



Research Article

Multi-target computational pharmacology and molecular docking study of chromone-based flavonoids from *Phyllanthus* genus

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Received: 15-05-2026

Accepted: 07-05-2026

Published: 30-09-2026

Abstract

Background: Natural products are valuable sources of drug discovery, especially for multifactorial diseases. Chromone-based flavonoids from the *Phyllanthus* genus possess antioxidant, anti-inflammatory, and anticancer activities, but their multi-target molecular interactions remain insufficiently understood. **Objective:** The present study aimed to investigate the multi-target therapeutic potential of major chromone-based flavonoids (quercetin, rutin, kaempferol, and luteolin) from *Phyllanthus* species through an integrated computational pharmacology approach. **Methods:** Molecular docking was performed using AutoDock Vina against 22 protein structures representing eight key therapeutic targets associated with oxidative stress, inflammation, and cancer progression, including matrix metalloproteinases (MMPs), nitric oxide synthase (NOS), nuclear factor-kappaB (NF-κB), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), phosphoinositide 3-kinase catalytic subunit alpha (PIK3CA), epidermal growth factor receptor (EGFR), and prostaglandin E2 (PGE-2). Protein-ligand interactions were analyzed using BIOVIA Discovery Studio Visualizer, while ADMETlab was employed to predict pharmacokinetic and toxicity profiles. **Results:** All flavonoids showed favorable binding to multiple therapeutic targets. Rutin exhibited the strongest affinity for NOS (-11.2 kcal/mol) and PIK3CA (-9.8 kcal/mol), while luteolin bound most strongly to MMPs (-9.8 kcal/mol), EGFR (-9.7 kcal/mol), and IL-6 (-7.7 kcal/mol). ADMET analysis predicted acceptable drug-likeness and safety, with rutin and quercetin showing comparatively favorable toxicity profiles. These findings indicate their potential to modulate multiple pathways involved in oxidative stress, inflammation, tumor progression, and metastasis. **Conclusion:** Study highlights the polypharmacological potential of *Phyllanthus*-derived flavonoids, particularly rutin and luteolin, as multi-target therapeutic candidates. Molecular docking and ADMET analyses support their promise and provide a foundation for future molecular dynamics simulations and experimental validation.

Keywords: Chromone-based flavonoids, *Phyllanthus* genus, Molecular docking, Multi-target pharmacology, Natural product drug discovery

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Website:
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DOI: <https://doi.org/10.47552/ijam.v17i3.7366>

Introduction

Natural products have historically served as a cornerstone in drug discovery, offering structurally diverse and biologically active scaffolds for the development of therapeutic agents. A substantial proportion of approved drugs are either directly derived from natural sources or inspired by natural product scaffolds, highlighting their enduring relevance in pharmaceutical research. Among these, chromone-based compounds have emerged as a particularly significant class due to their broad spectrum of

pharmacological activities and favorable safety profiles. Chromones (4H-1-benzopyran-4-one) constitute a privileged chemical scaffold in medicinal chemistry, characterized by a rigid planar structure and versatile substitution patterns that enable interactions with multiple biological targets, thereby supporting their role in modern drug design strategies (1,2).

Flavonoids, a major subclass of polyphenolic compounds abundantly found in plants, are structurally derived from the chromone nucleus and represent an important group of bioactive molecules with well-documented pharmacological effects. Compounds such as quercetin, Kaempferol, luteolin, and rutin are widely distributed in medicinal plants and are recognized for their potent antioxidant capacity and regulatory effects on intracellular signaling pathways. These chromone-based flavonoids exert their biological effects through modulation of key molecular targets involved in oxidative stress and inflammation, including nuclear factor-kappa B (NF-κB), tumor necrosis factor-alpha (TNF-α),

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and interleukin-6 (IL-6), which are critically implicated in the pathogenesis of cancer and inflammatory diseases (3,4). Dysregulation of these pathways contributes to enhanced cellular proliferation, angiogenesis, and resistance to apoptosis, thereby underscoring the importance of identifying multi-target inhibitors capable of modulating these signaling cascades.

