Journal of Integrated
SCIENCE & TECHNOLOGY

Computation studies of phytocompounds of *Papaver somniferum* and *Boswellia serrata* for diabetes management

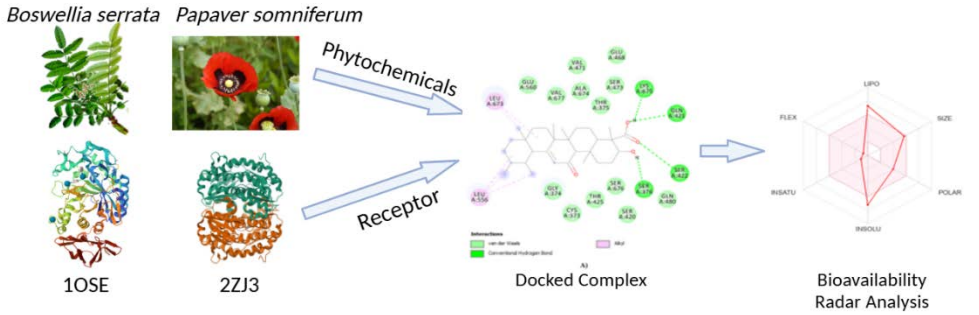
Madhura Roy[1+], Garvit Satija[2+], Ritika Luthra[3], Shreeja Datta[4], Arpita Roy[5*], Mohamed A.M. Iesa[6], Sarvesh Rustagi[7], Devvret Verma[8], Vaseem Raja[9], Cheng Wan Hee[10], Humaira Jan[11], Swetha Raj[12]

[1]Centre for Translational and Clinical Research, School of Chemical and Life Sciences, Jamia Hamdard University, India. [2]School of Pharmaceutical Education and Research, Jamia Hamdard University, Delhi, India. [3]Department of Chemical and Biomolecular Engineering, New York University Tandon School of Engineering, New York, USA. [4]Department of Biotechnology, Delhi Technological University, Delhi, India. [5]Department of Biotechnology, School of Engineering & Technology, Sharda University, Greater Noida, India. [6]Umm Al-Qura University, Faculty of Medicine at Al-Qunfudah, Department of Physiology. [7]School of Applied and Life Sciences, Uttaranchal University Dehradun, Dehradun, Uttarakhand, India.[8]Department of Biotechnology, Graphic Era Deemed to be Unversity, Dehradun, India 248002.[9]Department of Biotechnology, University Centre for Research and Development, Chandigarh University Gharuan, Mohali, Punjab- India,140413. [10]Faculty Health and Life Sciences, INTI International University, Persiaran Perdana BBN, Putra Nilai, Nilai 71800, Negeri Sembilan, Malaysia [11]School of Biological Sciences, University of Kashmir, Hazratbal, Srinagar, 190006, Kashmir, India. [12]Center for Global Health Research, Saveetha Medical College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Chennai, India

Received on: 28-Aug-2024, Accepted and Published on: 15-Nov-2024

Article

ABSTRACT



Natural bioactive compounds derived from medicinal plants have been extensively studied for their anti-diabetic properties. *Papaver somniferum* and *Boswellia serrata* are one of important medicinal plants that have bioactive compounds which could be utilized against diabetes. Therefore, an in-silico investigation of their function as anti-diabetic agents was conducted in this study, against two receptors i.e. alpha-amylase and glutamine-fructose-6-phosphate transaminase 1 (GFAT-1). The phytocompound-receptor docked complex was evaluated with known inhibitors of both important proteins responsible for diabetes. The molecular binding energy and inhibition constant were calculated, as well as the pharmacodynamics and pharmacokinetics characteristics were evaluated. Selected forty compounds were studied via Lipinski's rule. Out of 40 compounds one compound i.e. 3-O-Acetyl-11-Keto-Boswellic Acid, was eliminated since it violated two of the parameters of Lipinski's rule. Molecular docking (MD) analysis were performed on 39 identified components where (+-)-Teframedine and Morphine were found to be the potential inhibitors of alpha-amylase and GFAT-1, respectively. Morphine and (+-)-teframedine also demonstrated a good potential in bioavailability analysis and they can be taken orally. However, the solubility and lipophilicity parameters were not followed by 11-keto-boswellic acid, ursane, 3-acetyl-boswellic acid, and -amyrin, suggesting that these 4 substances are less bioavailable when taken orally. Further, these compounds should undergo in-vitro studies to support these results.

Keywords: Diabetes mellitus, alpha-amylase, GFAT-1, Molecular Docking, health care, global health

INTRODUCTION

One of the most common metabolic diseases, DM is characterized by abnormally elevated blood glucose levels, accounting for about 80% of the total fatalities occurring every year, as per the World Health Organisation (WHO) data (who. int). According to the statistical data of 2020, 463 million people were diagnosed with diabetes worldwide, with around 77 million from India and the International Diabetes Federation (IDF) has anticipated that these figures would climb up to 642 million over the next two decades. Currently, the most common medications used to treat diabetes include insulin and oral hypoglycemic agents like biguanides, α-amylase inhibitors meglitinides, thiazolidinediones, sulfonylureas, and gliptins.[1] However, owing to the numerous undesirable side effects like hepatocellular damage, hypoglycemia, dizziness, neurological disorders, etc caused by

*Corresponding Author: Dr. Arpita Roy, Email: arbt2014@gmail.com
+Authors contributed equally

Cite as: *J. Integr. Sci. Technol., 2025, 13(2), 1040.*
DOI: 10.62110/sciencein.jist.2025.v13.1040

these drugs, novel entities with fewer or no adverse effects must be evaluated.[2]

