Insights from chemoinformatics studies of phytochemical derivatives of *Aegle marmelos Correa*: Implications for diabetic therapy

Pillappan Ramkumar[1]*, Vangalapti Bheemesh[2], Anjali K.[3] and Rajeshwari A.[4]
1. Nitte Gulabi Shetty Memorial Institute of Pharmaceutical Sciences, Nitte (Deemed to be University), Deralakatte, Mangalore, INDIA
2. Department of Pharmacology, American University of Barbados, Bridgetown, BARBADOS
3. Vijnana Foundation for Innovation Research in Science and Technology, Udupi, INDIA
4. Department of Biochemistry, Adichunchanagiri Institute of Medical Sciences, Adichunchanagiri University, Karnataka, INDIA
*Dr.Ramkumar.pharm@gmail.com

Abstract

Rapid advances in the field of diabetes have resulted in the discovery of numerous chemotherapeutic agents. However, most of these drugs result in severe side effects causing physical and mental trauma to patients. In order to eliminate the side effects, the search for better and safer drugs has resulted in the discovery of anti-diabetic properties of many phytochemicals. Recently, phytochemicals from A. marmelos have garnered more interest for their anti-glycemic properties. Herein we present a process for utilizing efficient and inexpensive computational strategies for identifying and validating specific phytochemicals in the A. marmelos extracts and to further understand their potency as anti-diabetics. Screening programs have revealed that phytochemical agents from A. marmelos have shown in vitro or in vivo antidiabetic activity.

In this comprehensive study, we employed α-glucosidases viz., α-amylase, maltase-glucoamylase and sucrase-isomaltase as bio-chemical targets explore the underlying antagonistic mechanisms of A. marmelos phytochemicals. Further, we have delineated the important interactions responsible for the binding of ligands to the active site. The present study provides potent phytochemicals which will be employed in the testing their efficacy against diabetes in vitro.

Keywords: *A. marmelos*, Phytochemical, α-Glucosidases, Molecular docking, ADME studies.

Introduction

Diabetes mellitus, a metabolic disorder of the endocrine system, is one of the World's oldest diseases known to man. It is caused by inherited and/or acquired deficiency or inadequate secretion of hormone insulin [Type I or insulin-dependent diabetes mellitus (IDDM)] or due to an inadequate response of target cells to insulin [Type II or noninsulin-dependent diabetes mellitus (NIDDM)], or by a combination of these factors that ultimately culminates in hyperglycemia[6]. Being a metabolic disorder, diabetes affects carbohydrate, fat and protein metabolism which on a long term leads to severe complications that are more fatal than the primary disease[2,6]. Accordingly, because of the huge premature morbidity and mortality associated with the disease, prevention of both acute and chronic complications is vital[2].

In the past decade, several major studies have focused on the need for strict control of glycemia to prevent and/or reduce the risk of these secondary complications[2]. One of the mechanisms to control hyperglycemia is to inhibit the action of the α-glucosidase enzymes present in the brush border of the small intestines. These inhibitors establish control over hyperglycemia by inhibiting the breakdown of polysaccharides into monosaccharides and are extremely useful in type 2 diabetes mellitus. Synthetic drugs like acarbose, miglitol and voglibose are prescribed as monotherapy, in conjunction with other anti-diabetic drugs with lifestyle modification[5]. Unfortunately, regular use of these agents is associated with side effects like flatulence and diarrhea which contribute towards compromised therapeutic benefit and reduction in the quality of life[3].

Many people now rely upon alternative and complementary medicines for the management of diabetes and many plants have been observed to be useful[7]. *Aegle marmelos* Correa (syn. *Feronia pellucida* Roth, *Cratarea marmelos* L., family Rutaceae) commonly known as Bilwa or bael is an indigenous tree of India but is today found growing also in Pakistan, Ceylon, Burma, Thailand and China. The English name for Bael, is stone apple, as its rather large fruit is like pale yellow to golden orange when ripe. Bael has an important place in the various folk systems of medicine and is considered as an emblem of fertility. According to the traditional Indian system of medicine, the Ayurveda, bael is regarded to be a healing tree that gives strength to the body. In fact, as per Charaka (1500 BC), no drug has been longer or better known or appreciated by the inhabitants of India than bael[13].

Scientific studies carried out in the recent past indicate that the plant possessed anti-bacterial, anti-fungal, anti-cancer, cardioprotective, anti-pyretic, analgesic, anti-diarrheal, antioxidant, hepatoprotective, wound healing and anti-cholestremic effects[1]. Studies have also shown that the leaf and fruit extracts possess antidiabetic effects in chemically induced diabetic rats and to mediate the antidiabetic effects by multiple mechanisms[14,16]. Mechanistic studies have shown that the ethanolic extract of the raw bael fruit and bael

pods possessed α-amylase and α-glucosidase inhibitory activities in cell-free assays. Studies have also shown that phenylethyl cinnamides isolated from the bael leaf possess varying degree of α-glucosidase inhibitory effects *in vitro* with the best effect being observed for anhydroaegeline.

