


**Research Article**

## Systems Pharmacology and Molecular Docking Reveals the Potential Beneficial effect of *Rabdosia serra* in Treating liver Cancer

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### Abstract

**Introduction:** The folk herb *Rabdosia serra* (Xi Huang Cao) has been used to treat several diseases, including jaundice, hepatitis, acute cholecystitis, and enteritis, for many years. Moreover, it is also one of the components of the Dan Shi Tong capsule, a medication that relieves the damp-heat symptoms in the gallbladder and liver. This research aimed to carry out a series of comprehensive pharmacological evaluations of the mechanism of action of this plant for the treatment of hepatocellular carcinoma (HCC).

**Methods:** This study determined the potential anticancer benefit of *R. serra* by predicting the molecular targets of the key components and intersecting the herbal targets with disease targets associated with liver cancer. The anti-hepatocellular carcinogenic value of *R. serra* and the potential influence on other liver disorders and malignancies were demonstrated using a systems pharmacology approach and molecular docking.

**Results:** Fishing for drug targets turned up 451 targets related to 20 important metabolites. A 216 intersected target set was produced by crossing drug targets (451) with HCC-associated elite targets (5725). These data were then used to analyse the protein-protein interaction (PPI) network and GO and KEGG pathways. A combination of these results revealed that the target factors (PIK3R1, RELA, EGFR, and EP300) were implicated in more than four signaling pathways, including the PI3K-Akt, mitogen-activated protein kinase (MAPK), Wnt, and p53 signaling routes. These findings were validated by molecular docking, which showed stable combinations between the five metabolites (linoleic acid, quercetin, caffeine, rutin, and methyl rosmarinate) and the four molecular targets (PIK3R1, RELA, EGFR, and EP300).

**Conclusion:** These findings establish the theoretical foundation for future study into the active drug-like components and mechanisms of action of *R. serra* in treating HCC and other hepatic disorders.

**Keywords:** *Rabdosia serra*; systems pharmacology; hepatocellular carcinoma; hepatoma; molecular docking

### Introduction

Liver cancer (hepatoma) continues to be a global health challenge and a leading cause of cancer deaths worldwide, with a prediction of over 1 million cases by 2030 by the World Health Organization. Hepatocellular carcinoma (HCC) is the most common form of liver cancer, while hepatoblastoma mainly affects young children [1, 2]. HCC incidence remains a major oncologic challenge in many world areas, including Europe, the United States and Asian countries [3]. While liver transplant and resection can be curative

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in an early stage, it is often diagnosed at advanced stages of HCC, for which highly effective therapies are lacking [4, 5]. Recent years have seen a great diversification of treatment methods, such as lenvatinib, regorafenib, and sorafenib, approved as first or second-line treatment for advanced HCC patients [6]. Moreover, catheter-based intraarterial therapies have been demonstrated to be an attractive therapeutic option for patients who may have previously had other alternatives [7]. While we acknowledge that these are inspiring, their effectiveness is worth pointing out, which confers limited survival benefits.

Since irinotecan and topotecan, clinical derivatives of the plant alkaloid camptothecin, have been widely used as anticancer drugs for the past 20 years [8], the efforts to develop new medicines in oncology should continue focusing on natural products and the use of natural phytochemical compounds [9]. These natural therapies using plant-derived extracts may reduce adverse side effects compared with traditional cancer treatments [10]. In addition, the ability of phytochemicals to inhibit tumor formation by antioxidant, antiproliferative, and pro-apoptotic effects on a variety of conditions, including leukemia, prostate, breast, colon, brain, melanoma, and pancreatic cancers, has also been well documented [11]. However, the relative number of natural plant-based therapeutics, partially attributed to challenges associated with extraction, isolation, and their structural complexity, has steadily declined over the past several decades [12]. Thus, finding novel natural compounds through systems pharmacology based on big data simultaneously with low toxicity and high selectivity for killing cancer cells is an important area in cancer research [13].

*Rabdosia serra* (Maxim), a perennial plant, is found across South and Southeast Asia [16]. It is now demonstrated to have various pharmacological effects and has been used as a folk medicine for jaundice, hepatitis, acute cholecystitis and enteritis [17]. The bioactive molecules contained in the plant include diterpenoids (the most important active constituents contributing to the pharmacological efficacy), triterpenoids, flavonoids, phenolic acids and volatile oils [18]. Furthermore, *R. serra*, a valuable substance against jaundice and hypochondriac discomfort, treats damp heat in the liver and gallbladder in Traditional Chinese Medicine [19]. The top five chemicals tested in this investigation based on their degree values, linoleic acid, quercetin, caffeic acid, rutin, and methyl rosmarinic acid, were shown to interact with liver cancer-related molecular targets, which will be described in detail in the following sections in this paper.

Chinese medicine offers a wide range of potential avenues for investigation in regulating liver function and modulating abnormalities in numerous organ systems. Recently, research has focused on novel drug discovery for treating liver cancers via systems pharmacology [20]. As a result, we believe that

elucidating the structure and molecular targets of the complex components of herbal plants and discovering or repurposing existing medications will be an alternate development avenue for cancer treatment.

