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Integrated in silico dissection of ABC transporter-mediated hepatoprotective by apigenin and luteolin from *Eclipta prostrata* using network pharmacology, molecular docking and ADME-toxicity profiling

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Abstract

Liver disease poses a significant global health challenge, necessitation the discover of safer, multi-target natural hepatoprotective agents. In this work, the hepatoprotective attributes of Apigenin and Luteolin, major flavonoids from *Eclipta prostrata* L., using an integrated in silico framework. A combination of network-based target exploration, pharmacokinetic and toxicological prediction, and structure-based molecular docking were employed to elucidate their mechanisms. ADME-toxicity predictions indicated favourable drug likeness, good oral absorption, and low toxicity for both compounds, suggesting a promising safety profile for therapeutic application. Network and Venn analysis identified 12 common overlapping targets, including XDH, MAOA, ALOX5, GSK3B, PARP1, ABCG2, TOP1, ESR1, ACHE, PTGS2, ABCC1, AND CETR linking these phytochemicals to lover-associated pathological mechanisms. Functional enrichment analysis using gene ontology and KEGG pathway revealed involvement in xenobiotic detoxification, oxidative stress management, ABC transporter activity, bile secretion and metabolic balance. Molecular docking demonstrated stable and strong interaction of Apigenin and Luteolin with key ABC transporters (CFTR, ABCC1 and ABCG2), mediated by hydrogen bonding, pi stacking, and hydrophobic forces. Apigenin exhibited the highest affinity for CFTR Luteolin showed comparable binding and strong interaction with ABCG2, suggesting the role in enhancing toxic efflux and effector hepatoprotective. These finding indicate the Apigenin and Luteolin may act as promising natural hepatoprotective molecules through transporter modulation, antioxidant and anti-inflammatory pathway. The study provides molecular insight supporting the development of natural multi target apoptotic agent, with experimental validation recommended for clinical translation.

1. INTRODUCTION

Liver disease continues to represent a major global health burden, resulting in substantial morbidity and mortality worldwide due to the cirrhosis, hepatitis and drug induced liver injury (DILI) (Duo et al., 2025; Feng et al., 2025; Zhang et al., 2025). As the central organ responsible for xenobiotic metabolism and detoxification, the liver is particularly vulnerable to oxidative stress arising from exposure to reactive oxygen species, metabolic bu-products and liver injury (Jadhav et al., 2025). conventional hepatoprotective agent, such as silymarin and ursodeoxycholic acids, provide limited therapeutic efficacy and may cause adverse effect, emphasizing the need for safer, multi target natural alternatives (Jaffar et al., 2024; Lee et al., 2022; Okovityi et al., 2022; Pandey et al., 2023; Rajappa et al., 2024; Tighe et al., 2020).

Eclipta prostrata (L.) L. (Asteraceae), has long been utilized in ayurvedic and traditional Chinese medicinal system and is widely recognized for its strong hepatoprotective properties (Pan et al., 2021; Timalsina & Devkota, 2021; Vinyagam et al., 2020). Phytochemical analyses have disclosed that its major bioactive constituents include the flavonoid composition, with Apigenin and luteolin as prominent constituents, which are widely recognized for their antioxidant and anti- inflammatory properties and liver-protective activities. These flavonoids act by modulating key molecular aims involved in oxidative

stress, inflammation, and detoxification, thereby supporting hepatic function (Wang et al., 2024; Yao et al., 2023).

Accumulating evidence indicates that Apigenin and luteolin are capable of modulating ATP-binding cassette (ABC) transporters, such as p-glycoprotein (ABCB1), MRP2 (ABCC2), and BCRP (ABCG2), which are essential for the hepatic efflux of xenobiotics and bile acids (Fan et al., 2020; Li et al., 2020; Sharma et al., 2020; Tvrdý et al., 2021; Zhu et al., 2021). Dysregulation of these transporters is closely linked with hepatotoxicity and impaired drug clearance. Thus, natural compounds competent of restoring ABC transporter activity could offer a new therapeutic strategy for liver protection.

To systematically explore the hepatoprotective potential of these flavonoids, computational tools such as network pharmacology, molecular docking, and ADME–toxicity prediction have become increasingly valuable (Bergen et al., 2025; Han et al., 2025; Jadhav et al., 2025; Xiao et al., 20 25)). These in silico methods enable identification of target pathways, prediction of molecular interactions, and evaluation of pharmacokinetic safety profiles prior to experimental validation.

Hence, the present investigation seeks to evaluate the hepatoprotective potential of Apigenin and Luteolin derived from *Eclipta prostrata* using an integrated in silico approach combining network pharmacology, molecular docking, and ADME–toxicity profiling. The central hypothesis is that these flavonoids modulate ABC transporter–mediated hepatic detoxification pathways, thereby enhancing liver protection against oxidative and xenobiotic stress. The outcome of this investigation is anticipated to yield molecular-level insights that facilitate the development of natural, multi-target hepatoprotective agents.

2. MATERIALS AND METHODS

2.1 Ligand Acquisition and Optimization

2.1.1 Retrieval of Phytochemical Structures and Energy Minimization

Apigenin and luteolin where identified as major compound of Eclipta prostrata using the IMPPAT database (IMPPAT | IMPPAT: Indian Medicinal Plants, Phytochemistry and Therapeutics) (Azene et al., 2025; Ingle et al., 2024; Kaur et al., 2025; Sinha et al., 2022). The structure was downloaded from the PubChem (PubChem) (SDF/SMILES) and opened in the Molegro Molecular viewer (MMV) to check the chemical layout and convert them into the 3D format. Before further analysis, both structures were energy-minimized MMV to remove the stain and stabilize the molecular geometry ((Dittrich et al., 2020; Liebschner et al., 2023; Tsypin et al., 2023). Drug likeness was assessed through the mole soft (Molsoft L.L.C.: Drug-Likeness and molecular property prediction.), where key physio chemical properties (Molecular weight, LogP, H-bond donors/acceptors and TPSA) were found within acceptable range,

allowing both ligand to be considered suitable for docking and pharmacology studies ((Gu et al., 2024; Pirie et al., 2024; Raj et al., 2024).

