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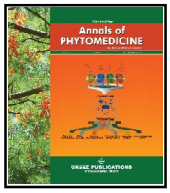

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Network pharmacology-based validation of traditional therapeutic claim of *Boerhavia diffusa* L. in the alleviation of kidney dysfunction

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Abstract

Since history, medicinal plants and their derived products have been playing an immense role in the alleviation of several diseases due to their multi-mechanistic and therapeutic action exhibited by various phytochemicals present in the plants. Based on the facts, the present study is associated to explore the multi-mechanistic and therapeutic action of *Boerhavia diffusa* L. (*B. diffusa*) based on its metabolites. In this study, network pharmacology analysis was performed to determine the interaction of *B. diffusa* metabolites against several genes involved in the pathophysiology of kidney disease and associated complications. Gene ontology analysis was performed to determine several pathophysiological pathways in the alleviation of kidney disease. Furthermore, *in silico* analysis was performed between quercetin and the most prominent genes screened from network pharmacology analysis. The results showed that *B. diffusa* alleviates acute or chronic kidney dysfunction *via* regulation of several pathophysiological pathways such as oxidative stress, inflammatory stress, glomerulonephritis, polycystic kidney syndrome, hypertension, diabetic retinopathy, positive regulation of cell death, *etc*. *In silico* analysis showed that quercetin exhibited prominent interaction with CAT, PPARA and TNF-a genes in form of conventional hydrogen bonding. Hence, it can be concluded that *B. diffusa* exhibitsa multi-mechanistic approach to alleviating kidney dysfunction and can be a promising agent for the management of kidney disease.

1. Introduction

As a principal excretory organ, the kidneys perform an essential role in the excretion of exogenous and endogenous toxins and metabolite, balance of electrolytes and body's fluids, regulate blood pressure, *etc*. It is often subacted to several medications or toxin aggressions, which causes several difficulties against the normal function of the kidney (Gaurav *et al*., 2022; Khan *et al*., 2022). Although, several modern medicines have been used for the alleviation of kidney dysfunction; however, the effective regimen for treatment of the kidney disease and its associated complication are still far perfection (Gautam *et al*., 2021). Medicinal plants and their derived products have been used for treating varieties of diseases due to their multi-mechanistic and therapeutic action exhibited by the numerous phytochemicals present in the plant matrix (Ansari *et al*., 2020). There is exponential growth in the utilization of medicinal plants and their derived products have been seen in the last few decades due to their easy availability, accessibility and economic in nature. Medicinal plants have been acknowledged as anexcellent source for the discovery and development of new drugs and the most effective and therapies for restoring the biologics' normal function against the harmful effect of different acute and chronic illnesses (Mehrotra, 2020). It has also been reported that the synergy effect among phytochemicals is the most effective approach which makes them most valuable source comparable to the modern medicine (Uddin and Veeresh, 2020).

Considering the above acts, quality, efficacy and safety-based scientific validation of medicinal plants and their derived products are critically needed to obviate the misconception about medicinal plants regimen among healthcare professionals. There are various computational, analytical and biological approaches for the scientific validation of medicinal plants (Amrutanand *et al*., 2021; Gaurav *et al*., 2020).

In silico techniques contribute an essential role in drug designing and development for the treatment of various diseases. Based on the strength of the ligation between the drug molecules and the particular targeted gene or protein, *in silico* techniques provide a significant contribution in the assessment of the therapeutic potential of drug molecules. Additionally, network pharmacology research reveals the several therapeutic mechanisms of various medications or active pharmaceutical components involved in the treatment of the disease. Network pharmacology (NP) exploreshow different drugs or phytomolecules interact and operate the expression of various genes (Ali *et al*., 2022). Network-based strategies are exponentially used for the exploration of multi-mechanistic and therapeutic action of phytochemicals and their role in the alleviation of any acute and chronic illness (Leem *et al*., 2022).

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Boerhaviadiffusa L (*B. diffusa*) is a traditional Indian medicinal plant that has been used for several illnesses such as hepatoprotection, immunomodulation, anticancer, antifibrinolytic, antidiabetic, anti-inflammation, nephroprotective activity, *etc*. It contains various phytochemicals such as flavonoid glycosides, rotenoids, flavonoids, xanthones, lignans, purine nucleosides, ecdysteroids and steroids in the root part of the plant (Mishra *et al*., 2014; Oburai *et al*., 2015). Since history, the aqueous extract of plant roots has been used traditionally for medical uses. Several studies of *B. diffusa* have been investigated for nephroprotective effects against drug-induced nephrotoxicity (Oburai *et al*., 2015; Sawardekar and Patel, 2015; Tiwari *et al*., 2016). Still, there is a need to explore the molecular mechanism involved in the pathophysiology of kidney disease. Based on the above facts, the study has been associated with network pharmacology-based exploration of multi-mechanistic and therapeutic action of *B. diffusa*in the alleviation of kidney disease.

