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Original article

Network pharmacology based anti-diabetic attributes of bioactive compounds from *Ocimum gratissimum* L. through computational approach

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ABSTRACT

The present research was framed to determine the key compounds present in the plant *Ocimum gratissimum* L. targeting protein molecules of Diabetes Mellitus (DM) by employing *In-silico* approaches. Phytochemicals previously reported to be present in this herb were collated through literature survey and public phytochemical databases, and their probable targets were anticipated using BindingDB ($p \geq 0.7$). STRING and KEGG pathway databases were employed for pathway enrichment analysis. Homology modelling was executed to elucidate the structures of therapeutic targets. Further, Phytocompounds from *O. gratissimum* were subjected for docking with four therapeutic targets of DM by using AutoDock vina through POAP pipeline implementation. 30 compounds were predicted to target 136 protein molecules including aldose reductase, DPP4, alpha-amylase, and alpha-glucosidase. Neuroactive ligand-receptor interaction, MAPK, PI3K-Akt, starch and insulin resistance were predicted to have potentially modulation by phytocompounds. Based on the phytocompound's binding score with the four targets of DM, Rutin scored the lowest binding energy (-11 kcal/mol) with Aldose reductase by forming 17 intermolecular interactions. In conclusion, based on the network and binding score, phytocompounds from *O. gratissimum* have a synergistic and considerable effect in the management of DM via multi-compound, multi-target, and multi-pathway mechanisms.

1. Introduction

Diabetes Mellitus (DM) is a familiar metabolic condition that has been impacting millions of people globally (Raffel and Goodarzi, 2014). DM implicates a significant risk to human health thereby becoming the ninth leading basis of death globally. In the past three decades the incidence rate of diabetic patients has doubled. DM is considered as one of the rapidly emerging diseases across the globe. According to statistics, there were 463 million diabetics worldwide in 2019 and 693 million are expected to have the disease by 2045.From international federation. Asia account for maximum number of T2DM (Type 2 Diabetes Mellitus) and it is more prevalent in developing countries leading to major socio economic challenge(Zhao et al., 2022).The most common affected age group are between 40 and 60 years i.e., working aged individuals which have negative impact on growth of the country consequently affecting productivity and national economy(Okaiyeto and Oguntibeju, 2021). In diabetes, due to impaired metabolism, the body's regulation of glucose is hindered, it is characterised by hyperglycemia, involving a relative lack of insulin secretion, resistance or both i.e., the sugars in food are not used by the body for energy and thus increase the blood glucose level in the body. This happens when the pancreas is not able to produce the required amount of insulin or even when the body is not able to properly process the glucose by resisting insulin (American Diabetes Association, 2010). Type 1 DM (T1DM) and Type 2 DM (T2DM) are the two main categories into which DM is traditionally sepa-

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rated.Factors like viral infection, genetic inheritance, unhealthy eating habits and lifestyle, etc. can all account to impaired insulin secretion and loss of tissue insulin sensitivity, resulting in an increase in the blood glucose level (Roglic et al., 2016). T1DM is mainly defined as an absolute insufficiency of insulin whereas, T2DM is distinguished by resistance to insulin in the tissue, β-cell dysfunction and relatively insufficient insulin secretion (Nyenwe et al., 2011; Roglic et al., 2016; Sun et al., 2022). The enzyme human alpha-glucosidase is essential for the degradation of glycogen to glucose in lysosomes (Kishnani and Chen, 2013). Type 2 Diabetes Mellitus (T2DM) develops as this enzyme produces an unwelcome increase in blood glucose levels (Rines et al., 2016). The inhibition of this enzyme will prevent glucose levels from rising too high and help to regulate DM (Lech et al., 1973). This is the target enzyme that will be considered for the study to identify the inhibitors. Furthermore, "glucagon-like peptide 1 (GLP-1)" a typical enzyme produced by the proglucagon gene in the L cells of the small intestine is accountable for triggering the liberation of glucose-dependent insulin from the pancreatic islets (Müller et al., 2019). It is also reported for its attribute to decrease the gastric emptying and interfering with the improper release of glucagon at post-meal condition (Marathe et al., 2013). Hence, its agonists play a potential role in the release of insulin. Dipeptidyl peptidase 4 (DPP-4) is a ubiquitous molecule which is commonly found to be expressed on the cellular surfaces among the various types of cells and also involved in the process of host deactivation of other bioactive peptides, such as, GIP and GLP-1. The current treatment for DM includes extreme utilisation of oral hypoglycemic agents, viz., DPP4, glucosidase, amylase, protein tyrosine phosphatase 1B (PTP1B), sodium-glucose co-transporter (SGLT) inhibitors, PPARG and GLP-1 agonists, etc., which work through expression regulation and a number of pathways, including lowering hepatic glucose intake,raising the amount of insulin that the pancreatic beta cells secrete and enhancing the sensitivity of the insulin (Meloni et al., 2013). Despite considerable advances in the treatment of DM with these synthetic medications, researchers continue to look for new natural anti-diabetic agents (Hsia et al., 2016).According to the World Health Organisation (WHO), traditional medicine is still practised by 80% of the population worldwide, including the majority of developing countries and some developed ones.

Traditional Medicine (TM) mainly refers to knowledge of medicines developed by older generations and indigenous cultures involving the use of natural or spiritual remedies to treat various ailments(Haux, 2022). It is usually practised in exclusion from allopathy, inclusive of but not limited to traditional Indian medicine (Ayurveda), traditional Arabic medicine (Unani), Traditional Chinese Medicine (TCM), etc. These systems have certain differences in approach and varied sources but a similar core. Though allopathic medicine is focused on immediate relief and suppression of symptoms, the effects on long-term health improvement and the risk of side effects of the synthetic drugs increase the demand for more natural alternative medicines(Raja Ikram and Abd Ghani, 2015). Traditional Medicines (TMs) and folklore medicine have similar therapeutic aims of mitigating symptoms and avoiding complication, but their approaches to understanding, diagnosing, and managing diabetes are vastly different (Modak et al., 2007). Utilisation of herbs has grown into a well-developed, well-coordinated medical practice that treats and prevents disease using a variety of modalities (Chauhan et al., 2015). Because of the vast variety of plants found around the world, the potential for using them as medicine is enormous (Ekor, 2014).Treatment of various diseases with plants in various formulations such as crude extracts, whole plants and so on was often encouraged by cultural and geographical influences (Sofowora et al., 2013). Herbal drugs are gaining traction around the world because they are made from non-synthetic ingredients and have less side effects (Ekor, 2014). Identification, isolation and analytical characterization of phytocompounds for their various medicinal uses has given basis for designing drugs with huge potential activity profile of most of the plant derived medicines and plant extracts with various phytocompounds which are secondary metabolites (Njan et al., 2023).A contemporary method for locating active ingredients and potential molecular targets in a large range of herbal formulas or basic herbs is the core concept of network pharmacology. This integrated strategy acts as a standard for the initial screening of compounds that are bioactive. found in medicinal plants as well as a new therapeutic approach for active chemical research in the future found in disease-treating mechanisms. Incorporating network pharmacology into conventional medicine will therefore provide distinctive and innovative possibilities for locating active ingredients, biomarkers, and conventional medicine's scientific foundations based on the complex biological systems of the human body. (Noor F et al., 2022).