The genus *Phyllanthus* (family: Phyllanthaceae) comprises over 600 species widely distributed across tropical and subtropical regions and has long been utilized in traditional medicine systems such as Ayurveda, Traditional Chinese Medicine, and ethnomedicine. Several species, including *Phyllanthus amarus* Schumach. & Thonn., *Phyllanthus niruri* L., *Phyllanthus urinaria* L., *Phyllanthus fraternus* G.L.Webster, and *Phyllanthus emblica* L. are known for their hepatoprotective, antiviral, antioxidant, and anti-inflammatory properties.(5) Phytochemical investigations of these species have revealed a rich repertoire of secondary metabolites, including lignans, alkaloids, tannins, and flavonoids, many of which possess chromone-derived structural frameworks. The therapeutic efficacy of *Phyllanthus* species is largely attributed to these bioactive constituents, which act through diverse molecular mechanisms to mitigate oxidative stress and regulate immune responses (6,7).

In recent years, computational approaches such as molecular docking and in silico ADMET prediction have gained prominence as efficient tools in early-stage drug discovery. Molecular docking enables the prediction of binding affinity and interaction profiles between small molecules and biological targets, thereby facilitating the identification of potential lead compounds. Concurrently, ADMET analysis provides critical insights into pharmacokinetic behavior and toxicity, which are essential determinants of drug candidacy. These approaches are particularly valuable in natural product research, where large numbers of bioactive compounds can be screened rapidly against multiple targets. Previous studies have demonstrated the potential of flavonoids to interact with key oncogenic and inflammatory proteins, including matrix metalloproteinases (MMPs), epidermal growth factor receptor (EGFR), phosphoinositide 3-kinase (PI3K), and nitric oxide synthase (NOS), highlighting their relevance as multi-target therapeutic agents (8,9).

However, despite extensive ethnopharmacological use and phytochemical characterization, a systematic and integrated evaluation of chromone-based flavonoids from the *Phyllanthus* genus against multiple disease-relevant molecular targets remains insufficiently explored. In particular, there is a need to elucidate their role in modulating interconnected signaling pathways associated with oxidative stress, inflammation, and cancer progression. Therefore, the present study aims to investigate the multi-target pharmacological potential of selected chromone-

derived flavonoids—quercetin, rutin, Kaempferol, and luteolin—using a comprehensive in silico approach integrating molecular docking and ADMET profiling, with the objective of identifying promising candidates for further drug development.

Phytochemical Basis of *Phyllanthus* Genus

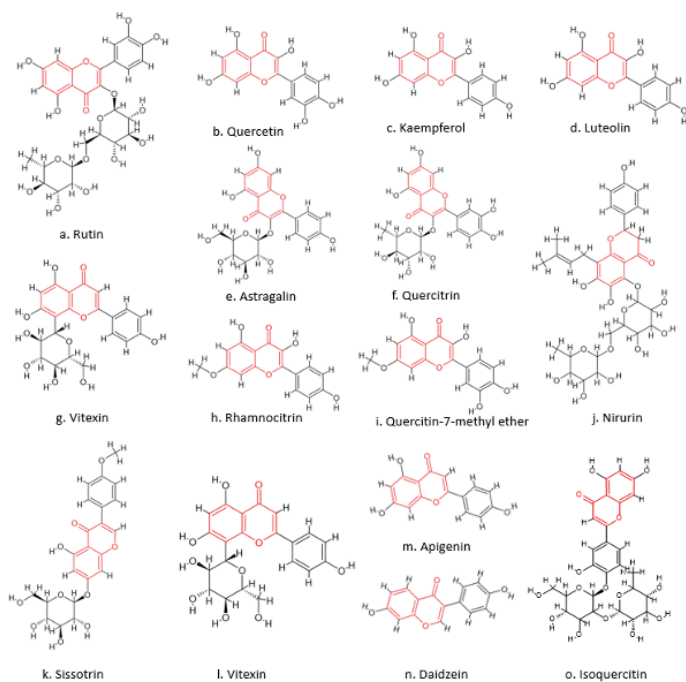
The genus *Phyllanthus* (family: Phyllanthaceae) comprises a diverse group of medicinal plants widely distributed across tropical and subtropical regions. Several species, including *Phyllanthus amarus*, *Phyllanthus niruri*, *Phyllanthus urinaria*, *Phyllanthus fraternus*, and *Phyllanthus emblica*, have been extensively utilized in traditional medicinal systems for the treatment of hepatic disorders, inflammatory conditions, metabolic diseases, and infections. Contemporary phytochemical and pharmacological investigations have validated many of these traditional claims, attributing their therapeutic potential to a rich array of secondary metabolites (6,7).

