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POTENTIAL DRUGS AGAINST MULTIDRUG RESISTANT BACTERIA FROM OCIMUM TENUIFLORUM: AN IN SILICO ANALYSIS

Mohideen A.P.[1*], Shamna K.P.[2]

[1]. Department of Basic Medical Sciences, College of Medicine, Prince Sattam bin Abdulaziz University, Al-Kharj, Saudi Arabia.
[2]. Deseeya Ayurvedic Pharmaceuticals Ltd., Kerala, India.

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Abstract

Antimicrobial resistance is a global concern threatening the whole world. Antimicrobial resistance pathogens cause more than two million illnesses and nearly 23000 deaths per year in the United States. antimicrobial resistance is linked to roughly 25,000 fatalities per year in Europe. The economic effects of antimicrobial resistance are significant, with an estimated $20 billion in extra medical spending in the United States each year. This leads to necessity for development of novel antimicrobial agents from various sources. Ocimum tenuiflorum is a popular plant with several biological properties. The present study focuses on investigating the antibacterial potential of the compounds present in Ocimum tenuiflorum by in silico techniques. Initially, compounds were screened for druglikeness analysis based on Lipinski rule of five (RO5). Molecular docking was performed against bacterial DNA gyrase and ligand interactions on the binding sites of the target protein was examined. PASS prediction for antibacterial activity was determined. From the analysis of 22 compounds, we identified four compounds showing higher binding energies, binding site interaction, druglikeness and PASS property. Thus, the compounds Apigenin, Gardenin B, Isothymusin and Cirsilineol can be used for treatment of multidrug resistance bacterial infections.

Keywords: *antimicrobial resistance, multidrug resistance, ocimum tenuiflorum, molecular docking, protein-ligand interactions*

Introduction

Antibiotics have changed medicine, enabling advances in a variety of areas, including safer childbirth, surgery, organ transplants, and myeloablative chemotherapy regimens. On the other hand, antimicrobial resistance threatens to halt and even reverse some of these gains **[***Marston HD et al., 2016*]. Antimicrobial resistance bacteria cause over 2 million illnesses and almost 23,000 deaths a year in the United States. About 25,000 people die from Antimicrobial resistance every year in Europe. The economic impact of Antimicrobial resistance is significant, with annual additional medical costs in the United States estimated at $20 billion **[***Kimera ZI et al., 2020*].

The full global effect of antimicrobial resistance is more difficult to quantify; as epidemiological data are sparse in many areas of the world. However, data that are available represent considerable concern. In this regard, the recent global emergence of resistance factors emanating from the United States (carbapenem-resistant Klebsiella pneumoniae), India (bacteria with the plasmid-mediated blaNDM-1 gene that confers resistance to carbapenems),4 and elsewhere (Escherichia coli

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Address for Correspondence:

Abubucker Peer Mohideen
Department of Basic Medical Sciences, College of Medicine, Prince Sattam bin Abdulaziz University, Al-Kharj, 11942, Saudi Arabia.
Tel: +966553201774
E-mail: peermdnnn@gmail.com

with the plasmid-mediated mcr-1 gene that confers resistance to colistin, originally described in China) demonstrate the widespread nature of the problem and the importance of improved global surveillance **[***Schar D et al., 2018*].

Cells that have been chosen for resistance to a particular cytostatic agent may develop cross-resistance to a variety of different medications, i.e., they may become multidrug resistant. The classic type of multidrug resistance, also known as pleiotropic drug resistance, which was first identified 20 years ago and is characterised by resistance to a wide spectrum of lipophilic cytotoxic medicines with no shared structure or cellular target **[***Ayukekbong JA et al., 2017*].