Inhibiting carbohydrate-hydrolyzing enzymes such as amylases, lipases, and maltases in the gut reduces glucose and fat absorption, which is one of the most therapeutically important strategies for managing diabetes.[3] A vital enzyme for digestion in the human body is pancreatic alpha-amylase (EC 3.2.1.1). The hydrolysis reaction of alpha-1,4 glycosidic bonds found in glycogen, maltodextrins, amylose, starch, and amylopectin is catalyzed by EC 3.2.1.1 and results in the formation of oligosaccharides, which are then split into monosaccharides by -glucosidase.[4] Hence, inhibiting alpha-amylase may help individuals to manage their diabetes, by retarding the elevation of blood glucose levels after consuming a carbohydrate-rich diet.[5] In addition to the glycolysis pathway, the hexosamine biosynthetic pathway—which utilizes glutamine as an amino source is also very important. It converts fructose-6-phosphate into glucosamine-6-phosphate. Glutamine-fructose-6-phosphate amidotransferase (GFAT-1) catalyzes this reaction by regulating the glucose entering the hexosamine pathway and acts as the rate-limiting enzyme.[6] Exceptionally high levels of sugar in the blood lead to a higher concentration of fructose-6-phosphate flowing into the hexosamine pathway and may result in the development of diabetic complications.[7,8] In addition, elevated human GFAT1 activity has been associated with insulin resistance in both animal and cellular models, which is a feature of Type 2 DM.[9,10] Thus, alpha-amylase and GFAT1 can strongly be considered significant targets for the treatment of Type 2 DM.[11]

Natural compounds have the potential to act as drug candidate and they can be used for generation of novel therapeutic agents.[12] Utilizing herbal remedies is a cost-effective therapeutic option, with fewer side effects, for several ailments.[13,14] Plant-based drugs possess many advantages concerning selectivity, efficacy, and reduced off-target toxicities.[15,16] In the last few years, the utilization of phytocompounds has drastically enhanced due to the various adverse effects exhibited by chemically synthesized drugs. Moreover, the drugs that are currently available in the market exhibit high levels of toxicity and thus, there is a need to replace chemically synthesized drugs with herbal compounds that have lower toxicity.[17] Previously, some studies have been published, that assess these two proteins as an important target for the management of this disorder. A study reported potential inhibitors of α-amylase extracted from the *Leucas ciliata Benth* (Lamiaceae) and *Streptomyces longisporoflavus* and *L. ciliata*,[18] followed by MD studies. The results identified flavonoid and alkaloid compounds as the potential inhibitors of α-amylase which could help in development of potential α-amylase inhibitors against diabetes. Okechukwu et al., 2020, showed MD on palmatine with α-amylase, alpha-glucosidase, and gliptins.[19] Furthermore, the binding energies were evaluated with those of widely used medications such as sitagliptin and acarbose, and it was established that palmatine has antidiabetic properties.

Ukwenya et al., 2021, carried out an in silico analysis where compounds derived from *Anacardium occidentale* were used against GFAT1.[20] The findings revealed that 8 compounds that met the RO5 and were within the acceptable range for Absorption, Distribution, Metabolism, and Excretion (ADME) criteria, demonstrating their suitability for application in the production of anti-diabetic medications. Davella et al., 2019, conducted a study for the evaluation of compounds extracted from *Rumex vesicarius* for anti-Type 2 Diabetes Mellitus activity.[21] The results showed that Physcion out of all the compounds had a better docking score (-7.66 kcal/mol). These investigations suggest that there is a scope for improvement in finding better inhibitors for activity against diabetes.[22]

Apart from this, it has been shown that phytochemicals extracted from *Boswellia serrata* gum resin possess anti-inflammatory properties and these have been used to treat several chronic inflammatory conditions.[23] It has previously been demonstrated that administering *Boswellia serrata* gum resin to LADA (Latent Autoimmune Diabetes in Adults) patients decreased blood levels of IA2 antibodies, one of the markers associated with LADA autoimmune diabetes. According to experimental research, it has also been demonstrated that *Papaver somniferum* comprises critical characteristics of therapeutic significance. It has been used as a sedative, analgesic, narcotic stimulant, nutrition, and more. It is even useful for headaches, cardiac asthma, cough, biliary colic, and insomnia.[24]

Thus, in this study, the aim was to find potential natural inhibitors against the two major protein targets, alpha-amylase, and GFAT-1, using computational techniques for the potentail treatment of diabetes using the two selected medicinal plant compounds.

Results and Discussion

ADME Analysis

The 40 shortlisted phytocompounds were initially subjected to preliminary assessment using molecular characteristics of the ligand (Table 1). This was done to exclude some of the compounds that did meet the criteria for selection. When the drug likeliness was calculated using Lipinski's Rule of 5, one compound, 3-O-Acetyl-11-Keto-Boswellic Acid, was eliminated since it violated two of the characteristics taken into account. The remaining 39 compounds were considered as potential candidates and were further investigated using molecular docking to anticipate the interactions of the protein-ligand complex.

Molecular Docking

The goal of MD studies is to identify conformations of the docked complex that have the lowest binding affinities and to anticipate the optimal configuration of the identified ligand with the target protein. All 39 of the ligands that complied with Lipinski's five conditions were subjected to MD to the active sites of the enzyme alpha-amylase and the protein GFAT-1.

Alpha-amylase protein

In case of alpha-amylase, the binding energy of standard drug i.e. acarbose showed a minimum binding energy of -4.05kcal/mol. GLN63, TRP59, GLU240, GLY306 and ASP300 formed conventional H-bonds. ALA198 and LEU162 demonstrated alkyl interactions. There were 14 van der waal attractive interactions and carbon-hydrogen bonds (Figure 1). The complexes with lowest binding energy of *Papaver somniferum* and *Boswellia serrata* were -8.31kcal/mol and -10.15 kcal/mol, respectively (Table 2).

