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In Silico Docking Studies of Potential Phytocompounds from *Musa* Flowers against Endometritis

Vaishnavi V.V. and Uma Gowrie S.*

Department of Plant Biology and Plant Biotechnology, Ethiraj College for Women (Autonomous), Affiliated to the University of Madras, Chennai 600 008, Tamil Nadu, India

**Corresponding Author*

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Abstract: India's extensive collection of medicinal plants is a vital source of bioactive compounds. World Health Organisation (WHO) reported that 80% of the global population, around 3.5 to 4 billion people, rely on plant-based medicine, which remains a safe and effective alternative to synthetic drugs. *Musa*, particularly its flowers, has anti-inflammatory properties with potential applications in addressing uterine inflammation. These properties arise from bioactive compounds like polyphenols and flavonoids that can combat inflammation, as well as the rich antioxidant content in *Musa* flowers which counteracts oxidative stress. Endometritis is a medical condition characterised by inflammation of the endometrium, the inner lining of the uterus. It often results from bacterial infection and can lead to symptoms such as pelvic pain, fever, and uterine tenderness. The objective of the present study was to analyse, validate and confirm the functional role of stigmasterol, Hexadecanoic acid Methyl ester and n-hexadecanoic acid through *in silico* docking against target protein molecule, Interleukin 1 Beta (IL-1β) and Tumour Necrosis Factor alpha (TNF-α). Metronidazole was used as the standard. The structure of ligands was retrieved from the PubChem Database and the target protein sequence was downloaded from Protein Data Bank. The stereochemical quality of the target protein was assessed using a Ramachandran plot, which indicated that 94.3% (IL-1β) and 65.1% (TNF-α) of the residues were located within the favoured regions. Additionally, non-bonded interactions among the atoms within the target protein were computed through ERRAT analysis, revealing an overall quality factor of 91.1765. Target protein and the ligand molecules were prepared in Autodock 4.2.6, Chain A of IL-1β and TNF-α with maximum number of residues in favoured regions was retained and active torsions were set in the ligand molecule for docking. The findings of the docking analysis were examined and visualised using several prominent web-based visualisation tools, including Protein-Ligand Interaction Profiler, Proteins Plus (DoG Site Scorer), and Pymol. Docking results of stigmasterol, hexadecenoic acid Methyl Ester, and n-hexadecanoic acid revealed binding energies of -8.63, -5.56, -5.27 kcal/mol respectively against IL-1β target protein and -6.41, -5.51, -5.26 kcal/mol against TNF-α target protein. The results obtained from these analyses strongly suggest that Stigmasterol exhibited notably high binding affinities towards the target protein IL-1β, which can be implicated in the treatment of endometritis.

Keywords: *Musa* flowers, Endometritis, Auto docking, Stigmasterol, n-hexadecanoic acid, IL-1β, TNF-α, Ramachandran Plot, Metronidazole

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Introduction

India's vast reservoir of medicinal plants represents an invaluable source of bioactive compounds that have been available in traditional medicine systems for centuries. These botanical resources have not only played a crucial role in meeting the healthcare needs of a substantial portion of the global population but also has an interest of modern scientific research. The World Health Organization (WHO) reported that plant-based medicines are continued to be a dependable and effective alternative to synthetic drugs for approximately 80% of the world's population. This reliance on natural remedies underscores the enduring importance of exploring the potential therapeutic applications of these plant-derived compounds (Divya *et al*., 2016).

Within this diverse botanical landscape, the *Musa* genus, which includes common banana plants, has garnered significant attention for its potential medicinal properties. In particular, the flowers of the *Musa* plant have been singled out for their intriguing attributes. Of which, their anti-inflammatory properties have emerged as an area of particular interest. These properties, underpinned by the presence of bioactive compounds such as polyphenols and flavonoids, holds the promise of addressing inflammatory conditions effectively (Krishnan and Sinija, 2016). Moreover, *Musa* flowers are rich in antioxidants, which not only contribute to their anti-inflammatory potential but also serve as defenders against oxidative stress, a common underlying factor in various health issues.

Banana has a rich traditional significance in India, where it is revered on various occasions and is highly valued for its medicinal properties (Murugavel *et al*., 2014). Musaceae, particularly the *Musa* species, offer a treasure trove of medicinal benefits through various plant parts, and their phytochemical constituents play a vital role in preventing and managing a wide range of diseases, including cancer and women's health issues. These natural remedies continue to be valued, especially in traditional and holistic medicine practices (Ojewole, 2006). In the sphere of women's health, endometritis stands as a significant medical concern. This condition, characterized by inflammation of the endometrial lining of the uterus, often arises from bacterial infections and can lead to distressing symptoms like pelvic pain, fever, and uterine tenderness. Recognizing the pressing need for innovative solutions in treating endometritis, the present study embarks on an exploratory journey into the specific bioactive compounds found in *Musa* flowers (Kitaya *et al*., 2018).

