International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 13, Issue 5, 2021

Original Article

BIOCOMPUTATIONAL AND PHARMACOLOGICAL ANALYSIS OF PHYTOCHEMICALS FROM *ZINGIBER OFFICINALE (GINGER), ALLIUM SATIVUM (GARLIC),* AND *MURRAYAKOENIGII (CURRY LEAF)* IN CONTRAST TO TYPE 2-DIABETES

RATUL BHOWMIK[1], SHUBHAM ROY[1], SOUNOK SENGUPTA[2], SAMEER SHARMA[3*]

[1]Department of Pharmaceutical Chemistry, SPER, Jamia Hamdard, New Delhi, India, [2]Department of Pharmacology, NSHM Knowledge Campus, Kolkata-Group of Institutions, Kolkata, West Bengal, India, [3]Department of Bioinformatics, BioNome Private Limited, Bengaluru, India
Email: sameer21.97@gmail.com

Received: 03 Jun 2021, Revised and Accepted: 03 Jul 2021

ABSTRACT

Objective: This study was aimed to analyze the inhibitory effect of the flavonoid class of phytochemicals present in ginger (*Zingiber Officinale)*, garlic (*Allium sativum),* and curry leaf (*Murrayakoenigii)* against some receptors of type-2 diabetes such as human aldose reductase receptor, mitogen synthase kinase receptor, as well as dipeptidyl peptidase receptor by implementing several *in silico* analysis techniques.

Methods: The 3D structures of the flavonoid class of phytochemicals of all the three plants were retrieved from the PubChem database in 3D SDF format and were converted to PDB format using PyMol software. These phytochemicals were subjected to *in silico* tools such as SwissADME, Pre-ADMET, and iMODS web server. The PDB-IDs of the targeted receptors human aldose reductase, dipeptidyl peptidase-IV, and mitogen synthase kinase were retrieved from Protein Data Bank in PDB format. All these receptors were then prepared for docking procedure using Autodock Tools. Now, both the prepared proteins and ligands were subjected to docking analysis using Pyrex (AutodockVina).

Results: Naringenin and kaempferol showed excellent docking results with the aldose reductase receptor. On the other hand, rutin showed the best docking score with dipeptidyl peptidase receptor-IV, whereas, epigallocatechin showed the best docking results with mitogen synthase kinase receptor. The ADME analysis showed that resveratrol had the best gastrointestinal absorption as well as high blood-brain barrier permeability.

Conclusion: Overall, the molecular docking results when analyzed showed a good binding affinity with the targeted receptors of diabetes. The ADME analysis and molecular docking results of the phytochemicals concluded that these compounds can be used as a potential cure for treating diabetes.

Keywords: Diabetes, Phytochemicals, ADME, Molecular docking

DOI: https://dx.doi.org/10.22159/ijap.2021v13i5.42294. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Ginger, scientific name *Zingiberofficinale*, family Zingiberaceae, is a flowering plant. Its rhizome is commonly consumed as folk medicine or as a spice in food. Based on scientific evidence ginger can be used as an Antiplatelet, antimicrobial, anticancer agent [1]. The ginger extract can be used to prevent autoxidation of fat at an earlier stage i.e. as an antioxidant agent [2]. Garlic, scientific name *Allium sativum*, Family Amaryllidaceae is a bulbous type flowering plant. It is commonly used as a flavoring agent in food as well as in traditional medicine. Meta-analysis Animal studies and epidemiological studies have proved that garlic consumption can reduce the expression of cancer, for example, stomach, colon, esophagus, cervix, skin, lung, breast, and uterine cancers. Clinical data shows that along with cancer garlic is also effective as an antifungal, antimicrobial, antioxidant, antidiabetic, and antihypertensive drug [3, 4]. The curry tree, scientific name *Murrayakoenigii*, family Rutaceae is a tropical and sub-tropical plant. Due to its characteristic aroma and chemical constituents, it is used as a flavoring agent in Indian dishes. The essential oil present in *Murrayakoenigii* leaves shows mosquitocidal-Antibacterial activity, Antifungal activity, and Antiprotozoal activity [5]. This study is mainly based on the phytochemical screening of the three above-mentioned plants. Flavonoids are a group of phytochemicals with different types of phenolic structures. Their antioxidant effects of flavonoids can cure various diseases like Alzheimer's disease (AD), cancer, atherosclerosis, etc. A significant amount of flavonoid intake can maintain coronary heart disease [6]. Chemically flavonoids contain A, B, and C ring systems. B ring when linked in position 3 of the ring C are called isoflavones similarly when B ring is linked in position 4 are called neoflavonoids. When the B ring is linked in position 2 of the C ring, it can be further subdivided into several subgroups like flavones, flavonols, flavanones, flavanonols, flavanols, or catechins and anthocyanins [7]. In this study, we have mainly selected the important flavonoid phytochemicals of the three plants i.e. Ginger, Garlic, and Curry leaves to carry out a comparative molecular docking analysis against some important receptors aldose reductase, dipeptidyl peptidase-IV, and mitogen synthase kinase. Moreover, this study also included pharmacological analysis of our selected phytochemicals to predict and analyze drug-likeness properties of the phytochemicals.

