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EXPLORING THE PHYTOCHEMICALS POSSESSING ANTIDIABETIC PROPERTY OF *MENTHA LONGIFOLIA* THROUGH IN SILICO DOCKING APPROACH

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ABSTRACT

Diabetes is a chronic metabolic disorder characterized by high blood glucose level in the body due to alteration in carbohydrate metabolism. Prevalence of diabetes is expected to cross 123 million by 2035. Two enzymes, α-amylase and α-glucosidase play a major role in starch digestion. Inhibition of these enzymes results in significant reduction of type 2 diabetes. The plant, *Mentha longifolia* possess good medicinal values such as, antimicrobial and antioxidant property. It can also be used as an antidiabetic agent. In order to test this hypothesis, the phytochemical constituent of *Mentha longifolia* was obtained from the previous literature study. *In silico* docking study was carried out for all the phytochemical against α-amylase and α-glucosidase. Trans-piperitol and menthol are found to be the top two compounds with good binding energy.

KEYWORDS :**Diabetes, *Mentha longifolia*, α-amylase, α-glucosidase, Trans-piperitol and menthol.**

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INTRODUCTION

Diabetes is a chronic metabolic disorder characterized by high blood glucose level in the body due to alteration in carbohydrate metabolism[1]. It is of two types, type 1 and type 2. Type 1 (insulin dependent) is a case where the body fails to synthesize insulin. Conversely, in type 2 (insulin independent) diabetes our body doesn't make use of insulin that is secreted[2]. South East-Asia (sea) region is home to more than 72 million adults with diabetes in 2013 and is expected to exceed 123 million in 2035 out of which nearly 95% of people have type 2 diabetes[3]. There are number of ways diabetes can be targeted. But, the most practical approach involves targeting the carbohydrate metabolism by the inhibition of enzyme α-amylase and α-glucosidase[4]. Our body system makes use of glucose as a major source of energy. Initially salivary amylase catalyzes the hydrolysis of starch molecule into different oligosaccharide. When oligosaccharide reaches gut these are in turn hydrolysed to di and trisaccharide by the action of pancreatic amylase. Resultant disaccharides are converted to individual glucose molecule by glucosidases[5]. Human salivary and pancreatic α-amylases share a high degree of amino acid sequence similarity with 97% identical residues overall and 92% in the catalytic domains[6]. Drugs like Acarbose are most widely used as α-amylase inhibitors[7]. Although it inhibits α-amylase it is found to have many gastrointestinal complications including vomiting, indigestion, diarrhoea etc.[8]. Therefore a search for new type of compounds can be a novel idea to circumvent this problem. So, an attempt has been made to find some natural and comparatively safer inhibitors of α-amylase and α-glucosidase. This study deals with the identification of potent inhibitor of α-amylase and α-glucosidase present in *Mentha longifolia*.

METHODOLOGY

All computational investigations were carried out using Schrodinger products: Maestro, GLIDE, QikProp running on Red Hat Enterprises Linux 5.3 platform.

Phytochemicals in Mentha longifolia

It has been reported from many researches that *Mentha longifolia* possess 41 phytochemicals[9,10]. These compounds are believed to act as a good inhibitor of α-amylase and α-glucosidase. The list of phytochemicals identified is shown in Table 1.

Table 1
Phytochemicals of *Mentha longifolia*

S.NO	Compound Name
1	α-pinene
2	α-thujene
3	α-fenchene
4	Camphene
5	β-pinene
6	Sabinene
7	Myrcene
8	Limonene
9	1,8-cineole
10	z-b-ocimene
11	3-octanone
12	γ-terpinene
13	P-cymene
14	Terpinolene
15	3-octanol
16	1-octenol-3
17	Menthone
18	Menthofurane

19	Isomenthone
20	B-bourbonene
21	Linalool
22	Methyl acetate
23	Isopulegone
24	Neoisomenthol
25	Terpinen-4-ol
26	Menthol
27	Pulegone
28	α-humulene
29	Trans-piperitol
30	α-terpineol
31	Germacrene d
32	Carvone
33	Piperitone
34	d-cadinene
35	γ-cadinene
36	Myrtenol
37	Carveol
38	Germacrene b
39	Caryophyllene oxide
40	α-calacorene
41	Thymol

Ligand preparation

The chemical structures of all the 41 phytochemicals from *Mentha longifolia* were taken from pubchem database. LigPrep module of Maestro was used for ligand preparation[11]. This will convert the 2D structure of ligand into 3D, add hydrogen, generate conformers, minimize the ligand and give low energy 3D output structure of ligand. The ligands were energy minimized using OPLS 2005 force field.

