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Original Research Article

In silico ADMET Profiling of Flavonoids as Potential Phosphodiesterase-5 Inhibitors in the Management of Erectile Dysfunction

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Abstract

Purpose*:* Erectile dysfunction (ED) affects millions of men globally, and its pharmacological management relies mainly on agents such as sildenafil, tadalafil, avanafil, and vardenafil. Although effective, these drugs are associated with adverse effects, creating a need for therapeutic alternatives with improved safety, efficacy, and bioavailability profiles. This study evaluated the preclinical absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles of the flavonoids apigenin, kaempferol, and naringin as potential oral therapeutic candidates for ED.
Methods*:* In silico ADMET profiling was conducted using SwissADME and ProTox-II to predict key pharmacokinetic and safety parameters, including solubility, gastrointestinal absorption, blood–brain barrier permeability, cytochrome P450 interactions, drug-likeness, and toxicity risks. Sildenafil served as the reference standard.
Results*:* Apigenin and kaempferol exhibited favorable oral bioavailability and drug-likeness, consistent with Lipinski's, Veber's, Egan's, and Muegge's rules. These properties were supported by their optimal molecular weights, moderate topological polar surface areas, and minimal molecular flexibility (apigenin: 270.24 g/mol, TPSA 90.90 Å2; kaempferol: 286.24 g/mol, TPSA 111.13 Å2). Naringin, however, displayed limited absorption potential due to its higher molecular weight (580.53 g/mol) and large polar surface area (225.06 Å2). All compounds demonstrated acceptable predicted safety profiles, with no signals for mutagenicity or hepatotoxicity.
Conclusion: The findings indicate that apigenin, kaempferol, and naringin may offer safer, more accessible alternatives or adjuncts to conventional ED medications such as sildenafil. Their favorable predicted pharmacokinetic and toxicity profiles support further exploration, and experimental validation in in vitro and in vivo models is recommended to confirm therapeutic potential.

Keywords: Flavonoids; adsorption; distribution; toxicity; In silico; Apigenin; Kaempferol; Naringin

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INTRODUCTION

Erectile dysfunction (ED), historically referred to as impotence, is defined as the recurrent or persistent inability, partial or complete, to achieve or maintain an erection sufficient for satisfactory sexual intercourse activity under appropriate stimulation.[1] It is a highly prevalent condition, affecting approximately 40% of men aged between 40 and 70 years.[2] The erectile response involves psychological, hormonal, neurological, vascular, and cavernosal factors; hence impairment in any of these can lead to ED pathology.[3] Beyond its physiological aspects, ED markedly diminishes quality of life, adversely affecting mental health, self-esteem, interpersonal relationships, and overall well-being.[4-6] The disorder also impacts sexual partners, who may experience emotional distress, decreased self-worth, and reduced sexual satisfaction.[7]

The advent of phosphodiesterase type 5 inhibitors (PDE5i), including sildenafil, tadalafil, vardenafil, and avanafil, revolutionized the pharmacological management of ED.[8] Despite their clinical efficacy, these agents are associated with adverse and toxic side effects such as priapism, headache, myalgia, dyspepsia, rhinitis, visual disturbances, and blood pressure fluctuations, with some reports suggesting association with melanoma and prostate cancer.[9] These safety concerns highlight the need to explore alternative therapeutic options for ED management with potentially improved safety, efficacy, and bioavailability. Numerous phytochemicals, including flavonoids, alkaloids, saponins, terpenoids, and polysaccharides, have demonstrated potential to enhance erectile function and are commonly employed in traditional medicine for ED management.[10]

Among these bioactive phytochemicals, the flavonoids apigenin (5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one), kaempferol (3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one), and naringin (4′,5,7-trihydroxyflavanone-7-rhamnoglucoside) are widely distributed secondary metabolites present in medicinal plants and herbs.[11-13] These compounds have exhibited diverse pharmacological properties,[14] including vasodilatory, antioxidant, cytoprotective, and anti-inflammatory effects,[15-19] which might support their development as therapeutic agents for ED management. Critically, no previous work has systematically assessed the absorption, distribution, metabolism, and excretion (ADME) and toxicity profiles of these compounds, specifically in the context of PDE5 inhibition, leaving uncertainty about their suitability as viable oral therapeutic candidates for ED management.

A critical determinant of clinical success in drug discovery is the ADME properties of candidate molecules, while toxicity evaluation is essential for assessing potential risks to humans and the environment.[20] Advances in computer-aided drug design have enabled accurate prediction of ADMET profiles, serving as an efficient and cost-effective complement to experimental testing.[21] Characterizing the ADMET properties of apigenin, naringin, and kaempferol is thus fundamental for predicting pharmacokinetic behavior, optimizing dosing, and mitigating toxicity risks. This study, therefore, employs in silico tools to predict the ADME parameters and toxicity profile of these flavonoids, thereby providing evidence which supports their potential development as safe and effective oral therapeutic agents for ED management.

