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In silico Exploration of Essential Oil Constituents in Combating Multidrug-Resistant *Staphylococcus aureus* Infected Wounds

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ABSTRACT

This research explores the multifaceted pharmacological actions of essential oils and its constituents, derived as secondary metabolites from aromatic plants, with a particular focus on their potent wound healing and antibacterial activities, elucidating their significance in therapeutic approach towards infected wounds. An *in silico* screening was carried out to identify the interaction between the bioactive essential oil contituents (EOC) such as cinnamaldehyde, citral, geraniol, linalool, and p-cymene, docked against various target proteins associated with antibiotic resistance and wound healing, including mec A (PDB ID- 4DK1), nor A (PDB ID- 7LO8), TGF- β1 (PDB ID- 1PY5), TGF- β2 (PDB ID- 1M9Z), VEGF (PDB ID-3QTK), GSK-3β (PDB ID-1Q5K) and MMP-9 (PDB ID-5UE4). The docking was done with AutoDock V 4.0 using five EOCs against seven receptors and the binding energy was gaged. The binding energy of EOCs were observed to be ranging from -5.3 kcal/mol to -2.55 kcal/mol. Notably, all the screened EOCs exhibited favourable binding affinity with GSK-3β, indicating their potential role in the inflammatory phase of wound healing. Additionally, towards antibiotic resistance, all EOC displayed adequate binding affinity with norA, suggesting their potential in modulating multidrug resistant efflux pumps. Compliance with Lipinski's rule, positions these EOC as promising candidates for drug development, particularly in the context of wound healing and antibiotic resistance. This study holds the promise of contributing novel insights to the field of wound care and combating antibiotic resistance, paving the way for innovative approaches in addressing the challenges posed by multi-drug resistant *Staphylococcus aureus* (MDRSA) infected wounds.

Keywords: Essential oil constituents, Wound healing, Antibiotic resistance, MDRSA.

INTRODUCTION

Wound infections pose a significant and persistent challenge to global healthcare. Wound infections can occur as a result of various factors, including surgical procedures, traumatic injuries, chronic conditions, or compromised immune systems. The consequences of untreated or poorly managed wound infections are substantial, leading to increased morbidity, prolonged hospital stays, escalating healthcare costs, and, in severe cases, mortality [1]. The rise of multidrug-resistant bacteria, such as *Staphylococcus aureus*, further complicates the management of wound infections[2]. Traditional antibiotic therapies are becoming less effective due to the emergence of resistant strains, emphasizing the urgent need for alternative and innovative treatment approaches[3]. Effective wound management involves a multi-faceted approach that includes infection control, inflammation reduction, and promotion of tissue repair [4]. In recent years, researchers have explored alternative treatments, including the use of natural compounds like essential oil owing to their multitude of therapeutic effects such as anti-inflammatory, antioxidant, analgesic, antimicrobial and antihyperlipidemic activities and it can be well ascribed to their potential bioactive constituents [5].

Essential oils are secondary metabolites produced by aromatic plants and are extremely intricate natural combinations that can include about 20 to 60 different components at wildly varying amounts. In comparison to other components present in trace amounts, they are characterised by two or three primary constituents at relatively high concentrations (20–70 percent). The biological qualities of the EO are typically determined by these key elements, comprising majorly of two groupings of the components with unique biosynthetic origins. Terpenes and terpenoids make up the primary group, whereas aromatic and aliphatic components make up the other category [6]. Essential oil presents an ideal alternative to current antibiotics due to their broad-spectrum antimicrobial potential, unique mechanisms of action and low propensity to instigate antibiotic resistance. These agents also attribute to increased cell growth and cell migration properties necessary for wound healing, indicating the scope of EO to serve as endearing options to mitigate associated squeals allied to impaired wound healing [7].

