicals 4,8,13-Cyclotetradecatriene-1,3-diol, 1,5,9-trimethyl-12-(1-methylethyl) possess great binding affinity with 1PHO, 4a(2H)-Phenanthrenecarboxaldehyde, 1,3,4,9,10,10a-hexahydro-6-methoxy-1,1-dimethyl-7-(1-methylethyl) with 5I5H, 4,8,13-Cyclotetradecatriene-1,3-diol, 1,5,9-trimethyl-12-(1-methylethyl) with 5UW2 and (Z)-4-Nitro-alpha-(p-nitrophenyl)cinnamic acid with 6NTW. Thus, our study suggests that ethanol leaf extract of *L. camara* contains many phytochemical compounds and may be utilized as a therapeutical source for developing beneficial drugs. However, further studies need to be carried out to isolate, and purify the compounds and analyze their pharmacological activity.

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