In ayurveda, *Ocimum gratissimum L.* (Clove basil) is known for its long usage since ages. It is mostly an aromatic herb that belongs to Lamiaceae family (Cimap.res.in. 2021) and is a widespread perennial herbaceous plant mostly found in Asia, Africa and South America having a strong aromatic smell (Ugbogu et al., 2021). It is known for its numerous therapeutic potential where it has been used not only as a spice, herb, flavouring agent, in preparation of condiments, but also for its various medicinal properties (Martins et al., 2021). It is indigenous to south East Asia and central Africa and they are perfectly adapted to tropical and subtropical regions. Natural bioactive components derived from plants are serving as an alternative source for a wide range of diseases. More than 50% of therapeutic drugs that are used now in the market for various medications include plant derivatives or similar molecules related to them(Ugbogu et al., 2021). In traditional medicine, it has been used as an anti-diarrhea agent, a treatment for cold and bronchitis, a treatment for conjunctivitis by its direct instilment in the eyes, the leaf oil is used for skin infections, etc. (Wynn, 2007). It also produces certain essential oils possessing antifungal activity (Mahajan et al., 2021). *O. gratissimum* has been recommended for many pharmacological benefits as the plant possesses anti-oxidative, antimicrobial, anti-inflammatory, antimalarial and antidiabetic properties. Researchers have also demonstrated several biological properties such as, antioxidant, antimicrobial and cytotoxic effect on cancer cells of *O. gratissimum* extracts for its potential applications in the food industry (Onyebuchi and Kavaz, 2020). Modern medicine has proved this plant to have antimicrobial activity against microbes like *Escherichia coli, Candida albicans, etc.,* (Martins et al., 2021). One of the many properties of this plant includes the anti-diabetic compounds found in this plant and their hypoglycemic activity (Okoduwa et al., 2017). A phenylpropanoid, eugenol from *O. gratissimum* is also reported as non-toxic potential inhibitor of advanced glycation end products by either inhibiting α-glucosidase and subsequently, stopping the production of glucose from complex carbohydrates or by inhibiting competitively the binding of sugar to serum albumin (Singh et al., 2016). *Studies in both in vitro and in vivo have revealed a therapeutic substance* eugenol from *O. gratissimum* to be involved in lowering the blood glucose concentration through the inhibition of alpha-glucosidase (Alabi et al., 2021a). Identifying medicinal compounds as inhibitors of alpha-glucosidase, alpha-amylase, DPP-4 and aldose reductase, and gene set molecular pathway enrichment of these inhibitors using *in-silico* methods was the main focus of the present research (Nweze and Eze 2009; Shittu et al., 2016). Network based study and poly-pharmacology are the latest developmental fields which have promising approaches for a very economical drug development process(Hopkins, 2008). Network pharmacology approach can help in providing a full or a partial understanding of pharma-

cological data using systems biology and network theory concepts, hence it is presently being considered as the next paradigm of drug discovery (Zhang et al., 2019). It integrates systematic data to provide interactions between compounds and their targets. Network pharmacology can include processes like screening of active components, enrichment analysis, finding targets and employing disease targets database. It is considered a bottom-up approach in finding phytopharmaceuticals in a more time-efficient manner to propose hypotheses of mechanisms that can further be validated experimentally (Jiashuo et al., 2022). The capability of network pharmacology not only comprises virtual computing and high throughput data analysis, but also involves network construction based on the interactions and network topology analysis. There is mounting evidence that network pharmacology may be able to predict the interactions between the effective chemical bioactive components found in herbal medicines and the targeted genes for particular diseases using the knowledge of metabolomics. As a result, this technique could confirm that the active elements of medicines that network pharmacology predicted indeed exist.(Yu S et al.,2023).There is mounting evidence that network pharmacology may be able to predict the interactions between the effective chemical bioactive components found in herbal medicines and the targeted genes for particular diseases using the knowledge of metabolomics. As a result, this technique could confirm that the active elements of medicines that network pharmacology predicted indeed exist.(Yu S et al.,2023).This multi-component, multi-target synergy, multi-channel approach is therefore a robust technique to methodically predict mechanisms involved in diseases and the consequences of various drugs on them at a molecular level(Hopkins, 2008; Kibble et al., 2015; Wang et al., 2022; Zhang et al., 2020).When it comes to dietary proteins, molecular docking has basically been used to examine the relationships that exist between enzymes and their substrates, which can help in the control of enzyme activity in foods, as well as to investigate chemicals that are antinutritional such as trypsin inhibitors.(Vidal-Limon et al.,2022).This method has so far shown promising in analysis of multi-target influences of various ethnomedicinal plants following the notion of "multicomponent, network-targeted therapies" for the management of wider classification disease and disorders. Molecular mechanisms between the potential targets of a disease and bioactive components of herbal plants are made easier by network pharmacology by eradicating the idea of "one gene, one target and one disease"(Qasim et al., 2023).

2. Materials and methods

2.1. Collection and druggability of phytocompounds

Bioactive phytochemicals from *O. gratissimum* were shortlisted from the Phytochemical Interactions DB (PCIDB, 2021) and published articles (Supplementary Table 1). Detailed characteristics viz., canonical smiles, molecular weight, molecular formula,number of donors and acceptors for hydrogen bonds, logP values of selected phytocompounds were gathered from PubChem Chemical compounds database(Kim et al., 2016) and the database was constructed. Duplication of plant compounds was eliminated during database construction. The Phytocompounds' drug similarity score was predicted using the "Lipinski's rule of five model" on the MolSoft(https://molsoft.com/mprop/) web server.

2.2. Target identification

The chosen phytochemicals' canonical smiles were entered into BindingDB (Liu et al., 2007), "a public, online-accessible and an experimentally determined protein–ligand interactions database" with a probability score of ≥ 0.7, to identify phytocompounds targeting aldose reductase, DPP4, alpha amylase, alpha glucosidase and other protein targets related to DM(Durai et al., 2020).The likely protein targets' gene IDs were gathered from UniProt. (Bateman et al., 2021).

2.3. Gene set enrichment analysis

The biochemical pathways and protein–protein interactions implicated in the DM were identified using STRING 11.0v (Szklarczyk et al., 2019) and the Kyoto Encyclopaedia of Genes and Genomes (KEGG) pathway database.(FDR ≤ 0.05) by submitting the set of probable protein target's gene IDs. To comprehend how proteins interact with one another STRING 11.0v (Szklarczyk et al., 2019) and the Kyoto Encyclopaedia of Genes received a set of proteins (gene IDs). Utilising the genomics (KEGG) pathway database (Kanehisa, 2000), it was possible to identify the metabolic pathways in DM that are likely responsible for the modification brought on by phytoconstituents.

2.4. Network construction

Based on the data from enrichment analysis, an interaction network between Compound-Protein (C-P), Protein-Protein (P-P), and Compound-Protein-Pathway(C-P-P) was constructed using the Cytoscape 3.6.1 version software, which is a modelling software used to integrate biomolecular interaction networks(Shannon et al., 2003). The interaction among the compounds, active constituent and target genes were visualised and unconnected nodes were removed. The networks were analysed by the "Network Analyser" by treating it as direct command. In order to enforce the topological parameter "Edge Count" for "low values to small sizes" and "low values to bright colours," both nodes and edges have to be at least one.

2.5. Homology modelling, validation, and active site determination

In the present study, bio-actives modulate four prospective therapeutic targets of DM,i.e.The chosen enzymes were aldose reductase, DPP4, alpha amylase, and alpha glucosidase. From the RCSB Protein Data Bank (PDB), X-ray crystal structures of aldose reductase (PDB ID: 3RX2), DPP4 (PDB ID: 4FFW), and alpha glucosidase (PDB ID: 5KZW) were discovered (Fig. 1). Human alpha amylase's 3D X-ray crystal structure is not currently accessible in the protein data bank. Therefore, its homologous structure was assembled using modeller9.10v (Eswar et al., 2006), using structures with PDB ID: 3OLD (Qin et al., 2011)and 5E0F (Burley et al., 2021)as a template builder and with NCBI protein accession number BAA14130.1 as the query sequence(Wu et al., 2020). Further, PROCHECK (Laskowski et al., 1993) and ERRAT (Colovos and Yeates, 1993)online servers were utilised to validate the modelled and selected structures for their amino acid distribution and overall quality respectively.The structurally conserved regions of the alpha amylase protein are what give it its enzymatic activity. The major domain of the protein, which is the catalytic domain in charge of the enzymatic activity, is present.A glycosidic bond on the polysaccharide substrate is hydrolyzed in the active site of the catalytic domain.Aldose reductase has a catalytic domain called AKR domain and the active site is in this domain. Key residues which take part in enzymatic activity include Tyr residue which is conserved and acts a catalytic base and Lys residue takes part in substrate binding activity. Alpha glucosidase is an enzyme which is involved in degradation of glycogen in lysosomes. Alpha glucosidase consists of Binding site at D404, R600, D616 and H674 residues and Active site on E521 and D518 residues. DPP4 enzyme is a protein which is involved in many physiological pro-

