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IN SILICO MOLECULAR DOCKING AND ADME PROFILING OF SELECTED SIDDHA HERBAL PHYTOCONSTITUENTS AGAINST PHOSPHODIESTERASE-5 AND NITRIC OXIDE SYNTHASE TARGETS FOR APHRODISIAC ACTIVITY

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ABSTRACT

Background: Male sexual dysfunction, including erectile dysfunction, reduced libido, and impaired reproductive performance, represents a growing global health concern that adversely affects quality of life and psychosocial well-being. Penile erection is primarily regulated by nitric oxide (NO)-mediated vasodilation and cyclic guanosine monophosphate (cGMP) signaling pathways. Phosphodiesterase-5 (PDE-5), which hydrolyzes cGMP, and Nitric Oxide Synthase (NOS), which catalyzes nitric oxide production, are recognized as key therapeutic targets for the management of erectile dysfunction. Siddha medicine describes several medicinal plants under the concepts of Thaathu Viruthi (enhancement of reproductive tissues) and Aanmai Perukki (promotion of virility), which are traditionally used to improve sexual vigor, fertility, and reproductive health. **Objective:** The present study aimed to evaluate the aphrodisiac potential of selected Siddha medicinal phytoconstituents through molecular docking and ADME profiling against PDE-5 and NOS targets. **Materials and Methods:** Major phytoconstituents, namely Aegeline, Arginine, L-DOPA, Smilagenin, and Quercetin, derived from Aegle marmelos, Prunus dulcis, Mucuna pruriens, Smilax china, and Hibiscus rosa-sinensis, respectively, were selected based on their traditional use and reported pharmacological activities. Molecular docking studies were performed using AutoDock Vina against PDE-5 (PDB ID: 2ZOB) and NOS (PDB ID: 2FLQ). Pharmacokinetic characteristics and drug-likeness properties were evaluated using SwissADME. **Results:** Among the investigated compounds, Smilagenin demonstrated the strongest binding affinity toward PDE-5 (-9.1 kcal/mol) and NOS (-10.6 kcal/mol), indicating superior interaction stability with both molecular targets. Quercetin (-8.1 kcal/mol) and Aegeline (-7.4 kcal/mol) also exhibited significant binding affinity against PDE-5, while Aegeline (-10.3 kcal/mol) and Quercetin (-9.3 kcal/mol) showed strong interactions with NOS. ADME analysis revealed favorable pharmacokinetic profiles, high gastrointestinal absorption, and acceptable drug-likeness characteristics for most compounds. **Conclusion:** The findings suggest that Smilagenin, Aegeline, and Quercetin possess promising aphrodisiac potential through modulation of nitric oxide signaling and cGMP-mediated erectile pathways. The study provides scientific evidence supporting the traditional Siddha use of these medicinal plants in enhancing male reproductive health and highlights their potential for further development as natural therapeutic agents for sexual dysfunction.

KEYWORDS: Aphrodisiac activity, Siddha medicine, Phosphodiesterase-5, Nitric Oxide Synthase, Molecular docking, ADME profiling, Erectile dysfunction, Male reproductive health.

INTRODUCTION

Sexual health is an essential component of overall well-being and quality of life. Male sexual dysfunction, particularly erectile dysfunction (ED), reduced libido, infertility, and impaired reproductive performance, has emerged as a significant global health challenge affecting millions of men worldwide. Epidemiological studies indicate that the prevalence of erectile dysfunction is steadily increasing due to aging, metabolic disorders, cardiovascular diseases, diabetes mellitus, hormonal

imbalance, psychological stress, and unhealthy lifestyle practices. The condition not only affects physical health but also has profound psychological and social consequences, leading to reduced self-esteem, interpersonal difficulties, and diminished quality of life.

Penile erection is a highly coordinated neurovascular phenomenon involving the integration of neural, vascular, endocrine, and psychological factors. At the molecular level, nitric oxide (NO) serves as the principal mediator of erectile function. Nitric oxide released from endothelial cells and non-adrenergic non-cholinergic neurons activates soluble guanylate cyclase, resulting in increased production of cyclic guanosine monophosphate (cGMP). Elevated cGMP concentrations promote relaxation of corpus cavernosum smooth muscles, thereby facilitating increased penile blood flow and erection. The enzyme Phosphodiesterase-5 (PDE-5) regulates this process by hydrolyzing cGMP into inactive metabolites, ultimately terminating the erectile response. Similarly, Nitric Oxide Synthase (NOS) plays a critical role in catalyzing nitric oxide production, making both PDE-5 and NOS important therapeutic targets for the management of erectile dysfunction.