Wound healing is a complex fragile biological process and the biology of wound healing is accurate and substantially programmed, through overlapping phases of hemostasis, inflammation, proliferation and remodelling [8]. Transforming Growth Factor-beta (TGF- β), Vascular Endothelial Growth Factor (VEGF), Glycogen Synthase Kinase-3β (GSK-3β), and Matrix Metalloproteinase-9 (MMP-9) stand as pivotal players in the intricate orchestration of wound healing processes[9]. TGF- β aligns various cellular events, promoting cell proliferation, differentiation, and extracellular matrix synthesis [10]. VEGF, a key angiogenic factor, stimulates the formation of new blood vessels crucial for nutrient supply to healing tissues [11]. GSK-3β influences diverse cellular pathways, regulating inflammation and cell survival[12], while MMP-9 facilitates tissue remodeling by degrading extracellular matrix components [13]. Together, these proteins create a dynamic network, coordinating the stages of inflammation, proliferation, and tissue remodeling essential for effective wound healing [14]. Understanding their significance provides valuable insights for developing targeted therapies that harness the complex mechanisms of these proteins, potentially revolutionizing wound care strategies.

Multidrug-resistant *S. aureus* (MDRSA) is the most prevailing pathogen associated with nosocomial infections where *mecA* and *norA* genes are contemplated to be the significant contributors to their antibiotic resistance [15]. MecA, as a crucial component of the staphylococcal chromosomal cassette carrying methicillin resistance, confers resistance to beta-lactam antibiotics, rendering traditional treatments ineffective. Understanding and targeting mecA are imperative for developing alternative therapeutic approaches to combat MDRSA infections[16]. On the other hand, norA, a multidrug efflux pump, plays a critical role in the resistance of S. aureus to various antibiotics. Inhibition of norA function is a promising avenue to enhance the effectiveness of existing antibiotics against MDRSA [17]. A comprehensive understanding of mecA and norA allows for the development of targeted interventions, potentially overcoming the challenges posed by multidrug resistance in *S. aureus* infections and offering novel strategies for more effective treatment regimens.

In unravelling the sophisticated molecular interactions between EOCs and key proteins associated with wound healing and antibiotic resistance, this research not only underscores the potential therapeutic implications but also lays the foundation for innovative strategies in mitigating MDRSA-infected wounds, heralding a promising frontier in the pursuit of effective and targeted therapeutic interventions.

MATERIALS AND METHODS

The *in silico* screening to analyse the interaction of bioactive EOC; *viz.*, cinnamaldehyde, citral, geraniol, linalool and p-cymene with target proteins like mec A (PDB ID- 4DK1), nor A (PDB ID- 7LO8), TGF- β1 (PDB ID- 1PY5), TGF- β2 (PDB ID- 1M9Z), VEGF (PDB ID-3QTK), GSK-3β (PDB ID-1Q5K) and MMP-9 (PDB ID-5UE4) were done by using AutoDock 1.5.6 (www.mgltools.scripps.edu) according to the procedure followed by Archana *et al.* (2022) [18]. The ligands were also analysed for their lipophilicity and violation of Lipinski rule of five using the SwissADME online web tool.

Preparation of Ligand Structure

The structures of the ligands including β-caryophyllene, cinnamaldehyde, citral, eugenol, geraniol, linalool and p- cymene were downloaded from PubChem Compound Database (National Center for Biotechnology Information; https://pubchem ncbi.nlm.nih.gov/) in Spatial Data File (.SDF) format as shown in figure 1. Then they were processed using Marvin View 17.25.0 (www.chemaxon.com) and modified to Tripos Mol 2 format. The modifying tools of AutoDock Tools (ADT) for ligands were used for processing them in terms of detection of roots, root expansion and choosing the number of rotatable bonds. Following the preliminary preparations, the ligand molecules were transformed to PDBQT format for using them in AutoDock4.