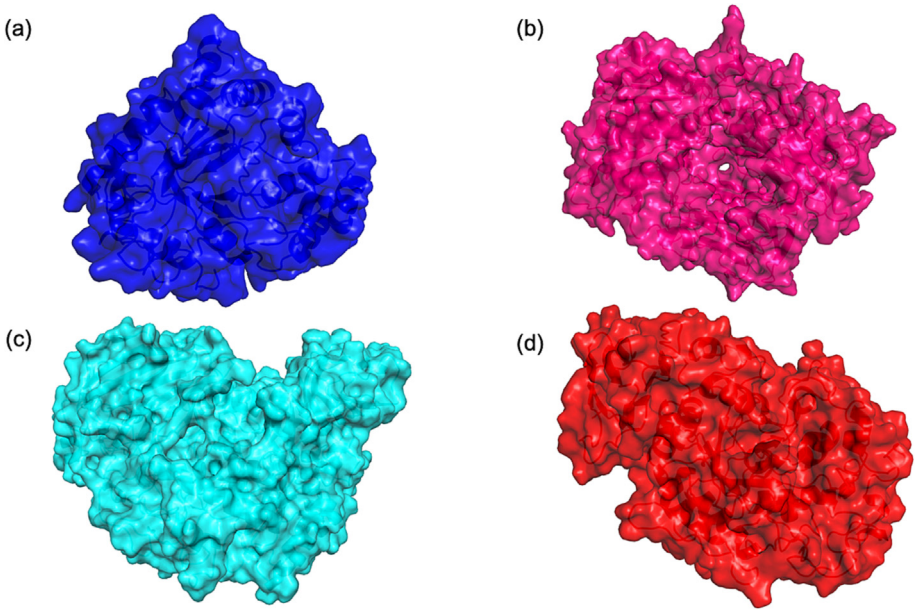


Fig. 1. 3D representation of (a) Aldose reductase (PDB ID: 3RX2), (b) DPP4 (PDB ID: 4FFW), (c) Alpha glucosidase (PDB ID: 5KZW) (d) Modelled Alpha-Amylase.

cesses, which range from immunological process and glucose metabolism. The three types of DPP4 domains that perform the proteolytic cleavage of peptides are the N-terminal Cytoplasmic Domain, Transmembrane Domain, and C-terminal Extracellular Domain.

2.6. Docking studies

Prior to the synthesis of any compound, all predictions and back validation of hits has to be confirmed. Molecular docking is a computational tool that can be employed to build the interaction among drug moiety and target protein at an atomic level followed by predicting the best confirmation that fits protein binding site (Othman et al., 2021).Molecular docking studies with 4 potential therapeutic targets of DM was executed out using AutoDock vina by POAP pipeline(Samdani and Vetrivel, 2018).The compounds from the enrichment analysis were taken as input compounds for the study. The compounds were prepared using POAP with minimization parameters of 5000 minimization steps with MMF94 forcefield. On the basis of the active sites of the target proteins, grid box was assigned using AutoDock Tools(Achutha et al., 2021). The exhaustiveness of the molecular docking process was kept at 50. Higher exhaustiveness provides higher accuracy as it increases the number of steps in searching for an optimal docked pose with the lowest binding energy(Muhammad and Fatima, 2015).

3. Results

3.1. Mining of phytocompounds and their druggability

Thirty bioactive phytocompounds from *O. gratissimum* were screened from various databases and other open-source records and identified from PCIDB and published articles. These phytoconstituents were recognized as alkaloid, terpenes, and steroids.Herbal medication is typically taken orally, where it is digested, distributed, metabolised, and expelled to the intended organ or tissue as determined by ADME analysis.Phytocompounds meeting the demand were selected as potential active phyto components for binding. Similarly,The majority of the diabetes protein molecules that were targeted were surface proteins and enzymes.The overall drug-likeness characteristics of shortlisted phytocompounds are given in Supplementary Table 1.

3.2. Target identification

Potential targets' gene names and Uniprot IDs were found in the Uniprot database. We obtained thirty potential compounds from *O.gratissimum* that were predicted to target one hundred and forty-six protein molecules (Supplementary Table 2). Among them, twenty-two compounds predicted to inhibit aldose reductase, fifteen for DPP4, six for alpha amylase and thirteen for alpha glucosidase. Additionally, these substances were forecast to target 136 different protein targets. (Supplementary Table 3).

3.3. Gene-set enrichment analysis

One hundred and thirty-six protein targets were found to affect sixty five biological pathways by the KEGG pathway enrichment analysis.(Supplementary Table 4). A peer literature review of sixty-five pathways identified eleven molecular pathways to be potentially involved in DM. Among them, Neuroactive ligand-receptor interaction, MAPK, and PI3K-Akt scored the lowest FDR value via modulating twelve, twelve, and thirteen protein molecules respectively. Following these pathways, starch and sucrose metabolism, insulin resistance, cell cycle, oocyte meiosis, regulation of lipolysis in adipocytes, AMPK, cAMP, and p53 signalling pathways were identified (Table 1).

3.4. C-P, P-P, and C-P-P network construction

Luteolin, Apigenin, Apigenin 7,4′-Dimethyl Ether, Salvigenin, Nevadensin, Isothymusin, Cirsimaritin, Xanthomicrol, Hymenoxin, Quercetin 3-O-Glucoside, and Kaempferol 3-O-Rutinoside were found through examination of the network that was built between C-P (Fig. 2), P-P (Fig. 3), and C-P-P (Fig. 4). These were potentially enriched within the network via targeting major protein molecules involved in DM viz., ARK1B1, EGFR, DPP4, GAA, ADORA1, HGF, PTGS1, and PTPN1 and by modulating Neuroactive ligand-receptor interaction, MAPK and PI3K-Akt as major intracellular signalling pathways.

Table 1
Enrichment analysis of targets modulated by the phytocompounds from O. gratissimum.

KEGG ID	Pathway description	Gene count	FDR	Matching proteins in your network (labels)
hsa04080	Neuroactive ligand-receptor interaction	12	1.70E-05	OPRD1, ADRA2A, ADRB2, GABRA5, DRD2, ADORA1, GABRA3, CHRM5, GABRA1, OPRM1, GABRA2, HTR2A
hsa04010	MAPK signalling pathway	12	3.05E-05	HGF, FLT3, CDC25B, IGF1R, EGFR, NTRK2, KIT, MAPT, RPS6KA3, TNF, PGF, VEGFA
hsa04151	PI3K-Akt signalling pathway	13	3.05E-05	HGF, FLT3, CDK6, CDK2, IGF1R, EGFR, NTRK2, KIT, GSK3B, PIK3CG, IL2RA, PGF, VEGFA
hsa00500	Starch and sucrose metabolism	4	0.0014	PYGM, SI, GAA, AMY2A
hsa04931	Insulin resistance	6	0.0014	PYGM, GSK3B, PTPN1, RPS6KA3, PPARA, TNF
hsa04110	Cell cycle	6	0.0023	CDC25B, CDK6, CDK2, GSK3B, ABL1, CDK1
hsa04114	Oocyte meiosis	5	0.0094	CDK2, IGF1R, AR, RPS6KA3, CDK1
hsa04152	AMPK signalling pathway	5	0.0102	CFTR, IGF1R, PPARG, HMGCR, FASN
hsa04024	cAMP signalling pathway	6	0.0142	CFTR, ADRB2, PDE4D, DRD2, ADORA1, PPARA
hsa04923	Regulation of lipolysis in adipocytes	3	0.0286	ADRB2, PTGS1, ADORA1
hsa04115	p53 signalling pathway	3	0.0467	CDK6, CDK2, CDK1

FDR, False Discovery Rate.

