



RESEARCH ARTICLE

Anti-hyperglycemic and anti-hyperlipidemic effect of *Syzygium aromaticum* (L.) Merr. & L.M.Perry via *in vitro*, *in vivo* and *in silico* models

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Abstract

Diabetes mellitus (DM) is one of the most prevalent endocrine disorders, projected to affect over 300 million people by 2025. Despite the availability of several anti-diabetic drugs, their adverse effects have prompted the search for safer alternatives. The present study investigates the anti-hyperglycemic and anti-hyperlipidemic effects of the ethanolic extract of *Syzygium aromaticum* (L.) Merr. & L.M.Perry (clove). Dried clove powder was extracted using ethanol and subjected to phytochemical screening, revealing the presence of various bioactive constituents like phenols, terpenoids, alkaloids, etc. The extract was evaluated for *in vitro* anti-diabetic activity using α -amylase and α -glucosidase inhibition assays in our laboratory at Trichy. Gas chromatography-mass spectroscopy (GC-MS) analysis identified major phytochemicals, including eugenol. *In vivo* studies were conducted on streptozotocin (STZ) induced diabetic albino rats, divided into five groups. Treatments included eugenol (10 mg/kg body weight), ethanolic extract (300 mg/kg body weight) and glibenclamide (3 mg/kg body weight) as a standard drug. The treated groups exhibited significant improvement in glucose and lipid profiles compared to diabetic controls. Docking studies further confirmed eugenol's strong binding affinity to pancreatic amylase and glucosidase, supporting its inhibitory potential. Pancreatic α -amylase had a glide score of -6.8, pancreatic α -glucosidase had a score of -7.9 and the AMP-activated protein kinase (AMPK) had a value of -7.3 kcal/mol. This effect may be the reason for its antidiabetic nature. The ethanolic extract of *S. aromaticum* and its key constituent eugenol demonstrated potent anti-hyperglycemic and anti-hyperlipidemic effects, suggesting their potential use as natural therapeutic agents for diabetes management.

Keywords: anti-hyperglycaemic activity; anti-hyperlipidemic activity; eugenol; *in silico* analysis; *Syzygium aromaticum*

Introduction

Diabetes mellitus (DM) is a serious endocrine condition marked by high blood sugar levels brought on by insufficient pancreatic insulin secretion, either alone or in combination with concurrent impairment of insulin action. Currently, from the global population of 150 million people, approximately 10 % are affected by diabetes. (1). According to the reports of the World Health Organisation, there were 171 million cases of DM in 2000 and that figure was projected to rise to 360 million by 2030 (2). It has also been estimated that 75 % of the people affected by diabetes will reside in underdeveloped nations by 2025 (3). Globally, the prevalence of diabetes is rising which ultimately is increasing the economic burden on national and international health care.

The genesis of the condition has been linked to a number of causal factors, including hormones, medications, heredity, race, lifestyle, nutritional status, stress, infection, hormonal imbalance and altered immunological function as well as metabolic and physiological imbalances. In urban India, 30 % of the diabetes affected persons are under the age of 40 years. The frequency of diabetes varies greatly between urban and rural areas, suggesting that urbanisation plays a significant role in both the disease's genesis and its progression. In urban India, 30 % of diabetics are under 40 years old. According to a national research conducted in 2000, 12.2 % of urban individuals over 20 years old had the condition. According to a study on the incidence of diabetes in India, there are notable regional variations: the North of the country has the lowest prevalence of the disease, while Western

and Southern India have the greatest. Further correlations between industrialisation and physical exercise and these regional variations were found (4). Low socio-economic groups have greater rates of the problems because of behavioural variables as well as poor management of hypertension and glucose.

There are several oral hypoglycemic medications available in the market, which on consumption, shows adverse side effects. Currently, herbal medications are associated with safety as opposed to synthetic pharmaceuticals. Plants make up 25 % of all medications in affluent nations, whereas approximately 80 % of all drugs in developing nations contain plant ingredients (5).

India has a rich diversity of medicinal plants and therefore contributes more to the economy and the traditional healthcare system.

Clove or *Syzygium aromaticum* (L.) Merr. & L.M.Perry, is a dried flower bud native to the Indonesian Maluku islands and a member of the myrtaceae family, which has since been cultivated in many regions across the world (6). It contains a rich profile of bioactive compounds, including eugenol, flavonoids and phenolic acids, which have been reported to possess antioxidant (7, 8) and antimicrobial properties (9, 10). These phytochemicals have also been suggested to play a role in modulating carbohydrate and lipid metabolism, thereby showing potential in managing hyperglycemia and hyperlipidemia. However, despite its widespread traditional use in managing blood sugar and cholesterol levels, scientific validation through integrated *in vitro*, *in vivo* and *in silico* approaches remains limited. They are also thought to be among the spices that have the potential to replace chemical preservatives in many foods, particularly in the processing of meat. Many studies have reported the antimicrobial, antiviral, anticarcinogenic and antifungal properties of various aromatic herbs, such as mint, cinnamon, oregano, clove, thyme and kaempferol. Additionally, clove contains flavonoids and phenolic acids (9). The essential oil extracted from clove flower buds can contain up to 18 % of essential oil, consisting of eugenol, eugenol acetate and β -cariofileno (11). Therefore, this study aimed to investigate the anti-hyperglycemic and anti-hyperlipidemic effects of *S. aromaticum* using these complementary models to bridge the existing knowledge gap.

Materials and Methods

Plant material and extraction

The fresh samples of *S. aromaticum* was collected locally. *Syzygium aromaticum* that had been shade-dried, mechanically pulverised and kept in an airtight container. Using a Soxhlet apparatus and hot percolation technique, *S. aromaticum* was extracted. As a solvent, ethanol was employed. Six hundred mL of ethanol were used to extract about 100 g of material powder. The extract was dried out at a regulated temperature of 40–50 °C. For 24 hr, 30 g of powdered material were steeped and dissolved in 75 mL of ethanol. After that, the filtrate was collected by letting them evaporate in liquid nitrogen.

Phytochemical Screening

Using standard phytochemical procedures, the freshly prepared various crude extracts of *S. aromaticum*-leaves were subjected to a preliminary phytochemical analysis to identify the presence or absence of phytoconstituents such as tannins, reducing sugar, flavonoids, steroids and alkaloids (12).

In vitro analysis

The ethanolic extract of *S. aromaticum* was subjected to *in vitro* analysis by the inhibitory action of α -amylase and α -glucosidase enzymes (13, 14)

Gas chromatography-mass spectrometry (GC-MS) analysis

The temperature of the instrument was initially adjusted to 110 °C and maintained for 2 min. After this, the temperature of the oven was increased to 280 °C, maintaining it there for 9 mins at a rate of 5 °C per min. A 250 °C injection port temperature and a 1 mL/min helium flow rate was guaranteed. Seventy eV was the ionisation voltage. The samples were split 10:1 during injection. The mass spectrum was scanned over an m/z range of 45–450. By using GC-MS, the chemical components were determined. From the relative peak area of each component in the chromatogram, the percentage of each component was determined.

