Research Article

www.ijrap.net

(ISSN Online:2229–3566, ISSN Print:2277–4343)

HYDROALCOHOLIC EXTRACT OF *ARTOCARPUS ALTILIS* PROMOTES THE GLUCOSE UPTAKE: AN *IN SILICO* AND *IN VITRO* APPROACH

Archana M. Patil [1], Sarvanan Kaliyaperumal [2], Mrityunjaya B. Patil [3]*, Vrunda J. Kumbhar [4]

[1] Department of Pharmacognosy, Maratha Mandal's College of Pharmacy, Belagavi, Karnataka, India

[2] Faculty of Pharmacy, Bhagwant University, Ajmer, Rajasthan, India

[3] Department of Pharmacognosy, KLE College of Pharmacy, Belagavi, KLE Academy of Higher Education and Research, Belagavi, Karnataka, India

[4] Department of Pharmacology, KLE College of Pharmacy, Belagavi, KLE Academy of Higher Education and Research, Belagavi, Karnataka, India

Received on: 28/01/23 Accepted on: 22/02/23

***Corresponding author**
E-mail: patil9367@gmail.com

DOI: 10.7897/2277-4343.140242

ABSTRACT

Background: In various herbal formulations, *Artocarpus altilis* is used to manage diabetes and is listed as an insulin sensitiser. As a result, the current research attempted to identify the likely lead hits to promote glucose uptake using a computational approach, followed by an experimental assessment of a hydroalcoholic extract of the *Artocarpus altilis* Plant in yeast cells. Methods: The baker yeast was used for the *in vitro* assay for glucose uptake, while the *in silico* study involved retrieving phytoconstituents from public sources, predicting for likely targets of diabetes, and then predicting for likely side effects and ADMET profile. In addition, PyRx 0.8's Autodock Vina predicted each ligand's affinity for binding to the glucose transporter. 13 phytoconstituents from *Artocarpus altilis* were found to have antidiabetic properties. At 500 g/mL, the extract demonstrated the highest glucose uptake in yeast cells. Network pharmacology identified 2, 4, 5', 7'-tetrahydroxyflavanone and 2, 4, 5', 7'-tetrahydroxyflavane phytoconstituents from *Artocarpus altilis* as specific targets that were modulated in the MAPK signalling pathway, PI3-Akt signalling pathway, and insulin signalling pathway. These targets included INSR, AKT1, PTPN, and IGFR1. Conclusion: Here, the *in vitro* and *in silico* methods used in the present study illustrated the potential role of phytoconstituents from *Artocarpus altilis* in promoting glucose uptake.

Keywords: *Artocarpus altilis*, network pharmacology, and molecular docking.

INTRODUCTION

Ayurveda and Unani medicine is mentioned in our earliest works, and there is a wealth of information about the benefits of herbal medicines. The Charaka Samhita (1000 B.C.), one of the earliest works on Indian medicine, describes using more than 2000 plants. [1] *Artocarpus altilis*, a plant from the Moraceae family, is one of the most adaptable medicinal plants. It is frequently referred to as breadfruit because it resembles freshly baked bread. The tropical breadfruit tree bears fruit twice yearly, from July through September and March through June. The majority of Artocarpus species contain phenolic chemicals, including flavonoids, the lectin jacalin, and stilbenoids. [2]

It is widely distributed throughout North and South America, Central and South America, Africa, particularly in Senegal, Ghana, and Liberia, India, primarily in the coastal regions of Karnataka and Kerala, Southeast Asia, Malaysia, Madagascar, the Maldives, Seychelles, Indonesia, Sri Lanka, Northern Australia, and South Florida, and it is a member of the Kingdom Plantae. Subkingdom: Mracheobionata, Class: Magnoliopsida, Subclass: Hamamelididae, Order: Rosales, Family: Moraceae, Division: Magnoliophyta *altilis* is a species of Artocarpus. [3]

The phytoconstituents from *Artocarpus altilis* are used in Artocarpus extracts and metabolites from leaves, stem, fruit, and bark for various biological activities, including antibacterial, antitubercular, antidiabetic, antiviral, antifungal, antiplatelet, antiarthritic, and tyrosinase inhibitory. [4] Diabetes mellitus (DM) is one of the most common chronic diseases in the 21st century in terms of a variety of lifestyle factors. Type I diabetes, or insulin dependence, is the most prevalent form of the illness, followed by type II diabetes, or non-dependent insulin, which is brought on by the death of the pancreatic beta cells that produce insulin. It may also be brought on by related obesity or other external factors. [5] The most recent information on diabetes worldwide is provided by the International Diabetes Federation (IDF). According to the most recent IDF and WHO reports, 422 million adults worldwide will have diabetes in 2022. Type 1 diabetes affects 1.1 million people overall, including kids and teenagers. According to the IDF, 643 million adults will have diabetes by 2030. [6]

Additionally, glucose transporters (GLUT) play a vital role in glucose uptake across the plasma membrane. GLUT, as such, because of its high Km (~ 17 mM) for glucose, appears well suited for the glucose uptake by β-cells of the liver in proportion to its concentration in the blood. [7] As a result, the hydroalcoholic extract made from *Artocarpus altilis* has been evaluated for its ability to increase glucose uptake by yeast cells. Additionally, this study presents a technique for building a network of disease targets called pathway enrichment analysis. To forecast the potential binding mode of phyto compounds, a network of interactions between phytoconstituents, targets, pathways, molecular docking, and pharmacokinetic studies was created.