2.2 ADME and Toxicity profile

pharmacokinetic behaviour of Apigenin and luteolin was evaluated using Swiss ADME (SwissADME), were key parameter including gastrointestinal absorption, lipophilicity (LogP), Topological polar surface area (TPSA), hydrogen bond donor and acceptors and bioavailability score for examined (Azzam, 2022; Bakchi et al., 2022; Fagerholm & Hellberg, 2025). compound suitability was sacked against Lipinski's rule of five to determine the oral drug-likeness, and both ligands matched acceptable range in most criteria, indicating good potential for systemic absorption and drug development feasibility (Bakchi et al., 2022). Toxicological assessment was performed using prTox-II (ProTox-3.0 - Prediction of TOXicity of chemicals) where predictive models where used to estimate acute toxicity (LD50), hepatotoxicity, mutagenicity, cytotoxicity and carcinogenic risk (Banerjee et al., 2024; Bergen et al., 2025; Lee et al., 2025; Sá et al., 2022).. The compound was classified under the safe toxicity class with no severe alert flagged in primary prediction filters, suggestion that apigenin and luteolin passes a favourable safety profile for further biological facilitation (Banerjee et al., 2024).

2.3 Network pharmacology Analysis

2.3.1 Prediction of Potential Molecular Targets

Two screening approach were used to identify potential target. in the first step Swiss target prediction(SwissTargetPrediction) was used for ligand-based prediction where the smiley of Apigenin and luteolin were uploaded and protein with higher probability score shortlisted (Daina & Zoete, 2024; Galati et al., 2021; He et al., 2025; Shaikh et al., 2021). In the second step diseases related target were collected from the Gene Cards (GeneCards - Human Genes | Gene Database | Gene Search) by searching terms like hepatotoxicity, liver injury and detoxification (Ayyadurai et al., 2023; Bergen et al., 2025; Datta et al., 2023; Teschke & Xuan, 2022; Zhu et al., 2025). Gene where filter based on the relevance score and only those strongly linked to the liver function was selected. The result from both methods were then compared and common high confidence gene were taken forward for the further network and docking studies (Jadhav et al., 2025).

2.3.2 Identification of common target by using Venn diagram

After obtaining the target and genes, both datasets were compared to find the gene common to the two lists. A Venn diagram (Venny 2.1.0) tool was used to visualize their intersection between the ligand predicted target and the hepatotoxicity related genes (Bao et al., 2020; Sindhu et al., 2024; Wen et al., 2024; Yang et al., 2023). The intersecting genes from the diagram were selected as final potential target, as they were related both to the compound and to liver associate pathways. The common targets were then taken forward for network construction and docking analysis.

2.3.3 PPI network construction

The common target was imported into STRING (STRING: functional protein association networks) to generate a protein-protein interaction (PPI) network, using homo-sapiens as selector Organism with confidence score ≥ 0.7 (Szklarczyk et al., 2022, 2024). The interaction file was then exported and visualized in ytoscape_v3.10.3, where network parameters, including node degree and centrality were analysed to identify the key hub genes (Doncheva et al., 2022; Majeed & Mukhtar, 2023; Zhou et al., 2023). The core nodes were considered significant for their potential involvement in the hepatoprotection and detoxification pathways and were used for further pathway and docking evaluation.

2.3.4 GO and KEGG enrichment analysis

The shortlist target genes was suspected to GO (Gene Ontology) and KEGG enrichment analysis using ShinyGO (ShinyGO 0.85), with homo sapiens selected as the reference species (Agbana et al., 2023; Arba, 2025; Trivedi et al., 2023). Enriched biological process (BP), molecular functions (MF), cellular component (CC) as well as KEGG pathway, were identified using an FDR < 0.05 cut off. The top ranked pathway related to detoxification, bile acid transport, oxidative regulation and ABC transporter activity were recorded and the generator enrichment plots were used to interpret the hepatoprotective relevance of apigenin and Luteolin (Barzegari et al., 2024; Dhongadi et al., 2023; Jadhav et al., 2025; Liu et al., 2025).

2.4 Molecular docking

The ABC transporter proteins, selected for their role in hepatic detoxification, where download from RCSB protein Data Bank (PDB) (rcsb.org) (Burley, 2021; Burley et al., 2022, 2024; Rose et al., 2020; Wankowicz, 2025). The structures were cleaned using Molegro Molecular viewer (MMV) by removing water molecules, co crystallised ligands and unwanted heteroatom (Dere et al., 2025). The minimized ligand structure where the docked against the prepared protein receptors using Swissdock (SwissDock), producing multiple finding confirmations ((Bugnon et al., 2024; Gu et al., 2025; Hossain, 2024; Martis & Téletchéa, 2025). The finest binding pose for each protein-ligands complex was selected based on affinity and full fitness score (Sarıgün et al., 2025). Protein-ligand interaction such as hydrogen bonding and hydrophobic contacts were subsequently examined and visualized using BIOVIA studio visualizer to interpret active site engagement and docking stability (Baroroh et al., 2023; Errington et al., 2025; Tran-Nguyen & Camproux, 2025; Verma et al., 2025; Wu et al., 2024).

3 RESULT AND DISCUSSION

3.1 ADME profile and drug likeness evaluation

SwissADME analysis (Table 1) confirmed that Apigenin and Luteolin comply with Lipinski's rules, with no violation, indicating favourable oral bioavailability. both molecules exhibited high GI absorption, tolerable

LogP values and moderate TPSA, suggesting good membrane permeability. This bioavailability score (0.55) for both compounds further supports their potential as orally active hepatoprotective activity. The absence of blood brain barrier permeability predicts reduced CNS toxicity, which is desirable for liver targeting molecules. Overall, both compounds demonstrate drug like behaviour with acceptable physicochemical balance, making them suitable for further talking and biological investigation.

Table 1
ADME- drug likeness profile of Apigenin and Luteolin

Parameter	Apigenin	Luteolin
Molecular Weight (g/mol)	270.24	286.24
LogP	3.22	2.78
H-Bond Donors	3	4
H-Bond Acceptors	4	5
TPSA (Å²)	90.9	111.13
Lipinski Rule Violations	0	0
Bioavailability Score	0.55	0.55
GI Absorption	High	High
BBB	No	No
Result Summary	Drug-like	Drug-like

3.2 Toxicity evaluation

The toxicity is screening outcomes presented in Table 2 indicate the both Apigenin and luteolin fall under toxicity class 5, reflecting minimal acute toxicity with high LD 50 threshold (2500 mg/kg for Apigenin and 3919 mg/kg for Luteolin). Both compounds were predicted to exhibit no hepatotoxic or cytotoxic and immunologically safe, supporting their suitability for liver related therapeutic applications. Carcinogenicity and mutagenicity remained inactive for Apigenin, whereas luteolin show only low risk prediction, which is still with-in tolerable range for natural bio-active compounds. In this analysis, the safety index recommended that both flavonoid permits positive pharmacological tolerance with negligeable toxicity concerns, reinforcing their potential for further biological evaluation.

