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Research Article

NETWORK PHARMACOLOGY AND MOLECULAR DOCKING-BASED EXPLORATION OF RUBIACEOUS PLANTS FOR BREAST CANCER: PHYTOCHEMICALS, PRECLINICAL STUDIES, AND REGULATORY PERSPECTIVES

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ABSTRACT

Objective: Cancer remains a global health challenge due to the limitations of conventional therapies, including drug toxicity and resistance. This study aims to explore the anticancer potential of Rubiaceous plant species by investigating their bioactive phytochemicals, molecular targets, and pharmacological pathways, with a particular focus on breast cancer.

Materials and **Methods:** A network pharmacology approach was employed to identify therapeutic compounds and their molecular targets. Disease-related targets were sourced from GeneCards and the Therapeutic Target Database (TTD). Cytoscape and STRING were used to construct interaction networks. Gene Ontology (GO) and KEGG pathway enrichment analyses were performed to elucidate biological functions and pathways. Molecular docking studies were conducted to assess the binding affinities of key phytoconstituents.

Results: A total of 1,435 biological processes and 173 pathways were associated with breast cancer. Molecular docking revealed Quercetin as the most potent compound with a binding affinity of -34.92 kcal/mol. Other compounds such as Acacetin, Resveratrol, and Apigenin exhibited lower, but significant, binding affinities. Rubiaceous plants, including *Alibertia myrciifolia*, *Anthocephalus cadamba*, and *Camptotheca acuminata*, were identified to contain flavonoids, alkaloids, and anthraquinones with demonstrated anticancer effects, including apoptosis induction and DNA damage.

Conclusion: Rubiaceous plants exhibit promising anticancer potential through multi-target mechanisms. Regulatory oversight is crucial to ensure the safety and efficacy of these herbal therapies. Further research is warranted to isolate active compounds, understand their molecular mechanisms, and validate their clinical relevance for integration into modern oncology.

Keywords: Breast Cancer, Rubiaceae plants phytochemicals, Cell lines, Network pharmacology, Molecular docking, Regulatory guidance.

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INTRODUCTION

A century ago, cancer was considered relatively rare; however, its incidence has surged dramatically in recent decades, largely attributed to changes in lifestyle, environmental factors, and increased life expectancy. Once regarded as one of the most feared diseases of the 20th century, cancer continues its relentless rise in the 21st century. Alarmingly, one in four individuals now faces a lifetime risk of developing cancer [1]. Among various cancer types, breast cancer stands out as a major global health concern, characterized by its complex pathogenesis and heterogeneous clinical behaviour, which presents significant challenges in diagnosis, treatment, and prevention [2]. As the global burden of breast cancer continues to escalate, a deeper understanding of its multifactorial nature is essential for the development of effective and targeted therapeutic strategies [3].

Anticancer drugs often exhibit significant toxicity, affecting not only tumor cells but also the normal cells in the affected body tissues. Consequently, the search for novel anticancer agents is increasingly focused on terrestrial plants [4,5]. Since ancient times, plants have been used as a useful resource for the discovery and development of new medicines. There are an estimated 250,000 flowering plant species in the world today, with roughly 155,000 of those species found in tropical areas. Bioactive phytocompounds derived from plants are increasingly expected to play a significant role in drug development. Despite the vast diversity of plant species, only a limited number have been thoroughly explored for their biological activities and bioactive compounds. Systematic research into these underexplored plant resources holds significant potential for identifying novel biomolecules with desirable pharmacological properties, offering both scientific and commercial benefits [6].

With the exception of Antarctica, the Rubiaceae family is widely dispersed throughout the world's major regions, with low to mid-altitude wet forests exhibiting the most growth. With 13,143 species spread across 611 genera, it is the fourth largest angiosperm family [7,8]. Various flowering plants in the Rubiaceae family are referred to as the coffee, madder, or bedstraw families. Antioxidant, anticancer, antimalarial, antimicrobial, antidiabetic, antihypertensive, and anti-inflammatory properties have been reported by numerous plants of the Rubiaceae family [9].

The Rubiaceae family has been a focal point of phytochemical research due to the natural presence of terpenoids, anthraquinones, and indole alkaloids. Notably, several members of this family are well known for their alkaloid content [9]. Rubiaceae family plants are rich in alkaloids, flavonoids, terpenoids, and iridoids, many of which exhibited potent anti-cancer properties [10-12]. These phytochemicals frequently target critical molecular pathways involved in cancer progression, such as inflammation, oxidative stress, and angiogenesis [13,14].

As natural products continue to be a promising source of novel therapeutic agents, the Rubiaceae family holds great potential for contributing to the discovery and development of novel anti-cancer

agents. Moreover, the relatively low toxicity of these plant-derived compounds compared to conventional chemotherapy makes them attractive candidates for complementary cancer treatments [6,15].

Network pharmacology offers a systematic approach to predicting the potential mechanisms of drug action [16] by constructing a "component–gene target–disease" network, supported by gene ontology (GO) [17] and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses [18]. In addition, molecular docking technology allows for the prediction of binding modes and affinities between drug ligands and their target proteins [19]. In this study, we employed an integrated network pharmacology and molecular docking approach to investigate the potential pharmacological mechanisms of isolated phytoconstituents from Rubiaceae family plants in the treatment of breast cancer. This included the identification of key bioactive compounds, prediction of their therapeutic targets, and exploration of underlying biological pathways, thereby providing a theoretical basis for the development of novel therapeutic agents for breast cancer.

This research aims to comprehensively explore the anticancer potential of medicinal plants from the Rubiaceae family, with a particular focus on their phytochemical constituents, pharmacological activities, and regulatory perspectives, supported by network pharmacology and molecular docking approaches.

Search scheme

A comprehensive search of electronic databases, including Web of Science, Scopus, PubMed, and Google Scholar, was conducted to identify the most relevant literature. The search utilized terms and phrases such as "Rubiaceae Anticancer herbs," "Molecular docking," "Network pharmacology," "Mechanism of action," "Animal models," "*in vitro* activity," and "*in vivo* activity." The total number of relevant articles extracted and analyzed was based on the combination of these keywords and phrases. Due to language limitations, only English-language literature was considered.

Inclusion criteria and data extraction

Specific anticancer plants were chosen using the second set of criteria, with an emphasis on phytochemicals which are well examined. Sixteen plants were chosen based on the availability of publications that (a) investigated the anticancer and antitumor properties of herbal products derived from the Rubiaceae family through both *in vitro* and *in vivo*, (b) documented the anticancer/antitumor effects of active compounds derived from Rubiaceae plants, and (c) evaluated the *in vivo* anticancer properties of the herbal anticancer products from Rubiaceae family.

Taxonomic classifications of rubiaceae

Although the Rubiaceae family is widely distributed, it is primarily found in tropical regions. It is one of the largest in the Magnoliopsida class and ranks fourth among Angiosperms in terms of species diversity. There are 637 genera and more than 13,000 species. There are still some unanswered questions regarding the taxonomic categorization of the Rubiaceae family. The four subfamilies of the Rubiaceae family – Rubioideae, Cinchonoideae, Antirheoideae, and Ixoroideae are separated by Robbrecht's classification. Rubioideae, Cinchonoideae, and Ixoroideae are the three subfamilies into which recent research indicates this family should be divided. This is because molecular investigations have demonstrated that Antirheoideae is polyphyletic and lacks a standardized occurrence of a chemical marker, leading certain authors to reject the family as a subfamily. Because of the number of species, the subfamilies were divided into 43 tribes, which are intermediate clades between genus and subfamily [20,21].

Isolated anticancer phytoconstituents of rubiaceous family plants

The Rubiaceae family of plants is a rich source of secondary metabolites with significant therapeutic potential, making them valuable for drug discovery. These metabolites, characterized by diverse structural features, have been isolated and classified into various phytochemical groups. Their therapeutic efficacy has been extensively evaluated through both *in vitro* and *in vivo* studies. The presence of numerous bioactive metabolites with distinct structural properties highlights the potential of Rubiaceae plants in the development of novel therapeutic agents. Table 1 provides a summary of bioactive phytoconstituents from medicinal plants in the Rubiaceae family with notable anticancer properties. It includes details on plant species, plant parts utilized, extraction solvents, and identified chemical compounds such as alkaloids, flavonoids, triterpenoids, anthraquinones, and phenolic compounds that have demonstrated potential in inhibiting cancer cell growth.

METHODS

The Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) (http://tcmspw.com/tcmsp.php) and based on a literature survey identify isolated anticancer phytoconstituents of rubiaceous family plants. Disease-related targets were identified using the Therapeutic Target Database [22] (http://db.idrblab.net/ttd/) and GeneCards: The Human Gene Database (https://www.genecards.org/) [23], which were cross-referenced with proteins regulated by bioactive compounds from Rubiaceae plants, as predicted through SwissTargetPrediction (http://www.swisstargetprediction.ch/) [24]. Network construction and protein-protein interaction (PPI) analysis were conducted using Cytoscape 3.7.2 [25] and STRING databases to explore the underlying mechanisms of action. Additionally, GO and KEGG enrichment analyses were performed to elucidate the potential therapeutic pathways of these bioactive compounds [26].

Screening of compound components from Rubiaceae family plants

A literature survey was conducted to explore the active components and drug targets of plants from the Rubiaceae family. Drug molecules with oral bioavailability ≥30% and drug similarity ≥0.18 were identified as active compounds. The corresponding target gene information was retrieved and annotated using the UniProt database (https://www.uniprot.org/) [27]. In addition, active components and related targets were screened from the literature [16] with further target annotation performed using the UniProt and GeneCards databases [28].

Acquisition of disease targets

The keyword "Breast cancer" was used to identify disease-related targets from the Therapeutic Target Database and GeneCards database. The intersection of target genes between the active components of Rubiaceae family plants and breast cancer-related genes was then determined.

Construction of the component-target-GO-KEGG network diagram

The components and disease-related targets of Rubiaceae family plants for breast cancer treatment were imported into Cytoscape 3.7.2 to construct and visualize a "component-target-disease" network [29]. A network diagram of the hub nodes was generated to highlight key interactions [30]. A "Components-Core Targets-GO-KEGG" network was built to visualize the interactions between components, core targets, biological processes, and signaling pathways.

"Components-Core Targets-GO-KEGG" network was constructed. In this network, target molecules including components, BPs, signaling pathways, and disease-related genes are represented as nodes, while their interactions are depicted as edges.

