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Molecular Docking and Dynamic Simulation Studies of compounds from *Rumex vesicarius* against Maltase-Glucoamylase to treat type 2 Diabetes

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ABSTRACT

The growing number of diabetes cases in India has lately been worrisome, and the potential of certain herbal plants in Indonesia to be anti-diabetic medication candidates has to be appropriately addressed. The Maltase-Glucoamylase objective was investigated with the aim of molecular docking and dynamic simulations of Indiian herbal substances (*Rumex vesicarius*). In this study the patented medicine, Acarbose, has been utilised as a control. The findings indicate that the affinity to acarbosis (-9,35 and 8,75 kcal/mol respectively) is greater for all the luteoline and apigenin compounds. The study of the binding site indicates that luteoline and apigenine compounds mostly dock at comparable locations than acarbose, which imply a similar cure between the drugs. The MD simulation study of maltose-glucoamylase (MGA) with luteoline and apigenine further verified the stability of ligand protein complexes. As with other compounds, they have higher binding affinities than acarbose, but have mostly been found in different locations than acarbose, which indicate that, in contrast to luteoline and apigenin compounds, other compounds have no significant anti-diabetic potentials through inhibiting MGA.

Keywords
Autodock, Dynamics simulation, Molecular docking, *Rumex vesicarius*, Maltase-Glucoamylase, type 2 diabetes

Introduction

One of the world's most important public health issues is diabetes mellitus (DM). There are 415 million people with diabetes according to the International Diabetes Federation, likely to reach 642 million by 2040 (IDF Diabetes Atlas,2015). DM is a multifactorial chronic metabolic disease that may be categorised mainly as Type 1 (insulin-dependent DM) or Type 2 (non-insulin-reliant DM) (Salsali A et al,2006). DM is a type 1 metabolic disorder. Type 2 DM is the most prevalent type of DM, which is the consequence of interplay between comportant and environmental risk and genetic risk factors (Wilke T et al,2015, Olokoba et al, 2012), accounting for over 90% of all diabetes patients. In diabetic patients, the risk of common infection and cancer, increased morbidity and mortality, and different types of short- and long term consequences are increasing (Muller L.M et al, 2005, Garg S.K et al, 2014). DM is characterised by absolute or relative insulin secretion deficit, increased resistance to insulin, and/or impairment in the action of insulin in the target tissue (Taylor et al, 1994, Cheng et al, 2014).

One of the objectives of intestinal glucosidase is the N-terminal catalytic domain of maltase-glucoamylase (MGA). In the human family, MGA hydrolyzes linear alpha-1,4-linked substrates of oligosaccharides which play a key part in glucose production of human lumen and are effective therapeutic targets for diabetes and obesity type 2. Therefore, herbal medicines have

been used to substitute pharmaceutical medications, such as acarbosis and miglitol, to block the activity of the enzyme, which frequently have an unfavourable impact for certain diabetic people. Tests revealed that the alkaloid components having a hypoglycemic impact on many animal investigations and small scale human studies included extracts from Momordica charantia, Tinopora cordifolia and Zingsooo-officinales plants (Heymann et al, 1995). In addition, the effectiveness of synthetic agents with high IC50 values is low (Sim L et al, 2008). So, a lot of effort was made to look for safer and more efficient inhibitors.

Rumex vesicarius L. is an edible, green leafy plant which belongs to the Polygonaceae family. It is locally known as Chukkakoora (Quézel P et al, 1962). This bush, born in northern Asia [Pakistan and India] (Sankar N R et al, 2011), grows every year during the wet seasons of the autumn and spring. It was regarded a dietary herbal additive because of its abundance, ß-carotenes (Bélanger J et al,2010), vitamins, proteins, lipids and organic acids (particularly vitamin C). A excellent supply of minerals including K, Na, Ca, Mg, Fe, Mn and Cu (Saleh N A M et al, 1993, Al Rumaih et al, 2002, Filho J M B et al,2008). The plant as a whole is medical and heals many illnesses, it is an invigorating, tonic and works as an aphrodisiac (Gopal R et al, 2008). It is utilised in tumour, hepatic illness, poor digestion, stroke, calculations, cardiac disorders, pains, stroke, hiccough, flatulence, asthma, bronchitis, dyspepsia, pilts, skin, leucoderma, toothache and nausea therapy. Finally, bile diseases and cholesterol levels may also be reduced by the plant (Mostafa H A M et al, 2011).