MATERIALS AND METHODS

Ligand preparation

All the important flavonoid phytochemicals of the plants *Murrayakoenigii, Allium sativum,* and *Zingiberofficinale* were retrieved from the PubChem database in the form of 3D Standard Data Format (3D SDF) [8, 9]. PyMol was then used for converting the ligand from 3D SDF to Protein Data Bank (PDB) format [10].

Protein preparation

The targeted receptor molecules were selected and downloaded in PDB format from the protein data bank database [11]. The protein molecules were then loaded in Autodock Tools software [12]. Firstly, the extraction of the co-crystallized ligand was done to validate the protein. Immediately, after this, protein preparation of the protein was started by removing water molecules, removing chains or heteroatoms not required, repairing missing atoms, the addition of hydrogen atoms, computing charges (Kollman charges) and finally converting it into pdbqt format. Finally, generation of the grid box was done keeping the co-crystallized ligand at the center. The dimension of the grid box was saved for docking using AutodockVina as a config. txt file. The co-crystallized was then removed from the prepared protein pdbqt file.

ADMET and drug-likeness analysis

SwissADME and Pre-ADMET web servers were used to predict drug-likeness and ADMET properties of our selected phytochemicals [13]. Lipinski's rule was used to virtually screen the best hit compounds

from our selected list of phytochemicals. According to Lipinski's rule of five, a compound, to qualify as a ligand, should have less than 500 Da molecular weight, high lipophilicity i.e. value of Log P less than five, hydrogen bond donors less than 5, and hydrogen bond acceptors less than 10. Compounds violating any two rules of Lipinski's were eliminated for further screening. Other than Lipinski's rule, physicochemical analysis, as well as Drug-likeliness properties of all the ligand molecules, were also taken into consideration for the drug screening process.

Boiled-egg

For predicting blood-brain barrier permeability as well as gastrointestinal absorption of our selected phytochemicals, BOILED EGG was used. According to BOILED-Egg plot analysis, compounds found in the yellow region were considered to be having higher blood-brain barrier permeability, whereas compounds found in the white region of the plot were considered to be having higher gastrointestinal absorption properties. The BOILED-Egg plot analysis was performed using the SwissADME webserver.

Molecular docking analysis

The molecular docking analysis was mainly performed to predict the interaction as well as inhibitory activity of our selected phytochemicals against our targeted protein receptors. The docking study was carried out using PyRx (AutoDockVina) [14, 15]. The prepared ligands were docked with the prepared protein receptors. The results of docking were displayed in the terms of binding affinity. The binding affinity represents the binding energy. The binding energy exhibits the extent of binding of a particular compound. Furthermore, the best type of conformation would be the one that would bind with its target. The molecule with the best binding affinity along with good ADMET properties was chosen as the best hit compounds. The structural analysis of the compounds was done by using Discovery Studio Visualizer 2021 [16].

Molecular dynamic simulation

It is a computer-based simulation technique for the analysis of atoms or molecules' physical movements. A few crucial hydrogen bond interactions can be identified using MD simulations. MD simulations aid in advancements in protein docking or virtual screening. In this study, the iMODS server was used for the molecular dynamic simulation. the iMODS server helps in exploring the normal mode analysis and produces accessible information of pathways which may be with macromolecules or between homologous structures.

RESULTS AND DISCUSSION

Ligands

Naringenin, catechin, epigallocatechin, epicatechin, resveratrol, quercetin, apigenin, quercetrin, rutin, kaempferol, morin, and myricetin were the flavonoid phytochemical chosen for the study. The structures of these phytochemicals were retrieved from the PubChem database in the form of 3D SDF format.

