In Silico Investigation Of The Potential Roles Of *Rosmarinus Officinalis* Oil As A Natural Antibacterial Agent Via Molecular Docking

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ABSTRACT

Background and Objective: The purpose of this study was to assess the antibacterial characteristics of rosemary essential oil against extended-spectrum β-lactamases-producing bacteria, especially *Enterobacter*, and to identify compounds with the strongest affinity to β-lactamase for combating antibiotic-resistant infections, using molecular docking.

Materials and Methods: Due to the emergence of multidrug-resistant bacteria and increase of antibacterial resistance within pathogenic bacteria, bacteria of the genus *Enterobacter* that produce extended-spectrum β-lactamases were selected using double disc test. The Gas chromatography-mass spectrometry method was not carried out because the nine ligands were selected only based on the literature and the antibacterial characteristics of compounds derived from *Rosmarinus officinalis* oils were assessed using molecular docking simulations to assess the binding affinity of nine rosemary essential oil components to β-lactamase.

Results and Conclusion: *Enterobacter* strains were resistant to most antibiotics, particularly those in the beta-lactam family, based on the antibiotic susceptibility test; the CTX-M15 gene was identified using Illumina sequencing at the National Research Center for Antibiotic Resistance, Clermont-Ferrand, France. Molecular docking analysis revealed that all bioactive compounds presented in *Rosmarinus officinalis* might include antibacterial effects, albeit with various binding affinities. From these, rosmarinic acid demonstrated the highest affinity as ΔG -8.2 (kcal.mol $^{-1}$), followed by carnosol -7.2, carnosic acid -7.0, β-caryophyllene -5.9, verbenone -5.4, camphor -5.0, 1,8-cineol -4.9, α-pinene -4.6 and β-myrcene -3.9 kcal/mol $^{-1}$. Certain components showed binding affinities similar to those of the standard inhibitor, avibactam, with rosmarinic acid advancing it. Thus, an industrially developed molecule must contain the concentrations of each component in rosemary essential oil, with high concentrations of rosmarinic acid, carnosol and carnosic acid, to ensure it is sufficiently effective against bacteria that produce extended-spectrum beta-lactamases. Therefore, increasing attention is directed to plant-derived compounds that show antibacterial characteristics without undesirable adverse effects typically induced by conventional pharmaceuticals.

Conflict of interest: The authors declare no conflict of interest.

What is "already known":	• Rosemary (Rosmarinus officinalis) contains bioactive compounds with reported antimicrobial properties against a range of pathogenic microorganisms. • Extended-spectrum β-lactamase (ESBL)-producing bacteria, particularly members of the Enterobacteriaceae family, are important contributors to resistance against β-lactam antibiotics. • Molecular docking is a computational approach used to predict the binding affinity and interactions of bioactive compounds with bacterial resistance-associated proteins, including β-lactamases.
What this article adds:	• This study investigated nine literature-selected compounds associated with R. officinalis for their predicted binding interactions with β-lactamase using molecular docking. • Rosmarinic acid exhibited the highest predicted binding affinity (−8.2 kcal/mol), followed by carnosol (−7.2 kcal/mol) and carnosic acid (−7.0 kcal/mol). • The findings identify promising candidate compounds for further investigation against ESBL-producing Enterobacter strains; however, their antibacterial efficacy requires experimental validation, as the study did not include GC–MS characterization or establish compound-specific antibacterial activity.

1. INTRODUCTION

Rosemary is cultivated in almost all regions of the Mediterranean Basin. It is widely used for its therapeutic characteristics [1] because it contains bioactive compounds with several activities, including antibacterial [2], antioxidant, antiparasitic, antifungal and anticarcinogenic activities [3]. Nowadays, antibiotic resistance is a serious public health concern worldwide [4]. According to several researchers, rosemary essential oil (EO) is a potential alternative antimicrobial agent to combat various harmful microorganisms, including *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Aeromonas hydrophila*, *Bacillus cereus*, *Clostridium perfringens* and *Salmonella* Choleraesuis [5]. The pharmacological effects of EO extracted from this plant are majorly due to its high phenolic component content [6].

