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FUNCTIONAL ANNOTATION AND NETWORK ANALYSIS OF PROTEIN IN RESPECT WITH DIABETES TARGETING *ALOE VERA* PLANT COMPOUNDS BY BIOINFORMATICS TOOLS

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ABSTRACT

Diabetes mellitus is a complex metabolic condition caused by insulin deficiency or malfunction. Diabetes is a serious human disease that affects people from all walks of life in numerous countries. *Aloe vera* is known for its magical powers, which include medicine, health, beauty and skin care products. The applications of *Aloe vera* is in cosmetics and health products, as well as its *anti-oxidant, anti-cancer, anti-inflammatory, laxative* and *anti-atherosclerotic* properties. Therefore, the *In-silico* study is worth mentioning to expand the effective anti-diabetic drugs of this plant. This research aims to discover the network between proteins and biologically active compounds and their functional annotations, cellular pathways, molecular and biological pathways. When using the STRING 9.1 tool to analyze protein-protein interactions, six enrichment pathways were identified in Arabidopsis and other species. According to the results, the CYP proteins of different species in seed plants are very similar to the CYP proteins of other organisms, so they must come from a common ancestor. The data obtained from the chain shows that the number of nodes is 11, the number of edges is 21, and the average node degree is 3.82. The local clustering coefficient is 0.863, the expected number of edges is 10, and the p value of the enriched ppi is 0.00197. The regulatory network analysis found many transcription factors, including FMO2, FMO5, CBR3, CYP3A4, MA OA, CYP2D6, HSD11B1, FMO4, FMO3, MAOB, FMO1, FMO2, FMO5, CBR3, CYP3A 4, CYP2D6, FMO4, FMO3, MAOB, FMO1CBR3, HSD11B1 CYP3A4, CYP2D6, pump, CYPs4ACYPsACYPs4DACYPs (diabetes type 2DDM/5 and PDM) It plays a role in the patient with type 2 diabetes.

Keywords: Antidiabetics, *Aloe vera,* Plant metabolites, STRING, STITCH.

1. INTRODUCTION

The second most prevalent chronic disease is type 1 diabetes (T1D) among adolescents. Diabetes-related morbidity and premature death are the main sources of pain [1] and medical expenses Diabetes was expected to affect more than 20 million peoples in the United States in 2005. Approximately 30% of these individuals had undetected cases [2]. Diabetes affects an estimated 77 million people in India, making it the world's second most affected country behind China. India accounts for one-sixth (17%) of all diabetics worldwide. Effective treatment is available, but one must balance the insulin dose, nutrition, and exercise, and receive feedback on the performance of blood sugar control levels. Therefore, even for the most determined teenagers, always applying and sticking to such a complex and rigorous treatment plan is a problem. Young people's spontaneity, longevity and particularity are not conducive to effective management of diabetes. On the other hand, paying more attention to diabetes control can help control blood sugar [3], and lowering the concentration of hemoglobin A1c (HbA1c), in turn, can reduce the risk of diabetes complications [1]. In addition to the complexity of treatment and periodic interruptions in adolescents' lives, the painful acupuncture required to control blood sugar, the inconvenience of carrying or using a blood glucose meter, and injecting insulin further hinder compliance.

The variability of the response to the drug is observed in patients with DM2, which means that some patients with DM2 appear to be resistant to certain drugs, while others are more sensitive to other drugs. The variability of systemic drug exposure is the main determinant of interindividual variability of drug response [4]. The

interindividual variability of the metabolism of these drugs are several important factors that can affect their pharmacokinetics.

