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Network Pharmacology of *Thalictrum simplex* var. *brevipes*: Linking Chemical Constituents to Hepatitis Treatment Targets

Chiu-Fai Kuok and Pedro Fong*

Faculty of Health Sciences and Sports, Macao Polytechnic University, Macao, 999078, China

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ABSTRACT

Thalictrum simplex var. *brevipes* has been used for the treatment of hepatitis. However, its chemical constituents and their corresponding bioactivities remain uncertain. This study aims to identify chemical constituents of *T. simplex* var. *brevipes* and to develop a network pharmacology model to enhance the understanding of *T. simplex* var. *brevipes* in the treatment of hepatitis. SwissTargetPrediction was employed to identify potential therapeutic targets of the identified compounds. Hepatitis-associated genes were sourced from the GeneCards database, and Venn analysis was conducted to reveal overlaps between these hepatitis genes and the predicted targets. Common targets were then subjected to protein-protein interaction (PPI) analysis using STRING. Key genes were further validated through KEGG pathway analysis. Finally, a compound-target-pathway network was constructed using Cytoscape (version 3.7.2), integrating hepatitis-linked genes with the common targets. The 13 identified compounds shared 423 unique common targets with hepatitis, with each compound having over 70 associated targets. The protein-protein interaction (PPI) network highlighted key hepatitis-related targets, specifically HSP90AA1, SRC, and EGFR. KEGG analysis revealed that 213 pathways were linked to these common targets, including significant pathways related to hepatitis B and C. This study indicated that the potential therapeutic effects of *T. simplex* var. *brevipes* may derive from its diverse compounds, which can influence targets and pathways related to hepatitis treatment.

Keywords: Hepatitis, Kyoto Encyclopaedia of Genes and Genomes, Network Pharmacology, Protein-Protein Interaction, *Thalictrum*

Introduction

Life expectancy has increased significantly as a result of medical improvements. By 2050, two billion individuals will be over the age of sixty.[1] Every five years, a twofold increase in age-related diseases like Alzheimer's, cancer, and heart disease will coincide.[2] This presents issues, with an increasing number of degenerative diseases straining the healthcare system, both socially and economically. As a result, attempts must be made to intervene in the aging process and promote healthy aging for the elderly population to remain productive. Several hypotheses attempt to explain the mechanism of aging. Cellular senescence, telomere shortening, chronic inflammation, increased oxidative stress, stem cell depletion, diminished function, and mortality are all consequences of the aging process.[3] Senescence-associated secretory phenotypes (SASPs) release inflammatory factors, including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), a crucial transcription factor, Tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6).[4] These can cause chronic inflammation and a reduction in immunological function, leaving the body unable to manage inflammatory factors as it ages. Chronic inflammation related to cell aging occurs systemically.[5]

*Corresponding author. Email: pedrofong@mpu.edu.mo
Tel: +853 85993427

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Hepatitis remains a significant global health concern, driving ongoing research into effective treatments and preventive strategies.[1] Among various traditional remedies, *Thalictrum simplex* var. *brevipes* has been used in China for managing hepatitis.[2] However, knowledge about its chemical constituents and potential pharmacological mechanisms is limited. In contrast, another species, *Thalictrum foliolosum*, has demonstrated hepatoprotective activity in animal studies,[3] though further research on this species is scarce. This study aims to identify the chemical constituents of *T. simplex* var. *brevipes* and develop a network pharmacology model to enhance our understanding of its role in hepatitis treatment. Network pharmacology is an integrated approach that combines systems biology and pharmacology to explore how herbal compounds interact with biological systems.[4] This method typically begins with the prediction or identification of potential therapeutic targets for the compounds under study. These targets are then systematically mapped to those associated with specific diseases, allowing researchers to establish connections between herbal remedies and their therapeutic applications.[5] To further elucidate these interactions, protein-protein interaction (PPI) analysis is employed. This analytical technique examines how proteins interact within a biological system, providing crucial information about the networks of interactions that govern cellular functions. By identifying key proteins that engage with the bioactive compounds of a herb, PPI analysis helps to uncover potential therapeutic targets and elucidate mechanisms of action. This comprehensive understanding can lead to more effective treatments by revealing how herbal compounds modulate biological pathways and affect disease processes, ultimately enhancing our ability to harness natural remedies in modern medicine.[6]

In addition, biological pathways are studied to understand metabolism, cell signalling, and disease processes. Analysing KEGG pathways provides information on how specific compounds from herbs affect these metabolic and signalling pathways, contributing to their biological activity and therapeutic effects. Overall, network pharmacology examines the influence of multiple compounds from herbs on various targets and pathways within the body, enhancing our

understanding of the complex mechanisms underlying their therapeutic actions. This study innovatively integrates chemical analysis and network pharmacology to identify the constituents of *Thalictrum simplex* var. *brevipes* and their potential therapeutic effects on hepatitis.