2. Materials and Methods

2.1 Screening of *B. diffusa* phytochemical constituents

Several phytochemical constituents of *B. diffusa* reported in the published articles were screened for the study. The selected phytochemical constituents were such as linalool, quercetin, gallic acid, apiole, limonene, ferulic acid, caffeic acid, stigmasterol, hexadecanoic acid, phytol, β-sitosterol, fluvalinate, squalene, menthol, α-pinene, eugenol, vanilin, propionic acid, silanamine and catechin.

Table 1: Selected phytochemicals of *B. diffusa* from the different reported databases

S.No.	Identified Compound	Reference
1.	Linalool	(Ahamad *et al*., 2017; Kaviya *et al*., 2022)
2.	Quercetin	(Ahamad *et al*., 2017; Kaviya *et al*., 2022)
3.	Gallic acid	(Ahamad *et al*., 2017)
4.	Apiole	(Ahamad *et al*., 2017)
5.	Ferulic acid	(Ahamad *et al*., 2017)
6.	Caffeic acid	(Ahamad *et al*., 2017; Kaviya *et al*., 2022)
7.	Limonene	(Kaviya *et al*., 2022)
8.	Hexadecanoic acid	(Pereira *et al*., 2009)
9.	Phytol	(Kaviya *et al*., 2022)
10.	Stigmasterol	(Pereira *et al*., 2009)
11.	β-Sitosterol	(Pereira *et al*., 2009)
12.	Squalene	(Pereira *et al*., 2009)
13.	Fluvalinate	(Pereira *et al*., 2009)
14.	Menthol	(Kaviya *et al*., 2022)
15.	α-Pinene	(Kaviya *et al*., 2022)
16.	Eugenol	(Kaviya *et al*., 2022)
17.	Vanilin	(Kaviya *et al*., 2022)
18.	Propionic acid	(Kaviya *et al*., 2022)
19.	Silanamine	(Pereira *et al*., 2009)
20.	Catechin	(Ahamad *et al*., 2017)

2.2 Network pharmacology analysis

2.2.1 Selection of potential kidney disease targets

Several genes related to kidney disease and associated complications were screened from gene cards (https://www.genecards.org) platform. A total of 200 genes were selected with their unique gene ID. The gene ID for each gene was obtained from the uniport gene directory (https://www.uniprot.org), which is a common platform to access the gene information related to genomics, proteomics and transcriptomics (Casas *et al*., 2019; Zhang *et al*., 2019).

2.2.2 Determination of compound and protein interaction

The compound-gene network's integration analysis was used to look into possible gene expressions that interacted with one another. The selected targets were imported to the STRING database (https://string-db.org), a tool primarily used to determine the enrichment and function of the selected genes. In this study, a compound and protein network was developed to determine the interaction of phytochemicals with the selected genes involved in the pathophysiology of the kidney. The integration analysis was also conducted using cytoscape version 3.8.2. The number of nodes, edges, average node degree and average local cluster coefficient was all calculated to create a protein-protein interacting (PPI) and compound-protein interactions (CPI) network. Every conceivable functional connection between of network of different proteins, proteins and chemicals was included in the study (Li *et al*., 2021; Yi *et al*., 2018).

2.3 *In silico* autodock analysis for determination of the kidney dysfunction activity of *B. diffusa*

2.3.1 Accession of the target protein

RCSB protein data bank contained information about the 3-D structure of the specified protein (http://www.rcsb.org/pdb; ID-TNF, PPARA, and CAT, respectively).

2.3.2 Ligand preparation of *B. diffusa*

The software was used to download the ligands' 3-D SDF file format from pubchem (https://pubchem.ncbi.nlm.nih.gov/compound/47965) and convert them to PDB and PDBQT formats (BIOVIA Discovery Studio Visualizer 2021). Then, using autodock, they were examined for molecular docking by varying torsion, ionization, level of freedom and stereochemical variation (Rahman *et al*., 2019).