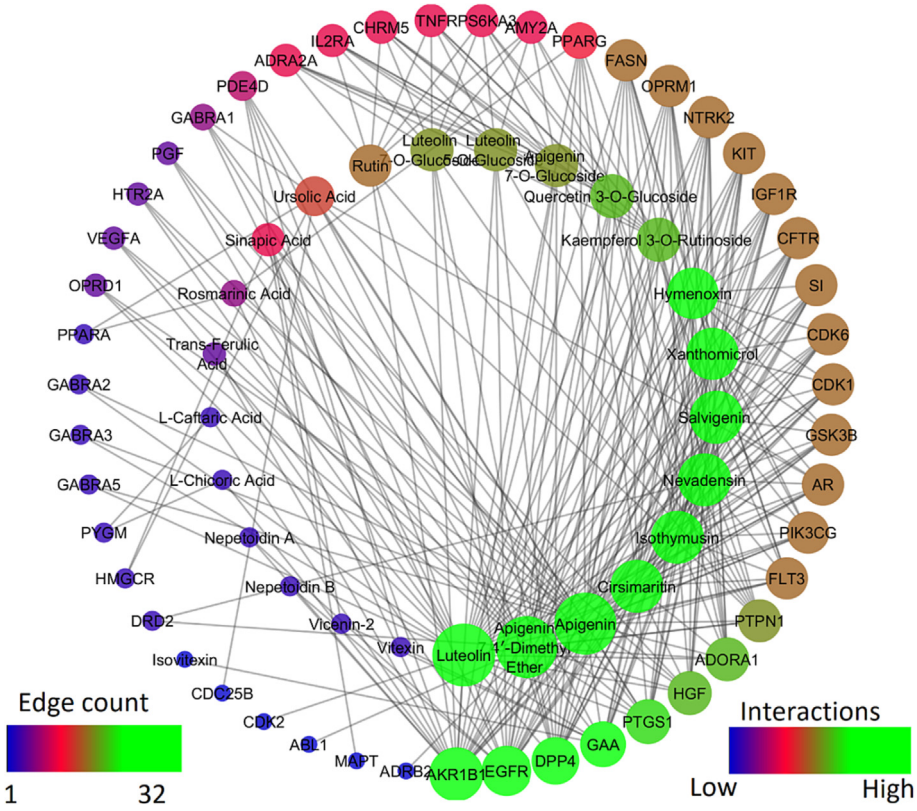


Fig. 2. Network interaction between Phytocompounds-Protein targets.

3.5. Homology modelling, validation, and active site determination

Human Lysosomal Alpha-Amylase Model No. 3 was the protein that was modelled, and it had the lowest DOPE score of 62,602.046875 with 92.49% overall quality. It was discovered that the RMSD between model3 and the 3LOD PDB template was 0.172 and the RMSD with the 5E0F PDB template was 0.329. Fig. 5 depicts the distribution and superimposition of amino acids. The Ramachandran plot in PROCHECK analysis for the human lysosomal alpha-amylase model showed that 90.8% of residues were in core regions, which are the regions with the most favoured, 8.3% were allowed,(additionally allowed) 0.9% were generously allowed regions, and 0.0% meant no residues were in disallowed regions.For a decent model structure that was obtained at a high resolution, one would assume that this fraction would be larger than 0.0% in forbidden zones. A mere 0.0% of the residues in the human lysosomal alpha-amylase model were discovered there. This result implies that the model's stereochemical quality was accurately predicted.

3.6. Docking studies

To acquire the optimum conformation and investigate potential ligand interactions at the target proteins active sites, as well as to assess potential inhibitory effects on the target protein, molecular docking was performed. The potential therapeutic compounds

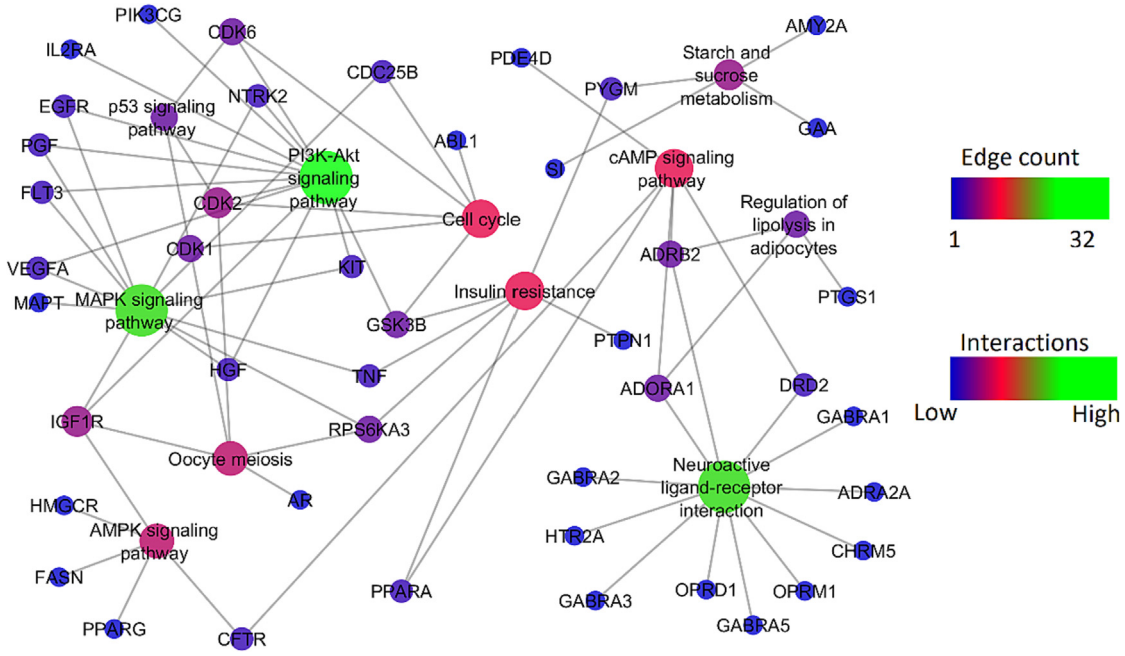


Fig. 3. Network interaction between Protein targets-Pathways.

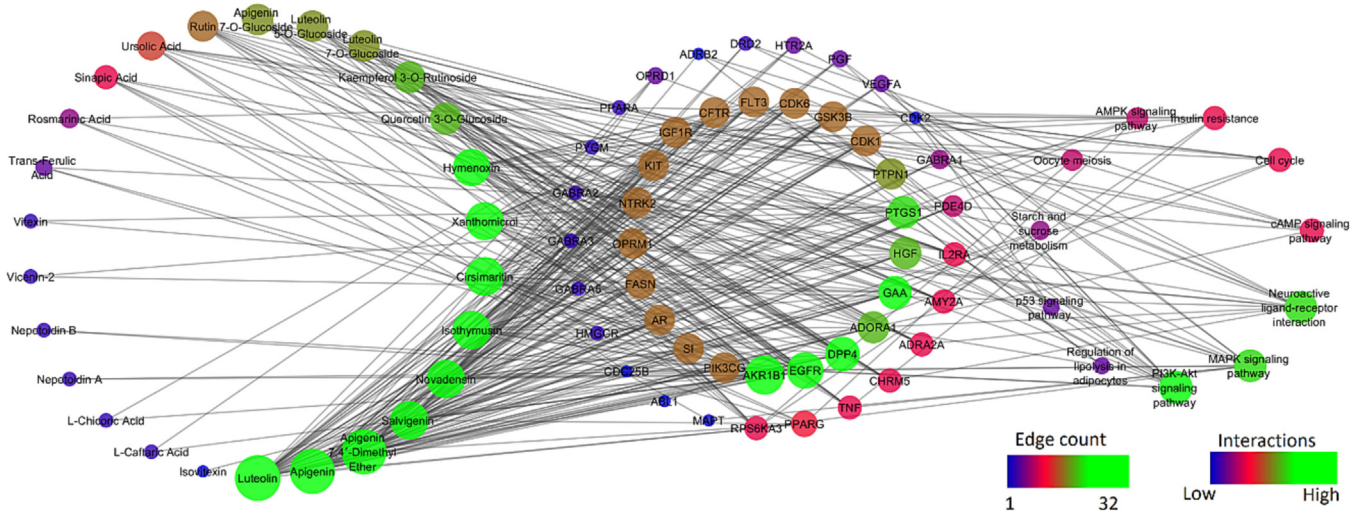


Fig. 4. Network interaction between Phytocompounds-Protein Targets-Pathways.