PPI network of target protein interaction

The overlapping genes between the active component targets of Rubiaceae family plants and breast cancer-related target genes were imported into Online STRING to construct a visualized PPI network. A confidence score of 0.150 was set to ensure the highest reliability from the STRING database [26]. The expanded target proteins of Rubiaceae family plants obtained from STRING were then imported into Cytoscape v3.7.2 for further network visualization and analysis.

Table 1: Potential anticancer phytoconstituents identified in key medicinal plants of the Rubiaceae family

Sr. No.	Genus	Plant species	Parts used	Extract/fraction	Class	Active components	References
1	*Alibertia*	*Alibertia myrciifolia*	Aerial parts	Hexane	Flavonoids	Acacetin, Apigenin, Lethedocin	[31]
2	*Anthocephalus*	*Anthocephalus cadamba*	Barks	Methanol (MeOH)	Alkaloids	Cadambine	[32]
			Fruits	--	Indole alkaloids Triterpenoid	Vallesiachotamine, Cadambine, Vincosamide, Dihydrocadambine Ursolic acid, Oleanolic acid	[33]
3	*Camptotheca*	*Camptotheca acuminate*	Stems	--	Alkaloids	Camptothecin	[34]
			Leaves, Seeds	MeOH	Alkaloids	Camptothecin	[35]
4	*Cephaelis*	*Carapichea ipecacuanha*	--	--	Alkaloids	Cephaeline	[36]
5	*Cinchona*	*Cinchona succirubra*	Barks	90% MeOH	Alkaloids	Liriodenine	[37]
		Cinchona ledgeriana				Cinchophylline, Liriodenine	[37]
6	*Corynanthe*	*Corynanthe pachyceras*	Barks	DCM (Dichloromethane: MeOH (1:1)	Alkaloids	Corynantheidine, Corynantheine, Dihydrocorynantheine, Corynanthine	[38]
7	*Coussarea*	*Coussarea hydrangeifolia*	Leaves	EtOH–Water (7:3 v/v)	--	Quinic acid, Cinnamic acid derivatives	[39]
		Coussarea paniculata	Twigs	DCM: MeOH (1:1)	Lupane triterpenoids Triterpenoids	3-Deoxybetulonic acid Lupeol, Lupeyl acetate, Betulin, Betulinic acid, 3-*epi*-betulinic acid, 3-*epi* -betulinaldehyde, Oleanolic acid,	[40]
8	*Coutarea*	*Coutarea hexandra*	Fruits	80%EtOH	Triterpenoids	23,24-Dihydrocucurbitacin	[41]
9	*Crossopteryx*	*Crossopteryx febrifuga*	Stem Bark	DCM	Triterpenoids	Betulic acid	[42]
10	*Emmenopterys*	*Emmenopterys henryi*	Twig, leaves	95% EtOH	Triterpenoids	Pomolic acid	[43]
11	*Exostema*	*Exostema acuminatum*	Roots	--	Flavonoid	3′-hydroxy-5,7,4′ -trimethoxy- 4-phenylcoumarin, 8-hydroxy-5,7,4′ -trimethoxy- 4-phenylcoumarin	[44]
12	*Galium*	*Galium asparagifolium*	--	--	Glycoside	Galiumic acid	[45]
13	*Gardenia*	*Gardenia lucida*	Gum resin	MeOH	Coumarins Flavonoids	Acerosin Gardenin D, Gardenin B	[46]
		Gardenia thunbergia	Aerial part	n-hexane, DCM	Triterpenoids Phenol	Lupeol Syringaldehyde	[47]
		Gardenia sessiliflora	Leaves, Twigs	MeOH	Triterpenoids Flavonoids	23-Deoxojessic acid, Sootepin A Apigenin	[48]
14	*Guettarda*	*Guettarda pohliana*	Leaves, Roots	--	Iridoids	Secoxyloganin, Sweroside, Loganin	[49]
15	*Hamelia*	*Hamelia patens*	Aerial parts	70% MeOH	Flavonoids Triterpenoids	Rutin, Isoquercetin, Soyasaponin Bb	[50]
16	*Hedyotis*	*Hedyotis biflora*	Whole plant	MeOH	Triterpenoids Glucoside	Oleanolic acid, Ursolic acid	[51]
		Hedyotis diffusa	Whole plants	95% EtOH	Triterpenoid	Ursolic acid, Oleanolic acid	[52]
17	*Heterophyllaea*	*Heterophyllaea pustulata*	Stem, leaves	MeOH	Anthraquinones	Rubiadin, Rubiadin-1-methyl ether, Soranjidiol	[53]
18	*Hymenodictyon*	*Hymenodictyon floribundum*	Stem Bark	80% EtOH	Coumarins Terpenoids	7-Hydroxy-6- methoxycoumarin 2,2,4-Trimethyl-3-(3,8,12,16-tetramethyl-heptadeca-3,7,11,15-tetraenyl)- cyclohexanol	[54]
19	*Ixora*	*Ixora coccinea*	Flower	MeOH	Peptides	Ixorapeptide I	[55]
20	*Knoxia*	*Knoxia roxburghii*	--	--	Anthraquinones	3-Hydroxymorindone	[56]
21	*Morinda*	*Morinda citrifolia*	Root bark	--	Anthraquinones	Rubiadin, Morindone	[57]
		Morinda coreia	Root	n-hexane, EtOH, MeOH	Anthraquinones	Soranjidiol, Nordamnacanthal, Damnacanthal	[58]
		Morinda elliptica	Root	DCM	Anthraquinones	Damnacanthal, Nordamnacanthal	[59]
			Leaves	80% MeOH	Flavonoids	Quercetin, Quercetin-7,4'-dimethylether	[60]
		Morinda umbellata	Vines	EtOH	Anthraquinones	3-hydroxy-2 hydroxymethyl anthraquinone, Rubiadin	[61]
22	*Mussaenda*	*Mussaenda recurvata*	Aerial part	--	Triterpenoid	Ursolic acid	[62]
23	*Nauclea*	*Nauclea orientalis*	Stem, leave	90% EtOH	Alkaloids	Antirhine, Alangine	[63]
		Nauclea pobeguinii	Bark	MeOH	Glycoside	Resveratrol	[64]

(Contd...)

Table 1: *(Continued)*

Sr. No.	Genus	Plant species	Parts used	Extract/fraction	Class	Active components	References
24	*Neonauclea*	*Neonauclea reticulate*	Stem	MeOH	Flavonoids	Ficusal	[65]
					Triterpenoid	Balanophonin	
					Phenolic acids	p-coumaric acid	
25	*Oldenlandia*	*Oldenlandia umbellate*	Aerial part	MeOH	Triterpenoid	Cedrelopsin	[66]
					Anthraquinones	Anthragallol 1,2-dimethyl ether,	
26	*Ophiorrhiza*	*Ophiorrhiza baviensis*	Aerial part	MeOH	Triterpenoids	Rutundic acid, 3ß,6ß,23– trihydroxyolean- 12-en-28-oic acid	[67]
		Ophiorrhiza pumila	--	95% EtOH	Saponins	Pumiloside, Deoxypumiloside	[68]
					Alkaloids	Camptothecin, Aknadinine	
		Ophiorrhiza mungos	Leaves	MeOH	Glycoside	Luteolin-7-O-glucoside	[69]
27	*Pentas*	*Pentas schimperi*	Root	MeOH	Anthraquinones	Damnacanthal	[70]
28	*Rothmannia*	*Rothmannia wittii*	Bark	n-hexane	Iridoids	Genipin	[71]
					Alkaloids	Garjasmine	
29	*Rubia*	*Rubia philippinensis*	Root	EtOH	Anthraquinones	Xanthopurpurin	[72]
		Rubia schumanniana	Root	70% MeOH	Triterpenoids	Zamanic acid, Maslinic acid, Ursolic acid	[73]
		Rubia yunnanensis	--	--	Alkaloids	Rubioncolin C	[74]
30	*Saprosma*	*Saprosma hainanense*	Stem	75% EtOH	Alkaloids	Marcanine A	[75]
31	*Uncaria*	*Uncaria macrophylla*	Stem, Bark	90% EtOH	Triterpenoids	Ursolic acid	[76]

GO and pathway enrichment analyses

R version 4.1.2 was used for GO functional annotation and KEGG pathway analysis of Rubiaceae family plants in the treatment of breast cancer, and the enrichment analysis results were visualized [77]. The GO database, including BP, molecular function, and cellular component (CCs), was used to explore the potential biological molecular mechanisms [78]. The KEGG database has also been used to identify biological functions and candidate targets [79].

Molecular docking verification

The structures of the active components from Rubiaceae family plants and key target proteins were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/)and the Protein Data Bank (PDB) (http://www.rcsb.org/pdb/home/home.do), respectively. Molecular docking was performed by analyzing the binding positions and binding energies of each ligand. The docking study focused on EGFR kinase (PDB ID: 1XKK), obtained from the PDB (https://www.rcsb.org). Protein preparation was carried out using Molsoft ICM Pro, which involved adding hydrogen atoms, removing water molecules, assigning partial charges, determining protonation states, and applying restraints [80]. After ligand removal, binding sites were identified, and a grid box was generated for docking [81,82]. Each bioactive compound from Rubiaceae family plants was docked into the designated binding site within the grid using Molsoft ICM Pro's Glide module, a rapid and efficient docking program designed for small-molecule docking. The program incorporates a scoring function that evaluates shape complementarity, electrostatic interactions, and van der Waals forces between the ligand and receptor [83]. Key interactions at the active site and corresponding docking scores were thoroughly analyzed [84].

RESULTS

Components and targets of rubiaceae family plants and breast cancer-related targets

According to the TCMSP database, 48 anticancer compounds from Rubiaceae family plants met the criteria of oral bioavailability (≥30%) and drug-likeness (≥0.18). A literature survey identified 77 potential isolated drug targets associated with Rubiaceae species. In addition, 517 disease-related gene targets were retrieved from the GeneCards and Therapeutic Target Database. By intersecting the targets of Rubiaceae-derived compounds (731 in total) with the disease-related targets, 89 common genes were identified, representing potential key targets for therapeutic intervention.

Network diagram

To explore the therapeutic potential of Rubiaceae plants in breast cancer treatment, a "component–target–disease" network was constructed, consisting of 166 nodes and 40 edges. This network illustrates the interactions between 77 isolated active anticancer compounds from Rubiaceae species and 517 disease-related gene targets. The detailed network representation is shown in Fig. 1.