The purpose of the current research was to discover, based on their historic usage in silico analysis, the MGA inhibiting action of *Rumex vesicarius* phyto-constituents.

Material & Methods

Data source:

A 'PubChem database' (https://pubchem.nlm.nih.gov) was utilised to create a three-dimensional arrangement of the phenolic compounds (Pereira D F et al,2011). The whole configuration of the MGA enzyme was obtained using a PDB database (https://www.rcsb.org/).The 3L4Y access number has been acquired from the PDB database (Kawser H M et al,2016).

Molecular docking studies:

Preparation of ligands:

From the IMPPAT database (https://cb.imsc.res.in/imppat/home/), 10 phytoconstituents apigenine, crysen, emodine, physcion, catechin, lutenoline, quercetine, rhein, tetramethylen sulphone and alloaromadendrene and from PubChem databse (https://pubchem.ncbi.nlm.nih.gov/) standard drug acarbose downloaded in Structure Data File (.SDF), and the 3D-SDF structure files were converted into .PDB format in open babel software (http://openbabel.org) (Fig.1).

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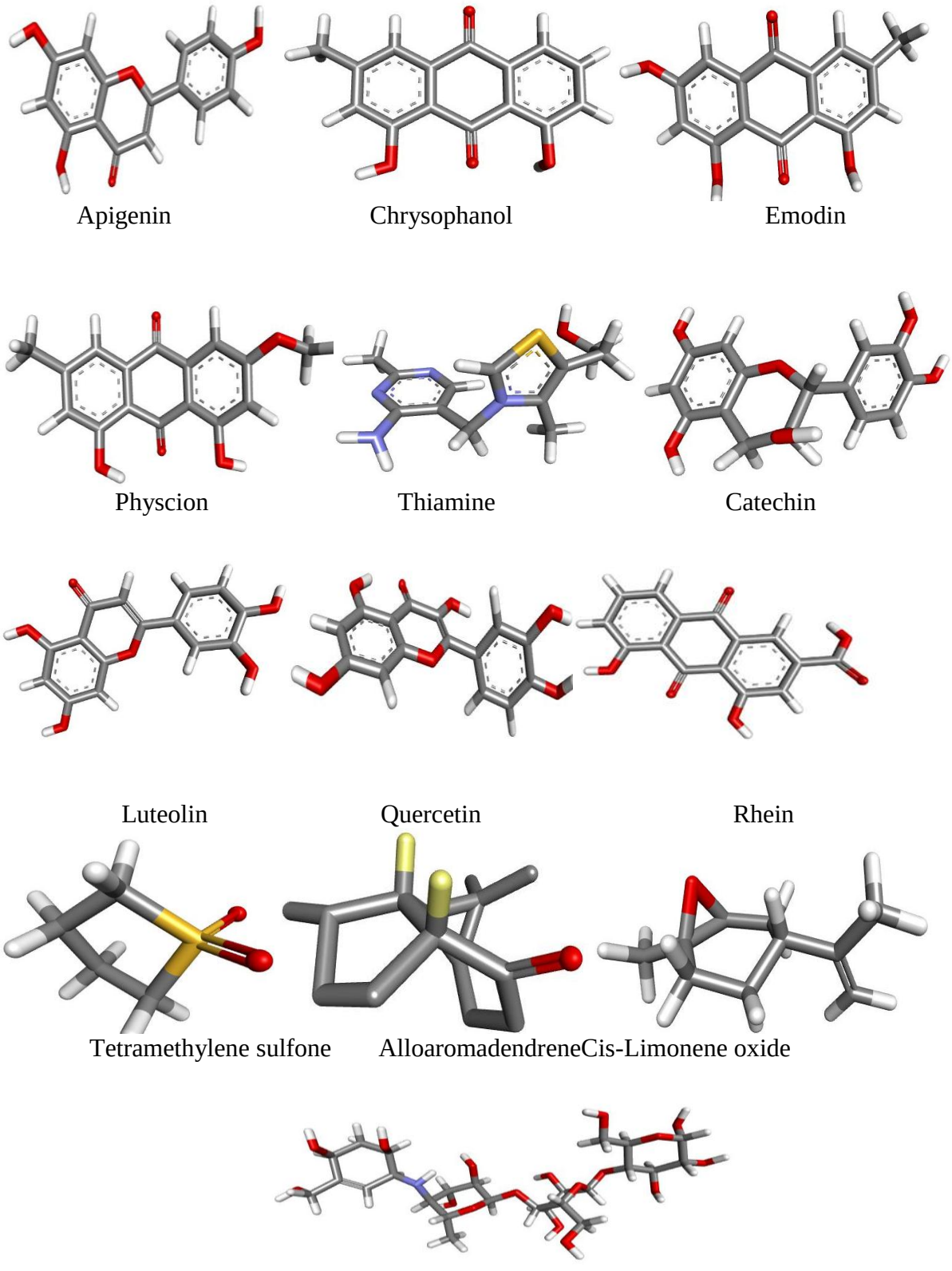