2.3.3 Selection of proteins for docking analysis

The structure of identified proteins has been built and optimized using autodock. The protein structure was downloaded for free and for work in PDB format with a resolution of 2.59Å with R-values of 0.263 and 0.208, respectively. Molecular docking was completed using the autodock vina and BIOVIA discovery studio visualizer programs. The command line and precondition were applied to handle the docking before the docking analysis (Eswaramoorthy *et al*., 2021; Islam *et al*., 2013)

3. Results

In this study, different phytochemicals of *B. diffusa* were screened from different reported literature and were proceeded for *in silico* docking analysis for determination of multi-mechanistic and therapeutic action of *B. diffusa* in the alleviation of kidney disease.

3.1 Network pharmacology analysis

Each screened metabolite of *B. diffusa* was explored to determine possible interaction with the targeted genes and the possible mechanism in the treatment of kidney disease. In this study, each gene and metabolite were represented in form of a network. During analysis, edges that were directly associated with the active metabolites were included for final assessment while edges that were not found to exhibit any interaction with the metabolites were removed from the study.

In PPI and CPI analysis, the results showed that the developed network exists 42 nodes and 367 edges while an average number of neighbors was found as 17.476. Target proteinssuch as TNF, CAT, PPARA, NOS3, JUN, IL6, NOS2 and others were shown to exhibit significant interaction with the metabolites of *B. diffusa* and play a significant role in oxidative stress, inflammation, or inflammation. It was discovered that limonen interacted with NOS2. It was found that β-sitosterol significantly interacted with CASP3 while menthol interacted with NOS, PTGS2, PON1, ILs, *etc*. Gallic acid also interacted with TRPM8 and CASP3 while apiole was found to exhibit significant interaction with TP53. Furthermore, linalool was found to interact with TP53, NOS2 and MAPK8 and stigmasterol interacted with EGFR, CAT and NR1H3.The complete network analysis of each metabolite and its respective gene has been represented in Figure 1.

Table 2: List of the genes found to exhibit strong interaction with the phytochemicals of *B. diffusa*

S. No.	Protein Name	UniProt ID	Protein code
1.	Aldo-keto reductase family 1 member B1	P15121	AKR1B1
2.	RAC-alpha serine/threonine-protein kinase	P31749	AKT1
3.	Polyunsaturated fatty acid lipoxygenase ALOX12	P18054	ALOX12
4.	Apoptosis regulator Bcl-2	P10415	BCL2
5.	Caspase-3	P42574	CASP3
6.	Caspase-8	Q14790	CASP8
7.	Catalase	P04040	CAT
8.	Catenin beta-1	P35222	CTNNB1
9.	Interleukin-8	P10145	CXCL8
10.	Epidermal growth factor receptor	P00533	EGFR
11.	Interleukin-1 beta	P01584	IL1B
12.	Interleukin 6	P05231	IL6
13.	Transcription factor AP-1	P05412	JUN
14.	Mitogen-activated protein kinase 1	P28482	MAPK1
15.	Mitogen-activated protein kinase 14	Q16539	MAPK14
16.	Mitogen-activated protein kinase	L7RXH5	MAPK3
17.	Mitogen-activated protein kinase 8	P45983	MAPK8
18.	Stromelysin-1	P08254	MMP3
19.	Nitric oxide synthase, inducible	P35228	NOS2

20.	Nitric oxide synthase, endothelial	P29474	NOS3
21.	Oxysterols receptor LXR-alpha	Q13133	NR1H3
22.	Nuclear receptor subfamily 1 group I member 2	O75469	NR1I2
23.	Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha isoform	P42336	PIK3CA
24.	Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit gamma isoform	P48736	PIK3CG
25.	Serum paraoxonase/arylesterase 1	P27169	PON1
26.	Peroxisome proliferator-activated receptor alpha	Q07869	PPARA
27.	Prostaglandin G/H synthase 1	P23219	PTGS1
28.	Prostaglandin G/H synthase 2	P35354	PTGS2
29.	Squalene monooxygenase	Q14534	SQLE
30.	Proto-oncogene tyrosine-protein kinase Src	P12931	SRC
31.	Tumor necrosis factor	P01375	TNF
32.	Tumor Protein P53	P04637	TP53
33.	Transient receptor potential cation channel subfamily M member 8	Q7Z2W7	TRPM8
34.	UDP-glucuronosyl transferase 2B17	O75795	UGT2B17
35.	Vascular endothelial growth factor A	P15692	VEGFA