PPI network

A total of 89 overlapping genes between the active component targets of isolated compounds from Rubiaceae plants and breast cancer-related target genes were entered into the STRING 12.0 database (https://string-db.org/) to construct a visual PPI network, using a confidence score threshold of 0.150. The resulting PPI network consisted of 89 nodes and 512 edges, as illustrated in Fig. 2.

GO and KEGG pathway enrichment analysis

A total of 1,435 GO BPs and 173 KEGG pathways were identified through enrichment analysis of the 89 overlapping genes, with a highly significant p-value ($p<0.0000000000000001$). Further classification of the GO terms revealed enrichment in 1,196 BPs, 114 CCs, and 125 molecular functions (MFs). The top 10 GO terms for BPs, MFs, and CCs are depicted in Figs. 3-5, respectively. The top 10 GO BPs arelisted as follows: (GO:0006468) response to protein phosphorylation, (GO:0016310) response to phosphorylation, (GO:0009410) response to Response to xenobiotic stimulus, (GO:0010243) response to

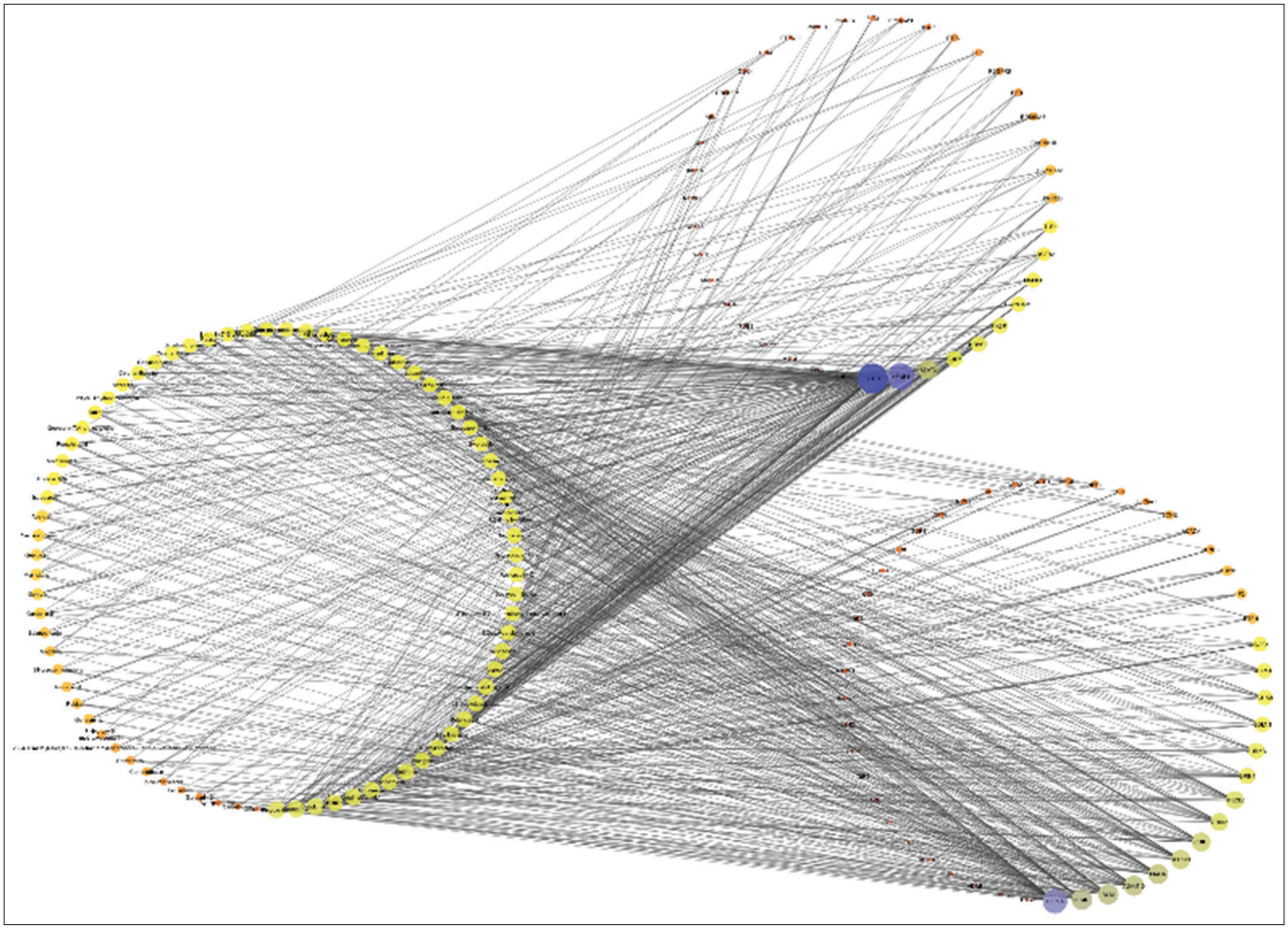


Fig. 1: The construction of the component-target-disease network diagram

Response to organonitrogen compound, (GO:1901698) responseto Response to nitrogen compound, (GO:0071417) response to Cellular response to organonitrogencompound, (GO:1901699) response to Cellular response to nitrogen compound, (GO:0042327) response to Positive regulation of phosphorylation, (GO:0001934) response toPositive regulation of proteinphosphorylation, and (GO:2000379) response toPositive regulation of reactive oxygenspecies metabolic process.

The top 10 KEGG pathways are as follows: Prostate cancer (hsa05215), Central carbon metabolism in cancer (hsa05230), MicroRNAs in cancer (hsa05206), Pathways in cancer (hsa05200), Neurotrophin signaling pathway (hsa04722), Hepatitis B (hsa05161), Chronic myeloid leukemia (hsa05220), HIF-1 signaling pathway (hsa04066), Thyroid hormone signaling pathway (hsa04919), and Pancreatic cancer (hsa05212). The resulting PPI network consisted of 89 nodes and 512 edges, as illustrated in Fig. 2. Fig. 6 illustrates the top 10 KEGG pathways.

Molecular docking verification

A molecular docking study was carried out using isolated phytoconstituents from Rubiaceous family plants as ligands, targeting the EGFR kinase domain. The docking analysis was performed using Molsoft ICM Pro. A total of 77 phytochemical structures were retrieved and docked against EGFR kinase (PDB: 1XKK), which is complexed with a quinazoline inhibitor (GW572016), to assess their binding conformations and binding affinities.

Among all docked compounds, Quercetin demonstrated the highest binding affinity, with a docking score of −34.92 kcal/mol. Other compounds such as Acacetin, Gardenin D, Resveratrol, Apigenin, Acerosin, Lethedocin, Xanthopurpurin, Cedrelopsin, and Soranjidiol showed comparatively lower binding affinities.

Visualization of ligand interactions within the binding pocket of PDB: 1XKK confirmed successful binding of all docked ligands at the identified active site (Fig. 7). Notably, 71 out of 77 docked Rubiaceous plant compounds exhibited appreciable binding affinity with the EGFR kinase domain. A 3D visualization of ligand interactions within the EGFR binding site, along with a detailed summary of specific interactions and binding affinities of the compounds, is presented in Table 2.

Preclinical studies on anticancer properties of Rubiaceae family plants

The anticancer properties of numerous plants and plant-based substances have been investigated to date. Certain plants and the substances they contain have been shown to be highly beneficial in treating one or more cancer types. The following plants have been chosen for their compounds' anticancer properties both *in vitro* and *in vivo* based on their activities.

A detailed overview of the anticancer properties of various plants from the Rubiaceae family, based on preclinical studies, is presented in Table 3. It highlights the plant species, parts used, and the bioactive compounds identified, emphasizing their potential for cancer treatment. Table 4 complements this information by showcasing the chemical structures of the key phytoconstituents linked to these plants' anticancer activities.

