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Exploring the Antidiabetic Potency of Phytochemicals of *Acacia arabica*– A Molecular Docking Approach

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Abstract: Diabetes mellitus (DM) is a metabolic disease that is concerned with the increased sugar level in the blood. Recent studies show that diabetes affects 643 million humans and is one of the most common chronic diseases that lead to complications in human health. In the present work, an attempt has been made to investigate the binding of phytochemicals derived from *Acacia arabica* in inhibiting oxidoreductase, alpha-amylase, and aldose reductase proteins to control Diabetes mellitus. Molecular docking studies have been carried out for 18 phytochemicals derived from Acacia arabica against the oxidoreductase, alpha-amylase, and aldose reductase proteins using AutoDock 4.2. An analysis of binding affinity, intermolecular interactions such as hydrogen bonding and hydrophobic contacts, and drug-likeness properties for all 18 phytochemicals have been carried out. It is found that the Catachin 5-gallate binds perfectly to the three proteins under study, viz oxidoreductase, alpha-amylase, and aldose reductase proteins, and have binding energies of -7.70, -10.0, and -13.90 kcal/mol respectively. The obtained results can be used to design a molecule that inhibits the proteins related to the causing of Diabetes mellitus.

Keywords: molecular docking; phytochemicals; *Acacia arabica*; oxidoreductase; alpha-amylase; aldose reductase; Diabetes mellitus.

1. Introduction

According to the data from the International Diabetes Federation (2021), diabetes has become a global burden to all, irrespective of age, gender, or geographical region. By the end of this decade, IDF projections show that there will be an increase in the affected population by 46%, and the numbers are most likely to hit 643 million by 2030 and 783 million by 2045. [1, 2]. Diabetes mellitus is a metabolic disorder caused by the loss of glucose homeostasis with disturbances occurring in carbohydrate, fat, and protein metabolism. These are caused by defects in insulin secretion, insulin action, or both [3]. Diabetes is a key factor and a co-disease for dangerous diseases such as kidney failure, diabetic neuropathy, hearing loss, heart attacks, stroke, blindness, depression, and dementia. Different types of Diabetes mellitus are type 1, type 2, maturity-onset diabetes of the young (MODY), gestational diabetes, and neonatal diabetes [4]. Diabetes is a condition that happens when blood sugar is too high, and more precisely, it develops when the pancreas doesn't make enough insulin or when the body is not responding to the effects of insulin properly [5].

Acacia arabica belongs to the leguminosae-mimosaceae family, sometimes referred to as babul, kikar, Indian gum, and Arabic gum. It is a multipurpose tree that is well-known around the world and has numerous applications. It is abundantly found in arid and semi-arid regions of the globe. It has been demonstrated that *Acacia arabica* works well as a medication to cure malaria, toothaches, diabetes, and sore throats [6-8]. Naturally occurring phytochemicals have various types of biological activity such as anti-inflammatory, anti-ulcer, Antibiotic, anti-viral, anti-cancer, and anti-diabetic activities. The hypoglycemic, antihyperglycemic activity [9], anti-fertility, antiplasmodial, and anti-HIV protease properties of *Acacia arabica* were also evaluated [10-13]. In vitro, antibacterial, antimicrobial, and immunomodulatory activities were also studied in detail. It is widely used to cure a wide range of illnesses, including leucoderma, biliousness, diarrhea, bronchitis, colds, and dysentery [14,15]. Phytochemicals from *Acacia arabica* showed good in vivo antidiabetic activity in alloxan-induced diabetic rats. Discovering novel drugs with enhanced efficiency for the diseases mentioned above is a complicated and time-consuming process. Modern drug discovery is mainly based on in silico and chemical-biological approaches. The use of computers in drug discovery and development is rapidly gaining popularity in recent days [16,17]. Hence, work was designed to check for the human system's antidiabetic activity of such phytochemicals. In order to carry out the work, a much-needed theoretical complement can be provided by molecular modeling, especially molecular docking.

Molecular docking is a structure-based technique that allows one to find the best match between two molecules, a macromolecule and a ligand (small molecule). It is a method that predicts the appropriate orientation of one molecule to a second when bound to each other to form a stable complex [18,19]. In turn, knowledge of the appropriate orientation may be used to predict the strength of association or binding affinity between two molecules [20,21]. To perform molecular dock screening, the first requirement is a three-dimensional structure of the protein (macromolecule), and the required structure has been determined using x-ray crystallography, NMR spectroscopy, cryo-electron microscopy, and homology modeling as well. The protein structure and a database of potential ligands (small molecules) are inputs to a docking program. The success of a docking program depends on two components: the search algorithm and the scoring function. The main aim of molecular docking is to computationally simulate the molecular identification process and accomplish an optimized conformation so that the free energy of the overall system is minimized [22-24].

Molecular docking is an attractive scaffold for understanding the drug-receptor interaction for rational drug design and discovery. It is one of the mechanistic studies that involves placing a molecule into the preferred binding site of the protein, especially in a non-covalent fashion, to form a stable complex of potential efficacy with enhanced specificity [25]. The information obtained from the molecular docking can be used to suggest the non-bonded interactions, binding free energy, and stability of protein-ligand complexes [26-28]. Currently, the docking technique is utilized to predict the tentative binding parameters of protein-ligand complexes with less binding energy for the optimized conformation [29,30]. Two approaches are particularly popular within the molecular docking community: the matching technique, which describes the protein and the ligand as complementary surfaces, and the second one simulates the actual docking process in which the ligand-protein pairwise interaction energies are calculated [31,32].

In the present study, we have selected 18 phytochemicals of *Acacia arabica* for docking at the binding site of the oxidoreductase, alpha-amylase, and aldose reductase enzymes to find

out the potential phytochemical, which can inhibit the diabetic enzymes and lead to design a compound in the development of a new anti-diabetic drug. ADME studies on phytochemicals are also theoretically carried out.