The wide spectrum of medications that are impacted by multidrug resistance pointed to the plasma membrane as the location of change early on. Dano demonstrated in 1972 that multidrug resistance cells expel impacted medicines at higher rates and that this extrusion is energy dependent. After much debate, the majority of researchers in the area now concur that this is the primary mechanism of resistance **[***Alonso CA et al., 2017*]. Each year, multidrug-resistant organisms cause a growing number of illnesses. 1 Multidrug-resistant organisms infections cause more than 2 million illnesses and 23,000 deaths in the United States each year, according to a widely quoted number. 1 However, due to inadequate national reporting rates and the lack of ICD-10 codes particularly for multidrug-resistant organisms infections, the real burden of multidrug-resistant organisms infections is unknown. As a result, we attempted to present an updated estimate of multidrug-resistant organisms -related mortality in the United States. We present an estimate of multidrug-resistant organisms mortality for the year 2010 based on data availability **[***Oyekale AS, To O, 2017*].

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

Antibiotics are antibiotics that are used to prevent and treat illnesses caused by bacteria. Antibiotic resistance develops when bacteria evolve in response to antibiotic treatment. Antibiotic resistance develops in bacteria, not people or animals. These bacteria may infect both humans and animals, and their illnesses are more difficult to treat than non-resistant bacteria's. Antibiotic resistance raises medical expenses, lengthens hospital stays, and raises fatality rates. As a result, new antibiotics are required to treat the infections **[***Caudell MA et al., 2017*].

Bioinformatics is primarily concerned with the development of algorithms and software to extract knowledge from biological data. Bioinformatics is widely used in the study of genomics, proteomics, protein 3D structure modelling, image analysis, drug creation, and many other fields. Precision and preventive medicine, which is primarily focused on discovering strategies to prevent, treat, and cure deadly infectious illnesses, is a prominent use of bioinformatics **[***Grundmann H, Gelband H., 2018*].

Docking is a method in molecular modelling that assumes the intended orientation of one molecule to a second molecule when they are linked together to create a stable complex. The strength of connection or binding affinity between the two molecules may be estimated using the orientations. In signal transduction, the interactions between physiologically relevant molecules such as proteins, nucleic acids, carbohydrates, and lipids are crucial. As a result, the sort of signal produced depends on the relative alignment of the two interacting proteins. As a result, docking is used to forecast (assume) both the strength and kind of signal that will be produced **[***Moremi N et al., 2017*].

Ocimum tenuiflorum, sometimes known as holy basil or tulsi, is a fragrant perennial plant belonging to the Lamiaceae family. It is a cultivated plant native to the Indian subcontinent and widely distributed in the Southeast Asian tropics. Tulsi is grown for its essential oil, as well as for religious and traditional medical uses **[***Bhavya et al., 2018*]. Since there are several reports on in vitro antibacterial activity of *Ocimum tenuiflorum*, no studies were reported on *in silico* validation and identification of specific compounds responsible for antibacterial actions. Therefore, the present study focuses on investigating the antibacterial potential of the compounds present in *Ocimum tenuiflorum* by *in silico* techniques. Molecular docking was performed against bacterial deoxyribonucleic acid

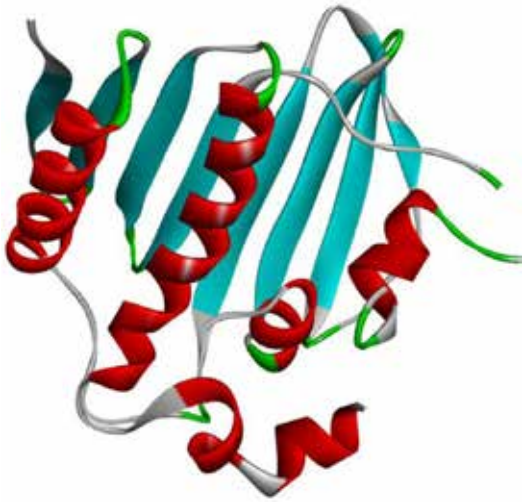

Figure 1. *3D structures of the DNA Gyrase*

(DNA) gyrase and ligand interactions on the binding sites of the target protein was examined.

Material and Methods

Target proteins Preparation: In this research, DNA gyrase subunit b (PDB ID: 1KZN) is applied as target protein and its 3D structures were attained from the Protein Data Bank (http://www.rcsb.org/). Using PyMol tool and the protein related ligands, water molecules, and co-crystal ligands were detached (Fig. 1), the target proteins are pictured. The proteins were set in Auto Dock Tools, an open source free software by accumulating charges and energy minimization was done in Swiss PDB viewer and additionally changed to pdbqt format.

