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Geraniol and Citronellal as Potential Inhibitors of *Fusobacterium nucleatum*: A Computational Study

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ABSTRACT
Fusobacterium nucleatum is associated with a wide range of oral and systemic infections, and the availability of effective inhibitors remains limited. The present study aimed to evaluate the inhibitory potential of two naturally occurring phytocompounds, geraniol and citronellal, against *Fusobacterium nucleatum* using computational approaches. Molecular docking analysis demonstrated that both compounds exhibit favorable binding interactions with the target protein. Citronellal showed comparatively higher binding affinity than geraniol, suggesting stronger inhibitory potential. ADMET analysis revealed that both compounds possess desirable pharmacokinetic properties, including high gastrointestinal absorption and acceptable bioavailability. These findings indicate that geraniol and citronellal may serve as promising therapeutic candidates against *Fusobacterium nucleatum*. However, further experimental validation is required to confirm their efficacy and safety.
Keywords: Fusobacterium nucleatum, Geraniol, Citronellal, Molecular docking, ADMET, In silico, medicine

1.INTRODUCTION

In recent years, in silico approaches have become an integral part of modern drug discovery, allowing researchers to identify potential lead compounds efficiently through molecular docking and computational analysis [1,2]. These techniques significantly reduce the time and cost associated with conventional drug development processes.
Natural compounds derived from plants have gained considerable attention due to their wide range of pharmacological properties and relatively low toxicity profiles. Citronellal, a key component of essential oils, has been reported to exhibit antimicrobial, antifungal, anti-inflammatory, and antioxidant activities [3]. Similarly, geraniol, a monoterpenoid alcohol present in various aromatic plants, is known for its diverse biological activities and therapeutic potential [4].
Fusobacterium nucleatum is a gram-negative, anaerobic bacterium commonly associated with oral infections such as gingivitis, periodontitis, and endodontic infections [5]. In addition to its role in oral diseases, it has also been implicated in systemic conditions, including colorectal cancer [6]. The growing concern of antimicrobial resistance highlights the urgent need for identifying novel and effective therapeutic agents [7].
Recent studies have emphasized the antimicrobial potential of monoterpenes and their applicability in oral healthcare [8,9]. These compounds are increasingly being explored as alternative therapeutic agents due to their effectiveness and safety profiles. In this context, the present study aims to investigate the inhibitory potential of geraniol and citronellal against *Fusobacterium nucleatum* using molecular docking and ADMET analysis.

2. MATERIALS AND METHODS

The outer membrane protein OmpA of *Fusobacterium nucleatum* was modeled using the SWISS-MODEL online server [10]. The three-dimensional structures of geraniol and citronellal were retrieved from the PubChem database in Structure Data Format (SDF) and subsequently converted into Protein Data Bank (PDB) format.Molecular docking was performed using the HEX docking server (version 8.0.0) to evaluate the interaction between the ligands and the target protein [11]. The binding energy (E-total) and hydrogen bond interactions were recorded to assess the strength of interaction.
Protein–ligand interactions were visualized using PyMOL software [12]. Pharmacological activity prediction was carried out using the PASS online server [13]. ADMET properties, including absorption, distribution, metabolism, excretion, and toxicity, were evaluated using the SwissADME tool [14]. All computational analyses were performed using default parameters unless otherwise specified.

3. RESULTS

TABLES:

TABLE 3.1 : In silico docking results based on binding residues and E-total are demonstrated

Phytochemicals	PubChem ID	Binding Residues	E-total
Geraniol	637566	TYR289 and ASP 290	-168.46
Citronellal	7794.	Arg 336	-175.70

TABLE 3.2: ADMET Pharmacokinetics of Citronellal and Geraniol provided by computational prediction methods

PARAMETERS	SWISS ADME(CITRONELLAL)	SWISS ADME(GERANIOL)
TPSA	17.07Å²	20.23Å²
INHIBITORS OF CYP1A2, CYP2C19, CYP2C9, CYP2D6 AND CYP3A4	NO	NO
GI ABSORPTION	HIGH	HIGH
Consensus Log $P_{o/w}$	2.71	2.78
Water solubility- class	Soluble	Soluble
BBB permanent	Yes	Yes
Lipinski	Yes; 0 violation	Yes; 0 violation
Bioavailability Score	0.55	0.55

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TABLE 3.3: Biological activity spectrum of Citronellal

PA	PI	ACTIVITY
0,904	0,001	Aldose reductase substrate
0,885	0,004	Protein-disulfide reductase (glutathione) inhibitor
0,883	0,006	CYP2J substrate

TABLE 3.4: Possible and adverse toxic effects of Citronellal

PA	PI	ACTIVITY
0,981	0,002	Skin irritation, moderate
0,980	0,002	Skin irritation, high
0,971	0,002	Skin irritative effect