Table 1: ADME Analysis of selected ligands

Plant Name	Phytocompounds	PubChem ID	Mol wt	H-bond acceptors	H-bond donors	LogP (XLOGP3) <5	Molar Refractivity	Lipinski Violation
Papaver somniferum	Sanguinarine	5154	332.33 g/mol	4	0	4.45	94.68	0
	(+-)-Carnegine	442186	221.30 g/mol	3	0	2.14	68.48	0
	(+-)-Teframidine	436140	323.34 g/mol	5	0	2.94	90.15	0
	Berberine	2353	336.36 g/mol	4	0	3.62	94.87	0
	Kaempferol	5280863	286.24 g/mol	6	4	1.9	76.01	0
	Linolenic acid	5280934	278.43 g/mol	2	1	6.46	88.99	1
	Morphine	5288826	285.34 g/mol	4	2	0.76	82.27	0
	Papaverine	4680	339.39 g/mol	5	0	2.95	97.16	0
	Reticuline	439653	329.39 g/mol	5	2	3.01	97.01	0
	1-Benzylisoquinoline	23345	219.28 g/mol	1	0	4.06	71.2	0
	Xanthaline	96932	353.37 g/mol	6	0	3.66	97.59	0
	Oripavine	5462306	297.35 g/mol	4	1	1.87	86.53	0
	1,2-Dehydroreticuline	440930	328.38 g/mol	4	2	2.38	98.27	0
	14-Hydroxycodeinone	9926820	313.35 g/mol	5	1	1.12	86.98	0
	2-(2-Furanyl)-3-methyl-2-butenal	555644	150.17 g/mol	2	0	1.91	43.42	0
	2-(4-Hydroxyphenyl) acetaldehyde	440113	136.15 g/mol	2	1	0.53	38.44	0
	3,4-Dimethoxyphthalic acid	68209	226.18 g/mol	6	2	0.92	53.34	0
	4-hydroxybenzaldehyde	126	122.12 g/mol	2	1	1.35	33.85	0
	4-Hydroxybenzoic acid	135	138.12 g/mol	3	2	1.58	35.42	0
	4,5-Dimethoxyphthalic acid	290988	226.18 g/mol	6	2	0.92	53.34	0
Boswellia Serrata	Alpha boswellic acid	637234	456.70 g/mol	3	2	8.41	136.65	1
	α-Campholenic-Acid	117235	168.23 g/mol	2	1	1.92	49.11	0
	Euphane	12312921	414.75 g/mol	0	0	12.12	136.83	1
	(−)-Camphene	440966	136.23 g/mol	0	0	4.22	45.22	1
	(+)-α-Phellandrene	443160	136.23 g/mol	0	0	3.21	47.12	0
	(1S,2R,4S)-(−)-Bornyl acetate	442460	196.29 g/mol	2	0	4.3	56.33	0
	11-Keto-β-boswellic acid	9847548	470.68 g/mol	4	2	7.2	137.11	1
	3-Acetyl-β-boswellic acid	11386458	498.74 g/mol	4	1	8.29	146.65	1
	3-O-Acetyl-11-Keto-β-Boswellic-Acid	11168203	512.72 g/mol	5	1		146.85	2
	α-Terpinene	7462	136.23 g/mol	0	0	4.25	47.12	0
	β-Pinene	14896	136.23 g/mol	0	0	4.16	45.22	1
	l-Idose	11030410	180.16 g/mol	6	5	-3.24	35.74	0
	Myrcene	31253	136.23 g/mol	0	0	4.17	48.76	0
	P-Cymene	7463	134.22 g/mol	0	0	4.1	45.99	1
	Serratol	101618281	290.48 g/mol	1	1	5.85	95.92	1
	Ursane	9548870	412.73 g/mol	0	0	11.47	134.45	1
	α-Amyrin	73170	426.72 g/mol	1	1	9.01	135.14	1
	2,3-Dihydroxyurs-12-en-28-oic acid	155934	472.70 g/mol	4	3	6.37	138.08	1
	Beta boswellic acid	168928	456.70 g/mol	3	2	8.26	136.91	1
	11-Keto-β-boswellic acid methyl ester	101695788	468.71 g/mol	3	0	8.32	140.27	1

Table 2: Molecular docking studies of selected ligands against alpha-amylase

Plant Name	Phytocompound	PubChem ID	Binding Energy (ΔG) (Kcal/mol)	Ligand Efficiency	Inhibition constant (μM)	Intermolecular energy	Vdw H bond desolvation energy
Papaver somniferum	(+-)-Teframidine	436140	-8.31	-0.35	0.8168	-8.31	-6.57
	Sanguinarine	5154	-7.65	-0.31	2.47	-7.65	-7.83
	Oripavine	5462306	-6.93	-0.32	8.29	-7.53	-6.96
	Berberine	2353	-6.91	-0.28	8.67	-7.5	-7.41
	Kaempferol	5280863	-6.81	-0.32	10.28	-8.3	-7.75
	(+-)-Carnegine	442186	-6.8	-0.43	10.35	-7.4	-5.48
	Morphine	5288826	-6.72	-0.32	11.96	-7.31	-6.73
	14-Hydroxycodeinone	9926820	-6.17	-0.27	30.13	-6.76	-6.33
	Reticuline	439653	-5.81	-0.24	55.02	-7.6	-6.9
	Xanthaline	96932	-5.75	-0.22	60.63	-7.54	-7.38
	1,2-Dehydroreticuline	440930	-5.57	-0.23	83.17	-7.36	-7.25
	Linolenic acid	5280934	-5.31	-0.27	128.49	-9.48	-8.76
	1-Benzylisoquinoline	23345	-5.07	-0.3	192.38	-5.67	-5.62
	2-(2-Furanyl)-3-methyl-2-butenal	555644	-4.94	-0.45	241.11	-5.53	-5.51
	Papaverine	4680	-4.92	-0.2	247.06	-6.71	-6.68
	4-Hydroxybenzoic acid	135	-4.5	-0.45	503.8	-5.39	-4.64
	4-hydroxybenzaldehyde	126	-4.39	-0.49	609.36	-4.98	-4.78
	2-(4-Hydroxyphenyl) acetaldehyde	440113	-3.99	-0.4	1200	-4.88	-4.81
	3,4-Dimethoxyphthalic acid	68209	-3.7	-0.23	1930	-5.49	-5.21
	4,5-Dimethoxyphthalic acid	290988	-3.69	-0.23	1960	-5.48	-5.18
Boswellia Serrata	Ursane	9548870	-10.15	-0.34	0.03607	-10.15	-10.15
	α-Amyrin	73170	-9.89	-0.32	0.05675	-10.18	-10.16
	Euphane	12312921	-9.68	-0.32	0.08031	-11.17	-11.17
	11-Keto-β-boswellic acid methyl ester	101695788	-9.53	-0.28	0.104	-10.12	-10.06
	11-Keto-β-boswellic acid	9847548	-9.09	-0.27	0.21846	-9.98	-10.24
	Beta boswellic acid	168928	-8.69	-0.26	0.42423	-9.59	-9.91
	3-Acetyl-β-boswellic acid	11386458	-8.55	-0.24	0.54242	-9.74	-10.11
	Alpha boswellic acid	637234	-8.43	-0.26	0.65758	-9.33	-9.68
	2,3-Dihydroxyurs-12-en-28-oic acid	155934	-7.99	-0.24	1.39	-9.18	-9.32
	Serratol	101618281	-7.05	-0.34	6.83	-7.64	-7.47
	(1S,2R,4S)-(−)-Bornyl acetate	442460	-5.64	-0.4	73.97	-6.23	-6.12
	l-Idose	11030410	-5.17	-0.43	163.43	-6.96	-5.87
	(+)-α-Phellandrene	443160	-4.86	-0.49	274.07	-5.16	-5.15
	β-Pinene	14896	-4.86	-0.49	274.82	-4.86	-4.86