Proteins

Glycogen Synthase Kinase, Dipeptidyl Peptidase-IV, and Aldose Reductase were the receptors chosen for the study. The PDB-Ids of the receptors Glycogen Synthase Kinase (PDB-Id: 3F7Z), Dipeptidyl Peptidase-IV (PDB-Id: 3F8S), an Aldose Reductase (1US0) were all retrieved from protein data bank (PDB) database in PDB format. These proteins were then prepared for docking using Autodock Tools as mentioned in the protein preparation process above.

ADMET and drug-likeliness analysis

Lipinski's rule of five analysis was carried out to predict the rigidity of the compounds for structure-based drug design. The physicochemical analysis, as well as the drug-likeness analysis of all our selected phytochemicals, are listed below.

Table 1: Physiochemical analysis

Ligand	Molecular formula	Molecular weight (g/mol)	Monoisotropic mass (g/mol)	Heavy atom count	Tropological polar surface area
Naringenin	C15H12O5	272.25	272.068473	20	86.99
Catechin	C15H16O7	308.28	308.0896029	22	111
Epigallocatechin	C15H14O7	306.27	306.0739528	22	131
Epicatechin	C15H14O6	290.27	290.079038	12	110.38
Resveratrol	C14H12O3	228.24	228.0786442	17	60.7
Quercetin	C15H10O7	302.04	302.042653	16	131.36
Apigenin	C15H10O5	270.24	270.052823	20	90.9
Quercetrin	C21H20O11	448.4	448.1005615	32	186
Rutin	C27H30O16	610.5	610.1533849	43	266
Kaempferol	C15H10O6	286.24	286.047738	21	111.13
Morin	C15H10O7	302.23	302.0426527	22	127
Myricetin	C15H10O8	318.23	318.0375673	23	148

Table 2: Lipinski's analysis

Ligand	Molecular formula	H-Bond donar	H-Bond acceptor	CLogP	Molar refractivity
Narigenin	C15H12O5	3	5	2.16	71.57
Catechin	C15H16O7	6	7	1.51	77.38
Epigallocatechin	C15H14O7	6	7	1.16	76.36
Epicatechin	C15H14O6	5	6	1.51	74.33
Resveratrol	C14H12O3	3	3	2.83	67.88
Quercetin	C15H10O7	5	7	1.49	78.03
Apigenin	C15H10O5	3	5	2.34	73.99
Quercetrin	C21H20O11	7	11	0.58	109
Rutin	C27H30O16	10	16	-1.26	141.38
Kaempferol	C15H10O6	4	6	1.84	76.01
Morin	C15H10O7	5	7	1.49	78.03
Myricetin	C15H10O8	6	8	1.14	80.06

BOILED-egg analysis

The BOILED-Egg analysis showed that resveratrol was the only compound showing both high blood barrier permeability property as well as good gastrointestinal absorption properties. The other compounds showing high gastrointestinal absorption other than resveratrol were apigenin, naringenin, kaempferol, morin, quercetin, epicatechin, epigallocatechin, catechin. The

least gastrointestinal absorption ability was shown by morin, quercetrin, and rutin.

Molecular docking analysis

Most of the phytochemicals showed good docking results for our three targeted receptors human aldose reductase, glycogen synthase kinase, and dipeptidyl peptidase-IV. For the aldose reductase receptor, the highest dock scores of about-10 and-9.9 with naringenin and kaempferol respectively. For the dipeptidyl peptidase-IV receptor, the highest dock score of about-9.7 was observed with rutin. Lastly, with mitogen synthase kinase receptor, the highest dock score of about-9.0 was observed with epigallocatechin. Thus, the compounds that showed the best dock score indicate good binding affinity with their respective receptor.

Table 3: Drug-likeness analysis

Ligands	Blood-brain barrier	GI absorption	Permeability glycoprotein substrate	LogS (scale insoluble<-10<poorly<-6<moderately<-4<soluble<-2very<0<highly) [Water solubility]
Naringenin	No	High	Yes	-3.49
Catechin	No	High	No	-2.02
Epigallocatechin	No	High	No	-2.08
Epicatechin	No	High	Yes	-2.22
Resveratrol	Yes	High	No	-3.62
Quercetin	No	High	No	-3.16
Apigenin	No	High	No	-3.94
Quercetrin	No	Low	No	-3.33
Rutin	No	Low	Yes	-3.3
Kaempferol	No	High	No	-3.31
Morin	No	High	No	-3.16
Myricetin	No	Low	No	-3.01