Materials and Methods

This study aims to develop a network pharmacology model to enhance the understanding of *T. simplex* var. *brevipes* in the treatment of hepatitis. The first step involved searching for all known chemical components of this plant across various online databases, including the Indian Medicinal Plants, Phytochemistry and Therapeutics (IMMPPAT) database, Dr. Duke's Phytochemical and Ethnobotanical Database, the Collection of Open Natural Products Database, TCMDatabase@Taiwan. Additionally, academic journal databases such as PubMed, EMBASE, Scopus, Google Scholar, and the China National Knowledge Infrastructure (CNKI) were utilised. Using the keywords "*Thalictrum simplex var. brevipes*" and its Chinese name, four compounds were identified, including oxyacanthine (11), thalcimine (12), abietin (13), and homoplantaginin (14).

Our previous phytochemical study has isolated ten compounds from *T. simplex* var. *brevipes*.[7] These compounds are chrysophanol (1), pulmatin (2), chrysophanein (3), thalictoside I (4), thalictoside II (5), acacetin 7-*O*-*α*-L-rhamnopyranosyl-(1→6)-*β*-D-glucopyranoside (6), 5,7-dihydroxy-4′-methoxyflavone-7-*O*-[6-*O*-(4-*O*-acetyl-*α*-L-rhamnosyl)-*β*-D-glucosyl (7), 5,7-dihydroxy-4′-methoxyflavone-7-*O*-[6-*O*-(4-*O*-acetyl-*α*-L-rhamnosyl)-3-*O*-*β*-D-glucosyl]-6-*O*-acetyl-*β*-D-glucoside (8), hydroxytyrosol (9), and *p*-tyrosol (10).[7] Combining these with four additional compounds: oxyacanthine (11), thalcimine (12), abietin (13), and homoplantaginin (14), identified through database searches, our total sample for network pharmacology analysis consists of 14 compounds (Figure 1).

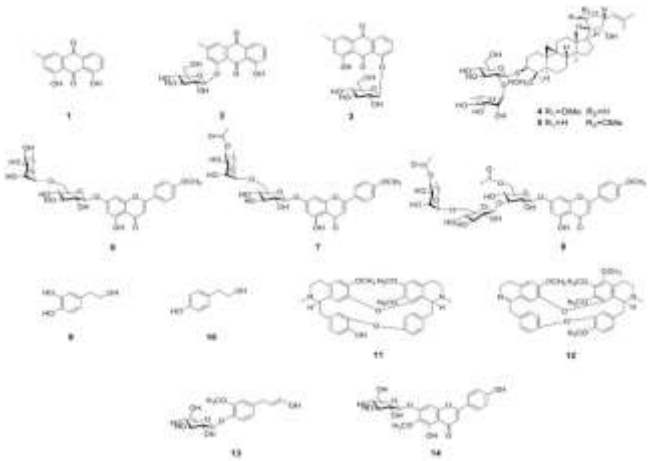

Figure 1: Structures of compounds 1–14.

The chemical structures of the 14 compounds were generated using ACD Lab ChemSketch Freeware (Advanced Chemistry Development, Inc., version 2024.2.3, 2024), which also facilitated the creation of their SMILES formats. These SMILES structures were then employed to identify therapeutic targets through SwissTargetPrediction,[8] focusing on targets specific to Homo sapiens. Subsequently, the UniProt IDs of the predicted targets were entered into the STRING database to analyse their protein-protein interactions (PPI),[9] maintaining the focus on Homo sapiens.

The GeneCards database{Citation} was used to identify genes associated with hepatitis, focusing on those with GeneCards Inferred Functionality Scores (GIFtS) of 55 or higher. GIFtS evaluate the functional relevance of genes to hepatitis, with higher scores indicating greater relevance to the disease. These scores are generated from integrated data sources, including experimental results, computational predictions, and literature-based evidence.[10] Venn analysis was conducted to identify the intersections between the predicted targets of the 14 compounds and those associated with hepatitis. This analysis can help reveal the potential mechanisms of action of *T. simplex* var. *brevipes* in the treatment of hepatitis.