from medicinal plants have been examined using a variety of computer-aided drug design methodologies. However, molecular docking seems to be a cost effective approach for assessing the interactions of ligands with respective receptors and also predicting the orientation of compounds in the binding sites of the selected protein target. In pursuit to identify possible binding of the compounds from *O. Gratissimum* with the selected therapeutic targets of DM, molecular docking studies were performed. In Supplementary Table 6, all of the chemicals' binding energies (kcal/-mol) and molecular interactions from molecular docking are listed. Considering the interactions of substances with active residues and the binding energy,selected compounds are tabulated in Table 2. Fig. 6 depicts the 2D ligand interaction diagram of the selected compounds in Table 2, and Fig. 7 provides the 3D representation of the complexes.Docking results obtained for each ligand with receptor were analysed on the bases of docking energy (Kcal/mol) and interaction of each ligand with functional residues of Alpha amylase (AMY2A), Aldose reductase(AR), Dipeptidyl peptidase IV(DPP4), Alpha glucosidase(GAA). The main interaction observed between the ligand and target proteins are Hydrophilic interaction, Hydrogen bonding and Binding energy.AMY2A showed more prominent binding with Urolisic acid via forming a single hydrogen bond with ASP 212 and hydrophobic interactions with the residues of amino acids.TRP74, LEU177, VAL178, ALA213, ILE250, HIS230.with binding energy of −10.8 Kcal/mol, In case of AR showed potent binding with Chicoric acid by ten hydrogen bonds TRP20, ASP43, HIS110, SER159,ASN160, LEU212, SER214, ASP216, LYS262, ARG268 and hydrophobic interactions with TRP20,TYR209,PRO215,ILE260,LYS262 with binding energy of −11 Kcal/mol, in DPP4 active binding is with Luteolin-5-O-Glucoside by nine hydrogen bonds ARG123, GLU203, ILE205, ARG356, TYR548, SER631, TYR663, ASN711, HIS741 and one hydrophobic interaction with PHE355,with binding energy of −9.1 Kcal/mol followed by GAA has more potent binding with

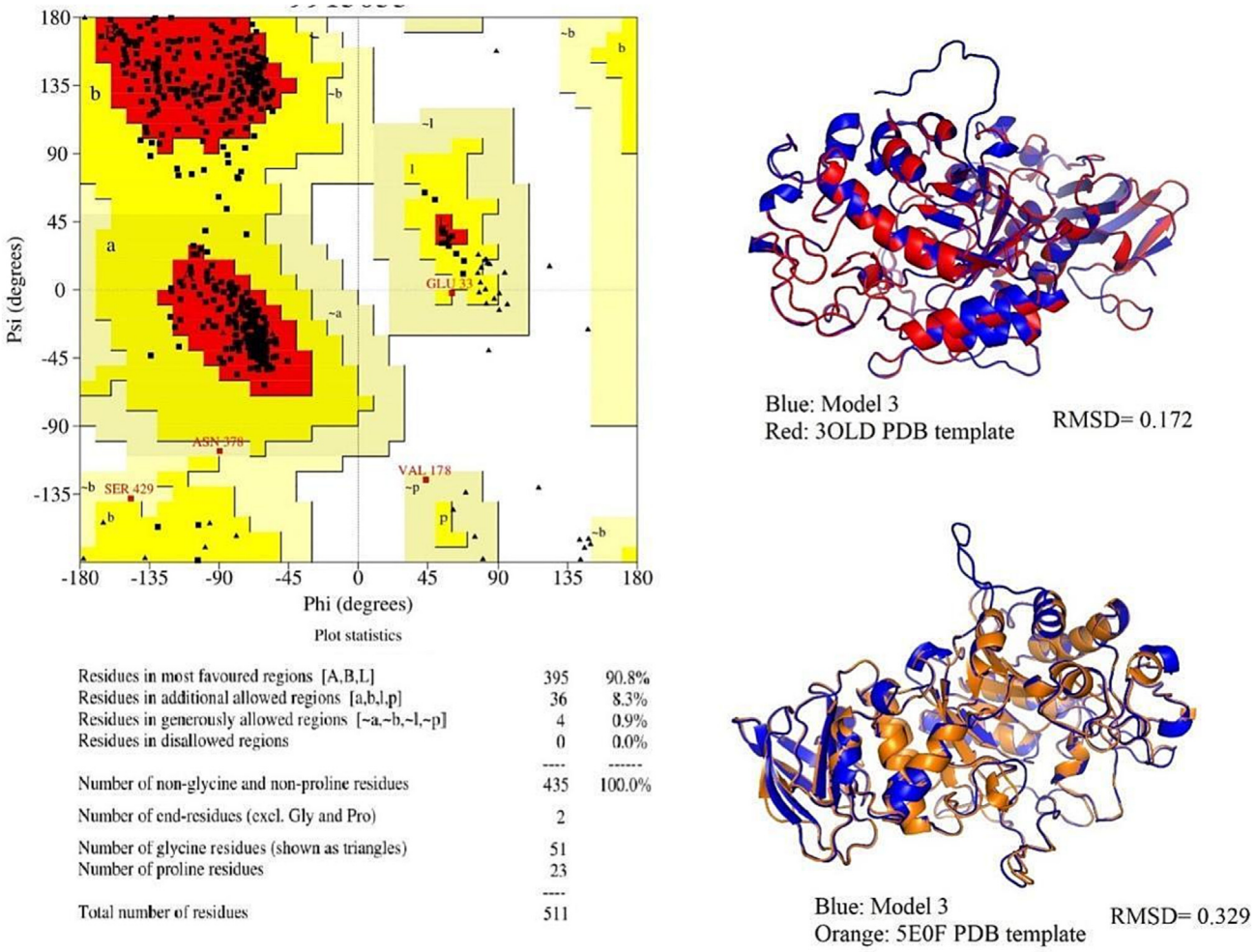


Fig. 5. The amino acid distribution and superimpose of model 3 and it superimpose with templates.

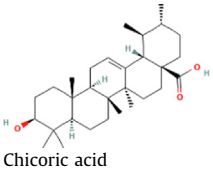
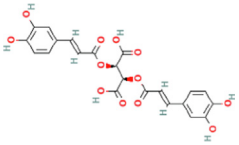
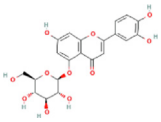
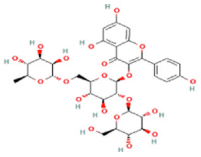
Kaempferol-3-O -Rutinoside with six hydrogen bonds VAL357,TYR360,MET363,ARG608,HIS717,GLU866 and four hydrophobic interactions with VAL200, TYR360, VAL588, LEU865 with binding energy of −9.2.Kcal/mol.