	α-Campholenic-Acid	117235	-4.85	-0.4	278.54	-5.74	-4.94
	α-Terpinene	7462	-4.72	-0.47	347.76	-5.02	-5
	(−)-Camphene	440966	-4.7	-0.47	360.85	-4.7	-4.7
	P-Cymene	7463	-4.4	-0.44	594.08	-4.7	-4.68
	Myrcene	31253	-3.9	-0.39	1380	-5.1	-5.08
Standard inhibitor	Acarbose	444254	-4.05	-0.09	1070	-10.61	-8.65

(+-)-Teframedine-alpha amylase complex demonstrated a minimum inhibition binding energy of -8.31 kcal/mol amongst all phytocompounds selected from *Papaver somniferum*. LEU673 and VAL677 exhibited alkyl interactions. There were 13 van der Waal attractive interactions present in the complex. ALA674 and SER422 formed conventional H-bonds (Figure 1(A)).

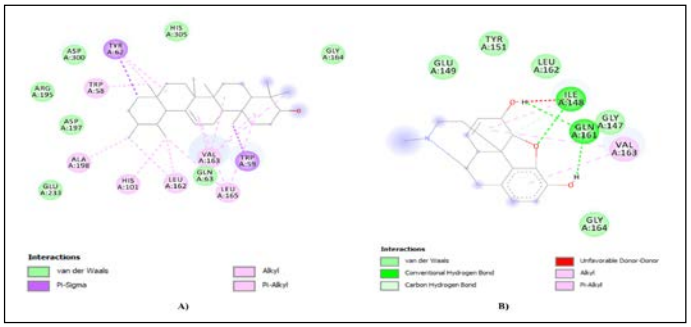


Figure 1. a) Interaction between (+-)-Teframedine & Alpha-amylase b) Interaction between Ursane & Alpha-amylase

In the case of *Boswellia serrata*, the Ursane-alpha amylase complex exhibited a minimum binding energy of -10.15 kcal/mol. HIS305, ASP300, ARG195, GLU233, ASP197, and GLN63 were shown to have van der Waal attractive interactions. There were 9 alkyl and pi-alkyl interactions present in the complex. TRP59 demonstrated a pi-sigma interaction (Figure 1(B)).

The second top-docked phytocompound of this plant was the α-Amyrin-alpha amylase complex, which demonstrated a minimum binding energy of -9.89 kcal/mol. As it can be seen in Figure 2(A), TYR62 and TRP59 exhibited pi-sigma bonds. TRP58, ALA198, HIS101, LEU162, VAL163, and LEU165 were shown to have alkyl and pi-alkyl interactions. There was a presence of 7 van der Waal attractive interactions in the complex.

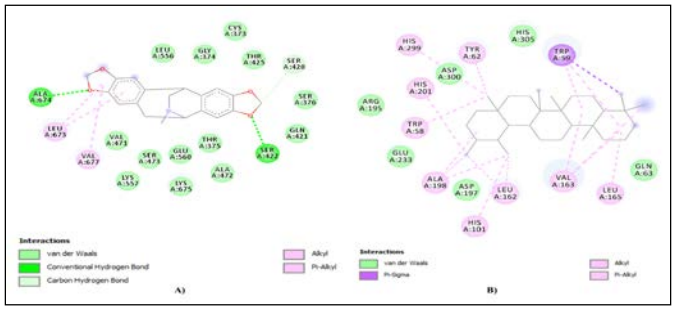


Figure 2. a) Interaction between α-Amyrin and Alpha-amylase b) Interaction between Morphine and GFAT1

GFAT1 protein

Metformin, a commonly used drug for GFAT-1, was taken as a standard inhibitor in this study. Metformin-GFAT1 complex was shown to have a most negative binding energy of -4.5 kcal/mol. VAL471 and ALA674 formed conventional H-bonds.LEU673, ALA472, SER473, LYS675, GLY374, and VAL677 were shown to have van der Waal attractive interactions. A salt bridge was observed between GLU560 and hydrogen.

The docking analysis exhibited the minimum binding energies of -8.01 kcal/mol and -9.97 kcal/mol among all the docked complexes of the two herbs, *Papaver somniferum* and *Boswellia serrata*, respectively (Table 3).