MATERIALS AND METHODS

Preparation of Extract

The *Artocarpus altilis* plant was gathered in Goa, India's Chorla region of the Western Ghats. The Raja Lakhamagouda Science Institute's Department of Botany performs plant authentication (College Road, Belgaum). Before being used, the samples were gathered, cleaned, drained, cut, dried, mixed, and sieved. A crude extract was made by combining 750 grams of powder with 70:30 ethanol and water, letting the mixture sit for 7 days, and stirring frequently. After filtering, the extract was added to a Soxhlet apparatus using the same solvent system and allowed to sit for three days while continually boiling. [8]

Phytoconstituents and their targets

Phytoconstituents for the *Artocarpus altilis* are obtained by text mining via a literature survey as they are missing in many phytoconstituents databases. Terms like *Artocarpus altilis* and bio-actives were used interchangeably to mine the phytoconstituents. Additionally, the targets for the construction of the network were retrieved from the Binding DB database (https://www.bindingdb.org/), which were then mapped with the aid of the STRING database (https://string-db.org/) to isolate the targets for Homo sapiens, a personal data set, which was composed of chemical identifiers like canonical SMILES, molecular formula, molecular weight, etc. were obtained from PubChem database (https://pubchem.ncbi.nlm.nih.gov/). [9]

ADMET profile, Druglikeness score, predicted toxicity profile

An ADMET profile of the compounds present all with the positive drug-likeness score was obtained from the admetSAR online tool (https://ngdc.cncb.ac.cn/databasecommons/database/id/3308), and the drug-likeness score of the phytoconstituents were retrieved from Molsoft software (https://www.molsoft.com/ the toxicity profile of the same phytoconstituents were also taken from the online tool referred to as passway2drug (http://www.way2drug.com/).

Disease targets the construction of a network

Disease targets for constructing the network were retrieved from the Gene Cards database (https://www.genecards.org/) and were submitted in Venny for isolating the common targets to that of phytoconstituents. Further, this list of common targets was submitted to the STRING online software where it presents the protein-protein interaction network, and pathways related to genes were also downloaded from the same in the form KEGG pathway (https://www.genome.jp/kegg/pathway.html). Further, considering the pathway, compound and targets, a Compound-Target-Pathway network was constructed in Cytoscape 3.7.2. [10]

Pathway enrichment

The directly linked pathway shown in the pathophysiology of Type 2 DM was chosen to construct the network looking into the modulations carried by phytoconstituent targets. Pathway enrichment analysis was carried out with KEGG pathway enrichment analysis. [11]

Hub genes identification

With the CytoHubba plugin of the Cytoscape software, the hub genes were identified with all the processes, and MCC was selected to represent the related results as it is suggested to be one of the best plugins for the selection of hub genes. [12]

Molecular Docking Analysis

To understand the binding mechanisms of active constituents of *Artocarpus altilis*, molecular modelling studies were accomplished for Artocarpin, 2,4,5,7-tetrahydroxy-6-(3-methyl-2-butenyl)flavone, Thiamin, 2,4,5,7-tetrahydroxyflavanone, Sitosterol, Ascorbic-acid, 2,4,5,7-tetrahydroxy-6-[3-methyl-1(E)-butenyl]flavone, Beta-carotene, Pantothenic-acid, 2,4,5,7-tetrahydroxyflavone, Niacin, Cycloartenyl acetate and Alpha-amyrin with target protein by AutoDock Vina by PyRx 0.8. Proteins were selected based on the Interaction network between the phytoconstituents-targets-pathways such as *IKBKB* and *KDR.* These are the two top modulated proteins seen in the top involved pathway, such as the PI3k-Akt signalling pathway, and to perform the docking study, we have selected the proteins that were highly involved in the relevant and key pathways in the pathogenesis of type-II diabetes mellitus. [13]

Preparation of ligand

The 3D structures of all ligand molecules were retrieved from the PubChem chemical database (https://pubchem.ncbi.nlm.nih.gov/) in structural data format is converted to PDB format by using Discovery Studio Visualizer (DSV) 2021.PubChem is a universal database that stores chemical structural information, including biological activities. Furthermore, we minimised the ligand's free energy using the MMFF94 force field. [14]

Preparation of target protein

We got the 3D x-ray crystallographic structures of the PI3-Akt signalling pathway protein (PDB ID: 4FHJ). These macromolecules were retrieved from PDB (https://www.rcsb.org/), a website in pdb format. The retrieved protein is associated with water molecules and hetero atoms. All hetero atoms, water molecules and native ligands were removed using Discovery Studio 2021 to avoid docking interference and saved in the PDB format. [15]

Determination of active pocket sites

The amino acids in a protein's active pocket site were determined using the Biovia Discovery Studio 2021, and the determination of the amino acids in the active pocket site was used to analyse docking evaluation results.