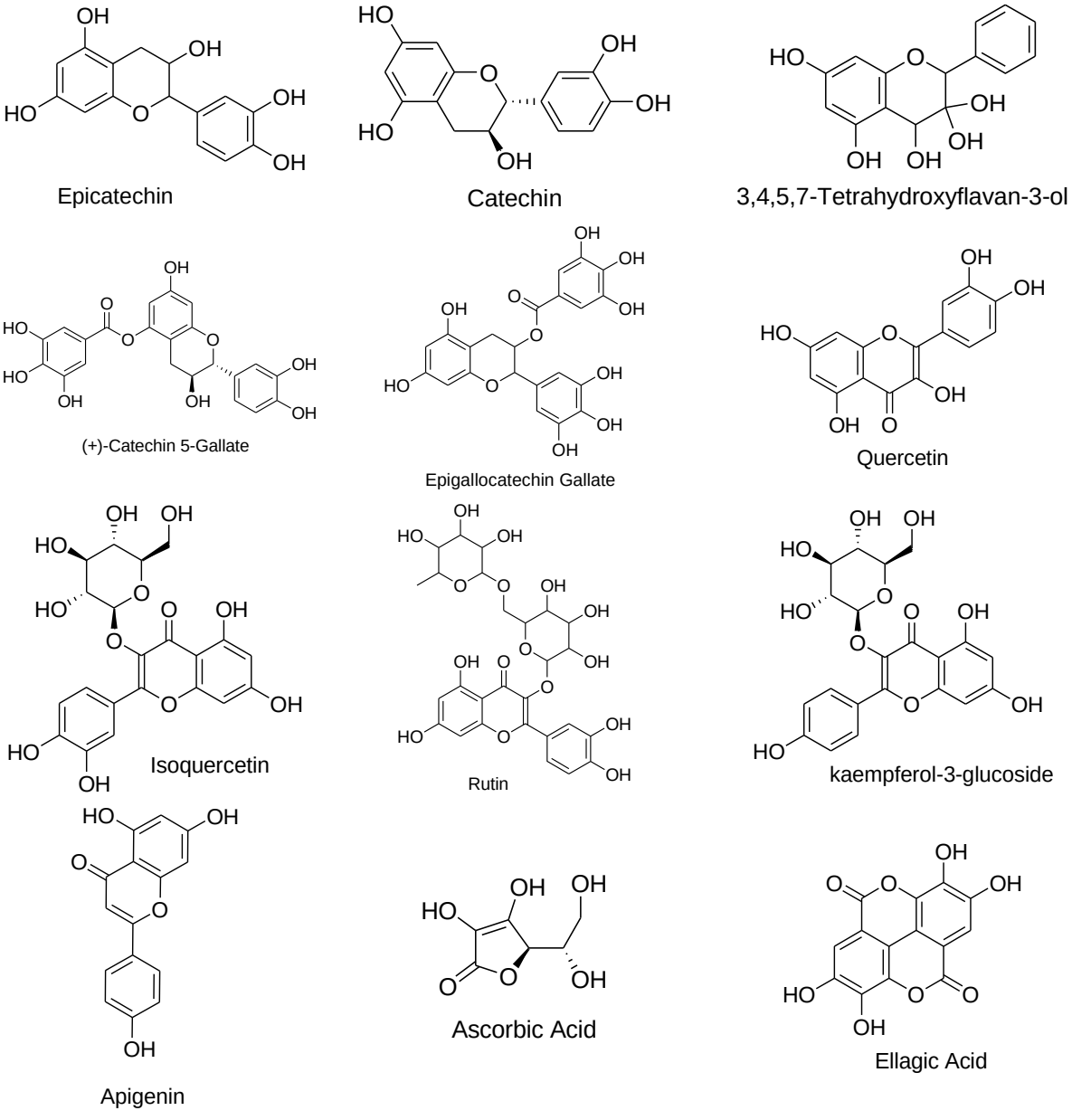
2. Materials and Methods

2.1. Software.

AutoDockTools-1.5.6 software (Scripps Research Institute) [33,34], Discovery Studio 4.0 client (Accelrys), and DruLiTo (NIPER).

2.2. Ligand generation.

The two-dimensional (2D) chemical structures of the selected flavonoids were obtained from PubChem data bank and energy minimized using MMFF94, then saved as a PDB file. The 2D structures of selected 18 phytochemicals of *Acacia arabica* are shown in Figure 1.



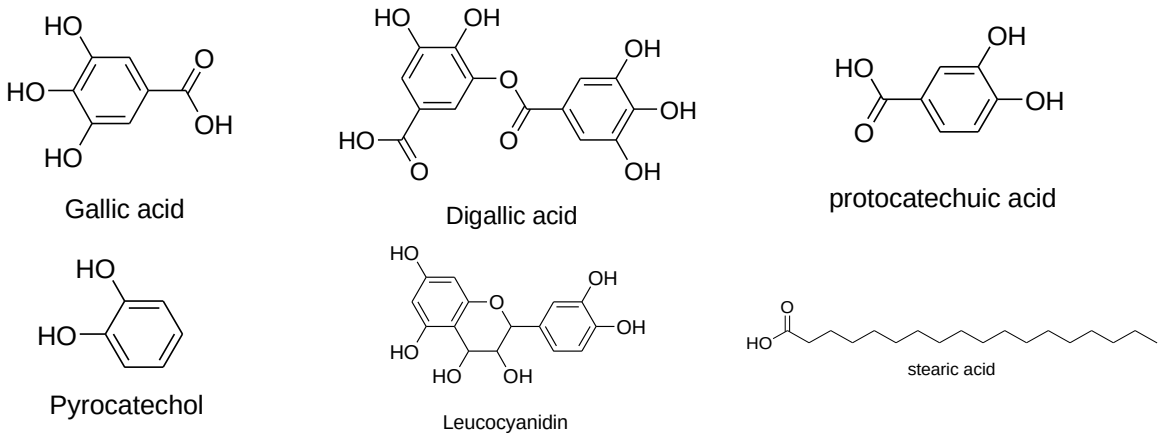


Figure 1. List of selected phytochemicals from *Acacia arabica*.

The 18 phytochemicals derived from *Acacia arabica* that is used in this study are (-) epicatechin (Pubchem id:72276), (-) epigallocatechin gallate (65064), (+) catechin (9064), (+) catechin-5-gallate (5276454), 3,4,5,7-tetrahydroxyflavan-3-ol (70700187), apigenin (5280443), ascorbic acid (54670067), ellagic acid (5281855), gallic acid (370), isoquercetin (5280804), kaempferol-3-glucoside (5282102), leucocyanidin (71629), m-digallic acid (341), protocatechuic acid (72), pyrocatechol (289), quercetin (5280343), rutin (5280805) and stearic acid (5281).

2.3. Preparation of oxidoreductase protein.

The three-dimensional structure of Oxidoreductase protein (FabG4 3-oxoacyl-(Acyl-carrier-protein) reductase: was obtained from the protein data bank [35] with PDB Code 3Q6I and its resolution is 2.59 Å. The ‘C’ and ‘D’ chains of 3Q6I are constituted of 21 and 30 amino acids, respectively. The chain ‘D’ was chosen for docking study since it contains the amino acids interacting with ligands such as nicotinamide-adenine-dinucleotide (QQ731). The docking site on the protein target was defined by establishing a grid box with the dimensions of 30:30:30 Å, centered at X: -11.926 Y: 17.308 Z: 1.396 Å.

2.4. Preparation of alpha-amylase protein.

The three-dimensional structure of Alpha-Amylase protein was obtained from the protein data bank with PDB code 1PPI with a resolution of 2.20 Å. The ‘A’ chain of 1PPI is constituted of 496 amino acids. The protein contains ligands such as Alpha-D-Glucopyranose (GLC1), Beta-D-Glucopyranose (BGC1), and Enopyranose (DAF2). The docking site on the protein target was defined by establishing a grid box with the dimensions of 66:60:60 Å, centered at X: 13.14 Y: 43.327 Z: 16.569Å.