Figure 1: 3D Structures of Phytoconstituents from the *R. vesicarius* and standard drug.

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Preparation of protein:

The 3D crystal human MGA (PDBID:3L4Y) structure was found from the protein database in PDB format, and downloaded in pdb format (Ceriello A et al,2016) to conduct the molecular docking study. The MGA structure may be classified into five primary domains: the Type-P Treefolio (Residues 29-80), the N Terminal Domain (Residues 81-296), the 8 barrel catalytic (Residues 297-681), with two variable inserted Domains 1 and 2 (Residue 395-445 and Domes 476-521, respectively) (Fig. 2). Only one chain, consisting of 875 residues and also an active site, was taken for molecular docking. The protein was separated from the ligands and water molecules, and the protein chemistry for missing hydrogen was rectified and protein energy was minimised. Optimization, adding of charges and hydrogen connections with the drug molecule and phytoconstituants were performed using Autodock technologies.

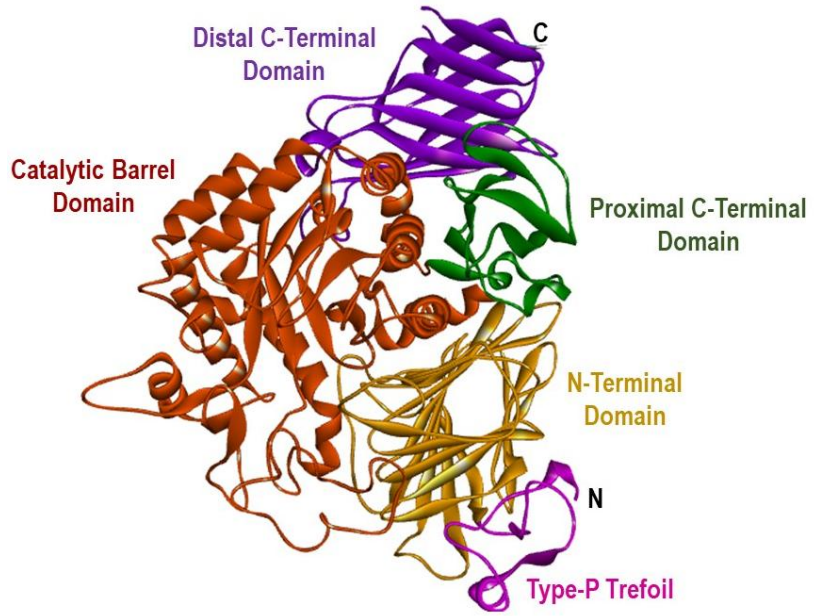

Figure-2: 3D crystal structure of the human Maltase-Glucoamylase (PDB ID: 3L4Y). Individual domains are colored as follows: trefoil Type-P domain (magenta), catalytic barrel domain (brown), distal C-terminal domain (violet), proximal C-terminal domain (green), N-terminal domain (yellow)

Protein and ligand docking:

The docking of Maltase-Glucoamylase with selected phytochemical molecules were performed by using Autodock 4. The docking calculations were verified using docking server. Gasitier partial charges were added to ligand. Nonpolar hydrogen atoms were merged and rotatable hydrogen bonds were defined. Docking calculations were carried out on receptor. Essential hydrogen atoms, kollaman charges and savlavation parameters were added affinity (grid) maps 25 Å grid points and 0.500Å were generated using the autogrid program. Autodock parameters set and distance dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms, respectively. Docking simulations were performed using Lamarckian algorithm (LA) method. Initial position torsion and orientation of the drug molecules were set

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randomly. All rotatable torsions were released during docking. Each docking experiment was derived from 10 different runs that were set to terminate after 250000 energy calculations (Xiao J B et al,2015). The population size was set to 150. During search the translational step 0.2 Å and quaternion and torsion step 5 were applied.