Table 3: Molecular docking studies of selected ligands against GFAT-1

Plant Name	Phytocompound	PubChem ID	Binding Energy (ΔG) (Kcal/mol)	Ligand Efficiency	Inhibition constant (μM)	Intermolecular energy	Vdw H bond desolvation energy
Papaver somniferum	Morphine	5288826	-8.01	-0.38	1.34	-8.61	-8.22
	Oripavine	5462306	-7.8	-0.35	1.92	-8.4	-7.74
	14-Hydroxycodeinone	9926820	-7.62	-0.33	2.58	-8.22	-7.95
	Xanthaline	96932	-7.43	-0.29	3.55	-9.22	-8.89
	(+-)-Teframidine	436140	-7.11	-0.3	6.17	-7.11	-6.66
	Sanguinarine	5154	-6.94	-0.28	8.22	-6.94	-6.75
	1,2-Dehydroreticuline	440930	-6.85	-0.29	9.55	-8.64	-8.48
	Reticuline	439653	-6.83	-0.28	9.85	-8.62	-7.7
	Kaempferol	5280863	-6.55	-0.31	15.78	-8.04	-7.76

	Berberine	2353	-6.45	-0.26	18.55	-7.05	-6.88
	Papaverine	4680	-6.21	-0.25	27.95	-8	-7.81
	1-Benzylisoquinoline	23345	-5.85	-0.34	51.76	-6.44	-6.38
	(+-)-Carnegine	442186	-5.47	-0.34	97.13	-6.07	-5.39
	4,5-Dimethoxyphthalic acid	290988	-5.18	-0.32	159.03	-6.97	-5.71
	3,4-Dimethoxyphthalic acid	68209	-5.1	0.32	182.42	-6.89	-5.74
	2-(2-Furanyl)-3-methyl-2-butenal	555644	-5.05	-0.46	199.4	-5.64	-5.5
	2-(4-Hydroxyphenyl) acetaldehyde	440113	-4.88	-0.49	266.24	-5.77	-5.66
	Linolenic acid	5280934	-4.87	-0.24	269.56	-9.05	-8.19
	4-Hydroxybenzoic acid	135	-4.81	-0.48	299.99	-5.7	-5.15
	4-hydroxybenzaldehyde	126	-4.73	-0.53	340.18	-5.33	-5.15
Boswellia Serrata	11-Keto-β-boswellic acid	9847548	-9.97	-0.29	0.04921	-10.86	-10.4
	3-Acetyl-β-boswellic acid	11386458	-9.79	-0.27	0.06629	-10.99	-10.56
	Beta boswellic acid	168928	-9.74	-0.3	0.07291	-10.63	-10.18
	Alpha boswellic acid	637234	-9.66	-0.29	0.08325	-10.55	-10.12
	Ursane	9548870	-9.11	-0.3	0.20913	-9.11	-9.11
	Euphane	12312921	-9.07	-0.3	0.22417	-10.56	-10.56
	11-Keto-β-boswellic acid methyl ester	101695788	-9.03	-0.27	0.24161	-9.62	-9.69
	α-Amyrin	73170	-8.9	-0.29	0.30115	-9.19	-9.05
	Serratol	101618281	-7.93	-0.38	1.55	-8.52	-8.52
	2,3-Dihydroxyurs-12-en-28-oic acid	155934	-7.65	-0.23	2.48	-8.84	-8.76
	(1S,2R,4S)-(−)-Bornyl acetate	442460	-6.53	-0.47	16.36	-7.13	-7.05
	α-Campholenic-Acid	117235	-5.4	-0.45	109.71	-6.3	-6
	l-Idose	11030410	-4.99	-0.42	220.59	-6.78	-6.54
	(+)-α-Phellandrene	443160	-4.9	-0.49	257.09	-5.2	-5.21
	β-Pinene	14896	-4.86	-0.49	276.08	-4.86	-4.85
	α-Terpinene	7462	-4.77	-0.48	320.18	-5.07	-5.07
	(−)-Camphene	440966	-4.73	-0.47	343.78	-4.73	-4.72
	P-Cymene	7463	-4.38	-0.44	615.47	-4.68	-4.68
	Myrcene	31253	-4.2	-0.42	828.66	-5.4	-5.39
Standard inhibitor	Metformin	4091	-4.5	-0.5	501.31	-4.5	-3.39

Amongst all the ten energy conformations obtained for the Morphine-GFAT1 complex from *Papaver somniferum*, -8.01 kcal/mol was the binding energy confirmation. GLU149, TYR151, LEU162, GLY147, and GLY164 demonstrated van der Waal interactions. ILE148 and GLN161 formed conventional H-bonds. Pi-alkyl and alkyl interactions were present (VAL163). Unfavorable donor-donor interactions were also observed (Figure 2(B)).

Figure 3(A) shows the best-docked complex from *Boswellia serrata*, i.e 11-Keto-β-boswellic acid, having a minimum binding energy of -9.97 kcal/mol. Three types of interaction can be seen i.e. conventional H-bond, van der Waal, and alkyl bonds. LYS675, GLN421, SER376, and SER422 were forming conventional H bonds. Alkyl interactions were observed with LEU673 and LEU556. Thirteen other van der Waal attractive interactions were found in the complex in addition to these interactions.

The second top-docked compound, 3-Acetyl-β-boswellic acid, which also belongs to *Boswellia serrata*, demonstrated the least binding energy of -9.79kcal/mol. LEU673 AND LEU556 were shown to have alkyl interactions. LYS675, GLN421, SER422, and GLN480 formed conventional H-bonds. Moreover, there were 15 van der Waal attractive interactions that were present in the complex (Figure 3(B)).