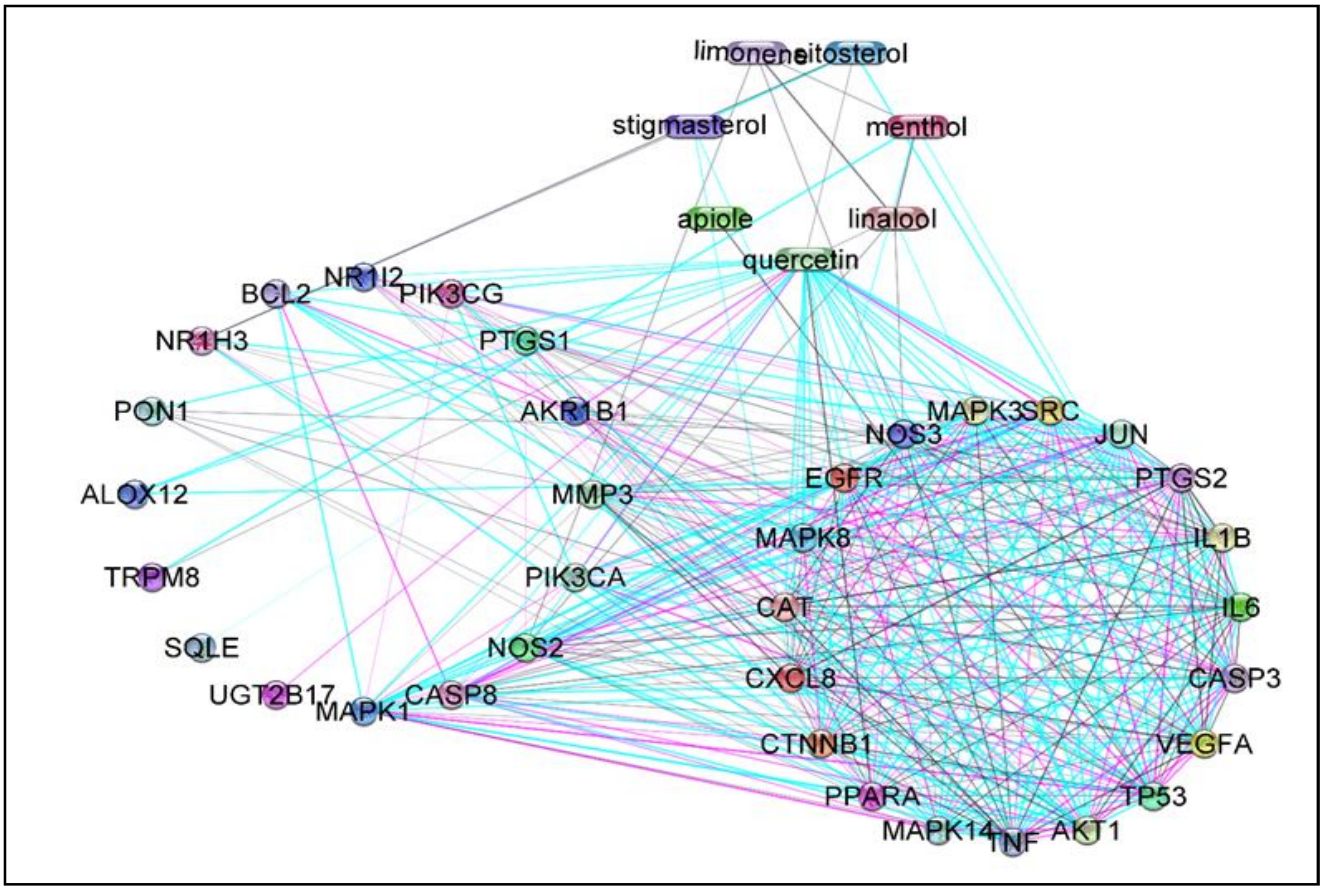

Figure 1: Compound and protein network showing interaction in form of the edges of black color (coexpression edges), light blue color (database edges) and purple color (experimental color).

In gene ontology analysis, the multiple physiological and pathophysiological functions of each gene in kidney dysfunction were evaluated using cytoscape dis gen net software. The outcome of the study suggested that the screened genes which were found to have significant interaction with the metabolites regulate several aspects of kidney dysfunction. It was observed in terms of the gene-disease analysis. Furthermore, the findings demonstrated that each gene plays an immense role in the regulation of vascular permeability, hyperlipidemia, diabetes mellitus, acute renal injury, fibrosis, hypertension, obesity, *etc*. It was also discovered that the metabolites and targets may be efficiently activeto control peroxidation, inflammation and inflammation brought by oxidative stress. The outcomes of the analysis have been summarized in Figure 2.