Among these phytoconstituents, flavonoids—structurally derived from the chromone scaffold—represent a key class of bioactive molecules responsible for the observed pharmacological effects. These chromone-based flavonoids exhibit potent antioxidant, anti-inflammatory, and anticancer activities through modulation of critical molecular pathways, including nuclear factor-kappa B (NF-κB), phosphoinositide 3-kinase (PI3K)/AKT signaling, and cytokine-mediated inflammatory cascades such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) (3,4). The ability of these compounds to interact with multiple biological targets highlights their relevance in polypharmacological drug discovery approaches.

Despite extensive phytochemical profiling of individual *Phyllanthus* species, comparative insights into the distribution and functional significance of chromone-based flavonoids across different species remain limited. A systematic consolidation of these constituents is therefore essential to understand their contribution to the therapeutic potential of the genus and to support rational drug discovery strategies. The phytochemicals investigated in this study were selected based on a comprehensive review of peer-reviewed literature and phytochemical databases. Quercetin, rutin, kaempferol, and luteolin were chosen because they are consistently reported in major *Phyllanthus* species, possess well-documented antioxidant, anti-inflammatory, and anticancer activities, and have experimentally validated chemical structures available in the PubChem database.(5,10) Their reported involvement in multiple disease-related molecular pathways justified their selection for subsequent molecular docking and ADMET analyses. (11,12) Accordingly, the major chromone-derived flavonoids identified in selected *Phyllanthus* species, along with their associated biological activities, are summarized in Table 1.

Table 1: Chromone-based flavonoids identified in selected *Phyllanthus* species and their biological activities

Species	Major Chromone-Based	Chemical Class	Key Biological Activities
<i>Phyllanthus amarus</i> Schumach.	Rutin, Quercetin, Kaempferol, Astragalin, Quercitrin	Flavonols / Glycosides	Antioxidant, hepatoprotective, anti-inflammatory, anticancer
<i>Phyllanthus niruri</i> L.	Rutin, Quercetin, Kaempferol, Astragalin, Nirurin, Quercitrin	Flavonols / Glycosides	Antiviral, antioxidant, anti-inflammatory, diuretic, hepatoprotective
<i>Phyllanthus urinaria</i> L.	Rhamnocitrin, Quercetin, Rutin, Astragalin, Kaempferol, Quercetin-7-	Flavonols / Methylated derivatives	Antioxidant, anti-inflammatory, anticancer, anti- <i>H. pylori</i>
<i>Phyllanthus fraternus</i>	Luteolin, Rutin, Quercetin, Astragalin, Vitexin, Daidzein,	Flavones / Isoflavones	Neuroprotective, anti-inflammatory, anticancer, antihypertensive
<i>Phyllanthus emblica</i> L.	Quercetin, Kaempferol, Rutin, Apigenin, Isoquercetin	Flavonols / Flavones	Antioxidant, immunomodulatory, anti-inflammatory, anticancer

Figure 1: Chemical structures of chromone-based flavonoids

Comparative Phytochemical Insights

The distribution of chromone-derived flavonoids across *Phyllanthus* species demonstrates a notable degree of conservation, particularly for quercetin, rutin, and Kaempferol, suggesting their central role in mediating the pharmacological properties of the genus. These compounds are well-documented for their ability to regulate oxidative stress and inflammatory responses, thereby contributing to hepatoprotective and anticancer effects. (5,13)

In contrast, certain species-specific constituents, such as rhamnocitrin in *Phyllanthus urinaria* and vitexin in *Phyllanthus fraternus*, may account for distinct biological activities, including antimicrobial and neuroprotective effects. (14,15) Additionally, the presence of glycosylated flavonoids such as rutin and astragalin is of particular significance, as glycosylation can enhance aqueous solubility and influence pharmacokinetic behavior, which may correlate with improved binding affinity and favorable ADMET profiles observed in computational studies (16).