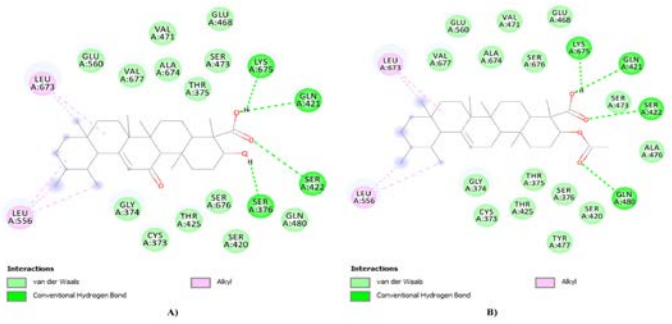


Figure 3. A) Interaction between 11-Keto-β-boswellic acid and GFAT1 B) Interaction between 3-Acetyl-β-boswellic acid and GFAT1

Bioavailability Radar

From *Boswellia serrata*, 11-keto-β-boswellic acid and 3-acetyl-β-boswellic acid were amongst the top two docked ligands against GFAT-1 protein that were studied. However, Morphine-GFAT-1 complex showed the minimum binding energy from a pool of phytocompounds obtained from *Papaver somniferum*. In case of alpha-amylase, ursane and α-amyrin of *Boswellia serrata* were amongst the top two obtained docked confirmations. (+-)-teframedine, On the other hand, exhibited the best results compared to all the phytocompounds chosen from *Papaver somniferum*. In order to conduct a thorough examination, bioavailability radar is a descriptive approach that takes 6 physical and chemical aspects into account when evaluating the drug-likeness of particular substances. It was noted that the ligand spectrum perfectly fit in the pink-colored areas in the cases of morphine and (+-)-teframedine, demonstrating that it is orally bioavailable. However, the solubility and lipophilicity parameters were not followed by 11-keto-boswellic acid, ursane, 3-acetyl-boswellic acid, and -amyrin, suggesting that these 4 substances are less bioavailable when taken orally. (Figure 4).

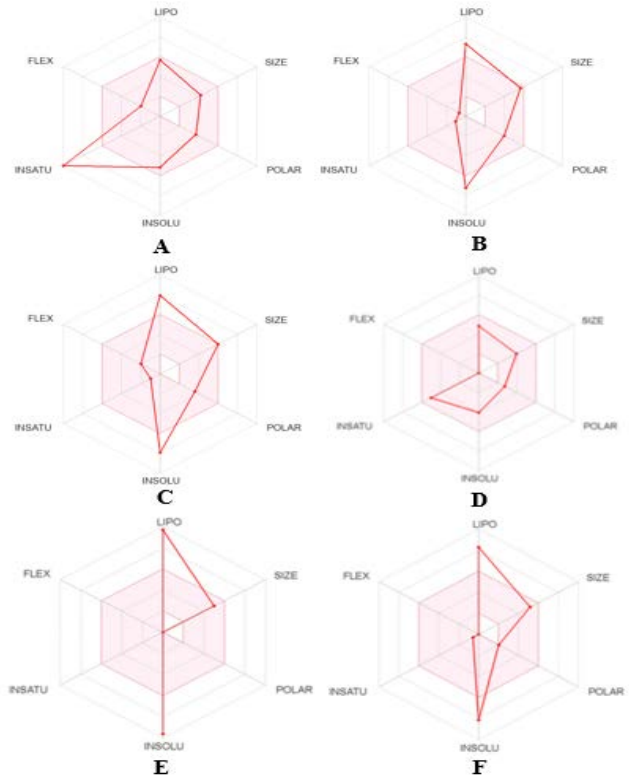


Figure 4. Bioavailability radars of (A) Morphine (B) 11-Keto-β-boswellic acid (C) 3-Acetyl-β-boswellic acid (D) (+-)-Teframedine (E) Ursane (F) α-Amyrin.

MATERIALS AND METHODS

Requirements for in silico investigations

IMPPAT database, PubChem, Protein Data Bank, Discovery studio visualizer Biovia, Alpha fold protein structure database, PyMOL, PyRx, SwissADME, and AutoDock v4.2.6 are the programs and datasets used in this investigation.[25]

Macromolecule

The 3D structures of alpha-amylase (PDB ID: 1OSE)[26] and GFAT-1 (PDB ID: 2ZJ3)[27], both being two major receptors involved in the progression of diabetes, were used for the investigation. Their structures were extracted from 'Protein Data Bank' in .pdb format.

Ligands

Two medicinal plants, *Papaver somniferum* (commonly known as opium poppy) and *Boswellia serrata*, owing to their therapeutic properties, were chosen for this study.[28] Fourty different phytocompounds present in the plants were selected using the IMPPAT (https://cb.imsc.res.in/imppat) database (Refer Table 1). To continue with docking studies, their 3-dimensional structures were downloaded from PubChem in the ".sdf" format and transformed into ".pdb" format using Biovia Discovery Studio's visualizer.[29]

ADME Analysis

The primary screening of the selected phytocompounds was done using the SwissADME (http://www.swissadme.ch/index.php) and their pharmacokinetic characteristics like ADME and toxicity were estimated using Lipinski's Rule of 5.[30] According to it, the molecular weight of the ligand should be <500 Dalton, H-bond donors should be <5, H-bond acceptors should be <10 in number, ligand should be highly lipophilic (LogP<5), and molar refractivity should be between 40-130.[31] Any ligand that exhibited more than 1 violation of Lipinski's rule was directly eliminated from further studies. Out of the forty phytocompounds, only 3-O-Acetyl-11-Keto-β-Boswellic-Acid was eliminated and remaining thirty-nine compounds were subject to MD.[32]

Molecular Docking

The MD of each selected ligand was carried out against alpha-amylase and glutamine-fructose-6-phosphate transaminase 1