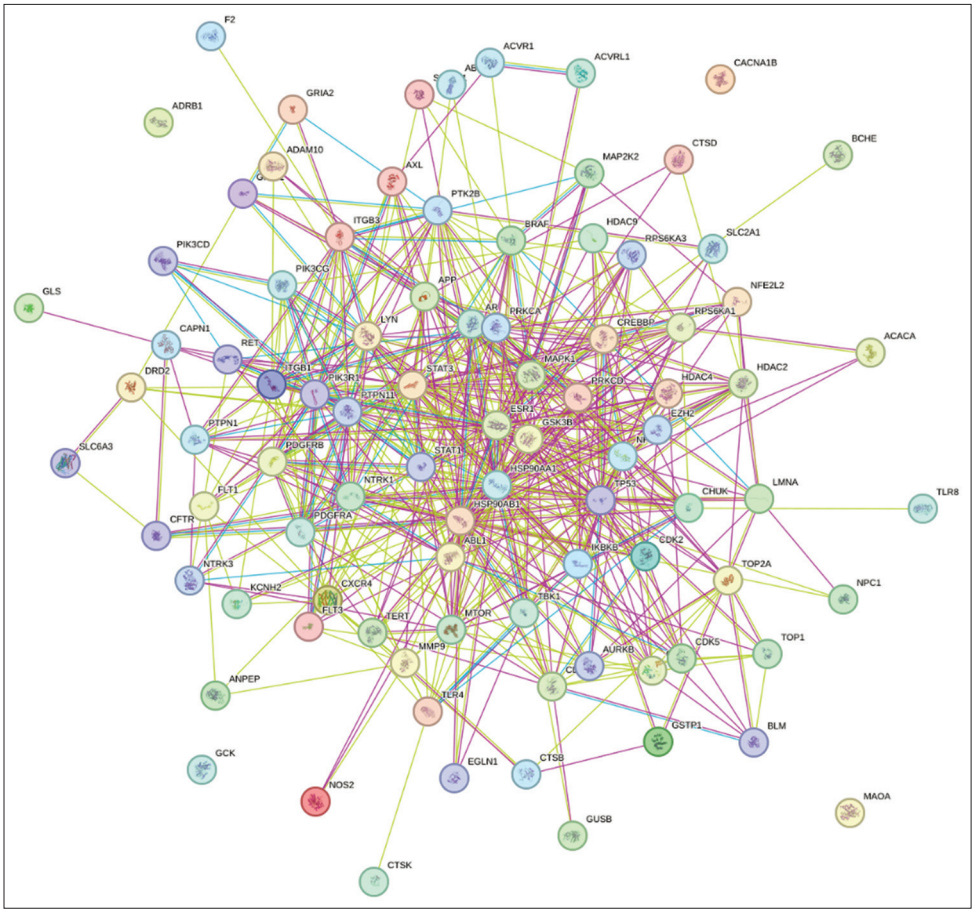


Fig. 2: Map of protein- protein interaction network

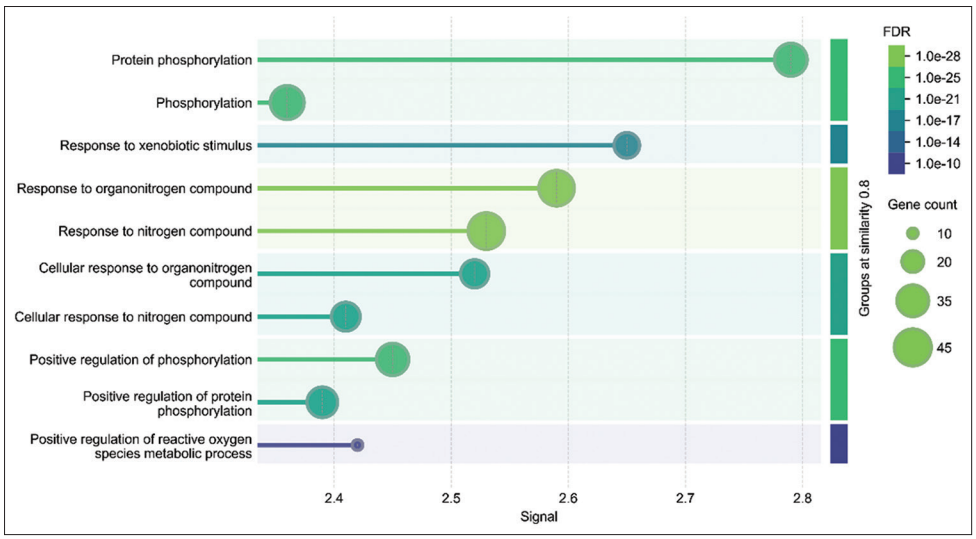


Fig. 3: Biological process (gene ontology) enrichment

Adina cordifolia

A. cordifolia, a plant native to Southeast Asia, is commonly known as Haldu [85]. It is found across countries like India [86], Burma, Sri Lanka, Bangladesh, and others [85]. The plant contains bioactive compounds such as cordifoline, benzoic acid, β-sitosterol, umbelliferone, and flavanones like 7,4-dimethoxy-5-hydroxyflavanone and 5,7-dimethoxy-4-hydroxyflavanone. Additional identified compounds include n-heneicosane, n-tricosane, n-pentacosane, and n-pentatriacontane. Its trunk produces an oleoresin rich in essential oils, and the bark has alkaloids, with a novel coumarin glycoside, adicardin, identified in the root bark [87]. *A. cordifolia* shows diverse therapeutic properties, including anticancer, antibacterial, hepatoprotective, and antidiabetic effects [86,88]. Swiss albino mice with Ehrlich Ascites Carcinoma (EAC) were used to test the anticancer potential of acetone and ethanol leaf extracts of *A. cordifolia*. Administered at 500 mg/kg for 14 days post-tumor inoculation, both extracts significantly reduced tumor volume, weight, and cell count, while decreasing body weight and extending survival time. The acetone extract exhibited stronger cytotoxicity at

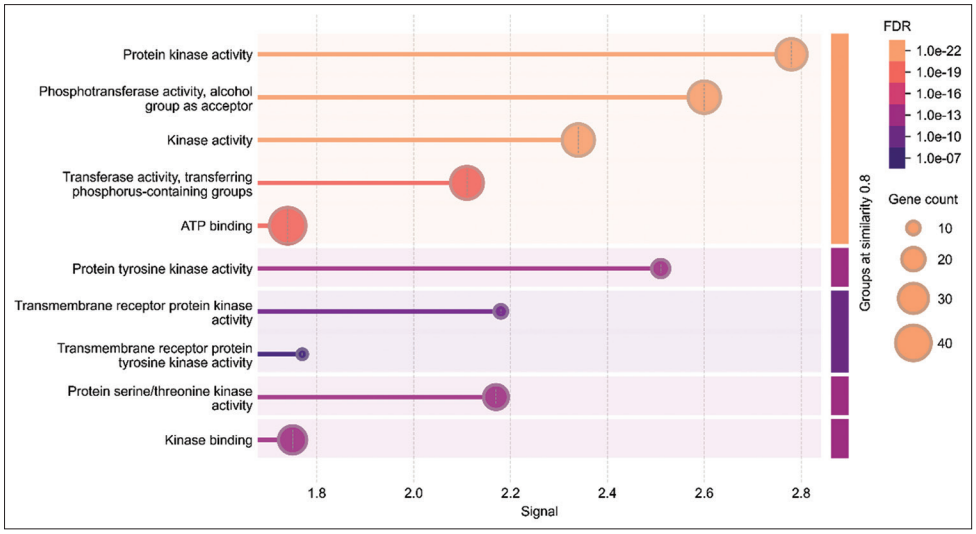


Fig. 4: Molecular function (gene ontology) enrichment

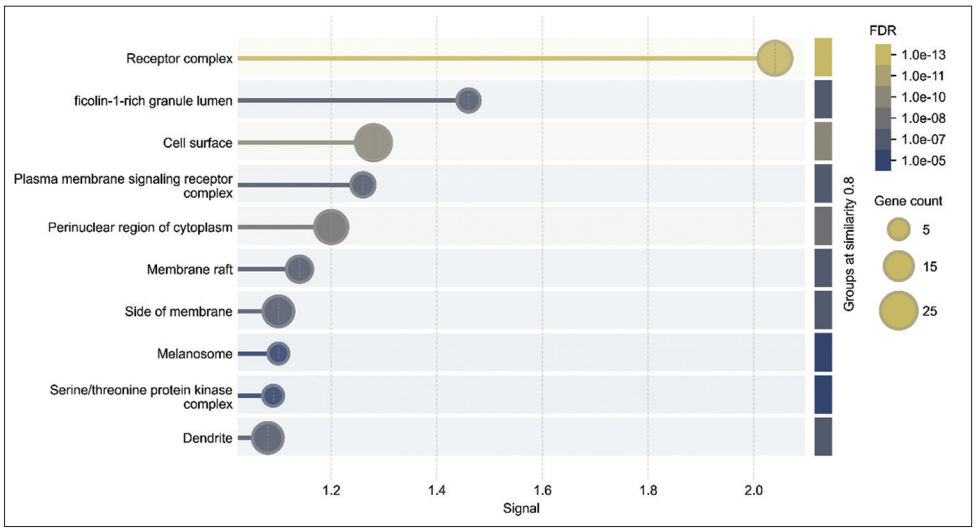


Fig. 5: Cellular component (gene ontology) enrichment

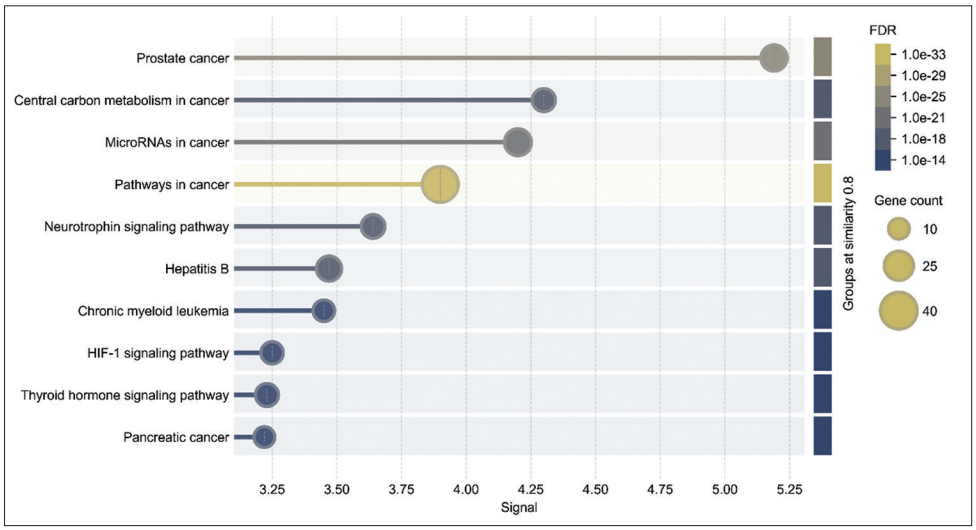


Fig. 6: Kyoto encyclopedia of genes and genomes pathways enrichment

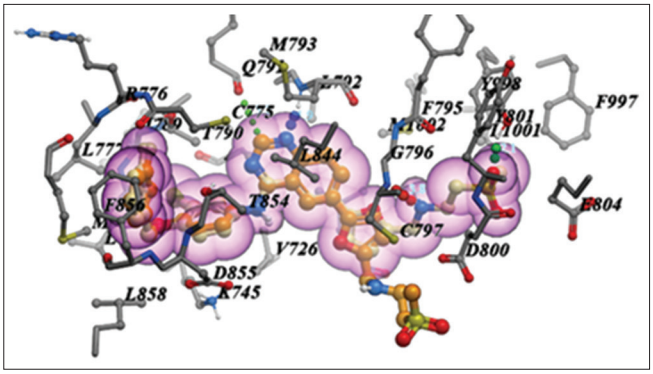


Fig. 7: Identified binding pocket in Protein Data Bank: 1XKK

200 µg/mL compared to the ethanol extract, demonstrating the notable anticancer potential of both extracts [89].

Borreria articularis

B. articularis, known as "Poaia" in Brazil [90], is native to Asia as well as naturalized in Africa and Australia [91]. Conventionally, it has been used to treat ailments like eye and gum inflammation, fevers, spleen disorders, conjunctivitis, hemorrhage, dysentery, and diarrhea [92]. In India, decoctions from its leaves, roots, and seeds are used for dropsy (Conserva and Ferreira, 2012). Along with β-amyrin, a novel triterpene, 3α-acetoxy-oleana-12-en-29-oic acid, was discovered in a chloroform extract of the aerial parts and roots [92]. The cytotoxicity of *B. articularis* leaves ethanolic extract utilizing Brine Shrimp Lethality Bioassay and MTT Assay on MCF-7 cells. The brine shrimp assay showed survival rates of 72–96% at concentrations ranging from 200 to 25 µL/mL, with an IC_{50} of 617.31 µL/mL.