Table 4: Molecular docking results with aldose reductase receptor

Ligand	PDB-ID	dock score
Narigenin	1US0	-10
Catechin	1US0	-9.2
Epigallocatechin	1US0	-9.6
Epicatechin	1US0	-9.4
Resveratrol	1US0	-8.8
Quercetin	1US0	-9.7
Apigenin	1US0	-9.7
Quercetrin	1US0	-8.3
Rutin	1US0	-10
Kaempferol	1US0	-9.9
Morin	1US0	-9.7
Myricetin	1US0	-8.7

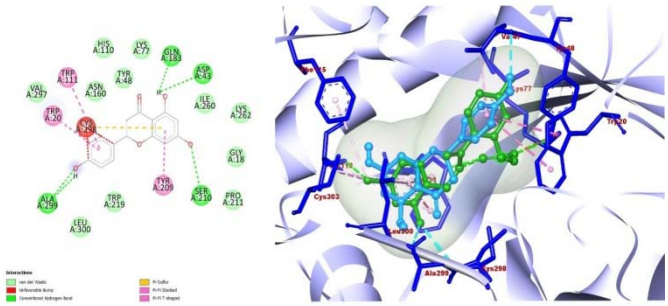

Fig. 1: The left-sided diagram shows the 2D amino acid interactions of Naringenin with human aldose reductase receptors. The right-sided diagram shows the binding analysis of Naringenin (light blue) at the active site of the co-crystallized/native ligand (deep green) of the receptor human aldose reductase. In the right-sided diagram, protein is represented in light violet color, whereas, the amino acid residues are represented in deep blue color

Table 5: Molecular docking results with mitogen synthase kinase receptor

Ligand	Pdbid	Dock score
Narigenin	3F7Z	-8.2
Catechin	3F7Z	-7.7
Epigallocatechin	3F7Z	-9
Epicatechin	3F7Z	-7.8
Resveratrol	3F7Z	-7.3
Quercetin	3F7Z	-8
Apigenin	3F7Z	-8
Quercetrin	3F7Z	-8.7
Rutin	3F7Z	-8.1
Kaempferol	3F7Z	-7.5
Morin	3F7Z	-7.8
Myricetin	3F7Z	-8

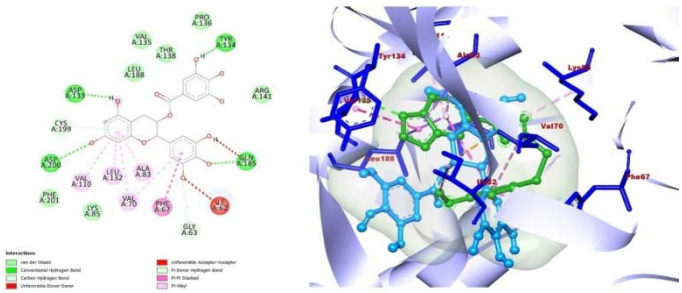

Fig. 2: The left-sided diagram shows the 2D amino acid interactions of epigallocatechin with mitogen synthase kinase receptor. The right-sided diagram shows the binding analysis of Epigallocatechin (light blue) at the active site of the co-crystallized/native ligand (deep green) of the receptor mitogen synthase kinase. In the right-sided diagram, protein is represented in light violet color, whereas, the amino acid residues are represented in deep blue color

Table 6: Molecular docking results with dipeptidyl peptidase-IV receptor

Ligand	Pdbid	Dock score
Narigenin	3F8S	-7.1
Catechin	3F8S	-7.7
Epigallocatechin	3F8S	-8.1
Epicatechin	3F8S	-7.5
Resveratrol	3F8S	-6.9
Quercetin	3F8S	-7.8
Apigenin	3F8S	-7.8
Quercetrin	3F8S	-8.8
Rutin	3F8S	-9.7
Kaempferol	3F8S	-7.7
Morin	3F8S	-7.7
Myricetin	3F8S	-8

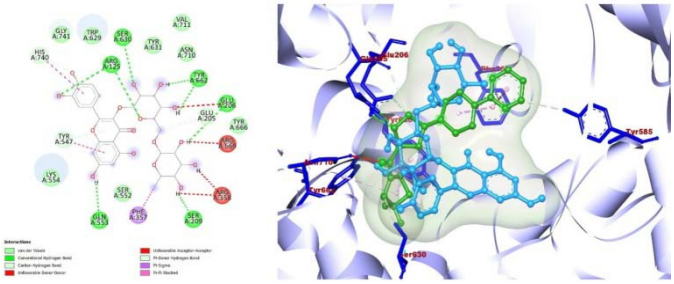

Fig. 3: The left-sided diagram shows the 2D amino acid interactions of Rutin with the dipeptidyl peptidase-IV receptor. The right-sided diagram shows the binding analysis of Rutin (light blue) at the active site of the co-crystallized/native ligand (deep green) of the receptor dipeptidyl peptidase-IV. In the right-sided diagram, protein is represented in light violet color, whereas, the amino acid residues are represented in deep blue color