Animals

We utilised male albino rats of 6–8 weeks of age, weighing 150–180 g, were used in the study. The animals were housed in hygienic, dry plastic cages and provided with water and a normal pellet diet. The institutional ethical committee of JJ College of Arts and Science College gave its approval for this investigation, which was conducted in the college's animal house. The animals were divided into 5 groups with 6 rats each. Commercially available eugenol is used for the treatment.

Group I: Normal rats (saline 2 mL/kg body weight).

Group II: Diabetic control rats (streptozotocin (STZ) induced as 60 mg/kg body weight.).

Group III: Diabetic induced animals were fed with *S. aromaticum* extract for 45 days (300 mg/kg body weight).

Group IV: Diabetic rats treated with Eugenol for 45 days (10 mg/kg body weight).

Group V: Diabetic rats treated with glibenclamide (3 mg/kg body weight).

At the end of the study the samples were collected for further biochemical analysis.

In silico analysis

Plant derived compounds (Ligands)

Using GC-MS, eugenol was identified from the ethanolic extract of *S. aromaticum* as one of the ligands for our investigation. These chemicals physiochemical characteristics and structures are taken from the PubChem database. A wide range of parameters, such as compound structure, name, fragments, molecular weight, chemical formula, X log P, hydrogen bond donor and acceptor count, can be searched for in the public database PubChem. Its own web editor uses the smiles format and we use this converter to convert our compounds into PDB format. The PubChem database is used to obtain Lipinski's characteristics, including molecular weight, log P and the quantity of hydrogen bond donors and acceptors.

Proteins

The RCSB-PDB database was utilised that contain a three-dimensional (3D) structural information of big biological macromolecules like proteins and nucleic acids. It offers both basic and sophisticated search options depending on sequence, structure and function annotations. Using the Swiss PDB viewer,

the heteroatoms are removed from the protein structure file and the C terminal oxygen is added. The protein structure file is available on PDB. The previous study, the PDB IDs for AMPK, α -amylase and α -glucosidase are 4zhx, 2qv4 and 3a4a respectively (15).

Docking Studies

AutoDock tools were used to automate docking by making grids, calculating docking scores and looking at conformers of activators that were bound to the active sites of AMPK, pancreatic α -amylase and pancreatic α -glucosidase as anti-diabetic targets. The ProDrug server made 3D coordinates and minimised energy. During docking, a genetic algorithm let all the torsions move freely and AutoGrid centered the grid map on certain protein residues.

Statistical analysis

The data show the number of experiments and their mean $\pm$ standard deviation (S.D). Given that the current study has examined more than two treatment groups. The statistical package of social science (SPSS) version 14.0 for Windows is used to do one way analysis of variance (ANOVA) in statistical analysis. A level of significance is defined as $p < 0.05$.

Result and Discussion

Phytochemical analysis of the *Syzygium aromaticum*

In the current investigation, *S. aromaticum* extract was gathered, dried and the leaves were extracted using ethanol as the solvent. Alkaloids, carbohydrates, tannins, terpenoids, steroidal glycosides, quinone, anthraquinone, saponin glycosides, flavonoids, total protein, fixed oil, phenols and coumarin are all tested for in *S. aromaticum* extract. The phytoconstituents found in the ethanolic extracts of *S. aromaticum* are shown in Table 1. In the present study, ethanolic extracts of *S. aromaticum* which contains

the alkaloids, carbohydrates, tannins, terpenoids, flavonoids, total protein, fixed oil, phenols and coumarin.

The biological actions of medicinal plants are not dependent on a single component, but rather on the synergistic effects of many chemicals, including alkaloids, terpenoids, tannins and saponins (16). The vast majority of secondary metabolites are found in the ethanolic extracts of *S. aromaticum* used in this investigation. *Syzygium aromaticum* contains phytochemicals (17). The phytochemical analysis reveals the presence of lipids, triterpenes, alkaloids, flavonoids, tannins, sterols and carbohydrates. There are a lot of secondary metabolites, including phenols, flavonoids, coumarins, saponins, tannins and sterols, in the *S. aromaticum* extract (18), these findings are in accordance with the results of the present study.

In vitro anti-diabetic activity of *Syzygium aromaticum*

The present study, evaluate the *in vitro* anti-diabetic activities of ethanolic and extract of *S. aromaticum* with the standard drug acarbose by an inhibitory activity of α -amylase and α -glucosidase enzymes. The results are shown in the Tables 2 and 3. The ethanolic extracts have an anti-diabetic activity by an *in vitro* study.

Ethnolic extract of *S. aromaticum* produced 21.4 % inhibition of α -amylase activity at 0.2 mg/mL and 91.1 % at 1 mg/mL concentration and its IC_{50} is found to be 0.53 mg/mL and the standard drug confirmed 30.2 % and 94.8 % at 0.2 mg/mL and 1.0 mg/mL respectively. The IC_{50} value of standard drug is 0.39 mg/mL against the α -amylase enzyme (Table 2).

Ethanolic extract of *S. aromaticum* showed 31.6 % and 89.1 % of inhibition on α -glucosidase at the concentration of 0.2 mg/mL and 1 mg/mL respectively and its IC_{50} is found to be 0.51 mg/mL. The acarbose as a standard confirmed 33.2 % of inhibition at 0.2 mg/mL and 97.3 % at 1 mg/mL concentrations and its IC_{50} is found to be 0.36 mg/mL (Table 3).

Table 1. Phytochemical analysis of *Syzygium aromaticum* of ethanolic extracts

S. No.	Phytochemical constituents	Name of the test	Ethanol
1.	Alkaloids	Mayer's test	+
2.	Carbohydrate	Molish test	+
3.	Tannin	Lead acetate test	+
4.	Terpenoids	Noller test	+
5.	Steroidal glycosides	Salkowaski test	-
6.	Quinones	H ₂ SO ₄ test	+
7.	Anthraquinone	Borntrager's test	+
8.	Saponin glycosides	Froth test	+
9.	Flavonoids	Schioda's test	+
10.	Total protein	Millon's test	+
11.	Fixed oil	Spot test	+
12.	Phenols	FeCl ₃ test	+
13.	Coumarin	NaCl test	+

+: present; -: absent

Table 2. *In vitro* anti-diabetic activity of ethanolic extract of *Syzygium aromaticum* by α -amylase method

S. No	Concentration of the sample (mg/mL)	% of inhibition of ethanolic extract	% of inhibition of acarbose
1	0.2	21.4	30.2
2	0.4	39.6	51.5
3	0.6	58.3	68.6
4	0.8	71.9	82.7
5	1.0	91.1	94.8
6	IC_{50}	0.53	0.39

Table 3. *In vitro* anti-diabetic activity of ethanolic extract of *Syzygium aromaticum* by α -glucosidase method

S. No	Concentration of the sample (mg/mL)	% of inhibition of ethanolic extract	% of inhibition of acarbose
1	0.2	31.6	33.2
2	0.4	49.3	55.7
3	0.6	62.2	69.2
4	0.8	75.7	86.4
5	1.0	89.1	97.3
6	IC_{50}	0.51	0.36

The carbohydrate metabolising enzymes α -amylase and α -glucosidase are responsible for converting oligosaccharides and disaccharides into monosaccharides (19–21). The inhibition of these enzymes decreases the absorption of glucose and lengthens the time it takes for carbohydrates to be digested (22). In the present study, the ethanolic extract of *S. aromaticum* strongly inhibits the α -amylase and α -glucosidase enzyme. This activity is due to the presence of various phytocomponents present in the extract. The α -amylase and α -glucosidase enzymes are inhibited in a dose-dependent manner by the aqueous extract of *Syzygium Cumini* seeds and *Psidium guajava* leaves (23). *Psidium guajava* leaf methanolic extract inhibits α -amylase and α -glucosidase in a concentration-dependent way (24). This may also be proved in the present study.

