Supplementary data

Table S1: Detail results of GO enrichment KEGG Pathways analysis for 13 hub target genes.

Target genes	Biological process	Cellular component	Molecular function	KEGG pathways
AKT1	Differentiation of osteoblasts Development of the maternal placenta Enhancement of protein phosphorylation Promotion of endothelial cell proliferation	Nucleus	Protein kinase activity	Resistance to EGFR tyrosine kinase inhibitors Hormonal resistance Diabetes-induced cardiomyopathy NF-κB signaling pathway ErbB pathway signaling Ras pathway signaling Rap1 pathway signaling
ABCG2	Lipid transport, Organic anion transport, Urate transport, Biotin transport	Nucleoplasm	Protein binding	Antifolate resistance ABC transporters Bile secretion
SRC	Protein degradation Adaptation to nutrient availability Inhibition of telomere maintenance by telomerase Cellular reaction to insulin signaling	Podosome	Protein kinase activity	Resistance to EGFR tyrosine kinase inhibitors Hormone resistance ErbB pathway activation NF-κB pathway signaling Chemokine-mediated signaling Mitophagy in animals Cellular endocytic process
CDK2	Progression from G1 to S phase in the mitotic cell cycle Transition from G2 to M phase in the mitotic cell cycle Suppression of transcription from the RNA polymerase II promoter Duplication of DNA	Chromosome, telomeric region	Magnesium ion binding	NF-κB pathway signaling Regulation of the cell cycle Meiotic division of oocytes p53 pathway activation PI3K-Akt pathway signaling Cellular aging and senescence Progesterone-induced oocyte maturation
CYP19A1	Suppression of chronic inflammatory response Steroid synthesis Estrogen production Androgen breakdown	Endoplasmic reticulum	Monooxygenase activity	Steroid hormone biosynthesis Metabolic pathways Cholesterol metabolism
EGFR	MAPK cascade, Bone formation Development of the embryonic placenta Enhancement of protein phosphorylation	Golgi membrane complex	Virus receptor activity	Resistance to EGFR tyrosine kinase inhibitors Hormonal resistance MAPK pathway signaling ErbB pathway activation Ras pathway regulation Cholesterol processing and metabolism Calcium-mediated signaling

S1 Table is continue…….

Target genes	Biological process	Cellular component	Molecular function	KEGG pathways
ESR1	Inhibition of transcription by RNA polymerase II Growth of antral ovarian follicles Development of epithelial cells Structural modification of chromatin	Chromatin	Sequence-specific DNA binding at the RNA polymerase II core promoter proximal region	NF-κB pathway activation Cholesterol processing and regulation Prolactin pathway signaling Thyroid hormone pathway modulation Calcium reabsorption influenced by endocrine and other regulatory factors
IGF1R	Development of the cardiac atrium Activation of the immune response Cellular signal transmission Transmembrane receptor tyrosine kinase signaling pathway	Plasma membrane membrane-bounded organelle	G-protein alpha-subunit binding	Resistance to EGFR tyrosine kinase inhibitors Hormonal resistance MAPK pathway activation Ras pathway regulation Cholesterol processing and metabolism HIF-1 pathway signaling
IL2	Inhibition of protein phosphorylation Adaptive immune system response Activation of leukocytes in immune defense Enhancement of immunoglobulin production	Extracellular region	Cytokine activity	Cytokine and receptor interactions Viral modulation of cytokine and receptor activity PI3K-Akt pathway signaling C-type lectin receptor pathway activation JAK-STAT pathway signaling NF-κB pathway activation Differentiation of Th17 cells
KDR	Formation of new blood vessels Development of ovarian follicles Branching in blood vessel formation Generation of blood vessels from precursor cells	Extracellular region	Protein tyrosine kinase activity	Resistance to EGFR tyrosine kinase inhibitors MAPK pathway activation Ras pathway regulation Cholesterol processing and metabolism Calcium-mediated signaling PI3K-Akt pathway signaling
MMP2	Formation of new blood vessels Growth and maturation of ovarian follicles Release of an oocyte from the ovarian follicle Transformation of the follicle into the corpus luteum	Extracellular region	Fibronectin binding	Hormonal resistance Migration of leukocytes across the endothelium GnRH pathway signaling Estrogen pathway activation Relaxin-mediated signaling AGE-RAGE pathway involvement in diabetic complications Heart disease associated with diabetes

S1 Table is continue……..