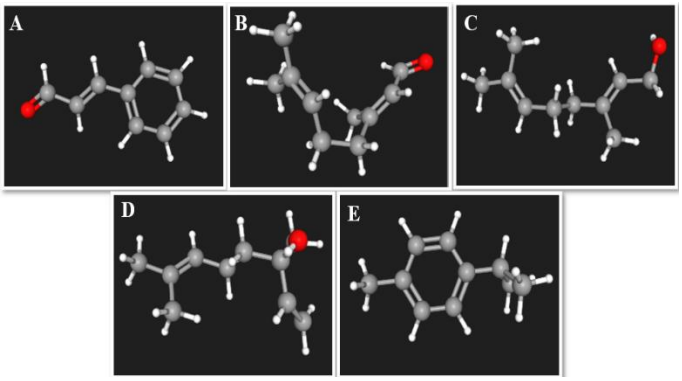

Figure 1: Structure of ligands: A. Cinnamaldehyde; B. Citral; C. Geraniol; D. Linalool; E. p-Cymene.

Preparation of Receptor Structure

Receptor structures for mec A (PDB ID- 4DK1), nor A (PDB ID-7LO8), TGF- β1 (PDB ID- 1PY5), TGF- β2 (PDB ID- 1M9Z), VEGF (PDB ID-3QTK), GSK-3β (PDB ID-1Q5K) and MMP-9 (PDB ID-5UE4) were downloaded from the database of the RCSB protein data bank (http://www.rcsb.org) in PDB format as shown in figure 2. The structure was prepared using Accelrys Discovery Studio Visualizer 3.5.0.12158 (Copyright© 2005-12, Accelrys Software Inc) for further processing and docking. Further, the macromolecule was processed in AutoDock 1.5.6 (Molecular Graphics Laboratory tools, www.mgltools.scripps.edu) according to the ADT tutorial's standard protocol and parameters.

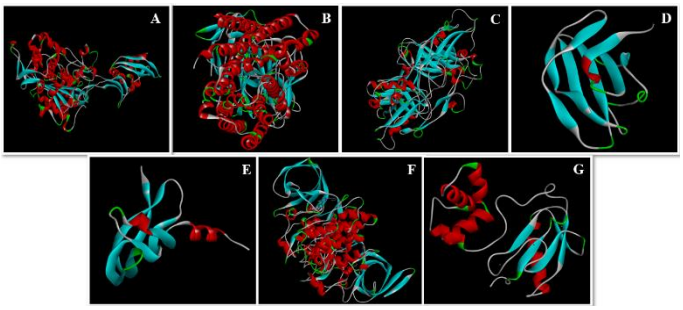

Figure 2: Structure of receptor proteins: A. mec A (PDB ID- 4DK1); B. nor A (PDB ID- 7LO8); C. TGF- β1 (PDB ID- 1PY5); D. TGF- β2 (PDB ID- 1M9Z); E. VEGF (PDB ID-3QTK); F. GSK-3 (PDB ID-1Q5K); G. MMP-9 (PDB ID-5UE4)

Docking Analysis

The docking studies were conducted using Autodock4 developed by the Scripps Research Institute (La Jolla, CA, www.autodock.scripps.edu). The grid map for the present study was computed with Autodock4. The processed file was saved in grid parameter file (gpf) format. Using the parameters optimised by ADT, the docking parameter file (dpf) was generated. The Lamarckian genetic algorithm was used for all docking runs.

Using discovery studio visualiser, the result of docking analysis was visualised. After studying each ligand's interactions with the protein and analysing their binding poses, the best and most energetically beneficial conformations of each ligand were selected. The docking log (dlg) file's RMSD table contained the binding energy for each molecule's optimal docked postures, which were specified in Kcal/mol.

All the ligands such as cinnamaldehyde, citral, geraniol, linalool and p-cymene were docked against different proteins of antibiotic resistance and wound healing such as mec A, nor A, TGF- β1, TGF- β2, VEGF, GSK-3β and MMP-9. Binding energies (Kcal/mol) of ligands obtained from RMSD table are illustrated in table 1 and graphically represented in Fig 3. The docked images are given in Fig 4. The results of lipophilicity and violation of Lipinski rule of five of ligands are tabulated in table 2.