Overall, the phytochemical diversity of *Phyllanthus* species underscores their potential as a valuable source of multi-target bioactive compounds. These findings provide a strong rationale for the subsequent molecular docking and ADMET analyses aimed at elucidating the mechanistic basis of their therapeutic effects.

Materials and Methods

Selection and Preparation of Ligands

The ligands were selected through a literature survey and phytochemical databases (PubMed, Scopus, Web of Science, and PubChem) based on their frequent occurrence in *Phyllanthus* species, reported pharmacological activities, and availability of validated 3D structures. Accordingly, quercetin, rutin, kaempferol, and luteolin were selected, while other phytochemicals were excluded due to limited evidence or lack of suitable structural data for molecular docking (5,17).

The three-dimensional (3D) structures of these ligands were retrieved from the PubChem database in SDF format. Ligand structures were subsequently converted to PDB format and subjected to energy minimization using UCSF Chimera, employing the default AMBER force field to obtain stable conformations suitable for docking analysis. Hydrogen atoms were added, and Gasteiger charges were assigned prior to docking preparation.

Selection and Preparation of Target Proteins

Target proteins associated with oxidative stress, inflammation, and cancer progression were selected based on their biological relevance and literature evidence. The protein structures were retrieved from the Protein Data Bank. Selected targets included nuclear factor-kappa B (NF- κ B), tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), matrix metalloproteinases (MMPs), nitric oxide synthase (NOS), phosphoinositide 3-kinase catalytic subunit alpha (PIK3CA), epidermal growth factor receptor (EGFR), and prostaglandin E2 (PGE-2)(18,19).

Protein preparation was performed using UCSF Chimera, which involved removal of co-crystallized ligands, water molecules, and heteroatoms. Missing hydrogen atoms were added, and appropriate protonation states were assigned. The prepared protein structures were then saved in PDB format for subsequent docking analysis.

Molecular Docking Protocol

Molecular docking simulations were carried out using AutoDock Vina, a widely used open-source docking program known for its improved scoring function and computational efficiency (20). The docking process was facilitated through UCSF Chimera by integrating AutoDock Vina tools.

Grid box parameters were defined to encompass the active binding site of each protein. The grid center coordinates were selected based on the position of the co-crystallized ligand, ensuring accurate targeting of the active site. Grid box dimensions were optimized to allow sufficient conformational flexibility of ligands within the binding pocket.

Docking exhaustiveness was set to 8, and grid box dimensions were defined based on the active site coordinates of co-crystallized ligands. Binding affinities were calculated in terms of binding energy (kcal/mol), and the best binding pose for each ligand-protein complex was selected based on the lowest docking score(21).

Docking Validation

To ensure the reliability of the docking protocol, validation was performed through a re-docking approach, wherein the native co-crystallized ligand was extracted and re-docked into the corresponding protein binding site. The predicted binding pose was compared with the experimentally observed conformation to assess the accuracy of the docking method. A low root mean square deviation (RMSD) value (< 2.0 Å) was considered indicative of a valid and reliable docking protocol (22).

Visualization of Protein-Ligand Interactions

The analysis and visualization of docking results were performed using BIOVIA Discovery Studio Visualizer. The binding interactions, including hydrogen bonding, hydrophobic interactions, π - π stacking, and van der Waals forces, were examined in detail to understand the molecular basis of ligand binding. Both two-dimensional (2D) and three-dimensional (3D)

interaction diagrams were generated to interpret ligand orientation within the active site (23).