Molecular dynamics simulation:

On the basis of the findings of the docking, structural analysis of the lowest energy value and docking complex chosen have been conducted. Based on these results. Groningen Chemicals Simulation Machine (GROMACS) 4.5.4 (Luthra T et al, 2017) package with GROMOS 96 force field (Mamidala et al, 2020) was used to simulate MDs. The PRODRG Server was used to produce topology files for ligands(Leiter L A et al, 2005). The most steep descended approach (1 000 ps) for protein-ligand complex was performed before minimizatiob (nsteps = 50,000). For the energy computation and electrostatic and Van der Waals interactions, the Particle Mesh Ewald (PME) technique was used, with a cut-off distances for the short range VdW (rvdw) set to 14Ao (Zhang L et al, 2016). Finally, a simulation of 10 ns molecular dynamics was performed for the nstep 1.000.000 protein-ligand complex. The RMSD/F/Gyration Radius (Rg) and Xmgrace (http://plasma-gate.weizmann.il/Grace/) root mean square deviation and fluctuation analysis were performed using the programme UCSF chimaera 1.10.1.

Results and Discussion

Molecular Docking Analysis:

In our investigations, we utilised the ten phytoconstituents apigenins, tetramethylene sulfone, chrysophane, emodium-physticum, catechins, luteoline, quercetin and alloaromadendrene from R. Vesicarius. These have been examined and proven experimentally for various biological activities from the earlier publication (Alves H M et al, 2014, Husain P N et al, 2011). In current study, we have identified the binding interaction and docking values of these chosen compounds by molecular docking with the target enzyma maltase-glucoamylase, as shown in Table 1. The drug development of new and effective inhibitors of the MGA may benefit from these findings.

There was good inhibition of luteolin −9,35 and epigenin −8,75 kcal/mol, when compared to other compounds and 3.18 kcal/mol relative to the ligands reference. Both compounds are extremely active and have demonstrated good interaction with the target enzyme MGA. In our investigations, we utilised the ten phytoconstituents apigenins, tetramethylene sulfone, alloaromadendrene, chrysophane, emodium, physticum, catechins, luteoline and quercetin from R. vesicarius. These have been examined and proven experimentally for various biological activities from the earlier publication (Husain P N et al, 2011). In current study, we have identified the binding interaction and docking values of these chosen compounds by molecular docking with the target enzyma maltase-glucoamylase, as shown in Table 1. The drug development of new and effective inhibitors of the MGA may benefit from these findings.

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The luteolin (-9.35 kcal/mol) and apigenin (-8.75 kcal/mol) exhibited excellent inhibition when compare to acarbose standard drug (−3,18 kcal per mol). These two chemicals are highly active and have shown excellent interaction with the MGA target enzyme.

Table-1. Table-1. Results of the docking of phytochemical compounds of R. vesicarius on the crystal structure of MGA

S.N	Compound Name	Binding energy	Hydrophobic Bond Interaction with Residues	No. of H bonds	Hydrogen Bond Interaction with Residues
1	Apigenin	-8.75kcal/mol	ALA:285,509,512,536,537, GLY:533,564, LYS:534,776, PHE:535,522, THR:508, ARG:520, ILE:523, ER:521,288, PRO:287,284,566, MET:567	3	ALA:536 GLY:533 LYS:508
2	Chrysophanol	-7.51 kcal/mol	PHE:535,522, ILE:523, ALA:536,509,285, LYS:534,776, ARG:520, LEU:286, SER:288,521, PRO:287	3	PHE:535 ILE:523
3	Emodin	-7.63 kcal/mol	LEU:286, THR:775,778, ARG:520, HIS:645, ALA:780,285, LYS:534,776, VAL:779, ASP:777, PHE:535	2	LEU:286 THR:775
4	Physcion	-8.16 kcal/mol	PHE:535,522, MET:567, SER:288,521, ALA:285,509,536,537, PRO:287, LEU:286, ARG:520, LYS:534,776, ILE:523	2	PHE:535
5	Thiamine	-7.87 kcal/mol	ARG:520, ALA:512,536,537,285,509, LYS:519,534,776, SER:521,	5	ALA:285,537 ARG:520 LYS:776