The chemical composition of Bael is very complex and the quantity of many of the constituents is dependent on the growing, harvesting, processing and storage conditions. Some of the important phytochemicals present are aegeline, aegelenine, marmelosine, marmelin, o-methyl halfordinol, alloimperatorin methyl ether, o-isopentenyl halfordinol, linoleic acid, cineole, p-cymene, citronella, citral, cuminaldehyde, D-limonene, eugenol, tannins, phlobatannins, flavon-3-ols, leucoanthocyanins, anthocyanins and flavonoid glycosides.

The conventional plant drug discovery methodologies are very time consuming, cumbersome and costly process. Nonetheless, there may be utility to increase research in the area of medicinal plants. There are several computational approaches for analyzing the diversity of compounds. These approaches have played a significant role in computer-aided drug design[18]. The field of drug design and discovery from medicinal plant require the application of such approaches for quicker and efficient progress so as to cope up with the continually demanding pharmaceutical needs. Bioinformatics offers a suite of essential techniques for analyzing and interpreting huge volumes of information generated using molecular biology based techniques[17].

Present study is directed towards comprehensive computational study on α-glucosidases viz., α-amylase, maltase-glucoamylase and sucrase-isomaltase to explore the underlying antagonistic mechanisms of *A. marmelos* extracts on these α-glucosidases. Thus, automated molecular modelling has been employed with the eventual aim to develop novel superior anti-diabetics agents with least side effects and to tailor these agents to possess the designed properties for individual therapy.

Material and Methods

Structure preparation: The crystal structures of α-amylase (PDB ID: 1B2Y, 2CPU), maltase-glucoamylase (PDB ID: 2QMJ) and sucrase-isomaltase (PDB ID: 3LPP, 3LPO) were obtained from Protein Data Bank and employed in molecular docking process. The protein was prepared employing the protein preparation module implemented in Schrödinger suite and accessible from within the Maestro (Maestro, version 9.2). H-atoms were added to the protein including the protons necessary to define the correct ionization and tautomeric states of amino acid residues such as Asp, Ser, Glu, Arg and His. Finally, the protein was refined with a restrained minimization performed using by Impref (Impact version 5.7,) and the OPLS2001 force field, setting a max RMSD of 0.30[12]. Prepared protein structures were used to generate Glide scoring grids for the subsequent docking calculations. To each of the crystal structures of protein, a grid box of default size (20 × 20 × 20 Å) was centered on the corresponding active site position. Default parameters were used and no constraints were included during grid generation. The receptor structure was manually defined by either selecting the amino acid residues that span the kinase domain or selecting the ligand present within the crystal structure.

Ligand preparation: All the ligands used were processed in the similar manner. The compound dataset was built with ChemDraw and 2D structures of dataset were incorporated into the Maestro (version 9.2, 2011) and processed with Ligprep module (version 2.4, 2010). The cleaning process was carried out with the following parameters: (a) the force field used was OPLS-2005, (b) all possible ionization states at pH 7.0 ±2.0 were generated with ionizer, (c) the desalt option was activated, (d) tautomers were generated for all ionization states at pH7.0±2.0, (e) chiralities, when present, were determined from the 3Dstructure and (f) one low-energy ring conformation per ligand was generated[12]. Conformations and sites for the resulting ligand structures were determined employing the Confgen graphic front-end. The parameter values used during this conformer generation were by default with the maximum number of conformers (100) per structure.

Docking Methodology: The aim of molecular docking is to evaluate the feasible binding geometries of a putative ligand with a target whose target site is known. The binding geometries often known as binding poses includes in principle, both the position of the ligand relative to the receptor and conformational state of the ligand and the receptor. There are three basic tasks any docking procedure must accomplish: (1) characterization of the binding site, (2) positioning of the ligand into the binding site (orienting) and (3) evaluating the strength of interaction for a specific ligand-receptor complex ("scoring").

The low-energy 3D structures of all compounds were employed in docking studies. Extra precision docking with receptor flexibility was used for all Glide docking runs with default settings for some parameters and no constraints of similarity scoring were applied. The protein was prepared using the protein preparation and refinement tool. All the Glide protocols were run using default parameters. An extensive search was carried out for generating all possible conformations. Minimization cycle for conjugate gradient and steepest descent minimizations were used with default value of 0.05 Å for initial step size and 1.0 Å for maximum step size.