Table 2 Toxicity assessment of Apigenin and Luteolin

Parameter	Apigenin		Luteolin	
LD50 (mg/kg)	2500mg/kg		3919mg/kg	
Predicted Toxicity Class		Class - 5		Class - 5
Hepatotoxicity		Inactive		Inactive
Carcinogenicity		Inactive		Low risk
Mutagenicity		Inactive		Low risk
Cytotoxicity		Inactive		Inactive
Immunotoxicity		Inactive		Inactive
Safety Profile	Safe		safe	

3.3 network pharmacology

3.3.1 Target identification and overlapping gene screening

Targets screening was initially performed using SwissTargetPridiction for Apigenin and luteolin generating 13 and 28 compound associated gene respectively. Disease related liver injury and hepatotoxicity genes retrieved from GeneCard resulted in a much large catalogue (> 400 genes). Intercepting both dataset using Venn analysis identified 12 common overlapping target (Table 3 and Fig. 1A), including XDH, MAOA, ALOX5, GSK3B, PARP1, ABCG2, TOP1, ESR1, ACHE, PTGS2, ABCC1 and CFTR.

These shared gene represent the core pharmacological nodes linking *Eclipta prostrata* phytochemicals with liver associated pathological mechanism.

3.3.2 Protein-Protein Interaction (PPI) Network Construction and Hub Gene Selection

PPI analysis using STRING database revealed robust connectivity among the overlapping target genes, establishing an extremely collaborative constellation (Fig. 1B). degree based network topology further ascertained hub genes with criticality, amongst which PTGS2, GSK3B, ABCG2, ABCC1, ESR1, CFTR materialized as dominant regulators (Fig. 1C). The hubs are pertinent in inflammation, detoxification, oxidative stress regulation, xenobiotic efflux and fibrotic signalling, demonstrating that both flavonoids wield multi nodes hepatoprotective behaviour rather than single target action.

Table 3
Identification of compound-associated, disease related and overlapping core target for Apigenin and Luteolin

Ligand	Apigenin	Luteolin
	NOX4, AKR1B1, CDK5R1/CDK5, XDH, MAOA, FLT3, CA2, CCNB3/CDK1/CCNB1/CCNB2, ALOX5, ADORA1, CA7, GLO1, APP, SYK, GSK3B, PARP1, TTR, MMP9, CA12, MMP2, CA4, MMP12, CD38, CYP1B1, ABCG2, AKR1B10, TNKS2, TNKS, TOP1, ARG1	**NOX4, AKR1B1, CDK5R1/CDK5, XDH, MAOA, FLT3, CYP19A1, ESR1, CCNB3/CDK1/CCNB1/CCNB2, ACHE, ADORA1, PTGS2, ESR2, CDK6, ADORA2A, SYK, GSK3B, ABCC1, HSD17B1, TTR, CSNK2A1, CFTR, CYP1B1, ABCG2, AKR1B10, TNKS2, TNKS**
GeneCards Disease-Related Genes	NAT2, CYP2E1, GPT, SLC17A5, GSTM1, CYP3A4, CYP2C9, CYP2B6, F2, CYP1A2, ABCB1, TPMT, TNF, GGT1, ALB, CYP2C19, NR1I2, POLG, CYP2D6, GSTP1, SLCO1B1, NFE2L2, CYP3A5, ABCG2, ALPP, MTHFR, CYP1A1, IL4, ABCB11, ABCC2, IL4R, UGT1A1, IL10, SOD1, DNM1L, CES1, HGF, LPL, GSS, HMOX1, NQO1, ABCB7, NR1H2, NR1I3, IL6, PPARG, APOA1, UGT2B7, CYP2C8, AKR1A1, RASGRP1, KCNIP4, ARHGAP24, EGFR, AHR, HLA-A, SLPI, PTGS2, INS, KRT18, NOS2, SOD2, CES2, ACHE, CASP9, NR1H4, SORD, PPIG, INSR, TP53, MAOB, XDH, LEPR, IGF1, SLCO1B3, CYP7A1, COMT, CD36, GYS1, NOS3, IGF2, CTLA4, GPX4, IRS1, IRS2, LEP, APOC3, GPX1, GYS2, RDH5, UCP1, ADRB3, GPX3, LMX1A, IRS4, ETNK2, MT-CO2, HLA-B, KDR, CYP2A6, ABCC3, NFKB1, PARP1, UGT1A4, IL2, MAPK8, ATP8B1, CAT, IL1B, BCHE, KRT8, MAPK1, SIRT1, HLA-DRB1, SMAD2, TGFB1, GSR, CPT1A, SDHB, TSPAN12, ESR1, MCL1, POMC, XPO1, CD33, NR0B1, CYP7B1, GCLC, COX5A, HRH2, PRL, GCLM, HLA-DQA1, SHBG, TTF2, CYP27A1, ERBB2, PTPN1, TGFA, ABCG1, HLA-C, LTC4S, HPX, BACH1, IL1RAPL2, AFP, GPT2, MDM2, STAT1, ALK, CAV1, SIRT3, ERCC1, MB, F3, APOC2, MKI67, OSMR, AASS, EHHADH, GSTM2, SLC26A1, CP, CFTR, GSK3B, TERT, TNFRSF1A, TNNI3, GLUL, CSF2, DLK1, COL18A1, TXNRD1, MMAB, GSTA1, BAAT, SPINK1, CUX2, APEH, OXA1L, RIPOR2, CD4, CRP, SEPSECS, FTCD, DNAL1, PDGFRA, NLRP3, SCARB1, ABCB4, HMGCS2, PDK4, SLC7A11, IL11, KYAT1, FIP1L1, ITPA, IFNG, SLC19A1, HMGCR, TNFSF10, CSF3, TYMS, HIF1A, POR, PPARA, CYCS, FDFT1, IFNA2, AADAC, EDNRA, EPHX2, UGT1A9, HLA-DQB1, APCS, FANCI, DNMT1, JUN, RPS6KB1, CASP3, TOP1, ABCC1, FASLG, NAT1, MT2A, SLC22A1, SLCO2B1, CCND1, HSP90AA1, BCL2, LDLR, AIFM1, BAX, EIF2AK2, GUSB, MAOA, TNFRSF10B, ALDOB, CCR5, GC, BID, CHKA, RBP4, ADH1B, SLC10A1, SLC22A2, FPGS, ADH1C, HLA-DRB5, RET, CASP8, MPO, ADA, CALR, EGF, CXCR2, ITGB2, ALOX5, ANPEP, APOE, ASS1, CD44, CYP17A1, G6PD, HSPA5, ICAM1, MAP3K5, MAPK3, MAPK9, P4HB, PCSK9, PLG, PNP, RB1, STAT2, ATP7B, CASP2, DHFR, HPRT1, KNG1, ODC1, PIK3C2A, PPARGC1A, ADIPOQ, CETP, DHODH, BAD, GOT1, SLC8A1, TFAM, WARS2, ADORA3, AOX1, CHGA, EIF3A, RIPK3, RPS27A, ADH7, AKR1D1, EPO, GGH, UBE2B, CXCL2, GDF6, PEX6, SLC22A7, IFNA1, IL18BP, SLC47A1, ADGRF5, MTOR, AKT2, CTNNB1, NTRK3, HSPB1, ITGB3, MAPK14, DPYD, ADAM17, CPT2, DNMT3B, EDNRB, FAS, HMGB1, IL2RA, IL6R, KCNH2, LMNA, TF, CCL2, CD40LG, CDC25C, HNF4A, KEAP1, NR3C1, OPRM1, PRKAA2, RHOA, SERPINA1, SQSTM1, STK11, EPCAM, ITGA5, TNFRSF1B, CD79A, CDK1, CHRNA2, CUL3, EPHA3, ERCC2, F8, F9, HSF1, KLK3, PPARD, TDO2, TFAP2A, TLR1, VEGFC, ALAD, ANXA5, APOB, CFL1, FTO, GZMB, IRF1, MTHFD1, NR1H3, OTC, PRDX2, PRKAA1, SGPL1, ACOX1, BCL2L11, CALM1, EGR1, EHMT2, HBB, PCK2, PDX1, PTPA, SLC1A5, TJP1, TKT, ATF3, BAK1, BMP6, CFD, CPOX, CXADR, CXCL10, E2F1, GNMT, HFE, HMBS, IDUA, NAGLU, NCOR1, PRDX5, SPTBN1, SQLE, UROD, ALAS1, CALCA, CD80, CXCL1, ENDOG, EPHX1, HBA1, HSPA4, IL17A, IL18, KLF6, KRT19, KRT7, PFKFB3, SELL, SET, UBC, ABCG8, AOC1, APOA5, BCL3, CPA6, NDUFS4, NR0B2, PNPLA3, S100A11, SULT2A1, TACR2, TCN2, TWNK, CABIN1, PAPSS2, SMN1, TRIT1, AKR7A2, CXCL5, GNRH1, GSTZ1, JUNB, KLRK1, KRIT1, MTF1, NCOA6, SLC10A2, CXCL9, DAPK2, FGF21, NPY4R, SESN2, SLCO1A2, CHRNA9, CROT, LACTB, CKAP2, PDLIM3, SH3BP5, SLC16A4, SLC51A	