The cytochrome P450 (P450) superfamily is an important enzyme system, primarily as monooxygenases [5]. P450 is a membrane-bound heme protein that plays an important role in the metabolism of drugs and other exogenous substances [6, 7]. Among the P450s found in humans, CYP2D6 and CYP3A4 are involved in the metabolism (oxidation) of 70-80% of approved drugs [8]. Large individual differences in P450 activity have been observed, especially CYP3A (40 times), CYP2D6 (100 times), CYP2B6 (50 times) and CYP2C9 (40 times) [9-11]. Therefore, regulating the expression or activity of P450 enzymes will lead to changes in drug distribution, which in turn affects the pharmacodynamic response. *Aloe vera* is known for its magical powers, including medicine, health, beauty and skin care products. It is found in beverages, body lotions, cosmetics and ointments, and in the form of gels for minor burns and sunburns. *Aloe vera* has applications in cosmetics and health products, as well as anti-oxidant, anti-cancer, anti-inflammatory, laxative and anti-atherosclerotic properties. It includes 75 active ingredients, which contain vitamins, enzymes, minerals, sugars, lignin, salicylic acid and amino acids [12, 13]. Many main ingredients such as: aloin, aloe acid, anthraphenol, babaloin, mannan and its derivatives, 8C-glusoly (2'O-cinnamoly), -7O-methlyaloediol A, alkaline phosphate, amylase, slow kinase, carboxypeptide Enzymes, catalase, pyrone phosphatase, phospho-pyranodase, pyrone phosphate, phosphatase have been found chromium, copper, iron, magnesium, arachidonic acid, linolenic acid, steroids, mannose, Glucose, Lamannose, aldose, vitamin A, B12, C, E, choline and folic acid, auxin and gibberellin [14].

2. MATERIAL AND METHODS

2.1. Sources and Selection of the targeting protein

The source of the plant, the geographic location of the collection, the chemical structure, and the biological activity of the pure *Aloe vera* compounds were obtained from bibliographic sources, including major natural product chemistry journals, master's and doctoral dissertations, chapters of Unpublished textbooks and conference reports. The following standards are used by Kumar et al. [15] and Gupta et al. [16]. If the IC_{50} is 0.06 mM, the pure compound is considered to have high activity, 0.06 mM, IC_{50} is active at 5 mM, and 5 mM, IC_{50} is weak at 10 mM, and the compound with IC_{50}10 MM is considered to have no activity. Choose weakly active compounds at most.

2.2. Protein and compounds network interaction

We use comprehensive network analysis to identify functional links between proteins in order to highlight the biological significance of enrichment pathways and linked genes. The STRING and STITCH databases (version: 11.0) are worldwide resources for predicting the functional link between proteins and cloud cluster networks, and they are used to investigate the interactions between proteins encoded by specific genes [17]. We use P protein and chemicals as our input gene set and conduct experiments to confirm species. We investigated protein interactions (PPI) between enriched genes and its interaction network between them. A complete score greater than 0.7 suggests a high level of confidence in the presence of a significant interaction.

3. RESULTS AND DISCUSSION

Protein-protein interactions are a core part of cell networks and are known to have many effects. It analyze the information flow network between all target proteins to determine how much information flows between the cytochrome protein and other proteins. Online STRING software was used to create a molecular genetic interaction network, and Cytoscape software was used to visualize the number of nodes 11, the number of edges 21, the average node degree 3.82, and the average value. The local clustering coefficient is 0.863, the expected number of edges is 10, and the p-value of the enrichment ppi is 0.00197. The nodes, lines and colors prove the rationality of the interactive network (Fig. 1). Through a large number of experiments, it has been observed that its genes are related to the expression of proteins. STRING conducted a co-expression analysis database, which shows the analysis of the biological, molecular, and cellular pathways shown in (Table 1-3). The findings indicate that more residues are involved in Protein signal intensity than in cytochrome protein networking pathway. The results are described by the colors shown in the prediction structure. Genes are primarily involved in cytokine reaction, oxidoreductase activity, N, N-dimethylaniline monooxygenase activity, and the GO term for monooxygenase activity. NADP binding, cofactor binding, oxidoreductase activity, acting on matched donors, with oxygenation or molecular reduction, flavin adenine dinucleotide binding, coenzyme binding, small molecule binding, primary amine oxidase