## Methods and Materials

### Compound Screening and Targeted Collection

The compounds needed for this project were obtained by literature matching and collecting the main active metabolites derived from *R. serra* based on China Knowledge Network (CNKI: <https://www.cnki.net/>), Bioinformatics Analysis Tool for Molecular Mechanisms in Chinese Medicine (BATMAN-TCM: <http://bionet.ncpsb.org.cn/batman-tcm/index.php>), Encyclopedia of Traditional Chinese Medicine (ETCM: <http://www.tcmip.cn/ETCM/index.php/Home/Index/>) and High-Entomology Database of Traditional Chinese Medicine (HERB: <http://herb.ac.cn/>) [19, 21]. Subsequently, the SMILES and other relevant information were gained from PubChem (<https://pubchem.ncbi.nlm.nih.gov/>). The names of the molecules and their chemical structure formulas were checked, and the oral bioavailability (OB) and drug-like (DL) information of the flavonoids were retrieved from TCMSP (<http://tcmsp.com/tcmsp.php>) to establish a database of flavonoids [22]. The Similarity Ensemble Approach (SEA: <https://sea.bkslab.org/>) with target species setting as *Homo sapiens* was then used to remove duplications were removed; the BATMAN-TCM (score >15, P<0.05) and HERB databases were applied to find relevant targets for the compounds [21, 23].

### Acquisition of Intersectional Targets between the Components of *Rabdosia serra* and HCC

The DisGeNET database (<https://www.disgenet.org/search>) was searched using "Liver carcinoma" to obtain relevant targets for liver cancer disease. The Bioinformatics & Evolutionary Genomics website was subsequently used to intersect targets with liver cancer targets and get a Venn diagram (<http://bioinformatics.psb.ugent.be/webtools/Venn/>) [24].

### Construction of Protein-Protein Interaction Network

The intersecting targets were imported into the STRING database under the "multiple proteins" option, the species of origin was selected as *Homo sapiens* for "organism," targets with the highest confidence score (>0.9) were set, and the free nodes were hidden [25]. The protein-protein interaction (PPI) network analysis of the effect of the components of *R. serra* on HCC was carried out. The higher the value, the more central the target is in the PPI network. The ".tsv" file was downloaded from the STRING database that generates information about the PPI network, which was further imported into Cytoscape 3.6.0. The cytoHubba function was chosen to filter the core targets.

## GO and KEGG Enrichment Analysis

The functional annotation, classification, and enrichment analysis of common targets were performed using Metascape and the organism was limited to *Homo sapiens* [26]. The key cancer gene pathways in Metascape were then shown using KEGG mapper, along with therapeutic targets for each of these pathways [27-29]. Further analysis of the genes was performed through the DAVID platform [30, 31].

## Component-Target-Pathway Network Construction

The components, intersecting targets and major pathways of *R. serra* were imported into Cytoscape 3.6.0 software to construct a component-target-pathway network map of *R. serra* components against liver cancer. The topological analysis was performed using the Network Analyzer function, and the top five components were selected for molecular docking validation based on their degree values.

## Molecular Docking

The 2D molecular structures of the ligands and their active components were obtained from PubChem, and the crystal structures of the primary target proteins were acquired from RCSB PDB (<https://www.rcsb.org/>) to verify the binding of the hub genes to their corresponding components. Autodock Vina 1.5.6 was used for molecular docking. The molecule with the lowest binding energy in the docked conformation was chosen; the lower the binding energy, the simpler it is for the active component to attach to the receptor. The molecular docking pattern is finally visualized by PyMOL 2.3.4.

## Results

### Target Prediction and Analysis

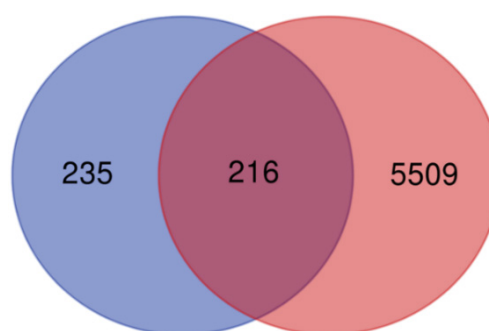
We found 23 components based on the literature review: BATMAN-TCM, HERB, and ETCM. In addition, the TCMSP database was searched, and only five components with oral bioavailability (OB)  $\geq 20\%$  were finally identified, while only three components with drug-likeness (DL)  $\geq 0.1$  were identified. Further, for the targets of the obtained compounds, a search of the potential targets based on the BATMAN-TCM (score  $>15$ ,  $P < 0.05$ ), SEA and HERB databases resulted in a total of 451 targets associated with 20 components. In contrast, the OB and DL values of 12 components obtained in the TCMSP database are shown in Table 1.

### Collection of Intersectional Targets

The dataset on liver cancer genes was retrieved from the DisGeNET database and paired with the constituent target ensemble we previously obtained, yielding 216 overlapping targets as prospective targets of *R. serra* constituents for the therapy of liver cancer using Venn diagram mapping (Figure 1).