Compound identification by gas chromatography-mass spectrometry (GC-MS) analysis

The present study investigates the presence of phytoconstituents in the ethanolic extracts of *S. aromaticum* by GC-MS method. The results of the GC-MS analysis of *S. aromaticum* are shown in Table 4. Gas chromatography-mass spectrometry analysis report is shown in Fig 1. Nearly 127 peaks were identified.

The present study investigates the presence of phytoconstituents in the ethanolic extracts of *S. aromaticum* by GC-MS analysis. The results of this GC-MS analysis of *S. aromaticum* are shown in Fig. 1 and Table 4. One hundred twenty six different phytoconstituents are identified in the ethanol extract of *S. aromaticum*. Some important compounds such as such as eugenol, caryophyllene, cyclohexane, isodene, nerolidol, cubenol, octadecenoic acid, hexadecanoic acid, arabinitol, etc.

The compounds which have the pharmacological activities such as eugenol have anti-microbial activity (25), antibacterial activity (26) and anti-inflammatory activity (27). The compound caryophyllene have anti-inflammatory activity and antidiabetic activity (24). The compound of n-hexadecanoic acid have an anti-inflammatory activity, the compound nerolidol which have anti-oxidant activity (28) and antifungal activity (29).

Effect of *Syzygium aromaticum* on diabetic markers

The effects of *S. aromaticum* ethanolic extract on glucose, insulin and HbA1C, three diabetes indicators are depicted in Table 5. When STZ was administered, insulin levels were lowered while glucose and HbA1C levels were raised. Following administration of the *S. aromaticum* ethanolic extract, the levels of the aforementioned indicators were considerably ($p < 0.05$) recovered by eugenol and glibenclamide.

The diabetic rats reduced insulin production can be attributed to the STZ, which destroys the Langerhans beta cells. Normally, there is an indirect relationship between blood glucose concentration and insulin levels. In the current study, the STZ's death of beta cells results in a decrease in insulin levels. After, the treatment of *S. aromaticum*, the levels of eugenol return to normal. The ethanolic extract of *S. aromaticum* has a hypoglycemic effect because it secretes insulin. The ethanolic extract of caryophyllene and *Psidium guajava* lowers the blood glucose level in STZ-induced diabetic rats (24). Eugenol activates the GLUT4-AMPK signalling pathway, which increases skeletal muscle glucose absorption and improves insulin sensitivity. This method lowers blood glucose levels in STZ-induced diabetic rats (30). The current study likewise notes a similar effect.

By stimulating the beta cells to regenerate and secrete more insulin, phytochemicals have a significant impact on stimulating the release of insulin. Alkaloids, terpenoids, flavonoids and phenols are among the different phytoconstituents found in the ethanolic extract of *S. aromaticum* used in this investigation. These substances primarily promote the release of β endorphins by stimulating the A1-adrenergic receptors. These substances enhance the muscle cells absorption of glucose. These phytoconstituents might encourage the regeneration of beta cells. Insulin secretion may be induced by this action (31). This kind of effect may lower the glucose levels in the STZ-induced diabetic rats.

A diabetic measure called HbA1c can be used to forecast the average blood glucose level in people with long-term diabetes (32). There is a direct correlation between rising glucose concentrations and rising HbA1c concentrations (33). Exercise and food have little effect on the HbA1c, which is the result of the excess glucose reacting with RBC. HbA1c forms slowly and is difficult to separate from other molecules. As a result, it is a useful marker for predicting if a patient has diabetes. The HbA1c level represents the actual blood glucose level (34). The current study treats the STZ induced diabetic rats with an ethanolic extract of *S. aromaticum*, which lowers their HbA1c content.

Effect of *Syzygium aromaticum* on glucose-6-phosphatase and fructose 1,6-bis phosphatase level

The ethanolic extract of *S. aromaticum* on fructose-1,6-bisphosphatase and glucose-6-phosphatase is displayed in Table 6. Rats with STZ-induced diabetes have higher concentrations of fructose-1,6-bisphosphatase and glucose-6-phosphatase. Following the administration of *S. aromaticum* ethanolic extract, eugenol significantly recovered the altered levels of the aforementioned markers, in line with the glibenclamide-treated rats.

Enzymes that metabolise carbohydrates are crucial for controlling blood glucose levels (35). An enzyme called glucose-6-phosphatase is involved in the processes of glycogenolysis and gluconeogenesis (36). The elevated amount of glucose-6-phosphatase in the current investigation may be caused by STZ-induced liver injury. This enzyme's level decreases during *S. aromaticum* treatment; this could be because of the influence of increased insulin concentration or liver cell regeneration. The process of gluconeogenesis and glycogenolysis may be slowed down by the rising concentration of glucose-6-phosphatase. This process is in favour of lowering blood glucose levels.

An enzyme that breaks down carbohydrates, fructose-1,6-bisphosphatase primarily participates in the gluconeogenesis process (36). The reduced insulin concentration in the STZ-induced rats causes a rise in this enzyme's level. The amount is lowered following *S. aromaticum* treatment. This decrease may reduce the production of glucose from sources other than carbohydrates. That could be the cause of the blood's lowering glucose levels.

Effect of *Syzygium aromaticum* on lipid profiles

The ethanolic extract of *S. aromaticum* on lipid profiles, including TC, TG, LDL, HDL and VLDL is displayed in Table 7. The delivery of STZ disrupted the metabolism of lipids, raising the levels of TC, TG, LDL and VLDL while lowering HDL. The administration of glibenclamide, eugenol and *S. aromaticum* ethanolic extract significantly ($p < 0.05$) normalises the abnormal lipid profile level.