activity, nucleotide binding, oxidoreductase activity, acting on pair donors, with oxygenation or reduction, flavin or reduced flavoproteins as a donor and conjugation of an oxygen atom, steroid hydroxylase activity, anionic bond, heterocyclic bond, cyclic organic compound bond, ionic bond, oxidoreductase activity, action with the CHOH group of the donor, NAD or NADP as acceptor, heme binding, secondary iron ion binding metabolism in plants, by protein-protein interaction network and modulus/cluster analysis as shown in table 4. Further, the analysis regulatory network found many transcription factors including FMO2, FMO5, CBR3, CYP3A4, MA OA, CYP2D6, HSD11B1, FMO4, FMO3, MAOB, FMO1, FMO2, FMO5, CBR3, CYP3A 4, CYP2D6, FMO4, FMO3, MAOB, FMO1CBR3, HSD11B1CYP3A4, CYP2D6, play a role in CYP3A4 pumps, involving CYP2D6, play a role in CYP3A4, involving the pumps, CYP3A4/5 and P-glycoprotein (Pgp) in patients with type 2 diabetes (T2DM) (Table 4). In addition, enzyme activity may be regulated by genetics and some external factors, for example, the activity of CYP3A and CYP2C decreased due to the increase of pro-inflammatory drugs [18]. It is believed that acute or chronic diseases can stimulate the inflammatory process, leading to changes in the expression of certain CYPs and leading to genotype-phenotype mismatches, which is an important environmental factor [19]. Therefore, it can be assumed that diabetes may be a potential environmental factor affecting CYP450 enzyme activity. In addition, it may lead to mispredictions of the potential clinical response to the administered drug, especially in the case of prodrugs and drugs with narrow therapeutic index. In order to fully understand the biochemistry of metabolites, drugs and other compounds, the current challenge is to integrate various sources of chemical knowledge into a single resource and link it to protein knowledge. For example, in order to link phenotypic observations of cell line screening with molecular events, their interaction with proteins in the context of cellular networks is essential.