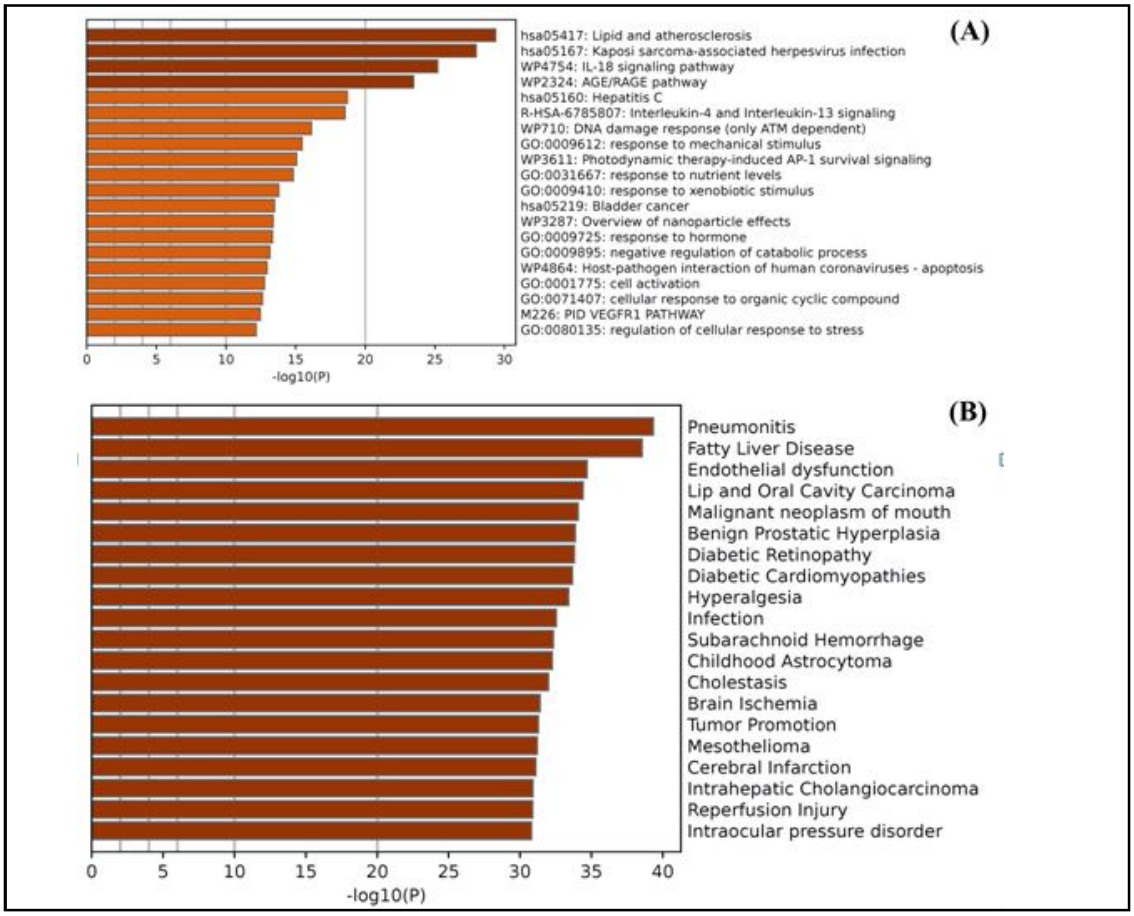

Figure 2: Gene ontology analysis of the potential genes showed interaction with the metabolites of *B. diffusa*.

3.2 *In silico* docking analysis

In silico docking analysis was performed to evaluate the biological interaction of quercetin with catalase (CAT), peroxisome proliferator-activated receptor alpha (PPARA) and tumor necrosis factor alpha (TNF-α). In this analysis, quercetin was selected as the most prominent metabolite which interacts with the several targeted genes involved in the pathophysiology of kidney disease. During analysis for the preparation of the protein, the spacing angstrom central grid box dimensions for each protein such as CAT, PPARA and TNF-α was set to X-center: 23.008, 6.714, – 1.171, Y-Center: 27.196, 3.096, 65.631, Z-Center: 73.653, 1.636, 127.508, respectively. The results of the *in silico* studies revealed that quercetin exhibited strong interaction with each protein with binding energy (affinity kcal/mol) of – 9.3, – 7.2 and – 6.5 kcal/mol, respectively. The grid box dimension and the binding energy of quercetin with each protein have been mentioned in Figure 3.