2.5. Preparation of aldose reductase protein.

The protein data bank accession code for the three-dimensional structure of Aldose reductase is 3G5E with a resolution of 1.80 Å. The ‘A’ chain of 3G5E is constituted of 316 amino acids. The protein contains ligands such as Dihydro-Nicotinamide-Adenine-Dinucleotide Phosphate (NDP318). The docking site on the protein target was defined by establishing a grid box with the dimensions of 50:50:50 Å, centered at X: 14.243 Y: 0.074 Z: 23.805 Å.

2.6. Molecular docking studies.

For all three proteins, a similar preparation procedure has been followed. AutoDockTools-1.5.6 software [36-39] was used to load the proteins to create a PDBQT file that is free from water molecules and natural ligands. The best structure with the lowest docked energy was chosen after the docking search was completed. Nine runs with AutoDockTools-1.5.6 were performed in each case per each ligand structure, and for each run, the best pose was recorded. The intermolecular interactions of 3Q6I, 1PPI, and 3G5E proteins, along with all the ligands under study, including hydrogen bonds and hydrophobic interactions, were analyzed using Discovery Studio 4.0 client. Binding mode analysis and interaction analysis of three proteins with selected phytochemicals were performed using AutoDockTools-1.5.6 software.

2.7. ADME analysis.

The physiochemical features of the selected 18 phytochemicals of the *Acacia arabica* plant were evaluated using the DruLiTo software to assess absorption, distribution, metabolism, and excretion [40]. The ADME studies were done using Lipinski's rule. Lipinski's rule of five is an important rule for the evaluation of drug-like properties of a compound that can be orally used in humans for treatment against disease. This rule addresses the compound's molecular weight, log P, and the proper number of hydrogen bonds between the donor and acceptor [41].

3. Results and Discussion

Molecular Docking studies were performed to obtain the number of possible orientations for the ligand at the binding site of proteins because docking of small molecule compounds into the binding site of a receptor and estimating the binding affinity of the complex is instrumental for the structure-based drug design. AutoDockTools-1.5.6 is an open-source program for drug discovery, molecular docking, and virtual screening, offering multicore capability, high performance, enhanced accuracy, and ease of use. The parameters chosen for the docking can be judged by the docking tool's ability to reproduce the binding mode of a ligand to a protein when the structure of the protein-ligand complex is known. The nine different orientations of the selected 18 compounds to the three different proteins viz 3Q6I, 1PPI, and 3G5E were carried out. The binding energy of the best orientation of the compounds is presented in Table 1.

The active site of the target protein shows the maximum number of interactions with the protein and ligands. The complete data set was docked and found to bind at the same active site position. Amino acids are intimately involved in the binding of ligands to proteins and form a complex. Intermolecular interactions such as hydrogen bonding and hydrophobic interactions are predominant in stabilizing energetically-favored ligands in an open conformational environment of protein structures. The significant interactions were identified after an in-depth analysis of amino acids in the active site of the target protein and atoms of the ligand compounds. The identified interactions are tabulated (Table 2-7) and include hydrogen and hydrophobic interactions of the best orientations, as shown in Figure 2-4.

Table 1. The binding affinity of selected phytochemicals of *Acacia arabica* with FabG4 3-oxoacyl-(Acyl-carrier-protein) reductase, alpha-amylase, and aldose reductase.

Compounds	Binding Energy (Kcal/mol)		
	FabG4 3-oxoacyl-(Acyl- carrier protein) reductase (3Q6E)	Alpha-amylase (1PPI)	Aldose reductase (3G5 E)
(-) Epicatechin	**-7.7**	**-9.5**	-11.1
(-) Epigallocatechingallate	**-7.8**	-8.9	-11.0
(+) Catechin	-7.1	-9.0	-11.2
(+) Catechin-5-gallate	**-7.7**	**-10.0**	**-13.9**
3,4,5,7-tetrahydroxyflavan-3-ol	-6.7	-8.2	**-13.2**
Apigenin	-7.3	**-9.5**	**-11.9**
Ascorbic acid	-4.6	-5.8	-11.4
Ellagic acid	-6.8	-8.5	-6.5
Gallic acid	-5.3	-5.8	**-12.5**
Isoquercetin	-7.1	-9.0	-7.6
Kaempferol-3-glucoside	-6.9	-8.9	-10.9
Leucocyanidin	-7.5	-8.9	-10.8
m-Digallic acid	-6.8	-8.0	-10.7
Protocatechuic acid	-5.3	-5.6	-7.6
Pyrocatechol	-4.3	-5.0	-6.4
Quercetin	**-7.9**	**-9.5**	-11.3
Rutin	-6.9	**-9.8**	-11.2
Stearic acid	-3.7	-4.7	-7.5
Natural ligands	-8.3(QQ731)	-9.2(GLC1, BGC1, DAF2)	-8.4(NDP318)

(+) Catechin-5-gallate showed the best binding affinity in all three enzymes. (-) epicatechin and quercetin showed the best binding affinity with oxidoreductase and alpha-amylase. Flavonoids, alkaloids, phenolics, sterols, and triterpenoids are recognized as bioactive antidiabetic agents [42]. Flavonoids can repair the damaged beta cells in alloxan diabetes rats, is reported [43]. Phenolics are found to be effective antihyperglycemic agents [44]. The previous studies showed that Gallic acid, pyrocatechol, (+)-catechin, (-) epigallocatechin-7-gallate, (-) epicatechin, quercetin, (+) catechin-5-gallate are the active principles for the anti-diabetic activity of *Acacia arabica* which act as secretagouge to release insulin [45]. Based on the evidence acquired from the literature, it is proved that *Acacia arabica* exerts their anti-diabetic action through a variety of mechanisms. A single herb can have numerous mechanisms of action, as the literature makes clear. These include the regeneration of pancreatic β cells, inhibition of the enzyme α-glucosidase, insulin production, and PPAR-γ ligand binding activity because the herb contains a range of phytoconstituents. This may, therefore, result in synergistic actions that lessen the effectiveness of hyperglycemia.

Table 2. Hydrogen bonding interactions of selected phytochemicals of *Acacia arabica* with FabG4 3-oxoacyl-(Acyl-carrier protein) reductase.