Banana flowers are a popular vegetable in Tamil Nadu, India often consumed raw with yogurt or cooked in curry. They offer a plethora of health benefits, including their ability to increase progesterone levels in the body when consumed with curd, alleviate urinary blockages when combined with coconut oil and spices, and treat menstrual disorders when the juice of flowers and leaf sheaths are mixed (Joseph *et al*., 2014). Plant-based foods are a valuable source of bioactive phytoconstituents, including phytochemicals that play a crucial role in preventing chronic diseases such as diabetes, coronary heart disease, hypercholesterolemia, and cancer. These phytochemicals such as vitamin E, vitamin C, phenolic compounds, flavonoids, and isothiocyanates, possess preventive properties like antioxidants, detoxification, immune stimulation, and neuropharmacological activities (Rao, 2003).

Phenolic acids, polyphenols, and flavonoids effectively scavenge free radicals, inhibiting oxidative mechanisms that lead to disease progression. Fruits and vegetables, including

bananas, are known to contain antioxidants and other chemical substances that protect the body against cancer. Flavonoids, natural plant compounds with a polyphenol structure found in various fruits and vegetables, reduce the risk of cardiovascular disease, prostate cancer, colorectal cancer, and renal cancer. Additionally, flavonoids inhibit cell growth and proliferation and induce cell toxicity (Luo *et al*., 2008). Polyphenols in the diet act as reducing agents, targeting multiple aspects of tumour growth and carcinogenesis, safeguarding body tissues from oxidative stress related to cancer (Jenshi Roobha and Aravindhan, 2011).

Furthermore, plant-derived compounds, including phytoestrogens like lignans, isoflavones, coumestans, resorcylic acid lactones, and certain flavonoids, are utilized traditionally to address women's health issues, such as menstrual disorders, menorrhagia, and endocrine-responsive cancers. The phytoestrogens present in *Musa* flowers act as alternatives to Hormone Replacement Therapy (HRT) by interacting with estrogen receptors, either stimulating or suppressing estrogen attachment, ultimately reducing the risk of breast and uterine cancers (Messina *et al*., 2014)

Through rigorous molecular docking analysis, this study seeks to provide not only validation but also confirmation of the therapeutic potential of these *Musa*-derived compounds in mitigating uterine inflammation. The aim of the study was to illuminate a promising path for the treatment of endometritis, a condition that can significantly impact women's health and well-being. The research methodology, findings, and insights into molecular interactions are expected to contribute to the growing body of knowledge on natural remedies and their application in modern healthcare. By bridging the gap in the cutting-edge of science, this study underscores the enduring relevance of India's medicinal plants and their potential to offer safe and effective solutions to pressing healthcare challenges. The primary objective of this research was to employ and further lead to advancement *in silico* docking techniques to delve deeper into the functional roles of phytocompounds from *Musa* flowers. These compounds will be selected for the interactions with key target proteins, including Interleukin 1 Beta (IL-1β) and Tumor Necrosis Factor alpha (TNF-α).

Materials and Methods

In this research study, we conducted docking analysis on three distinct Phyto-compounds, namely Stigmasterol, hexadecanoic acid methyl ester, and n-hexadecanoic acid (Fig. 1). Our investigation involved the utilization of Metronidazole (Fig. 2) as the reference standard for docking assessments against specific target proteins associated with endometritis, namely IL-1β and TNF-α (Figs. 3, 4).

Assessing Stereochemical Quality: *Ramachandran Plot*:

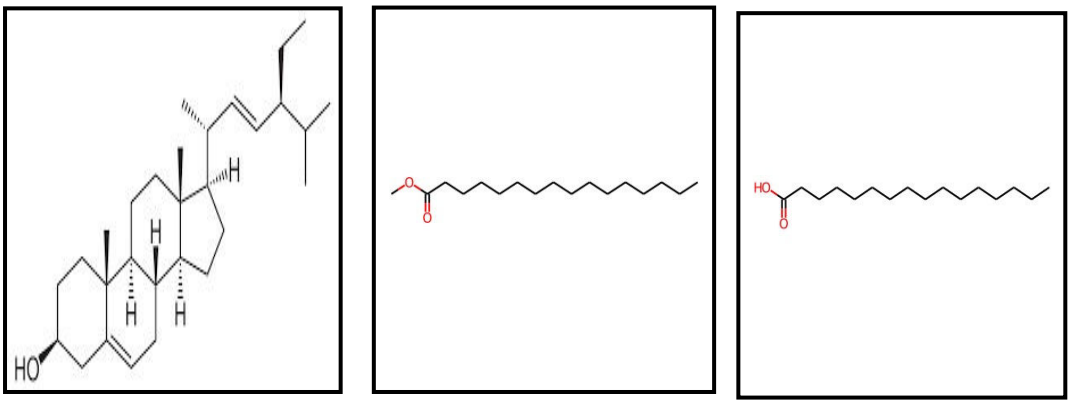
The stereochemical quality of the target protein molecules, IL-1β and TNF-α, was assessed using the PROCHECK server, which conducts a detailed examination of residue-by-residue geometry and overall structural geometry. This analysis included the generation of Ramachandran plots to evaluate the conformational quality of the proteins (Laskowski *et al*., 1993)

Analyzing Non-Bonded Interactions: *ERRAT Analysis*:

In addition to the Ramachandran plot analysis, ERRAT analysis was carried out to calculate non-bonded interactions among the atoms within the target protein molecules (IL-1β and TNF-α) which helps in assessing the overall structural integrity and reliability of these protein structures (Colovos and Yeates, 1993).