Ligand-protein docking study

For molecular docking interaction, we used AutoDock Vina by PyRx 0.8. The target protein and ligand PDB files were loaded into PyRx software, and AutoDock Vina preferences were obtained for both ligand and protein in PDBQT format. The grid box was generated to the active site, and the exhaustiveness was set to 100. After completion of the docking algorithm, the ligand-protein complexes with the best conformation and lowest binding affinity were selected and visualised in DSV 2021 for their hydrophobic interactions. [16]

Determination of glucose uptake capacity in yeast cells

For this test, yeast cells were suspended in millipore water (1% suspension), per the Cirillo method [17]. This suspension was kept in the dark and at room temperature (25 °C) for the entire night. The following day, a suspension of yeast cells was centrifuged at 4200 rpm for 5 minutes. Ten parts of the clear supernatant were

mixed with 90 parts of distilled water to produce a viable suspension of yeast cells. A series of concentrations were added to the mixture after the test agent had been dissolved in millipore water for about 25 mg. Finally, 1 mL of a 5 mM glucose solution was added. After that, the mixture was incubated at 37 °C for 10 minutes. The reaction was initiated by adding 100 L of yeast suspension and 1 mL of DNS reagent to the mixture of glucose and *Artocarpus altilis* extract after 60 minutes at 37 °C. Test tubes were incubated, cooled to room temperature and centrifuged (5 min, 3500 rpm). Using a spectrophotometer set at 520 nm, the glucose concentration in the supernatant solution was calculated. Glibenclamide was a commonly prescribed medication. On the same wavelength, absorbance for the control was also recorded. The formula used to calculate the percentage increase in glucose uptake by yeast cells was calculated as

$$\text{\% increase in glucose uptake} = \frac{\text{absorbance of control} - \text{absorbance of sample}}{\text{absorbance of control}}$$

RESULTS

Drug-likeness and ADMET profile of bioactive phytoconstituents

As a result of text mining, as described in the method, about 13 phytoconstituents from the chosen plant were discovered. The PubChem DB was used to screen these phytoconstituents for their chemical ID and other chemical identifiers. They were subsequently tested for drug-likeness; the results are shown in Table 1. The screened phytoconstituents were also investigated for their ADMET profiles and predicted for their various Absorption, Distribution, Metabolism, and Excretion properties in addition to the various toxicity shown in Table 2 in the form of a heatmap.

Molecular docking analysis

To understand the putative binding mode and interaction with amino acid residues at the binding site, docking studies were carried out, and binding affinity is represented in Table 3. Standard drug pioglitazone showed a binding affinity of -8.3 Kcal/mol; it formed a hydrogen bond with ARG 288, GLY 284, LEU 230, ARG 288, CYS 285, ILE 341, as seen in Figure 1 (a,b). Interestingly 2,4,5,7-tetrahydroxyflavone mimics the binding affinity at -9.5 Kcal/mol, interacting with ARG 280, ARG 288, LEU 330, ILE 341, and CYS 285; this compound was highly interactive with the target nodes as seen in the network. Compound 2,4,5,7-tetrahydroxy-6-(3-methyl-2-butenyl) flavone showed hydrogen bond interaction with ILE 262 and ILE 341 pi-stacking interactions with CYS 285 as shown in Figure 2 (a, b).

Protein-Protein interaction network

With the targets retrieved at high confidence commonly from the Phytoconstituents and disease targets, we got the list of 102 targets presented in Figure 3. A list of the top 10 pathways involved in the disease Type-II Diabetes Mellitus from various methods like key pathway search and KEGG pathway database, KEGG mapper the list of these pathways is given in **T**able 4 and Identified Top 10 hub genes from the list of the target is represented in Figure 4 where MCC algorithm for obtaining these genes was applied.

Interaction network between the Phytoconstituents-Targets-Pathways

The interaction network constructed had 125 nodes, where 13 nodes are phytoconstituents, 10 are pathways and the remaining count of 102 stands for the target. Phytoconstituents 2,4,5',7'-tetrahydroxyflavanone were found to be highly involved in various pathways, among which 10 targets were seen involved in modulating the PI3-Akt signalling pathway with *KDR, INSR, PGF, AKT1, BCL2, NOS3, IL6, IGF1R, FLT1*, and *FGFR1.* Secondly, the highly modulated pathway was the MAPK-signaling pathway with 8 involved targets, the Insulin-signaling pathway with 4 targets involved, the network representation of protein targets, and the pathways mentioned in Figure 5.