Name of the compounds	Interacting atoms of compounds	Interacting amino acids	Atoms of interacting amino acids	Distance (Å)
(-) Epicatechin	H	HIS5	O	2.02
(-)Epigallocatechingallate	H	HIS5	O	2.58
	H	CYS7	O	2.06
	H	CYS7	O	2.31
(+) Catechin	O	CYS7	HN	2.18
	H	HIS5	O	1.91
	H	CYS7	O	2.42
	O	THR8	O	2.52
(+) Catechin-5-gallate	H	PHE1	O	1.99
	O	ASN3	HD22	2.39
	H	HIS5	HE2	2.57
3,4,5,7-Tetrahydroxyflavan-3-ol	No interaction	-	-	-
Apigenin	H	CYS7	O	3.00
	H	THR8	O	2.55
Ascorbic acid	H	PHE1	O	1.84

Name of the compounds	Interacting atoms of compounds	Interacting amino acids	Atoms of interacting amino acids	Distance (Å)
	H	VAL2	O	3.01
	H	HIS5	O	2.05
	O	CYS7	HN	2.14
Ellagic acid	H	THR8	O	2.85
	H	CYS7	SG	2.68
Gallic acid	O	CYS7	HN	1.98
	H	HIS5	O	1.95
	H	PHE1	O	2.15
Isoquercetin	O	CYS7	HN	2.24
	H	CYS7	O	2.33
Kaempferol-3-glucoside	O	ASN3	HD21	2.44
	O	CYS7	HN	2.20
Leucocyanidin	O	CYS7	HN	2.31
	H	CYS7	O	2.21
m-Digallic acid	O	CYS7	HN	1.98
	H	HIS5	O	2.36
Protocatechuic acid	O	CYS7	HN	1.90
	H	VAL2	O	2.38
	H	HIS5	O	1.98
Pyrocatechol	O	CYS7	HN	1.90
	H	VAL2	O	2.38
	H	HIS5	O	1.98
	H	HIS5	O	1.92
Quercetin	O	CYS7	HN	2.22
	H	PHE1	O	2.12
	H	THR8	O	2.77
Rutin	O	CYS7	HN	2.25
	H	HIS5	O	2.23
	H	PHE1	O	2.09
Stearic acid	O	GLN4	HE22	2.59
Natural ligand(QQ731)	O13	LEU13	HN	2.08

The amino acid residues that are significant for binding interaction and thus comprising the binding pocket of the target protein are HIS5, CYS7, THR8, PHE1, GLN4, VAL2, HIS10, ASN3, ALA14, GLN4, ILE10, LEU6, CYS11, THR8, GLY8, LEU13, LEU16, and LEU17. These are the important amino acids present in the binding pocket of protein. The standard natural ligand QQ731 interacted with LEU13 amino acid. Interaction of the drug molecules shown in Table 2 such as (-)-Epicatechin interacts with the prominent amino acid HIS5 and (-)-Epigallocatechingallate with two amino acids HIS5 and CYS7, (+) Catechin-5- gallate with three amino acids PHE1, ASN3 and HIS5 and Quercetin with three amino acids such as CYS7, THR8, and PHE1.

Table 3. Hydrophobic interactions of selected phytochemicals of *Acacia arabica* with FabG4 3-oxoacyl-(acyl-carrier-protein) reductase.

Compound	Active site amino acid interactions (Distance in Å)
(-) Epicatechin	HIS5 (3.76, 4.19), VAL2 (5.21), CYS7 (4.24)
(-)Epigallocatechingallate	HIS5 (3.77, 4.16), VAL2 (5.20), CYS7 (4.24)
(+) Catechin	HIS5 (4.03), VAL2 (5.36), CYS7 (3.53)
(+) Catechin-5-gallate	HIS5 (3.70, 4.70), VAL2 (5.09), CYS7 (4.48)
3,4,5,7- tetrahydroxyflavan-3-ol	HIS5 (3.72), VAL2 (5.42), CYS7 (3.68)
Apigenin	HIS5 (4.63, 3.71), VAL2 (5.13), CYS7 (5.19)
Ascorbic acid	----
Ellagic acid	HIS5 (3.89, 4.07, 3.90, 4.73)
Gallic acid	VAL2 (4.95), CY7 (3.85)
Isoquercetin	HIS5 (4.39, 5.11), VAL5 (5.28), CYS7 (3.72)
Kaempferol-3-glucoside	HIS5 (5.54, 3.69), VAL2 (4.68), CYS7 (4.94, 4.26)
Leucocyanidin	HIS5 (3.68), VAL2 (5.43), CYS7 (3.56)
m-Digallic acid	HIS5 (3.95), VAL2 (4.95), CYS7 (3.92)
Protocatechuic acid	VAL2 (4.97), CYS7 (3.84)
Pyrocatechol	VAL2 (3.89), CYS7 (4.35)
Quercetin	HIS5 (4.22, 3.66), VAL2 (5.28), CYS7 (3.57)

Compound	Active site amino acid interactions (Distance in Å)
Rutin	HI5 (4.39, 5.11), VAL2 (5.28), CYS7 (3.73)
Stearic acid	LEU (5.29), LEU17 (5.36), HIS10 (4.56), ALA14 (3.71)
Natural ligand (QQ731)	HIS10 (5.12), LEU17 (5.15), LEU17 (5.43)

The compounds (-)-epicatechin, (-)-epigallocatechingallate, (+)-catechin-5-gallate, and quercetin show four hydrophobic interactions each and have the highest binding affinities of -7.7, -7.8, -7.7 and -7.9 Kcal/mol respectively. The standard natural ligand QQ731 shows four hydrophobic interactions. It may be due to the binding site having more hydrophobic amino acids than hydrophilic amino acids. The contribution of hydrophobic interaction is predominant compared to the hydrogen bonding interactions involved in the protein-ligand complexes. The protein-ligand interactions are shown in Figure 2.