Utilization of Computational Tools:

Various software tools were employed in the *in silico* analysis of protein-ligand interactions. This analysis involved the installation and utilization of software applications like Autodock 4.2.6, MGL tools, and Open Babel to study the interactions between proteins and ligands (Morris *et al*., 2009).



A B C

Fig. 1: Structure of Phytocompounds (A) Stigmasterol, (B) Hexadecanoic acid Methyl ester, (C) n-hexadecanoic acid present in Musa florets.

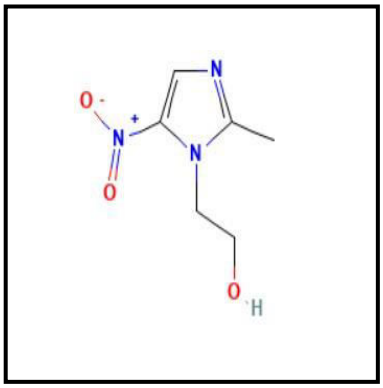


Fig. 2: Structure of synthetic drug Metronidazole.

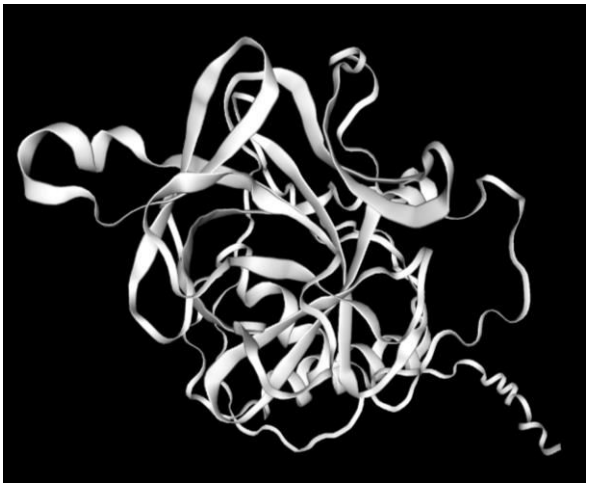


Fig. 3: Three-Dimensional structure of the target protein IL-1β of endometritis.

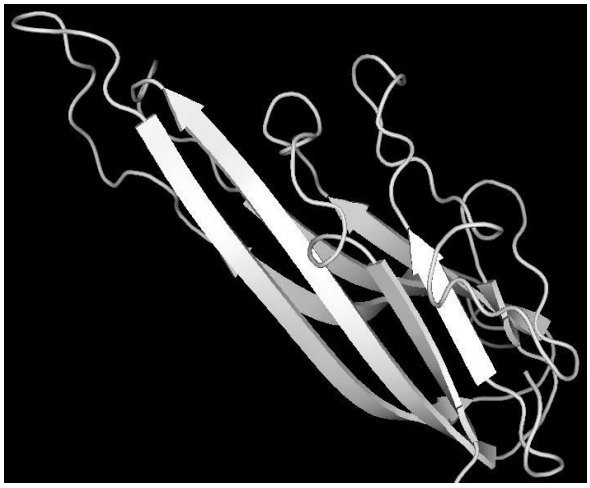


Fig. 4: Three-Dimensional structure of the target protein TNF-α of endometritis.

Preparation of target proteins:

The three-dimensional structure of IL-1B is not available in the Protein Data Bank (PDB). To obtain its 3D structure, a process called homology modeling was employed. In this approach, the 3D structure of TNF-α, with a known PDB ID of 1TNF, was retrieved from the Protein Data Bank (PDB) database at www.rcsb.pdb. The amino acid sequence of IL-1β was extracted from the UniProtKB database, accessible at www.uniprot.org, in FASTA format. This sequence was then submitted to SWISS-MODEL, an automated protein homology modelling server known for generating three-dimensional structures of target proteins based on their sequences and related structures (Sangeetha and Gowrie, 2023). Subsequently, the 3D structure of the target protein was subjected to validation using the ERRAT online server tool. This validation step was crucial to ensure the quality and reliability of the generated 3D structure, particularly in the context of subsequent docking studies (Ravi *et al*., 2016).