Furthermore, the interaction of quercetin was defined in form of the conventional hydrogen bond exhibited by each protein. The analysis showed that – OH and C=O groups of the quercetin remained the most prominent function group that produces conventional hydrogen bonds. Quercetin produced conventional hydrogen bond with CAT protein *via* interaction with amino acids such as GLN B:398, HIS D: 63 and ASP D:59 while it showed interaction with PPARA *via* interaction with amino acids such as GLN A: 413, ASP A: 419, HIS A: 416.

Furthermore, it showed a conventional hydrogen bond with TNF-α protein *via* interaction with amino acids such as PHE B:144 and ASP B:140, respectively. It has been noted that the stability of protein-ligand complexes with higher binding affinities than ordinary medicines is greatly influenced by the formation of conventional hydrogen bonds. Another vander Waals bonds include the carbon-hydrogen bond, the unfavorable donor-donor bond, the pi-cation, the pi-donor hydrogen bond, the pi-sulfur bond, and the alkyl and pi-alkyl bonds. Unfavorable bonding has been shown in studies to impact the drug's action and stability.

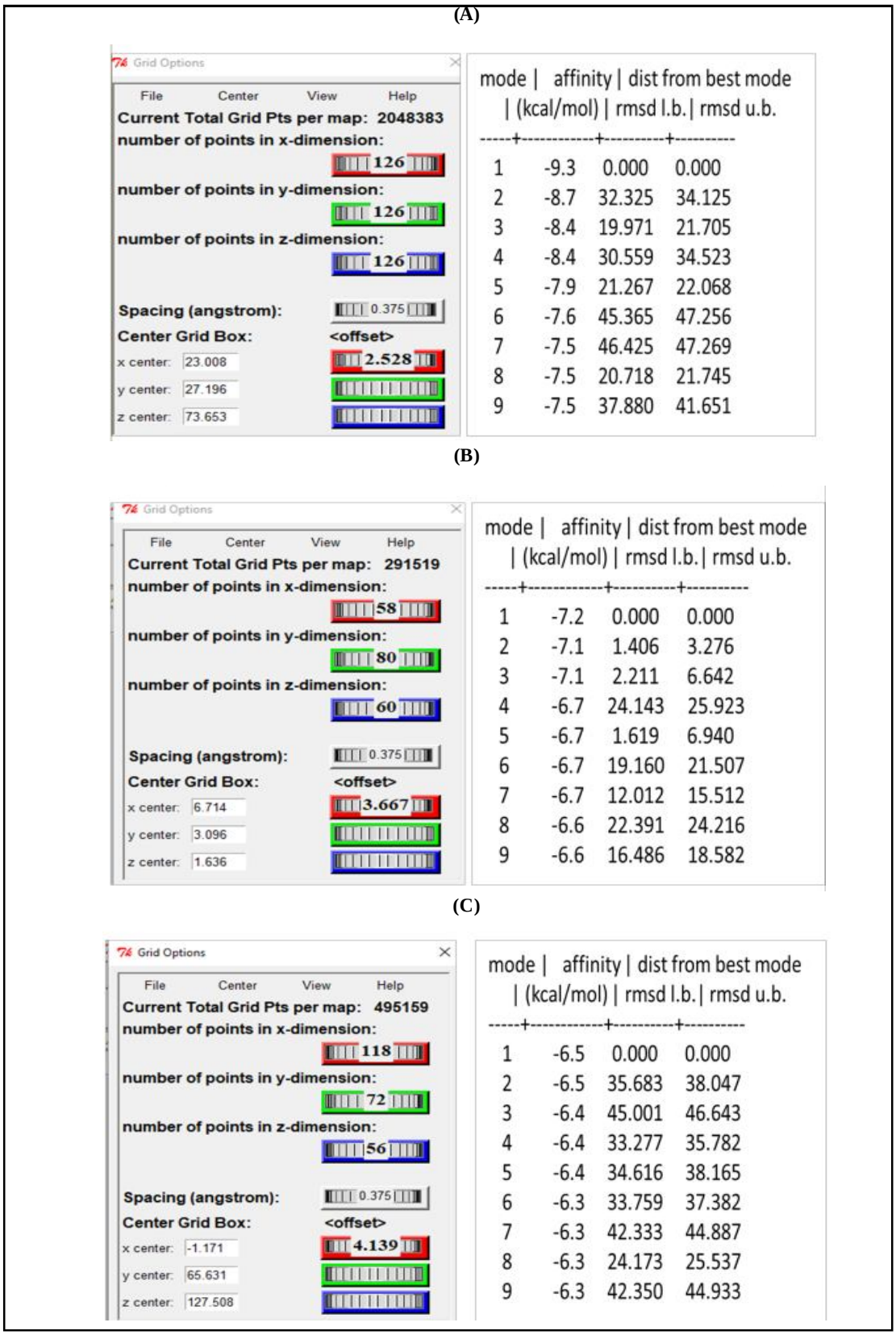

Figure 3: Representation of grid box dimensions (left side) and the binding energy (right side) of quercetin with CAT (A), PPARA (B) and TNF-α (C).

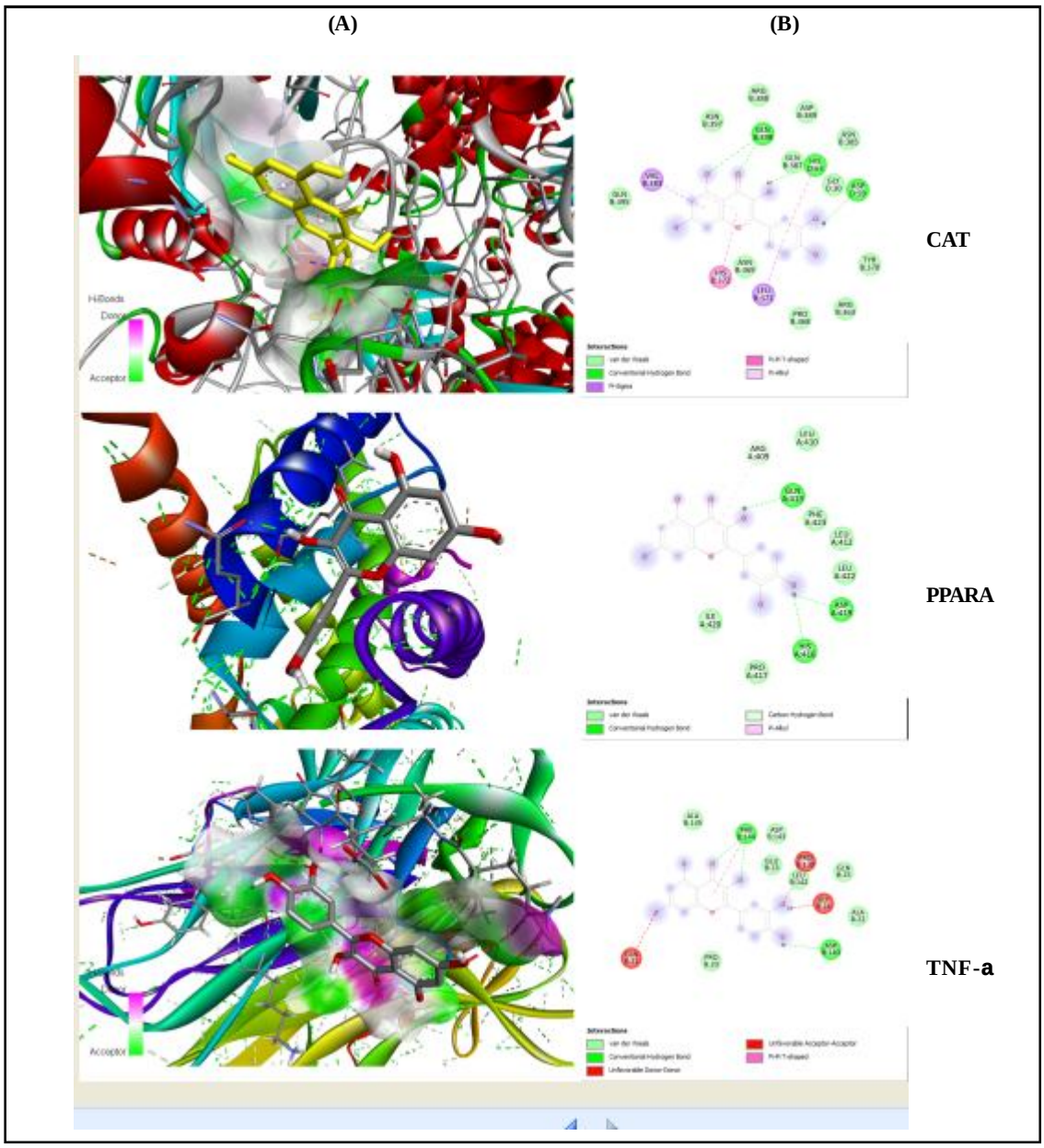

Figure 4: ***In silico*** **analysis of quercetin with CAT, PPARA and TNF-α. Column A represents the 3D structure of protein and ligand while column B represents the 2D figure of ligand and their respective formation of conventional hydrogen bonds in green balls.**