Ligand	Apigenin	Luteolin
	NOX4, AKR1B1, CDK5R1/CDK5, XDH, MAOA, FLT3, CA2, CCNB3/CDK1/CCNB1/CCNB2, ALOX5, ADORA1, CA7, GLO1, APP, SYK, GSK3B, PARP1, TTR, MMP9, CA12, MMP2, CA4, MMP12, CD38, CYP1B1, ABCG2, AKR1B10, TNKS2, TNKS, TOP1, ARG1	NOX4, AKR1B1, CDK5R1/CDK5, XDH, MAOA, FLT3, CYP19A1, ESR1, CCNB3/CDK1/CCNB1/CCNB2, ACHE, ADORA1, PTGS2, ESR2, CDK6, ADORA2A, SYK, GSK3B, ABCC1, HSD17B1, TTR, CSNK2A1, CFTR, CYP1B1, ABCG2, AKR1B10, TNKS2, TNKS
Common Overlapping Genes (Venn Intersection)	XDH, MAOA, ALOX5, GSK3B, PARP1, ABCG2, TOP1, ESR1, ACHE, PTGS2, ABCC1, CFTR	

3.3.3 GO, KEGG and Clustering functional pathway interpretation

GO enrichment (Fig. 2A) molecular biology (MB) revealed that the identified target genes were predominantly involved in xenobiotic response, oxidative stress management, transmembrane efflux and cellular detoxification, indicating a strong association with hepatoprotection. Molecular function (Fig. 2B) term further highlight ATP binding, ABC transporter activity, oxidoreductase functions and anion transport, suggesting improved toxin clearance and antioxidant defence. KEGG pathway analysis (Fig. 3A&B) consistently positioned ABC transporter as the top entrenched pathway. followed by metabolic and inflammatory signalling cascades including phenylalanine metabolism, arachidonic acid metabolism, NF-kP signalling, bile secretion and serotonergic pathway, confirming multi-pathway regulatory potential. Dendrogram clustering (BP, MF, KEGG) further grouped this function into integrated modules linked to detoxification, efflux transport, inflammatory suppression and metabolic restoration, were hub nodes such as ESR1, PTGS2, GSK3B, ABCC1, ABCG2, and CFTR play central regulatory role. collectively the enrichment results strongly support that Apigenin and Luteolin exert hepatoprotective action via transporter mediated, detoxification, toxin clearance oxidative and inflammation control and metabolic homeostasis, reinforcing the therapeutic potential in liver injury.

3.4 Molecular docking Analysis

Molecular docking was performed to assess the interaction strength and functional relevance of the screened target. Apigenin and Luteolin were individually docked against the three major ABC transporter protein involved in the hepatic xenobiotic clearance CFTR(2PZF), ABCC1(4C3Z) ana ABCG2(8QCM). The docking affinity value with the protein roles has summariser in Table 4 and the corresponding binding interaction views are illustrated in Fig. 4 and Fig. 5.