Preparation of ligands:

Stigmasterol, hexadecanoic acid methyl ester, and n-hexadecanoic acid were chosen as ligand molecules for docking studies due to their documented anti-inflammatory properties, which were sourced from the PubChem Database (https://pubchem.ncbi.nlm.nih.gov/) in SDF format. These compounds were then converted to PDB format using Open Babel. The preparation of the ligand molecule was performed using Autodock 4.2.6 and MGL tools. Additionally, we retrieved Metronidazole, an existing synthetic drug, to serve as a standard for comparing the effectiveness of the selected phytochemicals. The ligand were analyzed to identify three types of bonds: rotatable, non-rotatable, and unrotatable. Among these, rotatable bonds were deemed crucial for the docking process. Active torsions were subsequently configured, and the ligand was saved in .pdbqt format for using in molecular docking (O'Boyle *et al*., 2011).

Molecular Docking:

The active binding site in the target protein was identified using existing literature. The central grid point coordinates were set as the reference, defining the grid dimensions saved in "grid.txt." AutoGrid 4 (autogrid4.exe) was used with a Grid Parameter File (.gpf) to generate grid maps. Molecular docking was conducted with AutoDock 4.2.6, employing a rigid docking method and a Lamarckian genetic algorithm (population size: 150). The receptor's binding site was within a 5 Å grid with 0.375 Å spacing. AutoDock 4 (autodock4.exe) was executed for 10 runs, and the run with the most negative Genetic Algorithm value was chosen. Final conformations were clustered and ranked based on AutoDock scoring, considering crucial residues. PyMol was used for analysis, revealing binding energies and contacts for each ligand (Norgan *et al*., 2011; Valli *et al*., 2017).

Results

The functional role of Interleukin-1 beta (IL-1β) and tumour necrosis factor alpha (TNF-α) in endometritis was investigated by examining their interactions with stigmasterol, hexadecenoic acid methyl ester, and n-hexadecanoic acid as ligand molecules.

Ramachandran plot:

The validation of two target protein molecules, Interleukin-1 beta (IL-1β) and Tumour Necrosis Factor Alpha (TNF-α), was conducted using Ramachandran plots. For IL-1β, the analysis revealed that approximately 94.3% of its residues occupied the highly favoured regions denoted as [A, B, L]. Additionally, about 4.9% of the residues were situated in regions that were also permitted but to a lesser extent, marked as [a, b, l, p]. Moreover, 0.8% of the residues were located in generously allowed regions within certain limits, represented as [~a, ~b, ~l, ~p] and no residues was found in regions categorized as disallowed. In the case of TNF-α, the assessment also utilized a Ramachandran plot, revealing that approximately 65.1% of its residues were positioned within the

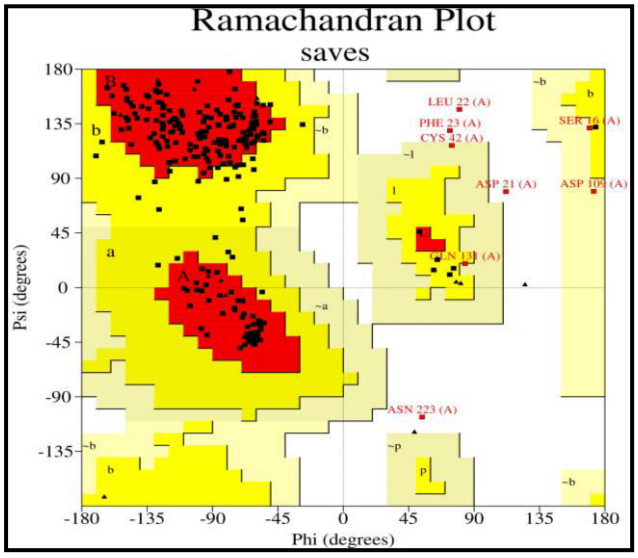


Fig. 5: Ramachandran plot of the target protein molecule, IL-1β.

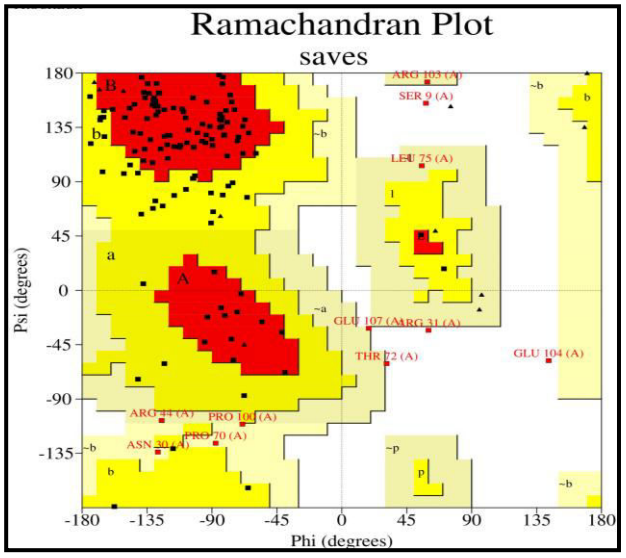


Fig. 6: Ramachandran plot of the target protein molecule, TNF-α.