			PHE:522,535,641, PRO:284,287, MET:567, 6LEU:286, ILE:532		
6	Catechin	-8.18 kcal/mol	LYS:534,776, ARG:520, HIS:645, LEU:286, ALA:285,291,536,537, SER:288,521, PHE:522,535, PRO:287, MET:567, ILE:523	4	LYS:534 ARG:520 ILE:523 MET:567
7	Luteolin	-9.35 kcal/mol	GLY:533,564, LYS:776, ARG:520, ALA:285,509,512,536,567, PRO:284,287,566, LYS:534, 776, PHE:535, SER:521, ARG:520	3	ARG:520 LYS:776 GLY:533
8	Quercetin	-8.26 kcal/mol	PHE:522,535, SER:288,521, ILE:523, ALA:285, 509,780, LYS:534,776, HIS:645, ASP:777, LEU:286, VAL:779, THR:775,778, ARG:520	3	PHE:535 THR:775 SER:521
9	Rhein	-7.17 kcal/mol	LEU:286, LYS:534,776, ARG:520, ALA:285,509,780, PHE:535, HIS:645, ASP:777, VAL:779, THR:775,778	2	LEU:286 LYS:534
10	Tetramethylenesulfone	-5.37 kcal/mol	MET:567, PRO:284,287,566, ALA:285,537, GLY:533,564, ILE:565,PHE:641	1	MET:567
11	Alloaromadendrene	-8.64 kcal/mol	LEU:286, ARG:520, LYS:534, ALA:285,291,536,537, PHE:522,535, ILE:523,	0	0

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			PRO:284,287, GLY:533, MET:567, SER:288		
12	Cis-Limoneneoxide	-7.35 kcal/mol	PHE:641,522,535, ALA:536,537, ILE:523,565, PRO:284,287,566, SER:521, GLY:533	0	0
13	Acarbose(standard drug)	**-3.18** kcal/mol	PRO:112, HIS:113,489, GLN:92,117, VAL:111,116, SER:118, PHE:119, LYS:100, GLN:92, GLU:90, TYR:263, ASP:261, MET:236, TRP:490, ASP:261	6	PRO:112, HIS:113, TYR:263, ASP:261, VAL:116, TRP:490

Luteolin binding energy analysis against MGA:

On the basis of lowest binding energy values (Kcal/mol) and hydrogen/hydrophobic interaction analysis the luteolin-MGA docked complex was examined. In the active areas of the target protein was selected best from all docking complexes based on the least binding energy values as well as the pattern of binding interaction (**Fig. 4**). The results revealed that, compared to other docking complexes, luteolin-MGA predicts the most binding energy values (-9.35 Kcal/mol) (**Table. 1**). Moreover, in comparison with previous docking complexes the value of intermolecular energy (-10.8 Kcal/mol) also was excellent.