Retrieval and Preparation of Ligands: Bioactive compounds present in *Oscillatoria* sp. were recognized and recovered by utilising KNApSAck database (http://www.knapsackfamily.com/KNApSAcK/). For the study, total of 22 bioactive compounds were utilised (Table 1). By identifying its torsion root, assigning charges, correcting torsion angle, optimising using universal force field (UFF) , the preparation of ligand is achieved and last of all changing into pdbqt format to produce 3D atomic coordinates of the molecules [*Rédei GP, 2008*].

Table 1.

Compounds used in the study

No	Compound name	No	Compound name
1	(+)-alpha-Pinene	12	Gardenin B
2	Camphor	13	beta-Elemene
3	(Z)-beta-Ocimene	14	delta-Cadinene
4	Borneol	15	(+)-Limonene
5	linalool	16	Germacrene D
6	alpha-Terpinene	17	Elemol
7	beta-Caryophyllene	18	alpha-Elemene
8	Copaene	19	Zerumbone
9	beta-Cubebene	20	Isothymusin
10	alpha-Caryophyllene (obsol.)	21	Cirsilineol
11	Apigenin	22	beta-Gurjunene

Screening of the of Ligands for Druglikeness: To estimate the compound's drug likeness, SwissADME (http://swissadme.ch/index.php) is utilised. The druglikeness of a molecule is a dangerous condition for validating it as a possible agonist for therapeutic targets [*Daina A, 2017*]. All the compounds identified in KNApSAck database were screened for druglikeness property using the Lipinski's Rule of Five.

Determination of Functional Sites of Targets: Exact assessment of the active (Functional) site is compulsory for significant docking analysis. The amino acid residues in the active pocket site format Computed Atlas of Surface Topography of proteins online server [*Tian W, 2018; Prasad S, Shanthi S, 2020*]. Computed Atlas of Surface Topography of proteins is a simple and handy tool to study protein regional anatomy and active site pockets**.** Determining the active site is a serious for setting the grid box former to docking.

Molecular docking and Protein-Ligand Interaction Analysis: All the compounds were docked using the PyRx tool via autodock wizard. Throughout the docking process, it was believed that the ligands were flexible and the protein was rigid. The grid parameter configuration file is created in PyRx using the grid boxes for 1KZN (x = 17.279, y = 30.688, z = 48.041) [*Dallakyan, S., Olson, A.J., 2015*]. Followed by docking, the ligand with the greatest binding energy (most negative) was identified as having the highest binding affinity. The ligands with a greater binding energy (-7*Kcal/mol*) were identified, and the interaction between the ligand and the protein at the binding sites was analysed using Biovia Drug discovery studio 2019.

Prediction of Activity Spectra for Substances for Antibacterial Activity: The antibacterial mechanisms of the selected compounds were predicted using Prediction of activity spectra for substances (PASS) online server [*Hasan M, 2019, Shamna KP, 2021*]. PASS algorithms are useful to predict a nu-

Table 2.

Amino acid residues in the active sites

Target Protein	Amino acid residues in binding sites
DNA gyrase (PDB ID: 1KZN)	GLU-58, ILE-60, GLN-72, ASP-73, ASP-74, VAL-133, GLN-135, LYS-162, THR-163, GLY-164, THR-165, MET-166

Figure 2. *Binding sites of DNA Gyrase analysed using Computed Atlas of Surface Topography of proteins*

merous physiological properties for a huge number of compounds. The compounds activity is predicted and quantified as probable activity and probable inactivity. The compounds that possess probable activity greater than probable inactivity are those that are viable for the particular biological activity.

Results

Binding site analysis: Computed Atlas of Surface Topography of proteins is an online program for evaluating the amino acid residues in a protein's binding site. Computed Atlas of Surface Topography of proteins was used to examine the functional pockets in target proteins (DNA Gyrase). Figure 2 is the representation of amino acid residues present in the active sites. Grid box for docking was developed by covering the functional sites of the target proteins (Table-2).