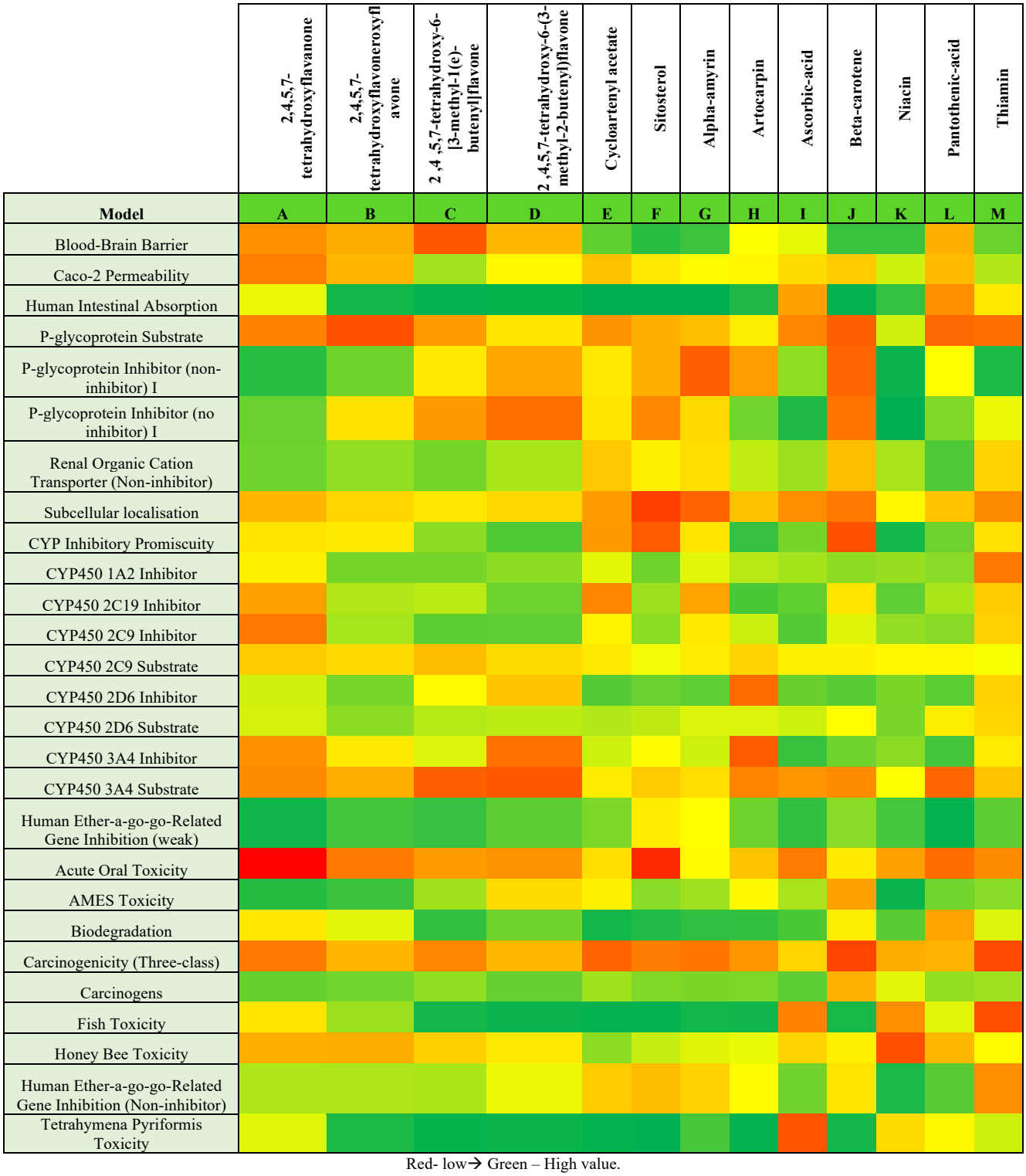
Glucose Uptake assay in yeast cells

One key finding in controlling blood glucose levels is maintaining plasma glucose concentration in humans. The yeast cell's ability to absorb glucose is determined by how glucose is transported across the cell membrane with an exogenous molecule. *Artocarpus altilis* leaves aqueous extract aids in glucose uptake at a concentration above 400 µg/ml, as shown in Figure 6.

Table 1: Drug-likeness properties of selected drugs and ligands

Phytoconstituents	Molecular formula	MW	Number of HBA	Number of HBD	MolLogP	MolLogS Log(moles/L)	mg/L	DLS
Artocarpin	$C_{15}H_{12}O_6$	436.19	6	3	6.97	-5.67	0.94	1
2 ,4,5,7-tetrahydroxy-6-(3-methyl-2-butenyl)flavone	$C_{15}H_{10}O_6$	354.11	6	4	5.04	-4.62	8.47	0.87
Thiamin	$C_{20}H_{18}O_6$	265.11	4	3	0.29	-1.22	16005.16	0.87
2,4,5,7-tetrahydroxyflavanone	$C_{20}H_{18}O_6$	288.06	6	4	2.25	-2.87	393.00	0.8
Sitosterol	$C_{32}H_{52}O_2$	414.39	1	1	8.45	-6.34	0.19	0.78
Ascorbic-acid	$C_{29}H_{50}O$	176.03	6	4	-1.59	-0.05	157906.58	0.74
2 ,4 ,5,7-tetrahydroxy-6-[3-methyl-1(E)-butenyl]flavone	$C_{30}H_{50}O$	354.11	6	4	4.89	-4.50	11.21	0.66
Beta-carotene	$C_{26}H_{28}O_6$	536.44	0	0	13.93	-6.08	0.45	0.64
Pantothenic-acid	$C_6H_8O_6$	219.11	5	4	-1.75	-0.85	30762.00	0.62
2,4,5,7-tetrahydroxyflavone	$C_{40}H_{56}$	286.05	6	4	3.03	-3.21	175.14	0.33
Niacin	$C_6H_5NO_2$	123.03	3	1	0.51	-0.46	42288.00	0.3
Cycloartenyl acetate	$C_9H_{17}NO_5$	468.4	2	0	9.07	-5.99	0.48	0.17
Alpha-amyrin	$C_{12}H_{17}N_4OS$	426.39	1	1	7.77	-6.03	0.39	0.1

Table 2: heatmap representation of ADMET profile of bioactive phytoconstituents



Red- low→ Green – High value.