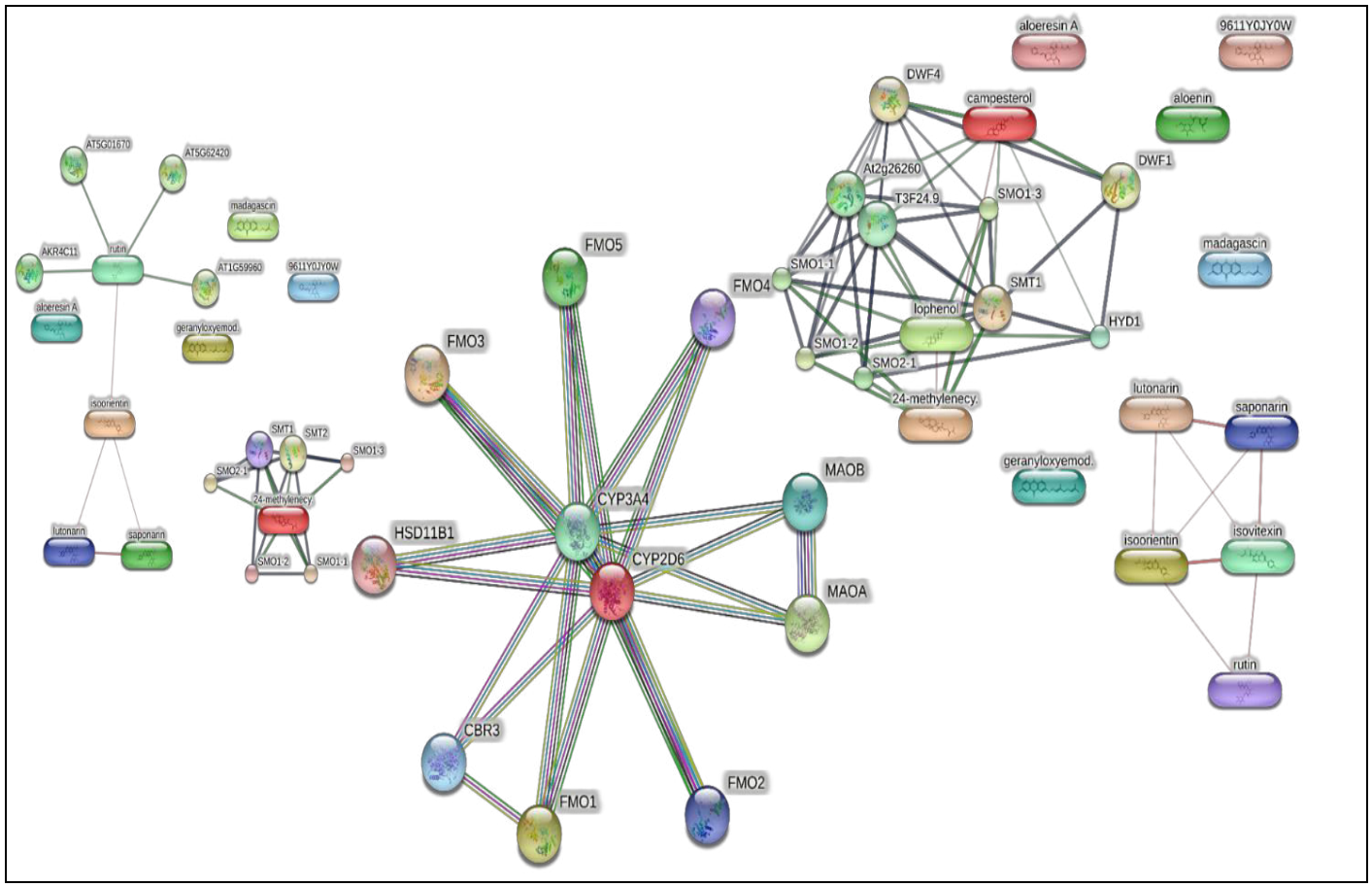

Fig. 1: STRING and STITCH database representing the interaction of CYP2D6 CYP3A4 protein with the compounds

Table 1: Network coordinates of CYP2D6 and CYP3A4

Node1	Node2	Node1 annotation	Node2 annotation	score
CBR3	CYP2D6	Carbonyl reductase [NADPH] 3; it has low NADPH-dependent oxidoreductase activity against 4-benzoylpyridine and menadione (in vitro); it belongs to short-chain dehydrogenase/reductase (SDR) cells Pigment P450 2D6 family; responsible for the metabolism of many drugs and environmental chemicals that it oxidizes.	Participate in themetabolism of antiarrhythmic drugs, adrenergic receptor antagonists, tricyclic antidepressants and other drugs; Cytochrome P450 series two.	0.937
CBR3	CYP3A4	Carbonyl reductase [NADPH] 3; Has low NADPH-dependent oxidoreductase activity towards 4-benzoylpyridine and menadione (in vitro); Belongs to the short-chain dehydrogenases/reductases (SDR) family	Cytochrome P450 3A4. It performs a variety of oxidation reactions (e.g. caffeine 8-oxidation, omeprazole sulphoxidation, midazolam 1'-hydroxylation and midazolam 4-hydroxylation) of structurally unrelated compounds, including steroids, fatty acids, and xenobiotics.	0.921
CBR3	FMO1	Carbonyl reductase [NADPH] 3; Has low NADPH-dependent oxidoreductase activity towards 4-benzoylpyridine and menadione (in vitro); Belongs to the short-chain dehydrogenases/reductases (SDR) family	Catalyzes the N-oxygenation of secondary and tertiary amines	0.689
CYP2D6	CBR3	Cytochrome P450 2D6; Responsible for the metabolism of many drugs and environmental chemicals that it oxidizes. It is involved in the metabolism of drugs such as antiarrhythmics, adrenoceptor antagonists, and tricyclic antidepressants; Cytochrome P450 family 2	Carbonyl reductase [NADPH] 3; Has low NADPH-dependent oxidoreductase activity towards 4-benzoylpyridine and menadione (in vitro); Belongs to the short-chain dehydrogenases/reductases (SDR) family	0.937
CYP2D6	CYP3A4	Cytochrome P450 2D6; Responsible for the metabolism of many drugs and environmental chemicals that it oxidizes. It is involved in the metabolism of drugs such as antiarrhythmics, adrenoceptor antagonists, and tricyclic antidepressants; Cytochrome P450 family 2	Cytochrome P450 3A4; Cytochromes P450 are a group of heme-thiolate monooxygenases. The enzyme also hydroxylates etoposide. Catalyzes 4-beta-hydroxylation of cholesterol. May catalyze 25-hydroxylation of chol […]	0.948
CYP2D6	FMO1	Cytochrome P450 2D6; Responsible for the metabolism of many drugs and environmental chemicals that it oxidizes. It is involved in the metabolism of drugs such as antiarrhythmics, adrenoceptor antagonists, and tricyclic antidepressants; Cytochrome P450 family 2	Dimethylaniline monooxygenase [N-oxide-forming] 1; This protein is involved in the oxidative metabolism of a variety of xenobiotics such as drugs and pesticides. Form I catalyze the N-oxygenation of secondary and tertiary amines	0.959
CYP2D6	FMO2	Cytochrome P450 2D6; Responsible for the metabolism of many drugs and environmental chemicals that it oxidizes. It is involved in the metabolism of drugs such as antiarrhythmics, adrenoceptor antagonists, and tricyclic antidepressants; Cytochrome P450 family 2	Inactive toward certain tertiary amines, such as imipramine or chloropromazine.	0.930
CYP2D6	FMO3	Cytochrome P450 2D6; Responsible for the metabolism of many drugs and	Plays an important role in the metabolism of trimethylamine	0.961