MATERIALS AND METHODS

Pharmacokinetic and Drug-Likeness Prediction

The pharmacokinetic and drug-likeness properties of apigenin, kaempferol, and naringin, were predicted using the SwissADME web tool (http://www.swissadme.ch/, accessed on 20 September, 2025), and compared with those of sildenafil (standard reference). The analysis covered key parameters including gastrointestinal (GI) absorption, blood–brain barrier (BBB) permeability, P-glycoprotein (P-gp) substrate potential, lipophilicity (Log Po/w), aqueous solubility (Log S), and cytochrome P450 inhibition profiles. Additionally, physicochemical descriptors, such as molecular weight, topological polar surface area (TPSA), number of rotatable bonds, were determined, alongside drug-likeness rule (Lipinski, Ghose, Veber, Egan, and Muegge rules) and medicinal chemistry filters (PAINS alerts, Brenk alerts, and synthetic accessibility).[22] Canonical Simplified Molecular Input Line Entry System (SMILES) notations of all compounds were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov, accessed on 20 September, 2025) for input into SwissADME web tool. The results were exported in a unified csv file format and visualized using bioavailability radar plots and the Brain or Intestinal Estimated permeation method (BOILED-Egg) model to aid interpretation of oral bioavailability and central nervous system (CNS) permeability.[23]

Toxicity Prediction

Toxicity profiles were predicted using the ProTox-II platform (version 3.0; https://tox.charite.de/protox3/, accessed on 20 September, 2025), a validated web-based tool for in silico assessment of small-molecule toxicity.[24] Canonical SMILES strings of all compounds were submitted into the server to estimate oral toxicity (LD50), organ-specific toxicity, and major toxicological endpoints including carcinogenicity, mutagenicity, hepatotoxicity, nephrotoxicity, and immunotoxicity. The tool classifies compounds into six toxicity categories based on predicted LD50 (mg/kg) (mg/kg), ranging from Class I (highly toxic; LD50 ≤ 5 mg/kg) to Class VI (non-toxic; LD50 > 5000 mg/kg).[25] The results were compared and represented in tabular format to provide a relative safety assessment of the flavonoids against sildenafil.

RESULTS AND DISCUSSION

Physicochemical Properties

Table 1 summarizes the key physicochemical descriptors of the evaluated compounds including molecular formula, molecular weight, number of heavy atoms, number of aromatic heavy atoms, number of rotatable bonds, hydrogen bond acceptors, hydrogen bond donors, molar refractivity, and topological polar surface area (TPSA).[27] In contrast to sildenafil's mixed aromatic–aliphatic framework (Csp^3 = 0.5; 15 aromatic atoms), apigenin and kaempferol had fully aromatic, planar structures (Csp^3 = 0; 16 aromatic atoms each), making them the smallest and most basic molecules with molecular weights nearly 40–45% lower and significantly fewer heavy atoms. Compared to sildenafil, which had seven rotatable bonds, they were far less flexible due to their rigidity, with just one rotatable bond.

Table 1: Physicochemical Properties

Parameter	Apigenin	Kaempferol	Naringin	Sildenafil
Formula	C15H10O5	C15H10O6	C27H32O14	C22H30N6O4S
Molecular weight (g/mol)	270.24 g/mol	286.24 g/mol	580.53 g/mol	474.58 g/mol
No. heavy atoms	20	21	41	33
No. aromatic heavy atoms	16	16	12	15
Fraction Csp3	0	0	0.52	0.5
No. rotatable bonds	1	1	6	7
No. H-bond acceptors	5	6	14	8
No. H-bond donors	3	4	8	1
Molar Refractivity	73.99	76.01	134.91	134.56
TPSA (Å2)	90.90 Å2	111.13 Å2	225.06	121.8 Å2

Conversely, naringin was significantly larger and more complex than sildenafil, with a greater molecular weight (580.53 g/mol), more heavy atoms, and a significantly higher Csp^3 fraction (0.52), which suggests a more three-dimensional shape. Furthermore, it had the highest polarity and a TPSA of 225.06 Å2, which was nearly twice as high as that of sildenafil (121.8 Å2), and significantly higher than apigenin and kaempferol (90.90 Å2 and 111.13 Å2, respectively). It also had a higher number of hydrogen-bond acceptors and donors than all other evaluated compounds. Molar refractivity was also highest for naringin (134.91), slightly exceeding that of sildenafil (134.56) and nearly double that of apigenin and kaempferol (73.99 and 76.01, respectively).

Lipophilicity

Table 2 presents the lipophilicity profiles of the compounds, a property that critically influences membrane permeability, absorption, and tissue distribution.[28] Apigenin and kaempferol showed moderate lipophilicity, with Consensus Log Po/w values of 2.11 and 1.58, respectively, which was comparable to that of sildenafil, with Consensus Log Po/w value of 1.94. In contrast, naringin was the least lipophilic, with a Consensus Log Po/w value of -0.87.