Although synthetic PDE-5 inhibitors such as sildenafil, tadalafil, and vardenafil have revolutionized the treatment of erectile dysfunction, their long-term use may be associated with adverse effects including headache, dizziness, flushing, visual disturbances, hypotension, and drug interactions. Furthermore, these agents primarily provide symptomatic relief without addressing broader aspects of reproductive health and vitality. Consequently, there is growing interest in the identification of plant-derived bioactive compounds with improved safety profiles and multifunctional therapeutic benefits.

Traditional medical systems have historically played an important role in the management of sexual disorders. Siddha medicine, one of the oldest indigenous systems of medicine practiced in South India, emphasizes the maintenance of physical, mental, and reproductive health through the equilibrium of the three fundamental humors: Vatham, Pitham, and Kabam. According to Siddha literature, reproductive strength and sexual vitality are closely associated with the nourishment of the seven body constituents (Udal Thathukkal), particularly Sukkilam (reproductive tissue). Siddha therapeutics describes several formulations and medicinal plants under the concepts of Thaathu Viruthi (enhancement of reproductive tissues), Aanmai Perukki (promotion of virility), and Kayakalpam (rejuvenation therapy), which are traditionally used to improve libido, semen quality, fertility, and sexual performance.

Among the medicinal plants extensively documented in Siddha texts, Vilvam (Aegle marmelos), Vathumai (Prunus dulcis), Punaikali (Mucuna pruriens), Parangipattai (Smilax china), and Semparuthi (Hibiscus rosa-sinensis) are recognized for their rejuvenating and aphrodisiac properties. These plants contain diverse classes of bioactive phytoconstituents including alkaloids, flavonoids, steroidal saponins, phenolic compounds, amino acids, and antioxidants that may influence reproductive physiology through modulation of hormonal balance, nitric oxide signaling, antioxidant defense mechanisms, and neuroendocrine pathways. Previous pharmacological investigations have reported fertility-enhancing, spermatogenic, antioxidant, adaptogenic, and libido-promoting activities for these medicinal plants, supporting their traditional therapeutic relevance.

Advances in computational drug discovery have facilitated the identification of potential bioactive compounds through molecular docking and pharmacokinetic prediction studies. Molecular docking provides valuable insights into ligand–protein interactions, binding affinity, and target specificity, thereby enabling the rapid screening of phytoconstituents against disease-related molecular targets. In addition, ADME (Absorption, Distribution, Metabolism, and Excretion) profiling serves as an essential tool for evaluating pharmacokinetic behavior, oral bioavailability, and drug-likeness characteristics during the early stages of drug development.

Despite the extensive traditional use of Siddha medicinal plants for improving male reproductive health, scientific evidence elucidating their molecular interactions with PDE-5 and NOS remains limited. Furthermore, comparative pharmacokinetic evaluation of their major phytoconstituents has not been comprehensively investigated. Therefore, the present study was undertaken to evaluate the molecular docking interactions and ADME profiles of selected phytoconstituents from Siddha medicinal plants against PDE-5 and NOS targets, with the aim of providing scientific validation for their traditional aphrodisiac use and identifying promising lead compounds for the management of male sexual dysfunction.

MATERIALS AND METHODS

Study Design

The present study was designed as an in silico molecular docking and pharmacokinetic investigation to evaluate the aphrodisiac potential of selected phytoconstituents obtained from Siddha medicinal plants traditionally used for enhancing male reproductive health. Molecular docking was performed to assess the binding interactions of selected phytoconstituents against Phosphodiesterase-5 (PDE-5) and Nitric Oxide Synthase (NOS), two key molecular targets associated with erectile function and sexual performance. In addition, ADME profiling was carried out to evaluate the pharmacokinetic suitability and drug-likeness characteristics of the selected compounds.