In convergence criteria for the minimization, both the energy change criteria and gradient criteria were used with default values of 10^{-7} kcal/mol and 0.001 kcal/mol respectively[13]. Then, all conformations were considered for docking. We docked the ligands flexibly, allowing for the flip of 5- and 6-membered rings, writing out maximum of one poses per ligand and also enabling the post-docking minimization of

the ligands. During the docking process, the G-score was used to select the best conformation for each ligand. G-score is based on the ChemScore but includes a steric-clash term and adds buried polar atoms devised by the Schrodinger to penalize electrostatic mismatches:

G-score = 0.065*vdW + 0.130*Coul + Lipo + Hbond + BuryP + RotB + Site.

***In silico* ADME Studies:** The drug discovery mainly aims at the generation of innovative small molecular entities demonstrating high target affinity and selectivity together with a fair absorption, distribution, metabolism and excretion (ADME) profile, lead and/or drug likeness. Such chemical molecules usually are potential to enter higher phases of the drug development process[14].

Herein, QikProp the prediction program was used to calculate ADME (Absorption, Distribution, Metabolism and Excretion) properties[15]. It is quick and accurate method and predicts physically significant descriptors and pharmaceutically relevant properties of organic molecules. Ligprep minimized ligands were processed by employing as source in Qikprop 3.2.

Results and Discussion

The objective of the current study was to identify the specific phytochemicals that have molecular attributes requisite to inhibit glucosidases and to explore the inhibitory mechanism of these phytochemicals. To achieve this, we employed here a computational strategy composed of rationale drug identification and evaluation. Molecular modelling techniques reveal the mechanisms and all the crucial interactions required in the inhibition of glucosidases.

To describe the overall molecular features of the ligands that govern their inhibitory activity here, we employed 24 diverse compounds that were identified in *A. marmelos* in previous phytochemical profile studies[12] (Table 1).

All the ligands were built using ChemDraw and energetically minimized using OPLS_2005 force field by ligprep. Protein preparation and refinement studies were performed on α-amylase, maltase-glucoamylase and sucrase-isomaltase using the protein preparation module. Finally, energetically minimized structures were used as active site in molecular docking process. The reliability of the docking method was validated by redocking the bound molecule into the active sites of each protein (Figure 1). The RMSD of superimposition was 0.21 and the inhibitor was docked to the same place, confirming the accuracy of Glide docking program in reproducing the experimentally observed binding mode for these α-glucosidases.

Molecular docking is a simulation process that predicts the conformation of a receptor-ligand complex, in which the receptor can be either a protein or a nucleic acid and the ligand is a small molecule[11]. Visualizing this simulation as analogous to the key-and-lock problem is possible, in which the lock is the receptor and the key is the ligand. The goal here is to adjust the position of the key in the lock.

All 24 inhibitors were employed in the exploring of bioactive conformation, by docking flexibly into the active site of α amylase, maltase-glucoamylase and sucrase-isomaltase. All the docking poses were visually inspected to rank the different host conformations of the complex. Molecular docking analysis of the five potential leads showed that they share common intermolecular interactions with the proteins. The key residues of amylase involved in the interaction with the ligands were Asp300 and Gln63 involved in H-bond interaction. Hydrophobic interactions with Ile51, Try59, Leu165 and Thr163 were consistent with all top hits (Table 2 and figure 2).

Table 1
Binding mode of bioactive ligands to Amylase

Ligand	Glide Score	H Bond Interaction	H Phobic Interaction	Glide Energy
Delphidin	-8.77	O…NH (Gln63) O…NH (His299) O…NH (Arg195) OH…O (Glu233)	Ile51, Try59, Leu165, Thr163	-43
Quercitrin	-8.1	O…NH (Gln63) OH…O (Asp300) OH…O (Asp300)	Val49, Ile51, Try59, Leu165, Thr163	-37.2
Leucocyanidin	-7.5	OH...O (Try59) O…NH (Gln63) OH…O (Asp197) O…OH (Glu233)	Ile51, Try59, Leu165, Thr163	-41
Ellagic acid	-5.68	OH…N (His 305) OH…O (Asp197) OH…O (Asp197)	Try59, Leu162, Leu165	-37.2