Target genes	Biological process	Cellular component	Molecular function	KEGG pathways
MMP9	Development of the skeletal system Enhancement of protein phosphorylation Protein breakdown (proteolysis) Regulation of programmed cell death (apoptosis)	Extracellular region	Endopeptidase activity	Hormonal resistance IL-17 pathway signaling TNF pathway activation Leukocyte migration across the endothelium Estrogen pathway modulation Relaxin-mediated signaling Diabetes-related heart disease
PTGS2	Prostaglandin biosynthetic process, Angiogenesis, Response to oxidative stress, Embryo implantation	Nuclear inner membrane	Peroxidase activity	Arachidonic acid metabolism Metabolic processes NF-κB pathway signaling Clearance of apoptotic cells (efferocytosis) VEGF pathway involvement in blood vessel formation C-type lectin receptor pathway activation Retrograde endocannabinoid signaling Serotonin synapse regulation Production of ovarian steroids Oxytocin-mediated signaling

Table S2: Interaction data of all residues and gene targets enlisting Binding affinity, RMSD, 2D structure and amino acid interactions.

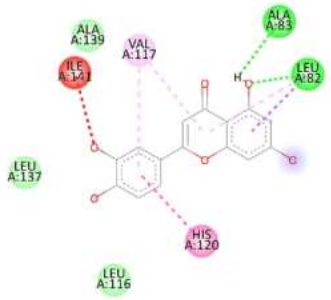
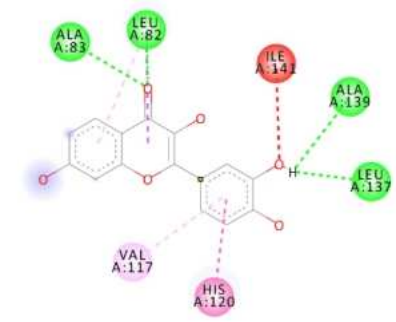
Sr. no.	Protein-ligand	BA	RMSD	2D	Interactions
1	MMP2 with luteolin-7-olate	-8.3	0.3456 Å		H (ALA A:83, LEU A:82), HIS A:120, LEU A:116, LEU A:137, ILE A:141, ALA A:139, VAL A:117
2	MMP2 with fisetin	-8.3	1.2345 Å		H (ALA A:83, LEU A:82, ALA A:139, LEU A:137), ILE A:141, HIS A:120, VAL A:117

Table S2 is continue…….

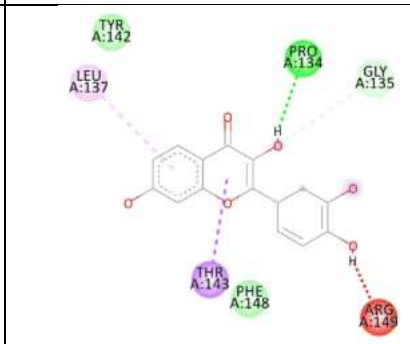
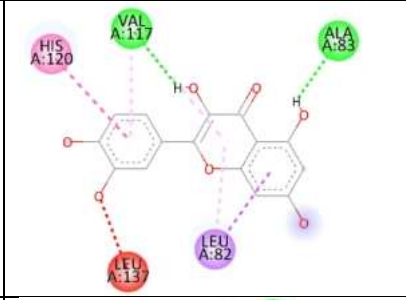
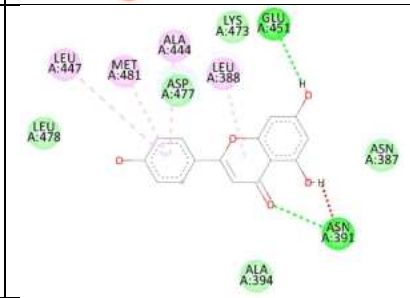
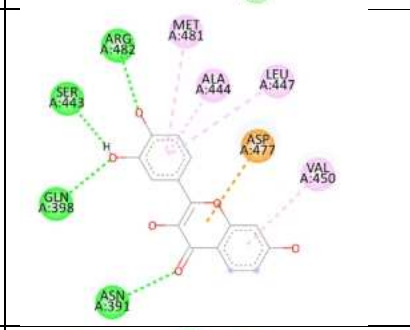
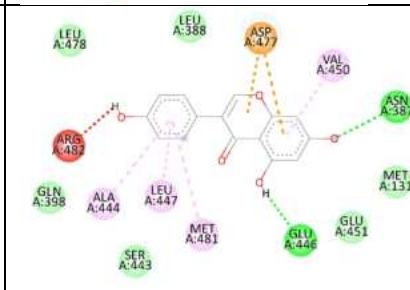
Sr. no.	Protein-ligand	BA	RMSD	2D	Interactions
3	MMP2 with luteolin	-8	2.3456 Å		H (PRO A:134), GLY A:135, ARG A:149, PHE A:148, THR A:143, LEU A:137, TYR A:142
4	MMP2 with quercetin	-8.7	1.9876 Å		H (VAL A:117, ALA A:83), LEU A:82, LEU A:137, HIS A:120
5	ABCG2 with apigenin	-7.8	2.1234 Å		H (GLU A:451, ASN A:391), ASN A:387, ALA A:394, LEU A:478, LEU A:447, MET A:481, ASP A:477, ALA A:444, LEU A:388, LYS A:473, GLU A:451
6	ABCG2 with fisetin	-7.5	1.8765 Å		H (ASN A:391, GLN A:398, SER A:443, ARG A:482, MET A:481, ALA A:444, LEU A:447, ASP A:477, VAL A:450
7	ABCG2 with genistein	-9.7	0.4321 Å		H (ASN A:387, GLU A:446), MET A:131, GLU A:451, MET A:481, LEU A:447, SER A:443, ALA A:444, GLN A:398, ARG A:482, LEU A:478, LEU A:388, ASP A:477, VAL A:450