Table 2: Lipophilicity

Parameter	Apigenin	Kaempferol	Naringin	Sildenafil
Log Po/w (iLOGP)	1.89	1.7	1.96	3.03
Log Po/w (XLOGP3)	3.02	1.9	-0.44	1.48
Log Po/w (WLOGP)	2.58	2.28	-1.49	1.93
Log Po/w (MLOGP)	0.52	-0.03	-2.77	1.2
Log Po/w (SILICOS-IT)	2.52	2.03	-1.64	2.06
Consensus Log Po/w	2.11	1.58	-0.87	1.94

Water Solubility

The water solubility, a major determinant of oral bioavailability, is summarized in Table 3. Solubility influences both gastrointestinal absorption and the attainment of therapeutic plasma concentrations, particularly for orally administered compounds.[28] SwissADME predicts aqueous solubility using three approaches: the ESOL model,[29] the Ali method,[30] and the SILICOS-IT predictor, providing comprehensive insights into solubility behavior for drug-likeness assessment.

Table 3: Water Solubility

Parameter	Apigenin	Kaempferol	Naringin	Sildenafil
Log S (ESOL)	-3.94	-3.31	-2.98	-3.59
ESOL Solubility	3.07e-02 mg/ml; 1.14e-04 mol/l	1.40e-01 mg/ml; 4.90e-04 mol/l	6.04e-01mg/ml; 1.04e-03 mol/l	1.22e-01mg/ml; 2.58e-04 mol/l
ESOL Class	Soluble	Soluble	Soluble	Soluble
Log S (Ali)	-4.59	-3.86	-3.82	-3.64
Ali Solubility	6.88e-03 mg/ml; 2.55e-05 mol/l	3.98e-02 mg/ml; 1.39e-04 mol/l	8.77e-02 mg/ml; 1.51e-04 mol/l	1.08e-01 mg/ml; 2.27e-04 mol/l
Ali Class	Moderately soluble	Soluble	Soluble	Soluble
Log S (SILICOS-IT)	-4.4	-3.82	-0.49	-5.83
SILICOS-IT Solubility	1.07e-02 mg/ml; 3.94e-05 mol/l	4.29e-02 mg/ml; 1.50e-04 mol/l	1.87e+02 mg/ml; 3.21e-01 mol/l	7.08e-04 mg/ml; 1.49e-06 mol/l
SILICOS-IT class	Moderately soluble	Soluble	Soluble	Moderately soluble

Naringin was consistently the most water-soluble molecule in all three solubility models, exhibiting significantly higher solubility than sildenafil and the two aglycone flavonoids, particularly in the SILICOS-IT model where its anticipated solubility surpassed sildenafil's by many orders of magnitude. In both ESOL and Ali forecasts, kaempferol frequently matched or marginally surpassed sildenafil and generally exhibited superior solubility than apigenin. Sildenafil varied from "soluble" in ESOL and Ali to "moderately soluble" in SILICOS-IT, where its solubility was significantly lower than that of the flavonoids except apigenin. Apigenin was the least soluble overall, falling to "moderately soluble" in the Ali and SILICOS-IT models.

Pharmacokinetic Properties

Table 4 summarizes the predicted pharmacokinetic paarmeters derived from SwissADME. These include gastrointestinal (GI) absorption, blood–brain barrier (BBB) permeability, P-glycoprotein (P-gp) substrate status, cytochrome P450 inhibition (CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4), and skin permeability (Log Kp).[31] None of the evaluated compounds were predicted to cross the BBB. Apigenin, kaempferol, and sildenafil exhibited high GI absorption, indicating potential for oral bioavailability, whereas naringin demonstrated low GI absorption, suggesting restricted oral uptake.

Table 4: Pharmacokinetics

Parameter	Apigenin	Kaempferol	Naringin	Sildenafil
GI absorption	High	High	Low	High
BBB permeant	No	No	No	No
P-gp substrate	No	No	Yes	Yes
CYP1A2 inhibitor	Yes	Yes	No	No
CYP2C19 inhibitor	No	No	No	No
CYP2C9 inhibitor	No	No	No	Yes
CYP2D6 inhibitor	Yes	Yes	No	No
CYP3A4 inhibitor	Yes	Yes	No	Yes
log Kp (skin permeation)	-5.8 cm/s	-6.7 cm/s	-10.15 cm/s	-8.14 cm/s

Drug-Likeness

Drug-likeness and bioavailability scores (Table 5) provide qualitative estimate of a molecule's likelihood to reach systemic circulation.[32] SwissADME applies drug-likeness using five rule-based filters, Lipinski, Ghose, Veber, Egan, and Muegge,each defining physicochemical boundaries characteristic of orally active drugs.[27] Adherence to these criteria indicates that apigenin and kaempferol possess favorable drug-like profiles, while naringin violates multiple rules, consistent with its high molecular weight and polarity.