Selection of Medicinal Plants

The medicinal plants selected for the present investigation were based on their extensive use in Siddha literature under the concepts of Thaathu Viruthi (enhancement of reproductive tissues), Aanmai Perukki (promotion of virility), and Kayakalpam (rejuvenation therapy). The selected plants included Vilvam (Aegle marmelos), Vathumai (Prunus dulcis), Punaikali (Mucuna pruriens), Parangipattai (Smilax china), and Semparuthi (Hibiscus rosa-sinensis). These plants have traditionally been employed to improve libido, semen quality, fertility, reproductive strength, and overall sexual wellness.

Table 1: Major Alkaloids/Bioactive Constituents and Family of Selected Plants Used for Aphrodisiac Activity.

Compound	Molecular Weight g/mol	Molecular formula	H- bond donor	H- bond acceptor
Vilvam	*Aegle marmelos*	Rutaceae	Aegeline, Skimmianine, Marmeline, Fagarine	Improves reproductive function, antioxidant protection of testicular tissue, enhances libido
Vathumai (Almond)	*Prunus dulcis*	Rosaceae	rich in Arginine, Flavonoids, Tocopherols, Phytosterols	Enhances nitric oxide production, improves sperm quality and sexual vigor
Punaikali (Poonaikali)	*Mucuna pruriens*	Fabaceae	L-DOPA, Mucunine, Mucunadine, Prurienine, Nicotine (trace)	Increases dopamine levels, testosterone production, spermatogenesis, and libido
Parangipattai	*Smilax china*	Smilacaceae	Smilagenin, Sarsapogenin, Diosgenin-related steroidal saponins	Adaptogenic activity, enhancement of reproductive health and sexual stamina
Semparuthi	*Hibiscus rosa-sinensis*	Malvaceae	Alkaloids (trace), Flavonoids, Quercetin, Anthocyanins, Hibiscetin	Improves reproductive hormone balance and antioxidant protection

Ligand Preparation

The chemical structures of the selected phytoconstituents, namely Aegeline, Arginine, L-DOPA, Smilagenin, and Quercetin, were retrieved from the PubChem database in Structure Data File (SDF) format. The downloaded structures were converted into Protein Data Bank (PDB) format using Open Babel software. Energy minimization was performed to obtain stable conformations suitable for docking studies. Hydrogen atoms were added and the optimized ligand structures were subsequently converted into PDBQT format using AutoDock Tools for molecular docking analysis.

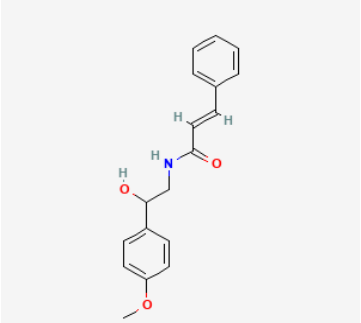
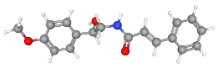
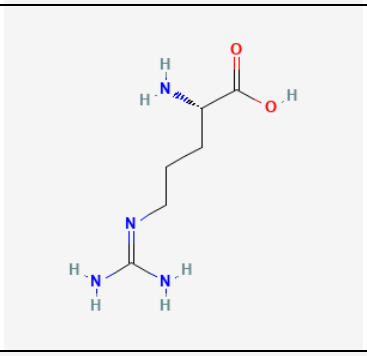
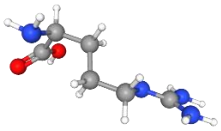
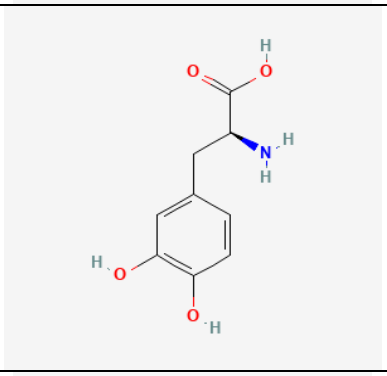
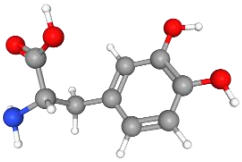
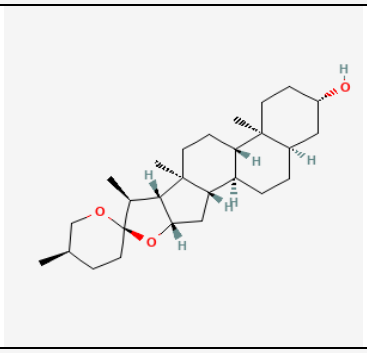
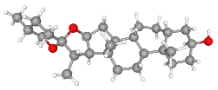
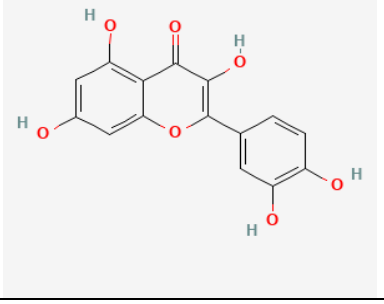
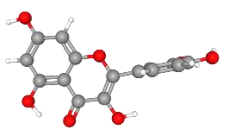
The identified phytochemicals along with their Molecular weight, Molecular formula, H-bond donor, H-bond acceptor, Rotatable bonds were listed in table 1.