ADMET Prediction

The pharmacokinetic and toxicity profiles of the selected ligands were evaluated using the online platform ADMETlab 3.0, which employs machine learning-based models trained on extensive experimental datasets (24). Key parameters assessed included:

- Absorption (intestinal permeability, oral bioavailability)
- Distribution (blood–brain barrier permeability)
- Metabolism (cytochrome P450 interactions)
- Excretion properties
- Toxicity endpoints (AMES toxicity, carcinogenicity, hepatotoxicity)

These predictions provided insights into the drug-likeness and safety profiles of the compounds, facilitating their evaluation as potential therapeutic candidates.

Data Analysis

Docking results were expressed as binding affinity values (kcal/mol), and comparative analysis was performed across all ligands and target proteins. Compounds exhibiting lower binding energy

values were considered to have stronger binding affinity and potential biological activity. ADMET results were interpreted qualitatively to identify compounds with favorable pharmacokinetic and toxicity profiles (25).

Results and Discussion

Molecular Docking Analysis

To elucidate the multi-target therapeutic potential of chromone-based flavonoids, molecular docking studies were performed against key proteins involved in cancer progression, inflammation, and oxidative stress. The selected ligands—quercetin, rutin, Kaempferol, and luteolin—demonstrated notable binding affinities across all targets, supporting their polypharmacological behavior.

Interaction with Matrix Metalloproteinases (MMPs)

Matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, are critical mediators of extracellular matrix degradation and tumor metastasis. Docking analysis against multiple MMP structures, including **PDB IDs: 1GKD, 1GKC, 4H3X, 8K5Y, and 8H78**, revealed strong binding affinities for all flavonoids.

A comprehensive summary of docking interactions across all targets is presented in Table 2.

Table 2: Molecular docking scores (kcal/mol) of selected flavonoids against multiple target proteins

Sr.no	Target Protein	Proteins PDB ID	Native/ Unique ligand	Docking Score with Quercetin	Docking Score with Rutin	Docking Score with Kaempferol	Docking Score with luteolin
1	Matrix metallo-proteinases (MMPs)	1GKD	STN	-9.6	-9.1	-9.0	-9.4
2		1GKC	NFH	-9.4	-8.6	-8.8	-9.5
3		4H3X	10B	-9.7	-8.6	-9.1	-9.8
4		8K5Y	VP6	-9.4	-9.0	-9.7	-9.5
5		8K5X	VOZ	-8.5	-8.5	-8.4	-8.5
6		8H78	L2U	-9.1	-9.0	-9.1	-8.6
7	Nitric Oxide Synthase (NOS)	4NOS	HEM	-9.1	-11.2	-9.2	-9.6
8		6AV2	HEM	-8.9	-11.0	-9.0	-8.9
9	NF-κB	6M2D	SO4	-5.1	-5.4	-5.0	-4.9
10		6M2C	ZN	-5.9	-5.4	-5.4	-6.1
11		6Z6V	NAG	-5.5	-6.3	-5.3	-5.6
12		6W9G	1PE	-5.9	-6.2	-4.9	-5.3
13	TNF-α	7JRA	VGY	-6.1	-5.7	-6.1	-6.2
14		7KP9	A7G	-5.9	-6.4	-6.3	-6.4
15	IL-6	4CNI	TAM	-6.3	-6.8	-7.4	-7.7
16	PIK3CA	5UBR	85S	-7.9	-8.6	-7.6	-8.1
17		5DXT	5H5	-9.2	-9.8	-8.7	-9.4
18		6PYS	P5J	-8.9	-9.0	-8.5	-9.0
19	EGFR	3EQP	T95	-9.6	-8.8	-9.3	-9.7
20		1U4D	DBQ	-9.2	-8.1	-9.1	-9.2
21	PGE-2 and Inflammatory Mediators	2ZB4	NAP	-9.0	-10.1	-8.8	-8.9
22		8BWR	P2E	-8.2	-9.4	-8.4	-8.0

Key findings from Table 2 are further summarized and discussed below.

Among the tested compounds, luteolin exhibited the highest binding affinity (−9.8 kcal/mol against 4H3X), followed by

quercetin and Kaempferol. These interactions were stabilized by hydrogen bonding and hydrophobic contacts within the catalytic zinc-binding domain of MMPs.