Table S2 is continue…….

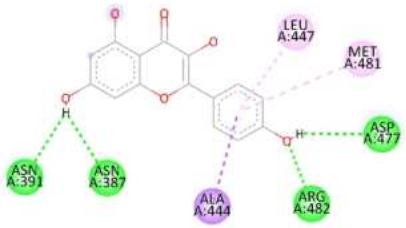
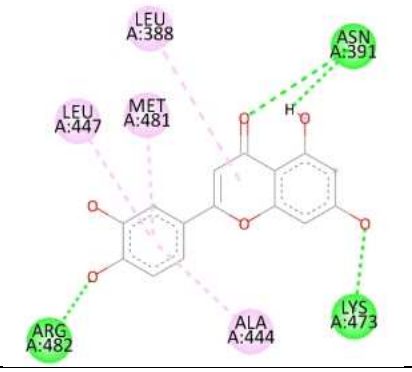
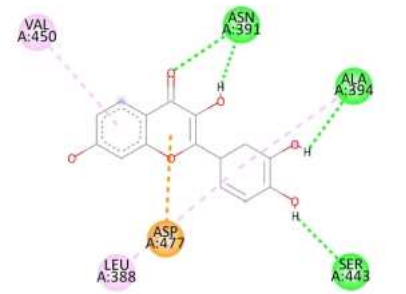
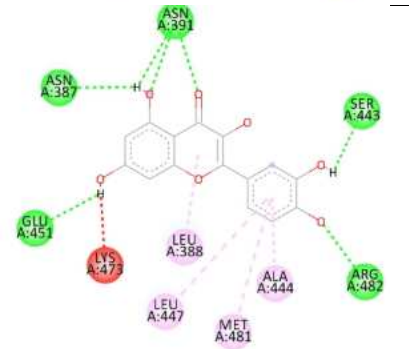
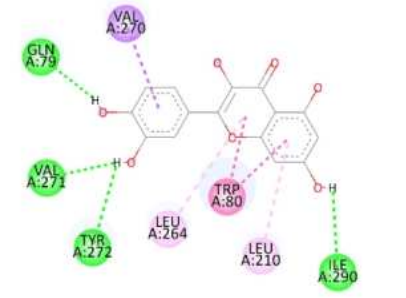
Sr. no.	Protein-ligand	BA	RMSD	2D	Interactions
8	ABCG2 with kaempferol	-9.2	2.4567 Å		H (ASP A:477, ARG A:482, ASN A:387, ASN A:391), ALA A:444, LEU A:447, MET A:481
9	ABCG2 with luteolin-7-olate	-9.5	1.6543 Å		H (ASN A:391, LYS A:473, ARG A:482), ALA A:444, LEU A:447, MET A:481, LEU A;388
10	ABCG2 with luteolin	-8.2	0.9876 Å		H (ASN A;391, ALA A;394, SER A;443), ASP A;477, LEU A;388, VAL A;450
11	ABCG2 with quercetin	-8	2.3456 Å		H (GLU A;451, ASN A;387, ASN A;391, SER A;443, ARG A;482, ALA A;444, MET A;481, LEU A;388, LEU A;447, LYS A;473
12	AKT1 with quercetin	-8.1	2.7654 Å		H (TYR A;272, VAL A;271, GLN A;79, ILE A;290), VAL A;270, LEU A;210, TRP A;80, LEU A;264

