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Network Pharmacology Approach to Evaluate the Therapeutic Effects of *Caesalpinia bonduc* (L.) Components for the Nephroprotective Activity

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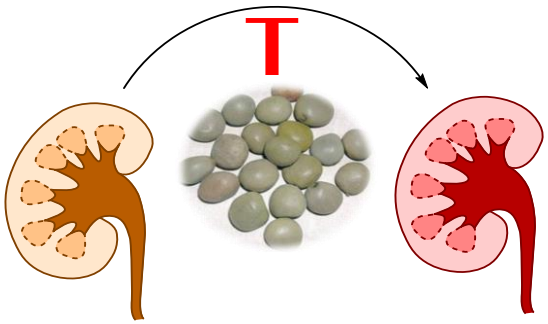
Abstract: *Caesalpinia bonduc* (L.) (Family: Caesalpiniaceae) commonly known as Bonduc Nut and Fever Nut is the main ingredients in Hjam-hbras formulation, a single herb formulation documented in Buddha Shakamuni for treating renal diseases. *C. bonduc* seed extract is also scientifically validated for having renal protective effects but its exact mechanism by which it showed renal protective effect is still unknown. In this study, we aimed to evaluate the nephroprotective mechanism of action of *C. bonduc* seed by performing Network pharmacology analysis. ADMET property analysis reveals 21 out of 190 phytochemicals of *C. bonduc* seeds has passed the good ADMET criteria. Network pharmacology analysis identified 197 mutual common nephroprotective targets for these 21 phytochemicals. The PPI analysis discovered that AKT1, PIK3CA, SRC, PIK3R1, HSP90AA1, MAPK1, PTPN11, FYN, EGFR and STAT3 are the top 10 genes sorted by degree value. GO enrichment analysis showed various processes, functions, and cellular components involved in nephroprotection while the KEGG enrichment analysis showed the associated pathways HIF-1 signaling pathway, Thyroid hormone signaling pathway etc. involved in nephroprotection. This study provides bioinformatic insights via Network pharmacology analysis could pave the way for understanding the effectiveness of *C. bonduc* as nephropotective agent.



Keywords: *Caesalpinia bonduc, Hjam-hbras formulation, nephropotection, network pharmacology, renal*

Introduction

Investigating nephroprotective herbal remedies takes one into a world where the complex web of plant components interacts with the kidneys' sensitive anatomy and physiology, providing a therapeutic opportunity for the avoidance and management of kidney diseases. Herbal medicine studies have recently centered on nephroprotection, a broad concept including many measures to protect the kidneys.[1-3] Currently, Indian medicinal plants have a significant impact on the treatment of numerous disorders in India. The prominent traditional medical systems utilized in India include Ayurveda, Siddha, and Unani.[4,5] The Traditional Knowledge Digital Library (TKDL) is a repository that documents India's traditional knowledge, particularly relating medicinal and ethnobotanical plants, as well as various formulations and preparations used in Indian systems of medicine.[6] We use this library to search plants and formulation having their major role in treating alignment related to kidney.

Hjam-hbras is a therapeutic single/compound formulation whose knowledge for treating diseases of the kidney is well known since 1000 years and is found in Buddha Shakamuni documents which was retrieved from the online search in TKDL.[7] *Caesalpinia bonduc* (L.) (Synonym: *Caesalpinia bonducella*; Family: Caesalpiniaceae) commonly known as Bonduc Nut, Fever Nut and Nicker Nut is the main ingredients in Hjam-hbras formulation. *C. bonduc* is a well-known Indian medicinal plant containing several nonpolar and polar phytoconstituents that are divided in different types of phytochemicals including, flavonoid[8] terpenoids, polysaccharides, and derivatives of phenolic acids however, cassane furanoditerpenes[9,10] and diterpenes of cassane[11,12] and norcassane[11] are the most significant substances. *C. bonduc* seed extract showed renal protective effects against paracetamol intoxication.[13] Apart from this, it is also showed various therapeutic properties like antidiabetic,[14-16] antimicrobial,[17] used for the treatment of hyperthyroidism,[18] Poly Cystic Ovary Syndrome (PCOS)[19,20] and several other complications/disorders. The presence of different phytoconstituents could be the main reasons behind its pharmacological effect mainly the nephrprotective effect. Network pharmacology analysis is a new powerful tool that could help to provide a correlation between plant secondary metabolites and disease/metabolic targets and helps us in understanding mechanism of action behind its traditional use.[21-23] Network pharmacology together with systems modeling has been successfully used to evaluate the nephroprotective mechanism of action of various traditional medicines and formulations.[23-28] Hence the main objective of our study is to decipher the nephroprotective mechanism of *C. Bonduc* seeds through network pharmacology analysis.

Results and Discussion

Analysis of phytochemicals

A total of 190 phytochemicals of *Caesalpinia bonduc* seeds had been obtained from PubMed® and Scopus based research articles. The chemical information of each of these phytochemicals was obtained from the public database like SciFinder® (https://scifinder-n.cas.org) or Pubchem (https://pubchem.ncbi.nlm.nih.gov/).