These findings are consistent with previous reports indicating that flavonoids such as quercetin and luteolin inhibit MMP activity, thereby suppressing tumor invasion and metastasis (26). The strong interaction observed in the present study supports the potential of chromone-based flavonoids as anti-metastatic agents.

Interaction with Nitric Oxide Synthase (NOS)

Nitric oxide synthase (NOS), particularly inducible NOS (iNOS), plays a crucial role in inflammation and oxidative stress. Docking studies performed on **PDB IDs: 4NOS and 6AV2** demonstrated significant binding affinities, with rutin showing the strongest interaction (−11.2 kcal/mol with 4NOS) which is comparable to or better than several reported synthetic inhibitors of NOS, suggesting its potential as a competitive natural inhibitor.

The enhanced binding affinity of rutin may be attributed to its glycosylated structure, which facilitates multiple hydrogen bonding interactions within the heme-containing active site. These interactions are critical for enzyme inhibition and stabilization of the ligand–protein complex.

Flavonoid-mediated modulation of nitric oxide pathways has been widely reported, where compounds such as quercetin and rutin reduce excessive nitric oxide production, thereby attenuating oxidative stress and inflammation (3). The present findings reinforce the role of rutin as a potent anti-inflammatory and antioxidant agent.

Interaction with NF-κB, TNF-α, and IL-6

The transcription factor NF-κB and pro-inflammatory cytokines TNF-α and IL-6 are central regulators of inflammatory signaling and cancer progression. Docking analysis against **NF-κB (PDB IDs: 6M2D, 6M2C, 6Z6V, 6W9G)**, **TNF-α (7JRA, 7KP9)**, and **IL-6 (4CNI, 1N26, 8IOW)** revealed moderate binding affinities ranging from −4.9 to −7.7 kcal/mol.

Among the tested ligands, luteolin showed the highest affinity for IL-6 (−7.7 kcal/mol with 4CNI), while rutin demonstrated relatively stable interactions across NF-κB and TNF-α targets.

Although the binding energies were lower compared to enzymatic targets, these interactions remain biologically relevant, as partial inhibition of transcription factors and cytokines can significantly modulate downstream signaling cascades. Previous studies have demonstrated that flavonoids inhibit NF-κB activation and suppress TNF-α and IL-6 production, thereby reducing inflammation and tumor progression (4,25,27).

Interaction with PIK3CA and EGFR

The PI3K/AKT and EGFR signaling pathways play pivotal roles in cancer cell proliferation, survival, and resistance to apoptosis. Docking studies performed on **PIK3CA (PDB IDs: 5UBR, 5DXT, 6PYS)** and **EGFR (3EQP, 1U4D)** revealed strong binding affinities for all flavonoids.

Notably, rutin exhibited the highest binding affinity toward PIK3CA (−9.8 kcal/mol with 5DXT), while luteolin showed strong interaction with EGFR (−9.7 kcal/mol with 3EQP). These interactions were characterized by hydrogen bonding with key active site residues and stabilization within the ATP-binding pocket.

These findings are in agreement with previous studies demonstrating that inhibition of PI3K and EGFR pathways effectively suppresses tumor growth and proliferation (8,28).. Thus, chromone-based flavonoids may serve as **potential kinase inhibitors in cancer therapy**.

Interaction with PGE-2 and Inflammatory Mediators

Prostaglandin E2 (PGE-2) is a key inflammatory mediator produced via the COX-2 pathway. Docking analysis against **PDB IDs: 2ZB4 and 8BWR** revealed strong binding affinities, particularly for rutin (−10.1 kcal/mol with 2ZB4).

The inhibition of PGE-2 signaling suggests that these flavonoids may exert anti-inflammatory effects by modulating prostaglandin synthesis. Similar anti-inflammatory mechanisms have been reported for flavonoids, which inhibit COX-2 activity and reduce prostaglandin production (29).

Comparative Binding Affinity and Structure–Activity Relationship

A comparative analysis of docking results in Table 3 indicates that rutin consistently exhibited superior binding affinity across multiple targets, followed by luteolin, quercetin, and Kaempferol.