Table 5: Drug-likeness

Parameter	Apigenin	Kaempferol	Naringin	Sildenafil
Lipinski	Yes; 0 violation	Yes; 0 violation	3 violations; MW>500, NorO>10, NHorOH>	Yes; 0 violation
Ghose	Yes	Yes	4 violations; MW>480, WLOGP<-0.4, MR>130, #atoms>70	1 violation; MR>130
Veber	Yes	Yes	1 violation; TPSA>140	Yes
Egan	Yes	Yes	1 violation; TPSA>140	Yes
Muegge	Yes	Yes	3 violations; TPSA>150, H-acc>10, H-don>5	Yes
	0.55	0.55	0.17	0.55

Medicinal Chemistry

Table 6 summarizes the medicinal chemistry parameters of the studied compounds. Pan Assay Interference Structures (PAINS) identify substructures prone to non-specific binding and false-positive results during high-throughput screening.[27] Structural alerts highlight fragments associated with chemical reactivity, metabolically instability, or toxicity.[33] Additionally, the Rapid Elimination of Swill (REOS) filter screens out non-drug-like moieties and reactive groups, enhancing the selection of viable lead compounds.[34] All evaluated flavonoids were PAINS-free and passed Brenk filters, indicating acceptable chemical robustness and drug-likeness.

Toxicity Predictions

Predicted toxicological profiles of the compounds are summarized in Table 7. Apigenin, kaempferol, and naringin were classified as toxicity class V (LD_{50} > 2000 mg/kg), indicating low acute oral toxicity, whereas sildenafil was categorized as class IV (LD_{50} ≈ 1000 mg/kg). None of the flavonoids were predicted to be mutagenic, carcinogenic, or hepatotoxic. These findings suggest the flavonoids, although relatively more toxic than sildenafil, fall within safety margins, thus supporting their potential suitability for further drug pharmacological evaluation.

Table 6: Medicinal Chemistry

Parameter	Apigenin	Kaempferol	Naringin	Sildenafil
PAINS	0	0	0	0
Brenk	0	0	0	0
Lead-likeness	0	0	1	1
Synthetic Accessibility	2.96	3.14	6.16	3.95

Table 7: Prediction of Toxicity

Tested Toxicities	Test Compounds			
	Apigenin	Kaempferol	Naringin	Sildenafil
Predicted LD50	2500 mg/kg	3919 mg/kg	2300mg/kg	1000 mg/kg
Hepatotoxicity	Inactive	Inactive	Inactive	Inactive
Neurotoxicity	Inactive	Inactive	Inactive	Inactive
Nephrotoxicity	Active	Active	Active	Inactive
Respiratory toxicity	Active	Active	Active	Active
Cardiotoxicity	Inactive	Inactive	Active	Inactive
Carcinogenicity	Inactive	Inactive	Inactive	Inactive
Immunotoxicity	Inactive	Inactive	Active	Inactive
Mutagenicity	Inactive	Inactive	Inactive	Inactive
Cytotoxicity	Inactive	Inactive	Inactive	Inactive
BBB-barrier	Inactive	Active	Inactive	Active
Ecotoxicity	Active	Inactive	Inactive	Inactive
Clinical toxicity	Inactive	Inactive	Active	Inactive
Nutritional toxicity	Inactive	Active	Active	Active
Toxicity Class	V	V	V	IV

Bioavailability Radar Plot

Figure 1 displays the bioavailability radar plots for all evaluated compounds. Each radar summarizes six critical physicochemical parameters, lipophilicity (LIPO), size (SIZE), polarity (POLAR), insolubility (INSOLU), unsaturation (INSATU), and molecular flexibility (FLEX), which collectively describe oral bioavailability and drug-likeness.[26] Optimal parameter ranges include molecular weight (150–500 g/mol), topological polar surface area (TPSA 20–130 Å2), aqueous solubility (Log S < 6), fraction of sp^3 carbons ≥ 0.25, number of rotatable bonds ≤ 9, and lipophilicity (XLOGP3) between –0.7 and +5.0.26 The bioavailability radar for oral bioavailability prediction of apigenin showed desired INSATU = insaturation as per Csp3 as 0.00, FLEX as per number of rotable bond 1, INSOLU Logs (ESOL) as -3.94 (soluble), SIZE as molecular weight (g/mol) of 270.24, POLAR as TPSA (Å2) 90.90, and LIPO as XLOGP3 value of 3.02 (Figure 1A). The bioavailability radar for oral bioavailability prediction of kaempferol showed desired INSATU = insaturation as per Csp3 as 0.00, FLEX as per number of rotable bond , INSOLU Logs (ESOL) as -3.31 (soluble), SIZE as molecular weight (g/mol) of 286.24, POLAR as TPSA (Å2) 111.13, and LIPO as XLOGP3 value of 1.90 (Figure 1B). The bioavailability radar for oral bioavailability prediction of naringin showed desired INSATU = insaturation as per Csp3 as 0.52, FLEX as per number of rotable bond 6, INSOLU Logs (ESOL) as -2.98 (soluble), SIZE as molecular weight (g/mol) of 580.53, POLAR as TPSA (Å2) 225.06, and LIPO as XLOGP3 value of -0.44 (Figure 1C). The bioavailability radar for oral bioavailability prediction of sildenafil showed desired INSATU = insaturation as per Csp3 as 0.50, FLEX as per number of rotable bond 7, INSOLU Logs (ESOL) as -3.59 (soluble), SIZE as molecular weight (g/mol) of 474.58, POLAR as TPSA (Å2) 121.80, and LIPO as XLOGP3 value of 1.48 (Figure 1D).