ADMET prediction

The obtained phytochemicals were then screened for their ADMET profile. A good drug candidate should always have good efficacy as well as appropriate ADMET properties at a therapeutic dosage. Additionally, compounds should not possess blood-brain barrier (BBB) penetration properties in order to avoid any CNS toxicities. Evaluation of the ADMET

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S.N	Name	Molecular Weight	Caco-2	BBB	CYP1A2-inh	CYP1A2-sub	CYP2C19-inh	CYP2C19-sub	CYP2C9-inh	CYP2C9-sub	CYP2D6-sub	CYP3A4-inh	CYP3A4-sub	CL	Carcinogenicity	Genotoxic Carcinogenicity	LogP	nHA	nHD	PAINS	Lipinski
1	Rosenonolactone	316.2	-5.0	0.7	0.0	0.6	0.1	0.9	0.2	0.2	0.3	0.9	0.5	5.7	0.8	0.0	3.0	3.0	0.0	0.0	Accepted
2	Phenanthro[3,2-b]furan-1,2,4aβ(2αH)-triol, 1α,3,4,5,6,8,9,11b-octahydro-4,4,7,11bα-tetramethyl	332.2	-4.7	0.9	0.1	0.6	0.0	0.9	0.0	0.9	0.8	0.0	0.4	12.7	0.0	0.0	2.7	4.0	3.0	0.0	Accepted
3	Caesaldekarin I	334.2	-4.8	0.6	0.1	0.6	0.1	0.8	0.1	0.0	0.1	0.9	0.5	10.5	0.7	0.0	2.2	4.0	3.0	0.0	Accepted
4	δ-Cesalpin, 14-deoxy	350.2	-4.9	0.9	0.0	0.2	0.0	0.7	0.0	0.3	0.4	0.0	0.4	11.8	0.1	0.0	1.9	5.0	4.0	0.0	Accepted
5	Phenanthro[3,2-b]furan-1,2,4aβ,7 (2αH)-tetrol, 1α,3,4,5, 6,6aα ,7,11 ,11 aβ,11b-decahydro-4,4,7β,11bα-tetramethyl	350.2	-4.9	1.0	0.0	0.2	0.0	0.8	0.1	0.5	0.4	0.0	0.5	9.3	0.2	0.0	1.8	5.0	4.0	0.0	Accepted
6	Dehydrodiconiferyl alcohol	358.1	-4.8	0.4	0.1	0.7	0.0	0.8	0.1	0.7	0.8	0.5	0.8	8.8	0.3	1.0	1.8	6.0	3.0	0.0	Accepted
7	β-Caesalpin	364.2	-4.9	1.0	0.0	0.3	0.0	0.8	0.0	0.4	0.2	0.0	0.4	6.8	0.2	0.0	1.4	6.0	4.0	0.0	Accepted
8	Caesall D	374.2	-4.7	0.5	0.1	0.1	0.1	0.7	0.4	0.1	0.2	0.6	0.5	8.7	0.9	0.0	2.8	5.0	2.0	0.0	Accepted
9	Phenanthro[3,2,-b]furan-1,2,4aβ (2αH)-triol, 1α,3,4,5,6,6 aα ,7 ,11, 11aβ,11b-decahydro-4,4,11bα-methyl-7-methylene-, 2-acetate	374.2	-4.7	0.5	0.1	0.1	0.1	0.8	0.4	0.3	0.6	0.1	0.6	10.2	0.6	0.0	2.7	5.0	2.0	0.0	Accepted
10	Norcaesalpinin E	376.2	-4.8	0.6	0.1	0.1	0.1	0.7	0.2	0.1	0.2	0.6	0.5	7.2	0.9	0.0	2.4	6.0	2.0	0.0	Accepted
11	Caesalmin B	388.2	-4.8	0.8	0.0	0.1	0.1	0.8	0.1	0.0	0.2	0.6	0.6	7.8	0.6	0.0	3.0	6.0	1.0	0.0	Accepted
12	Caesalmin E1	392.2	-4.9	0.8	0.0	0.1	0.0	0.7	0.1	0.1	0.1	0.4	0.5	7.2	0.9	0.0	2.5	6.0	3.0	0.0	Accepted
13	Phenanthro[3,2-b]furan-1,2,4aβ,7(2αH)-tetrol, 1α,3,4,5,6,6aα,7,11,11aβ,11b-decahydro-4,4,7β,11bα-tetramethyl-, 2-acetate	392.2	-4.8	0.9	0.0	0.1	0.0	0.9	0.1	0.3	0.4	0.1	0.7	6.7	0.4	0.0	2.3	6.0	3.0	0.0	Accepted
14	Caesalpinin I	402.2	-5.0	0.8	0.1	0.1	0.1	0.7	0.1	0.1	0.2	0.6	0.5	6.2	0.1	0.0	1.8	7.0	1.0	0.0	Accepted
15	Bonducellpin D	404.2	-5.0	0.7	0.1	0.1	0.0	0.6	0.0	0.0	0.2	0.4	0.4	6.2	0.3	0.0	2.1	7.0	2.0	0.0	Accepted
16	(+)-Bonducellpin C	420.2	-4.8	0.8	0.0	0.3	0.1	0.8	0.1	0.0	0.2	0.6	0.6	8.2	0.6	0.0	2.5	7.0	2.0	0.0	Accepted
17	Cassabonducin H	422.2	-4.9	0.8	0.0	0.1	0.0	0.8	0.0	0.1	0.2	0.5	0.6	7.1	0.9	0.0	2.1	7.0	3.0	0.0	Accepted
18	Caesalmin K	436.2	-5.0	0.4	0.0	0.1	0.0	0.7	0.0	0.1	0.2	0.2	0.3	5.1	0.3	0.0	1.9	8.0	3.0	0.0	Accepted
19	7-Acetoxybonducellpin C	462.2	-4.9	0.8	0.0	0.1	0.1	0.8	0.1	0.0	0.1	0.5	0.7	6.3	0.3	0.0	2.8	8.0	1.0	0.0	Accepted
20	Caesaldekarin G	364.2	-4.7	0.6	0.0	0.9	0.2	0.9	0.1	0.0	0.0	0.8	0.8	6.9	1.0	1.0	2.2	5.0	2.0	0.0	Accepted
21	δ-Cesalpin	366.2	-5.1	0.5	0.0	0.1	0.0	0.7	0.0	0.1	0.2	0.0	0.2	5.7	0.9	0.0	1.7	6.0	5.0	0.0	Accepted
			Absorption	Distribution	Metabolism									Excretion	Toxicity		Physicochemical Property			Medicinal Chemistry	