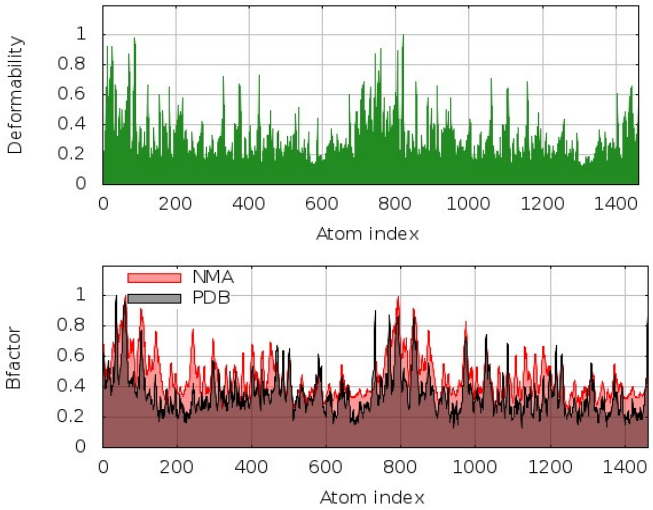

Fig. 4: B-factor or mobility (The main-chain deformability is a measure of the capability of a given molecule to deform at each of its residues)

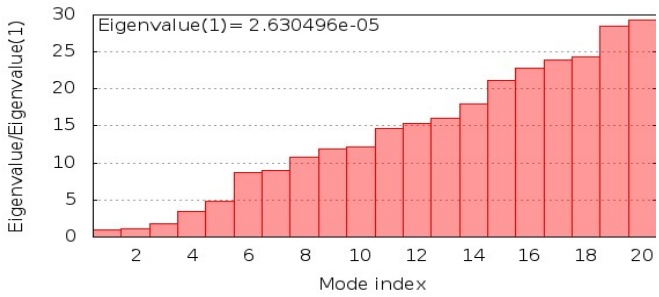

Fig. 5: Eigenvalues (The eigenvalue associated to each normal mode represents the motion stiffness. Its value is directly related to the energy required to deform the structure. The lower the eigenvalue, the easier the deformation)

Fig. 6: Variance (individual (red) and cumulative (green) variances)

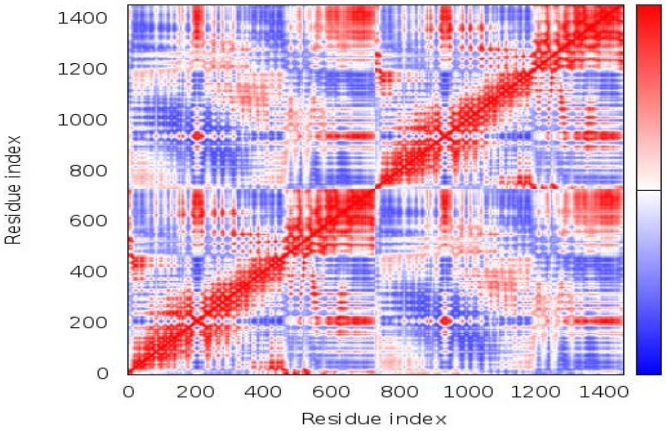

Fig. 7: Covariance map (correlated (red), uncorrelated (white) or anti-correlated (blue) motions of coupled residues)

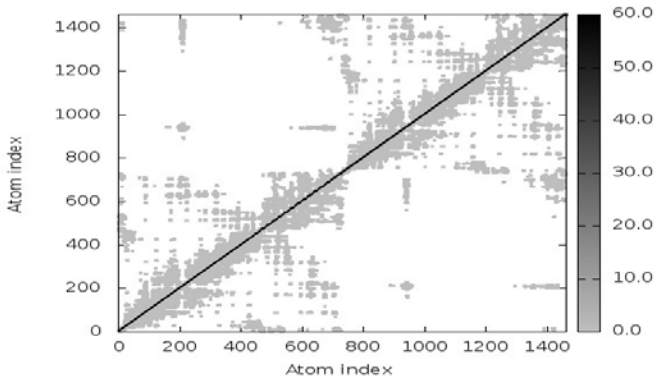

Fig. 8: Elastic network (Each dot denotes one spring within the respective atoms pair. The dots are colored based on the stiffness where the dark grey dots indicate the stiffer springs and vice versa)