Based on the development of antimicrobial resistance in bacterial infections, this investigation assessed the antibacterial efficacy of compounds in *Rosmarinus officinalis* oil. Thus, it is essential to investigate structurally distinct antibacterial agents with fewer adverse effects that can eradicate drug-resistant mutations [7]. However, drug investigation is a challenging process, but virtual screening and molecular docking (VS) are the methods in computer-aided drug design (CADD) that have significantly decreased the expenses and lead times connected to medicine development by forecasting the most favorable conformation, position and direction of a small molecule (potential medication) for simplifying further lead optimization. This is the preferred technique [8], when the three-dimensional (3D) structure of the protein target is accessible.

Studies have shown that Gram-negative bacteria are generally more resistant than Gram-positive bacteria [9]. Therefore, the current study focused on a bacterium that best represents antibiotic resistance in Gram-negative bacteria, namely, bacteria that produce extended-spectrum beta-lactamases (ESBLs). The main goal of molecular docking is to design interactions between a target macromolecule (protein) and a small molecule (ligand) [10]. Understanding the precise location and mode of ligand binding facilitates the logical design of modifications to maximize the interactions between proteins and ligands [10].

2. MATERIALS AND METHODS

2.1. Strains of Bacteria

Totally, ten Enterobacteriaceae strains were isolated from patients with various infections in various laboratories, Batna, Algeria. Only ESBL-positive bacterial isolates were selected for the characterization of antimicrobial activity. Three strains belonging to the Genus *Enterobacter* were selected; their molecular identification was carried out at the National Research Center for Antibiotic Resistance, Clermont-Ferrand, France. Thus, the identified species was *E. hormaechei hoffmannii*.

2.2. Bacterial Culture

MacConkey agar (BioMerieux, France) was used to cultivate strains at 37 °C ±1 for 24 h. The authors screened ESBL production using double-disc synergy test (DDST) with third-generation cephalosporins (cefotaxime, ceftazidime, aztreonam and cefepime) and clavulanic acid [11]. Isolates were identified using biochemical examinations and the identifications were verified using mass spectrometry (MS) with VITEK MS (Bio-Merieux, France).

2.3. The Extraction Process

The plant, *R. Officinalis*, was collected, stored out of the sun, dried in a temperature-controlled area and then processed into a powder. The extraction process involved steam distillation, as heat caused the plant cells to burst, releasing molecules that created an azeotropic odor. The distillation process involved immersing the plant raw material (rosemary) in 100 ml of purified water and transferring it over a heat source. The mixture was then heated to boiling. The Gas chromatography-mass spectrometry (GC-MS) method was not carried out. The nine ligands were selected only based on the literature.

2.4. Assessment of Antimicrobial Activity

The antibacterial characteristics of the extract from the extracted oil were assessed against various ESBL-producing bacterial strains of pathogenic enterobacteria using filter paper disk diffusion method (6-mm diameter) [11]. Antibacterial activity was assessed by the presence of an inhibition zone around the disk.

2.5. Molecular Docking

To estimate the affinity between the β-lactamase and the nine components of rosemary EO, molecular docking calculations were carried out using AutoDock Vina [14]. The 3D structure of the β-lactamase target (PDB ID: 5FA7) was achieved from the RCSB protein databank. Ligand structures were modeled and geometry optimized at the optimized and modeled DFT/B3LYP/6-31G(d,p)

levels using Gaussian 09 package [15]. Prior to docking, water molecules, except those preserved in the active site and co-crystallized, ligands were removed from the receptors and hydrogen atoms were added. The receptor was treated as rigid, whereas the ligands were considered flexible. Receptor and ligand structures were converted to PDBQT format using AutoDock Tools 1.5.6, the authors treated the ligands as flexible included. the authors removed water molecules (except those in the active site) and all cocrystallized ligands but preserved the hydrogens. The authors removed water molecules (except those in the active site) and all cocrystallized ligands but preserved the hydrogens. The docking search space was defined by a grid box centered at x = -25 y= -5 and z = 21 Å, with dimensions of 19 × 19 × 17 Å. The exhaustiveness parameter was set to 50 and a random seed of 2013 was used. Nine docking poses were generated for each ligand and ranked based on the predicted binding affinity calculated using AutoDockTools. The topranked pose was then used for interaction analysis and visualization using Discovery Studio Visualizer [16]. For validation, a re-docking procedure was carried out using co-crystallized ligand 5VR ([[(3R,6S)-6-(acetamidocarbamoyl)-1-methanoyl-piperidin-3-yl]amino] hydrogen sulfate; $C_9H_{16}N_4O_7S$), extracted from the β-lactamase crystal structure (PDB ID: 5FA7). The ligand was re-docked into a similar binding site using described docking parameters and the resulting top-ranked pose was superimposed on its original crystallographic conformation. The calculated all-atom RMSD between the re-docked and crystallographic poses was 2.29 Å (2.2899 Å), indicating a reasonable reproduction of the crystallographic binding orientation. Avibactam, a known β-lactamase inhibitor, was additionally included as a reference compound for comparaison of the predicted docking scores.