The common targets identified between the herbal compounds and hepatitis were entered into the STRING database for protein-protein interaction (PPI) analysis. The physical subnetwork was chosen as the network type because it includes only interactions that have been experimentally validated or strongly predicted to occur through direct physical contact, allowing for a more focused analysis. The network edges were configured to reflect confidence scores, emphasising the strength and reliability of the predicted interactions. A minimum required interaction score of 0.900 was established, and targets with no interactions were excluded from the analysis. The key genes were further analysed through the Kyoto Encyclopaedia of Genes and Genomes (KEGG) pathways using the STRING online platform to validate the roles of these genes in various metabolic and signalling pathways related to hepatitis.[11]

A compound-target-pathway network was built using the genes linked to the hepatitis pathway identified in the KEGG analysis, as well as the common targets shared by all the compounds and hepatitis. This network was created using Cytoscape (Cytoscape Consortium, version 3.7.2, 2019).[12]

Results and Discussion

SwissTargetPrediction was employed to predict potential targets for all 14 compounds. However, no target could be identified for hydroxytyrosol. This may be due to several factors: hydroxytyrosol might lack sufficient structural similarity to known ligands in the database, it may not have enough experimental data linking it to active compounds for the algorithm to generate a prediction, the predicted interaction probabilities could be too low, or there may be limitations within SwissTargetPrediction that prevent it from covering all potential targets.

The number of targets predicted by SwissTargetPrediction for each of the remaining 13 compounds ranges from 92 to 98. These targets belong to various classes, primarily including proteases, lyases, oxidoreductases, hydrolases, isomerases, kinases, phosphatases, protein-coupled receptors, electrochemical transporters, nuclear receptors, and others. GeneCards identified 15,325 targets associated with hepatitis, with GIFtS ranging from 8 to 68. Among these, 3,659 targets had GIFtS values of 55 or higher, indicating their significant roles in hepatitis pathophysiology. The GIFtS predicts the degree of a gene's functionality, with higher scores indicating more functionally annotated information.[10] The diverse classes of hepatitis targets reflect the complexity of the disease, suggesting multiple biological processes and pathways are involved. Similarly, the predicted targets of the compounds also vary widely, indicating that these herbal compounds may interact with various mechanisms to exert their effects.[13]

There are 621 common targets between the 13 compounds and hepatitis, indicating potential synergistic therapeutic effects. After removing duplicates, 423 unique targets remain, offering a focused list for further investigation.

The Venn analysis revealed that all 13 compounds share over 70 common targets with hepatitis (Figure 2). Among these, the two flavonoid glycosides, compounds **7** and **8**, had the highest number of common targets, with 87 and 86 targets, respectively. Compound **6** followed by 82 common targets. The PPI network of the common targets comprises 422 nodes and 319 edges, with an average node degree of 1.51 and a PPI enrichment p-value of less than $1x10^{-16}$ (Figure 3). This strong enrichment indicates a highly significant level of interaction among the identified proteins. The average node degree of 1.51 indicates that, on average, each protein interacts with approximately one and a half other proteins, which is a notable level of connectivity for a biological network.[14] The high number of nodes and edges suggests a robust network where proteins are not just isolated entities but rather part of a complex web of interactions.[15] These results indicated that the proteins associated with the herbal compounds interact more frequently with one another than would be expected by chance if a similar-sized group of proteins were randomly selected from the genome. This suggests that the proteins linked to the herbal compounds may share biological functions or pathways related to hepatitis.

The targets with the highest node degrees are HSP90AA1 (20), SRC (20), HSP90AB1 (19), EGFR (15), TP53 (13), PTPN11 (12), STAT3 (12), and FYN (10) (Figure 3). These proteins interact with a large number of other proteins, indicating their potential importance as hubs within the network. This connectivity implies that the herbal compounds could exert their therapeutic effects through a network of interconnected proteins, revealing potential mechanisms of action in the treatment of hepatitis.