BOILED-Egg Model

The BOILED-Egg model (Figure 2) was applied to visualize passive gastrointestinal absorption and BBB Ppermeability . Compounds positioned in the white region of the model exhibit high predicted intestinal absorption, whereas those in the yellow region represent BBB-permeant molecules. Apigenin, kaempferol, and sildenafil were localized within the white region, confirming high GI absorption, while naringin fell outside the model boundaries, consistent with limited intestinal permeability.

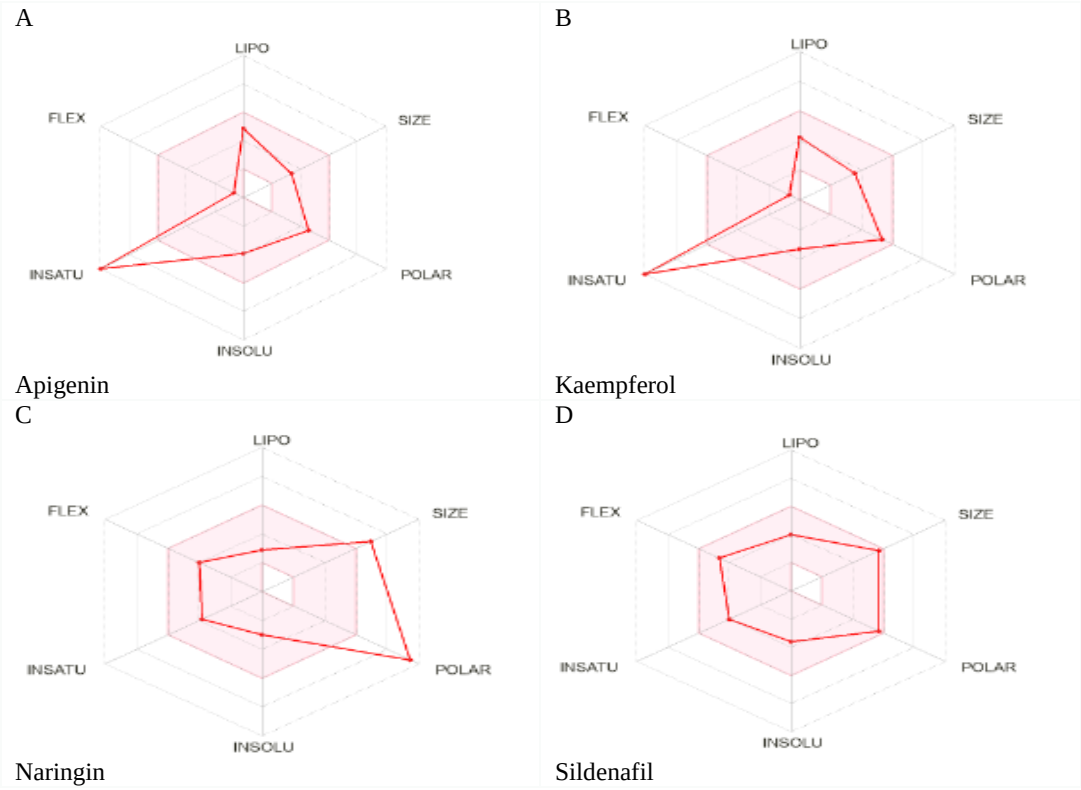

Figure 1: The bioavailability radar for the selected compounds. Pink area = Most desirable area for each of the bioavailability properties, LIPO = Lipophilicity, POLAR = Polarity, INSOLU = Insolubility, FLEX = Flexibility, SIZE = Molecular weight, INSATU = Unsaturation