RESULTS AND DISCUSSION

Table 1: Binding energy (Kcal/mol) of ligands such as cinnamaldehyde, citral, geraniol, linalool and p- cymene against different receptors of antibiotic resistance and wound healing

Receptors	PDB ID	Cinnamaldehyde	Citral	Geraniol	Linalool	p-Cymene
mecA	4DK1	-4.5	-4.78	-4.35	-3.93	-4.63
norA	7LO8	-5.2	-5.3	-5	-4.66	-5.12
TGFβ1	1PY5	-4.09	-3.84	-4.21	-3.39	-3.75
TGFβ2	1M9Z	-3.5	-2.85	-3.75	-3.03	-2.48
VEGF	3QTK	-3.01	-2.77	-2.84	-2.55	-2.89
GSK	1Q5K	-5.03	-4.86	-4.47	-5.07	-4.68
MMP9	5UE4	-4.94	-4.55	-4.13	-4.03	-4.28

Table 2: *In silico* analysis of essential oils constituents (ligands) for their lipophilicity and violation of Lipinski rule using SwissADME online web tool

Ligands	MW	MR	HA	HD	LOGP	Lipinski's rule
Cinnamaldehyde	132.16	41.54	1	0	2.01	Non violation
Citral	152.23	49.44	1	0	2.49	Non violation
Geraniol	154.25	50.4	1	1	2.59	Non violation
Linalool	154.25	50.44	1	1	2.59	Non violation
p-Cymene	134.22	45.99	0	0	4.47	Non violation

MW- Molecular weight in g/mol; MR- molar refractivity; HA- H acceptor; HD- H donar; Lipophilicity- LOGP

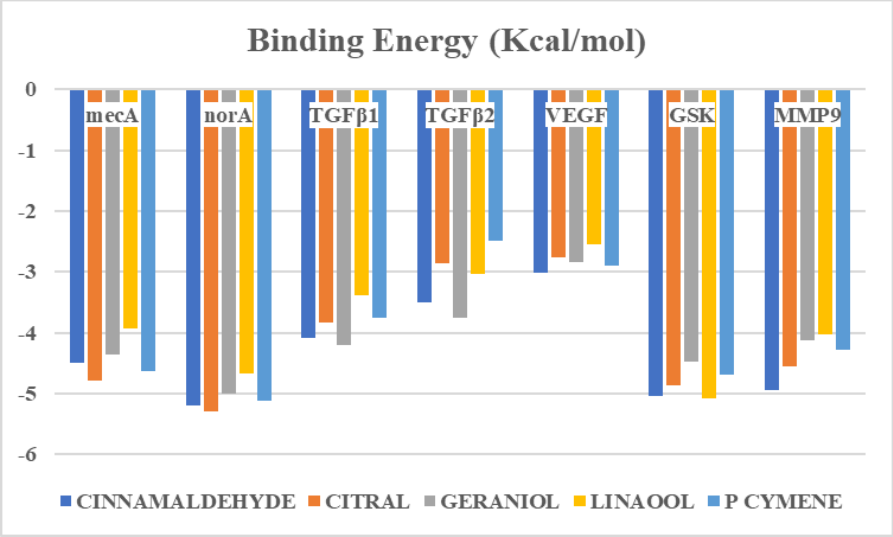

Figure 3: Graphical representation of binding energy (Kcal/mol) of ligands such as cinnamaldehyde, citral, geraniol, linalool and p- cymene against different receptors