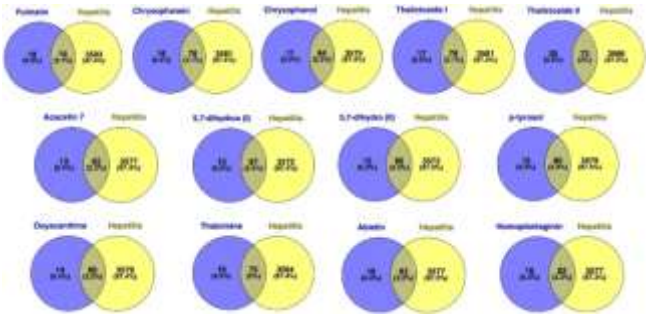

Figure 2: Venn diagram illustrating the predicted targets of 13 compounds from SwissTarget and hepatitis disease targets selected from GeneCards. Acacetin 7, 5,7-dihydrox (I), and 5,7-dihydrox (II) refer to Acacetin 7-O-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside, 5,7-dihydroxy-4′-methoxyflavone-7-O-[6-O-(4-O-acetyl-α-L-rhamnosyl)-β-D-glucosyl], and 5,7-dihydroxy-4′-methoxyflavone-7-O-[6-O-(4-O-acetyl-α-L-rhamnosyl)-3-O-β-D-glucosyl]-6-O-acetyl-β-D-glucoside, respectively.

A total of 213 KEGG pathways were identified as related to the common proteins of the compounds and hepatitis. The observed gene counts ranged from 2 to 95, indicating varying levels of representation, where pathways with fewer genes may suggest specific therapeutic targets, and those with higher counts may have broader implications.[16] The background gene counts varied from 5 to 1435, reflecting the complexity of the biological networks. This diversity helps contextualise the observed gene counts, revealing pathways that may be more significantly impacted by the herbal compounds.[17] The strength values ranged from 0.3 to 1.45, signal values from 0.33 to 4.37, and false discovery rates from 0.0362 to 6.32×10^{-40}. These values indicate strong, high-confidence associations between the proteins and pathways. Among these pathways, one associated with hepatitis B (HSA05161) showed a strength of 1.01, a signal of 3.02, and a false discovery rate of 1.88×10^{-21}. Another pathway related to hepatitis C (HSA05160) had a strength of 0.92, a signal of 2.28, and a false discovery rate of 1.69×10^{-15}. These values indicate that both pathways are significant and exhibit strong biological signals within the PPI network, with low false discovery rates suggesting the reliability of the pathway enrichment results. In addition to these two pathways, other highly significant pathways related to liver inflammatory diseases include the HIF-1 signalling pathway, ErbB signalling pathway, MAPK signalling pathway, Rap1 signalling pathway, and Chemokine signalling pathway. The compound-target-pathway network illustrates the interactions between 43 targets in the hepatitis B and C pathways and the 13 compounds (Figure 4). Thalcimine, chrysophanol, and thalictoside I show a higher number of interactions with these targets, indicating their potential significance. In contrast, thalictoside II and pulmatin exhibit fewer interactions. Among the targets, EGFR (Epidermal Growth Factor Receptor), GSK3B (Glycogen Synthase Kinase 3 Beta), and PRKCA (Protein Kinase C Alpha) have the highest levels of interaction, while IRAK4 (Interleukin-1 Receptor-Associated Kinase 4) and MAPK9 (Mitogen-Activated Protein Kinase 9) show the least. The Venn analysis indicates that compounds **6** (Acacetin 7-*O*-*α*-L-rhamnopyranosyl-(1→6)-*β*-D-glucopyranoside) exhibit the highest number of shared targets related to hepatitis (Figure 3). While the bioactivity of compound **6** is limited in the literature, related compounds such as acacetin, a natural flavone, have shown potential therapeutic effects for liver diseases. A systematic review of 47 publications highlights the impact of acacetin on various liver conditions,[18] including hepatocellular carcinoma, non-alcoholic fatty liver disease, and liver fibrosis. Its therapeutic effects may be attributed to its ability to promote lipolysis and fatty acid β-oxidation, as well as its role in modulating inflammation. Compounds **7** (5,7-dihydroxy-4′-methoxyflavone-7-*O*-[6-*O*-(4-*O*-acetyl-*α*-L-rhamnosyl)-*β*-D-glucosyl]) and **8** (5,7-dihydroxy-4′-methoxyflavone-7-*O*-[6-*O*-(4-*O*-acetyl-*α*-L-rhamnosyl)-3-*O*-*β*-D-glucosyl]-6-*O*-acetyl-*β*-D-glucoside) exhibit a high number of shared targets related to hepatitis (Figure 3). These two compounds are flavonoid glycosides with highly similar chemical structures (Figure 1). Although there is no direct link between these compounds and hepatitis found in the literature, other flavonoids with similar structures have demonstrated anti-inflammatory and antioxidant properties that may be relevant to liver health.[19,20] As such, the specific effects of these particular compounds on hepatitis have not been studied, and we may be the first to propose their potential therapeutic effects in this context. The PPI network reveals that HSP90AA1 has the highest number of interactions with herbal compounds related to hepatitis, followed by SRC and HSP90AB1 (Figure 3). The HSP90AA1 and HSP90AB1 gene encodes heat shock protein 90 alpha and beta, respectively. These proteins are involved in various cellular processes, such as protein folding, stabilisation, and degradation. They may play a significant role in liver disease and hepatitis by influencing liver cells' responses to stress and inflammation. Their expression can be altered in liver diseases, and they may interact with viral proteins in cases of viral hepatitis, potentially affecting viral replication and the immune response.[21]