Table 4. Gas chromatography-mass spectrometry (GC-MS) peak report for *Syzygium aromaticum*

Peak #	Retention time	Area	Area %	Height	Name
1	9.095	17377	0.00	6426	Cyclopentanecarboxaldehyde, 2,2,5-Trimethyl-, Trans-(.+
2	9.346	5351	0.00	2454	2-Propenoic Acid, 2-Methyl-, Ethenyl Ester
3	9.948	85994	0.02	35784	(+)-2-Bornanone
4	10.759	105346	0.02	31577	Benzoic Acid, 2-Hydroxy-, Methyl Ester
5	11.672	1220482	0.23	194790	2-Allylphenol
6	12.150	29966	0.01	9724	1,2-Propanedione, 1-Phenyl-
7	12.344	34970	0.01	7231	Acetone-Oxime
8	12.661	43736	0.01	12620	1-(4-Hydroxy-3-Methylphenyl)Ethanone #
9	13.103	1573482	0.30	631029	1h-Cyclopenta[1,3]Cyclopropa[1,2]Benzene, 3a,3b,4,5,6,7-Hex
10	13.423	218691171	41.59	20594749	Eugenol
11	13.570	6465459	1.23	2370224	Tricyclo[4.4.0.0(2,7)]Dec-3-Ene, 1,3-Dimethyl-8-(1-Methyleth
12	13.650	206198	0.04	69075	2,5-Methano-2h-Indeno[1,7-Bc]Oxete, Octahydro-1a-Methy
13	13.757	629758	0.12	109435	Cyclohexane, 1-Ethenyl-1-Methyl-2,4-Bis(1-Methylethenyl)-, [1S-(1.A.,2.Be
14	13.860	166780	0.03	50699	3-(2-Propenyl)Cyclopentene
15	13.959	622159	0.12	87451	Benzaldehyde, 4-Hydroxy-3-Methoxy-
16	14.052	385375	0.07	73965	4-Allylphenol
17	14.257	80637262	15.34	19378577	Caryophyllene
18	14.485	132026	0.03	31558	3,5-Cycloheptadien-1-One
19	14.613	842493	0.16	229631	1h-Cyclopenta[1,3]Cyclopropa[1,2]Benzene, 3a,3b,4,5,6,7-Hex
20	14.689	15856354	3.02	5951822	1,4,8-Cycloundecatriene, 2,6,6,9-Tetramethyl-, (E,E,E)-
21	14.786	793317	0.15	284172	1h-Cycloprop[E]Azulene, Decahydro-1,1,7-Trimethyl-4-Me
22	14.905	2537804	0.48	580546	1,6-Cyclodecadiene, 1-Methyl-5-Methylene-8-(1-Methylet
23	15.032	1520266	0.29	505127	1,6-Cyclodecadiene, 1-Methyl-5-Methylene-8-(1-Methylet
24	15.179	5218178	0.99	1348265	.A.-Farnesene
25	15.333	329865	0.06	109305	Isoledene
26	15.590	147302068	28.01	19025979	Phenol, 2-Methoxy-4-(2-Propenyl)-, Acetate
27	15.703	5806931	1.10	1605160	(3R,3ar,3br,4S,7R,7ar)-4-Isopropyl-3,7-Dimethyloctahydro-1H-Cyclopenta[1
28	15.833	336650	0.06	69434	9,10-Anthracenediol, 1,4,4a,5,8,8a,9,9a,10,10a-Decahydro-2,3,
29	15.946	186339	0.04	44944	Nerolidol
30	16.059	496548	0.09	52377	3-(3-Hydroxyphenyl)Propionic Acid
31	16.295	351979	0.07	83385	(Cyclopropyl)Trivinylsilane
32	16.370	1011173	0.19	335591	Phthalic Acid, Monoethyl Ester
33	16.432	3458937	0.66	1069884	(-)-5-Oxatricyclo[8.2.0.0(4,6)]Dodecane,,12-Trimethyl-9-Meth
34	16.616	529554	0.10	153447	Eugenol
35	16.688	620807	0.12	183786	Ledol
36	16.754	501754	0.10	154058	(1R,3E,7E,11R)-1,5,5,8-Tetramethyl-12-Oxabicyclo[9.1.0]Dodeca-3,7-Diene
37	16.819	161640	0.03	70761	Farnesene Epoxide, E-
38	16.925	1803722	0.34	471591	Di-Epi-1,10-Cubenol
39	17.012	591478	0.11	165490	Cubenol
40	17.099	1358263	0.26	300789	Tau.-Cadinol
41	17.256	1809036	0.34	281371	Tau.-Muurolol
42	17.404	482288	0.09	131638	Chrysantenyl 2-Methuylbutanoate
43	17.544	282703	0.05	51131	Cubenol
44	17.637	3934486	0.75	1223696	1-(2,3,4-Trimethoxyphenyl)Ethanone
45	17.776	411831	0.08	90804	1,4-Methanophthalazine, 1,4,4a,7,8,8a-Hexahydro-9,9-Dimethyl-, (1.A.,4.Al
46	17.844	341515	0.06	71230	3-Chloropropionic Acid, Heptyl Ester
47	17.930	251322	0.05	52908	Limonene Dioxide 2
48	18.025	139965	0.03	36033	7-Oxabicyclo[4.1.0]Heptane
49	18.130	81372	0.02	23496	Pentane, 3-Bromo-
50	18.213	420781	0.08	74176	9-Octadecenoic Acid (Z)-
51	18.333	160744	0.03	42861	4-Thujanol, cis-(.-.-)-
52	18.430	54138	0.01	14435	1,4-Pentadiene, 3-Methyl-
53	18.526	937413	0.18	256122	Phenol, 2-Methoxy-4-(2-Propenyl)-, Acetate
54	18.618	207933	0.04	55434	N-Dodecylpyridinium Chloride
55	18.730	45453	0.01	15383	2-Azetidinone
56	18.785	66999	0.01	20197	Ethyl 2,4-Dioxovalerate
57	18.856	151848	0.03	39563	Pseduosarsapogenin-5,20-Dien Methyl Ether
58	18.935	28293	0.01	10822	Cyclopentane methanol
59	19.030	56855	0.01	10831	Ethyl 2-Butynoate
60	19.087	81724	0.02	26861	(6Z)-Nonen-1-ol
61	19.158	221656	0.04	60889	2,6-Octadien-1-ol, 3,7-Dimethyl-
62	19.345	87782	0.02	15416	3-Octanol, 3,7-Dimethyl-
63	19.455	117075	0.02	23353	1-Buten-3-yne,-4-Trimethylsilyl
64	19.528	155826	0.03	29428	1,2-Benzenedicarboxylic acid, Bis (2-Methyl propyl) Ester
65	19.630	27059	0.01	11089	1-Butyne, 3-Chloro-
66	19.718	110771	0.02	29700	1,3,5-Cycloheptatriene
67	19.785	28070	0.01	9879	2-Tridecanone
68	20.016	272489	0.05	93536	Eicosanoic acid, Methyl ester
69	20.141	20140	0.00	6493	4-Hexenyl propionate
70	20.207	35997	0.01	9656	3,4-Pentadien-1-ol, 2,2-Dimethyl-