Both compounds successfully inserted into the catalytic cavity of all the three transporters farming staple binding architectures Apigenin exhibited the strongest affinity towards CFTR (-8.198 kcal/mol) followed by ABCC1 (-7.106) and ABCG2 (-6.077). likewise, luteolin displayed comparable potency, particularly toward CFTR (-8.081) and ABCG2 (-6.188), reflecting closed structural compatibility with the

transporter residues. These scores indicate a favourable ligand transporter fit implying that both phytochemicals may enhance transport efficiency and attenuate intracellular toxin build up during the hepatocellular stress.

Interaction profiling elevated that complex stabilization was mediator predominantly through conventional hydrogen bond, carbon hydrogen bond, van der Waals attractions and hydrophobic contract including π-Sigma, π-alkyl and π-π stacking. such as interaction promote firm anchoring inside the binding groove, reducing the probability of ligand displacement. Only minimal unfavourable donor-donor and acceptor-acceptor clashes were observed and were largely out balance by favourable bonding patterns confirming stable and strain free docking.

Structurally, Apigenin CFTR (Fig. 4A) displayed strong hydrogen bonding complemented with hydrophobic occupancy supporting it is high affinity. Apigenin ABCC1 (Fig. 4B) and Apigenin ABCG2 (Fig. 4C) interaction including multiple van der Waals and aromatic stabilising contact, enhancing cavity detention. For Luteolin enhanced π-stacking interaction in ABCG2 (Fig. 5C) suggested better aromatic compatibility, compare to apigenin whereas CFTR and ABCC1 complexes also demonstrated satisfactory stabilization.

In this docking outcome strongly correlated with network pharmacology Geo and KEGG enrichment result, confirming that Apigenin and luteolin effective target ABC mediated detoxification, bile/ion transport, xenobiotic efflux and redux regulations.

Table 4
Molecular docking score of selected Phyto ligands with ABC transporter proteins showing target role, binding strength (kcal/mol) and structural PDB ID

ligands	Pathway	Target protein	Common name	Role	PDB ID	Affinity (kcak/mol)
Apigenin	ABC transporter	CFTR	Cystic fibrosis transmembrane conductance regulator	Ion channel / transport	**2PZF**	**-8.198 (2)**
		ABCC1	ATP binding cassette subfamily C member 1	Transport protein	**4C3Z**	**-7.106 (1)**
		ABCG2	ATP binding cassette Super-family G member 2	ABC transporter	**8QCM**	**−6.077 (3)**
Luteolin		CFTR	Cystic fibrosis transmembrane conductance regulator	Ion channel / transport	**2PZF**	**-8.081 (2)**
		ABCC1	ATP binding cassette subfamily C member 1	Transport protein	**4C3Z**	**-7.003(3)**
		ABCG2	ATP binding cassette Super-family G member 2	ABC transporter	**8QCM**	**-6.188 (1)**

4 CONCLUSION

This analysis combined network pharmacology, ADME-tox profiling combined with molecular with molecular docking analysis was employed to assess the hepatoprotective potential of Apigenin and Luteolin derived from *Eclipta prostrata*. ADME-tox result confirmed good informed good drug likeness, strong absorption and low toxicity (class 5). Indicating favourable safety for oral publication. network and Venn analysis identified 12 overlapping liver related targets, with hub gene including ABCC1, ABCG2, CFTR, PTGS2, ESR, GSK3B, PARP1, TOP1, ALOX5, AND XDH. GO and KEGG enrichment demonstrate the involvement in xenobiotic detoxification, oxidative stress defence, ABC efflux activity, bile secretion and metabolic balance. Highlighting multi target therapeutic potential.

Docking result showed stable ligand- protein complex, where both flavonoids strongly interact with CFTR, ABCC1 and ABCG2 supported by hydrogen bonding, π-stacking and hydrophobic force. Apigenin exhibited highest affinity towards CFTR (-8.198 kcal/mol), while Luteolin showed comparable binding (-8.081 kcal/mol) and strong interaction with ABCG2 suggesting their role in enhancing toxic efflux and production of hepatocytes. In the end of the study the finding indicates that Apigenin and Luteolin may serve as promising natural hepatoprotective molecules acting through transporter modulation and

antioxidant, anti-inflammatory pathway. experimental validation is recommended to modulate this in silico insight into the therapeutic application.