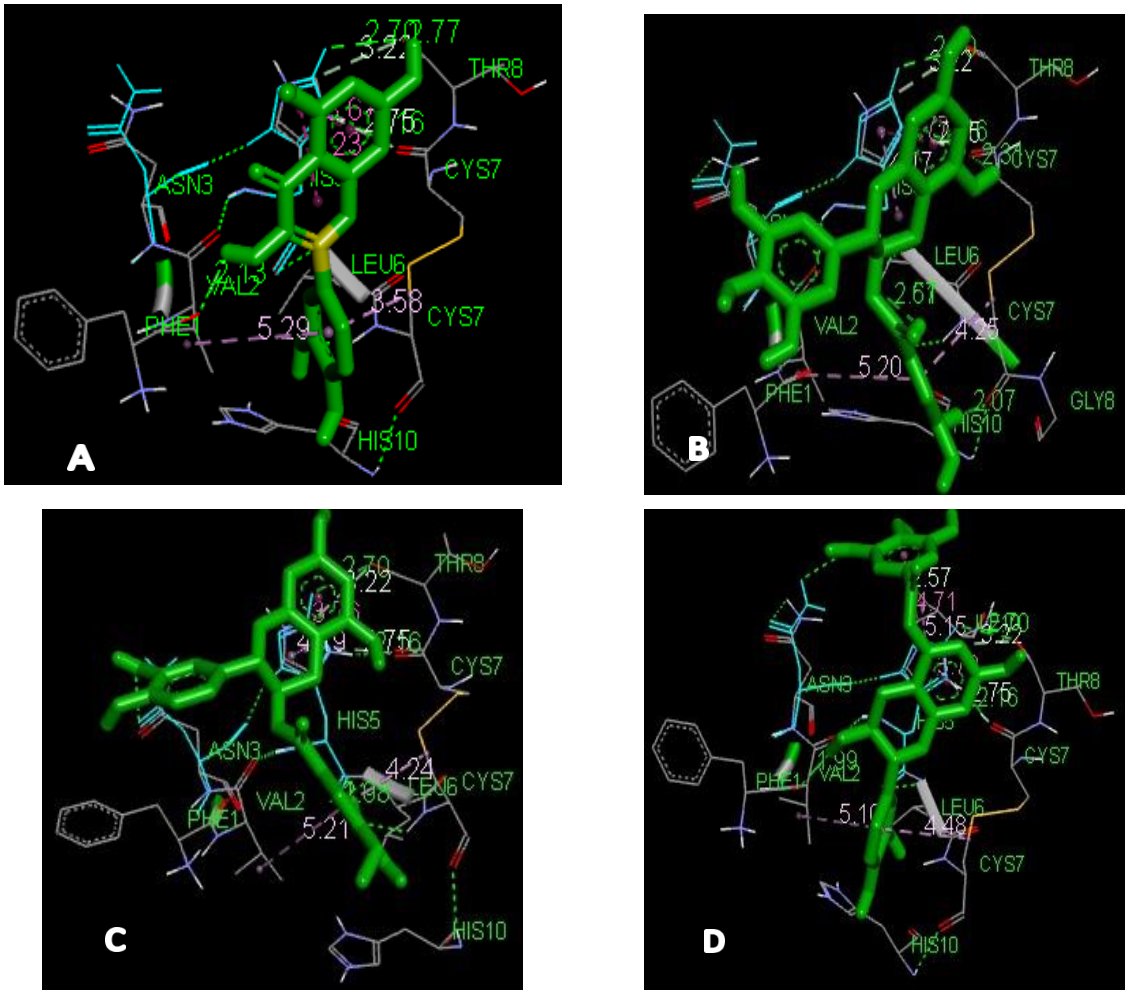


Figure 2. Binding orientation of most active phytochemicals and protein (FabG4 3-oxoacyl-(Acyl-carrier-protein) reductase) interactions are shown in the above figure. **(A)** Quercetin; **(B)** (-) Epigallocatechingallate; **(C)** (-) Epicatechin; **(D)** (+) Catechin-5-gallate.

Table 4. Hydrogen bonding interactions of selected phytochemicals of *Acacia arabica* with alpha-amylase (1PPI).

Compound	Atoms of compound involving interaction	Amino acid residue involving interaction	Atom amino acid residue involving interaction	Distance (Å)
(-)Epicatechin	O7	ARG195	HH11	2.78
	O2	HIS305	HD1	2.03
	H47	ASP197	OD1	2.28
	H47	GLU233	OE1	2.57
	H49	GLU233	OE2	2.65
	H49	ASP300	OD2	2.40
(-) Epigallocatechingallate	O11	TYR151	HH	2.46
	O8	ARG195	HH11	2.45

Compound	Atoms of compound involving interaction	Amino acid residue involving interaction	Atom amino acid residue involving interaction	Distance (Å)
	O8	ARG195	HH21	2.34
	O6	HIS299	HE2	1.87
	O2	HIS305	HD1	2.23
	O7	HIS305	HD1	2.48
	H46	GLU233	OE1	2.08
	H46	GLU233	OE2	2.16
	H48	GLU233	OE1	2.19
	H48	GLU233	OE2	2.40
(+) Catechin	H34	ASP197	OD1	2.28
	H34	ASP197	OD2	2.12
(+) Catechin-5-gallate	H44	ASP197	OD2	2.13
3,4,5,7-tetrahydroxyflavan-3-ol	H34	ASP300	OD1	2.17
	H35	ASP197	OD2	2.03
Apigenin	O5	ARG195	HH21	2.35
	H30	ASP197	OD1	2.14
	O3	GLN63	HE21	2.59
	H30	ASP197	OD1	2.14
Ascorbic acid	O4	GLY304	HN	2.65
	H18	ASP317	OD2	1.88
	H20	ASP317	OD2	1.96
Ellagic acid	O2	ARG346	HH11	2.38
	H27	ARG303	O	3.06
	H27	ASP356	OD2	2.04
	H28	SER310	O	2.18
Gallic acid	O1	ARG267	HH21	2.33
	O5	GLY304	HN	2.80
	H15	ASP317	OD1	2.96
	H18	ASN301	O	2.27
	H17	SER310	O	1.83
Isoquercetin	O12	ARG195	HH21	1.88
	O2	HIS305	HD1	1.93
	O5	HIS305	HD1	2.45
	O8	HIS305	HD1	2.71
	H52	GLU233	OE1	2.58
	H44	ASP300	OD2	2.74
Kaempferol-3- glucoside	O2	HIS305	HD1	1.95
	O8	HIS305	HD1	2.93
	O5	HIS305	HD1	2.49
Leucocyanidin	H35	GLU233	OE1	2.86
m-Digallic acid	O2	GLN63	HE21	2.74
	O3	GLN63	HE21	2.60
	O6	ARG195	HH21	2.42
	O9	HIS305	HD1	2.99
	H31	ASP300	OD1	2.07
	H32	ASP300	OD2	2.62
	H30	GLU233	OE1	2.92
Protocatechuic acid	O1	ARG267	HH21	2.76
	O4	GLY304	HN	2.86
Pyrocatechol	O1	ARG195	HH21	2.05
	H14	ASP197	OD1	2.26
	H14	GLU233	OE1	2.57
Quercetin	O4	GLN63	HE21	2.47
	H31	ASP197	OD2	2.13
	H31	ASP197	OD2	2.21
Rutin	O9	GLN63	HE21	2.65
	H61	GLU233	OE2	2.35
	H61	ASP300	OD2	2.98
	H59	ASP300	OD1	2.21
Stearic acid	-	-	-	-
Natural ligand (GLC1, BGC1, DAF2)	O2	GLY306	O	3.15
	N4	GLY304	O	3.36
	O6	ASP353	OD2	3.25
	O4	HIS30	HD1	2.56
	O2	HIS305	HD1	1.96
	O2	GLY306	HN	2.89
	O3	GLY306	HN	1.87
	O1	THR314	HG1	2.55
	O5	ARG346	HH11	2.40

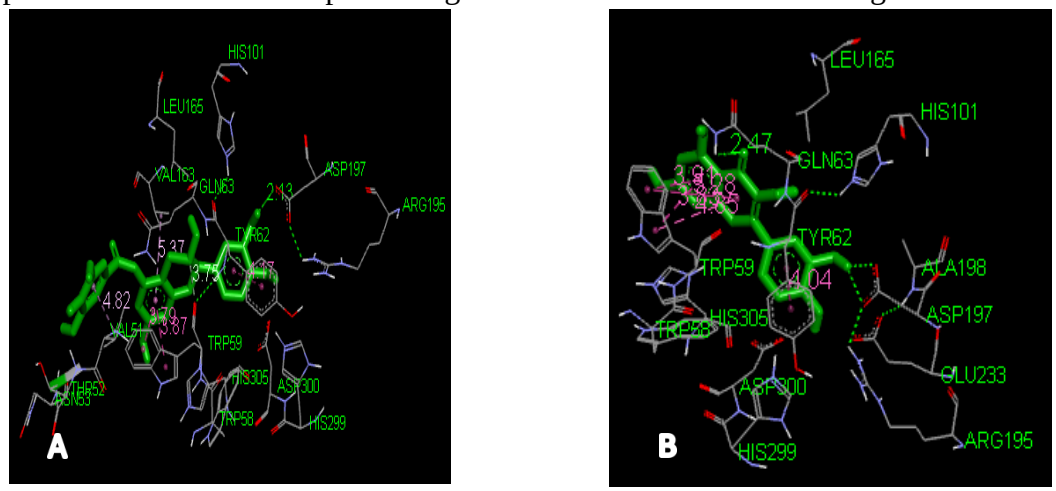
Compound	Atoms of compound involving interaction	Amino acid residue involving interaction	Atom amino acid residue involving interaction	Distance (Å)
	O1	ARG346	HH12	2.66
	O5	ASP353	HN	2.34