4. Discussion

Although several treatment approaches for diabetes have been developed, the morbidity rate is constantly increasing.The goal of the current study was to identify the molecular underpinnings of antidiabetic action of Phytoconstituents from *O. gratissimum* with the exploration of chemo-informatics and system biology approaches viz Target identification, target modelling, network pharmacology, gene set enrichment, and molecular docking exposes the network-based effects of multi-component medications by analysing drug-disease interactions in statistical databases (Patil et al., 2020). It also contains research on multi-target drugs with high efficacy and low toxicity (Reddy and Zhang, 2013). Prediction of the composition of active components and their targets at a multilevel network enables the locking of key drugs and disease targets and flexible and semi-flexible molecular docking reinforces the evaluation of the interactions force (Zhang et al., 2018, Ye et al., 2021).Data obtained from these approaches aids in the development of novel multi-targeted drugs that can be tested further in preclinical and clinical settings. Further, treatment with herbal constituents are often correlated with their ability to be used safely and purchasing herbal remedies seems to be having lower toxicity levels when compared to chemical drugs, although the corresponding material used in herbal remedies usually does not contain any special warnings(Chen et al., 2016).Protein–protein interaction networks have been also build to evaluate the physical connectivity among different proteins that gives insights of molecular mechanisms involved in the cellular function (Awan et al., 2022).

In the current research, we utilised multiple chemo-informatics and systems biology approaches to explore the molecular mechanisms of the well-known medicinal plant *O. gratissimum,* for the treatment of DM. This variety of basil's widespread use in medicine is supported by earlier research (Priyanka, C.et al.,2018)that found it had sedative, anthelmintic, antidiarrheal, antipyretic, antimutagenic, anti-ulcerative, gastroprotective, hepatoprotective, antibacterial, anti-stress, and anti-inflammatory actions.Its infusions are regarded as tonic and pectoral in Cameroon and are used to treat nausea, headaches, colds, and coughs. It is advised for the treatment of diarrhoea in Nigeria. Aqueous maceration of its leaves is used to treat purulent urethritis and haematuria, while the fresh juice from its leaves possesses anti diarrheic and antidysenteric effects.(Ugbogu, O.et al., 2021)The integrated bioinformatics methods were employed to recognize the prospective phytocompounds and pathways associated with DM. Plants show enormous versatility in their potential active components and their metabolic activities, these complex materials are referred to as secondary metabolites which have disease inhibiting or preventing capability.

Table 2
Targets and compounds with best docking score and details of interaction sites (Binding energy).

Targets	Compounds	Binding energy (Kcal/mol)	Interactions			
			Hydrophobic Interactions	Hydrogen Bonds	Salt bridges	pi - stacking
Alpha amylase (AMY2A)	Ursolic acid 	−10.8	TRP74, LEU177, VAL178, ALA213, ILE250, HIS320	ASP212	HIS116	
Aldose reductase (AR)	Chicoric acid 	−11.0	TRP20, TYR209, PRO215, ILE260, LYS262	TRP20, ASP43, HIS110, SER159, ASN160, LEU212, SER214, ASP216, LYS262, ARG268	LYS21	TYR209
Dipeptidyl peptidase IV (DPP4)	Luteolin-5-O-Glucoside 	−9.1	PHE355	ARG123, GLU203, ILE205, ARG356, TYR548, SER631, TYR663, ASN711, HIS741		PHE355
Alpha glucosidase (GAA)	Kaempferol-3-O -Rutinoside 	−9.2	VAL200, TYR360, VAL588, LEU865	VAL357, TYR360, MET363, ARG608, HIS717, GLU866	HIS584, HIS717	TYRE360

*Binding energy – AutoDock vina binding score.
The interactions of Ursolic acid with ALA212 and ALA213 of Alpha amylase (AMY2A)are part of the validated binding site of the protein (https://www.uniprot.org/uniprotkb/P15121/feature-viewer).

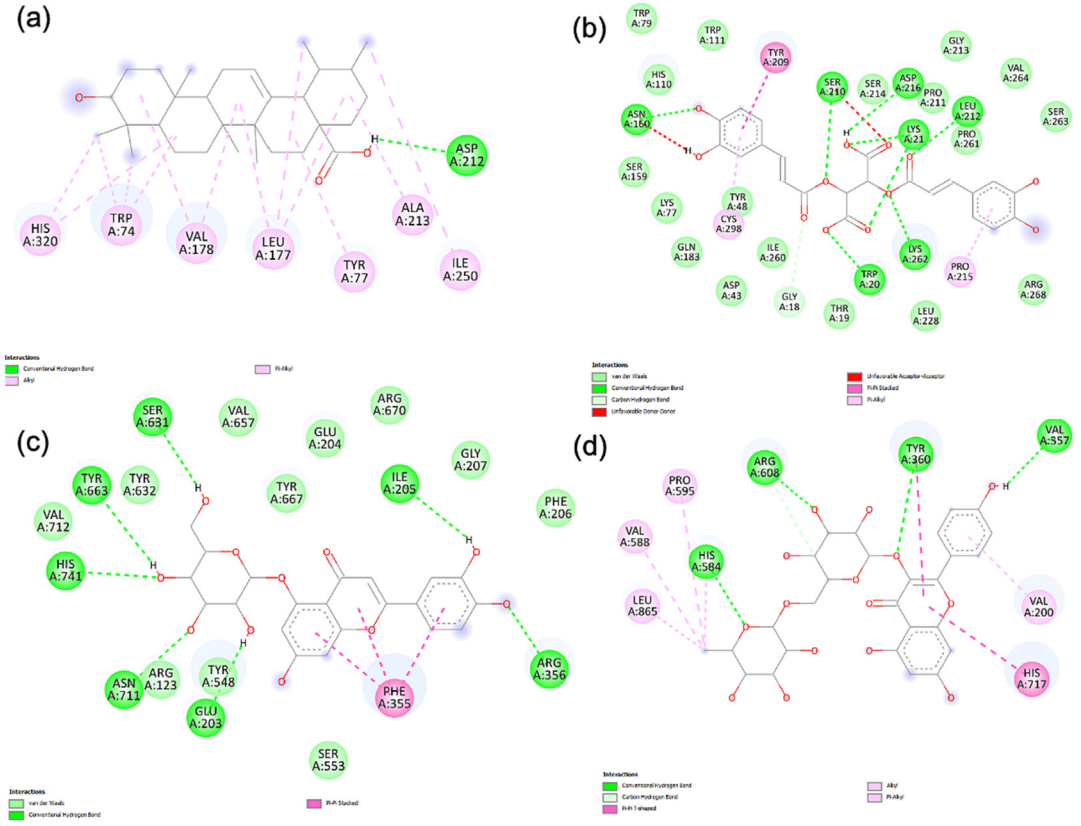


Fig. 6. 2D interaction diagram of target-ligand complexes (a). Alpha amylase with Ursolic acid (b). Aldose reductase with Chicoric acid(c). Dipeptidyl peptidase IV with Luteolin-5-O-Glucoside (d). Alpha glucosidase with Kaempferol-3-O –Rutinoside.