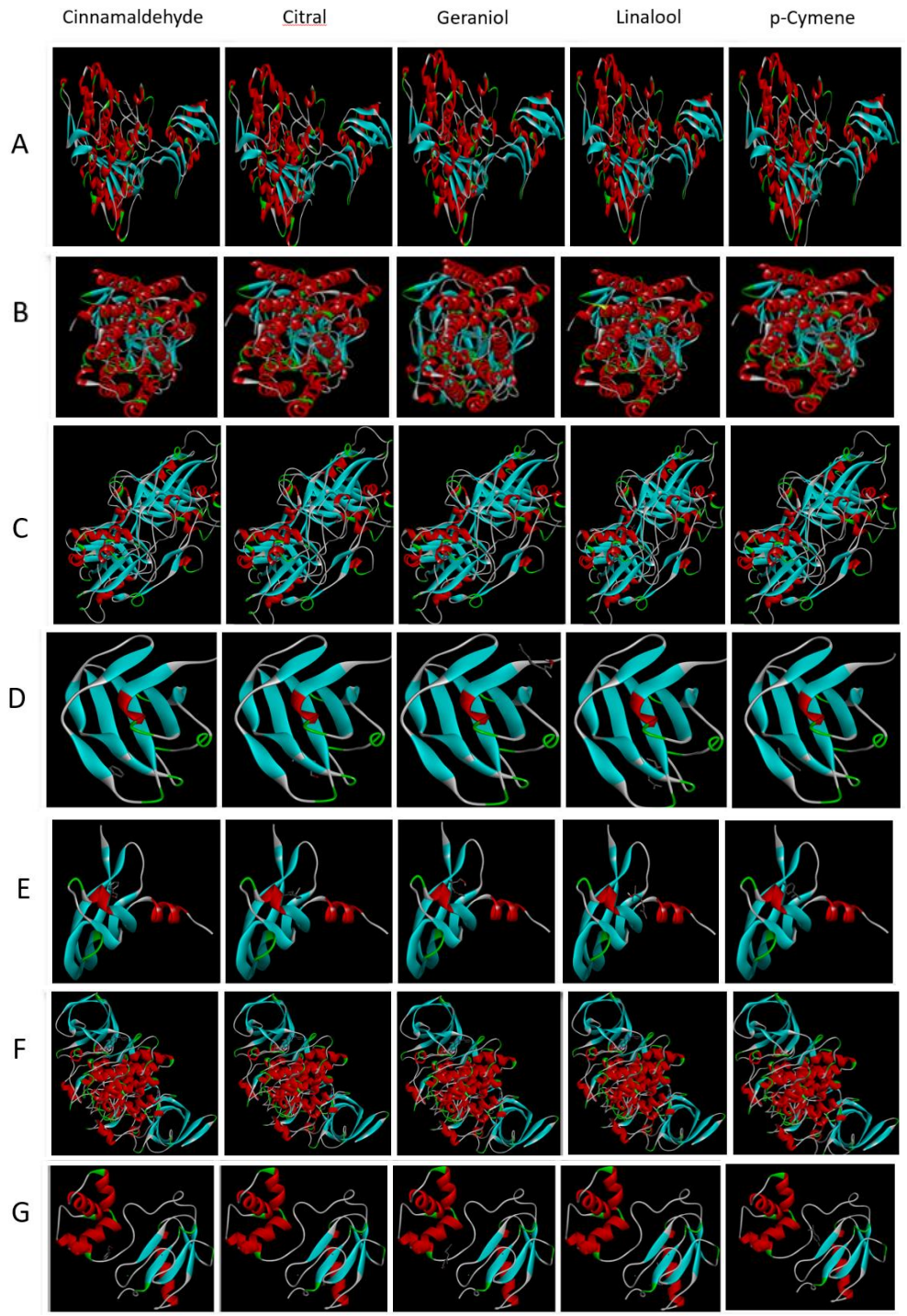

Figure 4: Docked images of ligands such as cinnamaldehyde, citral, geraniol, linalool and p- cymene against different receptors such as mec A (PDB ID- 4DK1), nor A (PDB ID- 7LO8), TGF- β1 (PDB ID- 1PY5), TGF- β2 (PDB ID- 1M9Z), VEGF (PDB ID-3QTK), GSK-3 (PDB ID-1Q5K) and MMP-9 (PDB ID-5UE4)

Molecular docking is an efficacious and steadfast computational model for the prediction of feasible binding approaches and learning the mechanism of ligand binding between proteins and small molecules [19]. The ligand molecules with the lowest binding energy were determined to be the most effective in modulating their respective receptors, as lower docking score (binding energy) is correlated with increased binding affinity [20]. In our study, we have docked bioactive EOC such as cinnamaldehyde, citral, geraniol, linalool and p- cymene with imperious proteins involved in antibiotic resistance and wound healing. The binding energy of EOCs were observed to be ranging from -5.3 kcal/mol to -2.55 kcal/mol.