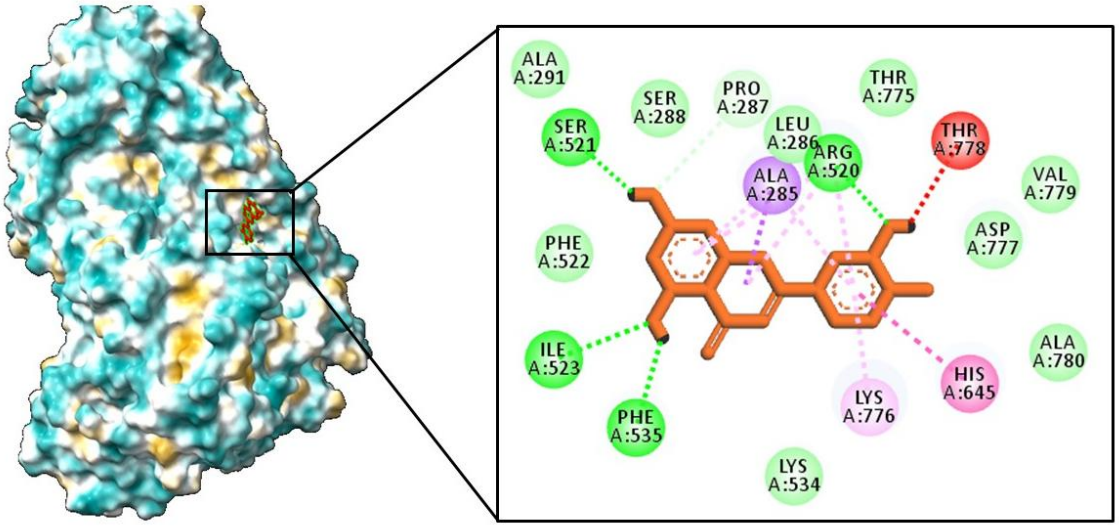

Figure 3. Interaction of luteolin in stick representation (brown) in surface representation form with active site residues of MGA. The luteolin compound is perfectly stacked inside the

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active site pocket of the enzyme with several hydrogen bonds and hydrophobic interactions. The hydrogen bond interactions were represented in green coloured broken lines.

Luteolin formed four hydrogen bonds at specific active site residues (Ser521, Ile523, Phe535, and Arg520) with target protein and four hydrophobic interactions (alkyl and Pi-alkyl) with Ala285, Thr778, Lys776, and His645 of MGA. Some other forming Van der Waals interaction with Luteolin were Ala291, Ser288, Leu286, Thr775, Val779, Asp777, ala780, Lys534, and Phe522 (**Fig. 3**).

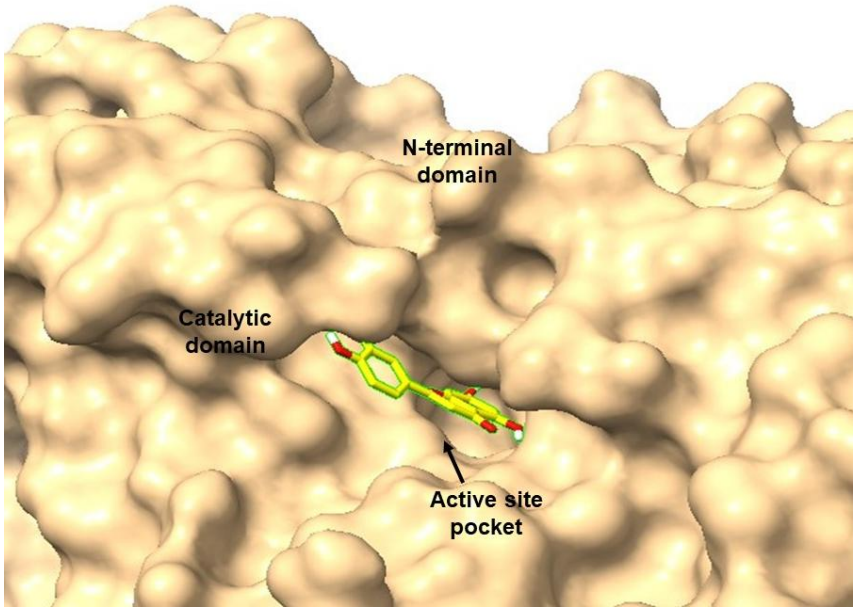

Figure 4. Surface representation of the MGA (light cyan) active sites with luteolin (yellow)

Molecular Docking Analysis

Apigenin binding energy analysis against Maltase-Glucoamylase:

Apigenin's binding energy was calculated at -8,75 Kcal/mol toward MGA (Table. 1). A map was designed and the important amino acid residues involved in contact were discovered in order to get a better understanding into apigenin interaction pattern with MGA target enzyme. The linkages between the three hydrogen bonds were made up of Ala536, Gly533 and Lys776 and the interactions were created via hydrophobic interaction: Ala285, 509, 512, 536, 537, Gly:33, 564, Lys534, 776, Phe535, 522, Thr 508, Arg520, Ile523, 288, Pro287, 284, 566, and Met567. Val111, Ser118, Lys100, Phe119, Gln92, Glu90, His98, His236 and His 489 were also additional amino acid remains creating Van der Waal's connections with apigenin (Fig. 5).