Figure 1: *ADME/Toxicity profile of the shortlisted phytochemicals from C. bonduc seeds.*

profile is, therefore, an important criterion for studying drug-like molecules to minimize their failure during the clinical stages of drug development.

Evaluation of ADMET profile is therefore the important criteria to study drug-like molecules in order to minimize their failure clinical stage of drug development. Based on the selection criteria of ADMETlab 2.0, 21 out of 190 phytochemicals of *C. bonduc* seeds were selected for target identification (**Figure 1**).

Putative protein targets for shortlisted phytochemicals

The human putative protein targets for the eligible phytochemicals were retrieved from Swiss Target Prediction (http://www.swisstargetprediction.ch), Similarity Ensemble Approach (https://sea.bkslab.org/), PharmMapper Server (https://www.lilab-ecust.cn/pharmmapper/) and SuperPred (https://prediction.charite.de/subpages/target_prediction.php) databases. A total of all the symbols/names of proteins were gathered and a total of 336 unique protein targets have been obtained after excluding the duplicate values for the particular phytochemicals was selected (**Figure 2**).

Caesalpinia bonduc seeds target network analysis

Network pharmacology serves as a powerful approach for exploring and identifying drug targets. In this study through network pharmacology analysis, we have identified multiple targets & pathways that are associated with the *C. bonduc* phytochemicals and this will help us to justify their mechanism responsible for nephroprotective effect. There were 197 mutual common targets between *C. bonduc* seeds phytochemicals targets and nephroprotective targets and these targets were considered as the potential therapeutic targets of *C. bonduc* seeds for nephroprotective activity (**Figure 3**). The STRING database (https://string-db.org/) is a used to analyze protein–protein interactions. From Protein−Protein Interaction network, 154 mutual targets (interaction score > 0.9 and except disconnected targets) with 194 nodes and 464 edges were sorted by centrality degree. Intelligent network pharmacology platform unique generate the PPI network for common targets **(Figure 4).**[29] The PPI analysis discovered that AKT1, PIK3CA, SRC, PIK3R1, HSP90AA1, MAPK1, PTPN11, FYN, EGFR and STAT3 as the

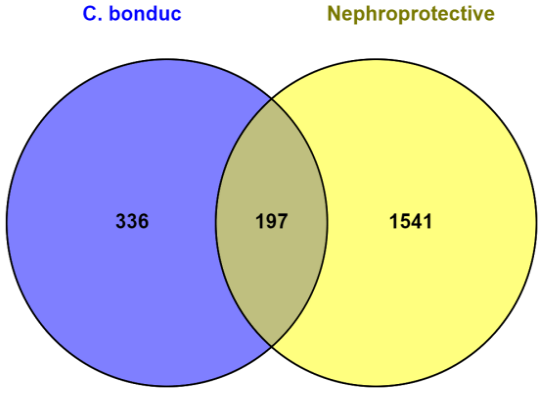

Figure 2: *Intersection of the Caesalpinia bonduc and nephroprotective-related targets. Blue and Yellow circles represent the predicted targets of Caesalpinia bonduc and nephroprotection respectively. The pale brown area reflects the common targets*

top 10 genes based on their degree values. These hub genes derived from the PPI network are illustrated in **Figure 5**. The top targets whose combined score is > 0.999 were selected for DAVID Pathway Analysis, the KEGG pathway and Gene Ontology (GO) enrichment analysis.

Gene Ontology (GO) enrichment analysis

Functional analysis of concerned genes can be possible with the help of GO analysis. It generally describes the role of selected genes in the BP-biological process (**Figure 6A**), CC-cellular component (**Figure 6B**) & MF-molecular function (**Figure 6C**). The top terms involved in the above mentioned three categories of gene ontology process i.e BP, CC & MF are represented in **Figure 6** has been developed by using ShinyGO,[30] an intuitive, graphical web application.

For *Caesalpinia bonduc* seeds, within the biological process ontology, the PPI network targets are primarily associated with process such as the transmembrane receptor protein tyrosine kinase signaling pathway, reg. of response to external stimulus, response to abiotic stimulus, cellular response to oxygen-containing compound, and reg. of phosphorylation among others. In the CC ontology, the targets are primarily located in extrinsic component on the cytoplasmic side of plasma membrane, cell body, and caveola. According to GO annotation for molecular function, the targets are mainly involved in activities such as nitric-oxide synthase regulator activity, 1-phosphatidylinositol-4-phosphate 3-kinase activity, phosphatidylinositol-4,5-bisphosphate 3-kinase activity, phosphatidylinositol-3,4-bisphosphate 5-kinase activity, 1-phosphatidylinositol-3-kinase activity, and insulin receptor substrate binding.