DISCUSSION

In this study, we have targeted three receptors. Glycogen Synthase Kinase (PDB-ID: 3F7Z); DPP4 (PDB-ID: 3F8S) and Aldose Reductase (PDB-ID: 1US0). Glycogen Synthase kinase or (GSK)-3 is a serine/threonine kinase that provides negative feedback in the hormonal regulation of glucose homeostasis, by phosphorylating and thus inhibits glycogen synthase (GS). Human GSK-3 presents in two isoforms, alpha and beta, encoded by two distinct genes. Insulin is responsible for the inactivation of GSK-3, both *in vitro* and *in vivo*. Phosphorylation of the specific serine residues is responsible for the inactivation mechanism. In addition, it has been reported that insulin receptor substrate (IRS)-1, a key molecule participating in insulin-signaling cascades can also be phosphorylated by GSK-3. In some experiments, it has been found that Lithium-ion (Li) can cause specific inhibition of GSK-3 [15, 17] and has been reported to have insulin-like effects on glucose metabolism, including increases in glucose uptake hence activation of GS activity. As a result, it stimulates glycogen synthesis in muscle, skin, and fat cells [17]. In skeletal muscle, insulin regulation is correlated by phosphorylating and inhibiting GYS1 activity and hence glycogen synthesis. Selective cell-permeable reversible inhibitors (INH) of GSK-3 were used to evaluate the role of GSK-3 in controlling glucose metabolism. Dipeptidyl-peptidase 4 (DPP4) is a type of glycoprotein of 110 kDa, which can be found on the surface of various cells. DPP4 is highly correlated with glucose metabolism. It is responsible for the degradation of increments such as GLP-1. Incretin hormones, glucagon-like peptide-1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP) are some of the major regulators of insulin secretion. Thus inhibition of DPP4 by the gliptin family of drugs gains high attention for the therapy of patients suffering from type 2 diabetes [18, 19]. Aldose reductase inhibitors are a class of drugs that can block the breakdown of glucose by inhibiting a specific metabolic pathway called the polyol pathway. The polyol pathway becomes hyperactive during the state of hyperglycemia. This pathway is responsible for the reduction of glucose to sorbitol via the enzyme aldose reductase (AR), utilizing the cofactor nicotinamide adenine dinucleotide phosphate (NADPH). This reduction reaction is responsible for increased sorbitol accumulation in the cells. Increases in sorbitol concentrations result in cellular and organ injury [20, 21]. So via inhibiting this enzyme we can prevent those complications. So basically all of these three receptors can be targeted as antidiabetic therapeutics. We have selected 3 plants *Zingiber Officinale(Ginger), Allium sativum (Garlic)* as well as*Murrayakoenigi (Curry leaf*) as lots of pharmacological evaluations of phytochemicals are already done on those plants.

More than 3000 publications in the past support the efficacy of garlic for the cure, prevention, and treatment of various types of diseases. Garlic has historically been used to treat various aches and pains, leprosy, deafness, diarrhea, constipation, parasitic infection, and fever and to relieve stomachache. It has also been used to lower food poisoning, tumors, blood pressure and as a mild anticoagulant [3]. In Ayurvedic medicine, garlic is used to treat respiratory problems, colic, and flatulence. Earache can be treated by using Garlic oil drops. Supplementation of garlic oil at 5 mg/kg body weight has been shown to have an anticoagulation effect in an animal study [20]. An aqueous extract obtained from 1 mg of a garlic preparation was as effective as an antioxidant, like 30 nmol ascorbic acids. In rat hepatocytes, garlic paste, garlic oil, allicin, and ajoene were found to significantly reduce cholesterol biosynthesis by inhibiting 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase and 14-a-demethylase. Garlic also lowers hyperlipidemia in animal studies [20]. In a randomized placebo-controlled trial in ten healthy adults, there was a significant improvement in plasma viscosity and capillary blood flow within 5 h of taking 900 mg of standardized garlic powder [22]. Aged garlic and garlic's diallyl sulfur compounds protected against acute chemically-induced hepatotoxicity in rats. Garlic cloves have shown antimicrobial properties against streptococci and anti-cariogenic properties against oral microorganisms with minor adverse effects [23].