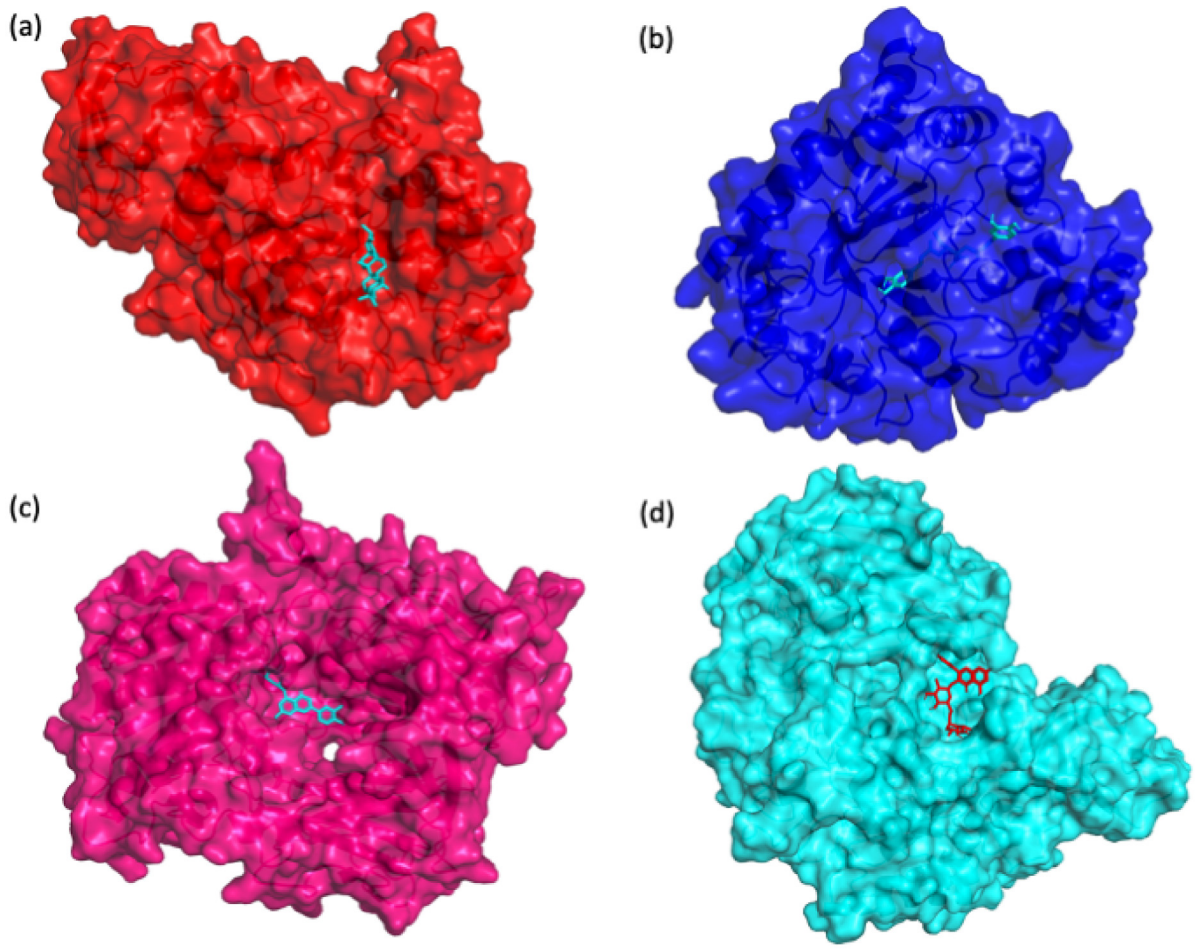


Fig. 7. 3D representation diagram of target-ligand complexes (a). Alpha amylase with Ursolic acid (b). Aldose reductase with Chicoric acid (c). Dipeptidyl peptidase IV with Luteolin-5-O-Glucoside(d). Alpha glucosidase with Kaempferol-3-O –Rutinoside.

In accordance with conventional medicine, tea the second most consumed beverage worldwide after water has long been considered a potential anti-diabetic. One of the key elements of tea is its polyphenols, which mostly consist of EGCG, EGC, ECG, and EC. Several GTPs may interact with numerous targets in the signalling network of complex diseases (such as diabetes, cancer, cardiovascular disease, etc.), according to the network pharmacology theory, having a synergistic effect. Three pathways—the p53 signal pathway, the neurotrophin signal pathway, and the T2DM pathway—were connected to DM out of the 147 pathways examined utilising a network pharmacology technique on GTPs. And they merged these three routes to produce a pathway for diabetes.(Zhang, S et al.,2014) We constructed a network among phytocompound, their protein targets and expected pathways.The findings suggested that alkaloid, tannin, flavonoids, and phenolic compounds are possible phytocompounds with the capacity to interact with various protein molecules and modify various protein molecules associated with DM (Talabi and Makanjuola, 2017).Initially, reported phytocompounds from *O. gratissimum,* were shortlisted and their essential information was obtained from PubChem chemical database. Utilising this information, the possible druggability and ADMET profile was predicted. Following this procedure, the study aimed to identify the probable protein targets using BindingDB with a probability score of $\geq$ 0.7. BindingDB is a freely open archive of experimental protein-small molecule interaction data (https://www.bindingdb.org). This database covers over a million of data entries that are largely derived from research papers, and progressively increasing US patents(Liu et al., 2007). Human alpha amylase's 3D X-ray crystal structure is not currently accessible in the protein data bank. Therefore, its homologous structure was assembled using modeller 9.10. Homology modelling reveals protein structural information but the degree to which a sequence resembles a template relies on quality. The approach is based on the observation that a protein's structural conformation is more conserved than its amino acid sequence, and that modest or moderate alterations in the sequence typically cause little change in the 3D structure (Vyas V et al.,2012).

Further, obtained list of protein targets of phytocompounds was submitted to the STRING database to obtain the protein–protein network and functional characterization (Szklarczyk et al., 2021). An equivalent internet tool Other researchers used STRING to imagine the regulatory network and protein–protein interaction network between tacrolimus and the target genes, resulting in the identification of 43 target genes. Network analysis also suggested the role of tacrolimus in liver transplantation. (Chen et al., 2021).The bioactive compounds of F. asafetida were also used to identify the mechanisms involved in the treatment of asthma. The compound target-pathway network was also explored by targeting several genes and modulating signalling pathways related

to asthma, and molecular docking was then used to identify a potential active compound to repress asthma. (Qasim et al., 2023).

In the present work, network interaction among phytocompounds, protein targets and pathway were constructed that reflects terpenes, steroid, alkaloids and flavonoids as a potential phytoconstituent against pathogenesis of DM which is in line with the research that have been reported(Singh et al., 2016) that claimed to still have antibacterial, anti-inflammatory, and antioxidant effects(Alabi et al., 2021b).Similar activities were reported for *Ocimum tenuiflorum (* Martiz R et al.,2022). and Berberine and polyphenols are two of the chemical constituents of *Rhizoma Coptidis* that by lowering insulin resistance in the liver, muscle, and adipose tissues, boosting insulin levels, enhancing cell dysfunction, and managing intestinal flora have been proven to have a vital role in regulating glucose metabolism.(W.Huang et al., 2021).A multifaceted network of functional connections among biomolecules is vital for cellular life. Protein–protein interactions are especially significant amongst these associations because of their flexibility, precision, and adaptability (Rao et al., 2014). After obtaining these interactions, The molecular pathways that may have been affected by the likely protein molecules of phytocompounds were found using the KEGG pathway database and finally molecular docking study was carried out with four potential therapeutic protein targets of DM to comprehend how active amino acid residues interact with biomolecules(Khanal et al., 2019). According to reports, computational biology techniques like protein network mapping and functional enrichment of biological pathways are used to explore the key genes involved in patients with familial hypercholesterolemia.(Awan et al., 2022). Additionally, In another study (Yuan, H et al.,2017)A novel network-based inference (NBI) technique, domain tuned-hybrid (DT-Hybrid), has been comprehensively examined using a previously validated drug-target interaction database obtained from Drug Bank. This technique uses domain-based information to give a solid recommendation strategy. Comparisons between various NBI techniques are also required in order to discover more active chemicals and pertinent processes.

Hence, network pharmacology is one of the advanced and powerful techniques that illustrate the molecular interactions of drugs. Earlier the drug discovery process was based on one disease one target approach but network pharmacology aids in multi-target approach thereby developing network models using rich computational tools and high throughput screening. Network pharmacology triggers the development of cost effective and feasible drug development.In recent years, network pharmacology has gained popularity as a potent method to clarify complicated interactions at a systematic and biological level. It has been utilised to treat numerous difficult chronic illnesses, including cancer, pancreatitis, Alzheimer's disease, diabetes mellitus, and other metabolic diseases, as well as cardio-cerebral ischemic diseases.The mechanistic investigations for DM therapy have frequently utilised network pharmacology.(Zhou, Z et al.,2020).