(GFAT-1) proteins using Autodock v4.2.6. Water molecules were eliminated, and polar hydrogens and Kollmann charges were added.[33] Further, gasteiger charges were computed, followed by the removal of hetatoms from the macromolecules to complete the preparation of both proteins. For alpha-amylase, the active site residues were arranged in a grid box with dimensions 48x60x44 and with a spacing of 0.375, and for GFAT-1, 60x60x64 and 0.375. The docking studies resulted in Lamarckian GA output. For each ligand, the process was performed three times, and among the 10 possible conformations, the ideal conformation with the lowest binding energy was selected. Using Biovia Discovery Studio Visualizer v19.1.0.18287, it was then converted into a 2-D graphic showing the interaction between the ligand and the active site residue.[34]

Bioavailability Radar

The filtration of a potent ligand molecule was continued using a more reasonable evaluation of physicochemical characteristics. The SwissADME (http://www.swissadme.ch/index.php) web-based tool was used to create bioavailability radars of ligands that performed more effectively than the standard molecule. The compounds were evaluated using six parameters: size, lipophilicity, saturation, polarity, and flexibility. Non-oral bioavailability was suspected in ligands that deviated from the established values, thus they were excluded from further testing.[35,36]

CONCLUSION

In the present study, forty phytocompounds from two different medicinal plants, *Papaver somniferum* and *Boswellia serrata*, were chosen against two receptor, i.e. alpha-amylase and glutamine-fructose-6-phosphate transaminase 1 which are involved pathogenesis of diabetes. These were screened for their drug likeliness, out of which thirty-nine were further evaluated using molecular docking studies. The docked complexes underwent comparison with the standard inhibitors of both proteins. In the case of alpha-amylase, thirty-five phytocompounds possessed higher binding energies than the standard inhibitor acarbose. Similarly, thirty-seven phytocompounds exhibited higher binding energies against GFAT-1 compared to its standard drug metformin. For bioavailability radar testing, the top compounds from each of the two plants docked against each protein were selected. Morphine and (+-)-Teframedine of *Papaver somniferum* was found to be orally bioavailable. In conclusion this study suggests that *Papaver somniferum* and *Boswellia serrata*, are probably better anti diabetic agents than metformin and phythochemicals analysed are probably better drug candidiates than metformin. Further in-vitro research should be done to find an effective and reliable treatment for diabetes. These phytochemicals can be employed as possible plant-based inhibitors against the targeted proteins.

ACKNOWLEDGMENTS

The authors would like to thank their universities for neassary support.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

REFERENCES

1. K.N. Sangeetha, S. Sujatha, V.S. Muthusamy, S. Anand, K. Shilpa. Current trends in small molecule discovery targeting key cellular signaling events towards the combined management of diabetes and obesity. Bioinformation. **2017**,13(12), 394.
2. S. P. Gurjar, A. Roy, A. Gupta. Competitive inhibition of catechol from *Andrographis paniculata* in the complex of ERK2 in lung metastasis. *J. Integr. Sci. Technol.*. **2023**, 12(1), 719.
3. K. Hamden, K. Mnafgui, Z. Amri, A. Aloulou, A. Elfeki. Inhibition of key digestive enzymes related to diabetes and hyperlipidemia and protection of liver-kidney functions by trigonelline in diabetic rats [published correction appears in *Sci Pharm*. **2014**, 82(2), 449-50.
4. S. Lordan, T.J. Smyth, A. Soler-Vila, C. Stanton, R.P. Ross. The α-amylase and α-glucosidase inhibitory effects of Irish seaweed extracts. *Food Chem*. **2013**,141, 2170–6.
5. S. Poovitha, M. Parani. In vitro and in vivo α-amylase and α-glucosidase inhibiting activities of the protein extracts from two varieties of bitter gourd (*Momordica charantia L.*). BMC Complement Altern Med. **2016**, 16, 185.
6. K.C. Chou. Molecular therapeutic target for type-2 diabetes. *J Proteome Res*. **2004**, 3(6), 1284–1288.
7. H. Zhang, Y. Jia, J.J. Cooper, T. Hale, Z. Zhang, S.C. Elbein. Common variants in glutamine: fructose-6-phosphate amidotransferase 2 (GFPT2) gene are associated with type 2 diabetes, diabetic nephropathy, and increased GFPT2 mRNA levels. *J. Clin. Endocrinol. Metab.* **2004**, 89, 748– 755.
8. D. Beriault, Y. Shi, G. Werstuck. Investigating the role of the hexosamine biosynthesis pathway in diabetic atherosclerosis. *Can J Cardiol.* **2013**, 29, S254.
9. K.A. Robinson, D.A. Sens, M.G. Buse. Pre-exposure to glucosamine induces insulin resistance of glucose transport and glycogen synthesis in isolated rat skeletal muscles. *Diabetes*. **1993**, 42, 1333– 1346.
10. L. Rossetti, M. Hawkins, W. Chen, J. Gindi, N. Barzilai. In vivo glucosamine infusion induces insulin resistance in normoglycemic but not in hyperglycemic conscious rats. *J. Clin. Invest.* **1995**, 96, 132– 140.
11. L. Herbert, D.A. McClain. Overexpression of glutamine: fructose-6-phosphate amidotransferase in transgenic mice leads to insulin resistance. *J. Clin. Invest.* **1996**, 97, 1235– 1241.
12. R. Luthra, A. Roy, S. Pandit, R. Prasad. Biotechnological methods for the production of ginsenosides. *S. Afr. J. Bot.* **2021**, 141, 25-36.
13. R. Luthra, G. Satija, A. Roy. Centellosides: pharmaceutical applications and production enhancement strategies. *Plant Cell, Tissue Organ Cult.* **2021**, 1-15.
14. A. Roy, S. Datta. Medicinal Plants against Ischemic Stroke. *Curr. Pharm. Biotechnol.* **2021**, 22(10), 1302-1304.
15. R. Zainul, D. S. Novel, H. Satriawan, Goh, K. W., Jakhmola, V., Rebezov, M., Faridah. In Silico Gene Transcription of 4-Hydroxycinnamic Acid from Broccoli Fruit (Brassica oleracea var. italica) with Estrogen Receptor Beta Protein. *Pharmacognosy Journal*, **2024**, 16(4).131
16. H. Assaggaf, N. El Hachlafi, M. El fadili et.al. GC/MS profiling, in vitro antidiabetic efficacy of Origanum compactum Benth. essential oil and in silico molecular docking of its major bioactive compounds. *Catalysts*, **2023**, 13(11), 1429.
17. Z. Rabiei, M.R. Bigdeli, Z. Lorigooini. A review of medicinal herbs with antioxidant properties in the treatment of cerebral ischemia and reperfusion. *J. Babol Univ. Medical Sci.* **2015**, 17(12), 47-56.
18. J. V. Akshatha, H. S. Santosh Kumar, H. S. Prakash, M.S. Nalini. In silico docking studies of α-amylase inhibitors from the anti-diabetic plant *Leucas ciliata Benth.* and an endophyte, *Streptomyces longisporoflavus*. *3 Biotech.* **2021**, 11(2), 51.
19. P. Okechukwu, M. Sharma, W.H. Tan, H.K. Chan, K. Chirara, A. Gaurav, M. Al-Nema, In-vitro antidiabetic activity and in-silico studies of the binding energies of palmatine and the standard compounds with the three receptors of alpha amylase, alpha glucosidase, and DPP-IV enzyme. *Pharmacia.* **2020**, 67(4), 363-371.
20. V.O. Ukwenya,; S.A. Adelakun,; O.O. Elekofehinti. Exploring the antidiabetic potential of compounds isolated from *Anacardium occidentale*