Table 2: Chemical properties of selected Ligands.

Compound	Molecular Weight g/mol	Molecular formula	H- bond donor	H- bond acceptor	Rotatable bonds
Aegeline	297.35	$C_{18}H_{19}NO_3$	7	3	2
Arginine	174.20	$C_6H_{14}N_4O_2$	5	4	4
L-DOPA	197.19	$C_9H_{11}N0_4$	3	5	4
Smilagenin	416.64	$C_{27}H_{44}O_3$	0	3	1
Quercetin	302.24	$C_{15}H_{17}O_7$	1	7	5

Each selected phytochemical was prepared for docking by obtaining its 2D and 3D structures from Pubchem database (https://pubchem.ncbi.nlm.nih.gov/) in SDF format and converted to PDB format, followed by energy minimization to ensure stable conformations and reduced steric hindrance. Each ligand was then parameterized with appropriate partial charges and rotatable bonds to enable flexible interactions with the target protein. The structures of the ligands are shown in Table 3

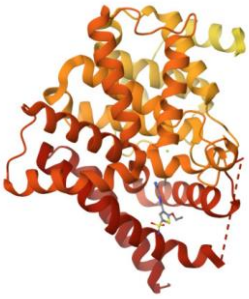
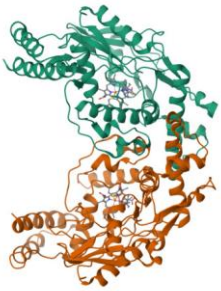
Table 3: 2D and 3D structure of the selected Ligands.

Compound	2D Structure	3D structure
Aegeline		
Arginine		
L-DOPA		
Smilagenin		
Quercetin		

Preparation of Target

The three-dimensional crystal structures of the target proteins were obtained from the Protein Data Bank (PDB). Phosphodiesterase-5 (PDE-5) was selected due to its role in regulating cyclic guanosine monophosphate (cGMP) degradation, while Nitric Oxide Synthase (NOS) was selected because of its involvement in nitric oxide production and vasodilation. The three-dimensional crystal structures of the target proteins were obtained from the rcsb.org. Water molecules, co-crystallized ligands, and unwanted heteroatoms were removed from the protein structures. Polar hydrogen atoms and Kollman charges were added using AutoDock Tools, and the prepared proteins were saved in PDBQT format.

Table 4: Selected targets and their action.

Target protein	PDB ID	Structure	Role in Aphrodisiac Activity
Phosphodiesterase-5	2ZOB		Regulates cGMP degradation and erectile function
Nitric oxide synthase	2FLQ		Catalyzes nitric oxide production and penile vasodilation

Molecular Docking Analysis

Molecular docking studies were performed using AutoDock Vina software to predict the binding affinity and interaction patterns between the selected phytoconstituents and target proteins. Grid boxes were generated around the active sites of the proteins to ensure accurate ligand binding simulation.

The docking protocol was executed using the Lamarckian Genetic Algorithm, and the best docking pose for each ligand was selected based on the lowest binding energy (kcal/mol). Lower binding energy values indicate stronger interaction and greater stability of the ligand–protein complex.