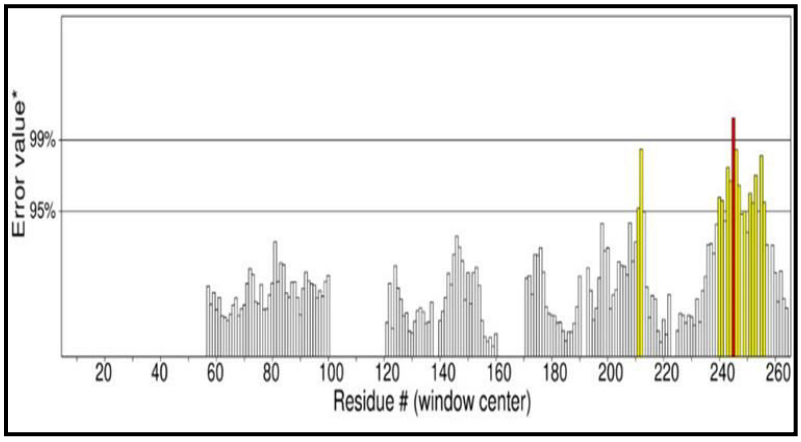


Fig. 7: ERRAT analysis of the target protein molecule, IL-1β.

highly favored regions [A, B, L]. Furthermore, around 27.9% of the residues were found in regions that were permitted for protein structure but were not as favored, designated as [a, b, l, p]. Additionally, 3.9% of the residues were situated in generously allowed regions within certain limits, indicated as [~a, ~b, ~l, ~p] and 3.1% of the residues were detected in regions considered disallowed for proper protein structure (Figs. 5, 6).

ERRAT Analysis:

The ERRAT analysis assessed the non-bonded interactions between atoms within IL-1β and TNF-α, resulting in quality factors of 91.1765 and 81.279, respectively. These quality factors provide an indication of the overall quality of the target protein molecules (Figs. 7, 8).

Preparation of target protein:

The target protein molecules, IL-1β and TNF-α, were prepared and docked with specific ligand molecules - stigmasterol, hexadecenoic acid methyl ester, and n-hexadecanoic acid. In this preparation, Chain A, containing a maximum number of residues at 96.6% for IL-1β and 93% for TNF-α, located within favoured regions, was retained. However, Chains B and C were excluded from the setup to streamline and reduce computation time.

Preparation of Ligand:

Auto grid calculation:

Auto Grid plays a pivotal role in the preliminary computational phase of docking simulations. This

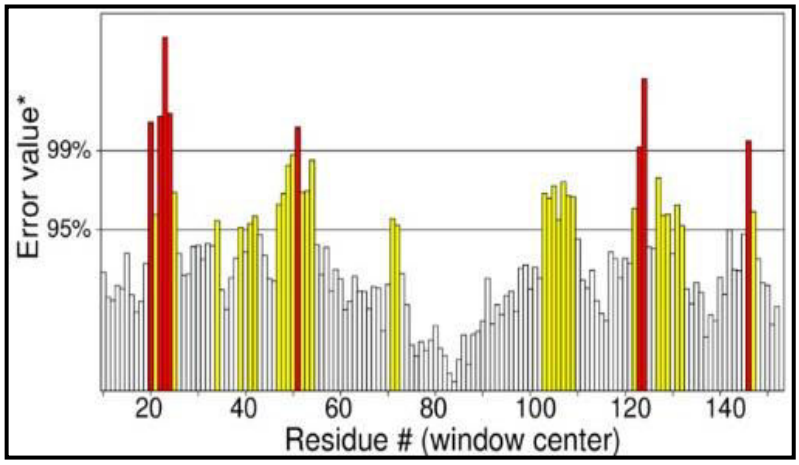


Fig. 8: ERRAT analysis of the target protein molecule, TNF-α.

Table 1: Docking result of ligands with the target protein molecule,IL-1β of endometritis

LIGANDS	ESTIMATED FREE ENERGY OF BINDING (KCal/Mol^{-1})	FINAL INTER MOLECULAR ENERGY, VDW + H BOND +DESOLV ENERGY, ELECTROSTATIC ENERGY (KCal/Mol^{-1})	NUMBER OF HYDROGEN BONDS	AMINO ACIDS INVOLVED IN HYDROGEN BOND INTERACTION
Stigmasterol	-8.63	-10.42, -10.37, -0.05	1	Glu 166
Hexadecenoic acid Methyl Ester	-5.56	-7.03, -6.99, -0.04	3	Ala 112, Tyr 113, Trp 108
n-hexadecanoic acid	-5.76	-7.23, -7.16, -0.08	2	Lys 190, Gln 197
Metronidazole (Standard)	-4.51	-5.41, -3.75, -1.65	4	Ala 112,Glu 166, Lys 190, Gln 197, Tyr 113

program is responsible for generating grid maps that depict the distribution of interaction energies. These maps are instrumental in guiding docking calculations, aiding in the determination of the overall interaction energy between Metronidazole and the target protein. This critical step facilitates a more precise and comprehensive understanding of the binding affinity between the ligand and the protein of interest, ultimately enhancing the accuracy of the docking process.