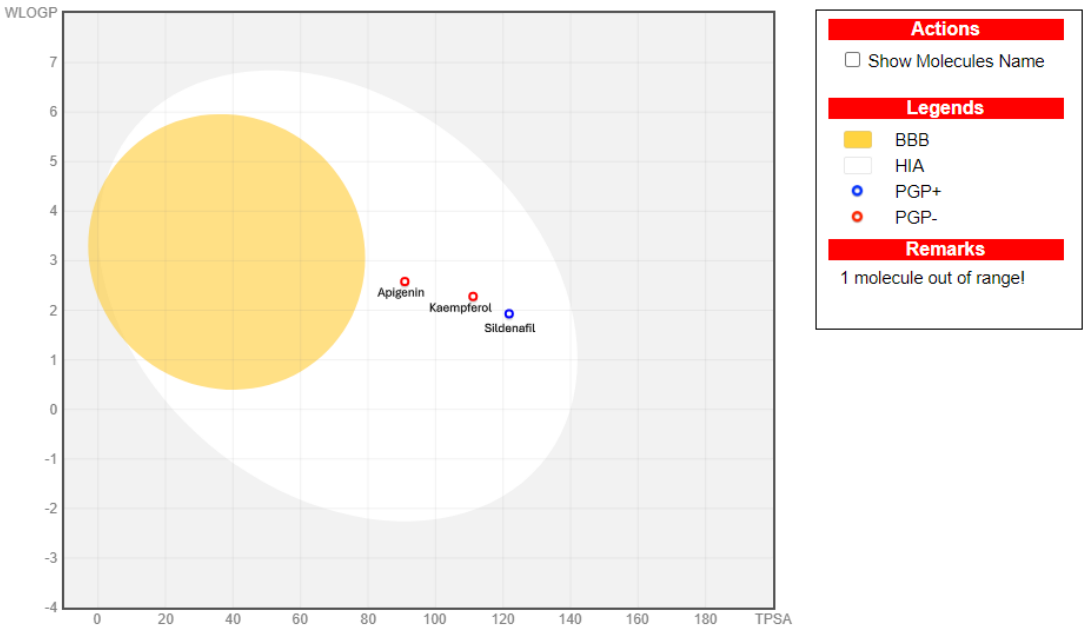

Figure 2: Boiled Egg Model of the apigenin, kaempferol, and sildenafil. Naringin is out of range.

Across all evaluated parameters, a coherent profile emerges in which apigenin and kaempferol demonstrate a balanced combination of moderate lipophilicity, acceptable solubility, and favorable drug-likenes. Their moderate consensus LogP values, high GI absorption, and compliance with all major drug-likeness rules indicate a good equilibrium between permeability and solubility, while relatively low synthetic complexity further strengthens their suitability for development.[35] In contrast, naringin's extremely high polarity (TPSA 225 Å2), low lipophilicity, and multiple rule violations severely limit membrane permeability and bioavailability, reflected in its low GI absorption and high P-gp efflux susceptibility, suggesting it is more likely to act as a pro-compound or require structural modification. Sildenafil, the benchmark PDE5 inhibitor, is more lipophilic, more permeable, has a lower toxicity class, and is pharmacokinetically optimized, which is consistent with previous studies.[36]

The therapeutic potential of apigenin, kaempferol, and naringin as PDE5 inhibitors hinges not only on their predicted binding affinities but also on whether their pharmacokinetic characteristics support meaningful pharmacodynamic action at peripheral vascular sites involved in penile erection. PDE5 is majorly expressed in cavernosal smooth muscle, where functional inhibition requires both sustained local concentrations and sufficient systemic exposure.[8] Apigenin and kaempferol exhibited physicochemical profiles consistent with oral bioavailability and effective access to peripheral tissues due to their moderate lipophilicity, advantageous topological polar surface areas, and high predicted gastrointestinal absorption. This increases the probability that their in silico PDE5 binding translates into in vivo relevance.[37] Their inability to cross the blood–brain barrier is also consistent with the peripherally limited action that ED treatments are intended to have.

On the other hand, absent formulation techniques to overcome its poor permeability, naringin's high molecular weight, extensive hydrogen-bonding characteristics, low anticipated GI absorption, and status as a P-gp substrate suggest restricted systemic availability, making effective PDE5 engagement less likely. Hence, only apigenin and kaempferol demonstrate observable pharmacokinetic properties that are close to those needed for pharmacologically significant PDE5 inhibition, when compared against sildenafil as a benchmark.

CONCLUSION

This study presents a comprehensive in silico assessment of apigenin, kaempferol, and naringin as prospective oral therapeutics for erectile dysfunction (ED). Apigenin and kaempferol exhibited favorable ADMET characteristics including high gastrointestinal absorption, moderate lipophilicity, and low acute toxicity, underscoring their potential as safe and efficacious PDE5 inhibitor candidates. In contrast, naringin displayed pharmacokinetic constraints, principally high molecular weight and polarity, suggesting the need for structural modification or advanced formulation to enhance bioavailability. Collectively, the findings highlight apigenin and kaempferol as potential leads for the rational design and preclinical development for ED management, pending in vitro or in vivo confirmation of their inhibitory activity against PDE5.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS DECLARATION

The authors hereby declare that the works presented in this article are original and that any liability for claims relating to the content of this article will be borne by them.