**Table 1:** Information of 12 flavonoid compounds from TCMSP

Components	CAS Number	Oral bioavailability, OB (%)	Drug-like, DL (%)
Caffeic acid	331-39-5	54.97	0.05
Isorhamnetin	480-19-3	49.6	0.31
Quercetin	117-39-5	46.43	0.28
Loliolide	06-02-5989	44.66	0.08
Linoleic acid	6144-28-1	41.9	0.14
Corosolic Acid	4547-24-4	18.56	0.74
Ursolic acid	77-52-1	16.77	0.75
Totarol	511-15-9	15.78	0.25
Chlorogenic acid	327-97-9	11.93	0.33
Rutin	153-18-4	3.2	0.68
Rosmarinic acid	20283-92-5	1.38	0.35
Methyl rosmarinate	99353-00-1	1.37	0.37



**Figure 1:** Intersecting targets between *Radosia serra* (Xihuangcao) components and liver cancer.

### Network Analysis and Construction

The STRING database was used to import the 216 intersection targets, and the disconnected nodes were removed to create a PPI network with a confidence level  $> 0.9$ . Figure 2 depicts the PPI network, which has 221 nodes and 438 edges with an average node degree value of 3.96. We next imported the network into Cytoscape 3.6.0 and utilised the cytoHubba plugin to identify the hub gene, as shown in Figure 3. The top ten genes calculated by the MCC algorithm were listed according to the scores: PIK3R1, PTK2, PTPN11, VEGFA, RHOA, CSK, EGFR, KDR, LPAR2, and LPAR1 (Table 3). The MNC, EPC, Degree, and Closeness algorithms were applied to determine the top 10 hub targets, and the results are displayed in Table 2. The targets in the table in black italics are important, and we chose the top objectives as docking targets based on the number of repetitions and the order of ranking (PIK3R1, RELA, EGFR and EP300).