71	20.414	4180010	0.79	797266	N-Hexadecanoic Acid
72	20.705	9672	0.00	4758	Heptanoic acid, Ethyl ester
73	20.745	17502	0.00	8627	1-Hexene, 3,5,5-Trimethyl-
74	20.834	479820	0.09	75812	Phenol, 4-[3-(Acetyloxy)-1-Propenyl]-2-Methoxy-, Acetate
75	21.036	212545	0.04	37266	(1S,2R,4R,7R)-4-Isopropyl-7-Methyl-3,8-Dioxatricyclo[5.1.0.02,4]Octane
76	21.154	354402	0.07	50459	Phenol, 4-[3-(Acetyloxy)-1-Propenyl]-2-Methoxy-, Acetate
77	21.399	84034	0.02	16306	2,2,4,4-Tetramethyl cyclobutan-1-ol
78	21.467	46216	0.01	13981	Propanedinitrile, Methyl-
79	21.574	105586	0.02	16975	2-Cyclobuten-1-one, 4-Hydroxy-2,3-Dimethoxy-4-[3-[(Tetra
80	21.772	228298	0.04	66755	9,12-Tetradecadien-1-ol, (Z,E)-
81	21.820	253018	0.05	59596	Methyl9-Octadecenoate
82	21.971	35832	0.01	10882	2-(3-Methyl-3-Nitrobutyl)-1,3-Dioxolane
83	22.036	74732	0.01	24391	Heneicosanoic acid, Methyl ester
84	22.166	463016	0.09	61051	9,12-Octadecadienoic acid (Z,Z)-
85	22.385	658835	0.13	60900	Octadecanoic acid
86	22.605	149370	0.03	27624	Cyclohexene, 1-Isopentyl-
87	22.721	378087	0.07	53846	5-Undecene, 3-Methyl-, (E)-
88	22.910	132370	0.03	24496	Z-4-Nonadecen-1-ol Acetate
89	23.009	68446	0.01	12935	Adipic Acid, Di(Trans-2-Methylcyclohexyl) Ester
90	23.223	168487	0.03	25181	Chloromethyl2-Chlorododecanoate
91	23.325	76818	0.01	14575	Cyclopentene, 1-Trimethylsilyl-2-Methyl-4-Methylene-
92	23.455	22522	0.00	5641	Nicolaoidesin A
93	23.522	68011	0.01	15619	Benzeneacetic acid, .A.-(1-Hydroxycyclopentyl)
94	23.653	117012	0.02	32806	Dichloroacetic Acid, Nonyl Ester
95	23.730	103208	0.02	22409	2-Pentadecanone
96	23.840	34858	0.01	9077	1,3-Hexanediol,
97	23.905	62091	0.01	17035	9-Eicosyne
98	24.047	41273	0.01	7091	1,3-Benzenedicarboxylic Acid, 5-(1,1-Dimethylethyl)-
99	24.216	36421	0.01	7166	2-Dodecen-1-ol, (E)-, TMS Derivative
100	24.329	17078	0.00	6048	Terephthalic Acid, 1-Cyclopentylethyl Propyl Ester
101	24.370	8158	0.00	4729	Methyl 3-Bromo-1-Adamantaneacetate
102	24.471	68466	0.01	18582	Hexadecane, 1-Iodo-
103	24.543	132369	0.03	38764	Cyclohexanecarboxylic Acid, 2-Tridecyl Ester
104	24.705	3815	0.00	1914	6,7,10-Trimethylbicyclo [5.4.0]undec-10-en-2-one
105	24.778	24046	0.00	7425	Isophthalic Acid, Monochloride, 2-Methylcyclohexyl Ester
106	24.825	12533	0.00	5959	4-Tert-Butylphenol, TMS Derivative
107	24.915	25699	0.00	5868	Succinic Acid, Cyclohexylmethyl 10-Chlorodecyl Ester
108	24.988	28888	0.01	11421	Methyl octylphenol -Ethoxycarboxylate
109	25.053	120642	0.02	29387	Hexanoic Acid, 2-Dimethylaminoethyl Ester
110	25.203	199002	0.04	43311	Dimethylmalonic Acid, Pentafluorophenyl Pentyl Ester
111	25.239	143019	0.03	43386	Tricyclo[3.1.0.0(2,4)]Hexane, 3,3,6,6-Tetraethyl-, Trans--
112	25.327	65137	0.01	15968	1-Bromo-1,1-Dideutero-2-Methyldecane
113	25.443	69187	0.01	13886	Arabinitol, Pentaacetate
114	25.564	41417	0.01	10714	Thymol, TBDMS Derivative
115	25.655	911675	0.17	194892	Benzene, 1-Methoxy-4-(2-Propenyl)-
116	25.790	85838	0.02	29992	3-[(Adamantan-1-ylmethyl)-Amino]-1-(4-Bromo-Phenyl)-Pyrrolidine-2,5-Dione
117	25.909	775897	0.15	226108	1,2-Benzenedicarboxylic acid, Dioctyl ester
118	26.025	89442	0.02	21309	Silane, Dimethyl(2-Methoxyethoxy)Butoxy-
119	26.136	23993	0.00	8487	Silane, Dimethyl(1-Phenylpropoxy)Ethoxy-
120	26.222	159354	0.03	48253	Cholest-22-Ene-21-ol, 3,5-Dehydro-6-Methoxy-, Pivalate
121	26.295	20143	0.00	7083	Methyl Octylphenol-Ethoxycarboxylate
122	26.411	151780	0.03	28145	1,3-Dioxolane, 4-Ethyl-5-Hexyl-2,2-Bis(Trifluoromethyl)-,
123	26.548	149653	0.03	37334	3-Octen-5-Yne, 2,2,7,7-Tetramethyl-, (E)-
124	26.644	27525	0.01	8809	1,4-Benzenediol, 2,5-Bis(1,1-Dimethylethyl)-
125	26.702	27651	0.01	9265	Methanol, [4-(1,1-Dimethylethyl)Phenoxy]-, Acetate
126	26.850	27533	0.01	10325	Tris(Tert-Butyldimethylsilyloxy)Arsane
127	26.945	37879	0.01	9306	Methyl 3-Bromo-1-Adamantaneacetate
		525802887	100.00	81788539	

Table 5. The activity of *Syzygium aromaticum* extract on the glucose, insulin and HbA1C level of diabetic and non-diabetic rats

Parameters	Group-I	Group-II	Group-III	Group-IV	Group-V
Glucose (mg/dl)	91.62 ± 1.49 ^a	264.49 ± 1.03 ^b	102.92 ± 1.92 ^c	104.44 ± 0.67 ^c	96.29 ± 0.99 ^{a, c}
Insulin (IU/L)	3.47 ± 0.32 ^a	0.61 ± 0.25 ^b	3.61 ± 0.62 ^c	3.60 ± 0.34 ^c	3.51 ± 0.84 ^a
HbA1C (%)	4.61 ± 0.89 ^a	9.32 ± 0.61 ^b	5.01 ± 0.53 ^c	5.04 ± 0.24 ^c	4.93 ± 0.72 ^c

Values are expressed as means ± SD for six rats in each group Values not sharing a common marking (a, b, c.....) differ significantly at $p \leq 0.05$ (DMRT).