Amongst the receptors of wound healing, binding energy was lowest towards the GSK-3β protein indicating that all the essential oil constituents might have good binding affinity towards GSK-3β protein. Linalool exhibited the lowest binding energy towards GSK-3β receptor followed by cinnamaldehyde, citral, p-cymene and geraniol. Glycogen synthase kinase 3 beta (GSK-3β) is a crucial molecule that modulates the Wnt pathway and is linked to inflammation, cell proliferation, differentiation, and glucose metabolism. Despite the fact that numerous proteins are involved in the wound healing process, research has indicated that inhibiting the GSK-3β protein can expedite the healing process [21]. Thus, our findings suggest that essential oil constituents might have role in the

modulation of GSK-3β protein indicating its possible role in inflammatory phase of wound healing.

There is a balance between the extracellular matrix component (ECM) precipitation and protease activity in the event of an acute wound. Nonetheless, metalloproteinase matrix (MMP) hyperactivity has a role in the development of chronic wounds. A rise in MMP indicates delayed healing. Specifically, MMP-9 has been suggested to be dynamically organized in certain pathogenic processes. Consequently, the development of an MMP inhibitor has proven to be an effective approach in the healing of wounds [22]. The binding energy of cinnamaldehyde was lowest among the screened EOCs followed by citral, p- cymene, geraniol and linalool against MMP-9 receptor.

Complex interactions between cells and growth factors are necessary for wound healing. Transforming growth factor-beta is a multifunctional cytokine which is essential for the proliferation and differentiation of fibroblasts into myofibroblasts, which helps wound closure during remodelling phase. It is a family of proteins that includes three isoforms: TGF-β1, TGF-β2, and TGF-β3. Furthermore, it has been discovered that TGF-β suppresses the production of collagenases, which are the enzymes accountable for the breakdown of collagen and the remodelling of the extracellular matrix. Thus, it can be inferred that TGF-β plays a vital part in coordinating the several cellular and molecular processes associated with wound healing [23]. In our study, we docked the selected EOC with TGF- β1 and TGF- β2, and found that all the compounds were having higher binding affinity for TGF- β1 than TGF- β2. Geraniol showed the maximum negative binding score followed by cinnamaldehyde, citral, p-cymene and linalool with TGF- β1.

Angiogenesis plays a vital role in the healing of wounds by forming new blood vessels from old ones by penetrating the wound clot and arranging into a microvascular network throughout the granulation tissue. Vascular endothelial growth factor plays a characteristic role is the promotion of angiogenesis. Angiogenesis is significantly elevated during the proliferative phase of wound healing primarily by VEGF[11]. The binding energies of EOCs were highest with VEGF receptor indicating its least affinity towards that receptor. Lowest binding energy was observed in cinnamaldehyde followed by p- cymene, geraniol, citral and linalool.

Microbial resistance to several antibiotic classes is primarily caused by bacterial multidrug efflux pumps. Efflux pumps can move different molecules with varied structures or they can be tailored to a single substrate. Inhibiting an efflux pump has the potential to both lessen the selection of resistant mutants and increase an antibiotic's clinical efficacy. NorA MDR efflux pump is responsible for the active expulsion of hydrophilic quinolones from the cells which makes *S. aureus* is less vulnerable to these drugs [24]. The binding energies of β-caryophyllene, cinnamaldehyde, citral, geraniol, linalool and p-cymene towards nor A were -5.2, -5.3, -5, -4.66 and -5.12 Kcal/mol respectively. Among the screened EOCs, citral exhibited the highest binding affinity followed by cinnamaldehyde, geraniol, p-cymene and linalool towards nor A indicating that these EOCs might have ability to modulate the efflux pump which could contribute to constraint the antibiotic resistance caused by nor A efflux pumps.