4. Discussion

Naturally derived medicines and their respective analogs have been exponentially used as a therapeutic agents for treating several acute and chronic ailments. Although, their origin has been betters explored as the traditional medicines which are being used for centuries for the management of diseases. In this study, some of the facts of *B. diffusa* have been explored based on the traditional aspects and molecular aspects of *B. diffusa* metabolites for the management of the disease including kidney disease. A network pharmacology study was performed to determine multi-mechanistic and therapeutic aspects of *B. diffusa*, the outcome of the study showed that among 20 screened metabolites of *B. diffusa*, 7 metabolites were found effective against the selected targets. Furthermore, out of 7 metabolites, quercetin was found the most prominent compound that showed significant interaction with the genes such as AKR1B1, AKT1, ALOX12, BCL2, CASP3, CASP8, CAT, CTNNB1, CXCL8, EGFR, IL1B, IL6, JUN, MAPK1, MAPK14, MAPK3, MAPK8, MMP3, NOS2, NOS3, NR1H3, NR1I2, PIK3CA, PIK3CG, PON1, PPARA, TNF, *etc*., which revealed that quercetin exhibited the multi-mechanistic action *via* regulation of several pathophysiological pathways. Gene ontology analysis was performed to determine the role of metabolites in pathophysiological pathways involved in various illnesses including kidney disease. The findings suggested that the metabolites of *B. diffusaal* leviate kidney dysfunction *via* regulation of several pathophysiological pathways such as oxidative stress, inflammatory

stress, glomerulonephritis, polycystic kidney syndrome, hypertension, diabetic retinopathy, positive regulation of cell death, reduction of vascular rigidity by decreasing the risk of lipid accumulation in blood vessels and atherosclerosis, *etc*., in a study conducted by Gaurav and his team have investigated through network pharmacology that quercetin inhibits the signaling pathways involved in inflammation, oxidative injury, glomerulonephritis and apoptosis (Gaurav *et al*., 2022). It reduces cell migration and invasion by suppressing the levels of the proteins MMP-2, p-Akt1, as well as MMP-9, thereby reducing the ability of various human cancer cells to metastasize (Lu *et al*., 2018).

Numerous renal pathologic diseases, such as glomerulosclerosis and nephrotic syndrome, have also been linked to PPARs. According to reports, PPAR ligands including antidiabetic thiazolidinedione PPAR gamma agonists and hypolipidemic PPAR alpha enhancers not only slow the advancement of renal impairment but also provide a variety of therapy options for illnesses linked to prediabetes. The PON polypeptide genes PON2 and PON3 play a significant part in dyslipidemia-induced CKD. With its capacity to interact with PONs targets, quercetin may be a useful treatment for CKD brought on by atherosclerosis (Ruan *et al*., 2008).

In silico analysis of the significantly active metabolite (quercetin) was explored for the biological interaction with the protein such as CAT, PPARA and TNF-α. It has been reported that CAT, PPARA and TNF-α are the most prominent gene which play role in the regulation of oxidative stress, polycystic kidney disease and inflammatory stress-induced kidney disease (Basist *et al*., 2022; Gaurav *et al*., 2022). The activity of quercetin was favored in form of the production of the conventional hydrogen bond. The formation of any kind of unfavorable bond between/in the protein-ligand complex reduces the stability of the complex as these types of bonds indicate a force of repulsion occurring between 2 molecules and an atom (Dhorajiwala *et al*., 2019).

5. Conclusion

The study concludes that *B. diffusa* metabolites and especially quercetin play a multi-mechanistic role in the alleviation of kidney dysfunction induced by oxidative and inflammatory stress *via* the regulation of several pathophysiological pathways. Hence, it can be demonstrated that can be *B. diffusa* a promising agent for the management of several kidney diseases.

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Conflict of interest

The authors declare no conflict of interest relevant to this article.

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