Borreria hispida

B. hispida, sometimes called "Gathiyu" or "Shankhlo," is a perennial herb that grows widely in India. It is frequently used as fodder and a hedge plant, and it is also eaten as a vegetable when food is scarce. It contains bioactive compounds like steroids, tannins, terpenoids, carotenoids, flavonoids, alkaloids, and glycosides, known for their therapeutic properties [91]. Human lung carcinoma (A549) and breast carcinoma (MCF-7) cell lines were both susceptible to the strong anticancer effects of the methanolic extract of *B. hispida* seeds, with IC_{50} values of 3.125 µg/mL and 1.56 µg/mL, respectively [93].

Canthium dicoccum

In India, *C. dicoccum* is referred to as Nalla Balusu in Telugu and Nallamandharam in Tamil. The Deccan Peninsula, which extends from Maharashtra to Assam and Meghalaya, is home to it (Meghashree *et al*., 2019) [96]. Valuable phytochemicals such as caryophyllene oxide, cedren-13-ol, spathulenol, and ledene oxide are found in the ethanolic extract of *C. dicoccum* [96]. Various *Canthium* species exhibit pharmacological activities, including anti-inflammatory, diuretic, antinociceptive, wound healing, antipyretic, antimicrobial, antioxidant, antidiabetic, and antitumor effects [97]. The ethanol extract of *C. dicoccum* leaves showed strong anticancer activity against the A549 lung cancer cell line, with IC_{50} values lower than the positive control. At 50 µg/mL, it achieved 21.17±0.156% cell inhibition. This anticancer effect is linked to phenolic compounds, with inhibition increasing at higher concentrations [99].

Canthium parviflorum

C. parviflorum Lam., known as Mullukaarai in Tamil, Carray Cheddie in Hindi, English, Kirma and Balusu in Telugu [99], is a shrubby plant found throughout the Western Ghats, peninsular India, and dry plains [100]. Researcher reported the 22 active compounds from this plant, including Biphenyl, 2-Methyl-4-heptanone, Di-isodecyl phthalate, 1,2,4,5-Tetroxane, Ethyl (9Z,12Z)-9,12-octadecanoate, 3,3,6,6-Tetraphenyl, 3-Oxo-alpha-Ionol, Methyl 7-hydroxy-2-methyl-3,5-octadienoate, 4-(2-Hydroxy-2,6,6-trimethylcyclohexyl)-3-buten-2-one, 1-Hexadecanol, n-Hexadecanoic acid, E-11-Hexadecanoic acid ethyl ester, Ethyl hexadecanoate, Phytol, Methyl linolenate, Ethyl linolenate, 2-Phenoxyl-2-phenylpropanic acid, All-trans-squalene, Gamma-tocopherol, DEPH (1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester), Stigmasterol, Gamma-stigmasterol, and Methyl cis-11,14,17-icosatrienoate [101]. The leaves and roots are used traditionally as astringents, diuretics, and febrifuges, and for treating diabetes, diarrhea, leucorrhea, fever, and constipation. Tribes in Orissa use its fruits for headaches [102,103]. In addition, flavonoids in ethanolic extracts at doses of 200 mg/kg and 400 mg/kg significantly inhibited the proliferation of Dalton's lymphoma ascites (DLA) and HeLa cells, with IC_{50} values of 61.24 µg/mL and 43.15 µg/mL, respectively [104].

Coffea arabica

C. arabica, a medium-sized tree from the Rubiaceae family [105], is the second-largest global commodity. Originally cultivated in Arabic countries, it later spread to Iran and India [106]. The primary chemical constituents include fructose, amino acids like asparagine and cysteine, and fatty acids like palmitic, linolenic, and stearic acid, decanoic acid, betalamic acid, and dopaxanthin. Secondary compounds include caffeine, flavonoids, trigonelline, polyphenols, and kahweol [107]. *C. arabica* exhibits various pharmacological effects, including antidiabetic, antiviral, antimicrobial, anticancer, antioxidant, and anti-inflammatory activities [105,108]. Methanolic extracts of *C. arabica* exhibited potential anticancer activity against the HT29 cell line, with an IC_{50} value of 101.26 µg/mL [109].

Galium verum

G. verum, or Lady's Bedstraw, is a perennial herb native to Europe, North Africa, and Asia [110,111]. Traditionally, it has been utilized for its diuretic, choleretic, spasmolytic, and diaphoretic properties, as well as for treating diarrhoea, psoriasis, skin injuries, and for its sedative and anticancer effects. Phytochemical studies revealed compounds like iridoid glycosides, phenolics, anthraquinones, triterpenes, tannins, saponins, essential oils, and vitamin C [112]. Deacetylasperulosidic acid, asperuloside, rutin, chlorogenic acid, ampeloside acid, and quercetin are important substances [113,114]. Using the MTT test, Pashapour *et al*. examined the effects of *G. verum* methanolic extract at doses ranging from 12.5 to 400 µg/mL over a 72-h period on the colon cancer cell line HT-29 and the fibroblast cell line AGO. In both cell lines, the maximum concentration (400 µg/mL) significantly reduced cell viability [115]. The petroleum ether extract of *G. verum* showed strong antitumor activity against A375 melanoma cells, reducing cell viability by 55% at 55 µg/mL, likely due to phenolic compounds like rutin and quercetin [116]. Chloroform and petroleum ether fractions of *G. verum* were tested for their anticancer properties against HepG2 (liver cancer) and HT29 (colon cancer) cell lines by Pashapour *et al*. At all doses, the petroleum ether fraction was cytotoxic to HT29 cells, but only at 3.125 µg/mL did it harm HepG2 cells [117].

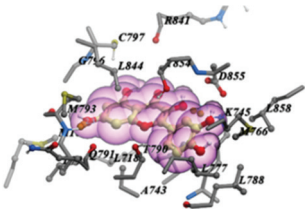
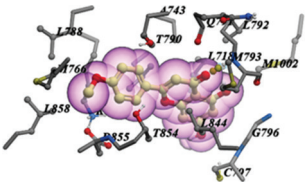
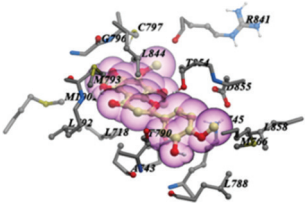
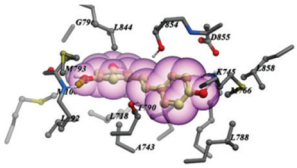
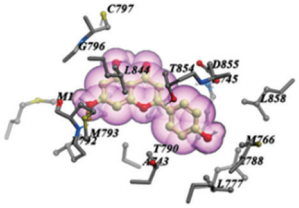
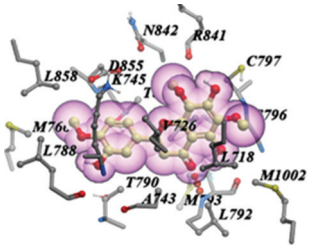
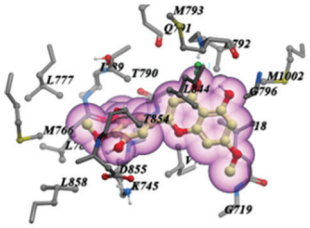
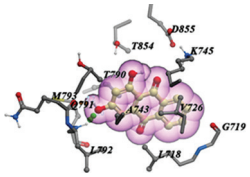
Gardenia gummifera

G. gummifera, a medium sized tree, is commonly found in dry forests throughout India [131], including in the states of Maharashtra, Karnataka, Andhra Pradesh, Kerala and Tamil Nadu [132]. The plant contains bioactive compounds, including β-sitosterol, D-mannitol, oleanolic aldehyde, 19-hydroxyerythrodiol, and erythrodiol (Vinaykumar *et al*., 2020) [134]. The resin from its leaf buds is known for medicinal properties, like being carminative, antispasmodic, stimulant, antioxidant, cardiotonic, and antiseptic. It is usually utilized to treat indigestion, ulcers, gas troubles, and cardiac issues, and to promote wound healing [118].

Gardenia jasminoides

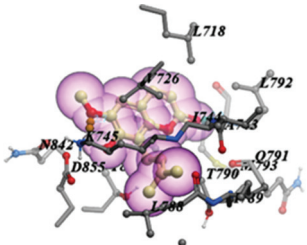
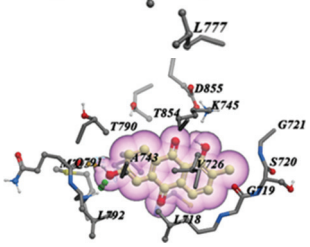
G. jasminoides Ellis, commonly known as gardenia or cape jasmine [135], is a widely cultivated evergreen shrub native to tropical and

Table 2: Molecular docking verification between core components and targets

Molecule name	3D view of ligand binding in the binding cavity	Dock score
Quercetin		−34.92
Acacetin		−30.43
Gardenin D		−30.2
Resveratrol		−29.88
Apigenin		−29.86
Acerosin		−29.75
Lethedocin		−27.88
Xanthopurpurin		−27.07

(Contd...)

Table 2: ***(Continued)***

Molecule name	3D view of ligand binding in the binding cavity	Dock score
Cedrelopsin		−26.7
Soranjidiol		−24.28

subtropical regions, especially southern China (Yin and Liu, 2018) [136]. Several compounds have demonstrated anticancer properties, including Hederagenin 3-O-β-D-glucuronopyranoside-6'-O-methyl ester, oleanolic acid 3-O-β-D-glucuronopyranoside, siaresinolic acid 28-O-β-D-glucuronopyranosyl ester, chikusetsusaponin IVa methyl ester, chikusetsusaponin, and chikusetsusaponin IVa butyl ester [136]. Extracts of *G. jasminoides* and key constituents such as geniposide, genipin, crocin, and crocetin [137] exhibit a wide range of pharmacological effects, including anti-hyperglycemic, anti-inflammatory, anti-arthritic, anticancer, antioxidant, anti-angiogenic, and antimicrobial activities [138]. The anti-proliferative effects of genipin on MDA-MB-231 human breast cancer cells were explored, revealing its ability to induce apoptosis by downregulating Bcl-2, upregulating Bax, and activating caspase-3. In addition, genipin enhanced the activation of JNK and p38 MAPK while suppressing the invasive and migratory behaviours of the cells. These results highlight genipin's potential as a chemopreventive agent for combating metastatic breast cancer [119].