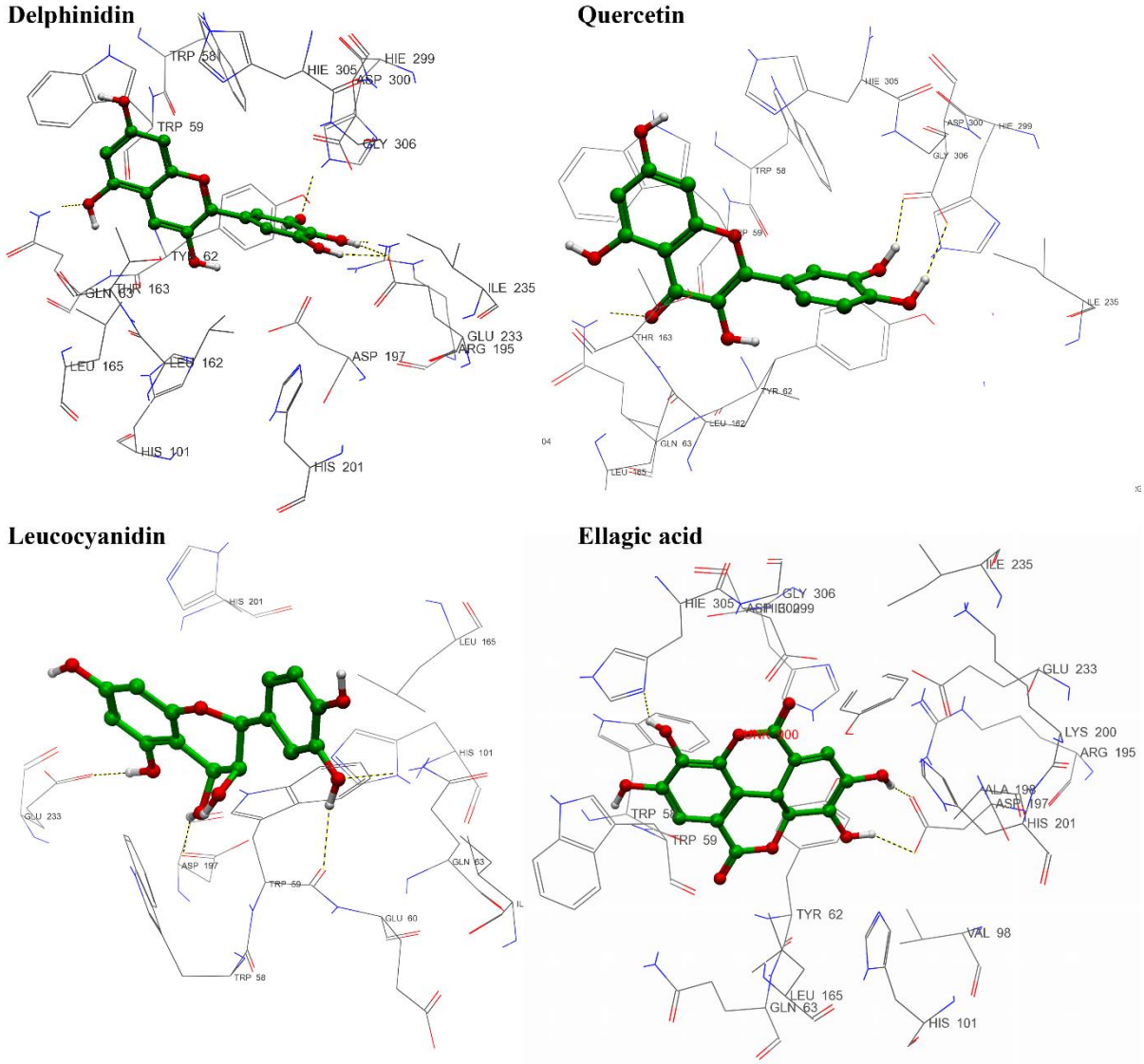

Figure 1: The reliability of docking method was validated by redocking the bound molecule into the active sites of each protein

Table 2
Binding mode of bioactive ligands to Sucrase-Isomaltase:

Ligand	Glide Score	H Bond Interaction	H Phobic Interaction	Glide Energy
Leucocyanidin	-6.5	OH…O (Glu678), O…NH (Arg682), OH…O (Tyr762), OH…O (Asp796)		-36.6
Delphidin	-6.2	OH…O (Glu678), OH…O (Ile 763)	Tyr762, Lys794, Lys672, Pro705, Phe665, Ile764	-40.1
Quercitrin	-5.9	OH…O (Ile763), O…NH (Lys672), OH…O (Glu678), OH…O (Asp796),	Tyr762, Lys794, Lys672, Pro705, Phe665, Ile764	-31.5
Ellagic acid	-5.2	O…NH (Lys672), OH…O (Glu678), O…NH (Arg682), OH…O (His686)		-35.9