Table 3: Binding affinity of Phytoconstituents of *Artocarpus altilis*

Compounds	Docking scores in Kcal/mol
	PDB ID: 5U5L
2 ,4,5,7-tetrahydroxy-6-(3-methyl-2-butenyl)flavone	-8.3
2 ,4 ,5,7-tetrahydroxy-6-[3-methyl-1(E)-butenyl]flavone	-8.2
cycloartenyl acetate	-7.8
ALPHA-AMYRIN	-9
ARTOCARPIN	-7.7
ASCORBIC-ACID	-5.6
BETA-CAROTENE	-8

NIACIN	-5.1
PANTOTHENIC-ACID	-5.1
sitosterol	-8.3
Pioglitazone	-8.3
2,4,5,7-tetrahydroxyflavone	-9.5
THIAMIN	-6.2

Table 4: Highly enriched molecular pathways

#term ID	Term Description	Observed gene count	Background gene count	False discovery rate	Matching proteins in your network (labels)
hsa04210	Apoptosis	5	132	0.0024	KRAS,BCL2,TNF,IKBKB,AKT1
hsa04020	Calcium signalling pathway	5	193	0.0096	NOS3,PRKCB,ADRB2,NOS2,ADRB1
hsa04910	Insulin signalling pathway	9	133	7.82E-07	GCK,KRAS,BRAF,INSR,FASN,MTOR ,PTPN1,IKBKB,AKT1
hsa04010	MAPK signalling pathway	14	288	1.37E-08	FLT3,KRAS,KDR,IGF1R,FLT1,BRAF, INSR,PRKCB,FGFR1,TNF,IKBKB,PG F,AKT1,VEGFA
hsa04650	Natural killer cell-mediated cytotoxicity	5	121	0.0018	KRAS,BRAF,PRKCB,PTPN6,TNF
hsa04064	NF-kappa B signalling pathway	4	101	0.0059	PRKCB,BCL2,TNF,IKBKB
hsa04115	p53 signalling pathway	4	72	0.0021	SERPINE1,CDK6,IGFBP3,BCL2
hsa04151	PI3K-Akt signalling pathway	17	350	2.36E-10	FLT3,KRAS,KDR,CDK6,IGF1R,FLT1, NOS3,INSR,MTOR,BCL2,IL6,FGFR1, IKBKB,PGF,AKT1,ITGB3,VEGFA
hsa04668	TNFsignallingg pathway	7	112	2.00E-05	MMP3,MMP14,MMP9,IL6,TNF,IKBK B,AKT1
hsa04930	Type II diabetes mellitus	6	46	2.96E-06	GCK,INSR,MTOR,PRKCD,TNF,IKBK B