Table 3.

Druglikeness analysis

Compound	Druglikeness analysis				
	MW (*g/mol*)	H-bond		MLogP	Rule of five
		acceptor	donor		
(+)-alpha-Pinene	136.23	0	0	4.29	yes; 1 violation
Camphor	152.23	1	0	2.3	yes
(Z)-beta-Ocimene	136.23	0	0	3.56	yes
Borneol	154.25	1	1	2.45	yes
Linalool	154.25	1	1	2.59	yes
Alpha-Terpinene	136.23	0	0	3.27	yes
Beta-Caryophyllene	204.35	0	0	4.63	yes; 1 violation
Copaene	204.35	0	0	5.65	yes; 1 violation
beta-Cubebene	204.35	0	0	5.65	yes; 1 violation
Alpha-Caryophyllene (obsol.)	204.35	0	0	4.53	yes; 1 violation
Apigenin	270.24	5	3	0.52	yes
Gardenin B	358.34	7	1	0.4	yes
Beta-Elemene	204.35	0	0	4.53	yes; 1 violation
Delta-Cadinene	204.35	0	0	4.63	yes; 1 violation
(+)-Limonene	136.23	0	0	3.27	yes
Germacrene D	204.35	0	0	4.53	yes; 1 violation
Elemol	222.37	1	1	3.56	yes
Alpha-Elemene	204.35	0	0	4.53	yes; 1 violation
Zerumbone	218.33	1	0	3.37	yes
Isothymusin	330.29	7	3	-0.07	yes
Cirsilineol	344.32	7	2	0.17	yes
Beta-Gurjunene	204.35	0	0	5.65	yes; 1 violation

Table 4.

Molecular docking analysis

Compound	DNA gyrase subunit (1KZN)
(+)-alpha-Pinene	-4.7
Camphor	-4.5
(Z)-beta-Ocimene	-5.4
Borneol	-4.4
Linalool	-5.5
Alpha-Terpinene	-5.8
Beta-Caryophyllene	-5.5
Copaene	-6
Beta-Cubebene	-6.5
Alpha-Caryophyllene (obsol.)	-6.2
Apigenin	-8.5*
Gardenin B	-7.3*
Beta-Elemene	-5.8
Delta-Cadinene	-7.4*
(+)-Limonene	-5.9
Germacrene D	-5.8
Elemol	-5.4
Alpha-Elemene	-5.9
Zerumbone	-6.4
Isothymusin	-7.8*
Cirsilineol	-7.2*
Beta-Gurjunene	-6

Note: **Compound showing binding energy higher than -7Kcal/mol*

Table 5.

Protein-Ligand interactions on binding site analysis

Compound	Protein-Ligand interactions		
	To No. of H-bonds	H-bond on binding sites	Interacting amino acid residue
Apigenin	5	1	A: THR-165
Gardenin B	2	2	A: ASP-74; GLU-58
delta-Cadinene	-	-	-
Isothymusin	3	2	A: ASP-74; THR-163
Cirsilineol	1	1	THR A: 165

Druglikeness analysis: Druglikeness property of the *Oscillatoria* bioactive compounds were investigated using the Lipinski's Rule of Five (RO5). Druglikeness of the compound is essential for the development of drugs. The parameters evaluated for druglikeness are molecular weight, H-bond acceptors, H-bond donors and MLogP. Compounds satisfying atleast two properties were considered to possess druglikeness. From the analysis, all the 22 compounds showed druglikeness property; few compounds showing 1 violation. Table 3 shows the druglikeness properties of the compounds used in the study.

Molecular docking and Protein-Ligand interactions: Inhibition of the target protein by bioactive compounds is calculated by binding energies expressed in *Kcal/mol*. 5 compounds i.e. apigenin, gardenin B, delta-Cadinene, isothymusin and cirsilineol showed binding energies higher than -7*Kcal/mol* (Table 4). These compounds were further used for protein-ligand interactions and PASS prediction.

Binding of compounds on the functional site of the target protein is essential for effective inhibition reactions. H-bond is a stable bond which confirms the effective binding of ligand to the target in

Table 6.