		environmental chemicals that it oxidizes and tricyclic antidepressants; Cytochrome P450 family 2	(TMA), via the production of TMA N-oxide (TMAO). Is also able to perform S-oxidation when acting on sulfide compounds	
CYP2D6	FMO4	Cytochrome P450 2D6.It is involved in the metabolism of drugs such as antiarrhythmics, adrenoceptor antagonists, and tricyclic antidepressants; Cytochrome P450 family 2	Dimethylaniline monooxygenase [N-oxide-forming] 4; This protein is involved in the oxidative metabolism of a variety of xenobiotics such as drugs and pesticides	0.929
CYP2D6	FMO5	Cytochrome P450 2D6. It is involved in the metabolism of drugs such as antiarrhythmics, adrenoceptor antagonists, and tricyclic antidepressants; Cytochrome P450 family 2	Dimethylaniline monooxygenase [N-oxide-forming] 5; In contrast with other forms of FMO it does not seem to be a drug-metabolizing enzyme	0.948
CYP2D6	HSD11B1	Cytochrome P450 2D6; Responsible for the metabolism of many drugs and environmental chemicals that it oxidizes. It is involved in the metabolism of drugs such as antiarrhythmics, adrenoceptor antagonists, and tricyclic antidepressants; Cytochrome P450 family 2	Corticosteroid 11-beta-dehydrogenase isozyme 1; Catalyzes reversibly the conversion of cortisol to the inactive metabolite cortisone. Catalyzes reversibly the conversion of 7-ketocholesterol to 7-beta-hydroxycholesterol.	0.928
CYP2D6	MAOA	Cytochrome P450 2D6; Responsible for the metabolism of many drugs and environmental chemicals that it oxidizes. It is involved in the metabolism of drugs such as antiarrhythmics, adrenoceptor antagonists, and tricyclic antidepressants; Cytochrome P450 family 2	Amine oxidase [flavin-containing] A; Belongs to the flavin monoamine oxidase family	0.951
CYP2D6	MAOB	Cytochrome P450 2D6; Responsible for the metabolism of many drugs and environmental chemicals that it oxidizes. It is involved in the metabolism of drugs such as antiarrhythmics, adrenoceptor antagonists, and tricyclic antidepressants; Cytochrome P450 family 2	Amine oxidase [flavin-containing] B; Catalyzes the oxidative deamination of biogenic and xenobiotic amines and has important functions in the metabolism of neuroactive and vasoactive amines in the central nervous system and peripheral tissues. MAOB preferentially degrades benzylamine and phenylethylamine	0.946
CYP3A4	CBR3	It performs a variety of oxidation reactions (e.g. caffeine 8-oxidation, omeprazole sulphoxidation, midazolam 1'-hydroxylation and midazolam 4- hydroxylation) of structurally unrelated compounds, including steroids, fatty acids, and xenobiotics.	Carbonyl reductase [NADPH] 3; Has low NADPH-dependent oxidoreductase activity towards 4-benzoylpyridine and menadione (in vitro); Belongs to the short-chain dehydrogenases/reductases (SDR) family	0.921
CYP3A4	CYP2D6	Cytochrome P450 3A4; Cytochromes P450 are a group of heme-thiolate monooxygenases. Acts as a 1,8-cineole 2-exo-monooxygenase.	Cytochrome P450 2D6;. It is involved in the metabolism of drugs such as antiarrhythmics, adrenoceptor antagonists, and tricyclic antidepressants; Cytochrome P450 family 2	0.948
CYP3A4	FMO1	The enzyme also hydroxylates etoposide. Catalyzes 4-beta-hydroxylation of cholesterol.	This protein is involved in the oxidative metabolism of a variety of xenobiotics such as drugs and pesticides. Form I catalyze the N-	0.963