REFERENCES

1. Mazzilli F. Erectile dysfunction: causes, diagnosis and treatment: an update. J Clin Med. 2022; 11(21):6429. https://doi.org/10.3390/jcm11216429
2. Argiolas A, Argiolas FM, Argiolas G, Melis MR. Erectile dysfunction: treatments, advances and new therapeutic strategies. Brain Sci. 2023; 13(5):802. https://doi.org/10.3390/brainsci13050802

3. Kaltsas A, Dimitriadis F, Zachariou A, Sofikitis N, Chrisofos M. Phosphodiesterase type 5 inhibitors in male reproduction: molecular mechanisms and clinical implications for fertility management. Cells. 2025; 14(2):120. https://doi.org/10.3390/cells14020120
4. Özkent MS, Hamarat MB, Taşkapu HH, Kılınç MT, Göger YE, Sönmez MG. Is erectile dysfunction related to self-esteem and depression? A prospective case–control study. Andrologia. 2021; 53(1):e13910.
5. De Nunzio C, Roehrborn CG, Andersson KE, McVary KT. Erectile dysfunction and lower urinary tract symptoms. Eur Urol Focus. 2017; 3(4-5):352-63. https://doi.org/10.1016/j.euf.2017.11.004
6. Alrumaihi F, Raut R, Yahia EA, Kumar V, Anwar S. A review on risk factors, diagnostic innovations, and plant based therapies for the management of erectile dysfunction. Uro. 2024; 4(2):60-88. https://doi.org/10.3390/uro4020006
7. Allen MS, Tostes RC. Cigarette smoking and erectile dysfunction: an updated review with a focus on pathophysiology, e-cigarettes, and smoking cessation. Sex Med Rev. 2023; 11(1):61-73. https://doi.org/10.1093/sxmrev/qeac007
8. Saikia Q, Hazarika A, Mishra R. A review on the pharmacological importance of PDE5 and its inhibition to manage biomedical conditions. J Pharmacol Pharmacother. 2022; 13(3):246-57. https://doi.org/10.1177/0976500X221129008
9. Paronetto MP, Crescioli C. Rethinking of phosphodiesterase 5 inhibition: the old, the new and the perspective in human health. Front Endocrinol. 2024; 15:1461642. https://doi.org/10.3389/fendo.2024.1461642
10. Sin VJ, Anand GS, Koh HL. Botanical medicine and natural products used for erectile dysfunction. Sex Med Rev. 2021; 9(4):568-92.
11. Singh A, Singh J, Parween G, Khator R, Monga V. A comprehensive review of apigenin a dietary flavonoid: biological sources, nutraceutical prospects, chemistry and pharmacological insights and health benefits. Crit Rev Food Sci Nutr. 2025; 65(23):4529-65. https://doi.org/10.1080/10408398.2024.2390550
12. Chen J, Zhong H, Huang Z, Chen X, You J, Zou T. A critical review of kaempferol in intestinal health and diseases. Antioxidants. 2023; 12(8):1642. https://www.mdpi.com/2076-3921/12/8/1642
13. Salehi B, Fokou PV, Sharifi-Rad M, Zucca P, Pezzani R, Martins N, Sharifi-Rad J. The therapeutic potential of naringenin: a review of clinical trials. Pharmaceuticals. 2019; 12(1):11. https://doi.org/10.3390/ph12010011
14. Venkateswara Rao P, Kiran SD, Rohini P, Bhagyasree P. Flavonoid: A review on Naringenin. J. Pharmacogn. Phytochem. 2017; 6:2778-83.
15. Bayram P, Aksak Karamese S, Ozdemir B, Salum C, Erol HS, Karamese M. Two flavonoids, baicalein and naringin, are effective as anti-inflammatory and anti-oxidant agents in a rat model of polymicrobial sepsis. Immunopharmacol Immunotoxicol. 2023; 45(5):597-606. https://doi.org/10.1080/08923973.2023.2197143
16. Thomas SD, Jha NK, Jha SK, Sadek B, Ojha S. Pharmacological and molecular insight on the cardioprotective role of apigenin. Nutrients. 2023; 15(2):385. https://doi.org/10.3390/nu15020385
17. Zhuang J, Wang J, Zhang B, Chai D, Zuo Z. The prophylactic effects of naringin on steroid-induced early-stage osteonecrosis in rats: a preliminary study. Cell Mol Biol. 2023; 69(5):94-104. http://dx.doi.org/10.14715/cmb/2023.69.5.16
18. Stabrauskiene J, Kopustinskiene DM, Lazauskas R, Bernatoniene J. Naringin and naringenin: Their mechanisms of action and the potential anticancer activities. Biomedicines. 2022; 10(7):1686. https://doi.org/10.3390/biomedicines10071686
19. Imran M, Salehi B, Sharifi-Rad J, Aslam Gondal T, Saeed F, Imran A, Shahbaz M, Tsouh Fokou PV, Umair Arshad M, Khan H, Guerreiro SG. Kaempferol: A key emphasis to its anticancer potential.