Evidence for the benefit of ginger as an antiemetic in pregnancy is some of the strongest. Preliminary studies suggest that ginger may be effective for mild to moderate nausea and vomiting of pregnancy when used at a recommended dose of 1-g dried ginger per day or its equivalent in the form of ginger syrup [24]. There are few investigations into ginger's capacity to alter blood clotting. One human study suggested that intake of 1-g ginger powder may have a synergistic effect on antiplatelet aggregation in hypertensive patients when used in combination with nifedipine. Findings from several animal studies suggest that ginger may have beneficial effects on blood pressure [25]. Streptozotocin (STZ) induced diabetic rats, specific extracts of ginger lowered blood glucose, cholesterol, and triglyceride levels and increased high-density lipoprotein cholesterol concentration [26]. In animals, ginger exhibited mixed results as an inhibitor of tumor formation in models of colon, bladder, lung, and skin cancer. *In vitro* studies of Ginger extracts and their chemical constituents indicate suppression of the growth of various common infectious bacteria including Staphylococcus aureus and Listeria monocytogenes [27]. The CO2 extract from ginger has high polyphenol content. It manifested very good scavenging of DPPH and reduced its reducing capacity. The extract can be used as an antioxidant at an earlier stage of fat oxidation [2].

Curry leaves have also been found to have a variety of health benefits. The ethanolic extract of the leaves showed fungi toxicity against *Colletotrichumfalcatum* and *Rhizoctoniasolani*. The acetone extract of the fresh leaves of Murrayakoenigii on fractionation gives three bioactive carbazole alkaloids named mahanimbine, murrayanol, and mahanine, which has shown mosquitocidal, antimicrobial activity[5]. Curry leaves powder supplementation (12 g providing 2.5 g fiber) was given for one month in 30 non-insulin-dependent diabetes mellitus patients. The results indicated a significant reduction in fasting and postprandial blood sugar levels at 15-day [28].

Due to the variety of health benefits of these three plants, we have chosen them for our drug repurposing study against some important diabetes type 2 receptors namely dipeptidyl peptidase-IV, aldose reductase as well as mitogen synthase receptor. The most important phytochemicals i.e. the flavonoid class of phytochemicals of these three plants was chosen as ligands for this study. Flavonoids are a group of phytochemicals with different types of phenolic structures. Their antioxidant effects of flavonoids can cure various diseases like Alzheimer's disease (AD), cancer, atherosclerosis, etc. A significant amount of flavonoid intake can maintain coronary heart disease [6]. These phytochemicals were subjected to various *in silico* techniques such as molecular docking and ADME-based pharmacological tools analysis. Through this study, we were finally able to screen and find out our hit compounds for each receptor, which showed a good binding affinity with our selected type two diabetes receptors. In short, we can conclude by saying that our hit phytochemicals, can be considered as lead candidates in binding with our targeted receptors, and thus can help to treat type 2 diabetes. Results obtained from this research study will serve as an insight for future preclinical as well as *in vivo* studies.

CONCLUSION

Zingier Officinale(Ginger), Allium sativum (Garlic) as well as *Murrayakoenigi (Curry leaf)* have been previously used as a cure to many diseases. The flavonoids phytochemicals obtained from these three plants have overall good showed a binding affinity with the receptors dipeptidyl peptidase-IV, aldose reductase, and mitogen synthase kinase. Naringenin and kaempferol showed excellent docking results with the aldose reductase receptor. On the other hand, rutin showed the best docking score with dipeptidyl peptidase receptor-IV, whereas, epigallocatechin showed the best docking results with mitogen synthase kinase receptor. The ADME analysis showed that resveratrol had the best gastrointestinal absorption as well as high blood-brain barrier permeability. Hence, we can conclude by saying that these phytochemicals can provide a cure to diabetic disorders. To find the effectiveness as well as to propose the exact mechanism, *in vitro* studies can be encouraged on these phytochemicals to understand the exact mechanism and potential cure for diabetes.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICTS OF INTERESTS

All authors have none to declare.