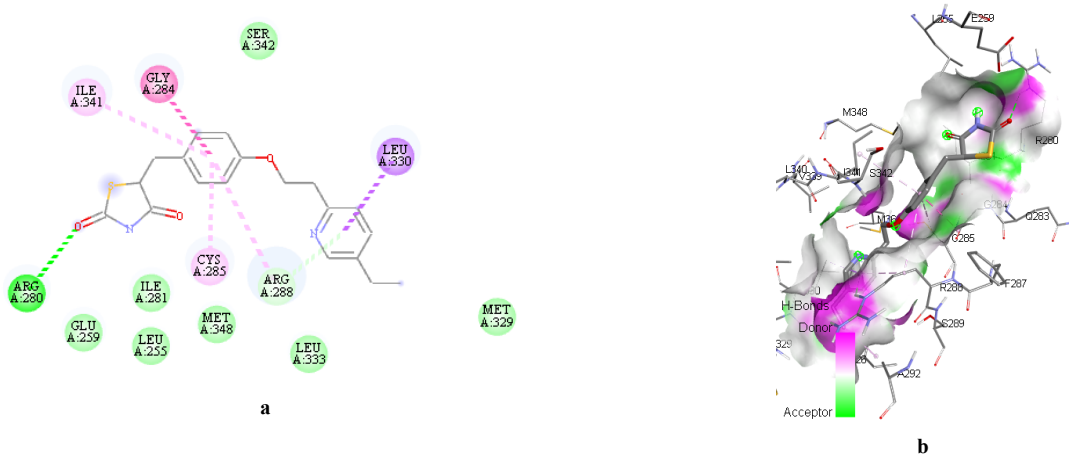


Figure 1: 2D and 3D pose of Pioglitazone in the binding pocket of 4FHJ

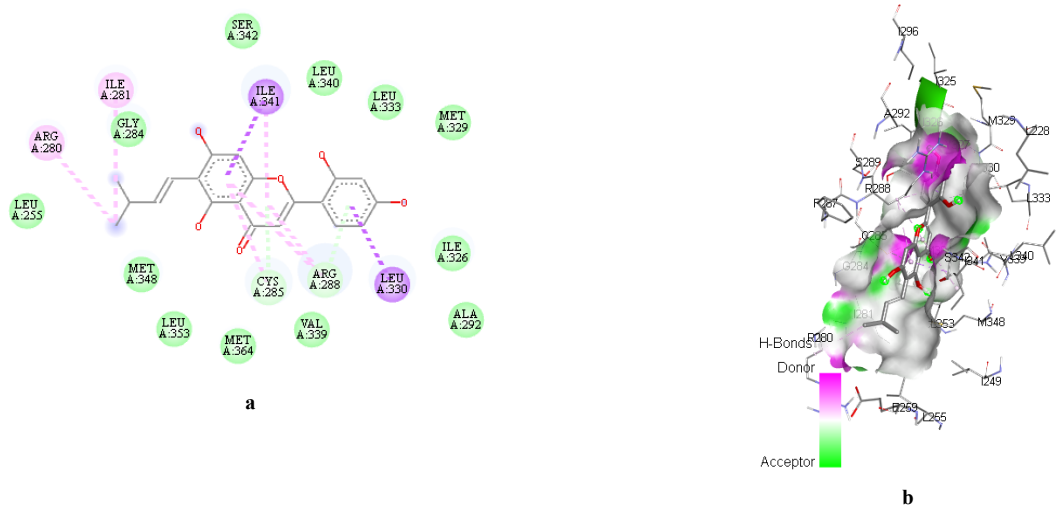


Figure 2: 2D and 3D pose of 2, 4, 5, 7-tetrahydroxy-6-(3-methyl-2-butenyl) flavone in binding pocket of 4FHJ

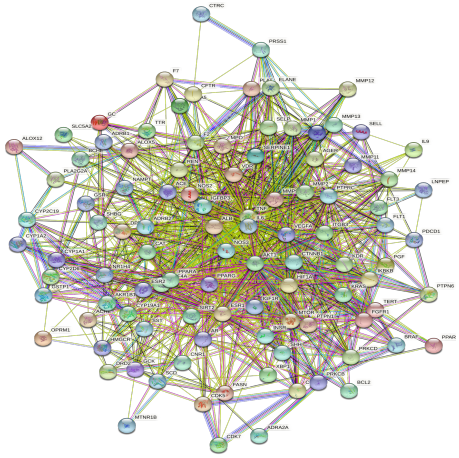


Figure 3: Protein-Protein interaction network

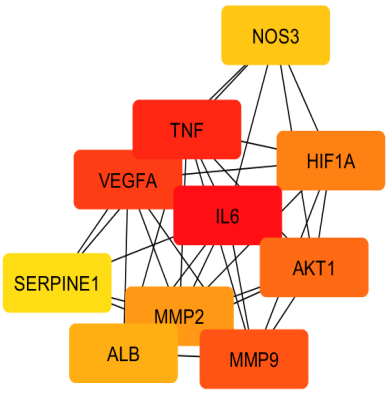


Figure 4: Top 10 hub genes

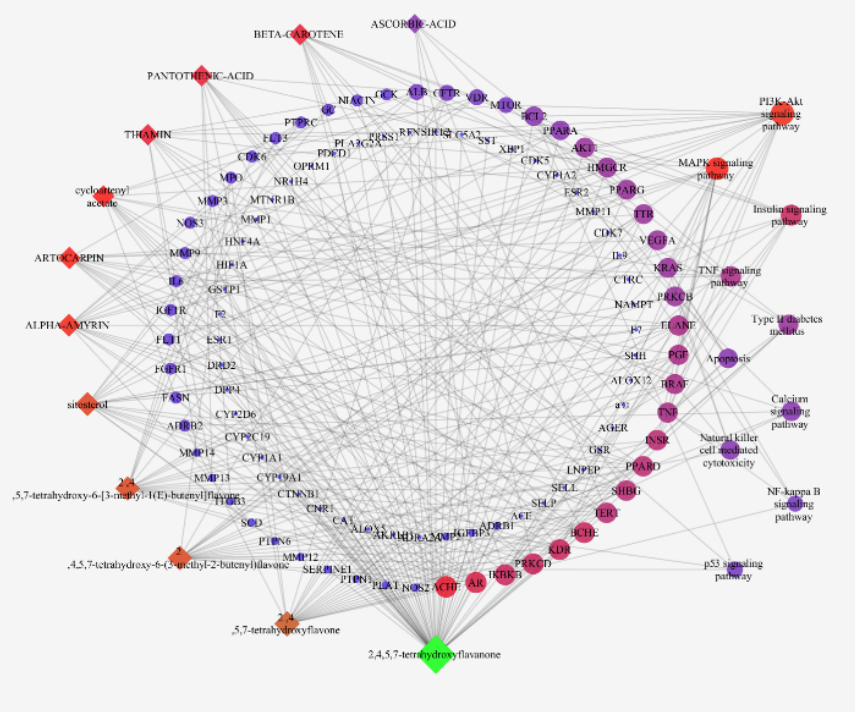


Figure 5: The network representation of protein targets and pathways

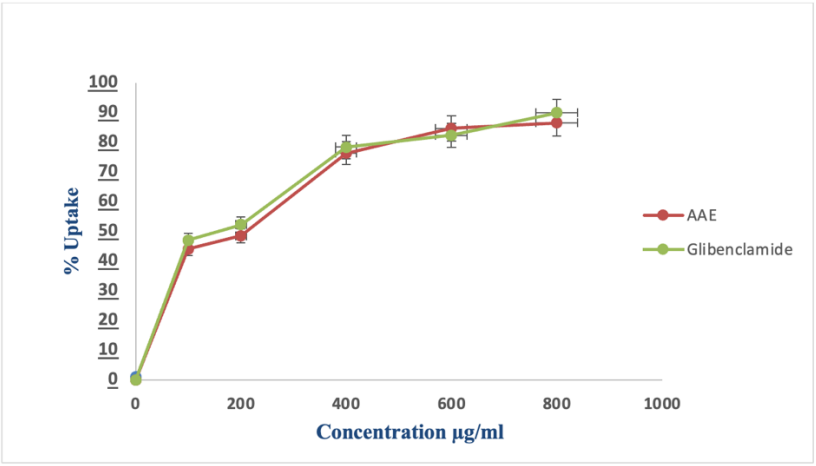


Figure 6: Glucose uptake assay in yeast cells.