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Figures

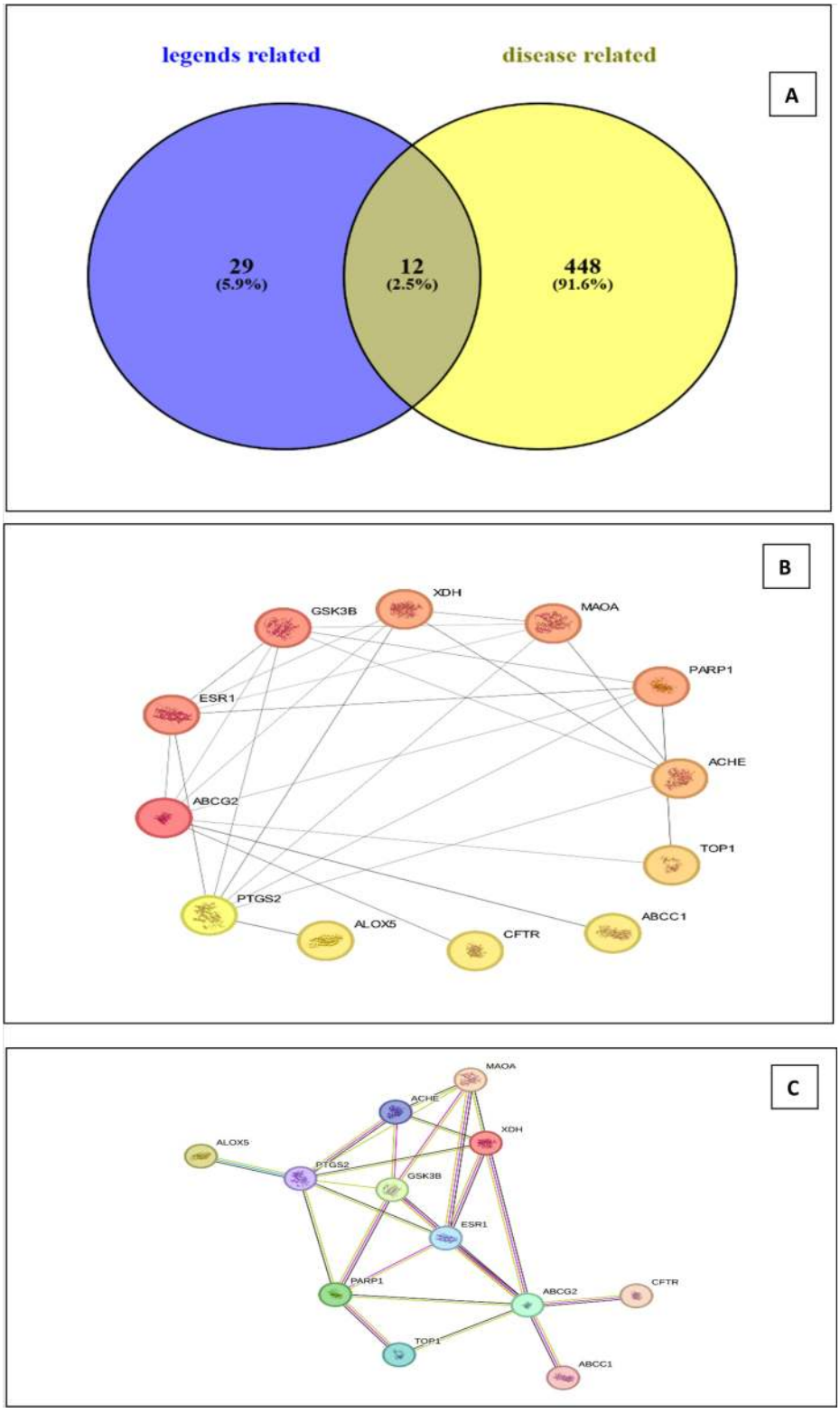

Figure 1

Venn diagram, A) Overlap between compound-predicted target and disease-associated hepatotoxicity genes, identifying 12 core intersection gene B) STRING based protein -protein interaction C) hub gene ranking

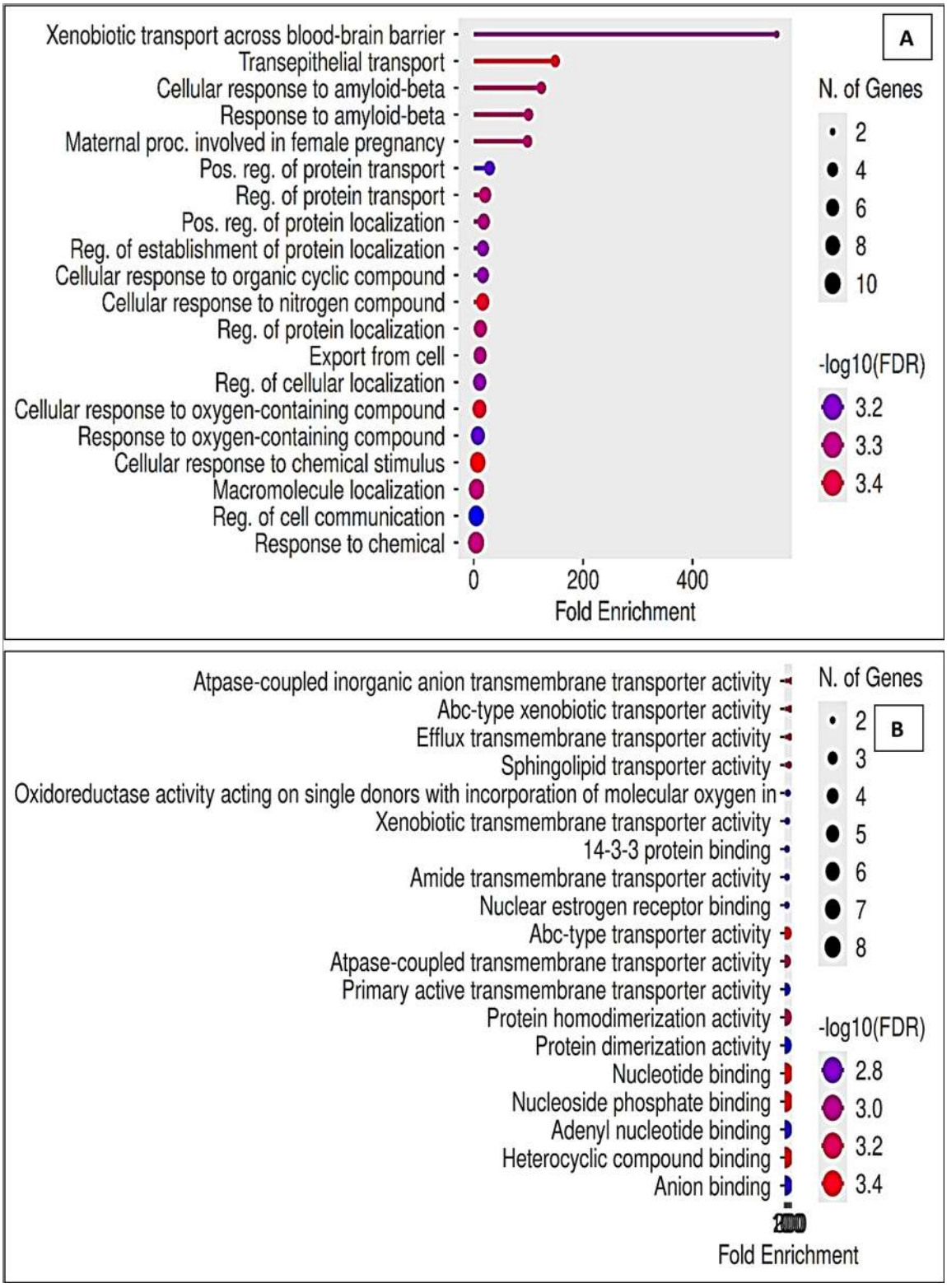

Figure 2

Gene Ontology (GO) enrichment clustering of common target gene. A) TOP enriched biological process B) molecular function