REFERENCES

1. Singletary K. Ginger: an overview of health benefits. Nutr Today 2010;45:171-83.
2. Stoilova I, Krastanov A, Stoyanova A, Denev P, Gargova S. Antioxidant activity of a ginger extract (Zingiber officinale). Food Chem 2007;102:764-70.
3. Rana SV, Pal R, Vaiphei K, Sharma SK, Ola RP. Garlic in health and disease. Nutr Res Rev 2011;24:60-71.
4. Zhou Y, Zhuang W, Hu W, Liu G, Wu T, Wu X. Consumption of large amounts of Allium vegetables reduces the risk for gastric cancer in a meta-analysis. Gastroenterology 2011;141:80-9.
5. Saini SC, Bala G, Reddy S. A review on curry leaves (Murraya koenigii): versatile multi-potential medicinal plant. Am J Phytomed Clin Ther 2015;3:363-8.
6. Pietta PG. Flavonoids as antioxidants. J Nat Prod 2000;63:1035-42.
7. Panche AN, Diwan AD, Chandra SR. Flavonoids: an overview. J Nutr Sci 2016;5:e47.
8. Kim S, Chen J, Cheng T, Gindulyte A, He J, He S, *et al.* PubChem 2019 update: improved access to chemical data. Nucleic Acids Res 2019;47. DOI:10.1093/nar/gky1033
9. Kim S, Thiessen PA, Bolton EE, Chen J, Fu G, Gindulyte A, *et al.* PubChem substance and compound databases. Nucleic Acids Res 2016;44:D1202–D1213.
10. DeLano WL. The PyMOL molecular graphics system. Version 2.3. Schrodinger LLC; 2020.
11. Berman HM, Westbrook J, Feng Z, Gilliland G, Bhat TN, Weissig H, *et al.* The protein data bank. Nucleic Acids Res 2000;28:235-42.
12. Forli W, Halliday S, Belew R, Olson A. AutoDock Version 4.2. Citeseer; 2012.
13. Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep 2017;7:42717.
14. Trott O, Olson AJ. AutoDock vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. J Comput Chem 2010;31:455-61.
15. Dallakyan S, Olson AJ. Small-molecule library screening by docking with PyRx. Methods Mol Biol 2015;1263:1.
16. DS Visualizer. v4. 0.100. 13345, Accelrys Software Inc; 2013.
17. Nikoulina SE, Ciaraldi TP, Mudaliar S, Carter L, Johnson K, Henry RR. Inhibition of glycogen synthase kinase 3 improves insulin action and glucose metabolism in human skeletal muscle. Diabetes 2002;51:2190-8.
18. Deacon CF. Corrigendum: physiology and pharmacology of DPP-4 in glucose homeostasis and the treatment of type 2 diabetes frontiers in endocrinology. Frontiers Endocrinol 2019;10:275.
19. Rohrborn D, Wronkowitz N, Eckel J. DPP4 in diabetes. Front Immunol 2015;6:1-20.
20. Alexiou P, Pegklidou K, Chatzopoulou M, Nicolaou I, Demopoulos V. Aldose reductase enzyme and its implication to major health problems of the 21st century. Curr Med Chem 2009;16:734-52.
21. Schemmel KE, Padiyara RS, D'Souza JJ. Aldose reductase inhibitors in the treatment of diabetic peripheral neuropathy: a review. J Diabetes Its Complications 2010;24:354-60.
22. Gebhardt R, Beck H. Differential inhibitory effects of garlic-derived organosulfur compounds on cholesterol biosynthesis in primary rat hepatocyte cultures. Lipids 1996;3:1269-76.
23. Salehi I, Vahidinia A, Bakhtiari A, Mohammadi P, Sukumaran A, Hosseini-Zijoud SM. The effect of fresh garlic on the lipid profile and atherosclerosis development in male rats fed with a high ghee diet. Int J Pharm Pharm Sci 2015;7:486-90.
24. Chrubasik S, Pittler MH, Roufogalis BD. Zingiberis rhizoma: a comprehensive review on the ginger effect and efficacy profiles. Phytomedicine 2005;12:684-701.
25. Kemkar K, LS, Sathiyanarayanan A, Mahadik K. 6-Shogaol rich ginger oleoresin loaded mixed micelles enhances *in vitro* cytotoxicity on mcf-7 cells and *in vivo* anticancer activity against dal cells. Int J Pharm Pharm Sci 2018;10:160-8.
26. Bhandari U, Kanojia R, Pillai KK. Effect of ethanolic extract of Zingiber officinale on dyslipidaemia in diabetic rats. J Ethnopharmacol 2005;97:227-30.
27. Norajit K, Laohakunjit N, Kerdchoechuen O. Antibacterial effect of five zingiberaceae essential oils. Molecules 2007;12:2047-60.
28. Iyer UM, Mani UV. Studies on the effect of curry leaves supplementation (Murraya koenigi) on lipid profile, glycated proteins and amino acids in non-insulin-dependent diabetic patients. Plant Foods Hum Nutr 1990;40:275-82.