3. RESULTS AND DISCUSSION

3.1. The Importance of Protein Choice

Based on the literature, extended-spectrum beta-lactamases (ESBLs) are produced by most Enterobacteriaceae and causing community-acquired and nosocomial illnesses, rendering strains resistant to beta-lactam antibiotics and leading to serious therapeutic failures [17]. The blaCTX-M-type enzymes have become an increasingly serious public health issue. They are spread worldwide and have become the most common ESBLs in human and animal Enterobacteriaceae [18]. Within various blaCTX-M types distributed internationally, blaCTX-M-15 has been reported in humans, animals and the environment. Several studies have identified ESBL-producing genes, in particular, the blaCTX-M-15 variant (CTX-M-1 group), in Algeria, Africa, the USA, Europe, Asia, Canada, France and the UK [19].

3.2. The Importance of Choosing a Ligand

This study aimed to demonstrate an innovative strategy from natural sources such as medicinal plants to eliminate resistant bacterial strains, especially those that produce ESBL enzymes, as a potential substitute for modern medication in treating bacteria that have developed antibiotic resistance [20]. Therefore, it is essential to comprehend how bioactive chemicals are distributed in rosemary EO (ROEO), which is responsible for its antimicrobial effects [21]. The choice of the rosemary plant was based on recent studies, indicating that it includes excellent broad-spectrum antibacterial activity [22].

Rosemary oil contains phenols, alcohols, aldehydes and ketones, which show activity [23]. Within these substances, phenols are the most active substances against bacteria because of the acidic characteristics of their hydroxyl groups [24]. Because alcohols are soluble in aqueous media, they effectively disrupt bacterial cell walls, making them particularly effective against bacterial strains [25]. The antibacterial process of ROEO is majorly due to cytoplasmic membrane disruption, mixed-force kinetics, proton and electron movements, active cellular transport and coagulation of intracellular contents, as well as cell death [26].

3.3. Molecular Docking

The antibacterial activities of EO extracted from *R. officinalis* and used against ESBL-producing and multidrug-resistant bacteria were assessed. The filter-paper diffusion technique showed that *R. officinalis* EO demonstrated anti-*E. hormaechei Hoffmannii* activity, creating a zone of inhibition around the disc impregnated with the extract, ranging from 2 to 4 in diameter. Each strain was assessed three times to provide significant verification of the presence of activity. Based on the absence of GC-MS analysis in the current study, the nine ligands were selected based on their persistence and antibacterial effects in rosemary oil, referring to published scientific literature.

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The current molecular docking analysis (**Table 1**) demonstrated that rosmarinic acid included further favorable predicted docking score/binding affinity under the computational conditions and the highest affinity within the EO components studied for β-lactamase (-8.2 kcal.mol^{-1}). This affinity was ensured by seven hydrogen bonds with active-site residues (Figure 1a). This results were similar to those of several studies, showing that the antibacterial characteristics of rosemary were primarily attributed to rosmarinic acid [27].

Table 1: Binding energy (ΔG) and non-bonded interactions between the nine components of rosemary essential oil and β-lactamase

Ligand	ΔG (kcal.mol^{-1})	H-Bonds		Hydrophobic interactions	
		interacting residue	length (Å)	interacting residue	length (Å)
Rosmarinic acid	-8.2	SER 70	2.38		
		SER 70	2.07		
		ASN 132	2.59		
		ASN 132	2.17		
		GLU 166	2.71		
		SER 237	2.36		
		THR 235	2.29		
Carnosic acid	-7.0	H_2O 693	2.70	TYR 105	4.88
		H_2O 693	2.61		
		SER 237	2.69		
		SER 237	2.24		
Carnosol	-7.2	H_2O 693	2.79	TYR 105	5.06
		H_2O 723	2.32	TYR 105	4.12
		SER 237	1.92		
β-caryophyllene	-5.9			TYR 105	3.93
				TYR 105	3.90
Verbenone	-5.4	H_2O 723	2.15	TYR 105	4.41
				TYR 105	4.55
				TYR 105	3.96
				TYR 105	4.72
β-myrcene	-3.9			TYR 105	4.71
				TYR 105	4.38
				TYR 105	3.79
Camphor	-5.0	THR 216	2.75	TYR 105	2.70
		THR 235	1.89	TYR 105	4.48
1-8 cineole	-4.9			TYR 105	2.70
				TYR 105	4.70
α-pinene	-4.6			TYR 105	4.96
				TYR 105	3.86
Avibactam (standard)	-7.4	HOH 750	2.41		
		HOH 545	2.47		
		ASN 104	2.38		
		SER 237	2.62		
		GLU 166	3.01		
		SER 70	2.74		