			oxygenation of secondary and tertiary amines	
CYP3A4	FMO2	Cytochrome P450 3A4; It performs a variety of oxidation reactions (e.g. caffeine 8-oxidation, omeprazole sulphoxidation, midazolam 1'-hydroxylation and midazolam 4- hydroxylation) of structurally unrelated compounds, including steroids, fatty acids, and xenobiotics.	Inactive toward certain tertiary amines, such as imipramine or chloropromazine. Can catalyze the S-oxidation of methimazole. The truncated form is catalytically inactive	0.933
CYP3A4	FMO3	Cytochrome P450 3A4; Cytochromes P450 are a group of heme-thiolate monooxygenases.	Dimethylaniline monooxygenase [N-oxide-forming] 3; Involved in the oxidative metabolism of a variety of xenobiotics such as drugs and pesticides. It N-oxygenates primary aliphatic alkylamines as well as secondary and tertiary amines. Plays an important role in the metabolism of trimethylamine (TMA), via the production of TMA N-oxide (TMAO). Is also able to perform S-oxidation when acting on sulfide compounds	0.967
CYP3A4	FMO4	Acts as a 1,8-cineole 2- exo-monooxygenase. The enzyme also hydroxylates etoposide. Catalyzes 4-beta-hydroxylation of cholesterol.	Dimethylaniline monooxygenase [N-oxide-forming] 4; This protein is involved in the oxidative metabolism of a variety of xenobiotics such as drugs and pesticides	0.946
CYP3A4	FMO5	In liver microsomes, this enzyme is involved in an NADPH-dependent electron transport pathway. The enzyme also hydroxylates etoposide. Catalyzes 4-beta-hydroxylation of cholesterol.	Dimethylaniline monooxygenase [N-oxide-forming] 5; In contrast with other forms of FMO it does not seem to be a drug-metabolizing enzyme	0.956

Table 2: Biological annotation of the CYP2D6 and CYP3A4 protein

Gene ID	Proteindescription	false discovery rate
hsa00982	Drug metabolism - cytochrome P450	1.30E-19
hsa00980	Metabolism of xenobiotics by cytochrome P450	6.69E-07
hsa04726	Serotonergic synapse	
hsa00360	Phenylalanine metabolism	0.00027
hsa00340	Histidine metabolism	0.00038
hsa00260	Glycine, serine and threonine metabolism	0.00073
hsa00350	Tyrosine metabolism	0.00073
hsa00380	Tryptophan metabolism	0.00073
hsa00330	Arginine and proline metabolism	0.00085
hsa01100	Metabolic pathways	0.00085
hsa05030	Cocaine addiction	0.00085
hsa00140	Steroid hormone biosynthesis	0.00091
hsa05031	Amphetamine addiction	0.0011
hsa05204	Chemical carcinogenesis	0.0013
hsa04728	Dopaminergic synapse	0.0034
hsa05034	Alcoholism	0.0039