DAVID AND KEGG PATHWAY ANALYSIS

KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway analysis along with other pathway analysis like reactome, wikipathways and Elsevier pathway collection showed that *C. bonduc* seeds have many more important pathways which are responsible for nephroprotective activity. *C. bonduc* seeds were associated with pathways like HIF-1 signaling pathway, Thyroid hormone signaling pathway,

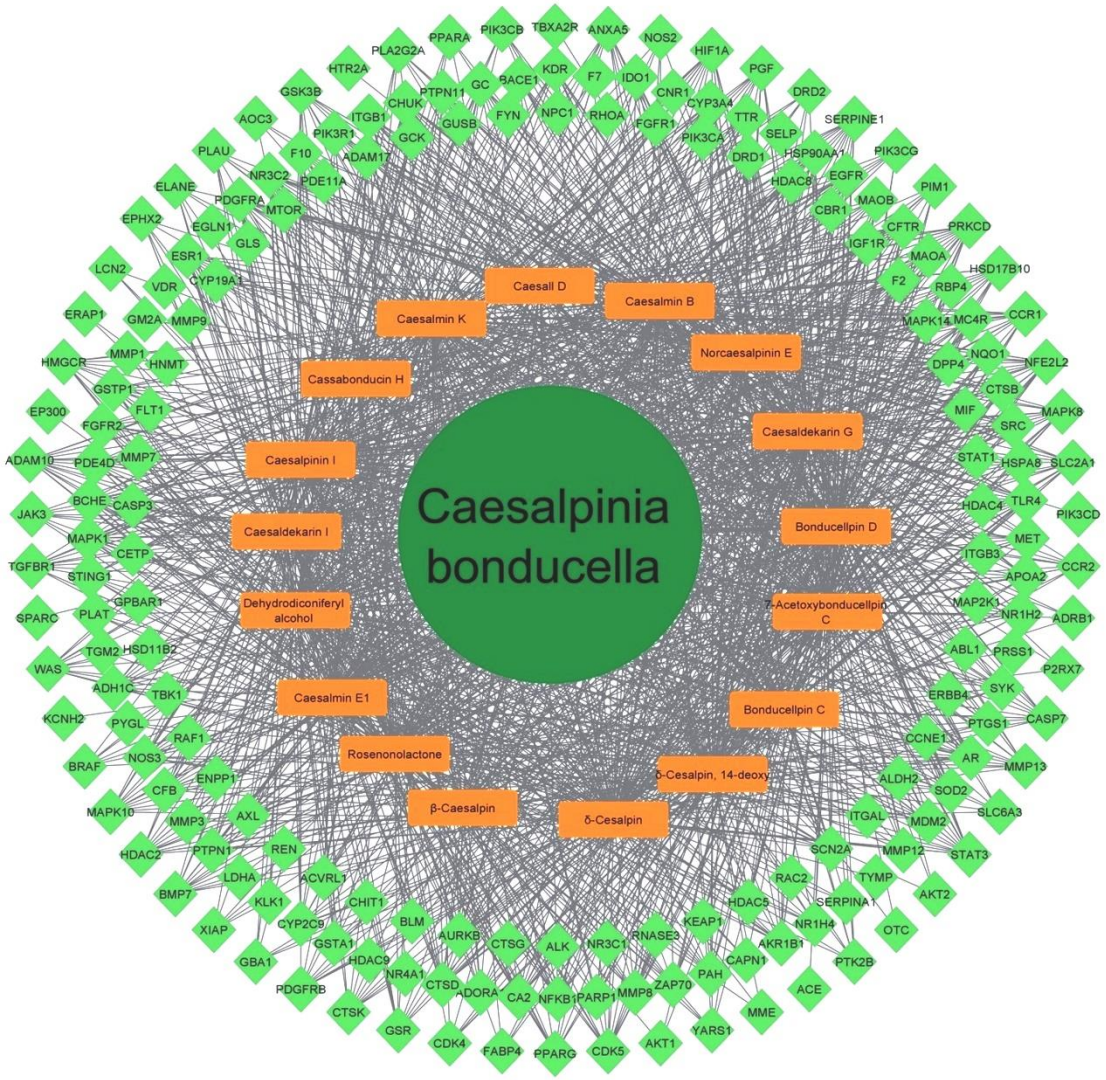

Figure 3: *Compound –Target Network of Caesalpinia bonduc seeds*

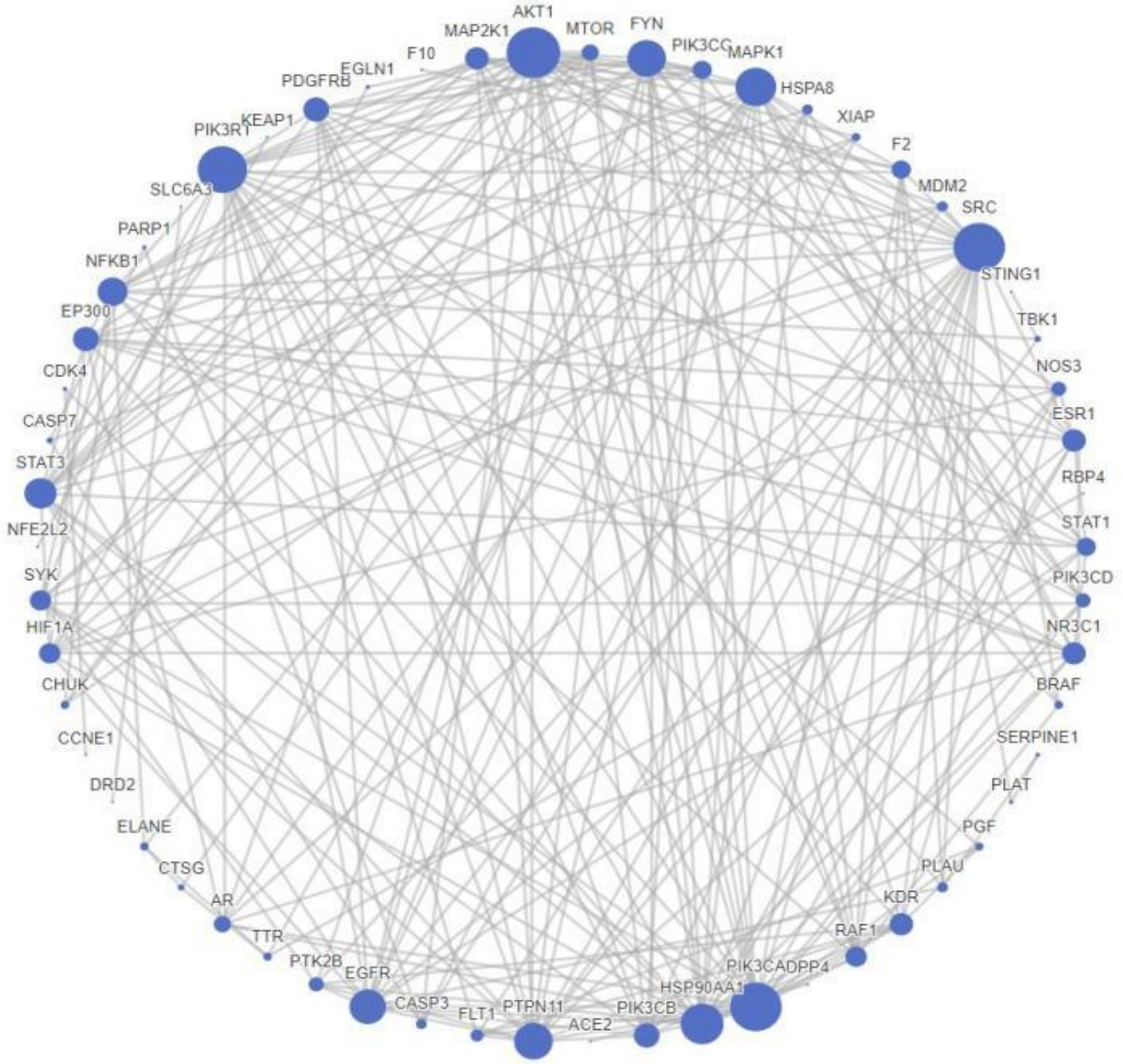

Figure 4: *PPI network for common Caesalpinia bonduc seeds targets*

Phospholipase D signaling pathway, Chemokine signaling pathways, FoxO signaling pathway etc. (**Figure 7,** developed by using ShinyGO, an intuitive, graphical web application).

Discussion

In our study we perform network pharmacological analysis which has been emerged as a reliable tool for identifying interactions and correlations between different pathways, so that to uncover the underlying mechanisms behind the nephroprotective effect of *C. bonduc* seeds. GO analysis helps us to identify pathways pathways. KEGG analysis showed that the PI3K-AKT, JAK-STAT, MAPK and Chemokine signaling pathways were significantly enriched. The PPI analysis discovered that AKT1, PIK3CA, SRC, PIK3R1, HSP90AA1, MAPK1, PTPN11, FYN, EGFR and STAT3 are the top 10 genes sorted by degree value. This study will provide research direction and reference for future clarification of the specific effective ingredients and mechanism of action of *C. bonduc* seeds as nephropotective agent. biologicalprocesses, molecular functions and cellular components of the proteins and genes influenced during nephroprotective activity.

KEGG analysis emphasizes on the pathways which plays important role in nephroprotectiive activity. β-catenin pathway, inflammasome pathway (NF-κB/NLRP3), STAT3 signaling pathways, PI3K/Akt pathway, ROS and SO pathways are some of the important pathways which plays important role in nephroprotectiive activity.[31,32] *C. bonduc* seeds was associated with pathways like renal cell carcinoma, PI3K-AKT signaling pathway, JAK-STAT signaling pathway, MAPK signaling pathway and Chemokine signaling pathways and hence of *C. bonduc* seeds showed it's nephroprotective effect though these pathways. For the aforementioned potential pharmacological effects, clinical trials involving humans could be considered for these plants. In summary, based on our network pharmacology studies, the key bioactive ingredients

of *C. bonduc* seeds showed nephropotective action through various signaling

Materials and Methods

Study design

The phytochemical constituents found in *Caesalpinia bonduc* seeds were retrieved from published literature and databases such as PubChem (https://pubchem.ncbi.nlm.nih.gov/), and SciFinder® (https://scifinder.cas.org/).[33,34] The ADMETlab 2.0 server (https://admetmesh.scbdd.com/), a free online tool used to predict absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties of these phytochemicals found in *C. bonduc* seeds.[35]