The current findings also showed that the compounds with the strongest affinity against β-lactamase were carnosol and carnosic acid following rosmarinic acid, with ΔG values of -7.2 and -7.0 kcal.mol^{-1}, respectively. These two components could form relatively stable complexes with the target (Table 1). In general, intramolecular nonbonded interactions between the nine components and the enzyme were either hydrogen bonding, hydrophobic interactions, or the two ones (**Figures 1a–1i**).

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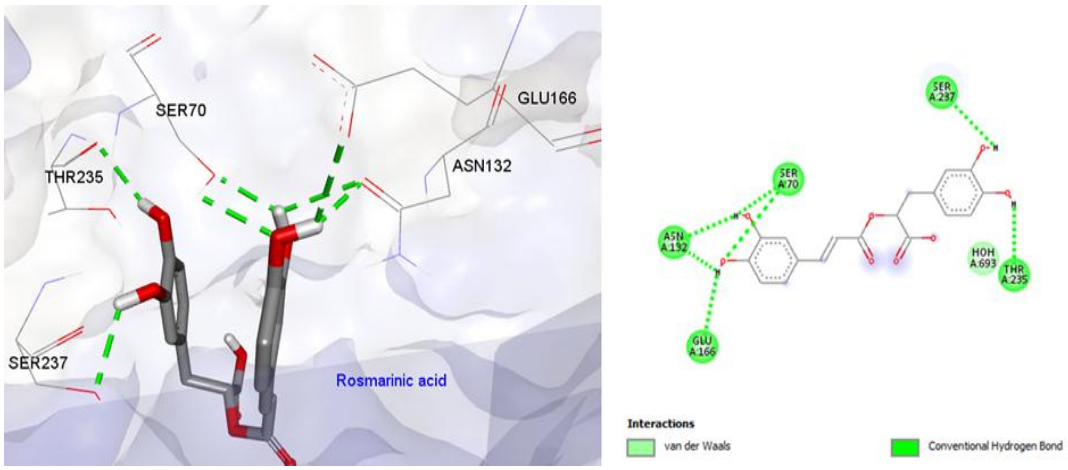


Figure 1a. The 3D and 2D presentations of rosmarinic acid and β-lactamase non-bonded interactions

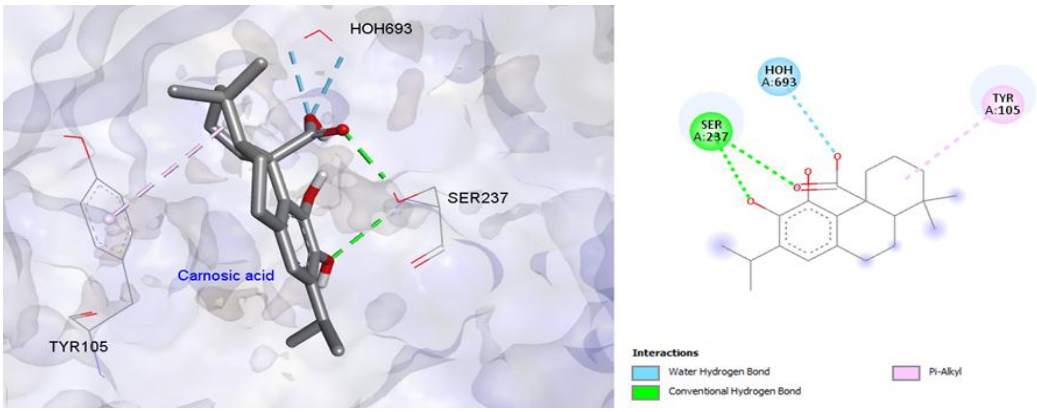


Figure 1b. The 3D and 2D presentations of carnosic acid and β-lactamase non-bonded interactions