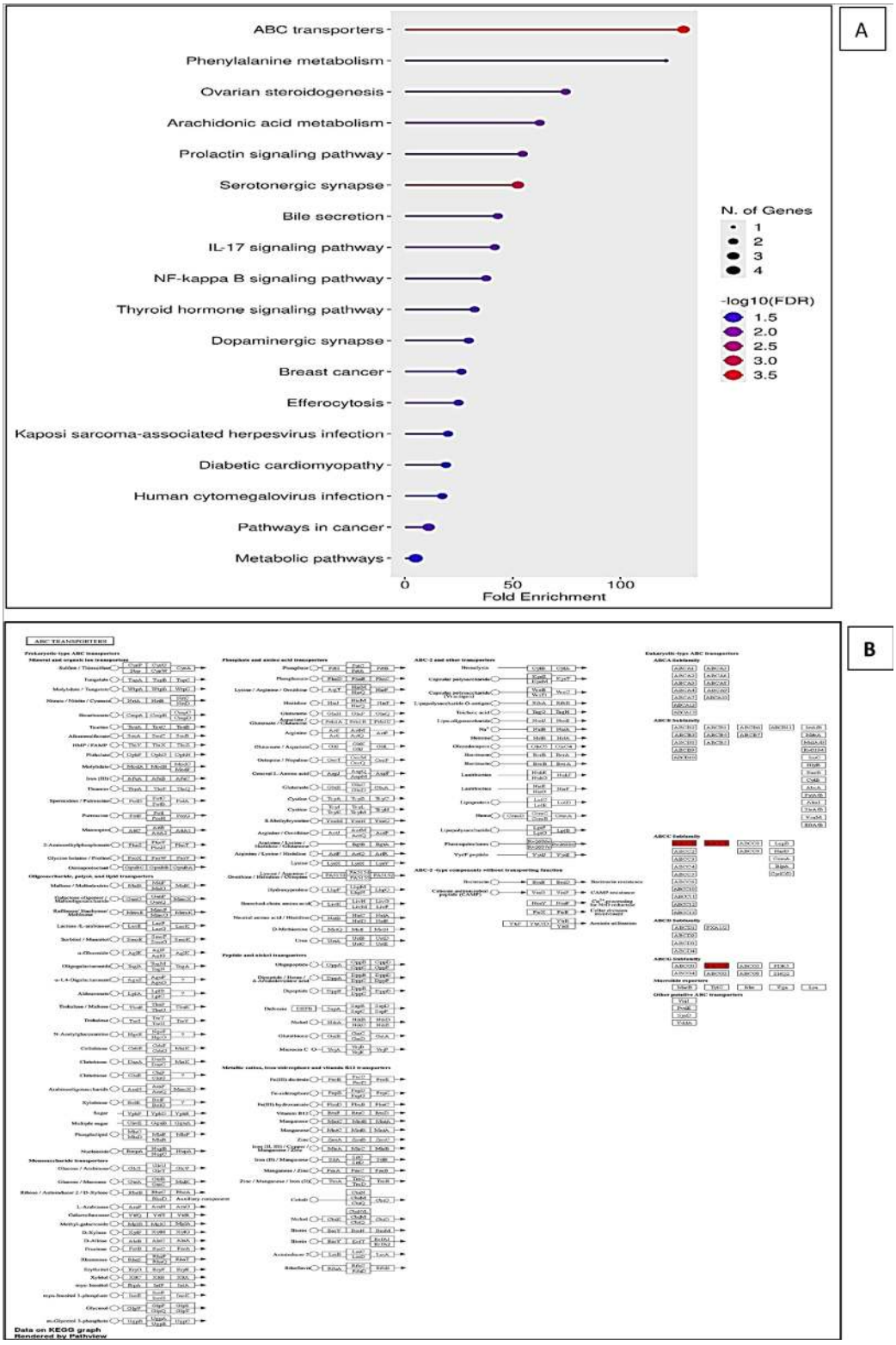

Figure 3

KEGG pathway and signalling map of target. A) KEGG bar plot showing top enriched pathway with transporters ranked B) KEGG pathway interaction map highlighting the signalling connectivity of enriched genes.