Guettarda pohliana

The roots of *G. pohliana*, also known as angelica-do-mato, contain quinovic acid, daucosterol, and triterpenoid saponins, which are derived from quinovic and cincholic acids [139]. The leaves also contain triterpenes with oleanane and ursane skeletons, as well as compounds such as loliolide, secoxyloganin, and steroids [140]. The cytotoxic activity of crude extracts and fractions from the leaves and roots of *G. pohliana* was evaluated against nine human cancer cell lines, including MCF-7, NCI-ADR, NCI-460, PCO-3, 786-0, OVCAR, HT-29, K-562, and UACC-62. The most potent fractions, exhibiting GI_{50} values below 1 mg/mL, were the hydromethanolic, ethyl acetate, chloroform, and hexane fractions derived from the leaves. These fractions demonstrated strong activity, particularly against the K-562 cell line. In addition, the chloroform and hydromethanolic fractions effectively inhibited the UACC-62 cell line [49].

Hedyotis corymbose

H. corymbose also known as *Oldenlandia corymbosa* (L.), is a weedy annual herb commonly found in fields across India, Nepal, Bhutan, Malaysia, and Africa [141]. The methanolic extracts of *O. corymbosa* are rich in bioactive compounds, including flavonols (quercetin, 3-methoxy quercetin, and 3,4-dimethoxy quercetin), phenolic acids (vanillic, syringic, melilotic, *p*-hydroxybenzoic, *p*-coumaric, ferulic, and caffeic acids), anthocyanidins (cyanidin and pelargonidin), iridoids, and alkaloids [142]. These compounds exhibited biological properties like anti-aging, anti-apoptotic, anticarcinogenic, anti-inflammatory,

and anti-atherosclerosis effects, and contribute to cardiovascular protection, improved endothelial function, and inhibition of angiogenesis and cell proliferation. The ethanol extract of *Hedyotis corymbosa* L. exhibited potent anticancer activity against the YMB-1 human breast cancer cell line, with an IC_{50} value of 6.51 μg/mL. The methylene chloride fraction exhibits even higher cytotoxicity, with an IC_{50} of 2.75 μg/mL. Asperuloside, the lead chemical, has inhibitory effects on human cell lines YMB-1, HL60, and KB, with IC_{50} values of 0.7, 11.0, and 104.2 μg/mL, respectively [120]. In addition, the ethanolic extract inhibits breast cancer cell migration and metastasis, with an IC_{50} of 400 μg/mL [121]. Nanoliposomes loaded with the extract display potential anticancer activity, as the bioactive compound rutin inhibits ER-α binding and selectively decreases the viability of breast cancer cells (T47D) compared to non-cancerous cells (NIH3T3) [122].

Hedyotis diffusa

H. diffusa, known as sheshecao in Chinese, is primarily found in Northeast Asia. It has traditionally been employed to treat inflammatory conditions like appendicitis, bronchitis, and urethritis [143,144]. Recent pharmacological advancements have highlighted its antitumor properties, demonstrating effectiveness against cancers of the lungs, colon, brain, pancreas, and bioactive substances such as polysaccharides, triterpenes, and anthraquinones are abundant in *H. diffusa* [145,146]. Methyl anthraquinones, a bioactive compound in *H. diffusa*, induce apoptosis in various cancers. At a dosage of 18.62 μM for 24 h, they activate the caspase-4/Ca^{2+}/calpain pathway, exhibiting an inhibitory effect on the MCF-7 breast cancer cell line. Methyl anthraquinone treatment significantly raised the proportion of apoptotic cells in MCF-7 cells as well as the S phase of the cell cycle [123]. Furthermore, in both *in vitro* and *in vivo* investigations, *H. diffusa* successfully suppressed the growth of cervical cancer HeLa cells and decreased the expression of the Ki-67 protein, suggesting its function in preventing the growth of cancer cells. *H. diffusa*-treated mice demonstrated strong tumour growth suppression and prominent apoptotic traits, which resulted in longer life periods [124].

Morinda citrifolia

M. citrifolia L. (Noni), a small evergreen tree native to Southeast Asia and Australia [148], is now found worldwide in tropical regions [149]. Known as noni in Malaysia, it has various names like Indian mulberry and hai ba ji [12,149]. Many compounds, like alcohols, phenols, acids, flavonoids, and terpenoids, are present in the plant (Kitic *et al*., 2024) [150]. Studies have shown its anticancer effects against lung, cervical, and breast cancer cells, along with antioxidant, antimicrobial, antifungal, hepatoprotective, hypoglycemic, and immunomodulatory properties [150]. Rengaswamy Gopal utilised the MTT assay to assess the anticancer effects of fruit extracts from *M. citrifolia* on HepG-2 cells. With an IC_{50} of 71.442 μg/ml, the methanolic extract was the most potent; nevertheless, only the chloroform extract had a significant impact on HepG-2 cells [125].

Mussaenda frondose

M. frondosa is a scrambling climber that grows 1-5 meters tall, with bright green oblong leaves, small orange tubular flowers, and creamy white bracts [151]. Butanedioic acid, quinic acid, hexadecanoic acid, caryophyllene, 4-((1E)-3-hydroxy-1-propenyl)-2-methoxyphenol, naphthalene, decahydro-2-methoxy, 1,2,3-benzenetriol, saponins, flavonoids, alkaloids, and tannins are among its chemical components [152]. The plant is used as an astringent, expectorant, and for treating jaundice, ulcers, leprosy, and asthma. It also serves as a diuretic, wound healer, anti-inflammatory, and has antimicrobial, hypolipidemic, and hepatoprotective properties [126]. An *in vitro* cytotoxicity study was conducted on the HepG2 cell line using the methanolic extract, flavonoid fraction, and phenolic fraction of *M. frondosa*, employing the MTT assay. The results revealed that both the flavonoid fraction and the methanolic extract exhibited higher efficacy against the HepG2 cell line compared to the phenolic fraction [126].

Neolamarckia cadamba

N. cadamba, or Kadam, is a large tropical deciduous tree from the Rubiaceae family, native to South Asia, including Myanmar, India, Nepal, and western China [153]. Triterpenes, saponins, flavonoids, triterpenoid glycosides, and indole alkaloids such as cadamine, isocadambine, cadambine, and isodihydrocadambine are among its main components [154]. The plant exhibited a wide range of medicinal properties, including anti-diabetic, antioxidant, antipyretic, anthelmintic, anticancer, antihyperglycemic, hepatoprotective, anti-inflammatory, antibacterial, antimicrobial, and analgesic activities [155]. The hydro-methanolic extract of *N. cadamba* showed anticancer activity against N1S1 rat hepatoma cells in the SRB assay, with −37.66% and −34.13% cell growth at 40 μg/mL and 80 μg/mL, respectively. The LC_{50}, TGI, and GI_{50} values were 75.92, 46.73, and 17.46 μg/mL, with phenolic compounds likely responsible for the antiproliferative effects [127]. Additionally, the dichloromethane extract exhibited anticancer potential against MCF7, A549, and HepG2 cells, with docking studies identifying three key bark constituents, especially 4-hydroxy-beta-ionone, as having strong binding affinity to HER2, VEGFR2, and EGFR proteins [128]. Purankar *et al*. further confirmed a dose-dependent reduction in cell growth in Wistar rats [129].

Ophiarrhiza mungos

O. mungos L., known as the Mongoose plant, is an Ayurvedic herb from the Rubiaceae family. It is ethnobotanically significant for containing camptothecin, a potent anticancer compound [156]. Australia, New Guinea, the Pacific Islands, and tropical and subtropical Asia are the native habitats of the genus Ophiorrhiza [157]. Traditionally, these plants are used for treating snake bites, tumors, and poisonous wounds, and they exhibited anti-helminthic, antibacterial, anti-ulcer, antiviral, and anti-venom properties [158]. The camptothecin alkaloid is key to the genus's notable anticancer effects [159]. The anticancer effects of alcohol and aqueous extracts of *O. mungos* L. leaves on Dalton's Ascitic Lymphoma (DAL) in mice were evaluated by Madhavan and Murali When taken orally at 400 and 800 mg/kg, the extracts significantly slowed the growth of tumors. The presence of camptothecin has been associated by the study with the significant anticancer activity [130].

Predicted anticancer mechanism of Rubiaceae family plants

Plants from various species have exhibited remarkable anticancer properties through diverse mechanisms. Many, such as *A. cordifolia*, *B. hispida*, and *C. dicoccum*, induce apoptosis, effectively disrupting cancer cell viability and promoting programmed cell death. Others, like *C. parviflorum*, *C. arabica*, *G. jasminoides*, and *H. diffusa*, inhibit cell proliferation by targeting specific phases of the cell cycle or key regulatory proteins, thereby slowing tumor growth. Some, including *A. cordifolia* and *C. dicoccum*, mitigate oxidative stress to prevent DNA damage and mutagenesis. Plants like *B. hispida* and *O. corymbosa* show promise in reducing metastasis by interfering with cancer spread pathways. Additionally, species such as *G. gummifera* and *G. pohliana* exhibited broad-spectrum cytotoxicity with low IC_{50} values, while *O. mungos* and *N. cadamba* target critical cancer pathways, including DNA replication and signaling proteins like human epidermal growth factor receptor 2, vascular endothelial growth factor receptor 2, and estimated glomerular filtration rate. These diverse mechanisms highlight the potential of these plants in cancer therapy.