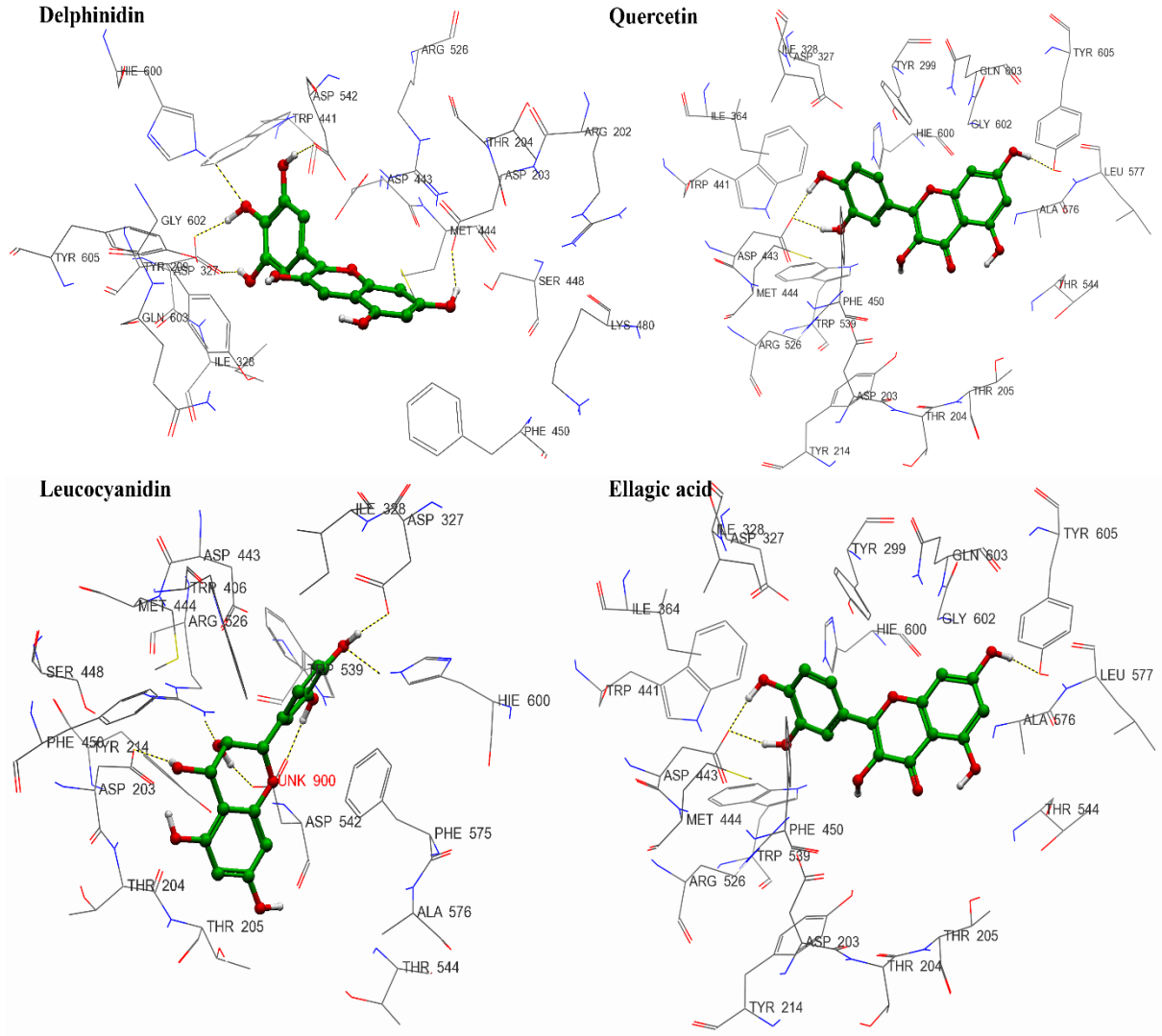

Figure 2: The key residues of amylase involved in the interaction with the ligands were Asp300, Gln63, involved in H-bond interaction. Hydrophobic interactions with Ile51, Try59, Leu165 and Thr163 were consistent with the all top hits.

Table 3
Binding mode bioactive ligands to Maltase- Glucoamylase

Ligand	Glide Score	H Bond Interaction	H Phobic Interaction	Glide Energy
Leucocyanidin	-7.6	OH…O (Asp203) O…NH (Arg526) OH…O (Asp542) OH...O (Asp 327)	Trp539, Trp406, Trp441, Ile 328, Tyr299, Phe 575	-45.3
Delphidin	-7.5	OH…O (Asp 203) OH…O (Asp 542) OH...O (Asp 327) O…NH (His 600)	Trp539, Trp406, Ile328, Tyr299, Phe575, Phe450	-45.1
Ellagic acid	-6.0	OH...O (Tyr605) OH…O (Asp203) OH…O (Thr 205)		-32.0
Quercitrin	-5.9	OH…O (Asp 443) OH...O (Tyr605) OH...O (Asp 542)	Trp406, Ile328, Ile364, Tyr299, Phe575, Tyr605	-34.8