Prediction of activity spectra for substances

Compound	Probable activity	Probable inactivity
Apigenin	0.391	0.032
Gardenin B	0.364	0.039
delta-Cadinene	0.385	0.034
Isothymusin	0.365	0.039
Cirsilineol	0.346	0.044

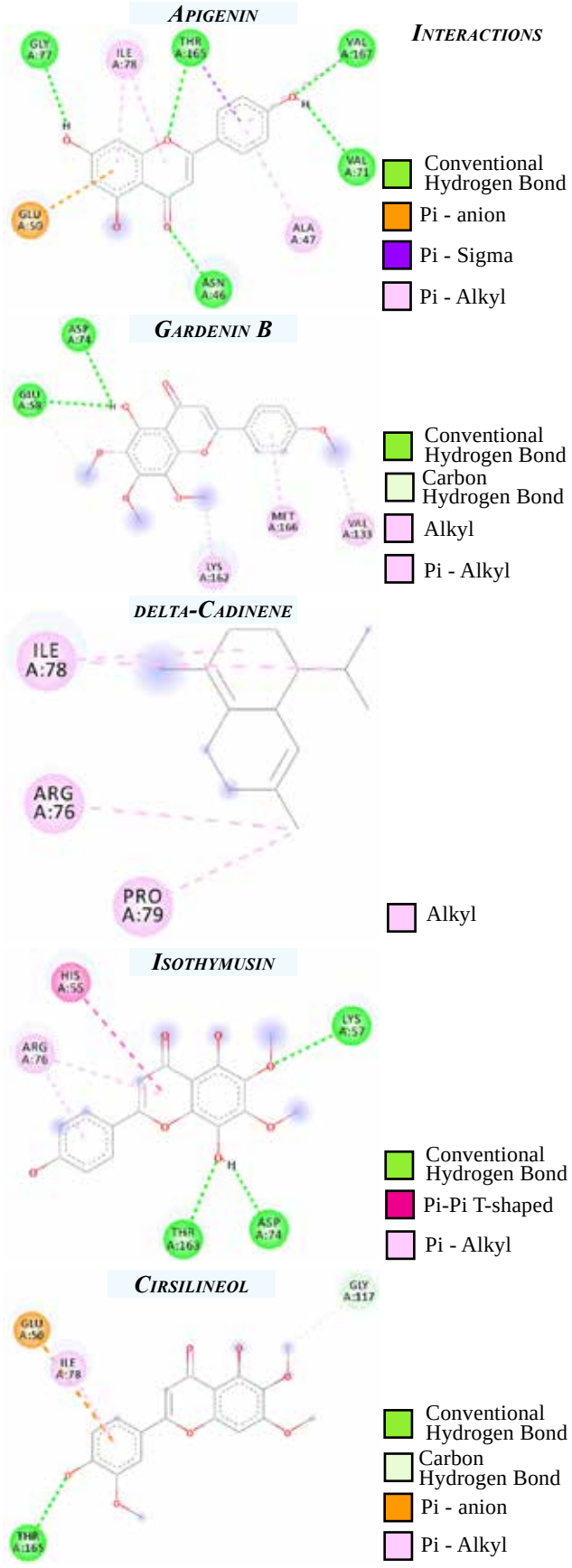

Figure 3. *Interaction of Apigenin, Gardenin B, delta-Cadinene, Isothymusin and Cirsilineol on DNA Gyrase*
Note: *Pi - Probable inaktivity*

biological systems. Therefore, the selected compounds were analysed for binding on the functional sites of the target protein and H-bond formations. All the compounds except delta-Cadinene showed H-bond formation (Figure-3). The major interacting amino acid residues are ASP-74 and THR-165 (Table 5).

PASS predictions: PASS prediction for antibacterial activity was carried out for the selected five compounds. All the compound showed probable activity values higher than probable inactivity. Probable activity and probable inactivity values of the compounds were presented in Table 6.

Discussion

DNA gyrase is a type II topoisomerase that may create negative supercoils into DNA while consuming adenosine triphosphate (ATP). It is required by all bacteria but not by higher eukaryotes, making it a promising target for antibacterial. [*Ashley A et al., 2017*].