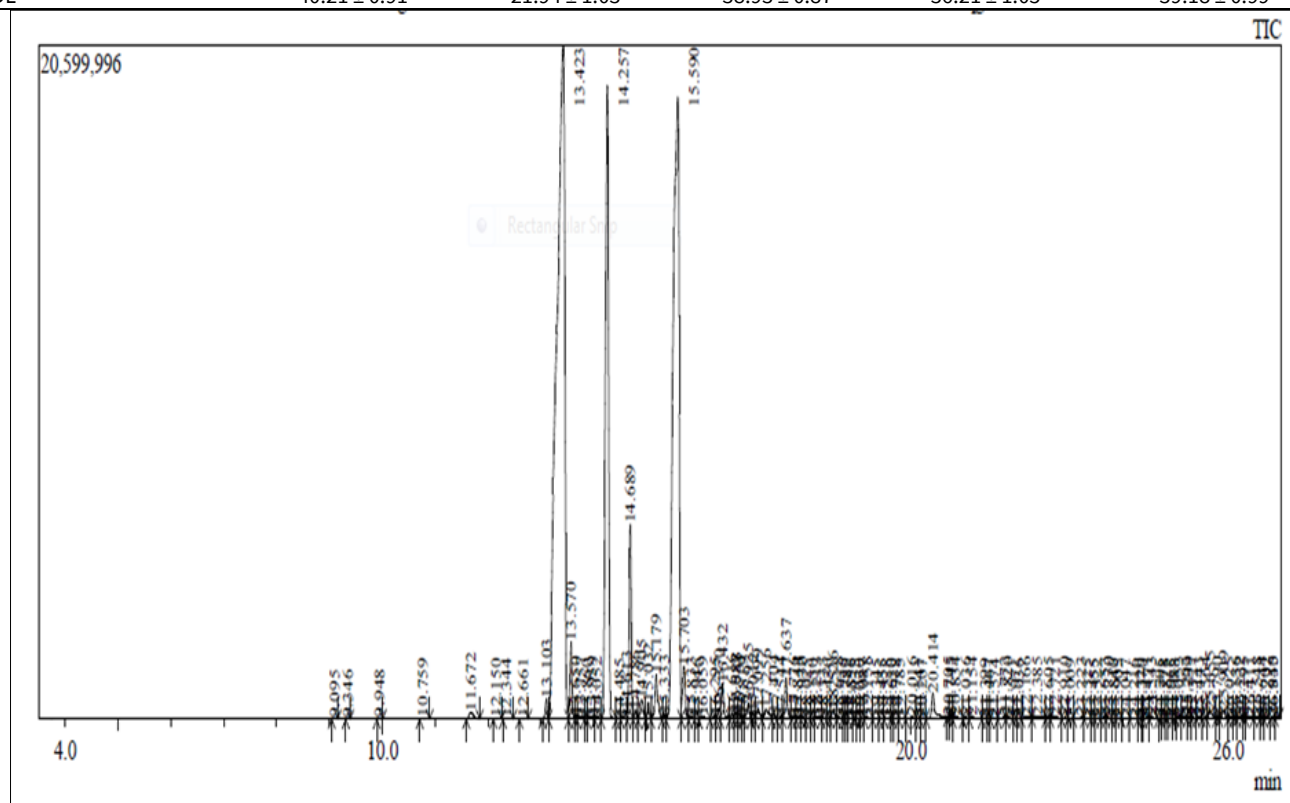
Table 6. The activity of ethanolic extract of *Syzygium aromaticum* extract on the glucose-6-phosphatase and fructose 1,6-bisphosphatase level in treated and untreated rats

Parameters	Group-I	Group-II	Group-III	Group-IV	Group-V
Glucose-6-phosphatase (µg of phosphorous liberated/mg/g tissue)	7.39 ± 0.36 ^a	21.16 ± 0.52 ^b	9.15 ± 0.21 ^c	9.19 ± 0.27 ^c	8.89 ± 0.15 ^c
Fructose 1,6-bisphosphatase (µg of phosphorous liberated/mg/g tissue)	36.74 ± 0.19 ^a	90.15 ± 0.73 ^b	41.29 ± 0.26 ^c	42.64 ± 0.31 ^c	41.02 ± 0.14 ^c

Values are expressed as means ± SD for six rats in each group Values not sharing a common marking (a, b, c.....) differ significantly at $p \leq 0.05$ (DMRT).

Table 7. The activity of *Syzygium aromaticum* extract on the lipid profile in diabetic and non-diabetic rats

Parameters	Group-I	Group-II	Group-III	Group-IV	Group-V
TC	97.82 ± 3.26 ^a	281.38 ± 4.14 ^b	104.18 ± 3.84 ^c	108.91 ± 3.97 ^c	102.17 ± 3.57 ^{a, c}
TG	80.19 ± 3.19 ^a	280.11 ± 3.53 ^b	91.91 ± 2.94 ^c	92.35 ± 2.43 ^c	83.11 ± 2.74 ^a
LDL	38.11 ± 1.19 ^a	196.14 ± 1.41 ^b	41.92 ± 1.01 ^a	43.04 ± 1.59 ^c	40.13 ± 2.02 ^a
VLDL	16.04 ± 0.62 ^a	56.02 ± 0.72 ^b	18.38 ± 0.51 ^a	18.47 ± 0.42 ^a	16.62 ± 0.56 ^a
HDL	40.21 ± 0.91 ^a	21.94 ± 1.03 ^b	38.93 ± 0.87 ^a	36.21 ± 1.05 ^{a, c}	39.18 ± 0.99 ^a



In silico analysis

Eugneol is a compound identified from GC-MS studies. This eugenol was used for docking analysis. The compound eugenol was selected for docking analysis against the pancreatic α -amylase (PDB-ID (2QV4)), pancreatic α -glucosidase (PDB-ID (3A4A)) and AMPK (PDB-ID (4ZHX)) enzyme. The structure of pancreatic α -amylase, pancreatic α -glucosidase and AMPK enzymes respectively were depicted (Fig. 2, 3 and 4). The outcome of the docking process is represented in Fig 5, 6 and 7. Initially, every compound was screened according to the score function. Pancreatic α -amylase had a glide score of -6.8, pancreatic α -glucosidase had a score of -7.9 and the AMPK had a value of -7.3 kcal/mol (Table 8).

Molecular docking, also known as virtual screening, has many benefits, such as a lower error rate, better usability and stability, a wide range of uses, low cost and easy scalability. The current study demonstrated that eugenol interacts with critical amino acid residues in the three target enzymes. It specifically interacted with ARG252, PHE335, PRO4 and ASP402 in pancreatic α -amylase; HIS280, PHE303, GLN353, ARG315, TYR158 and PHE178 in pancreatic α -glucosidase; and LYS31, LYS29, ILE46, VAL24 and GLY28 in AMPK, indicating a strong binding affinity at the active sites of these enzymes.

The crystal structures of α -amylase (PDB code: 1B2Y) and α -glucosidase (PDB code: 5NN8) have been utilised in docking studies with phenolic compounds, revealing interactions such as hydrogen bonds, halogen bonds, Van der Waals contacts and π - π interactions as the principal binding forces between inhibitors and target enzymes (43). The inhibitory effect of phenolic compounds on α -amylase and α -glucosidase, as evidenced in previous studies, aligns with the results of the current investigation, thereby reinforcing the potential of eugenol as a bioactive inhibitor of these essential enzymes in carbohydrate metabolism (43).