Table 3: Comparative analysis of binding affinities of selected flavonoids across target proteins

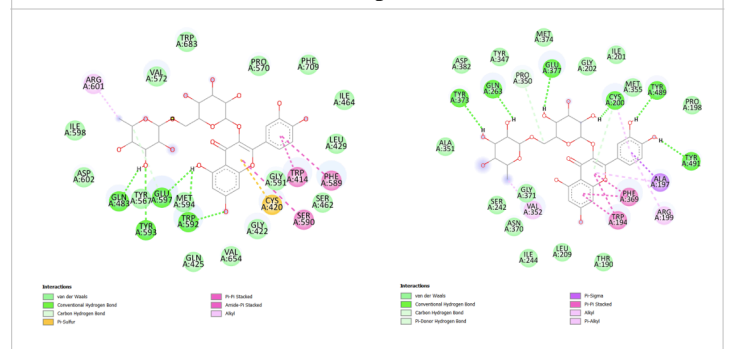
Target	Best Ligand	Binding Energy (kcal/mol)	Key Observation
MMPs	Luteolin	-9.8	Strong anti-metastatic potential
NOS	Rutin	-11.2	Highest interaction
NF-κB	Rutin	-6.3	Moderate inhibition
TNF-α	Luteolin	-6.4	Anti-inflammatory
IL-6	Luteolin	-7.7	Cytokine modulation
PIK3CA	Rutin	-9.8	PI3K inhibition
EGFR	Luteolin	-9.7	Anticancer signaling
PGE-2	Rutin	-10.1	Anti-inflammatory

The enhanced activity of rutin can be attributed to:

- Glycosylated structure
- Increased hydrogen bonding potential
- Improved interaction stability

Glycosylation has been shown to enhance ligand–protein interactions and influence pharmacokinetic properties, as reported in previous computational and pharmacological studies (24,30).

Figure 2: (A) Interaction of rutin with nitric oxide synthase (NOS; PDB ID: 4NOS) showing strong hydrogen bonding and binding stability; (B) interaction of luteolin with matrix metalloproteinase (MMP; PDB ID: 4H3X) illustrating π – π stacking and hydrophobic interactions supporting anti-metastatic potential.



ADMET and Toxicity Analysis

Table 4: Predicted ADMET and toxicity profiles of selected flavonoids

Toxicity Test	Quercetin	Rutin	Kaempferol	Luteolin
Mutagenicity (AMES Toxicity)	Moderate	High	Moderate	Moderate
Carcino-genicity	Moderate	Less	High	Moderate
Hek293/A549 Cytotoxicity	Moderate	Moderate	Less	Moderate
Drug-induced Nephrotoxicity	Less	Less	Less	Less
Drug-induced Neurotoxicity	Less	Less	Less	Less
Respiratory toxicity	Moderate	Less	High	High
RPMI-8226 Immuno-toxicity	Less	Less	Less	Less
Total Toxicity measures (In ratio Less:Moderate:High)	3:4:0	5:1:1	4:1:2	3:3:1

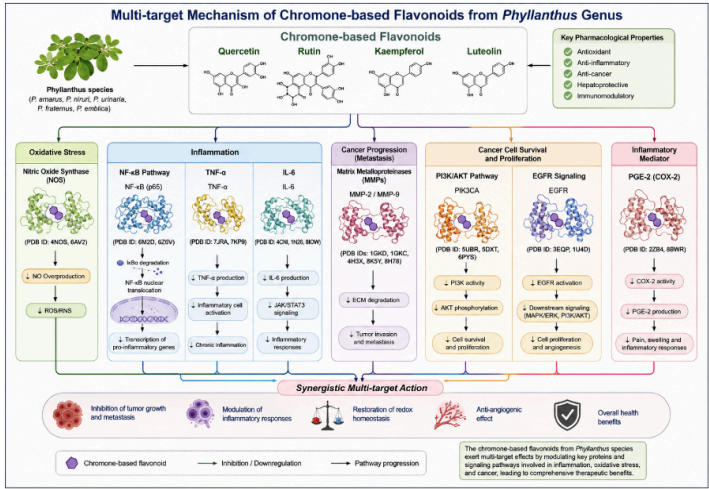
ADMET analysis revealed that all compounds possess **acceptable pharmacokinetic profiles**, with variations in toxicity endpoints.