Although the specifics of this process are still being researched, biochemical and structural evidence largely support a concept known as the "two-gate mechanism". The N-terminal domain of DNA gyrase subunit B (GyrB) (referred to as the N-gate), the GyrA–GyrB–DNA interface, where the DNA is cleaved (referred to as the DNA gate), and the C-terminal area of coiled coils, which forms the C or exit gate, are the three interfaces that can be in an open or closed conformation in DNA gyrase. At the interface of the N terminus of the GyrA dimer and the TOPRIM (topoisomerase-primase) domain of GyrB, the DNA G (or gate) segment connects with the enzyme, and DNA is wrapped **[***Mshana SE et al., 2016*]. The supercoiling reaction is expected to proceed as follows: at the interface of the N terminus of the GyrA dimer and the topoisomerase-primase domain of GyrB, the DNA G (or gate) segment connects with the enzyme, and DNA is wrapped around the enzyme in a right-handed supercoil of 130 base pairs. Wrapping DNA around the C-terminal domains of gyrase makes it easier for a second segment (the transported or T segment) from the same DNA molecule to reach the N gate, which is positioned above the G segment and ready for strand transit. The N gate is closed and the T segment is trapped when ATP binds to it **[***Kagambega A et al., 2018*]. The enzyme cleaves the G segment, establishing 4 bp apart DNA–phosphotyrosyl bonds, resulting in a double-strand break and GyrA's covalent attachment to the DNA. The T segment travels through the open DNA gate, the broken G segment, and finally the exit gate. The binding and hydrolysis of ATP drives the passage of the T segment through the G segment (strand passage). The N gate is opened when ATP is hydrolyzed and ADP is released, resetting the enzyme for the next supercoiling cycle. At the expense of two ATPs, one gyrase supercoiling cycle introduces two negative supercoils into the DNA molecule. In the absence of ATP, gyrase may catalyse the relaxing of negatively supercoiled DNA using a process that is virtually the opposite of ATP. Fluoroquinolones are a class of gyrase-targeted medications that have had a lot of success, but as bacteria become more resistant to them, we'll need to look for new chemicals as well as novel ways to block this enzyme. The process of supercoiling in gyrase makes it a good target for antibacterial medicines **[***Djeffal S et al., 2017*]. Thus, in the present study bioactive compounds present in *O. tenuiflorum* were investigated for its antibacterial mechanisms through molecular docking approaches.

O. tenuiflorum is a tropical plant that is endemic to the old world tropics and is frequently cultivated for its therapeutic value. It's a 30-60 *cm* tall, upright, heavily branched sub shrub with opposite leaf arrangement, no stipules, 5 *mm* petioles, dark green to green in colour, oval, serrate edge leaf. raceme type inflorescence Flowers: vertical, 5-7 *mm* in length, calyx: greenish in color; 5 in number, corolla: bilabiate in shape and covered with scattered hairs, white petals, stamens: 4, filament length is 1 *mm*, floral bracts: caudiform in shape, floral bracts: caudiform in shape, floral bracts: caudiform in shape, floral bracts: caudiform in shape, floral bracts: **[***Pavela R, Benelli G, 2016*] caudiform in shape, floral br The filaments are white in colour, and the ovary is missing. seed: plant produces a lot of seed; the seed is very small and white in colour, stem: stem is coated with minute hairs, style: single style; colour is white, fruit: none seed: plant produces a lot of seed; the seed is extremely small and white in colour, stem: stem is covered with minute hairs. Ram tulsi (the most common form, with broad brilliant green leaves

that are slightly sweet), purplish green-leaved (Krishna or Shyam tulsi), and common wild vana tulsi are the three primary morphotypes grown in India and Nepal **[***Pilas A et al., 2018*].