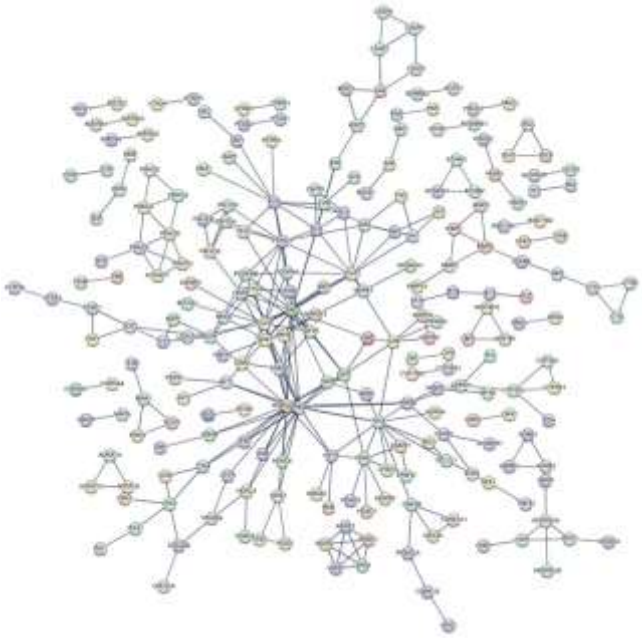

Figure 3: Protein-protein interaction network of common targets shared between the 13 herbal compounds and hepatitis. The thickness of the grey lines represents the confidence of the interactions, with thicker lines indicating stronger support from the data.

SRC encodes a non-receptor tyrosine kinase that plays a crucial role in various cellular processes, including signal transduction, cell growth, and differentiation.[22] Regarding liver disease and hepatitis, SRC may be involved in the regulation of inflammatory responses and the progression of liver injury.[23] SRC can interact with viral proteins in cases of viral hepatitis, which may affect viral replication and the host's immune response. Additionally, aberrant SRC activity has been linked to liver fibrosis and hepatocellular carcinoma, making it a potential target for therapeutic intervention in liver diseases.[23]

This study identified two KEGG pathways through which the 13 compounds may exert effects: HSA05161 and HSA05160. The former

pathway pertains to the "Hepatitis B" pathway, which encompasses various biological processes and interactions related to the Hepatitis B virus (HBV).[24] It illustrates the virus's life cycle, including how HBV enters liver cells and replicates, as well as detailing the host immune response triggered by the infection.[24] Similarly, the HSA05160 pathway relates to the "Hepatitis C" pathway, which includes various biological processes and interactions associated with the Hepatitis C virus (HCV).[25] It details HCV's life cycle, including how the virus enters hepatocytes and replicates within them, while outlining the immune responses triggered by HCV infection, particularly the activation of immune cells.[26] Both pathways are linked to mechanisms that can lead to liver inflammation, fibrosis, and potentially hepatocellular carcinoma.[24,25]