The docking results were analyzed using Discovery Studio Visualizer to identify hydrogen bonding interactions, hydrophobic interactions, van der Waals interactions, and amino acid residues involved in ligand binding.

ADME and Drug-Likeness Prediction

The pharmacokinetic properties of the selected phytocompounds were evaluated using the SwissADME web server to determine their drug-likeness, absorption, distribution, metabolism, and excretion characteristics. Parameters including gastrointestinal absorption, blood–brain barrier permeability, cytochrome P450 inhibition, P-glycoprotein interaction, skin permeation, Lipinski's rule of five, bioavailability score, and medicinal chemistry properties were analyzed.

RESULTS AND DISCUSSION

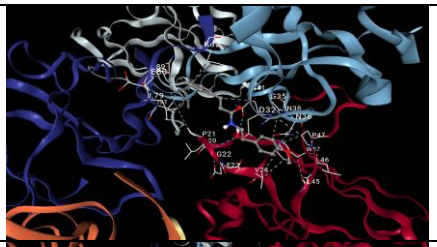
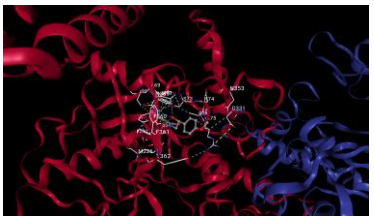
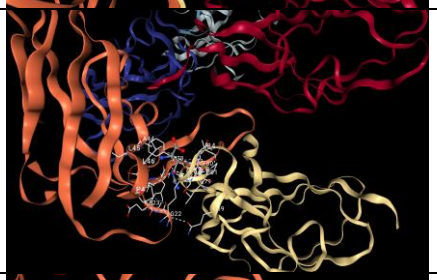
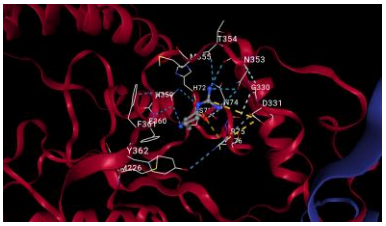
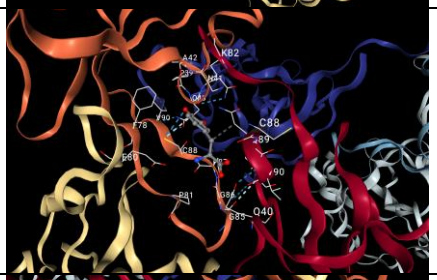
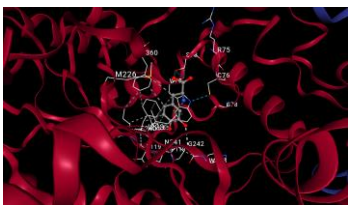
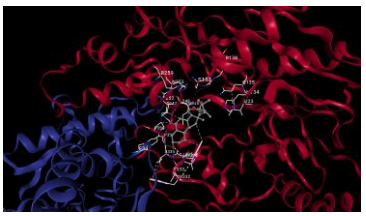
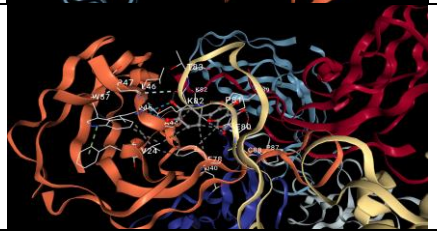
The aphrodisiac potential of selected Siddha phytoconstituents was evaluated through molecular docking studies against two crucial molecular targets involved in erectile physiology, namely Phosphodiesterase-5 (PDE-5) and Nitric Oxide Synthase (NOS). PDE-5 regulates the degradation of cyclic guanosine monophosphate (cGMP), while NOS catalyzes the production of nitric oxide (NO), a major mediator of penile vasodilation. Modulation of these targets enhances erectile function through increased blood flow and smooth muscle relaxation. Therefore, compounds exhibiting strong interactions with both targets may possess significant therapeutic potential in the management of male sexual dysfunction.

Table 5: Binding energies of different compounds.