O. tenuiflorum is native to the Indian subcontinent, including the Himalayas, Malesia, and other tropical and subtropical regions of Asia, but it is now widely grown and naturalised around the world, including the Caribbean, Pacific islands, and portions of Africa **[***Pola M et al., 2018*]. Various components of the plant, including as leaves, blossoms, and stems, have traditionally been used to cure a variety of ailments, including skin problems, colds, coughs, fevers, vomiting, and swelling. Anti-cancer, antibacterial, antiseptic, antispasmodic, antifungal, antiviral, anti-inflammatory, analgesic, and immunostimulatory effects have been identified for *O.tenuiflorum*. Eugenol, methyl cinnamate, camphor, and thymol are the primary chemical ingredients of *O.tenuiflorum*. In addition to treating jaundice and lowering blood pressure, whole powder is employed **[***Vyas P et al., 2018*].

Subbiah et al.,investigated that he antibacterial activity of plant extract against Gram negative (*Pseudomonas putida* and *Klebsiella pneumoniae*, *E.coli*) and Gram positive (*Staphylococcus aureus* and *Bacillus subtilis)* bacteria was discovered. Plant extract inhibitory zones against Gram negative and Gram positive bacteria were measured. The findings showed that ocimum tenuiflorum leaf extract has good antibacterial action against both Gram negative and Gram positive microorganisms. These findings indicate that *Ocimum tenuifloram* has antimicrobial properties **[***Subbiah R et al., 2020*].

A research by Samson *et al.* looked at the ability of *O. tenuifloram* to scavenge free radicals. The findings show that *O. tenuifloram* may scavenge radicals in a dose-dependent manner. The ethanolic extract of *O. tenuifloram* has 2,2-Diphenyl-1-picrylhydrazyl radical scavenging activity (IC50 = 28.89 *mg/ml*) as well as nitric oxide scavenging activity (IC50 = 26.92 *mg/ml*). The IC50 result of 27.63 *mg/ml* indicated that *O. tenuifloram* extract has superoxide scavenging action. The hydroxyl radical scavenging activity of O. sanctum extract was found to be dosage dependent, with an IC50 value of 661.11 *mg/ml*, while the dose dependent 2,20-azinobis(3ethylbenzthiazoline-6-sulfonic acid (ABTS) radical scavenging activity was found to be 8.82 mg/ml. These findings are in line with those of the current investigation **[***Das SK Brar MV, 2016*].

Ocimum tenuifloram juice and decoction, which contain a blend of herbs such as Tulsi, ginger, kalimirch, and lemon juice, are useful for treating seasonal flu and influenza. Is an excellent immunomodulator, and so aids in the prevention of asthmatic symptoms, as well as being high in anticonvulsant and anxiolytic compounds. Because of its antibacterial and antiviral qualities, tulsi can help fight infections and reduce fever. Tulsi is available in a variety of forms, including tinctures, capsules, herbal tea, and powders, and it is already a part of most people's diets **[***Chaudhuri L et al., 2017*]. Tulsi may assist to relieve anxiety, which in turn improves emotions, according to research studies. Tulsi pills taken twice a day for 60 days can help with anxiety, tension, and sadness. Tulsi's phytochemicals, which have strong antioxidant capabilities, aid in the prevention of skin, lung, liver, and oral cancers **[***Padalia S et al., 2017*].

Conclusion

From the analysis of 22 compounds we identified four compounds showing higher binding energies, binding site interaction, druglikeness and PASS property. Therefore, the compounds Apigenin, Gardenin B, Isothymusin and Cirsilineol can be used for development of novel antimicrobial drugs for treatment of multidrug resistance infections. Further studies are required to purify these compounds from plant extracts and validate its antibacterial action.

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Yerevan State Medical
University after M. Heratsi.

Address for correspondence:

Yerevan State Medical University
2 Koryun Street, Yerevan 0025,
Republic of Armenia

Phones:

(+37410) 582532 YSMU
(+37410) 580840 Editor-in-Chief

Fax: (+37410) 582532

E-mail: namj.ysmu@gmail.com, ysmiu@mail.ru

URL: http//www.ysmu.am

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Copy editor: Tatevik R. Movsisyan

Printed in "VARM" LLC
Director: Ruzanna Arakelyan
Armenia, 0018, Yerevan,
Tigran Mec 48, 43
Phone: (+374 91) 19 29 00,
E-mail: armana6@mail.ru