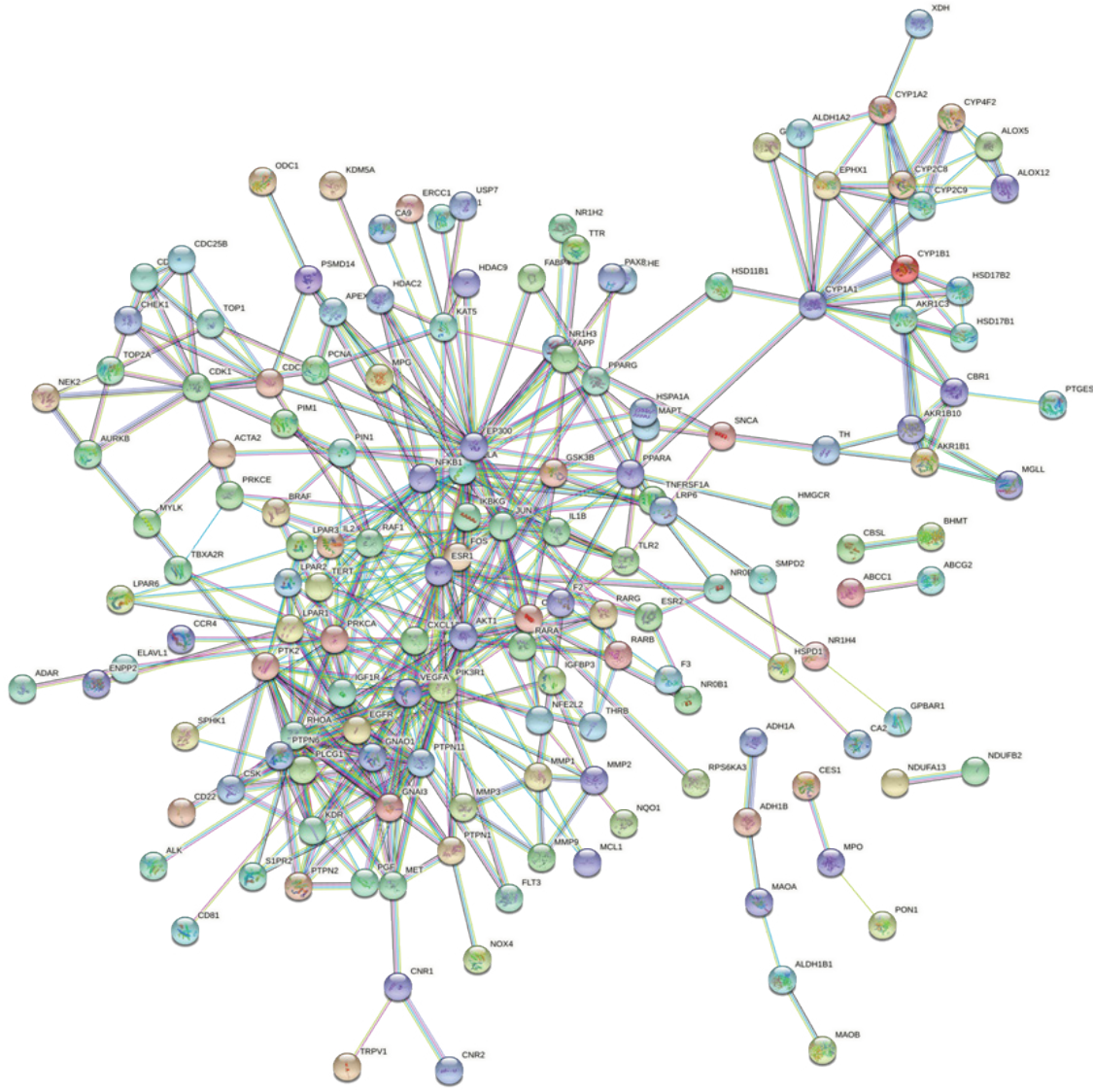


Figure 2: Protein-protein interaction (PPI) network

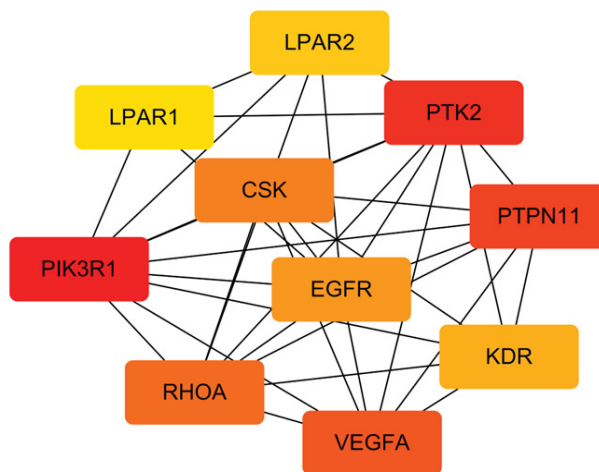


Figure 3: Top 10 hub targets by MCC.

**Table 2:** Top 10 targets in PPI network ranked by MCC method.

Rank	Name	Score
1	PIK3R1	2009
2	PTK2	1801
3	PTPN11	1796
4	VEGFA	1732
5	RHOA	1692
6	CSK	1440
7	EGFR	1268
8	KDR	786
9	LPAR2	510
10	LPAR1	499

**Table 3:** Different calculation methods and key genes

Category	Rank methods in CytoHubba				
	EPC	MCC	MNC	Degree	Closeness
1	PIK3R1	PIK3R1	PIK3R1	EP300	EP300
2	RELA	PTK2	EP300	PIK3R1	RELA
3	EGFR	PTPN11	RELA	RELA	PIK3R1
4	EP300	VEGFA	AKT1	AKT1	JUN
5	AKT1	RHOA	NFKB1	EGFR	AKT1
6	PTK2	CSK	ESR1	NFKB1	NFKB1
7	RHOA	EGFR	JUN	ESR1	ESR1
8	VEGFA	KDR	EGFR	VEGFA	VEGFA
9	ESR1	LPAR2	PTPN11	JUN	EGFR
10	PTPN11	LPAR1	RHOA	PTPN11	PRKCA

### Functional Classification and Enrichment Analysis of the Common Gene Sets

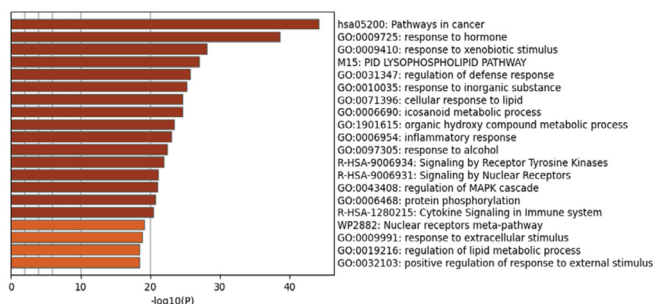
In the process and the KEGG/Wiki/Canonical route, the common *R. serra*-HCC targets were significantly enriched, according to the Metascape study (Figure 4). The top 20 enrichment terms by the p-value are pathways in cancer (hsa05200), response to hormone (GO:0009725), response to xenobiotic stimulus (GO:0009410), lysophospholipid pathway (M15-PID), regulation of defense response (GO:0031347), response to inorganic substance (GO:0010035), cellular response to lipid (GO:0071396), icosanoid metabolic process (GO:0006690), organic hydroxy compound metabolic process (GO:1901615), inflammatory response (GO:0006954), response to alcohol (GO:0097305), signaling by receptor tyrosine kinases (R-HSA-9006934), signaling by nuclear receptors (R-HSA-9006931), regulation of the mitogen-activated protein kinase (MAPK) cascade (GO:0043408), protein phosphorylation (GO:0006468), cytokine signaling in immune system (R-HSA-1280215), nuclear receptors meta-pathway (WP2882), response to extracellular stimulus (GO:0009991), regulation of lipid

metabolic process (GO:0019216), positive regulation of response to external stimulation (GO:0032103). Of these, the cancer pathway was the most significantly enriched.

We also used the KEGG mapper to visualize the herb's additional targets enriched for the cancer pathway (hsa05200, Figure 5). The typical herbal cancer targets are shown in green, whereas other herbal targets are highlighted in red. As shown in Figure 5, the targets EGRF, MET, Raf, and DAPK are associated with the MAPK signaling pathway, while the herb's major targets are also the PI3K-Akt route. There are also many drug targets in the Wnt and the JAK-STAT signaling pathway. Similarly, in the pathway analysis of HCC (Figure 6), GSK-3 controlled cell proliferation, differentiation, and survival, whereas TERT influenced telomerase activity and KEAP1-NRF2-associated targets influenced cell survival. Finally, one of the downstream targets associated with TP53 transcription was found to be the POLK target. Further, the DAVID platform was used to analyze the genes and select the "KEGG\_PATHWAY" and "WIKIPATHWAYS" options. As a result, 22 targets were involved in the PI3K-Akt signaling pathway ( $p < 0.05$ ), and 18 were involved in the PI3K-Akt-mTOR (the mechanistic target of rapamycin)-signaling pathway ( $p < 0.05$ ). The "DISGENET" and "OMIM\_DISEASE" options were further selected, and the higher Classification Stringency condition showed that this ensemble was also associated with Breast Carcinoma ( $p < 0.05$ , 26 targets), Adenocarcinoma ( $p < 0.05$ , 10 targets) and Diffuse Astrocytoma ( $p < 0.05$ , 6 targets).