- **Rutin** exhibited the most favorable safety profile
- **Quercetin** showed moderate but acceptable toxicity
- **Kaempferol and luteolin** showed relatively higher toxicity alerts

Importantly, all compounds demonstrated low nephrotoxicity and neurotoxicity risks, supporting their potential for therapeutic applications.

Despite favorable toxicity profiles, the relatively large molecular weight and glycosylation of rutin may limit its oral bioavailability, necessitating formulation strategies.

Figure 3: Multi-target mechanism of chromone-based flavonoids from *Phyllanthus* species; generated using AI-assisted tools and refined by the authors



Mechanistic Insights and Polypharmacology

The multi-target binding behavior observed in this study highlights the polypharmacological nature of chromone-based flavonoids. These compounds simultaneously modulate multiple pathways, including:

- Oxidative stress → NOS, NF-κB
- Inflammation → TNF-α, IL-6, PGE-2
- Cancer progression → MMPs, EGFR, PIK3CA

Such multi-target interactions are particularly advantageous in complex diseases like cancer, where single-target therapies often fail. The results strongly support the potential of *Phyllanthus*-derived flavonoids as multi-functional therapeutic agents.

These findings collectively reinforce the potential of chromone-based flavonoids as promising multi-target therapeutic candidates for complex diseases such as cancer and chronic inflammation.

Study Limitations

The present study is limited by its reliance on in silico approaches, including molecular docking and ADMET predictions, which provide only theoretical insights into ligand–protein interactions. Docking simulations are based on static protein conformations and do not fully account for protein flexibility, solvent effects, or dynamic biological environments, which may influence binding behavior (22). Additionally, docking scores represent approximate binding energies and may not directly correlate with actual biological activity. The absence of molecular dynamics simulations further limits the assessment of complex stability over time. Importantly, no experimental validation (in vitro or in vivo) was performed to confirm the predicted pharmacological effects. Moreover, ADMET predictions may not fully reflect real biological metabolism, particularly for glycosylated compounds such as rutin. These limitations highlight the need for further validation.

Future Perspectives

To the best of our knowledge, this study represents one of the first systematic multi-target docking analyses of chromone-based flavonoids from the *Phyllanthus* genus, integrating phytochemical distribution with computational pharmacology. The integration of docking and ADMET analysis provides a comprehensive framework for early-stage natural product-based drug discovery.

Future studies should focus on experimental validation of the identified lead compounds through in vitro assays and cell-based models to confirm their biological activity. Incorporation of molecular dynamics simulations and free energy calculations (e.g., MM-PBSA) would enhance the reliability of binding predictions. Further research on structure–activity relationship (SAR) optimization may improve potency and selectivity of chromone-based flavonoids. Given the promising multi-target activity, integration of network pharmacology approaches could provide deeper insights into pathway-level mechanisms. Additionally, development of advanced delivery systems, such as nanoformulations, may improve bioavailability and therapeutic efficacy. These approaches will facilitate the translation of computational findings into potential clinical applications.

Conclusion

In conclusion, the present study provides a comprehensive in silico evaluation of chromone-based flavonoids derived from *Phyllanthus* species, highlighting their significant multi-target therapeutic potential. Molecular docking analysis demonstrated strong binding affinities of key compounds, particularly rutin and luteolin, against critical proteins involved in cancer progression, inflammation, and oxidative stress, including MMPs, NOS, PIK3CA, and EGFR. The observed polypharmacological interactions suggest that these flavonoids can modulate multiple interconnected signaling pathways, thereby offering a promising

strategy for the management of complex diseases. Furthermore, favorable ADMET profiles support their potential as drug-like candidates. Overall, this study establishes a mechanistic basis for the traditional medicinal use of *Phyllanthus* and underscores the potential of chromone-based flavonoids as lead compounds for future therapeutic development, warranting further experimental validation.

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