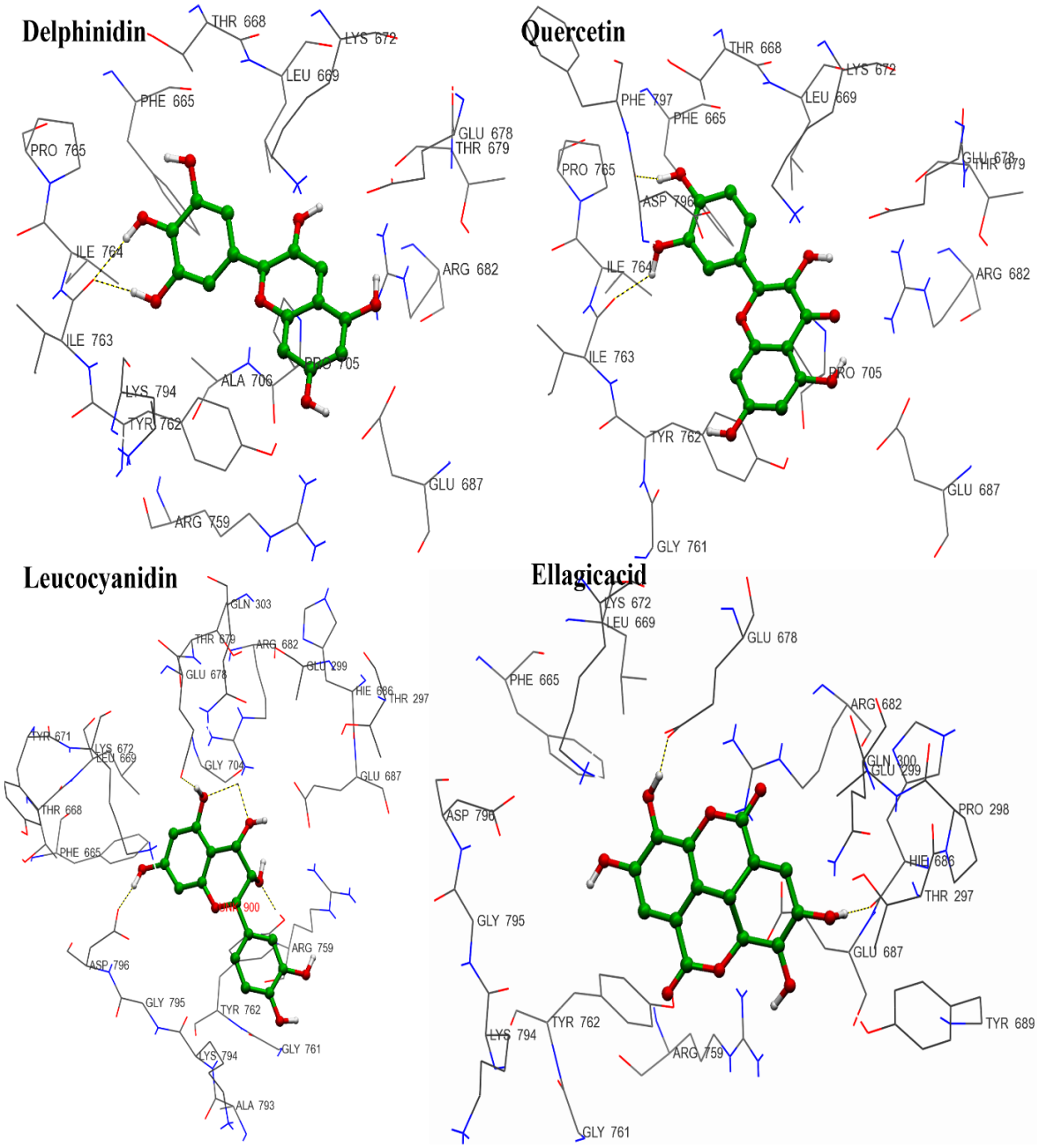

Figure 3: The main Maltase-Glucoamylase residues involved in the interaction with the ligands were Asp203, Arg526, Asp542 involved in H-bond interaction.

The main maltase-glucoamylase residues involved in the interaction with the ligands were Asp203, Arg526, Asp542 involved in H-bond interaction (Table 3 and figure 3). This hydrogen-bonding network places the inhibitor such that hydrophobic contacts are made with the side chains of Trp539, Trp406, Trp441, Ile 328, Tyr299, Phe575 and Tyr605 maltase-glucoamylase. The ligands shared hydrophobic interactions with Tyr299, Trp406 and Phe575. Docking analysis of the sucrase-Isomaltase reveals the presence of H-bond interactions between the ligands and Glu678, Arg682, Tyr762, Asp796, Glu678, Ile 763, Lys672 of the sucrase-Isomaltase active site.