Compounds	PDE-5		NOS	
	No. of Interactions	Highest Binding Free Energy (Kcal/ mol)	No. of Interactions	Highest Binding Free Energy Kcal/ mol
Aegeline	16	-7.4	10	-10.3
Arginine	20	-5.1	20	-6.0
L-DOPA	20	-5.9	20	-6.9
Smilagenin	20	-9.1	18	-10.6
Quercetin	20	-8.1	19	-9.3

The docking scores obtained in the present investigation indicate strong molecular interactions between the selected phytoconstituents and the active sites of PDE-5 and NOS. Compounds exhibiting docking scores below −7.0 kcal/mol are generally considered to possess significant binding affinity, suggesting potential biological activity against the selected targets.

Table 6: Docking interactions of Different compounds.

Compound	PDE-5	NOS
Aegeline		
Arginine		
L-DOPA		
Smilagenin		
Quercetin		

The docking results revealed significant differences in binding affinity among the investigated phytoconstituents. Among all compounds, Smilagenin demonstrated the strongest interaction with both molecular targets, exhibiting binding energies of -9.1 kcal/mol against PDE-5 and -10.6 kcal/mol against NOS. The highly negative binding energies indicate the formation of stable ligand–protein complexes and suggest superior inhibitory and modulatory potential. The steroidal structure of Smilagenin may facilitate extensive hydrophobic interactions within the active sites of both proteins, thereby enhancing binding stability and biological activity.

Aegeline exhibited considerable affinity toward both targets, particularly NOS, where it showed a docking score of -10.3 kcal/mol. The strong interaction observed for Aegeline suggests its potential role in enhancing nitric oxide-mediated vasodilatory responses. The compound demonstrated a comparatively lower but still significant affinity toward PDE-5 (-7.4 kcal/mol), indicating a possible dual mechanism of action involving both nitric oxide production and cGMP regulation.

Quercetin displayed favorable docking scores of -8.1 kcal/mol and -9.3 kcal/mol against PDE-5 and NOS, respectively. The multiple hydroxyl groups present in Quercetin facilitate hydrogen bond formation and improve interaction stability within the active binding regions of both proteins. In addition, the antioxidant properties of Quercetin may contribute to the preservation of endothelial nitric oxide activity by reducing oxidative stress.

L-DOPA demonstrated moderate binding affinity toward PDE-5 (-5.9 kcal/mol) and NOS (-6.9 kcal/mol). Although its direct interaction with the target proteins was comparatively weaker, L-DOPA remains pharmacologically important because it serves as a precursor of dopamine, a neurotransmitter closely associated with sexual motivation, libido, and reproductive behavior.

Arginine exhibited the lowest docking scores among the investigated compounds, showing binding energies of -5.1 kcal/mol and -6.0 kcal/mol against PDE-5 and NOS, respectively. Despite its relatively weaker docking performance, Arginine possesses established physiological significance as the primary substrate for nitric oxide synthesis. Therefore, its aphrodisiac effects may be mediated predominantly through enhancement of endogenous nitric oxide production rather than direct protein binding.

ADME PROPERTIES

Table 7: ADME properties of Different compounds.

Compounds	GI absorption	BBB permeant	P-gp	CYP1A2 inhibitors	CYP2C19 inhibitors	CYP2C9 inhibitors	CYP2D6 inhibitors	CYP3A4 inhibitors	Log Kp (cm/s)
Aegeline	High	Yes	No	No	No	No	No	Yes	-6. 61
Arginine	Low	No	Yes	No	No	Yes	No	Yes	-1. 90
L-DOPA	High	No	Yes	No	No	Yes	No	Yes	-2. 20
Smilagenin	High	Yes	Yes	No	No	Yes	No	Yes	-2.74
Quercetin	High	No	Yes	Yes	Yes	No	Yes	Yes	-7. 14

Drug-likeness

Table 8: Drug-likeness of the compounds.

Compounds	Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability
Aegeline	Yes 0 violations	Yes	Yes	Yes	No 1 violation	0.55
Arginine	Yes 1 violation	No 3 violations	Yes	No 1 violation	No 2 violations	0.55
L-DOPA	Yes 1 violation	Yes	Yes	Yes	No 2 violations	0.55
Smilagenin	Yes 1 violation	No 2 violations	Yes	No 1 violation	No 2 violations	0.55
Quercetin	Yes 0 violation	Yes	Yes	Yes	Yes	0.55

The consistently superior performance of Smilagenin against both targets suggests that it may be the principal bioactive constituent responsible for the aphrodisiac activity traditionally attributed to Smilax china. Similarly, Aegeline and Quercetin demonstrated strong binding affinities and may contribute significantly to the reproductive health benefits associated with Aegle marmelos and Hibiscus rosa-sinensis.