GeneCards and DisGeNET.[39,40] All targets were limited to human-specific entries. Subsequently, the targets were input into UniProt (https://www.UniProt.org/) to obtain functional annotations and standardized gene names. Cytoscape 3:2.1., the potential protein targets of phytochemicals were predicted using Swiss Target Prediction (http://www.swisstargetprediction.com/),[36] the Similarity Ensemble Method (https://sea.bkslab.org), SuperPred (https://prediction.charite.de/subpages/target_prediction.php)[3] [7] and PharmMapper Server (http://lilab.ecust.edu.cn/pharmmapper/submit_file.php).[38] Nephroprotection-related genes were chosen from network visualization program that was used to establish relationships between target proteins and phytochemicals, resulting in the construction of a graphical interaction network.[41]

Chemical databases

Molecular weight, molecular formula, chemical structure and SMILES for the phytochemicals of *Caesalpinia bonduc* are recovered from the databases like Pubchem (https://pubchem.ncbi.nlm.nih.gov/), SciFinder® (https://scifinder-n.cas.org) or from the reported literature. [42,43]

ADMET screening

Pharmacokinetic profile of phytochemicals can be identified with the help of ADMETlab 2.0, a free online tool that is used to the ADMET and drug-likeness properties. The *Caesalpinia bonduc* phytochemicals which was obtained from various databases were screened based on the selection criteria of ADMETlab 2.0.[35]