DISCUSSION

The yeast cell's ability to absorb glucose is determined by how glucose is transported across the cell membrane with an exogenous molecule. There have been continuous efforts to use network pharmacology to study the molecular mechanisms of herbal remedies in treating complex diseases. [18-20] For the treatment of DM, the use of *Artocarpus altilis* has been established. [21]

The molecular basis for *Artocarpus altilis* role in treating diabetes hasn't been fully elucidated. In order to understand the probable molecular processes of AAE in managing DM, the current study uses the network pharmacology approach. We built a network that integrated the interactions between phytoconstituents, their targets, and pathways. The findings suggest that flavonoids, stilbenoids, aryl benzofurans and alkaloids are possible phytoconstituents capable of interacting with several protein molecules involved in the pathogenesis of DM. One of these, 2, 4, 5, 7-tetrahydroxyflavone, flavonoids, may have a place in the pharmacotherapy of diabetes mellitus (DM) by focusing on the many protein molecules in the network as reported that phytoconstituents in *Artocarpus altilis* contains a large amount of flavonoids [2] were seen to be highly associated with DM. Furthermore, reports have been shown to explain how flavonoids are helpful in the treatment of diabetes. This may be because 2, 4, 5, and 7-tetrahydroxyflavones are primarily responsible for targeting the various protein molecules involved in the pathogenesis of DM, as shown by the current findings, and synergistic with other phytoconstituents.

Targeting The MAPK pathway, which is connected to various disease processes in the kidneys, can be triggered by processes brought on by hyperglycaemia (polyol pathway products, oxidative stress, and accumulation of advanced glycosylation end-products). [22]

The PI3K/AKT pathway is tightly regulated, and its disruptions are the root of many disorders, most notably insulin resistance. One of the most significant issues facing modern research is the need for more understanding of the systems controlling this signalling. Currently, regulatory-PI3K kinase subunits, IRS proteins, and kinase isoform Akt /PKB have been identified as three distinct signalling nodes. The leading cause of the decreased signal transmission efficiency and the associated illnesses is disturbances of any of these nodes. [23]

Insulin is involved in various metabolic processes, including storing glycogen in the liver and skeletal muscles, stimulating lipogenesis and inhibiting lipolysis, and inhibiting gluconeogenesis in the liver. However, the main metabolic effect of released insulin is increased glucose uptake via the insulin receptor signalling pathway. [24]

The IRS proteins are phosphorylated on tyrosine residues, which can then activate two important signalling pathways. The first pathway goes from Ras to mitogen-activated kinases (MAPK), which are important in controlling gene expression in cell growth and differentiation. The second mechanism, known as the phosphatidylinositol 3-kinase (PI3K) pathway, results in the phosphorylation of the AKT/PKB kinase, which gives insulin its metabolic effects. [25] Thus, activation of the PI3K-Akt signalling pathway, MAPK signalling pathway and insulin signalling pathway results in translocation and activating GLUT-4 protein, facilitating glucose uptake.

The current study identifies 2,4,5',7'-tetrahydroxyflavanone and 2,4,5',7'-tetrahydroxyflavone with other associated phytoconstituents to stimulate INSR, AKT1, PTPN, IGFR1 leading to activating the MAPK signalling pathway, PI3-Akt pathway, and insulin signalling pathway, causing activation of GLUT4 and finally glucose uptake in skeletal muscles, similarly *in vitro* glucose uptake in yeast cells assay supported these findings.

CONCLUSION

We identified two flavonoids, 2,4,5',7'-tetrahydroxyflavanone and 2,4,5',7'- tetrahydroxyflavone, to interact with a maximum number of protein molecules involved in the pathogenesis of insulin resistance and their binding affinity. These findings are supported by data from yeast cells' *in vitro* glucose uptake assay. However, the current findings are only based on *in vitro* and *in silico* data, and wet lab results are required for additional analysis.

ACKNOWLEDGMENT

The authors thank Principal Maratha Mandal's College of Pharmacy, Belagavi, for his constant support.