using computational aproach: ligand-based virtual screening. *In silico pharmacology*. **2021**, 9(1), 25.
21. R. Davella, E. Mamidala. In silico Molecular Docking Studies of compounds from *Rumex vesicarius* against GFAT1. *Biolife*. **2019**, 6(3), 6302.
22. S. Datta, R. Luthra, N. Bharadvaja. Medicinal Plants for Glioblastoma Treatment. *Anticancer Agents Med Chem.* **2022**, 22. 4739
23. Z. Franić, Z. Franić, N. Vrkić, N.N. Gabaj, I. Petek. Effect of extract from *Boswellia serrata* gum resin on decrease of GAD65 autoantibodies in a patient with Latent Autoimmune Diabetes in Adults. *Altern Ther Health Med.* **2020**, 26(5), 38-40.
24. M. Masihuddin, M. Jafri, A. Siddiqui, S. Chaudhary. Traditional uses, phytochemistry and pharmacological activities of *Papaver somniferum* with special reference of unani medicine an updated review. JDDT. **2018**, 8(5), 2069
25. S.P. Gurjar, A. Roy, A. Gupta. Understanding Pharmacokinetics, Bioavailability Radar, and Molecular Docking Studies for Selected Medicinal Plants Against Lung Cancer Receptors. In Harnessing Medicinal Plants in Cancer Prevention and Treatment. *IGI Global.* **2024**, 343-388.
26. C. Gilles, J. Astier, G. Marchis-Mouren, C. Cambillau, F. Payan. Crystal Structure of Pig Pancreatic α-amylase Isoenzyme II, in Complex with the Carbohydrate Inhibitor Acarbose. European Journal of Biochemistry, **1996**, 238(2), 561–569.
27. Y. Nakaishi, M. Bando, H. Shimizu, K. Watanabe, F. Goto, H. Tsuge, K. Kondo, M. Komatsu. Structural analysis of human glutamine:fructose-6-phosphate amidotransferase, a key regulator in type 2 diabetes. FEBS Letters. **2008**, 583(1), 163–167.
28. B. Haque, A. Gupta, A. Roy, A. Malik, & A. A. Khan. Green fabrication of Ag–Ni–Mn-Zn nanoparticles from watermelon peels and its antioxidant, dye degradation and molecular docking studies. Clean Technologies and Environmental Policy, **2024**, 1-28.
29. A. Roy, N. Sharma, R. Luthra. In-silico analysis of antiviral fungal inhibitors against Mpro receptor protein. *Vegetos*. **2024**. 1-14
30. H. Kashyap, G. Sekhon, A. Varshney, M. Khatri. In silico screening of potential antidiabetic phytochemicals from Tephrosia purpurea: A polypharmacology approach. *Biomed. Ther. Lett.* **2024**, 11 (2), 911.
31. A. Daina, O. Michielin, V. Zoete. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Sci Rep.* **2017**, 7(1), 42717.
32. A. Gupta, A. Roy, S. Pandit, N. Pandey, Rustagi, S. Evaluation of bioactive compounds obtained from *Ginkgo biloba* against crystal structure of myelin oligodendrocyte glycoprotein (MOG). *OBM Neurobiology*, **2023**, 7(4), 1-34.
33. A. Roy, A. Gupta, D. Verma. Evaluation of different phytochemicals from *Cannabis sativa* against Myelin oligodendrocyte glycoprotein receptor. *Vegetos.* **2023**. 1-11.
34. A. Gupta, A. Roy, V. Raja, S. Rustagi, S. Malik, & D. Verma. In-silico studies of phytoconstituents of *Bacopa monnieri* and *Centella asiatica* with Crystal structure of Myelin Oligodendrocyte Glycoprotein against primary demyelination in Multiple Sclerosis. *J. Integr. Sci. Technol.*, **2023**, 12(3), 764.
35. S.P. Gurjar, A. Gupta, A. Roy. Molecular docking studies of phytocompounds from *Artemisia monosperma* against ERK2 kinase in lung cancer. *J. Mol. Chem.*, **2023**, 3(2), 591-591.
36. U. Kaushik, S.C. Joshi. Formulation and evaluation of Momordica charantia fruit extract based transdermal drug delivery against diabetes. *Biomed. Ther. Lett.* **2024**, 11 (1), 905.