### Component-Target-Pathway Network Construction

A network of 20 flavonoid components, 216 crossing targets, and five significant pathways was created using Cytoscape 3.6.0 (Figure 6). There are 404 nodes and 1026 edges in the network diagram, with 20 green diamond nodes representing components of *R. serra*, 216 red inverted triangles representing intersection targets, five red triangles representing critical pathways, and the edges representing the relationship between components, targets, and pathways (Figure 7). To validate molecular docking, the top five components were chosen based on their degree values: rutin



**Figure 4:** Enrichment analysis of GO terms and KEGG pathways for key targets.

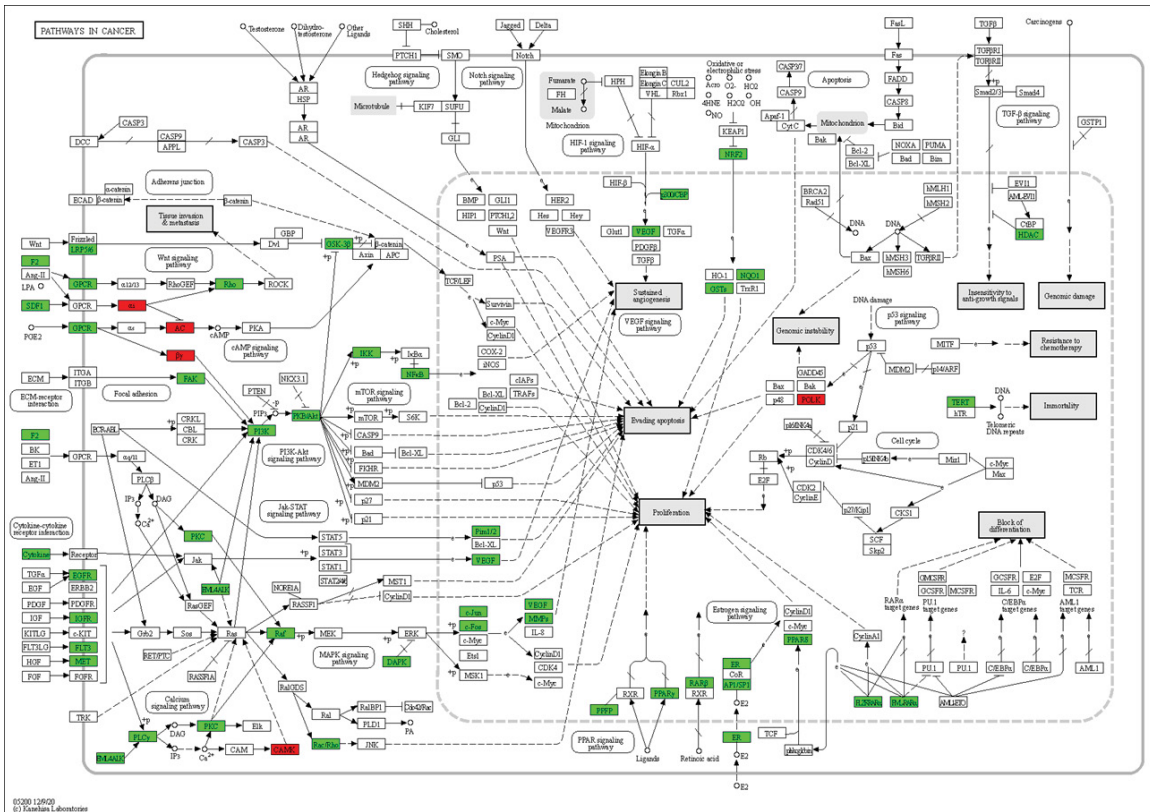


Figure 5: Genes involved in cancer pathway intersection (green) and other herbal targets involved in the pathway (red)