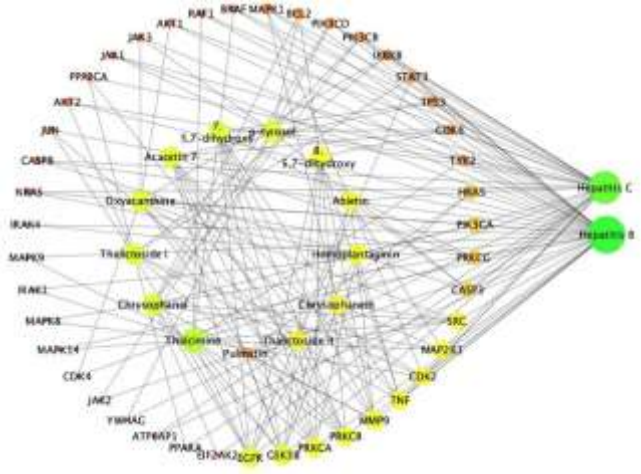

Figure 4: Compound-target-pathway network of the 13 compounds, their predicted targets, and the pathways associated with hepatitis B and C. The inner circles represent the 13 compounds, while the outer circle displays the targets. Larger nodes and a deeper green colour indicate a greater number of interactions, whereas smaller and brown nodes signify fewer interactions. Acacetin 7, 5,7-dihydrox (I), and 5,7-dihydrox (II) refer to Acacetin 7-O-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside, 5,7-dihydroxy-4′-methoxyflavone-7-O-[6-O-(4-O-acetyl-α-L-rhamnosyl)-β-D-glucosyl], and 5,7-dihydroxy-4′-methoxyflavone-7-O-[6-O-(4-O-acetyl-α-L-rhamnosyl)-3-O-β-D-glucosyl]-6-O-acetyl-β-D-glucoside, respectively.

This study reveals that the compounds thalcimine, chrysophanol, and thalictoside I exhibit a significantly higher number of interactions with key hepatitis-related targets, specifically EGFR, GSK3B, and PRKCA. EGFR is known to be involved in various cellular processes, including proliferation and survival, and its dysregulation has been implicated in liver diseases.[27] GSK3B is a pivotal regulator in multiple signalling pathways, including those linked to liver inflammation and cell apoptosis.[28] The GSK3B inhibitor has been found to prevent hepatitis C.[28] PRKCA also plays a significant role in various signal transduction pathways in the liver, influencing processes such as cell growth and differentiation.[29] The interactions with thalcimine, chrysophanol, and thalictoside I may indicate their potential to influence various signalling, possibly affecting liver cell function and the progression of hepatitis. Chrysophanol is a natural anthraquinone with therapeutic potential and various relationships with hepatitis.[30] It exhibits antiviral properties that may inhibit hepatitis virus replication and modulate immune responses.[30] Its anti-inflammatory effects could reduce liver inflammation and protect liver cells from damage.[31] Furthermore, chrysophanol shows hepatoprotective properties and interacts with key signalling pathways involved in liver disease.[30] However, no scientific studies have been found regarding the relationship between thalcimine and thalictoside I and hepatitis. This study may be the first to suggest their potential relationship, supporting further investigation.

Limitations

This study focused exclusively on the pathways that are directly implicated in the onset of hepatitis, omitting those that may be involved indirectly. This is because we aim to provide a clearer understanding of the mechanisms that lead to the disease. Future research could explore the indirect pathways to gain a more comprehensive view of the factors contributing to hepatitis development. We analyse hepatitis B and C together rather than separately to highlight the similarities and shared pathways between them. However, we recognise that future studies could benefit from examining the two diseases individually. This separation may provide more information for each condition. This study primarily relies on SwissTargetPrediction to identify compound targets. However, by incorporating additional databases such as SuperPred and PharmMapper, we could uncover a broader range of potential targets. Similarly, when identifying genes associated with hepatitis, our analysis could be enriched by utilising multiple datasets. For instance, expanding our search to include resources like DisGeNET, in addition to GeneCards, would allow us to capture a wider array of relevant genes.

Conclusion

This study identified potential targets for the 13 compounds from *T. simplex* var. *brevipes*, each associated with 92 to 98 predicted targets. In total, 423 unique common targets were found between these compounds and hepatitis. Venn analysis showed that each compound shared over 70 targets, particularly among the flavonoid glycosides. The protein-protein interaction (PPI) network highlighted the key targets, such as HSP90AA1, SRC, and EGFR, indicating their important roles in mediating the therapeutic effects of the plant in treating hepatitis. Additionally, 213 KEGG pathways were linked to these common targets, including significant pathways related to hepatitis B and C. These findings imply that *T. simplex* var. *brevipes* contains various compounds that may offer new possibilities for hepatitis treatment, supporting further investigation into their mechanisms and therapeutic potential. Understanding these interactions could lead to the development of novel strategies for managing hepatitis and improving patient outcomes.

Conflict of Interest

The author`s declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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