According to KEGG Analysis, the major targets were primarily centred in Neuroactive ligand-receptor interaction pathway followed by MAPK and PI3K-Akt signalling pathways were identified as enriched pathways by phytocompounds by targeting OPRD1, ADRA2A, ADRB2, GABRA5, DRD2, ADORA1, GABRA3, CHRM5, GABRA1, OPRM1, GABRA2, HTR2A, HGF, FLT3, CDC25B, IGF1R, EGFR, NTRK2, KIT, MAPT, RPS6KA3, TNF, PGF, CDK6, CDK2, GSK3B, PIK3CG, IL2RA, and VEGFA. Similar pathway analysis was reported by (Khanal P et al., 2019), Neuroactive ligand-receptor interaction has been identified as one of the key strategies for treating diabetes and preventing heart disease, which is a substantial risk factor for both insulin resistance and diabetes. Terpenoids and alkaloids are listed as the primary phytoconstituents in *T. cordifolia* by the Ayurvedic Pharmacopoeia of India, and they were engaged in modulating the several pathogenic protein molecules linked to DM.P13K-Akt is an important pathway for maintenance of homeostasis, regulated by various bioactive compounds that are mentioned earlier. Insulin-stimulated glucose utilisation is the main component of glucose metabolism and energy homeostasis in skeletal muscle via this pathway. Impaired P13K-Akt signalling pathway also controls the growth, survival, angiogenesis, and inflammation of cardiomyocytes in both healthy and pathological cases of DM, obesity, and cardiac hypertrophy. This might have a beneficial therapeutic impact on how proliferative diabetic retinopathy is managed thereby increasing the glucose absorption and insulin production (Patil et al., 2020).

Following these pathways, starch and sucrose metabolism, cell cycle, oocyte meiosis, regulation of lipolysis in adipocytes, AMPK, cAMP, and p53 signalling pathways were found to regulate via protein molecules PYGM, SI, GAA, AMY2A, GSK3B, PTPN1, RPS6KA3, PPARA, TNF, CDC25B, CDK6, CDK2, GSK3B, ABL1, CDK1, IGF1R, AR, CFTR, IGF1R, PPARG, HMGCR, FASN, CFTR, ADRB2, PDE4D, DRD2, ADORA1, PPARA, ADRB2, and PTGS1. It was hypothesised (Khanak and Patil 2020) that all phytoconstituents will consistently influence the p53 signalling pathway. Additionally, it prevents the formation of glycogen by blocking the enzymes phosphoglycerate mutase, hexokinases 1 and 2, and glucose-6-phosphate isomerase.

The pancreatic -cell mass is also maintained by the p53 signalling pathway. Additionally, this system controls pyruvate metabolism in the mitochondria and prevents embryonic deformity in diabetes circumstances. Three principal targets, CDK6, CDK2, and CDK1, are the primary modulators of the P53 signalling pathway in the current investigation.

Previous research indicated that the ARDS (Acute Respiratory Distress Syndrome) development was aided by the MAPK signalling pathway. The MAPK signalling pathway was used to create numerous inflammatory substances, including IL1b, TNF-a, and IL-6. The MAPK signalling pathway is the target of some anti-inflammatory drugs. In retinoblastoma, cardiomyocyte, and chorionic carcinoma cells, quercetin was discovered to control the activity of the MAPK signalling pathway. (Tao et al.,2020).Additional research suggests that baicalin may stop the growth and invasion of cancer cells by obstructing the p38 MAPK signalling pathway. (Yan H et al.,2015).

In essence, molecular docking is a conformational sampling technique where several docked conformations are investigated in an effort to forecast the potential correct one, which will then be experimentally verified by X-ray crystallography or by NMR analysis. In general, lower energy scores are thought to imply better protein–ligand binds than higher energy values.Since the goal of molecular docking is to identify the ligand-binding mode with the lowest energy, it can be conceptualised as an optimisation issue.(Pierri et al.,2010). Majority of the phytocompounds identified to act as antidiabetic hits, were flavonoids. AutoDockVina was used for docking because it could achieve a higher magnitude of speed when compared to AutoDock 4, and improved binding accuracy by using sophisticated gradient optimization in the local procedure (Trott and Olson, 2009). A phenolic compound Eugenol, constitutes 74.80 % from the essential oils of *O. gratissimum* which was discovered to reduce blood sugar levels by 38% in an *in-vivo* study largely by inhibiting alpha-glucosidase. Some *in-vivo reports* have verified the anti-hyperglycemic perspective of different solvent (aqueous, methanolic, ethanol) extracts of *O. gratissimum* leaves through high reduction of plasma glucose levels in induced diabetic rats (Antora and Salleh, 2017).

The number of compounds from *O. gratissimum* predicted to target the targets identified by DM were 6 for AMY2A, 22 for AR, 15 for DPP4, and 13 for GAA. The molecular interaction analysis of these small molecules with their respective targets was carried

out via a docking study of Ursolic acid, Chicoric acid, Luteolin-5-O-Glucoside, Kaempferol-3-O -Rutinoside with Alpha amylase (AMY2A), Aldose reductase (AR), Dipeptidyl peptidase IV (DPP4) and Alpha glucosidase (GAA)respectively. In our study, Luteolin-5-O-Glucoside with a docked score of −9.1 (Binding energy Kcal/-mol) can also be considered as potential drug moiety. The presence of Luteolin in *O.gratissimum* is strongly reported through LC-ESI–MS/MS analysis by (Venuprasad et al., 2014). Review (Ugbogu et al., 2021) reveals that Diverse experts have published various investigations on the hypoglycemic actions of *O. gratissimum* employing animal models and also suggest the mechanism of anti-hyperglycemic effect via inhibition of sodium-dependent glucose transporter In an *in-vivo* study conducted by (Casanova et al., 2014), phenolic acids, such as chicoric acid from *O. gratissimum* was investigated to exhibit profound hypoglycemic activity on diabetic mice with a 54 % reduction rate. Chicoric acid may increase insulin release from beta cells and increase muscle cells' sensitivity to insulin.(Casanova et al., 2014). Chicoric acid as revealed from our study was found to be a potential anti-diabetic molecule. Studies by (Othman et al., 2021) examined the influence of Hail Ocimum extract and respective total flavonoids against hepatorenal damage in experimental diabetes induced rats that lowered the glucose and insulin levels and revealed a protective effect in liver and kidney. In another recent study, neurotherapeutic compounds as lead phytocompounds from Using molecular docking, *O. gratissimum* demonstrated a multi-target inhibitory action against acetylcholinesterase (AChE), butyrylcholinesterase (BChE), and monoamine oxidase B (MAO-B) targets that may be significant for the management and treatment of neurodegenerative illnesses.(Njan et al., 2023). A study (Ojo et al., 2019),It discusses the potential use of phenolic and flavonoid chemicals found in *O. gratissimum* leaf extracts to treat erectile dysfunction by inhibiting erectile dysfunction-related enzymes in testicular and penile tissues in rats. A huge number of researchers have recently looked into the method of biodegradation at the molecular level. The reaction process has been studied using molecular docking. The contaminants are attached to the enzymes' active sites during this process (Liu Z et al., 2018).

5. Conclusion

From the present findings, *in-silico* approach suggests several probable mechanisms of *O. gratissimum* phytocompounds' anti-diabetic prospective. The phytocompounds were found to act through MAPK, PI3K-Akt, AMPK, cAMP, and p53 signalling pathways, cell cycle, oocyte meiosis, neuroactive ligand-receptor interaction, regulation of lipolysis in adipocytes, neuroactive ligand-receptor interaction, starch and sucrose metabolism, and insulin resistance. Further, the study demonstrated the interactions of phytocompounds with four major drug targets of DM viz., AMY2A, GAA, DPP4, and AR. The current study not only provides a theoretical framework for comprehending the DM's underlying molecular mechanisms but also leads to the development of potential targets and drugs to cater to the needs of DM suffering patients. The current study conclusions are based on the computational simulation, which can be further validated through *in-vitro studies*.

Author contributions

RH and ZB have been involved in the concept design. RH and SD have executed all the research work and carried out all the network constructions and analysis. RH has carried out all the data analysis and interpretations. RH, ZB and SD have written the manuscript. RM and SJ have critically reviewed the manuscript. ZB has supervised the entire work. The authors have read and approved the contents of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sjbs.2023.103766.

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