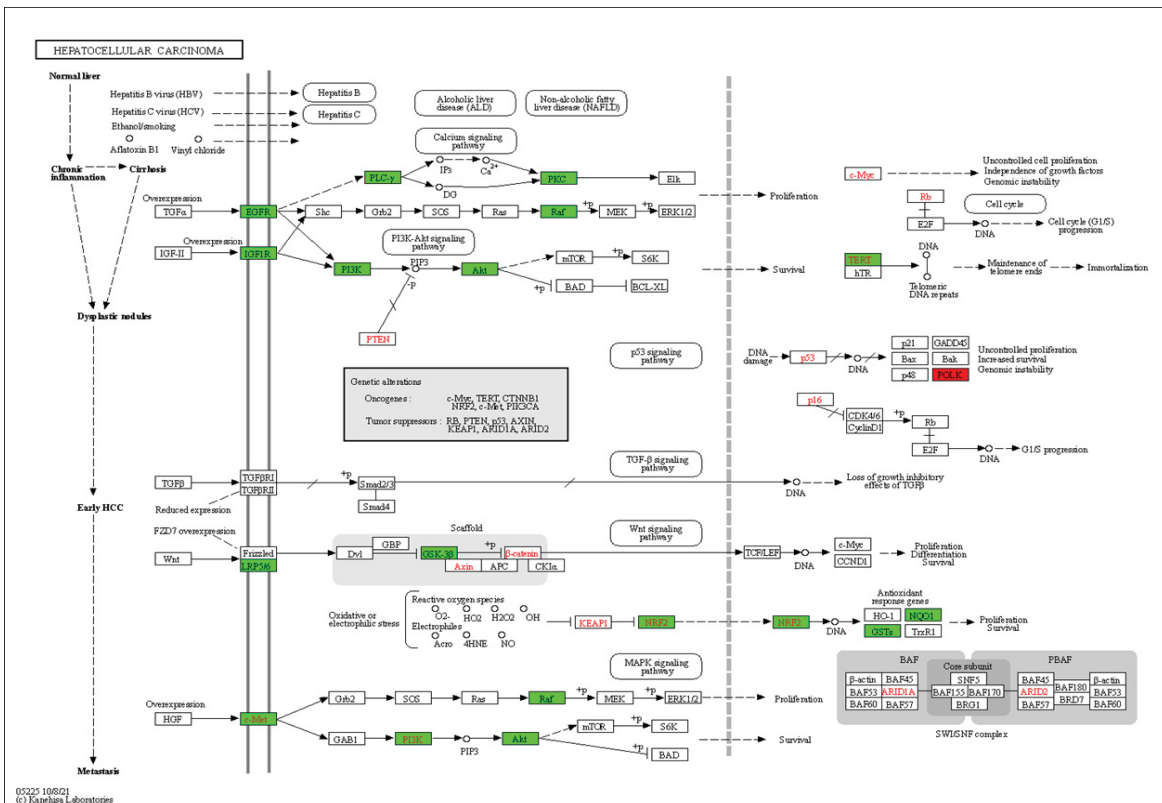


Figure 6: Genes involved in hepatocellular carcinoma intersection (green) and other herbal targets involved in the pathway (red)

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(degree:82), caffeic acid (degree:97), quercetin (degree:97), linoleic acid (degree:152), and methyl rosmarinate (degree:60).

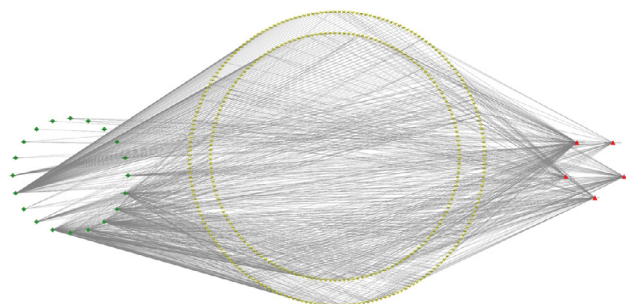
### Molecular Docking

Lower energy and a higher chance of contact resulted from a more stable ligand conformation when it binds to the receptor. The foundation for calculating interaction capacity is the binding energy of -5 kJ/mol. Linoleic acid (CAS: 6144-28-1), quercetin (CAS: 117-39-5), caffeic acid (CAS: 331-39-5), rutin (CAS: 153-18-4) and methyl rosmarinate (CAS: 99353-00-1) were selected as small molecule ligands, and EGFR (PDB ID: 5UGB), PIK3R1(PDB ID: 5LKZ), EP300 (PDB ID: 1H9O) and RELA (PDB ID: 3RCO) were molecularly docked as protein receptors (Figure 8). All five components' binding energies were negative, as shown in Table 4, demonstrating their capacity to attach to the target site spontaneously. However, all five parts showed binding solid affinities to the EGFR and PIK3R1. On the other hand, linoleic acid has a poor capacity to interact with EP300 and RELA. Based on the whole picture, molecular docking revealed that the chytid components exhibit superior binding potential to the key targets.

### Discussion

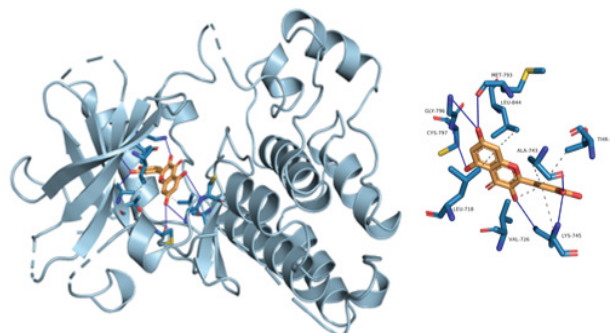
Hepatocellular carcinoma is the most prevalent type of primary liver cancer [32]. It occurs most commonly in chronic liver disease, typically brought on by infection with hepatitis B or hepatitis C and regular alcohol consumption [33]. Although surgery is now the most popular treatment option for HCC, the traits of multifocal growth and distant metastases prevent surgical treatment from being curative in most HCC patients [34]. In addition, the five-year survival rate for HCC patients is still poor due to metastasis, dissemination, and high recurrence rates [35]. Therefore, it is anticipated that systems pharmacology analysis will enable us to reevaluate the effectiveness value of the existing available medications or herbal remedies, enhancing cancer patients' outcomes and experiences.