Figure 1c. The 3D and 2D representations of carnosol and β-lactamase non-bonded interactions

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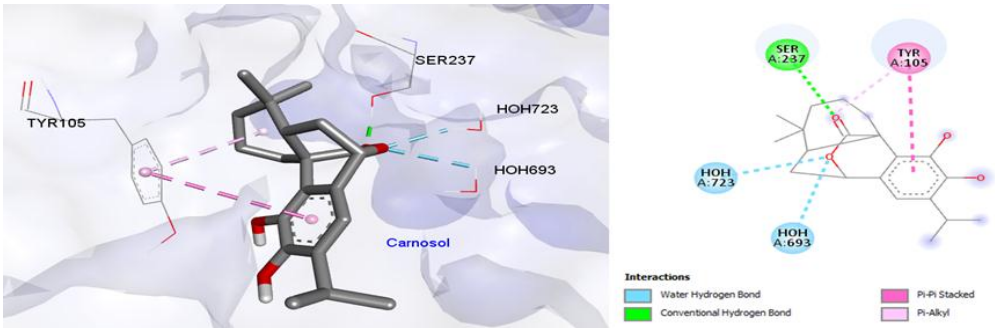


Figure 1d. The 3D and 2D presentation of non-bonded interactions between β-caryophyllene and β-lactamase

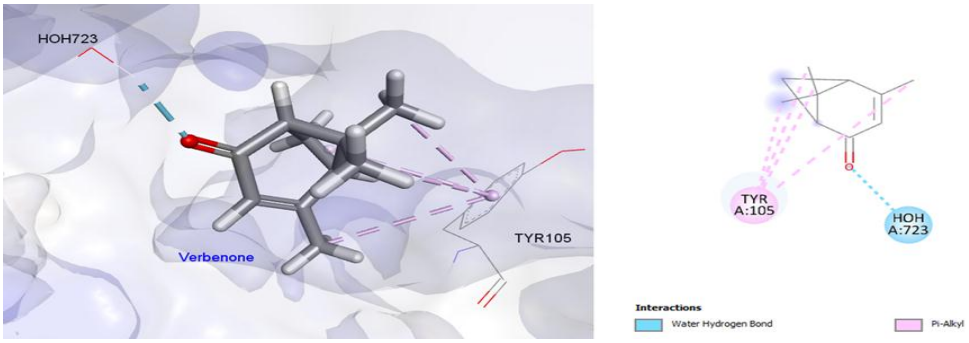


Figure 1e. The 3D and 2D representations of verbenone and β-lactamase non-bonded interactions

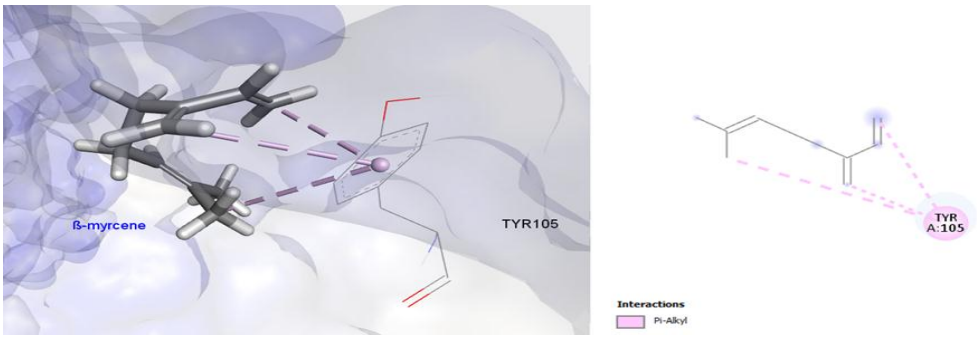


Figure 1f. The 3D and 2D presentation of non-bonded interactions between β-myrcene and β-lactamase