Protein preparation

The crystal structures of α- amylase and α-glucosidase were fetched from protein data bank[12, 13]. The X-ray structure of α- amylase with PDB ID 1HNY has a resolution of 1.8Å and that of α- glucosidase (2QMJ) is 1.9Å. (http:// www.rcsb.org). Proteins were prepared using protein preparation wizard module of Maestro prior to docking[14]. This will add hydrogen, missing side chains, change bond order, optimize the rings present in amino acid and subsequently restrained energy minimization was carried out using the OPLS 2005 force field and the heavy atoms were constrained.

Active Site identification

For α-amylase, active site was identified using sitemap module[15]. Since the structure of α-glucosidase is in complex with the ligand, the grid was generated keeping the ligand as a centre, with grid box dimension of 10x10x10Å.

Glide docking

The prepared ligands were docked to the proteins using glide module to find good binding energy[16]. Glide employs two scoring functions. Standard precision (SP) and Extra precision (XP). The ligands were docked with both SP and XP scoring terms. However SP and XP differ in their scoring function such as, XP are more accurate than SP[17]. For the atoms of protein with partial charges ≤ 0.25, the scale factor of 0.4 was applied for Van der Waals radii. The best pose ligands with good XP value are considered for ADME property analysis.

ADME analysis

One of the main factor concerns with drug design is pharmacokinetic parameter of a drug. The drug with valid absorption, metabolism, distribution and excretion/ Toxicity properties can easily pass through the clinical trials. QikProp was used to validate ADME properties[18]. QikProp validate the

accessibility of drug based on the Lipinski rule of five, to ensure drug likeliness of a compound based on pharmacokinetic parameters.

RESULTS AND DISCUSSION

Molecular docking

Docking approach is used to find the favourable interaction at which a ligand binds to the receptor. Individual docking score of 41 compounds are shown in Table 2. Two compounds trans-piperitol and menthol posses a good binding affinity with α-amylase and α-glucosidase. The ligand interaction diagram of trans-piperitol and menthol against α-amylase and α-glucosidase is shown in the Figure1 and 2 respectively. From Figure 1, it clearly shows that both trans-piperitol and menthol are making hydrogen bond interaction with GLN 63, TRP 59 and contribution of few hydrophobic groups of α-amylase. From figure 2, it is shown that trans-piperitol has a hydrogen bond interaction with ASP 327 and menthol is having hydrogen bond interaction with ASH 443 of α-glucosidase. Trans-piperitol and menthol belongs to the family of terpenoids. Role of terpeniods in type 2 diabetes is already been studied[19]. Hence *Mentha longifolia* can act as a potent antidiabetic target.

Table 2
Docking score of phytochemicals present in Mentha longifolia against α-amylase and α-glucosidase

S.No	Compound Name	α-amylase		α-glucosidase	
		Glide docking score (kcal/mol)			
		SP	XP	SP	XP
1	α-pinene	-3.456	-4.830	-4.51	-5.497
2	α-thujene	-3.544	-3.912	-3.305	-4.191
3	α-fenchene	-3.357	-4.418	-5.151	-5.291
4	camphene	-3.115	-4.568	-4.744	-4.984
5	β-pinene	-3.717	-4.741	-3.607	-5.483
6	sabinene	-3.282	-4.090	-5.156	-5.517
7	myrcene	-0.921	-1.820	-1.109	-1.474
8	Limonene	-2.983	-4.055	-4.860	-5.487
9	1,8-cineole	-3.303	-3.750	-4.130	-4.833
10	z-b-ocimene	-2.142	-2.250	-2.419	-2.579
11	3-octanone	-2.423	-3.601	-3.476	-3.670
12	γ-terpinene	-2.940	-4.699	-5.294	-5.761
13	P-cymene	-2.140	-2.424	-3.225	-3.300
14	terpinolene	-3.992	-5.222	-4.411	-4.977
15	3-octanol	-2.348	-2.423	-2.428	-2.551
16	1-octenol-3	-2.479	-2.533	-2.852	-2.924
17	Menthone	-4.344	-4.824	-4.278	-4.834
18	Menthofurane	-4.361	-4.801	-4.775	-4.981
19	Isomenthone	-4.344	-4.824	-4.278	-4.834
20	B-bourbonene	-4.941	-5.406	-4.813	-5.205
21	Linalool	-3.114	-3.515	-3.690	-4.026
22	Methyl acetate	-2.464	-2.679	-2.036	-2.251
23	Isopulegone	-3.749	-5.731	-4.553	-5.685
24	neoisomenthol	-4.886	-5.216	-5.011	-5.186
25	Terpinen-4-ol	-4.513	-5.251	-5.530	-5.565
26	Menthol	-5.635	-6.584	-4.962	-5.439
27	pulegone	-3.749	-5.131	-4.923	-5.566
28	α-humulene	-2.201	-5.330	-3.139	-3.242
29	Trans-piperitol	-4.355	-5.894	-5.186	-5.655
30	α-terpineol	-3.536	-5.122	-5.456	-5.951
31	Germacrene d	-4.036	-5.233	-4.981	-4.851
32	carvone	-4.478	-5.030	-4.493	-4.526
33	Piperitone	-4.239	-5.663	-4.538	-5.265
34	d-cadinene	-3.931	-4.497	-4.227	-4.430
35	γ-cadinene	-4.660	-4.823	-4.965	-5.049
36	Myrtenol	-4.033	-5.092	-4.305	-4.396
37	Carveol	-4.961	-5.581	-5.048	-5.264
38	Germacrene b	-3.548	-4.640	-4.931	-5.235
39	Caryophyllene oxide	-4.283	-5.355	-3.814	-4.718
40	α-calacorene	-3.979	-5.413	-4.283	-4.710
41	thymol	-5.191	-5.693	-4.518	-4.684