The important interacting amino acid residues present on the active site of the 1PPI protein were ASP19, ASP13, ASP356, ASP300, GLU233, GLN63, GLY304, HIS201, HIS305, TYR62, TYR151, ARG195, ARG303 and SER310 [46]. These are the amino acids that prominently contribute to the binding of protein-ligand complexes. Interaction of the drug molecules along with standard natural ligands shown in Table 4 such as natural ligand (GLC1, BGC1, DAF2) interacted with eleven amino acids, Catechin-5-gallate were found to interact with ASP197 amino acid, apigenin interacted with four amino acids such as ASP197, ASP197, ARG195, and GLN63, quercetin interacted with three amino acids like GLN63, ASP197 and ASP197 and Rutin interacted with four amino acids GLN63, GLU233, ASP300 and ASP300.

Table 5. Hydrophobic interactions of selected phytochemicals of *Acacia arabica* with alpha-amylase (1PPI).

Compound	Active site amino acid interactions (Distance Å)
(-) Epicatechin	VAL163 (3.43, 4.91), LEU165 (5.47)
(-) Epigallocatechingallate	VAL163 (3.47, 4.81), LEU162 (5.48)
(+) Catechin	TRP59 (3.81, 3.83), TYR62 (4.13)
(+) Catechin-5-gallate	TRP59 (3.87, 3.793), TYR62 (4.17), VAL163 (5.36, 4.81)
3,4,5,7- tetrahydroxyflavan-3-ol	TRP59 (5.54, 4.76), TYR62 (4.74), VAL163 (4.87), LEU165 (5.40)
Apigenin	TRP59 (4.92, 3.80, 5.42, 4.0), TYR62 (3.93)
Isoquercetin	TYR62 (4.23), VAL163 (3.42, 4.96)
Kaempferol-3-glucoside	TYR62 (4.05), VAL163 (3.43, 4.82), LEU165 (5.30)
Leucocyanidin	TRP59 (4.93, 5.17), VAL163 (4.90), LEU165 (5.42)
m-Digallic acid	TRP59 (4.32, 4.45), TYR62 (4.50), VAL163 (5.01)
Quercetin	TRP59 (4.85, 3.82, 5.27, 3.91), TYR62 (4.03)
Rutin	TRP59 (3.51, 4.06), TYR151 (4.84), VAL163 (4.89), HIS305 (5.12), LEU162 (5.11), ILE235 (4.65)
Stearic acid	LEU162 (5.15)

The compounds (+) catechin-5-gallate and quercetin show five hydrophobic interactions having the highest binding affinities (-10.0) and (-9.5) Kcal/mol, respectively. Similarly, rutin and apigenin show seven and four hydrophobic interactions, each having the highest binding affinities, -9.8 and -9.5 Kcal/mol, respectively. Since hydrogen bonding and hydrophobic interactions are major contributors to binding affinity, the standard natural ligands (GLC1, BGC1, DAF2) have no hydrophobic interactions. Thus, hydrogen bonding interactions were predominant in the four compounds, showing the highest binding affinities towards the target proteins. The binding site has more hydrophilic amino acids than hydrophobic amino acids. The protein-ligand interactions are shown in Figure 3.



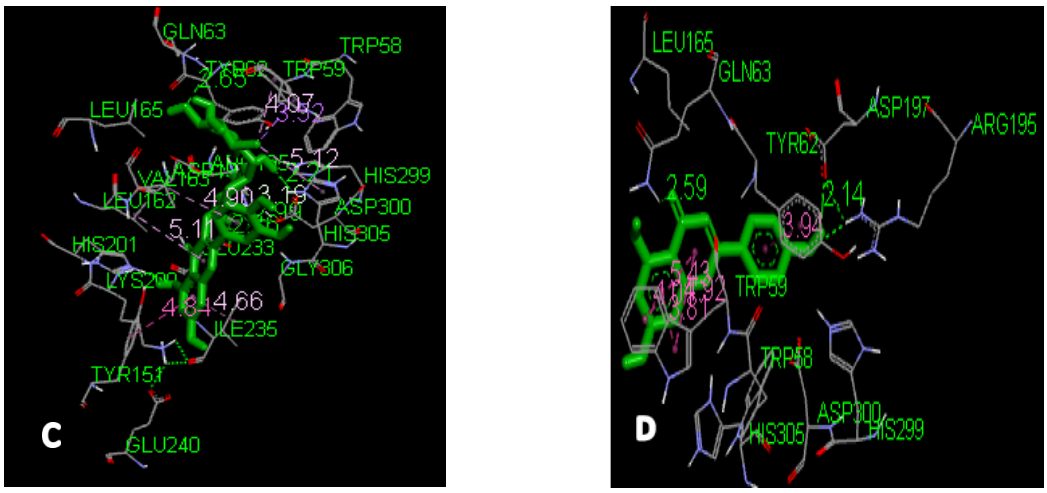


Figure 3. The binding orientation of most active phytochemicals and protein (Alpha-Amylae (1PPI)) interactions are shown in the above figure: **(A)** (+) Catechin- 5-gallate; **(B)** Quercetin; **(C)** Rutin; **(D)** Apigenin.

Table 6. Hydrogen bonding interactions of selected phytochemicals of *Acacia arabica* with aldose reductase (3G5E).