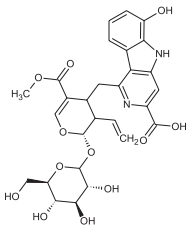
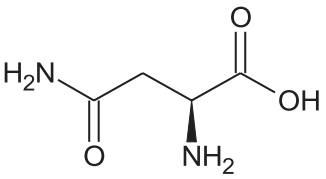
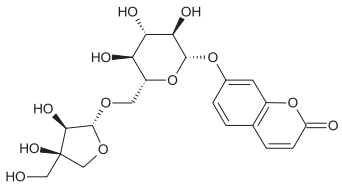
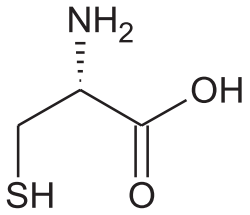
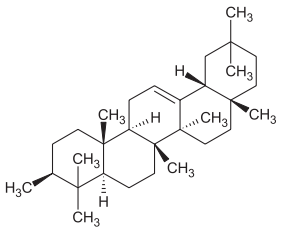
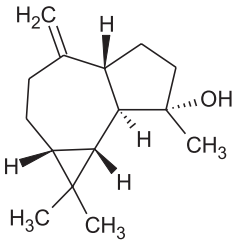
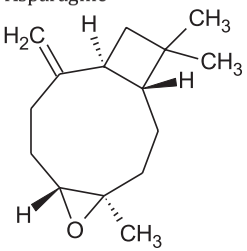
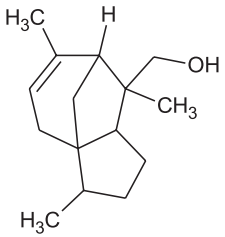
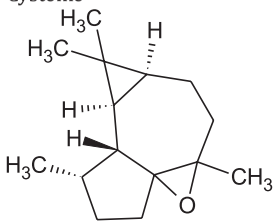
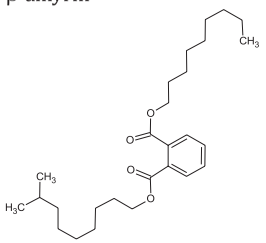
***In vivo* studies on anticancer herbal medicines from rubiaceae**

Several medicinal plants' anticancer effects have been assessed *in vivo* using a variety of animal models. There have been numerous reports of *in vivo* trials of anticancer plants in mice models. For instance, in tumor-bearing mice, dihydroartemisinic acid has been shown to inhibit tumor tissue growth, increase interferon-gamma levels, and decrease interleukin 4 levels [160]. Similarly, artesunate, a derivative of artemisinin, has been indicated to be a promising treatment for angiogenic Kaposi's sarcoma [161], suppress human prostate cancer xenograft [162], inhibit the growth of leukemia in mice [163], and

Table 3: Important anticancer medicinal plants from the Rubiaceae family, their active phytochemicals, and reported *in vitro* and *in vivo* activities

Sr. No.	Plant name	Common name	Parts used	Extract used	Active components	Dose concentration/ IC_{50} value	Cancer cell line applied to	Animal models applied to	References
1	*Adina cordifolia*	Haldu	Leaves	Acetone, EtOH	--	500 mg/kg	--	Swiss albino mice	[89]
2	*Borreria hispida*	Gathiyu	Seed	MeOH	--	3.125 µg/mL, 1.56 µg/mL	A549, MCF 7	--	[93]
3	*Canthium dicoccum*	Bellachi	Leaves	Petroleum ether, Ethyl acetate, EtOH	Phenolic compound	50 µg/mL	A549	--	[98]
4	*Canthium parviflorum*	Kirma	Leaves	EtOH	Flavonoid	200 mg/kg and 400 mg/kg	Hela	Swiss albino male mice	[104]
5	*Coffea arabica*	Coffea	Bean	MeOH	Chlorogenic acid	101.26 µg/mL	HT-29	--	[109]
6	*Galium verum*	Yellow bedstraw	Aerial part	MeOH	--	400 µg/mL	HT29, AGO	--	[115]
			Aerial part	Petroleum ether	Phenolic compound (Rutin, Isoquercitrin, Quercetol, Chlorogenic acid)	55 µg/mL	HaCaT, A375	--	[116]
			Whole plant	Chloroform and Petroleum Ether Fraction	--	>100 µg/mL	HepG2, HT29	--	[117]
7	*Gardenia gummifera*	Dikamali	Leaves	MeOH	Cycloartanes	30.98 µg/mL	MDA-MB-231	--	[118]
8	*Gardenia jasminoides*	Gandroya	--	--	Genipin	--	MDA-MB-231	--	[119]
9	*Guettarda pohliana*	Brazilian velvet	Root, leaves	--	Iridoids Secoxyloganin, Sweroside, Loganin	--	UACC-62, MCF-7, NCIADR, NCI-460, PCO-3, 786-0, OVCAR, HT-29, K-562	--	[49]
10	*Hedyotis corymbose*	Flat-top mille graines	Whole plant	EtOH	Asperuloside	6.51 µg/mL	YMB-1	--	[120]
			Whole plant	EtOH	Ursolic acid	400 µg/mL	--	--	[121]
			Leave	80% EtOH	Rutin	25 µg/mL	T47D, NIH3T3	--	[122]
11	*Hedyotis diffusa*	Snake-needle grass	--	--	Methylanthraquinone	18.62 µM	MCF-7	--	[123]
			Whole Plant	Water	--	5.0 mL/kg once daily for 10 days	--	Nude mice xenograft	[124]
12	*Morinda citrifolia*	Noni	Fruit	Aqueous, chloroform, MeOH	--	93.505, 94.808, 71.442 µg/mL	HepG-2	--	[125]
13	*Mussaenda frondose*	Dhobi tree	Leaves	MeOH	Flavonoids, Phenolic compound	125 µg/mL	HepG2	--	[126]
14	*Neolamarckia cadamba*	Bur-flower tree	Bark	Hydro-methanolic (80:20 v/v)	Phenolic compound	10–80 µg/mL	N1S1	--	[127]
			Stem Bark	n-hexane, DCM, 80% alcohol	Propanamide 2 hydroxy, 1,2 benzenedimethanol, 4-hydroxy-beta-ionone	--	MCF 7, A549, HepG2	--	[128]
			Stem bark	MeOH	--	200 mg/kg	--	Wistar rats	[129]
15	*Ophiorrhiza mungos*	Snake root	Leaves	95% EtOH	Camptothecin	400 and 800 mg/kg	--	Swiss albino mice	[130]

Table 4: Chemical structures of key phytoconstituents from Rubiaceae family

				
Cordifoline	Asparagine	Adicardin	Cysteine	β-amyrin
				
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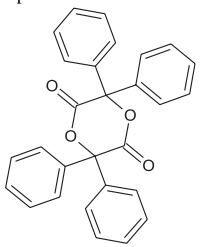	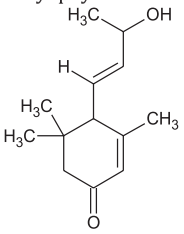	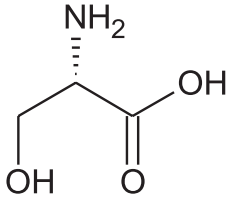	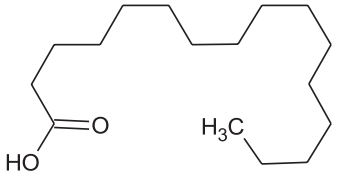	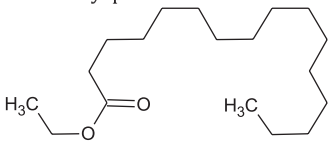
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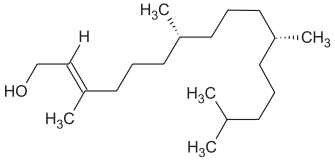	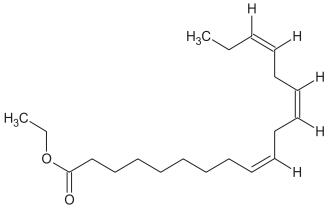	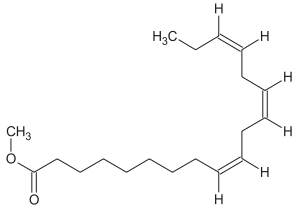	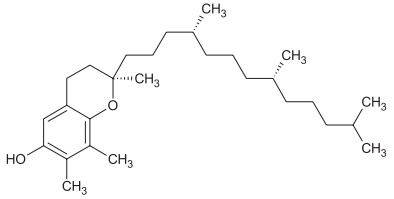	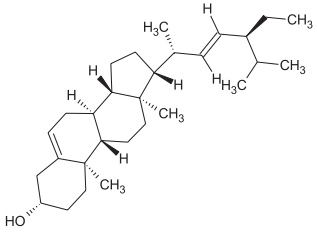
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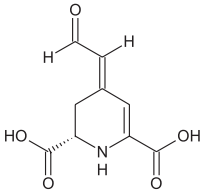	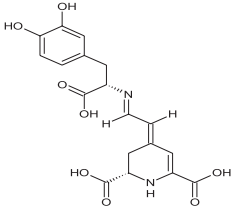	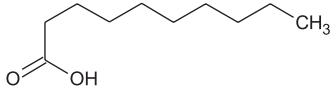	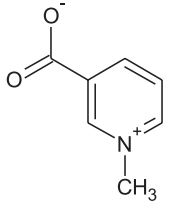	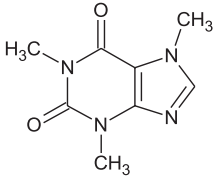