Table S2 is continue…….

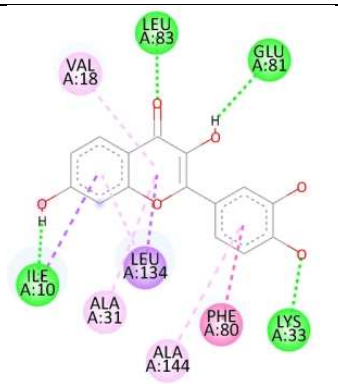
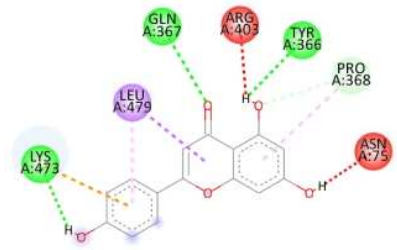
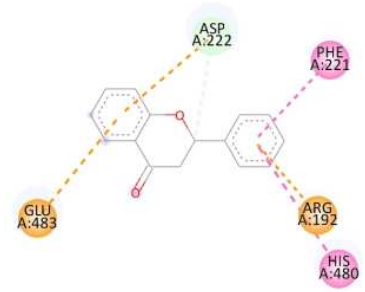
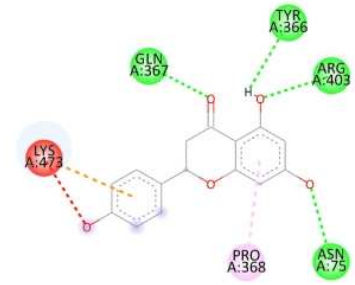
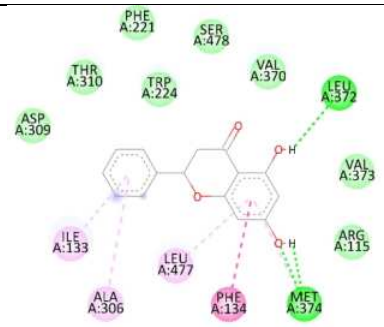
Sr. no.	Protein-ligand	BA	RMSD	2D	Interactions
13	CDK2 with fisetin	-9.6	2.6543 Å		H (LEU A;83, GLU A;81, LYS A;33, ILE A;10), VAL A;18, PHE A;80, ALA A;144, LEU A;134, ALA A;31
14	CYP1NA1 with apigenin	-8.5	2.5432 Å		H (LYS A;473, GLN A;367, TYR A;366), LEU A;479, ARG A;403, PRO A;368
15	CYP1NA1 with flavanone	-8.3	1.4567 Å		ASP A;222, PHE A;221, ARG A;192, HIS A;480, GLU A;483
16	CYP1NA1 with naringenin	-8.5	0.6789 Å		H (GLN A;367, TYR A;366, ARG A;403, ASN A;75), PRO A;368, LYS A;473
17	CYP1NA1 with pinocembrin	-8.3	2.9876 Å		H (LEU A;372, MET A;374), ASP A;309, THR A;310, PHE A;221, TRP A;224, SER A;478, VAL A;370, VAL A;373, ARG A;115, PHE A;134, LEU A;477, ALA A;306, ILE A;133

Table S2 is continue…….