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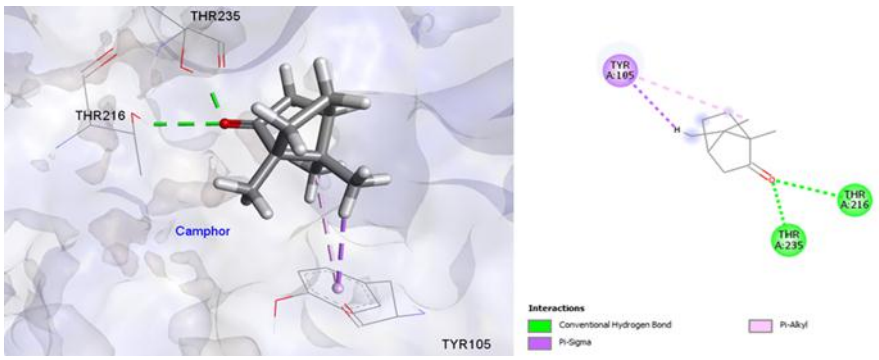


Figure 1g. The 3D and 2D representations of camphor and β-lactamase non-bonded interactions

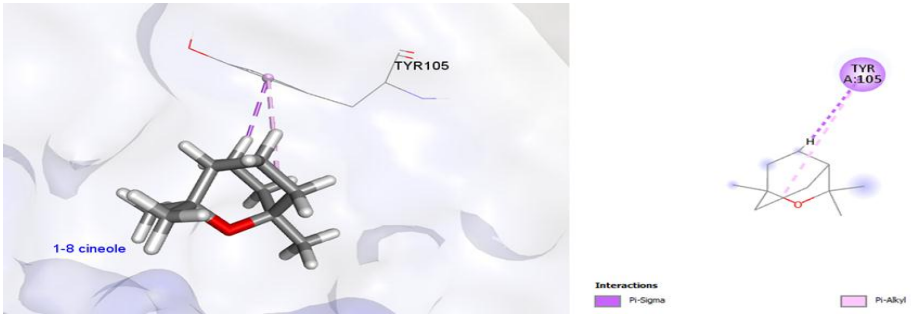


Figure 1h. The 3D and 2D presentations of 1-8 cineole and β-lactamase non-bonded interactions

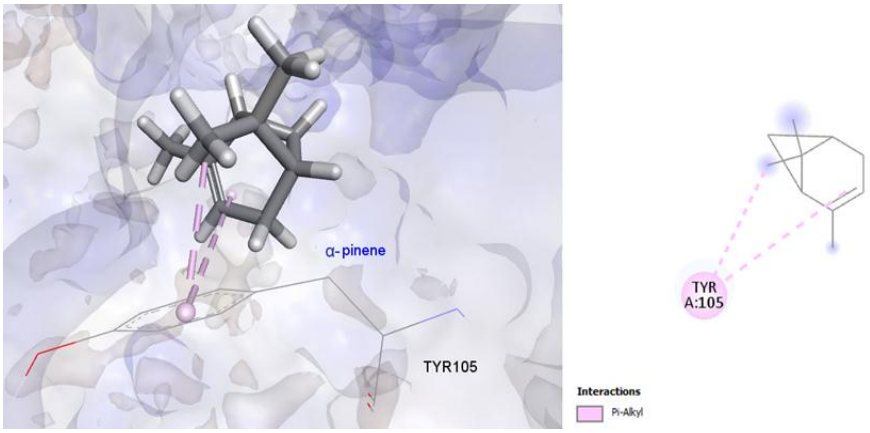


Figure 1i. The 3D and 2D representations of non-bonding interactions between α-pinene and β-lactamase

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Carnosol and carnosic acid are phenolic compounds in rosemary EO that may include antimicrobial and antioxidant effects [28]. Moreover, the current findings were similar to those of further research [29], demonstrating that rosmarinic acid, carnosol and carnosic acid are the phenolic compounds responsible for the biological activities of *R. officinalis* and Eucalyptus plants [30], particularly antibacterial activity. Based on the reports, these phenolic acids (rosmarinic acid, carnosic acid and carnosol) include good interactions with bacterial cell wall proteins that are widespread in Gram-positive and Gram-negative bacteria, including penicillin-binding proteins (PBP) and outer membrane protein A (OMPA), which explains the antibacterial characteristics of the selected phenolic acids [31]