Molecular Docking:

Phytocompounds like stigmasterol, Hexadecanoic acid Methyl ester, and n-hexadecanoic acid were subjected to docking studies against the target proteins IL-1β and TNF-α using Autodock 4.2.6. This analysis highlighted promising hydrophobic and hydrogen bond interactions between these compounds and various amino acid residues within the target proteins. The docking results revealed binding energies of -8.63, -5.56, and -5.76 Kcal/mol, along with inhibition constants of 472.33, 13.33, and 9.49 μM, respectively, when stigmasterol, Hexadecanoic acid Methyl ester, and n-hexadecanoic acid were docked against the IL-1β target protein (Table 1). When these compounds were docked against TNF-α, the binding energies were -6.41, -5.51, and -5.26 Kcal/mol, with inhibition constants of 19.91, 13.33, and 21.94 μM, respectively (Table 2). In comparison, Metronidazole exhibited binding energies of -4.51 and -3.81 Kcal/mol, with inhibition constants of 492.30 and 1.62 μM when

Table 2: Docking result of ligands with the target protein molecule, TNF-α of endometritis

LIGANDS	ESTIMATED FREE ENERGY OF BINDING (KCal/Mol^{-1})	FINAL INTER MOLECULAR ENERGY, VDW + H BOND +DESOLV ENERGY, ELECTROSTATIC ENERGY (KCal/Mol^{-1})	NUMBER OF HYDROGEN BONDS	AMINO ACIDS INVOLVED IN HYDROGEN BOND INTERACTION
Stigmasterol	-6.41	-8.65, -8.55, -0.10	2	Gln 47, Asp 45
Hexadecenoic acid Methyl Ester	-5.51	-7.03, -6.96, -0.07	3	Pro 139, Glu 135, Ile 136
n-hexadecanoic acid	-5.76	-6.74, -6.69, -0.05	3	Ala 134, Trp 28, Asn 46
Metronidazole (Standard)	-3.81	-4.70, -3.62, -1.08	5	Leu 26, Trp 28 Asn 46, Ala 134 Ile 136

docked against IL-1Band TNF-α, respectively.

Based on these findings, stigmasterol displayed the highest binding affinity with both target proteins, IL-1β. Hexadecanoic acid Methyl ester and n-hexadecanoic acid also exhibited maximum binding energies, comparable to the standard Metronidazole. The observed amino acid interactions further supported the binding affinity of these phytocompounds with the target proteins. Specifically, stigmasterol formed one hydrogen bond with Glu 186, while Hexadecanoic acid Methyl ester formed three hydrogen bonds with Ala 112, Tyr 113, and Trp 108, and n-hexadecanoic acid formed two hydrogen bonds with Lys 190 and Gln 197 when docked against IL-1β. When docked against TNF-α, stigmasterol formed two hydrogen bonds with Gln 47 and Asp 45, Hexadecanoic acid Methyl ester formed three hydrogen bonds with Pro 139, Gln 135, and Ile 136, and n-hexadecanoic acid formed three hydrogen bonds with Ala 134, Trp 28, and Asn 46. Metronidazole, on the other hand, formed four hydrogen bonds with Ala 112, Glu 166, Lys 190, Gln 197, Tyr 113 when docked against IL-1β and five hydrogen bonds with Leu 26, Trp 28, Asn 46, Ala 134, and Ile 136 when docked against TNF-α. The two-dimensional docking interactions between these phytocompounds and the standard compound with the target proteins were accurately visualized using BIOVIA Discovery Studio Visualizer. This analysis included the examination of protein-ligand docked complex interactions, ligand interactions, receptor-ligand interactions such as aromatic edges and faces, interpolated charges, hydrogen bonds, hydrophobicity, and ionizability (Figs. 9, 10)

The docking results revealed that the phytocompounds stigmasterol which is present in *Musa* flowers have the potential to bind effectively to the target proteins IL-1β. On the other hand, TNF-α showed significantly lesser potential to bind with the ligands. As a result, it has been observed that they possess strong anti-inflammatory activity similar to that of Metronidazole in the context of endometritis.