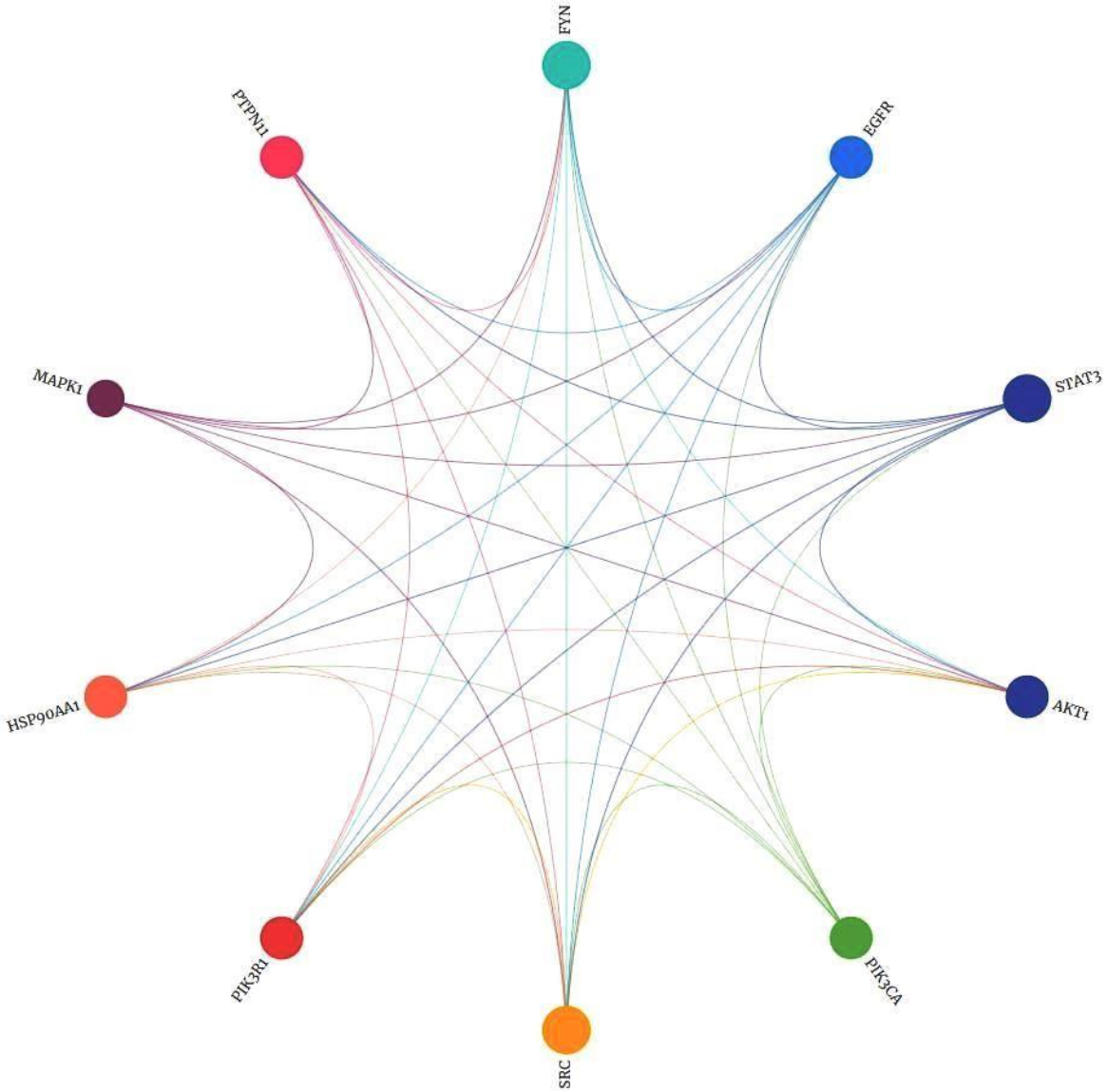

Figure 5: *Top 10 Hub genes obtained from PPI network*

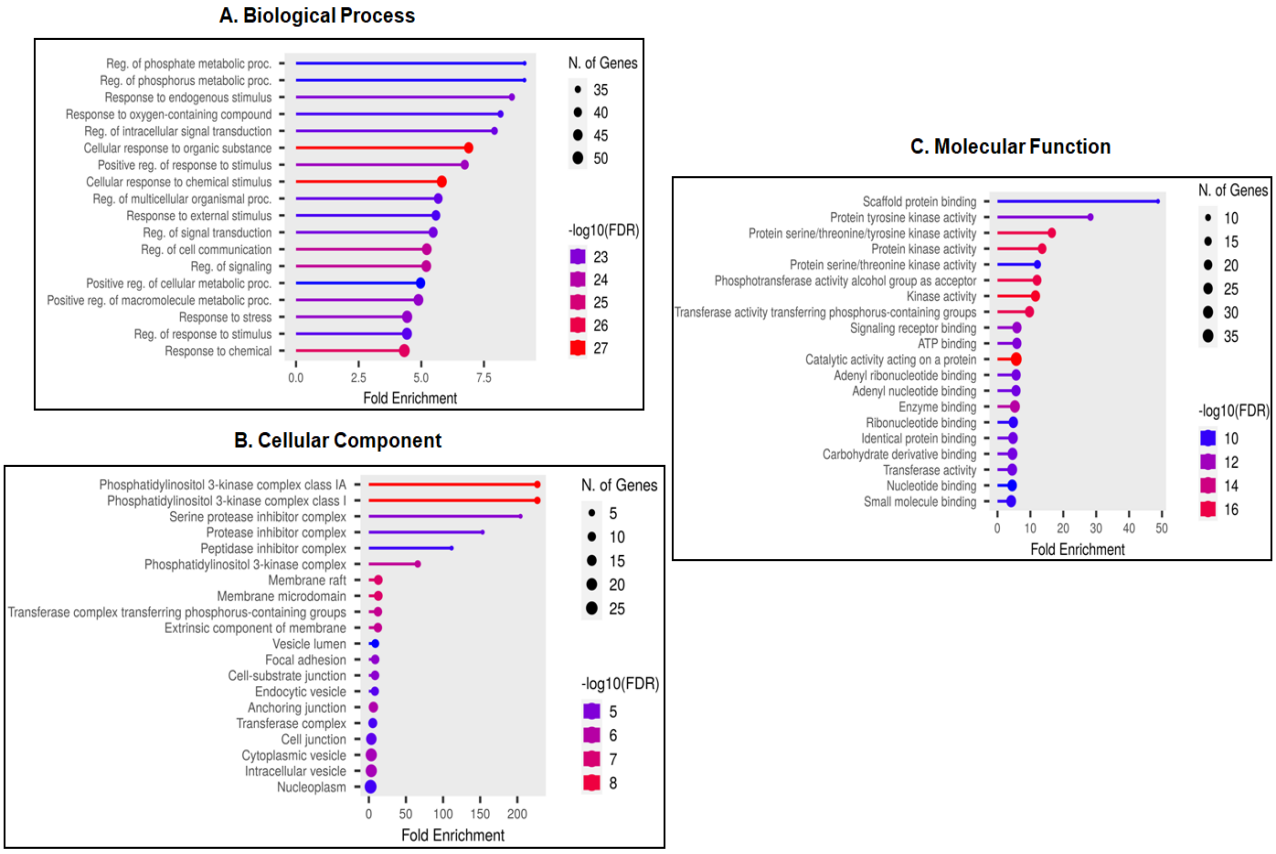

Figure 6: *GO function analysis of Caesalpinia bonduc seeds: BP-biological process (Figure 6A), CC-cellular component (Figure 6B) & MF-molecular function (Figure 6C).*