REFERENCES

1. Pandey MM, Rastogi S, Rawat AK. Indian traditional Ayurveda system of medicine and nutritional supplementation. Evid-Based Complementary Altern. Med. 2013.
2. Sikarwar MS, Hui BJ, Subramaniam K, Valeisamy BD, Yean LK, *et al*. A review on *Artocarpus altilis (*Parkinson) Fosberg (breadfruit). J. Appl Pharm Sci. 2014; 27;4(8):09:1-7.
3. Deivanai S, Bhore SJ. Breadfruit (*Artocarpus altilis* Fosb.): An underutilised and neglected fruit plant species. Middle East J. Sci. Res. 2010;6(5):418-28.
4. Jagtap UB, Bapat VA. Artocarpus: A review of its traditional uses, phytochemistry and pharmacology. J. Ethnopharmacol. 2010;27;129(2):142-66.
5. Alam U, Asghar O, Azmi S, Malik RA. General aspects of diabetes mellitus. Handb. Clin. Neurol. 2014;1;126:211-22.
6. International Diabetes Federation. IDF Diabetes Atlas, 10th ed. Brussels, Belgium: 2021. Available at: (https:// diabetesatlas.org/).
7. James DE, Piper RC. Insulin resistance, diabetes, and the insulin-regulated trafficking of GLUT-4. J. cell biol. 1994;1;126(5):1123-6.
8. Durairaj B, Thiruselvi M. Free radical scavenging activity from hydroethanolic extracts of *Artocarpus heterophyllus* seeds. Drug Invent. Today. 2018;1;10(8).
9. Khanal P, Patil BM. Reversal of insulin resistance by *Ficus benghalensis* bark in fructose-induced insulin-resistant rats. J. Ethnopharmacol. 2022;10;284:114761.
10. Xu X, Fang C, Wang Y, Lu F, Liu S. Integrating network pharmacology and metabolomics to elucidate the mechanism of action of huang qin decoction for treatment of diabetic liver injury. Front. Pharmacolo. 2022;13.
11. Noor F, Rehman A, Ashfaq UA, Saleem MH, Okla MK, *et al*. Integrating Network Pharmacology and Molecular Docking Approaches to Decipher the Multi-Target Pharmacological Mechanism of *Abrus precatorius* L. Acting on Diabetes. Pharmaceuticals. 2022;29; 15(4):414.
12. Chin CH, Chen SH, Wu HH, Ho CW, Ko MT, Lin *et al*. cytoHubba: Identifying hub objects and sub-networks from complex interactome. BMC Syst. Biol. 2014;8(4):1-7.
13. Jakhar R, Dangi M, Khichi A, Chhillar AK. Relevance of molecular docking studies in drug designing. Curr. Bioinform. 2020;1;15(4):270-8.
14. Sulimov AV, Kutov DC, Katkova EV, Ilin IS, Sulimov VB. New generation of docking programs: Supercomputer

validation of force fields and quantum-chemical methods for docking. J. Mol. Graph. Model. 2017;1; 78:139-47.
15. Peterson EA, Boezio AA, Andrews PS, Boezio CM, Bush TL, *et al*. Discovery and optimisation of potent and selective imidazopyridine and imidazopyridazine mTOR inhibitors. Bioorganic Med. Chem. Lett. 2012;1;22(15):4967-74.
16. Ounthaisong U, Tangyuenyongwatana P. Cross-docking study of flavonoids against tyrosinase enzymes using PyRx 0.8 virtual screening tool. TJPS. 2017;41(2017).
17. Cirillo VP. Mechanism of glucose transport across the yeast cell membrane. J. Bacteriol. 1962;84(3):485-91.
18. Zhang GB, Li QY, Chen QL, Su SB. Network pharmacology: A new approach for Chinese herbal medicine research. Evid-Based Complementary Altern. Med. 2013;2013.
19. Khanal P, Patil BM. Gene set enrichment analysis of alpha-glucosidase inhibitors from *Ficus benghalensis*. Asian Pac. J. Trop. Biomed. 2019;1;9(6):263.
20. Li W, Yuan G, Pan Y, Wang C, Chen H. Network pharmacology studies on the bioactive compounds and action mechanisms of natural products for the treatment of diabetes mellitus: A review. Front. Pharmacolo. 2017;23;8:74.
21. Djabir YY, Hardi H, Setiawati H, Lallo S, Yulianty R, *et al*. *Artocarpus altilis* leaf extract protects pancreatic islets and improves glycemic control in alloxan-induced diabetic rats. J. Rep. Pharm. Sci. 2021;1;10(1):87.
22. Barros JB, da Silva Santos R, da Silva Reis AA. Implication of the MAPK signalling pathway in the pathogenesis of diabetic nephropathy. Diabetes. 2019.
23. Taniguchi CM, Emanuelli B, Kahn CR. Critical nodes in signalling pathways: insights into insulin action. Nat. Rev. Mol. Cell Biol. 2006;7(2):85-96.
24. Newsholme EA, Dimitriadis G. Integration of biochemical and physiologic effects of insulin on glucose metabolism. Exp. Clin. Endocrinol. Diabetes. 2001;109(Suppl 2):S122-34.
25. Świderska E, Strycharz J, Wróblewski A, Szemraj J, Drzewoski J, *et al*. Role of PI3K/AKT pathway in insulin-mediated glucose uptake. Blood Glucose Levels. 2018; 5; 1: 1-8.

Cite this article as:

Archana M. Patil, Sarvanan Kaliyaperumal, Mrityunjaya B. Patil and Vrunda J. Kumbhar. Hydroalcoholic extract of *Artocarpus altilis* promotes the glucose uptake: An *in silico* and *in vitro* approach. Int. J. Res. Ayurveda Pharm. 2023;14(2):61-68
DOI: http://dx.doi.org/10.7897/2277-4343.140242

Source of support: Nil, Conflict of interest: None Declared