Table 3: Functional annotation of the CYP2D6 and CYP3A4 protein

#term ID	Protein description	false discovery rate
GO:0055114	Oxidation-reduction process	7.32E-13
GO:0006805	Xenobiotic metabolic process	1.84E-09
GO:0042737	Drug catabolic process	1.62E-07
GO:0017144	Drug metabolic process	4.02E-07
GO:0009822	Alkaloid catabolic process	9.79E-05
GO:0019748	Secondary metabolic process	0.0001
GO:0070995	NADPH oxidation	0.00011
GO:0016098	Monoterpenoid metabolic process	0.00019
GO:0042420	Dopamine catabolic process	0.00022
GO:0070989	Oxidative demethylation	0.00039
GO:0009404	Toxin metabolic process	0.001
GO:0042135	Neurotransmitter catabolic process	0.001
GO:0042759	Long-chain fatty acid biosynthetic process	0.0012
GO:0051186	Cofactor metabolic process	0.0012
GO:0044248	Cellular catabolic process	0.0013
GO:0070887	Cellular response to chemical stimulus	0.0018
GO:0008202	Steroid metabolic process	0.0027
GO:0042221	Response to chemical	0.003
GO:0006732	Coenzyme metabolic process	0.004
GO:0042446	Hormone biosynthetic process	0.0041
GO:1901575	Organic substance catabolic process	0.0074
GO:0006082	Organic acid metabolic process	0.0091
GO:0046496	Nicotinamide nucleotide metabolic process	0.0091
GO:1901565	Organonitrogen compound catabolic process	0.0091
GO:1901615	Organic hydroxy compound metabolic process	0.0091
GO:0044281	Small molecule metabolic process	0.0094
GO:0006766	Vitamin metabolic process	0.0097
GO:0006694	Steroid biosynthetic process	0.0104
GO:0006733	Oxidoreduction coenzyme metabolic process	0.0104
GO:1901361	Organic cyclic compound catabolic process	0.0104
GO:0008610	Lipid biosynthetic process	0.016
GO:0097164	Ammonium ion metabolic process	0.0196
GO:1901360	Organic cyclic compound metabolic process	0.0346
GO:0032496	Response to lipopolysaccharide	0.0472

Table 4: Cellular annotation of the CYP2D6 and CYP3A4 protein

Gene ID	Description	Matching proteins in your network
Go:001691	Oxidoreductase activity	Gene ID
Go:0004499	N,n-dimethylaniline monooxygenase activity	Go:0016491
Go:0004497	Monooxygenase activity	CYP2D6, HSD11B1, FMO4, FMO3,
Go:0050661	Nadp binding	MAOB, FMO1
Go:0048037	Cofactor binding	Go:0004499
Go:0016705	Oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen	FMO3, FMO1
Go:0050660	Flavin adenine dinucleotide binding	Go:0004497
Go:0050662	Coenzyme binding	FMO4, FMO3, FMO1
Go:0036094	Small molecule binding	Go:0050661
Go:0008131	Primary amine oxidase activity	FMO3, FMO1
Go:0000166	Nucleotide binding	Go:0048037
Go:0016712	Oxidoreductase activity, acting on paired donors, with	FMO4, FMO3, MAOB, FMO1

	incorporation or reduction of molecular oxygen, reduced flavin or flavoprotein as one donor, and incorporation of one atom of oxygen	
Go:0008395	Steroid hydroxylase activity	Go:0016705
Go:0043168	Anion binding	FMO3, FMO1
Go:1901363	Heterocyclic compound binding	Go:0050660
Go:0097159	Organic cyclic compound binding	Go:0050662
Go:0043167	Ion binding	Go:0036094
Go:0016616	Oxidoreductase activity, acting on the ch-oh group of donors, nad or nadp as acceptor	Go:0008131
Go:0020037	Heme binding	Go:0000166
Go:0005506	Iron ion binding	Go:0016712

4. CONCLUSION

In the analysis of protein-protein interactions with STRING 9.1 tools, six enrichment pathways were identified in Arabidopsis and other species. According to the results, there is a high degree of similarity between the CYP proteins of different species in seed plants and other organisms, so they should come from a common ancestor. In this study, the network analysis of CYP3A4 and CYP2D6 in seedlings and other organisms showed the similarity of these proteins in different families. The data obtained was the networking of the function and evolution of proteins in seedlings.. The study also concluded that the interaction of phytochemical networks with proteins can be used as potential therapeutic drug candidates for the prevention of diabetes.

Conflict of interest

None declared

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