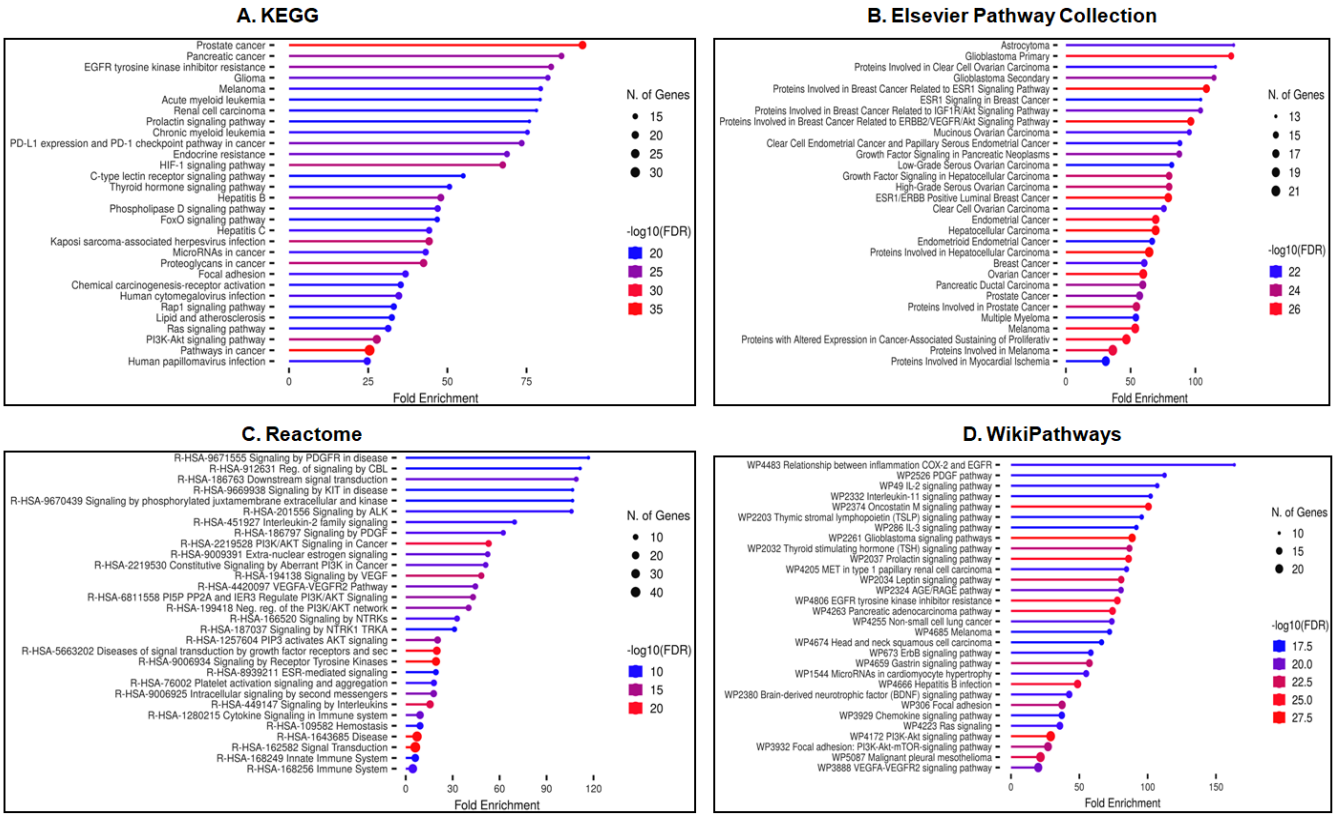

Figure 7: *Pathway enrichment analysis of Caesalpinia bonduc seeds*

Target genes prediction

The interaction between target proteins each compound was obtained from the databases like Swiss Target Prediction, Similarity Ensemble Approach, PharmMapper Server and SuperPred databases.

Identification of targets for nephroprotection

The nephroprotective targets were retrieved from databases like Gene Cards (https://www.genecards.com/), DisGeNET (https://disgenet.com/) & Mala Cards (https://www.malacards.org/).[23] The network between the target genes and active compounds has been created and visualized using the Cytoscape software. In order to shed light on the mechanism of action of specific medicinal plants, network visualizations of "compound target" network maps were created using the visualization program Cytoscape 3.2.[41] The software in particular visually integrates the network with expression profiles and connects the network to databases of functional annotations. This software was also used for network creation, editing, visualization, and analysis. In these networks each nodes represent the compounds while edges represent the interactions between the nodes.[44]

Protein-Protein interaction (PPI) network

The statistical depictions of the physical interactions between proteins within a cell are given by protein-protein interactions (PPIs). Graphs are typically used to model PPI networks, with the proteins acting as the nodes and the interacting proteins acting as the edges. The Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database (https://string-db.org/. version 11.0) was used to build the PPI network.[45] The organisms included in the database were designated as "Homo sapiens". From the PPI network, the target genes with confidence score >0.90 has been selected for further analysis.[28]

The criteria for the STRING analysis included text mining, co-expression, gene fusion, co-occurrence, databases, and interaction sources from experiments.

Gene ontology & DAVID pathway enrichment analysis

The shortlisted network's protein targets (identified by target name or UniProt id) were loaded into the DAVID (Database for annotation, Visualization, and Integrated Discovery) platform to elucidate their mode of operation (https://davidbioinformatics.nih.gov/tools.jsp).[46] DAVID is a freely accessible online bioinformatics resource that provides information on cellular components, biological functions, molecular roles, and biological pathways associated with the given genes.[47] Pathway analysis was performed on the annotated datasets corresponding to each compound's targets. Gene Ontology (GO) was used to examine the biological process and perform enrichment analysis on the gene sets.[48] Additionally, the KEGG database, which includes information on drugs, chemicals, diseases, genomes, and biological pathways, was utilized for further analysis.[49]

Conclusion

Hjam-hbras is a 1000 year old traditional formulation consisting of useful parts of *Caesalpinia bonduc* was found in traditional Buddha Shakamuni documents for treating diseases of the kidney. Network pharmacology analysis proves the effectiveness of *C. bonduc* as nephropotective agent by analyzing its ability of phytochemicals to influence diverse pathways and targets. This study provides bioinformatic insights that could pave the way for a deeper understanding of the mechanisms of action of the nephroprotection.

This comprehensive analysis not only affirms nephropotective efficacy but also lays the groundwork for further exploration into the intricate workings of this 1000 years old traditional knowledge. By elucidating the complex interplay between *C. bonduc* and the biological pathways associated with nephropotection, this study not only validates its therapeutic potential but also offers a roadmap for future research endeavors.

Author Contribution Declaration

The authors have no conflicts of interest regarding this investigation. Hanumant U. Bhusnar conceptualized the idea of the study, data analysis, manuscript writing and reviewing. Sushil Dagadu Patil confirmed the manuscript writing and manuscript writing and reviewing. Soma Das and Laxmikant B. Borse involved in data validation and manuscript reviewing. Attention: The authors have no financial conflicts of interest to disclose.

Funding sources

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Data Availability Declaration

The new data generated and analyzed is included in this article.

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