In this research, we analyzed the components of *R. serra*. The top five components (linoleic acid, quercetin, caffeic

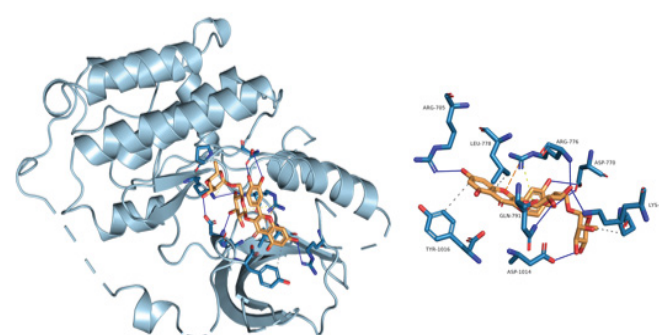


**Figure 7:** Network of flavonoid components-target-pathway (green diamonds: compounds, yellow circles: target; red triangle: pathway).

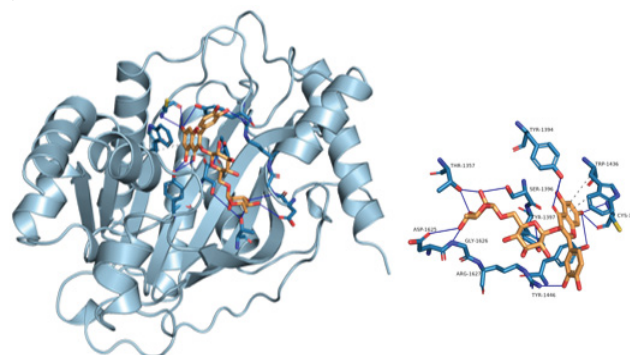
A) EP300-Quercetin



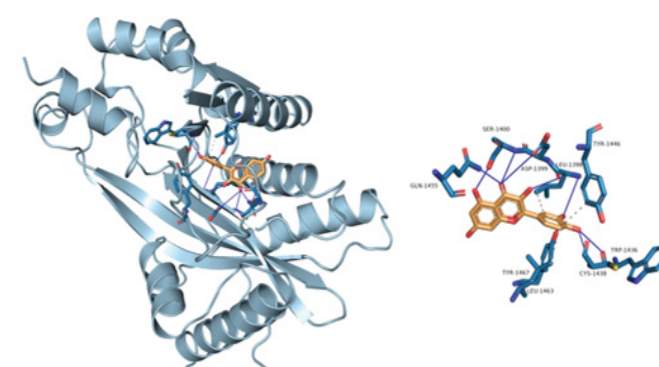
B) EGFR-Quercetin



C) EP300-Rutin



D) EGFR-Rutin



**Figure 8:** Component-target molecular docking interaction. The binding affinities are presented in Table 4.

acid, rutin, and methyl rosmarinat) were filtered based on the degree value from the network diagram created. Linoleic acid, an important unsaturated fatty acid, has an isomer called conjugated linoleic acid (CLA) [36]. Conjugated linoleic acid (CLA; cis-9, trans-11-18:2), one of the most desired unsaturated fatty acids with the healthiest features, is the unsaturated fatty acid [37]. Natural flavonoid quercetin has been a promising therapeutic ligand for human triple-negative breast cancer, which inhibits various target proteins, including heat shock factor 1 (HSF1), Nuclear factor kappa B (NF- $\kappa$ B), CYP3A4 and numerous kinases [38]. Inhibition of HSF1 can make the antiproliferative effects of simvastatin in HCC cells more noticeable since HSF1 supports the growth and progression of malignancy [39]. It has also been demonstrated that HSF1 directly triggers miR-135b expression, promoting HCC cell motility and invasiveness, whereas miR-135b increases HCC cell metastasis *in vivo* and migration and invasion *in vitro* [40].

Similarly, NF- $\kappa$ B is constitutively active in some malignancies controlling genes involved in cell survival and proliferation, and it is also a key regulator of inflammatory responses [41]. It has also been shown that NF- $\kappa$ B plays a crucial role in modulating the development of liver disorders and even cancer by activating survival and inflammation of damaged hepatocytes, inducing spontaneous liver injury, fibrosis, and HCC [42]. About half of all commercially available medications are metabolized by CYP3A4, an important CYP450 enzyme responsible for the oxidation and inactivation of the anticancer agent taxol [43]. Caffeic acid and its derivative, caffeic acid phenethyl ester CAPE, have shown therapeutic benefits of reducing multidrug resistance in cancer cells by locking the efflux function of human P-glycoprotein against lung and breast cancer cells [44]. Additionally, the C/EBP Homologous Protein (CHOP)-mediated apoptosis was induced in hepatocarcinoma when Hep3B cells were treated with caffeic acid phenethyl ester, and DR5 protein levels were elevated [45]. Rutin was non-toxic to hepatoma cells, dramatically blocking the binding between HCV-LP and hepatoma cells and preventing cell-culture-derived HCV (HCVcc) from entering hepatoma cells [46]. It has been reported as a hepatoprotective, antioxidant, and anti-inflammatory agent [47]. Among Rosmarinus acid derivatives, methyl rosmarinat provided notable antioxidant and AR-inhibiting properties [48]. As a result, the above-mentioned key components of *R. serra* may have a role in intervening in liver cancer by regulating cell proliferation and apoptosis, reducing oxidative stress, decreasing drug resistance build-up, and down-regulating inflammatory levels.