Compounds	Atoms of compound involving interaction	Amino acid residue involving interaction	Atom amino acid residue involving interaction	Distance (Å)
(-) Epicatechin	O	HIS110	HE2	2.11
	O	TRP11	HE1	2.18
	O	ALA299	N	2.92
(-) Epigallocateching allate	O	HIS110	HE2	2.78
	O	HIS110	HE2	2.26
	O	TRP111	HE1	2.03
	O	CYS298	SG	3.39
	O	LEU300	HN	2.96
(+) Catechin	O	LYS21	HZ1	2.24
	O	LY2S62	HN	2.09
	O	ASP43	OD2	3.03
	O	TYR48	OH	2.98
	O	ILE260	O	3.04
	O	SER214	OG	3.17
	O	ASP216	OD1	2.92
(+) Catechin-5- gallate	O	THR19	HN	2.57
	O	LYS21	HZ1	2.11
	O	TRP111	HE1	2.99
	O	SER159	HG	2.52
	O	ASN160	HD2	2.93
	O	ASN160	HD2	2.08
	O	SER210	HN	2.05
	O	LYS262	HN	2.04
	O	GLN183	OE1	3.30
	O	ASP43	OD2	3.09
	O	SER214	OG	2.97
3,4,5,7-tetrahydroxyflava n-3-ol	H	ASP43	OD2	2.68
	H	GLN183	OE1	2.89
Apigenin	O	TH919	HN	2.17
	O	TRP20	HN	2.12
	O	ASN160	HD22	2.35
	O	SER210	HN	2.53
	O	SER210	HN	2.89
	O	SER210	OG	2.76
Ascorbic acid	O	SER210	HN	2.92
	O	LYS262	HN	2.03
	O	LYS262	HN	2.74
	O	ASP43	OD2	3.07
	O	TYR48	OH	2.97
	O	ILE260	O	2.99
	O	SER214	OG	3.09
	O	ASP216	OD1	2.86
	O	ILE260	O	2.72

Compounds	Atoms of compound involving interaction	Amino acid residue involving interaction	Atom amino acid residue involving interaction	Distance (Å)
Ellagic acid	O	THR19	HN	2.93
	O	TRP20	HN	2.14
	O	LYS21	HZ1	2.13
	O	SER210	HN	2.06
	O	SER214	OG	3.02
	O	SER210	OG	2.82
Gallic acid	O	LEU300	HN	2.17
Isoquercetin	O	CYS80	SG	3.63
	O	LEU300	HN	2.28
	O	THR13	OG1	2.91
	O	THR113	OG1	2.87
Kaempferol-3-glucoside	O	ARG217	HH12	2.06
	O	ARG217	HH12	2.20
	O	ARG217	HH22	2.86
	O	LEU22	HN	2.64
	O	LEU227	HN	2.68
	O	LEU228	HN	1.79
	O	LEU212	O	2.97
	O	PRO225	O	3.17
	O	GLY213	O	3.05
	O	PRO22	O	3.10
	O	LYS2215	O	2.73
	O	PRO222	O	3.09
Leucocyanidin	O	ARG217	HH12	2.06
	O	ARG217	HH12	2.22
	O	ARG217	HH22	2.88
	O	LEU227	HN	2.55
	O	LEU227	HN	2.68
	O	LEU228	HN	1.78
	O	LEU212	O	2.93
	O	PRO225	O	3.16
	O	GLY213	O	3.03
	O	PRO225	O	3.11
	O	LYS221	O	2.75
m-Digallic acid	O	THR19	HN	2.46
	O	TRP20	HN	2.01
	O	TYR48	HH	2.65
	O	HIS110	HE2	2.98
	O	SER159	HG	2.68
	O	ASN160	HD22	1.99
	O	SER210	HN	2.52
	O	SER210	HN	2.51
	O	CYS298	SG	3.38
	O	SER210	OG	2.70
	O	GLN183	OE1	2.96
Protocatechuic acid	O	CYS80	SG	3.64
	O	LEU300	HN	2.27
	O	THR113	OG1	2.86
Pyrocatechol	O	THR113	OG1	2.83
Quercetin	O	LYS262	HN	2.69
	O	LYS262	HN	2.03
	O	ILE260	O	2.80
	O	ASP43	OD2	3.21
	O	TYR48	OH	2.97
	O	ILE260	O	3.04
Rutin	O	TYR48	HH	2.14
	O	HIS110	HE2	2.03
	O	TRP111	HE1	2.64
	O	VAL47	O	2.70
	O	VAL47	O	3.22
Stearic acid	O	THR113	OG1	2.72
Natural ligand (NDP318)	O48	ARG3	HE	2.15
	O5	ARG3	HH11	2.42
	O1A	ARG3	HH21	2.37
	O2B	ARG40	HE	2.47
	O1X	ARG40	HE	2.27
	O1X	ARG40	HH22	2.13
	O2X	ARG40	HH22	2.27

The significant interacting amino acid residues present on the active site of 3G5E protein were THR19, TRP20, TYR48, HIS110, SER159, ASN160, SER210, CYS298, VAL47, THR113, TRP111, ILE260, LYS262, LEU300 and GLN183. These are the prominent amino acids present in the binding pocket of protein. Interaction of the drug molecules and standard natural ligand NDP318 shown in Table 6 such as natural ligand NDP318 interacted with seven amino acids, catechin-5-gallate was found to interact with eleven amino acids, 3,4,5,7- tetrahydroxyflavan-3-ol were found to interact with two amino acids, apigenin with six amino acids and gallic acid with one amino acid.

Table 7. Hydrophobic interactions of selected phytochemicals of *Acacia arabica* with aldose reductase (3G5E).

Compound	Active site amino acid interactions Distance (Å)
3,4,5,7-Tetrahydroxyflavan-3-ol	TYR209 (3.73), HIS110 (5.43)
Apigenin	TYP309 (3.70)
Rutin	TRP20 (4.85)
Stearic acid	TRP20 (5.30, 4.65), TYR209 (4.00)
Natural ligand (NDP318)	ARG40 (5.07)