Molecules. 2019; 24(12):2277. https://doi.org/10.3390/molecules24122277

20. Reddy KA, Ashma M, Jyothi V, Jyostna TS. Molecular Properties Prediction of Phenothiazine Derivatives by Using Swiss ADME, PkCSM, Lazar and Protox. World J Pharm Sci. 2019; 7(11):65-71. [cited 2025 Oct. 1]. Available from: https://wjpsonline.com/index.php/wjps/article/view/molecular-properties-prediction-phenothiazine-derivatives
21. Riyadi PH, Sari ID, Kurniasih RA, Agustini TW, Swastawati F, Herawati VE, Tanod WA. SwissADME predictions of pharmacokinetics and drug-likeness properties of small molecules present in Spirulina platensis. IOP conference series: earth and environmental science 2021; 890(1):012021. IOP Publishing. https://doi.org/10.1088/1755-1315/890/1/012021
22. Yusuf SE. Pharmacokinetic Evaluation of Sulfadicramide through SwissADME: A Computational Insight into Drug-Likeness and Bioavailability. MAS J Appl Sci. 2025; 10(2):357-62. http://dx.doi.org/10.5281/zenodo.15741944
23. Mahanthesh M, Ranjith D, Sreedhara J, Kumar Wodeyar DS, Hebbar A, Sudharani R, Ramesh BK, Mahesh C, Doddamani PL, Ram J, Radha J. In Silico assessment of Tolfenpyrad utilizing Swiss-ADME, Pass and Molinspiration: A comprehensive analysis. Int J Vet Sci Anim Husb. 2024; 9(4):653-9.
24. Banerjee P, Eckert AO, Schrey AK, Preissner R. ProTox-II: a webserver for the prediction of toxicity of chemicals. Nucleic Acids Res. 2018; 46(W1):W257-63. https://doi.org/10.1093/nar/gky318
25. Suliman RS, Alghamdi SS, Ali R, Rahman I, Alqahtani T, Frah IK, Aljatli DA, Huwaizi S, Algheribe S, Alehaideb Z, Islam I. Distinct mechanisms of cytotoxicity in novel nitrogenous heterocycles: future directions for a new anti-cancer agent. Molecules. 2022; 27(8):2409. https://doi.org/10.3390/molecules27082409
26. Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep. 2017; 7(1):42717. https://doi.org/10.1038/srep42717
27. İslamoğlu F, Hacıfazlıoğlu E. Investigation of the usability of some triazole derivative compounds as drug active ingredients by ADME and molecular docking properties. Moroc J Chem. 2022; 10(4):J-Chem. https://doi.org/10.48317/IMIST.PRSM/morjchem-v10i3.30855
28. Nabati M, Bodaghi-Namileh V. Design of novel drugs (P3TZ, H2P3TZ, M2P3TZ, H4P3TZ and M4P3TZ) based on zonisamide for autism treatment by binding to potassium voltage-gated channel subfamily D member 2 (Kv4. 2). Int J New Chem. 2019; 6(4):254-76.
29. Delaney JS. ESOL: estimating aqueous solubility directly from molecular structure. J Chem Inf Comput Sci. 2004; 44(3):1000-5. https://doi.org/10.1021/ci034243x
30. Ali J, Camilleri P, Brown MB, Hutt AJ, Kirton SB. Revisiting the general solubility equation: in silico prediction of aqueous solubility incorporating the effect of topographical polar surface area. J Chem Inf Model. 2012; 52(2):420-8. https://doi.org/10.1021/ci200387c
31. Oyeneyin, Oluwatoba, Nureni Ipinloju, Nathanael Ojo, and Daniel Akerele. "Structural modification of ibuprofen as new NSAIDs via DFT, molecular docking and pharmacokinetics studies." Int J Adv Eng Pure Sci. 2021; 33(4): 614-626. https://doi.org/10.7240/jeps.928422
32. Bhuia MS, Eity TA, Chowdhury R, Ansari SA, Bappi MH, Nayeem MA, Akter F, Islam MT. Anxiolytic Activity of Morellic Acid: Modulation of Diazepam's Anxiolytic Effects, Possibly Through GABAergic Interventions. CNS Neurosci Ther. 2025; 31(2):e70276. https://doi.org/10.1111/cns.70276
33. Brenk R, Schipani A, James D, Krasowski A, Gilbert IH, Frearson J, Wyatt PG. Lessons learnt from assembling screening libraries for drug discovery for neglected diseases. ChemMedChem: Chem Enabl Drug Discov. 2008; 3(3):435-44. https://doi.org/10.1002/cmdc.200700139

34. Kralj S, Jukič M, Bren U. Molecular filters in medicinal chemistry. Encyclopedia. 2023; 3(2):501-11. https://doi.org/10.3390/encyclopedia3020035
35. Banerjee P, Kemmler E, Dunkel M, Preissner R. ProTox 3.0: a webserver for the prediction of toxicity of chemicals. Nucleic Acids Res. 2024; 52(W1):W513-20. https://doi.org/10.1093/nar/gkae303
36. Tahir A, Saleh YI, Muazu IK. Structure-Based Repurposing of Clinically Approved Compounds for PDE-5 Inhibition: Integrative Computational and Pharmacokinetic Evaluation. Al-Mustaqbal J Pharm Med Sci. 2025; 3(3):5. https://doi.org/10.62846/3006-5909.1036
37. Stielow M, Witczyńska A, Kubryń N, Fijałkowski Ł, Nowaczyk J, Nowaczyk A. The Bioavailability of Drugs—The Current State of Knowledge. Molecules. 2023; 28(24):8038. https://doi.org/10.3390/molecules28248038