The *mec A* gene is one of the crucial gene involved in antimicrobial resistance which is encoded by pencillin binding protein (PBP)2a conferring resistance to beta lactam antibiotics in *S. aureus*. Compounds that inhibit PBP2a offer pledging therapy against MRSA infections[25]. The results of *in silico* docking study revealed that among the screened EOCs, citral had the maximum negative binding score followed by p cymene, cinnamaldehyde, geraniol and linalool towards mec A.

Essential oil and its constituents are natural compounds with vast array of beneficial properties and various studies have unveiled modulatory effects of essential oil in the release of inflammatory cytokines [26], reactive oxygen species [27], antimicrobial activity [28], augmentation of reepithelialisation and collagen deposition [29] divulging its role in different phases of wound healing. There are previous studies that have reported the anti-inflammatory activity of cinnamaldehyde [30], citral [31], geraniol [32], linalool [33] and p-cymene [34]. The anti-inflammatory property of EOCs could be possibly due to the modulation of GSK-3β which can be correlated to our findings. Various research findings have also reported the antibacterial properties of cinnamaldehyde [35], citral [36], geraniol [37], linalool [38] and p-cymene [39]. The antibacterial activity of EOCs might be due to the its inhibitory action on nor A efflux pumps or *mec A* genes which can be associated with the findings of our study suggesting its possible role in the reversal of antibiotic resistance.

Lipophilicity is the characteristic that gives a chemical molecule its "drug-likeness" during the research and development phases. The lipophilicity of a substance, represented as Log P, indicates the drug molecules' absorption into the body [40]. Cinnamaldehyde, citral, geraniol, and linalool in our investigation showed a Log P value less than 4.15, which is indicative of its beneficial absorption into the body. A successful drug molecule should also include characteristics that fall within the permissible range of the following five Lipinski's criteria, according to the Lipinski's rule of five: molecular weight of 500, molar refractivity from 40 to 130, number of hydrogen bond donors: ≤ 5, number of acceptors of hydrogen bonds: ≤ 10, and lipophilicity (given as LogP): ≤ 4.15 [41]. It had been demonstrated that cinnamaldehyde, citral, geraniol, linalool and p-cymene adhered to the Lipinski rule of five making them potential candidates for drug development.

CONCLUSION

In conclusion, this *in silico* research sheds light on the promising potential of essential oil constituents in the realms of wound healing and combating antibiotic resistance. The docking studies conducted with various targets associated with critical domains of wound healing and antibiotic resistance have unveiled significant insights into the molecular interactions of essential oil components. Conspicuously, the observed robust binding affinities towards the GSK-3β protein suggest a potential modulatory role in inflammation, thereby accelerating the wound healing process. Equally compelling is the discovery of the favorable binding affinities of EOCs towards the norA protein, indicating a probable contribution to the reversal of antibiotic resistance. This finding underscores the multifaceted therapeutic potential of essential oils in addressing the pressing global challenge in wound care management and combating antibiotic resistance. Furthermore, the compliance of all screened essential oil constituents with Lipinski's rule adds a layer of confidence in their drug-like properties, enhancing their candidacy for further exploration and development as potential therapeutic agents. As we navigate the complex landscape of modern medicine, this research serves as a foundational step towards harnessing the therapeutic potential of natural compounds like essential oil and its constituents for the management of MDRSA infected wounds. The identified molecular interactions provide a basis for future *in vitro* and *in vivo* studies,

eventually emphasizing the way for the development of novel pharmaceutical interventions.

Conflict of interest

The authors declare that they have no conflict of interest.

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