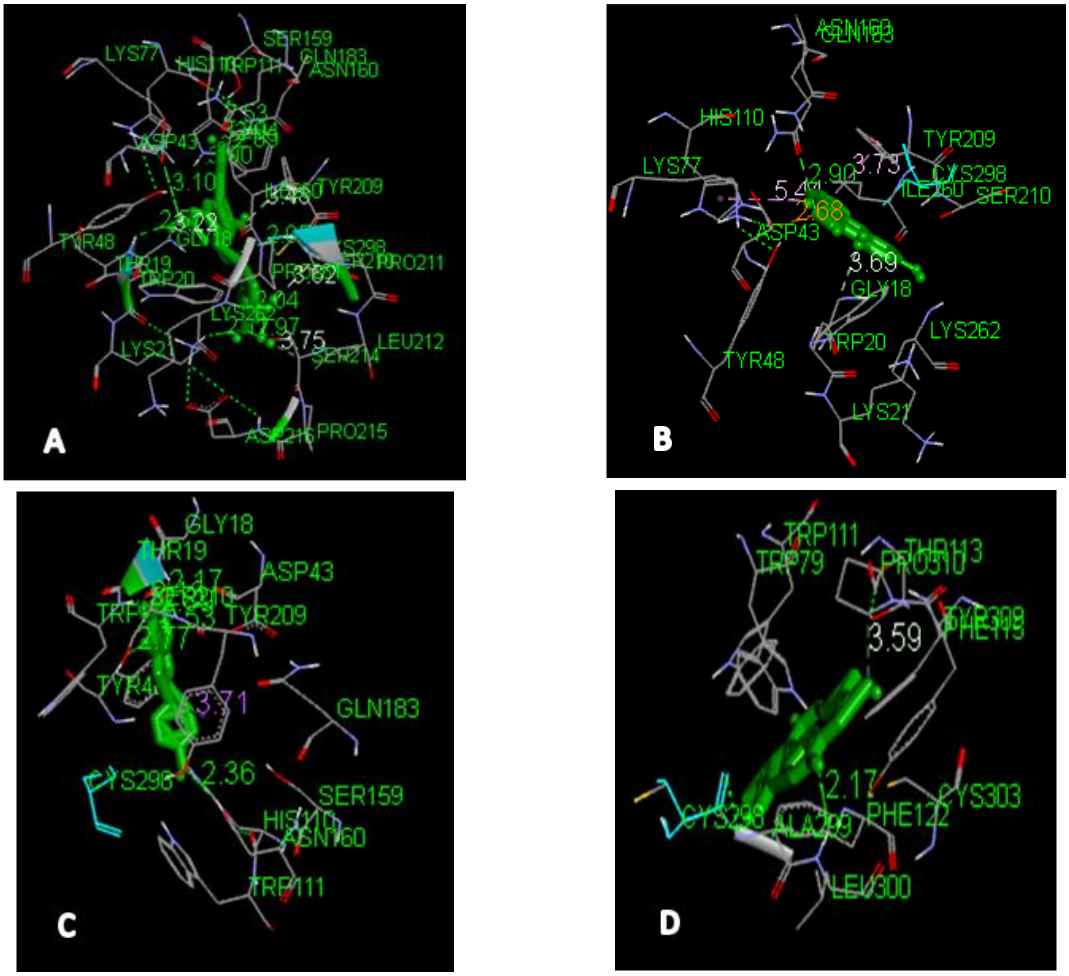


Figure 4. The binding orientation of most active phytochemicals and protein **(**Aldose reductase (3G5E)) interactions are shown in the above figure: **(A)** (+) Catechin-5-gallate; **(B)** 3,4,5,7-tetrahydroxyflavan-3-ol; **(C)** Apigenin; **(D)** Gallic acid.

Natural ligand NDP318 shows one only hydrophobic interaction, and out of the four most interacting compounds, Based on the binding score, the top four phytochemicals catechin-5-gallate (-13.9), 3,4,5,7-tetrahydroxyflavan-3-ol (-13.2), gallic acid (-12.5) and apigenin (-11.9) show hydrogen bonding 11, 2, 1 and 6 respectively. Catechin-5-gallate and gallic acid

didn't show any hydrophobic interactions. Thus, hydrogen bonding interaction was predominant in Catechin-5-gallate and Gallic acid, which made a major contribution toward the target protein. The compounds 3,4,5,7-tetrahydroxyflavan-3-ol and apigenin show two and one hydrophobic interactions, respectively. The overall strengths of these bonds determine the degree of affinity between the drug and the receptor. The protein-ligand interactions are shown in Figure 4. The results indicate that molecular modeling is a valuable tool for predicting the biological activity of selected compounds.

3.1. ADME studies.

18 phytochemicals from the *Acacia arabica* plant were screened for the drug likeliness properties using the DruLiTo software [47]. The results using Lipinski's rule of five are shown in Table 8.

Table 8. ADME studies of phytochemicals of *Acacia arabica.*

Sr. No.	Metabolites	MW	Log P	RB	HBA	HBD	Lipinski
1	3,4,5,7-Tetrahydroxyflavan-3-ol	290.08	0.734	1	6	5	Yes, 0 violation
2	Apigenin	270.05	1.138	1	5	3	Yes, 0 violation
3	Ascorbic acid	176.03	-0.178	2	6	4	Yes, 0 violation
4	(+) Catechin	290.08	0.852	1	6	5	Yes, 0 violation
5	(+) Catechin-5-gallate	442.09	2.087	4	10	7	No, 1 violation, HBD<5.
6	Ellagic Acid	302.01	1.366	0	8	4	Yes, 0 violation
7	(-)Epicatechin	290.08	0.852	1	6	5	Yes, 0 violation
8	Epigallocatechin Gallate	458.08	2.984	4	11	8	No, 2 violation, HBD<5, HBA<10.
9	Gallic acid	170.02	0.964	1	5	4	Yes, 0 violation
10	Isoquercetin	464.1	0.099	4	12	8	No, 2 violation, HBD<5, HBA<10.
11	Kaempferol-3-glucoside	448.1	-0.249	4	11	7	No, 2 violation, HBD<5, HBA<10.
12	Leucocyanidin	306.07	0.517	1	7	6	No, 1 violation, HBD<5
13	m-Digallic acid	322.03	1.77	4	9	6	No, 1 violation, HBD<5.
14	Protocatechuic acid	154.03	0.616	1	4	3	Yes, 0 violation
15	Pyrocatechol	110.04	1.083	0	2	2	Yes, 0 violation
16	Quercetin	302.04	1.834	1	7	5	Yes, 0 violation
17	Rutin	610.15	-0.735	6	16	10	No, 3 violations, MW <500, HBA<10, HBD <5.
18	Stearic acid	284.27	8.708	16	2	1	No, 2 violation, Log P <5, RB <10

MW: molecular weight (<500 Da); Log P: prediction octanol-water partition coefficient(<5); RB: rotable bound (1-10); HBA: hydrogen bond acceptor (<10); bHBD: hydrogen bond donor (<5); TPSA: topological polar surface area (<140 A).

According to Lipinski's rules of five, out of 18 phytochemicals, rutin showed 3 violations, stearic acid, epigallocatechin gallate, isoquercetin, and kaempferol-3-glucoside showed 2 violations, respectively. (+) catechin-5-gallate, leucocyanidin, and m-digallic acid showed 1 violation, respectively. Ascorbic acid, quercetin, gallic acid, (-) epicatechin, (+) catechin, 3,4,5,7-tetrahydroxyflavan-3-ol, apigenin, ellagic acid, protocatechuic acid and pyrocatechol had no violation. According to Lipinski's rule, the phytochemicals with zero violation will have good oral absorption.

4. Conclusions

Molecular docking studies have been carried out for the selected phytochemicals towards the FabG4 3-oxoacyl-(Acyl-carrier-protein) reductase, alpha-amylase, and aldose reductase proteins. The results obtained have enhanced binding affinities and increased hydrogen bonding interactions and hydrophobic contacts. The chosen three proteins show the better binding interaction with the selected 18 phytochemicals, from which one phytochemical of catechin-5-gallate showed highest binding affinity with all the three proteins and reported binding affinity were -7.70, -10.0, and -13.90 kcal/mol respectively. Subsequently, all the selected phytochemicals have shown better interaction with the respective proteins. Based on the analysis of hydrogen bonding interactions, hydrophobic contacts, binding affinity, and ADME studies, the phytochemical of catechin-5-gallate may precisely inhibit Diabetes mellitus. The oxidoreductase, alpha-amylase, and aldose reductase proteins will likely be a better target for diabetes, and catechin-5-gallate can be an appropriate drug to treat Diabetes mellitus in the future. Interestingly, the obtained results allow isolation of a particular compound from the plant extract of Acacia Arabica, which will be a potential inhibitor for Diabetes mellitus.

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Conflicts of Interest

No conflict of interest.

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