Discussion

The findings of this *in silico* docking study provided valuable insights into the potential therapeutic efficacy of specific bioactive compounds derived from *Musa* flowers in addressing endometritis. The study focused on the interaction of stigmasterol, hexadecanoic acid methyl ester, and n-hexadecanoic acid with target

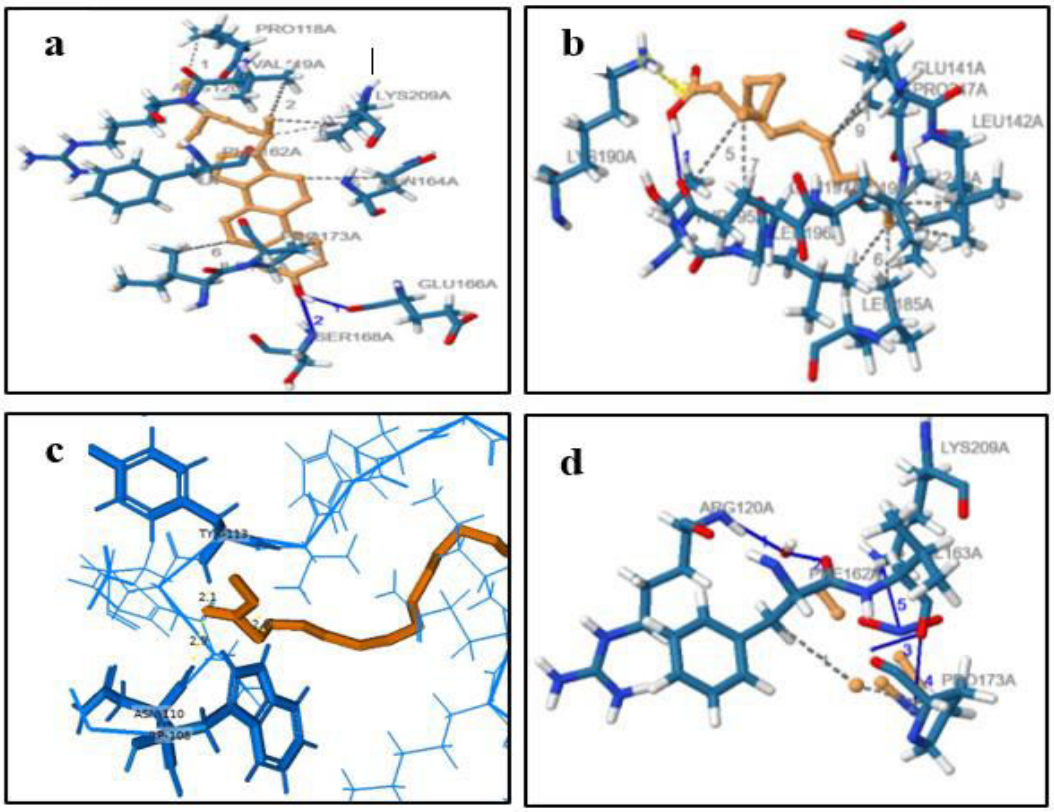


Fig. 9: Docking interaction of (a) Stigmasterol, (b) hexadecenoic acid Methyl Ester, (c) n-hexadecanoic acid and (d) Metronidazole with the target protein IL-1β of Endometritis.

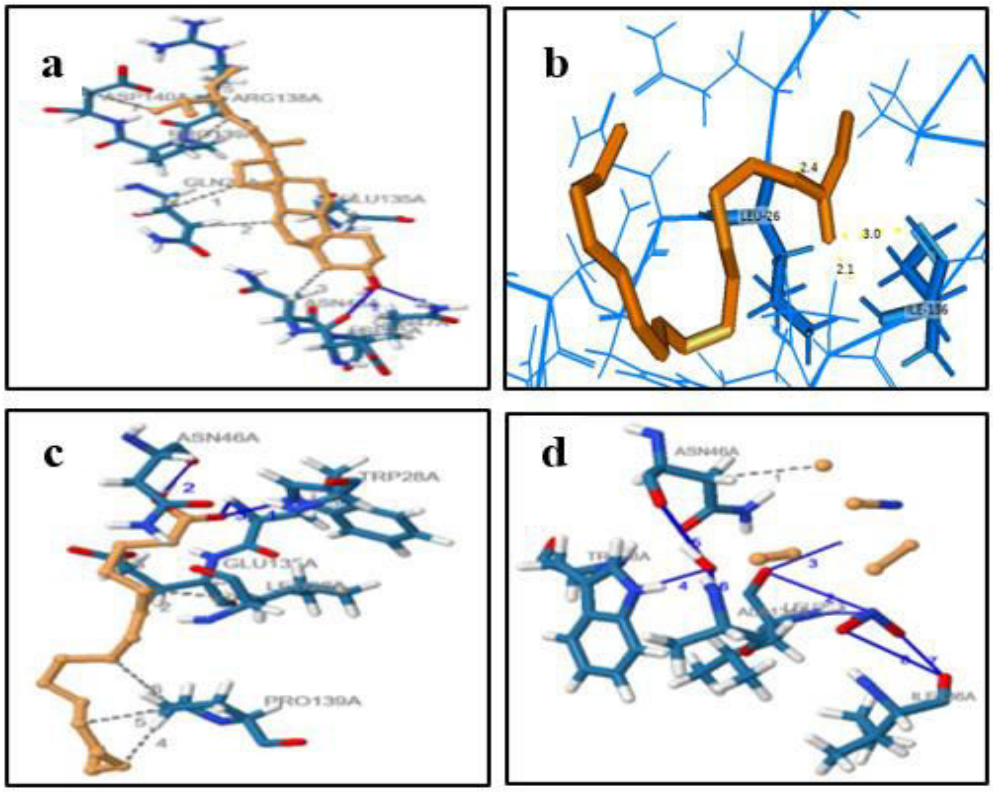


Fig. 10: Docking interaction of (a) Stigmasterol, (b) hexadecenoic acid Methyl Ester, (c) n-hexadecanoic acid and (d) Metronidazole with the target protein TNF-α of Endometritis.