Sucrase-isomaltase provides a mat of hydrophobic contacts that include the side chains of Tyr762, Lys794, Lys672, Pro705, Phe665 and Ile764. These interactions were in accordance with PDB data. We can conclude that the spatial arrangements of highly active molecule and that of the crystal ligand (Acarbose) are very similar emphasizing the validity of this study.

Finally, after visual inspection, the 4 most favorable compounds of diverse scaffolds with the best binding mode and structural diversities were selected for further analysis. Lipinski's rule of five is based on a set of property values (i.e. the number of hydrogen-bond donors and acceptors, the molecular weight and the log P) derived from the Food and Drug Administration-approved drugs which are known to have clinically acceptable ADME properties.

Table 4
ADME properties of selected molecules

Entry Name	MW	QPlogPC16	QPlogPo/w	QPlogS	QPlogH	% Oral Abs
Delphidin	304	11.2	-0.1	-2.3	-4.8	35
Quercitrin	302	10.7	0.4	-2.9	-5.0	53
leucocyanidin	306	11.0	-0.3	-2.2	-4.7	40
Ellagic acid	304	9.62	-1.3	-1.9	-3.7	36

Therefore, molecules that pass the Lipinski rule, are expected to be active in humans after oral administration[10]. Incorporating ADME predictions as a part of the drug development process can generate lead compounds that are more likely to exhibit satisfactory ADME performances during clinical trials[8]. The dataset was evaluated for drug-likeness of lead molecules by assessing their physicochemical properties and by applying Lipinski's rule of five. Their molecular weights were <500 daltons with <5 H-bond donors, <10 H-bond acceptors and a logP of <5; all these properties were well within the acceptable range of the Lipinski rule for drug-like molecules.

For the selected six lead compounds, the partition coefficient (QPlogPo/w) and water solubility (QPlogS), critical for estimating the absorption and distribution of drugs within the body, ranged between −2 to 6.5 and −6 to 0.5 respectively. Further, the percentage human oral absorption for all six compounds ranged from 25 to 100%. All these pharmacokinetic parameters were within the acceptable range defined for human use, thereby indicating their potential to act as drug-like molecules (Table 4).

Conclusion

Computational methods are playing an increasingly larger and more important role in drug discovery and development and can offer improved efficiency for the discovery of novel enzyme inhibitors. They are expected to limit and focus on chemical synthesis and biological testing, thereby greatly decreasing the traditional resource requirements. Till date, there are several therapeutics available for discoursing diabetes mellitus but most of them are synthetic treatment making the treatment costly and are often associated with side effects. Hence there is a burgeoning need for the successful development and application of natural anti-diabetics, in order to reduce the cost of treatment for diabetes mellitus.

Mounting evidence has indicated that *A. marmelos* demonstrated potent hypoglycemic activity better than the synthetic hypoglycemic drugs, thereby validating its ethnomedicinal uses. In the present work, we describe the identification of key phytochemicals that are involved in the hypoglycemic potential of *A. marmelos* extracts by employing computational drug-designing strategies. In order to identify key phytochemicals, we prepared a dataset of diverse phytochemicals that we have identified in our previous report and employed in the molecular modeling process. These ligands with considerable chemical diversity were docked into the active site of the α-glucosidases viz., α-amylase, maltase-glucoamylase and sucrase-isomaltase to investigate the binding modes and molecular interactions formed with catalytic amino acid residues as a positive indication of enzyme inhibition. The hit compounds were further filtered for drug-like properties based on Lipinski's rule of five. A post-docking analysis based on binding modes and molecular interactions produced four compounds as final hit compounds. The present study provides potent phytochemicals to be employed in testing their efficacy against diabetes *in vitro*.

Acknowledgement

The authors thank Nitte (Deemed to be University) for providing all the support to carry out this research work.

References

1. Balakumar S., Rajan S., Thirunalasundari T. and Jeeva S., Antifungal activity of Aegle marmelos (L.) Correa (Rutaceae) leaf extract on dermatophytes, *Asian Pacific Journal of Tropical Biomedicine*, **1(4)**, 309-12, 10.1016/S2221-1691(11)60049-X **(2011)**

2. Dal Canto E., Ceriello A., Rydén L., Ferrini M., Hansen T.B., Schnell O., Standl E. and Beulens J.W., Diabetes as a cardiovascular risk factor: An overview of global trends of macro and micro vascular complications, *European Journal of Preventive Cardiology*, **26(2)**, 5-32, 10.1177/2047487319878371 **(2019)**

3. Dirir A.M., Daou M., Yousef A.F. and Yousef L.F., A review of alpha-glucosidase inhibitors from plants as potential candidates for the treatment of type-2 diabetes, *Phytochemistry Reviews*, **21(4)**, 1049-79, 10.1007/s11101-021-09773-1 **(2022)**