Conclusion

We may conclude that *Syzygium aromaticum* has anti-hyperglycemic and hypolipidemic properties in its ethanolic extract and that it can be employed as a hypoglycemic medication. The ability of *S. aromaticum* to attach to several protein molecules involved in diabetes metabolism is demonstrated by the docking studies. Therefore, it can be concluded that *S. aromaticum* may be utilised as a powerful medication for diabetes and its associated complications in the near future.

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Authors' contributions

MR and VAA contributed to the conceptualisation of the study. MR, NR and DMMG were responsible for data curation. MR, NR and VAA contributed to the formal analysis and methodology. MR and NR prepared the original draft of the manuscript. AA, AS, AM and VAA reviewed and edited the manuscript. All authors have read and approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest: Authors do not have any conflict of interest to declare.

Ethical issues: None

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Table 8. Docking score and interaction of α amylase, α glucosidase and adenosine monophosphate activated protein kinase enzyme to the compound eugenol

S. No	Protein names	Docking score (kcal/mol)	Interaction
1	Human pancreatic α amylase (2QV4)	-6.8	ARG252, PHL 335. PRO4 and ASP402
2	Human pancreatic α glucosidase (3A4A)	-7.9	HIS280, PHE303, GLN353, ARG315, TYR158 and PHE 178
3	Adenosine monophosphate-activated protein kinase (4ZHX)	-7.3	LYS31, LY29, ILE46, VAL24 and GLY28

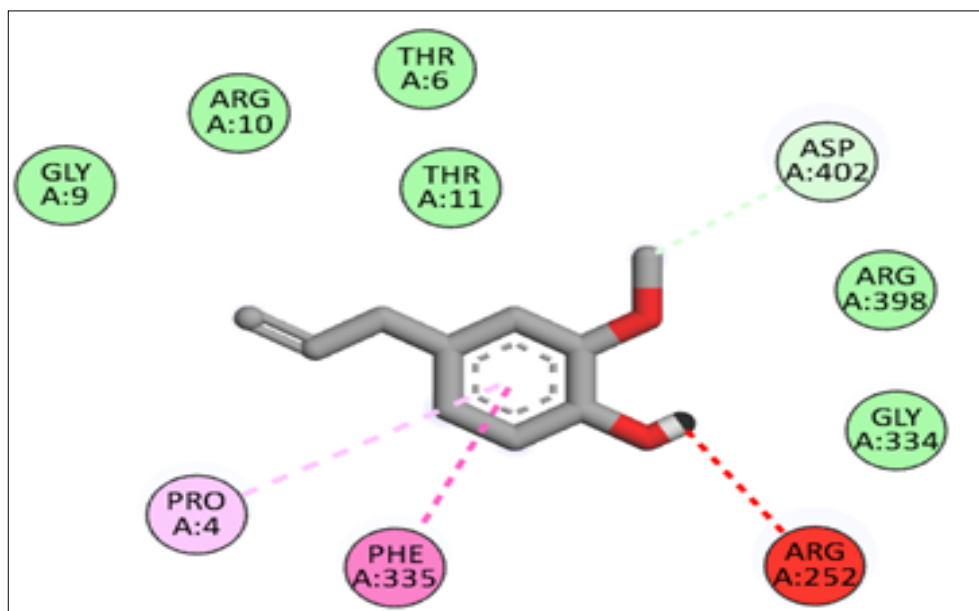


Fig. 2. The structure of human pancreatic α-amylase.

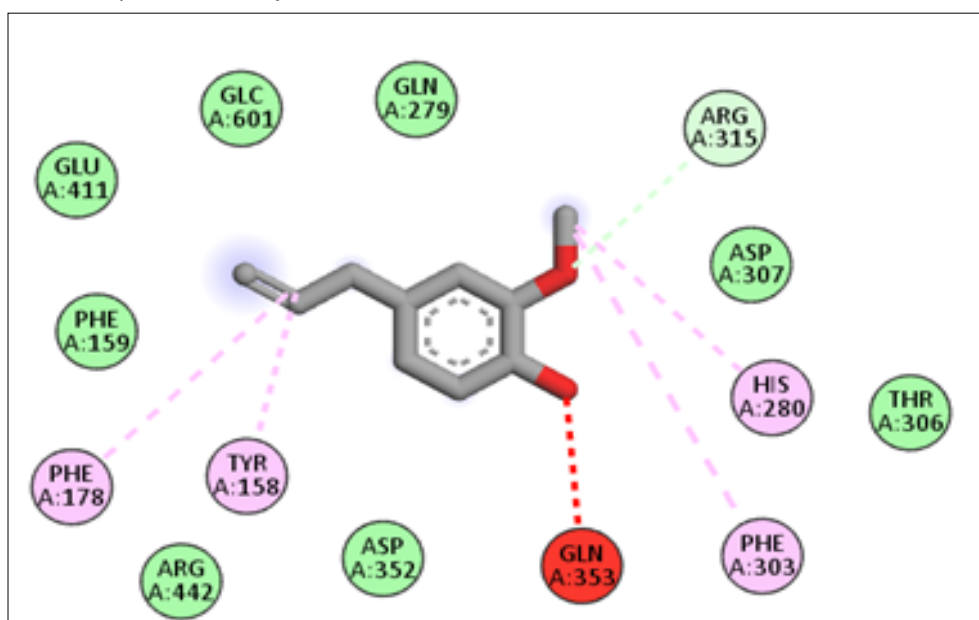


Fig. 3. The structure of human pancreatic α-glucosidase.

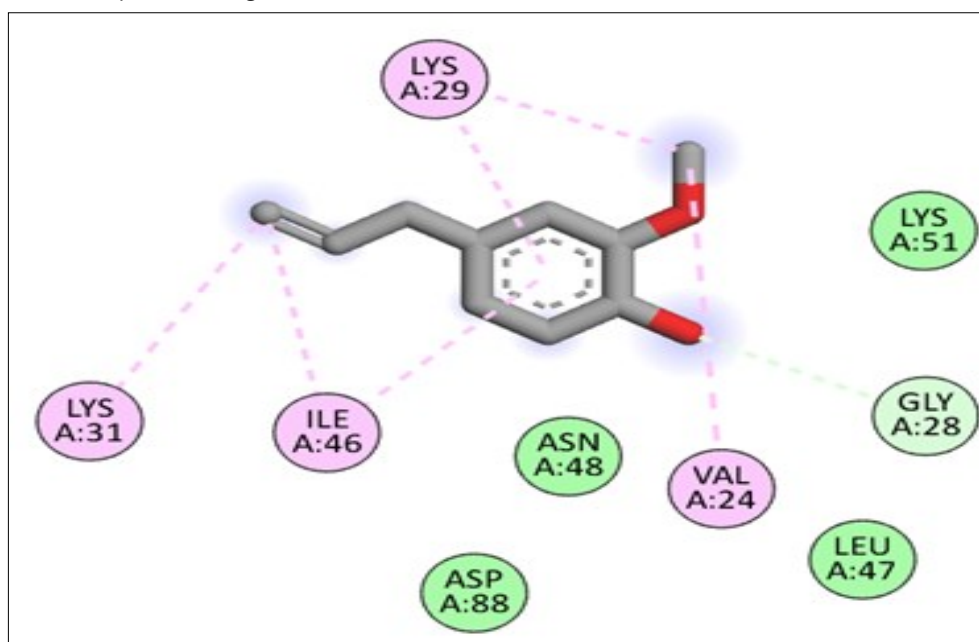


Fig. 4. The structure of adenosine monophosphate-activated protein kinase.