ADME Analysis

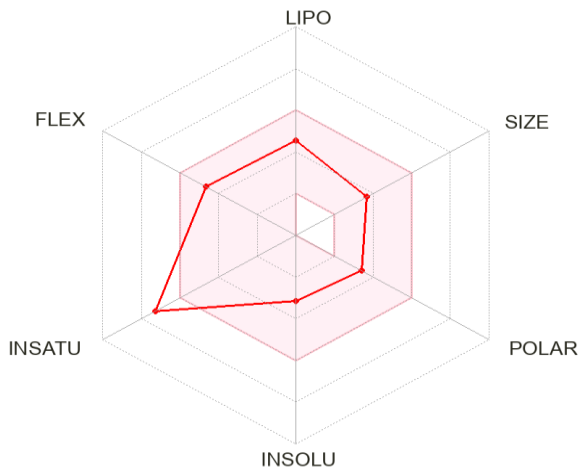
The pharmacokinetic evaluation demonstrated favorable drug-likeness characteristics for most of the selected phytoconstituents. High gastrointestinal absorption was predicted for Aegeline, Smilagenin, L-DOPA, and Quercetin, indicating their suitability for oral administration. Most compounds complied with Lipinski's Rule of Five and exhibited acceptable

bioavailability scores, suggesting promising pharmacokinetic behavior.

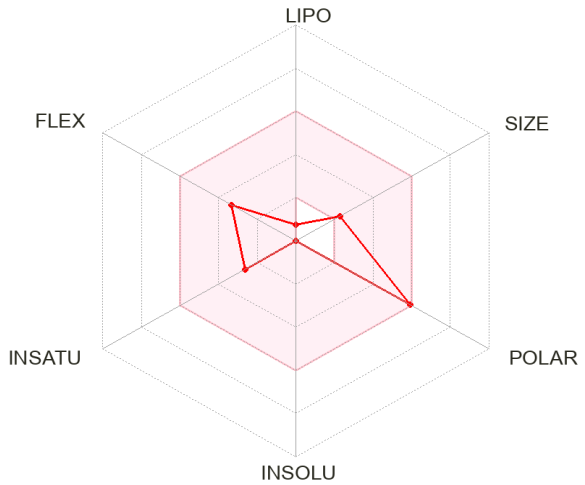
The combination of strong docking affinity and favorable ADME properties observed for Smilagenin, Aegeline, and Quercetin highlights their potential as lead molecules for the development of plant-derived aphrodisiac therapeutics. The findings also provide molecular evidence supporting the Siddha concept of Thaathu Viruthi and Aanmai Perukki, wherein these medicinal plants are traditionally employed to strengthen reproductive tissues, improve virility, and enhance sexual performance.

Overall, the study demonstrates that the selected Siddha phytoconstituents interact effectively with key molecular targets regulating erectile physiology and possess favorable pharmacokinetic profiles, thereby supporting their potential therapeutic application in the management of male sexual dysfunction.