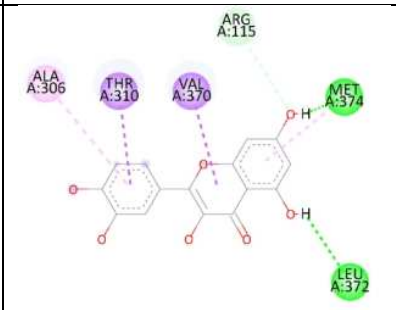
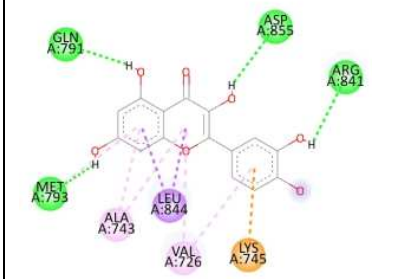
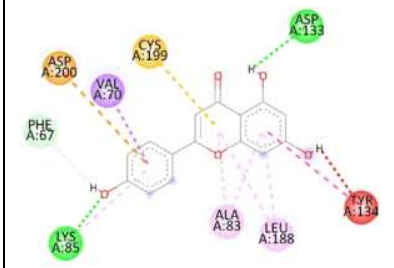
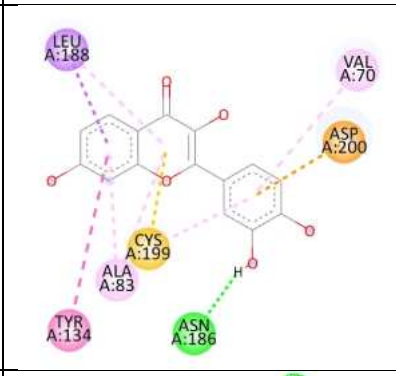
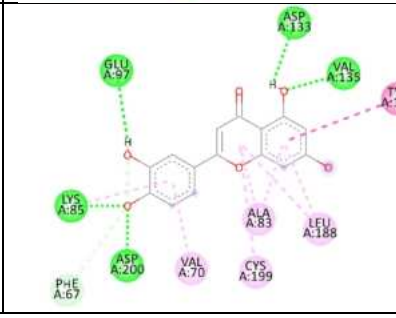
Sr. no.	Protein-ligand	BA	RMSD	2D	Interactions
18	CYP1NA1 with quercetin	-8	1.7654 Å		H (MET A;374, LEU A;372), ALA A;306, THR A;310, VAL A;370, ARG A; 115
19	EGFR with quercetin	-9.8	0.3456 Å		H (MET A; 793, GLN A;791, ASP A;855, ARG A;841), ALA A;743, LEU A;844, VAL A;726, LYS A;745
20	GSK3B with apigenin	-8.8	2.3456 Å		H (LYS A;85, ASP A;133), PHE A;67, ASP A;200, VAL A;70, CYS A;199, ALA A;83, LEU A;188, TYR A;134
21	GSK3B with fisetin	-9.1	1.9876 Å		H (ASN A;186), CYS A;199, ALA A;83, TYR A;134, LEU A;188, VAL A;70, ASP A;200
22	GSK3B with luteolin-7-olate	-8	0.5678 Å		H (ASP A;200, LYS A;85, GLU A;97, ASP A;133, VAL A;135), PHE A;67, VAL A;70, CYS A;199, ALA A;83, LEU A;188, TYR A;134

Table S2 is continue…….