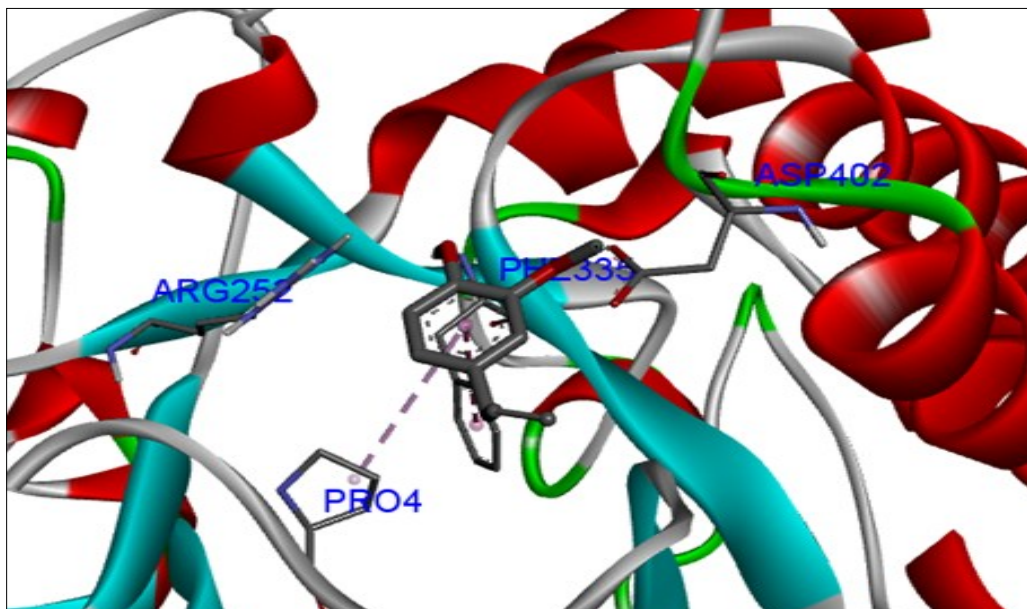


Fig. 5. The interaction between the eugenol and human pancreatic α -amylase.

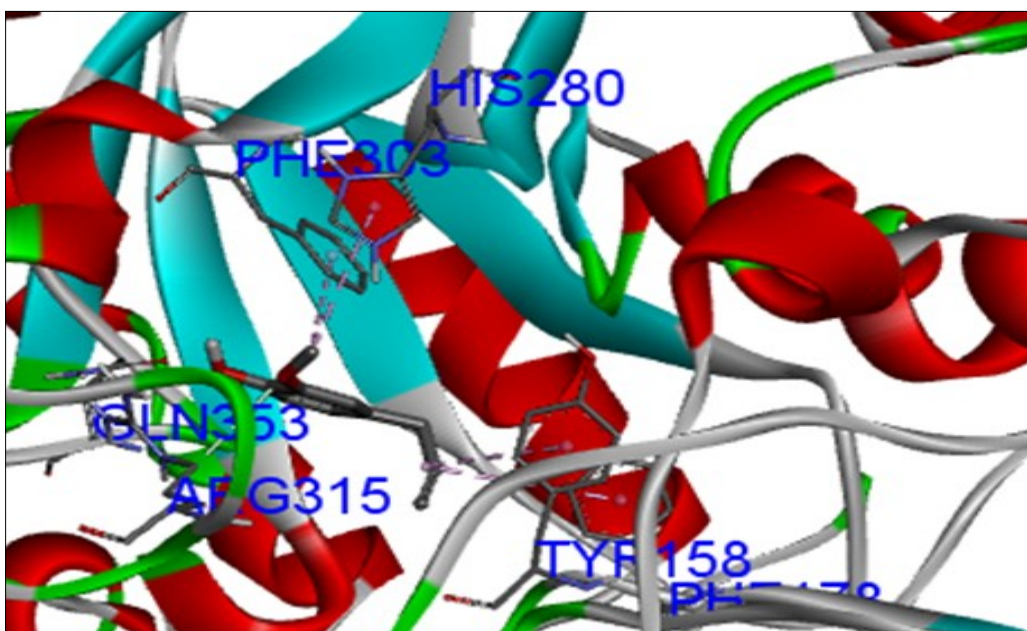


Fig. 6. The interaction between the eugenol and human pancreatic α -glucosidase.

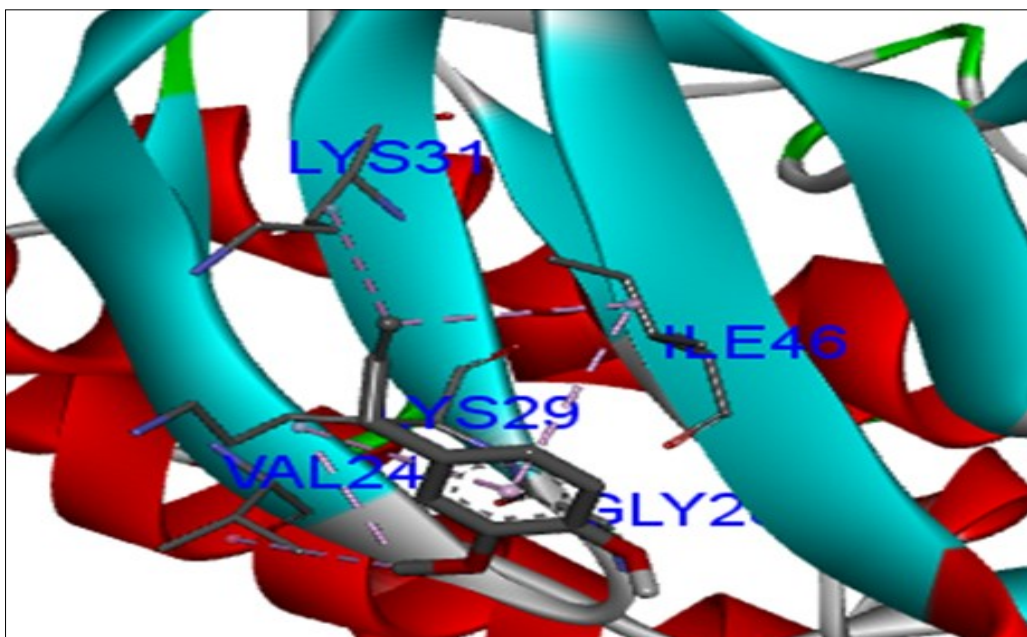


Fig. 7. The interaction between the eugenol and adenosine monophosphate-activated protein kinase.

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