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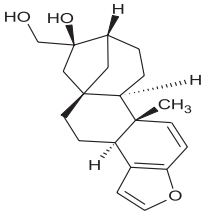
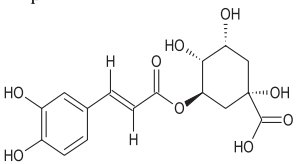
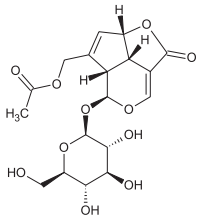
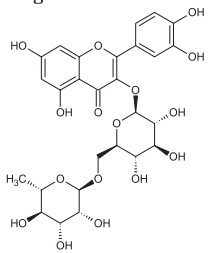
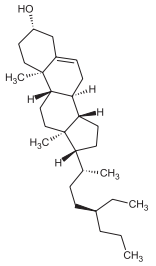
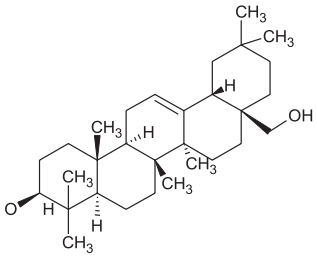
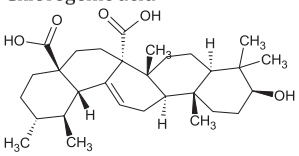
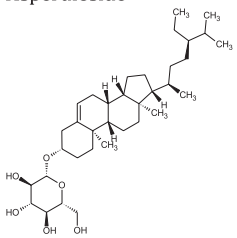
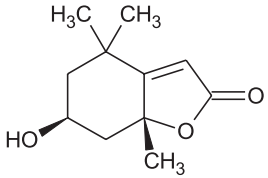
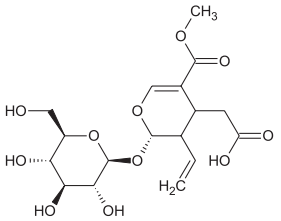
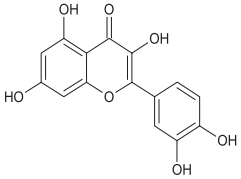
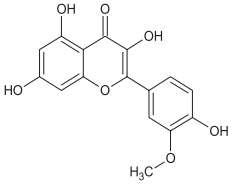
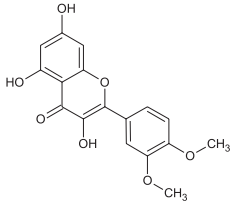
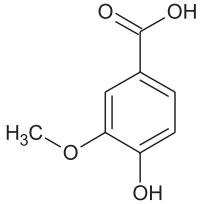
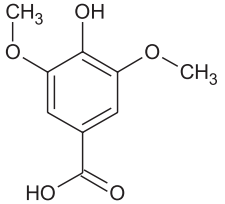
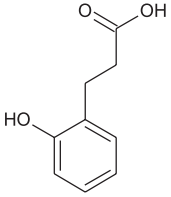
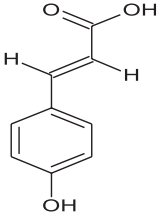
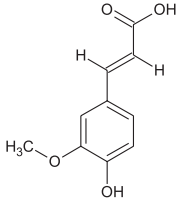
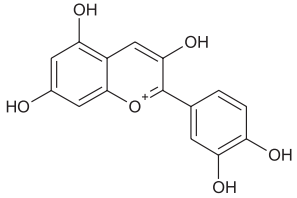
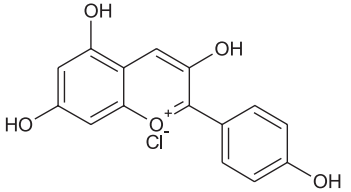
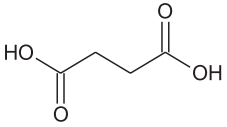
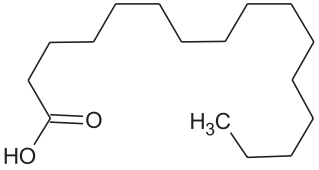
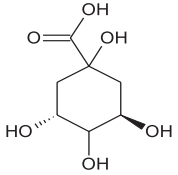
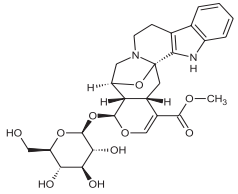
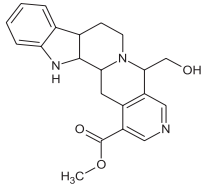
Betalamic acid 	Dopaxanthin 	Decanoic acid 	Trigonelline 	Caffeine 
Kahweol 	Chlorogenic acid 	Asperuloside 	Rutin 	Sitosterol 
Erythrodiol 	Quinovic acid 	Daucosterol 	Loliolide 	Secoxyloganin 
Quercetin 	3-methoxy quercetin 	3,4-dimethoxy quercetin 	Vanillic 	Syringic 
Melilotic acid 	p-coumaric acid 	Ferulic acid 	Cyanidin 	Pelargonidin 

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Table 4: ***(Continued)***

Butanedioic acid	Hexadecanoic acid	Quinic acid	Cadambine	Cadamine	
5,7-dimethoxy- 4-hydroxyflavanone	7,4-dimethoxy- 5 hydroxy flavanone	Deacetylasperulosidic acid	Camptothecin	Purpurin	
4-(2-Hydroxy-2,6,6-trimethylcyclohexyl) -3-buten-2-one	1,2 Benzenedicarboxylic acid, bis (2-ethylhexyl) ester	4-((1E)-3- hydroxy-1-propenyl)-2-methoxyphenol	Munjistin	Xanthopurpurin	

inhibit the growth of A549 and H1299 lung tumors when administered at a dose of 100 mg/kg [164].

Kumar and Kumar evaluated the anticancer effects of methanol extract of *Morinda tinctoria* leaves (MEMT) utilizing *in vitro* and *in vivo* models. MEMT exhibited significant cytotoxicity against EAC cells and improved survival rates in EAC-bearing mice. At doses of 200 and 400 mg/kg, MEMT enhanced lifespan, protected the hemopoietic system, reduced lipid peroxidation, and restored antioxidant enzyme levels in the liver while significantly decreasing solid tumor volume. The study used 5-Fluorouracil as a standard reference [165]. The anticancer potential of *Mussaenda macrophylla* (MMAE) aqueous extract in a mouse model of DLA. MMAE extended survival time and dramatically reduced tumor development. In DLA mice, it decreased lipid peroxidation while increasing glutathione levels and the activity of glutathione-s-transferase and superoxide dismutase. Additionally, MMAE reduced elevated alanine transaminase, aspartate aminotransferase, and creatinine levels while restoring decreased hemoglobin and red blood cell levels. Additionally, MMAE induced DNA damage and modulated pro- and anti-apoptotic gene expression, supporting its apoptosis-based anticancer effects [166].

Regulatory aspects of using rubiaceae-derived compounds in cancer therapy

A global survey conducted by the World Health Organization around 124 member states (64%) responded that they had laws or regulations on herbal medicines whereas around 125 member states, or almost 65% of member states responded that they have a registration system for herbal medicines. In the European Union, regulatory harmonization is ensured through legislation (Directive 2001/83/EC and 2004/24/EC), which governs herbal medicine marketing. In contrast, Africa has widespread use of traditional herbal medicines, but no legal framework to integrate them into drug legislation. In many African countries, herbal remedies are sold without proof of safety, efficacy, or quality. In sub-Saharan Africa, gaps in policy and regulation are evident, with some countries, such as Kenya and Ethiopia, lacking formal registration systems for herbal medicines. Despite Ethiopia's National Health Medicine policy and recent regulations (Regulation No. 1112/2019), traditional herbal medicines continue to be sold without restrictions or proven safety and efficacy [167].

The Department of AYUSH is the regulating authority for herbal medicines in India, which are governed under the Drug and cosmetic act (D&C) of 1940 and the Rules of 1945. A manufacturing license is required for producing or marketing herbal medicines [168]. Schedule T of the D&C Act outlines good manufacturing practices (GMP) for herbal manufacturers. The Ministry of AYUSH, established in 2014, focuses on the development of traditional health systems, evolving from the earlier Department of Indian Medicine and Homeopathy. Sections 33C to 33O provide details on manufacturing, registration, sale, licenses, GMP certification, and penalties [169]. From 2017, manufacturing and expiry dates on product labels became mandatory, and clinical trial approvals took around 3 months [170].

It is well known that to obtain marketing authorization, medications, including anticancer agents, must undergo phase III clinical research trials. According to the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) standards, a product cannot be marketed unless at least one Phase III controlled trial has produced statistically significant results. All medications must undergo all required testing stages in accordance with regulations set by international organizations such as the FDA and EMA unless exceptional circumstances apply. However, pharmaceutical companies have occasionally deviated from established practices by initiating human testing of new substances before the designated timeline. These actions are taken to accelerate the approval process in response to pressure from investors [171]. This indicates that there is insufficient information on the drug's efficacy, safety, and quality when it is submitted for approval.

Despite the fact that plant-based substances have been proven to be less hazardous than traditional synthetic substances, there is mounting data regarding the adverse effects of using these plants unregulated to treat various illnesses. The issue is that not enough information is accessible about the effectiveness, safety, and quality of herbal medications. For example, *Galium aparine* has demonstrated action against the Caco-2 and MCF-7 cell lines. In traditional medicine, *G. aparine* is utilized as a choleretic, a diuretic, to prevent diarrhea, and to treat gout, epilepsy, and some stomach issues [172]. There aren't many reports on the plant's anticancer properties, therefore the question still stands. Expert involvement and an advice process facilitated by regulatory bodies govern the development and marketing of cancer drugs worldwide [173].

There are multiple regulatory frameworks for prescribing drugs, but greater harmony is needed among regulatory agencies to improve the process. The United State FDA, for example, has recently adopted the International Council for Harmonization's guidelines on the nonclinical evaluation of anticancer drugs. The aim of these 41 questions and answers is to standardize the development of anticancer drugs. For more comprehensive oversight, it is recommended that regulatory bodies integrate scientific research with traditional knowledge while collaborating with other organizations that regulate anticancer herbal compounds [174,175].

Furthermore, it is clear that the profile of therapeutic substances in plants of the same species grown in various locations varies [176]. This requires focusing on producing reliable, superior plants with a steady metabolite profile that can be categorically categorised as safe or hazardous afterwards testing. Biotechnological and genetic studies of these anticancer plants, as well as *in vitro* cultivation, could help accomplish this objective [177,178].

CONCLUSION

This comprehensive research underscores the significant anticancer potential of Rubiaceous plants, particularly in the context of breast cancer. Through an integrative approach combining network pharmacology, molecular docking, and preclinical evidence, key bioactive phytoconstituents such as quercetin, resveratrol, and apigenin have been identified as promising candidates targeting breast cancer-related pathways, especially via EGFR kinase inhibition. GO and KEGG enrichment analyses revealed extensive involvement in cancer-related BPs and signaling pathways, supporting the relevance of these compounds in cancer modulation. While preclinical studies highlight the efficacy of Rubiaceae-derived phytochemicals in inducing apoptosis and suppressing tumor growth, further research is necessary to explore lesser-known species, validate mechanisms of action, and assess clinical safety. Importantly, the development of standardized formulations, supported by robust regulatory frameworks, is essential for the successful integration of these plant-based therapies into mainstream oncology. Moving forward, a multidisciplinary strategy combining ethnopharmacological knowledge with advanced computational and experimental tools holds promise for the discovery and development of novel, safe, and effective anticancer agents from the Rubiaceae family.

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AUTHORS' CONTRIBUTIONS

Mr. Omkar Tipugade and Dr. Jyotiram Sawale conceptualized and designed the study, with Mr. Omkar Tipugade handling data collection. Dr. Jyotiram Sawale conducted data analysis and prepared the initial draft of the article. Dr. Namdeo Jadhav supervised the study, contributed to data analysis and interpretation, and provided essential revisions. All authors have reviewed and approved the final version of the manuscript. The authors confirm that no paper mill and artificial intelligence was used.

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All data are available upon request.

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