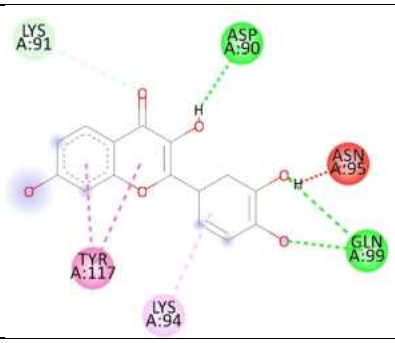
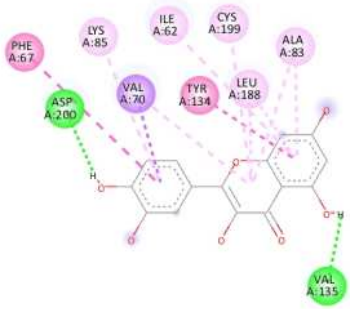
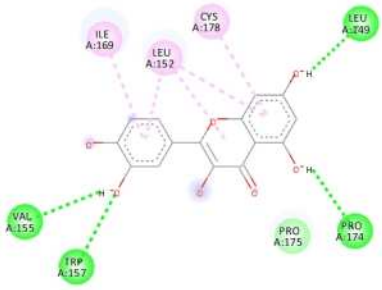
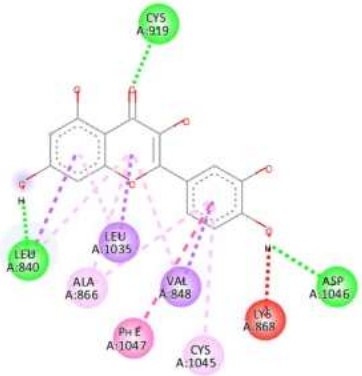
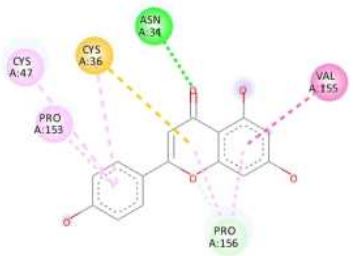
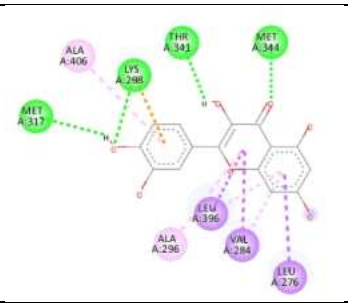
Sr. no.	Protein-ligand	BA	RMSD	2D	Interactions
23	GSK3B with luteolin	-7.8	2.1234 Å		H (ASP A;90, GLN A;99), ASN A;95, LYS A;94, TYR A;117, LYS A;91
24	GSK3B with quercetin	-9.6	1.8765 Å		H (VAL A;135, ASP A;200), PHE A;62, LYS A;85, ILE A;62, CYS A;199, ALA A;83, LEU A;188, TYR A;134, VAL A;70
25	IGF1R with quercetin	-8.3	2.4567 Å		H (LEU A;149, PRO A;174, TRP A;157, VAL A;155), PRO A;175, ILE A;169, LEU A;152, CYS A;178
26	KDR with quercetin	-8.7	0.9876 Å		H (LEU A;840, CYS A;919, ASP A;1046), LYS A;868, CYS A;1045, VAL A;848, PHE A;1047, LEU A;1035, ALA A;866
27	PTGS2 with apigenin	-7.8	1.0987 Å		H (ASN A;34), VAL A;155, PRO A;156, PRO A;153, CYS A;47, CYS A;36

Table S2 is continue…….

Sr. no.	Protein-ligand	BA	RMSD	2D	Interactions
28	SRC with quercetin	-9.7	0.8765 Å		H (MET A;317, LYS A;298, THR A;341, MET A;344), ALA A;406, ALA A;296, LEU A;396, VAL A;284, LEU A;276

Random Forest classification of compound bioavailability
We implemented a Random Forest classifier (scikit-learn, n_estimators=500, class_weight='balanced') to predict compound bioavailability using molecular weight (MW), hydrogen bond acceptors (HBA), hydrogen bond donors (HBD), and MLOGP. Performance was evaluated using stratified 5-fold cross-validation. The model achieved accuracy = 97%, precision = 98%, recall = 97%, F1 = 0.975, and AUC = 0.96.
The confusion matrix showed 467 true positives, 138 true negatives, 10 false positives, and 9 false negatives. Feature importance analysis indicated HBA (44.40%) as the most influential predictor, followed by MW (22.13%), HBD (16.93%), and MLOGP (15.07%). These details demonstrate model reliability and clarify the contribution of features to classification outcomes.

Compound–target prioritization framework
To address the need for a clear hierarchy, we integrated three parameters: (1) network centrality (degree, MCC, MNC from CytoHubba), (2) docking binding affinity (ΔG values), and (3) ADME/bioavailability scores. Each measure was normalized and combined into a composite Priority Score:
Priority Score = 0.4 × Centrality_norm + 0.4 × (−ΔG)_norm + 0.2 × ADME_norm.
This framework ranks compound–target pairs, highlighting top candidates such as Quercetin–EGFR (ΔG = −9.8), Genistein–ABCG2 (ΔG = −9.7), and Quercetin–SRC (ΔG = −9.7) for experimental validation.
The ranked results are presented in the revised Results and discussed for translational implications, ensuring a practical pathway from computational prediction to laboratory testing.