4. Halgren T.A., Murphy R.B., Friesner R.A., Beard H.S., Frye L.L., Pollard W.T. and Banks J.L., Glide: a new approach for rapid, accurate docking and scoring. 2. Enrichment factors in database screening, *Journal of Medicinal Chemistry*, **47(7)**, 1750-9, https://doi.org/10.1021/jm030644s **(2004)**

5. Kalra S., Selvam A.P., Shah A.V., Neelaveni K., Agrawal N., Das S., Dhandhania V.K., Jain S., Jha P.K. and Rava N., Prospective Multicenter Observational Study of Voglibose in Type 2 Diabetes-Victory, *Journal of US Endocrinology*, **16(1)**, 31–5, https://doi.org/10.17925/USE.2020.16.1.31 **(2020)**

6. Kharroubi A.T. and Darwish H.M., Diabetes mellitus: The epidemic of the century, *World Journal of Diabetes*, **6(6)**, 850-867, 10.4239/wjd.v6.i6.850 **(2015)**

7. Kifle Z.D., Prevalence and correlates of complementary and alternative medicine use among diabetic patients in a resource-

limited setting, *Metabolism Open*, **10**, 100095, 10.1016/j.metop.2021.100095 **(2021)**

8. Komura H., Watanabe R. and Mizuguchi K., The trends and future prospective of in silico models from the viewpoint of ADME evaluation in drug discovery, *Pharmaceutics*, **15(11),** 2619, 10.3390/pharmaceutics15112619 **(2023)**

9. Lai Y., Chu X., Di L., Gao W., Guo Y., Liu X., Lu C., Mao J., Shen H., Tang H. and Xia C.Q., Recent advances in the translation of drug metabolism and pharmacokinetics science for drug discovery and development, *Acta Pharmaceutica Sinica B*, **12(6)**, 2751-77, 10.1016/j.apsb.2022.03.009 **(2022)**

10. Lipinski C.A., Lombardo F., Dominy B.W. and Feeney P.J., Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings, *Advanced Drug Delivery Reviews*, **23(1-3)**, 3-25, https://doi.org/10.1016/j.addr.2012.09.019 **(2012)**

11. Mohanty M. and Mohanty P.S., Molecular docking in organic, inorganic and hybrid systems: A tutorial review, *Monatshefte für Chemie-Chemical Monthly*, **154(7)**, 683-707, https://doi.org/10.1007/s00706-023-03076-1 **(2023)**

12. Monika S., Thirumal M. and Kumar P.R., Phytochemical and biological review of Aegle marmelos Linn, *Future Science OA*, **9(3)**, FSO849, doi: 10.2144/fsoa-2022-0068 **(2023)**

13. Pathirana C.K., Madhujith T. and Eeswara J., Bael (Aegle marmelos L. Corrêa), a medicinal tree with immense economic potentials, *Advances in Agriculture*, **2020**, 1-3, https://doi.org/10.1155/2020/8814018 **(2020)**

14. Poonkothai M. and Saravanan M., Antibacterial activity of Aegle marmelos against leaf, bark and fruit extracts, *Ancient Science of Life*, **27(3)**, 15-8 **(2008)**

15. QikProp, Version 3.4, Schrödinger, LLC, New York, NY **(2011)**

16. Sabu M.C. and Kuttan R., Antidiabetic activity of Aegle marmelos and its relationship with its antioxidant properties, *Indian Journal of Physiology and Pharmacology*, **48(1)**, 81-8, https://pubmed.ncbi.nlm.nih.gov/15270373/ **(2004)**

17. Saito Y., Kitamura H., Hijikata A., Tomizawa-Murasawa M., Tanaka S., Takagi S., Uchida N., Suzuki N., Sone A., Najima Y. and Ozawa H., Identification of therapeutic targets for quiescent, chemotherapy-resistant human leukemia stem cells, *Science Translational Medicine*, **2(17)**, 17ra9, Doi: 10.1126/scitranslmed.3000349 **(2010)**

18. Shah M., Patel M., Shah M., Patel M. and Prajapati M., Computational transformation in drug discovery: A comprehensive study on molecular docking and quantitative structure activity relationship (QSAR), *Intelligent Pharmacy*, https://doi.org/10.1016/j.ipha.2024.03.001 **(2024)**

19. Teli M.K. and Rajanikant G.K., Pharmacophore generation and atom-based 3D-QSAR of novel quinoline-3-carbonitrile derivatives as Tpl2 kinase inhibitors, *Journal of Enzyme Inhibition and Medicinal Chemistry*, **27(4)**, 558-70, Doi: 10.3109/14756366.2011.603128 **(2012)**.

(Received 20th April 2024, accepted 22nd June 2024)