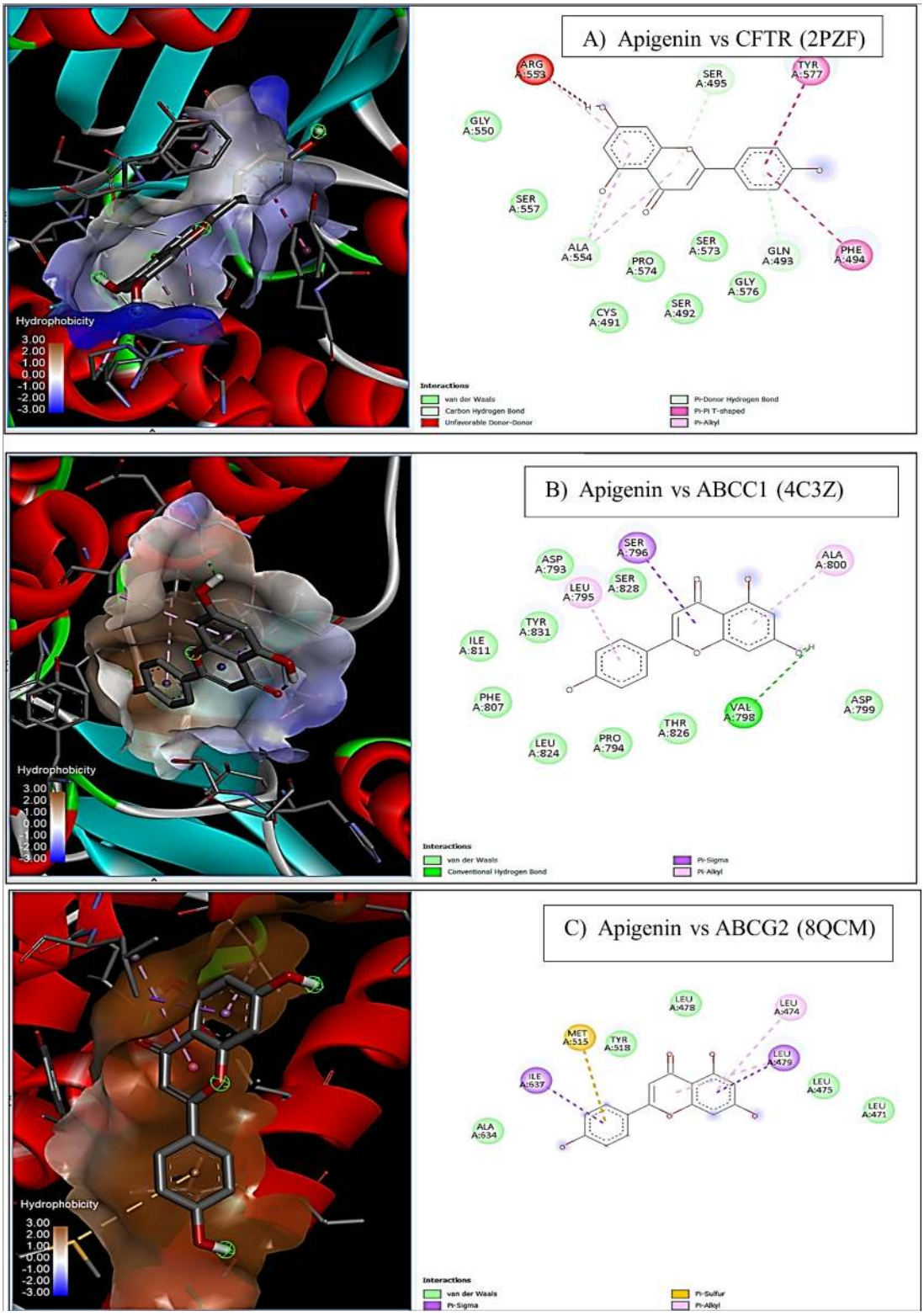

Figure 4

docking interaction profile of Apigenin with ABC-transporter targets (CFTR, ABCC1 and ABCG2). (A) Binding mode of Apigenin vs CFTR (PDB: 2PZF) showing hydrogen-bonding and pocket fit visualization. (B) Interaction of Apigenin vs ABCC1 (PDB: 4C3Z) represented with surface topology and ligand orientation within active cavity. (C) Docked conformation of Apigenin vs ABCG2 (PDB: 8QCM) highlighting hydrophobic contacts, van der Waals forces and π-stacking interactions

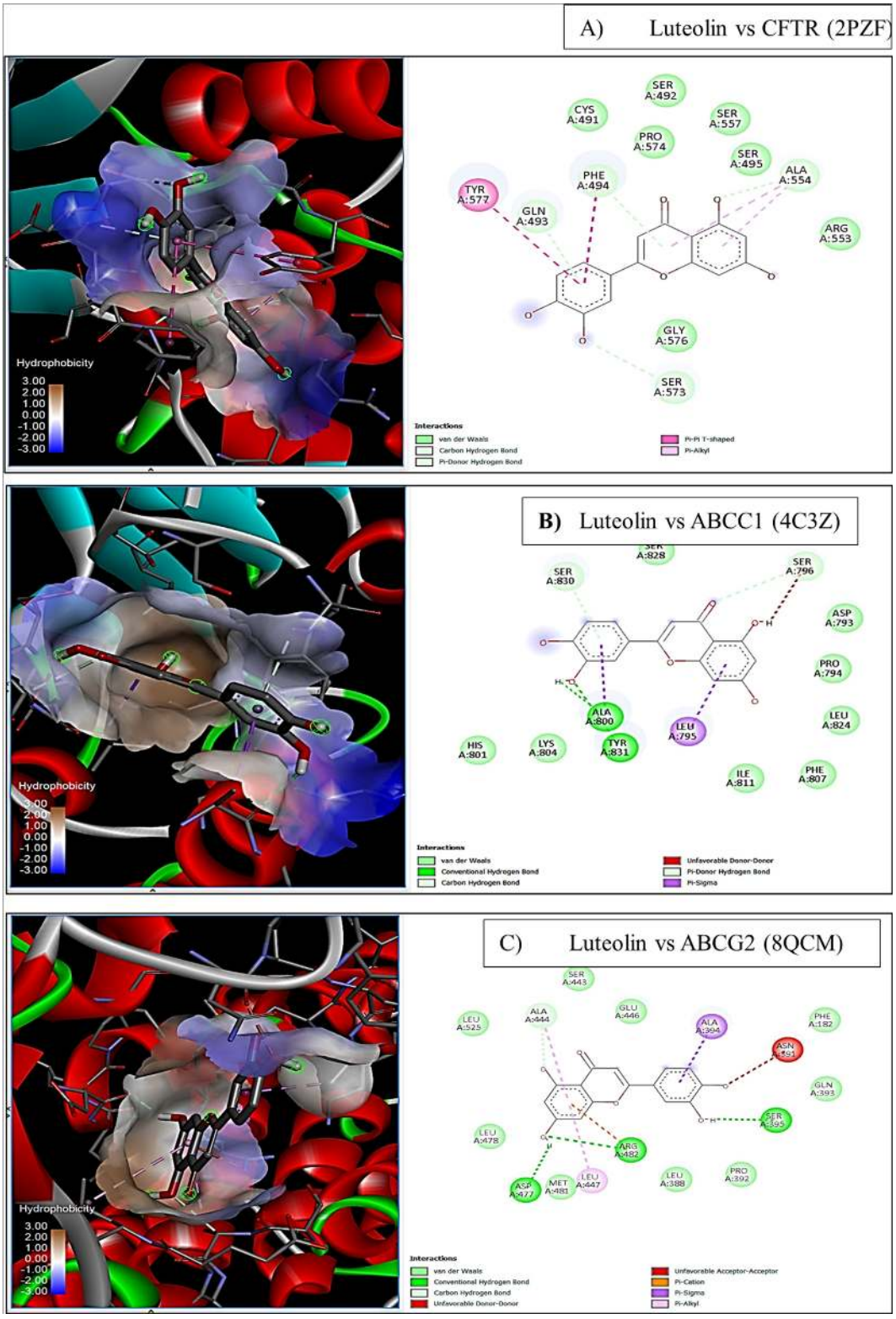

Figure 5

Molecular docking interaction profile of Luteolin with ABC-transporter targets (CFTR, ABCC1 and ABCG2). (A) Luteolin–CFTR complex (PDB: 2PZF) illustrating hydrogen bonding, ligand pose orientation and binding within the channel pocket. (B) Luteolin–ABCC1 complex (PDB: 4C3Z) presenting interaction surface mapping and ligand accommodation within the transporter active cavity. (C) Luteolin–ABCG2

complex (PDB: 8QCM) demonstrating hydrophobic interactions, van der Waals stabilization and π–stacking contributions within the core binding region.