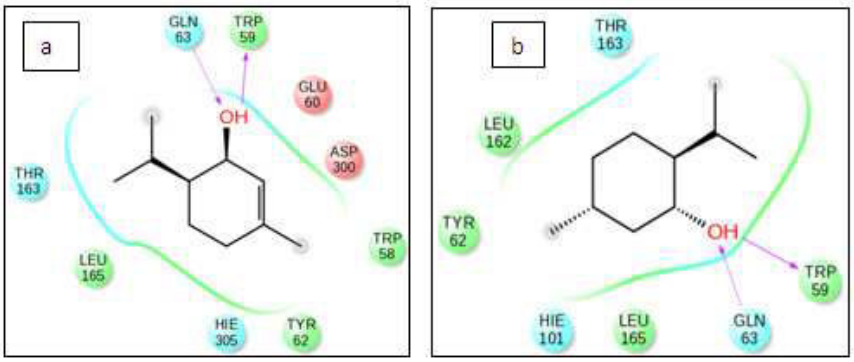

Figure 1
Ligand interaction diagram of trans-piperitol (a) and menthol (b) against α-amylase

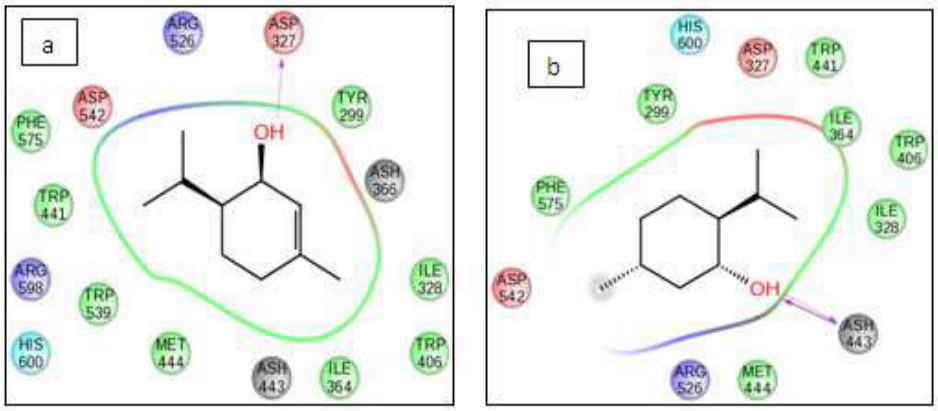

Figure 2
Ligand interaction diagram of trans-piperitol (a) and menthol (b) against α- glucosidase

ADME analysis

ADME properties for pharmaceutically relevant descriptors were analyzed. The Lipinski's rule of five was also evaluated for trans-piperitol and menthol. The values of the chosen descriptors are shown in Table 3. They are within the acceptable range defined for human. The two lead compounds did not violate any of the Lipinski's rule and has 100% oral absorption. These results show that the compounds Trans-piperitol and menthol have good drug likeliness.

Table 3
The ADME property of Trans-piperitol and menthol obtained from QikProp

S.NO.	Compound name	SASA	Logp o/w	% of Human oral absorption	Violation of Lipinski's Rule of five
1	Trans-piperitol	398	2.772	100	0
2	menthol	399	2.772	100	0

CONCLUSION

The phytochemical constituents of *Mentha longifolia* have already been reported. Three dimensional structures of α-amylase and α-glucosidase were retrieved from protein data bank. The active site of the enzymes was identified and is docked with the individual compounds of *Mentha longifolia*. Trans-piperitol and menthol were identified as a compound with good binding energy. Further, ADME properties of these compounds were studied. Thus, this study reports Trans-piperitol and menthol can be potential inhibitors of the enzymes involved in diabetes and further experimental researches on these compounds may uncover novel anti-diabetic drug molecules.

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