According to the core target network screening, PIK3R1, RELA, EGFR, EP300, and other core targets are among the targets of *R. serra* components that affect liver cancer. First

of all, aberrant PI3K signaling is a hallmark of cancer. As one of the key players in the PI3K pathway, which is linked to tumor growth and metastasis, PIK3R1 can control cancer cell proliferation [49]. In HCC clinical samples, PIK3R1 expression was elevated, and its silencing decreased the expression of p-PI3K, p-AKT, and p-mTOR, limiting cell proliferation, migrating, and expediting apoptosis in HCC cells [50]. It has also been demonstrated that mTOR signaling increases the production of new fatty acids [51]. As a potential target for cancer therapy, PIK3R1, therefore, deserves further exploration. Additionally, RELA, a protein-coding gene known as p53, is a widely expressed pleiotropic NF- $\kappa$ B subunit that stimulates the expression of the target gene IRF1 when RELA levels and baseline transcriptional activity are increased [52]. Furthermore, overexpression of RELA/p53 inhibits the growth of breast cancer cells by activating IRF1 in a manner that relies on RELA/p53 [53]. The RELA/p53 binding site in the Fas promoter was previously found and it has been demonstrated that tumor necrosis factor (TNF)-induced NF- $\kappa$ B-mediated elevation of Fas also further mediates the apoptosis [54]. Thus, regulating the expression of the RELA gene and related products is likely a potential therapeutic approach. Overexpression of the epidermal growth factor receptor (EGFR) and EGFR-activating mutations have been documented in numerous human tumors and are linked with poor clinical outcomes [55]. Additionally, EGFR promotes tumor stem/progenitor cell expansion and survival, supporting the use of EGFR-targeted drugs in managing resistant malignancies [56]. According to the abnormal Wnt signaling connected to HCC patients, proteins are usually regarded as the prominent oncogenes in HCC. They promote the signaling of growth factor receptors like EGFR to promote the survival of tumor cells [57]. As a histone acetyltransferase, EP300 plays a key role in regulating transcriptional activity through chromatin remodeling, thereby influencing cell proliferation and differentiation [58]. The mTOR complex 1 (mTORC1) is a key cell development and metabolism regulator. Acetyl-coenzyme A (AcCoA), a Leu metabolite, positively controls mTORC1 activity by acetylating raptor, an important mTORC1 regulator, at K1097 [59]. In conclusion, it is unequivocal that the anticipated action targets of *R. serra* are implicated in the etiology of HCC. As a result, we propose that the *R. serra* constituents may possess potential therapeutic benefits by acting on these critical targets.

Cirrhosis and chronic hepatitis account for over 90% of HCC cases [60]. The findings of the combined enrichment indicate that the therapies for treating HCC associated with *R. serra* components could have anticancer effects through essential pathways such as the PI3K/Akt, MAPK, Wnt,



calcium, and p53 signaling pathways. The balance between cell survival and apoptosis is maintained through the PI3K/PTEN/AKT/mTOR pathway, which also plays a significant part in the emergence of resistance to platinum compounds, taxanes, and fluoropyrimidines [61]. The kinase cascade that results from the activation of PI3K by EGFR, VEGFR, and PDGFR can further provide signals that promote cell growth, survival, and antigenicity through AKT and mTOR [61, 62]. It has been demonstrated that the PI3K-AKT-mTOR signaling route is necessary for the survival and proliferation of luminal breast cancers, making them highly vulnerable to the blockage of pathway elements [63]. This concurs with our findings on adenocarcinoma and breast cancer. The most common survival signals that encourage the growth of hepatocellular carcinoma are NF- $\kappa$ B, Akt, MAPK, and mTOR, and intricate connections between the mTOR and MAPK pathways have been shown in hepatocarcinogenesis [64]. The evolution of liver fibrosis is aided by the PI3K/Akt pathway, which controls HCC activation, cell proliferation, and collagen production. Liver fibrosis can proceed to cirrhosis, which causes organ failure and death [65]. Hepatitis, hepatic steatosis, hepatic fibrosis, as well as infection with the hepatitis B and C viruses are the primary risk factors for the development of HCC [66]. The Wnt pathway is closely linked to an oncogenic phenotype in many malignancies, including liver, breast, and colon. The Wnt ligand receptor FZD7 is implicated in the initiation and progression of HCC, and increased expression of NF- $\kappa$ B-related Wnt-1 may be a key mechanism in hepatocarcinogenesis. Hepatocarcinogenesis is usually linked with aberrant activation of the Wnt-catenin pathway [67]. As a transcription factor, p53 responds to stress signals and controls the expression of its target genes, causing a range of cellular responses to prevent tumor formation. P53 is the most mutated gene in human malignancies [68]. Due to the composition complexity and the target diversity, herbal compounding provides a promising field of research in drug discovery and development when a class of medications ameliorates the pathology of a type of organ.

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### Statement of Conflict

No conflict of interest

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