It is noteworthy that, in addition to previously highlighted compounds (rosmarinic acid, carnosic acid and carnosol), other compounds included affinity with ESBL enzymes with an almost similar difference in binding energy (ΔG), including β-caryophyllene -5.9 kcal.mol^{-1}, verbenone -5.4 kcal.mol^{-1} and camphor -5.0 kcal.mol^{-1}. These findings were similar to those of previous research, indicating that caryophyllene [10], verbenone and camphor are antibacterial agents [32], especially against enterobacteria. In addition, the skin readily absorbs camphor, resulting in a cooling sensation similar to menthol [33]. Other components such as 1,8-cineol and α-pinene interacted with the current target with ΔG values of -4.9 and -4.6 kcal.mol^{-1}, respectively. As reported by [34], presence of 1,8-cineol and α-pinene in the EO of rosemary makes it effective against a wide variety of fungal and bacterial infections, especially because α-pinene is the major chemotype in *R. officinalis*. In addition, several studies have shown that volatile substances (e.g., 1,8-cineol and α-pinene) increases the antibacterial activity of rosmary oil [35].

The current data demonstrated that β-myrcene included the least effective interaction with ESBL (ΔG = -3.9 kcal.mol^{-1}). However, this did not preclude its antibacterial activity, as reported in other studies [36]. The molecular docking results in the current study showed high affinity between microbial proteins (ESBL) and ligands in rosemary EO, particularly rosmarinic acid, carnosol and carnosic acid, which are well known for their bioactivities [37]. Based on the results of the predictions assessed by molecular docking and the current findings, *R. officinalis* can be recommended in the pharmaceutical sector as a natural antibacterial agent to treat infections caused by clinical or foodborne ESBL-producing isolates [38]. The molecule developed for industrial scale-up must contain the concentrations of each component in rosemary EO, with high levels of rosmarinic acid, carnosol and carnosic acid to ensure sufficient effectiveness against ESBL-producing bacteria.

Based on the results of scientific research worldwide, rosemary EO shows an interactive effect against several strains, including the most common agents that cause hospital-acquired (HA) and community-acquired (CA) diseases, by overcoming and decreasing the impermeability of the membrane. Examples include methicillin-resistant *S. aureus* (MRSA), *E. coli*, *P. aeruginosa* [39], *S. epidermidis*, *Streptococcus* sp., *Enterococcus faecalis*, *B. subtilis*, *A. hydrophila*, *B. cereus*, *C. perfringens* and *Salmonella* Choleraesuis [40].

Additionally, earlier published reports [41] have shown that rosemary includes the potential to inhibit several bacteria and may make bacteria further susceptible to common medicines by becoming further active on Gram-positive mutants, compared to Gram-negative mutants. This accurs possibly as a result of the presence of an outer membrane in Gram-negative [42] strains, which restricts hydrophobic chemicals ability to diffuse via its lipopolysaccharide (LPS) cover, as well as inducing its permeability and cell death [43]. The lipophilic ends of Gram-positive bacteria cell membrane contain acids, which facilitate the infiltration of the EO hydrophobic substances [44]. As described by [44] and [45], efflux systems such as the resistance-nodulation-cell division (RND) family are primary sources of resistance and multidrug resistance in Gram-negative bacteria.

4. CONCLUSION

The emergence of bacterial resistance to antibiotics leads to therapeutic failure and sometimes death in patients with bacterial infections. These findings have created an urgent need for a natural broad-spectrum antibacterial substance such as rosemary EO, which includes strong medicinal, antibacterial and antioxidant characteristics, as an innovative strategy for eliminating resistant bacterial strains. Therefore, researchers are

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searching for plant-based substitutes with antibacterial characteristics but with no undesirable side effects of synthetic drugs. Rosemary species include a promising future in healthcare and their therapeutic potentials should be further addressed in food science and human and animal medicines. These findings suggest a promising role for rosemary-derived compounds in addition to conventional antibiotics. Based on the limited number of isolates and the lack of GC-MS characterisation as well as the absence of direct enzyme inhibition assays and quantitative measurements of MIC/MBC, further *in vivo* investigations are needed to fully clarify their potentials in antibacterial therapy.

5. DECLARATION

5.1. Conflict of Interest

The authors declare no conflict of interest.

5.2. Funding

No funding was received for this study.

5.3. Author Contributions With

RA designed the study; RA and ML carried out the experiments; RA and B analyzed the data; RA and HR wrote the manuscript draft; and RA, ML and HR revised the manuscript. All the authors approved the final version of the manuscript.

5.4. Ethical Considerations

All ethical principles were addressed in carrying out and writing this manuscript.

5.5. Data Availability

In accordance with the principles of transparency and open research, the authors declare that all data and materials used in this study are available upon request.

5.6. Using Artificial Intelligence Chatbot

No AI chatbot was used in this study.