proteins, Interleukin-1 Beta (IL-1β) and Tumor Necrosis Factor alpha (TNF-α), implicated in uterine inflammation. The results indicated that stigmasterol exhibited notably high binding affinities towards IL-1β, suggesting its potential as a promising candidate for the treatment of endometritis (Kaur *et al.*, 2011). The stereochemical quality assessment through Ramachandran plot analysis and ERRAT analysis of the target proteins (IL-1β and TNF-α) ensures the reliability of the protein structures used in the docking simulations. The high percentage of residues located within favored regions in the Ramachandran plot, coupled with favorable ERRAT quality factors, underscores the structural integrity of the target proteins. These rigorous validation steps enhance the credibility of the subsequent docking analyses and affirm the reliability of the findings (Colovos and Yeates, 1993).

The molecular docking results had revealed that stigmasterol demonstrated the highest binding affinity with both IL-1β and TNF-α among the tested compounds. This suggests that stigmasterol, a bioactive compound found in *Musa* flowers, has the potential to effectively interact with the target proteins associated with endometritis. The observed hydrogen bond interactions between stigmasterol and key amino acid residues further support the specificity of its binding to the target proteins (Laskowski *et al*., 1993*)*. It is noteworthy that the binding energies of stigmasterol were comparable to, or even higher than, the standard drug Metronidazole. This underscores the potential of stigmasterol as a natural alternative for the treatment of endometritis, providing a basis for further exploration and development. The interactions between stigmasterol and the target proteins were visualized through advanced tools, allowing for a comprehensive understanding of the molecular mechanisms involved in the binding process (Xia, 2017).

Hexadecanoic acid methyl ester and n-hexadecanoic acid further exhibited substantial binding affinities, comparable to the standard drug, suggesting their potential as alternative therapeutic agents. The identified hydrogen bond interactions between these compounds and the target proteins contribute to the understanding of their binding mechanisms. The current study aligns with the growing recognition of the medicinal properties of plant-derived compounds and their potential applications in modern healthcare (Bikadi *et al*., 2009). By specifically focusing on endometritis, a significant women's health concern, the research contributes to addressing the unmet medical needs in this domain. The use of *in silico* docking techniques allows for a systematic and cost-effective screening of potential therapeutic compounds, providing a foundation for future experimental validations.

In conclusion, the *in silico* docking study provides compelling evidence for the potential anti-inflammatory activity of *Musa* floret-derived compounds, particularly stigmasterol, in the context of endometritis. These findings open avenues for further research, emphasizing the need for translational studies to validate the efficacy and safety of these compounds for clinical applications. The integration of Phyto compounds with modern scientific approaches represents a synergistic strategy for advancing healthcare solutions.

Novelty and significance of the present includes:

(1) This study uncovers new anti-inflammatory properties in compounds from *Musa* flowers (stigmasterol, Hexadecanoic acid Methyl ester, n-hexadecanoic acid) for treating endometritis.

(2) *Musa* flowers, with their rich variety of phytocompounds, can be considered as safe, natural dietary supplements for managing endometritis, without any side effects.

(3.) The significance of this study lies in *Musa* flowers' potential as an anti-inflammatory agent, with implications extending to the prevention and treatment of ovarian cancer. These flowers are rich in valuable secondary metabolites, marking a

novel avenue for addressing a broader spectrum of health challenges

Conclusion

This study provides evidence of the potential therapeutic benefits of phytocompounds derived from *Musa* species in the management of endometritis, a condition characterized by uterine inflammation. Through rigorous *in silico* molecular docking analyses, the research highlights the remarkable binding affinities of stigmasterol, hexadecanoic acid methyl ester, and n-hexadecanoic acid to key inflammatory proteins, Interleukin-1 Beta (IL-1β) and Tumor Necrosis Factor Alpha (TNF-α). Stigmasterol, in particular, emerges as a standout candidate with the highest binding affinity with IL-1β. These findings suggest that natural compounds from *Musa* species have the potential to serve as safe and effective alternatives to synthetic drugs for addressing endometritis. Moreover, the structural validation and detailed interaction analyses provide a strong foundation for further research and potential clinical applications. Although, the study underscores the importance of conducting subsequent *in vitro* and *in vivo* investigations to confirm the safety and efficacy of these phytocompounds, bringing us one step closer for developing natural remedies from plants.

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