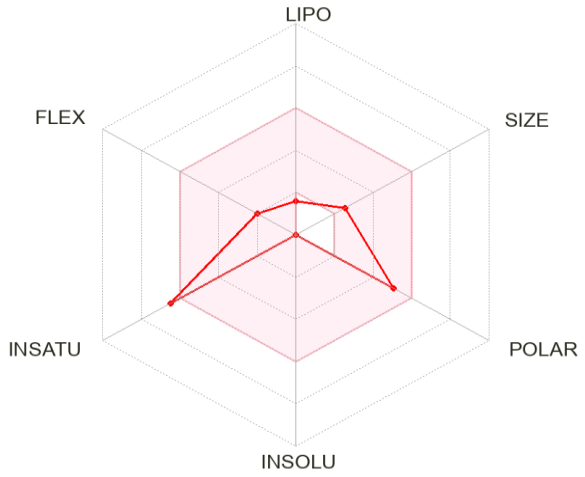
Aegeline



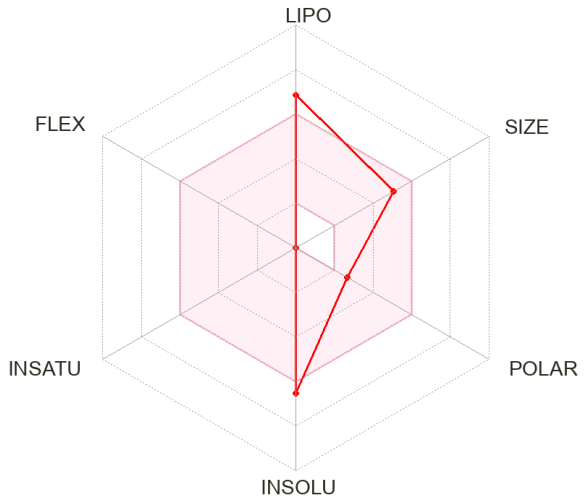
Arginine



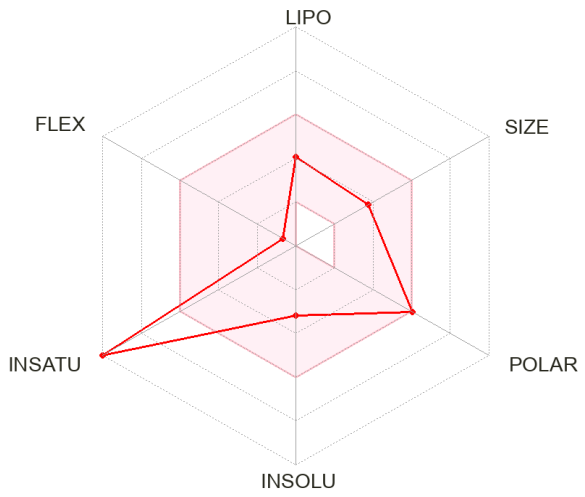
L-DOPA



Smilagenin



Quercetin



CONCLUSION

The present study scientifically evaluated the aphrodisiac potential of selected Siddha medicinal phytoconstituents through molecular docking and ADME profiling against two key molecular targets involved in erectile physiology, Phosphodiesterase-5 (PDE-5) and Nitric Oxide Synthase (NOS). The findings demonstrated that all selected compounds exhibited varying degrees of interaction with both targets, indicating their potential role in the modulation of male sexual function.

Among the investigated phytoconstituents, Smilagenin exhibited the strongest binding affinity against both PDE-5 (-9.1 kcal/mol) and NOS (-10.6 kcal/mol), suggesting superior interaction stability and greater therapeutic potential. Quercetin and Aegeline also demonstrated significant binding affinities toward both targets, whereas L-DOPA and Arginine showed moderate interactions. The strong binding affinities observed for Smilagenin, Aegeline, and Quercetin indicate their ability to influence nitric oxide signaling and cGMP-mediated erectile pathways, which are essential for penile vasodilation and erectile response.

The ADME analysis further revealed favorable pharmacokinetic characteristics, including good gastrointestinal absorption, acceptable bioavailability, and compliance with major drug-likeness criteria for most of the selected phytoconstituents. These findings support their potential suitability as orally active therapeutic candidates.

From a Siddha perspective, the investigated medicinal plants are traditionally categorized under Thaathu Viruthi, Aanmai Perukki, and Kayakalpa therapies, which are intended to strengthen reproductive tissues, improve virility, and enhance overall reproductive wellness. The present molecular docking findings provide a scientific basis for these traditional claims by demonstrating the interaction of their major phytoconstituents with molecular targets directly associated with erectile function.

Overall, the study provides computational evidence supporting the traditional use of Aegle marmelos, Prunus dulcis, Mucuna pruriens, Smilax china, and Hibiscus rosa-sinensis in the management of male sexual dysfunction. Among the investigated compounds, Smilagenin emerged as the most promising lead molecule and may be considered a potential candidate for further drug development. However, additional in vitro studies, animal experiments, mechanistic investigations, and clinical trials are necessary to validate the therapeutic efficacy and safety of these phytoconstituents before their application in clinical practice.

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