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بررسی سیلیکویی نقش‌های بالقوه روغن رزماری (Rosmarinus officinalis) به‌عنوان یک عامل ضدباکتریایی طبیعی از طریق داکینگ مولکولی

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واژگان کلیدی:

اثرات ضدباکتریایی، باکتری‌های تولیدکننده بتالاکتامازهای با طیف گسترده(ESBL) ، انتروباکتر، داکینگ مولکولی، اسید رزمارینیک، رزماری (Rosmarinus officinalis)

چکیده

مقدمه و هدف: هدف از این مطالعه، ارزیابی ویژگی‌های ضدباکتریایی اسانس رزماری در برابر باکتری‌های تولیدکننده بتالاکتامازهای با طیف گسترده(ESBL) ، به‌ویژه باکتری‌های جنس Enterobacter، و شناسایی ترکیباتی با بیشترین تمایل اتصال به آنزیم بتالاکتاماز، با هدف مقابله با عفونت‌های مقاوم به آنتی‌بیوتیک، با استفاده از روش داکینگ مولکولی بود.

مواد و روش‌ها: با توجه به ظهور باکتری‌های مقاوم به چندین دارو و افزایش مقاومت ضدباکتریایی در میان باکتری‌های بیماری‌زا، باکتری‌های جنس Enterobacterتولیدکننده بتالاکتامازهای با طیف گسترده، با استفاده از آزمون دیسک دوتایی انتخاب شدند. در این مطالعه، آنالیز کروماتوگرافی گازی-طیف‌سنجی جرمی(GC-MS)انجام نشد؛ زیرا ۹ لیگاند صرفاً بر اساس مطالعات پیشین انتخاب شدند. ویژگی‌های ضدباکتریایی ترکیبات مشتق‌شده از اسانس Rosmarinus officinalisبا استفاده از شبیه‌سازی‌های داکینگ مولکولی ارزیابی شد تا تمایل اتصال ۹ ترکیب موجود در اسانس رزماری به آنزیم بتالاکتاماز بررسی شود ..

یافته ها و نتیجه گیری: بر اساس نتایج آزمون حساسیت آنتی‌بیوتیکی، سویه‌های Enterobacterدر برابر اغلب آنتی‌بیوتیک‌ها، به‌ویژه آنتی‌بیوتیک‌های خانواده بتالاکتام، مقاوم بودند. همچنین، ژن CTX-M15 با استفاده از توالی‌یابی ایلومینا در مرکز ملی تحقیقات مقاومت آنتی‌بیوتیکی، واقع در کلرمون-فران فرانسه، شناسایی شد. نتایج آنالیز داکینگ مولکولی نشان داد که تمامی ترکیبات زیست‌فعال موجود در Rosmarinus officinalisممکن است دارای اثرات ضدباکتریایی باشند، اگرچه میزان تمایل اتصال آن‌ها متفاوت بود. در میان این ترکیبات، اسید رزمارینیک با انرژی اتصال ۲/۸- کیلوکالری بر مول، بیشترین تمایل اتصال را نشان داد. پس از آن، کارنوسول (۲/۷-)، اسید کارنوزیک (۰/۷-)، بتا-کاریوفیلن (۹/۵-)، وربنون (۴/۵-)، کافور (۰/۵-)، ۱،۸-سینئول (۹/۴-)، آلفا-پینن (۶/۴-) و بتا-میرسن (۹/۳- کیلوکالری بر مول) قرار گرفتند. برخی از ترکیبات، تمایل اتصالی مشابه با مهارکننده استاندارد، آویباکتام، نشان دادند و اسید رزمارینیک عملکرد اتصال مطلوب‌تری از آن داشت. بر این اساس، برای توسعه یک مولکول با کاربرد صنعتی، لازم است غلظت اجزای مختلف اسانس رزماری، به‌ویژه اسید رزمارینیک، کارنوسول و اسید کارنوزیک، به‌گونه‌ای تنظیم شود که اثربخشی بالقوه آن در برابر باکتری‌های تولیدکننده بتالاکتامازهای با طیف گسترده تأمین شود. ازاین‌رو، توجه فزاینده‌ای به ترکیبات مشتق‌شده از گیاهان با ویژگی‌های ضدباکتریایی و احتمال بروز عوارض جانبی نامطلوب کمتر نسبت به داروهای متداول معطوف شده است.

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