TABLE 3.5: Biological activity spectrum of Geraniol

PA	PI	ACTIVITY
0,966	0,001	Prenyl-diphosphate inhibitor
0,952	0,001	Undecaprenyl-phosphate mannosyltransferase inhibitor
0,953	0,003	Mucomembranous protector

TABLE 3.6: Possible and adverse toxic effects of Geraniol

PA	PI	ACTIVITY
0,025	0,009	Uterine rupture
0,137	0,076	Carcinogenic, group 2B
0,147	0,091	Carcinogenic, group 3

4.FIGURES:

Fig 4.1: Chemical structure of Geraniol

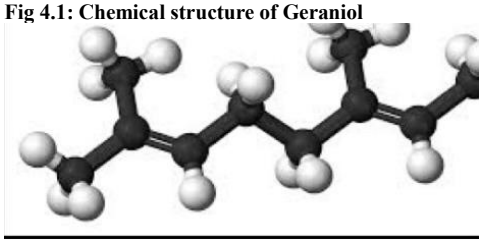

Fig 4.2: Chemical structure of Citronellal

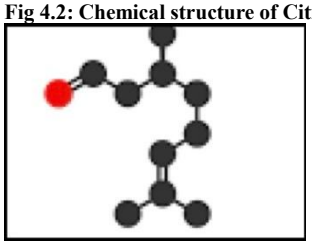

Fig 4.3: Morphology of Fusobacterium

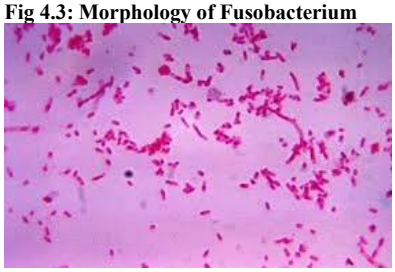

Fig 4.4: Molecular docking interaction of Geraniol with OmpA protein.

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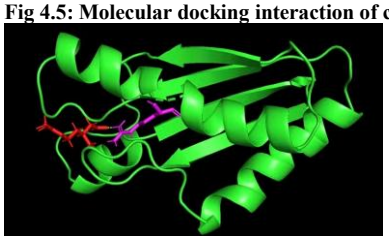
Fig 4.5: Molecular docking interaction of citronellal with OmpA protein of *Fusobacterium nucleatum*.



5. DISCUSSION

The molecular docking analysis revealed that both geraniol and citronellal exhibit significant binding interactions with the OmpA protein of *Fusobacterium nucleatum*. Citronellal demonstrated a higher binding affinity with an E-total value of −175.70 compared to geraniol (−168.46), indicating stronger interaction and potential inhibitory activity.

The interaction analysis showed that citronellal forms stable interactions with key amino acid residues, which may contribute to its enhanced inhibitory potential. In contrast, geraniol exhibited comparatively weaker interactions, suggesting a lower binding efficiency.

ADMET analysis indicated that both compounds possess favorable pharmacokinetic properties. High gastrointestinal absorption and acceptable bioavailability were observed, and both compounds satisfied Lipinski's rule of five [15]. These properties suggest that both compounds have good drug-like characteristics.

PASS analysis further supported the biological activity of these compounds, indicating potential antimicrobial and enzyme inhibitory properties. Citronellal demonstrated comparatively stronger predicted activity, whereas geraniol exhibited lower toxicity, suggesting a safer profile.

The findings of this study are consistent with previous reports highlighting the antimicrobial properties of monoterpenes and essential oil components. These compounds have been widely studied for their ability to disrupt microbial membranes and inhibit essential biological pathways [8,16].

Furthermore, recent literature supports the potential application of phytocompounds in the treatment of oral infections, particularly those caused by *Fusobacterium nucleatum* [9,17]. The stronger binding affinity observed for citronellal suggests that it may serve as a more effective therapeutic candidate.

However, it is important to note that the present study is limited to computational analysis. Experimental validation through in vitro and in vivo studies is essential to confirm the efficacy and safety of these compounds.

6. CONCLUSION

The present study demonstrates that geraniol and citronellal exhibit significant inhibitory potential against *Fusobacterium nucleatum*, with citronellal showing comparatively higher binding affinity. Both compounds displayed favorable pharmacokinetic properties, supporting their potential as therapeutic agents. These findings highlight the importance of natural phytocompounds in antimicrobial drug discovery and provide a basis for further experimental research.These findings may contribute to the development of novel antimicrobial agents for oral infections.

AUTHOR CONTRIBUTIONS

Author 1: Kaviya Selvaraj carried out the study by collecting data and drafted the manuscript after performing the necessary statistical analysis and in the preparation of the manuscript.

Author 2: Sathish Sankar aided in conception of the topic, designing the study and supervision of the study, correction and final approval of the manuscript.

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