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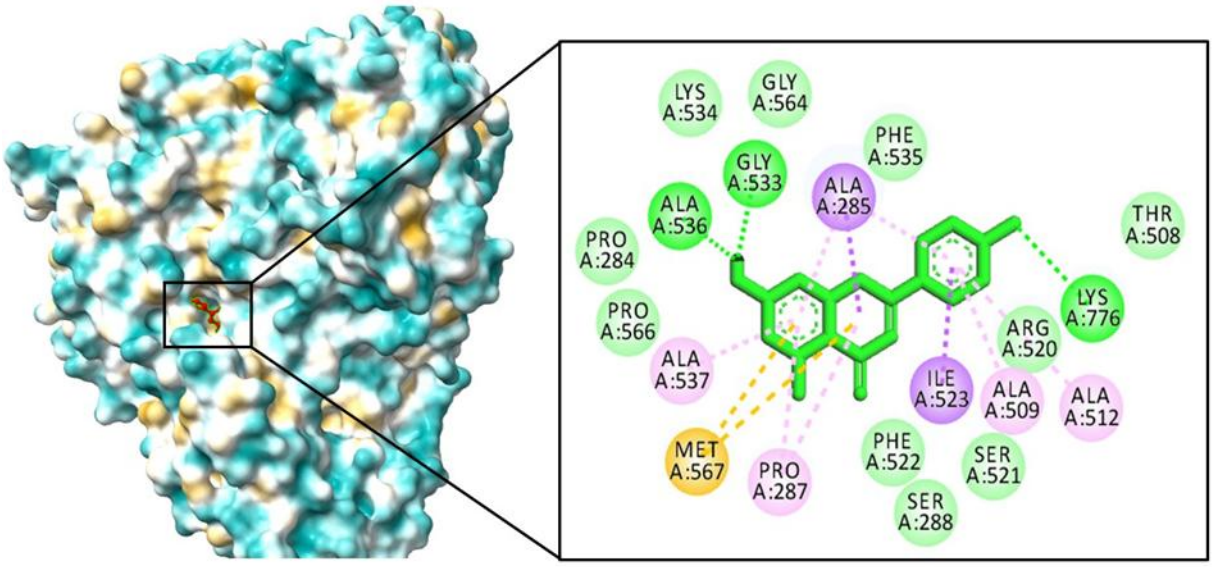

Figure- 5. Interaction of apigenin in stick representation (brown) in surface representation form with active site residues of MGA. The apigenin compound is perfectly stacked inside the active site pocket of the enzyme with three hydrogen bonds and hydrophobic interactions. The hydrogen bond interactions were represented in green coloured broken lines.

Molecular dynamic simulations analysis:

The top one ligand, namely luteolin, is chosen for the dynamic simulation research, based on docking investigations. The molecular dynamic simultaneous measurements were investigated based on root mean square (RMSD) deviation, root mean square (RMSF) fluctuation and time radius of rotational values.

Root Mean Square Deviation (RMSDs) estimation:

We performed 10 ns time dependent MD simulations using Gromacs 4.5.4 to assess the flexibility and overall stability of the docked complex. Using RMSD and RMSF graphs produced by Xmgrace software the deviations and the fluctuations in the complexes were determined.

The root mean square deviations (RMSDs) alone or in complex with luteolin ligand in the backbone of MGA, as a function of simulation time are shown in Fig. 6 in comparison to the original frame. It was found that modest fluctuations in RMSD values (up to 3.1 Å) alone were detected during the first 2000-5,000 ps (2-5 nm) by the balance of original protein structures. Thus, throughout the simulation period, a stable dynamic was maintained and the values for RMSD fluctuated with the acceptable limit of 3 A0. Likewise, following early variations of 1000 - 2000 ps, RMSD values of α-glucosidase with bound ligand Luteolin were within 3 A0 upper limit (1-2 ns). The entrance of the ligand into the binding site cavity caused a little change in RMSD values during the commencement of a simulation. During the simulation period, a constant state dynamic was maintained from 2 ns. This dynamic steady state states that ligand luteolin increases protein flexibility and stability. The development of complementary protein-

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ligand interactions resulted in the construction, as shown in steady RMSD values, of a stable protein-ligand complex

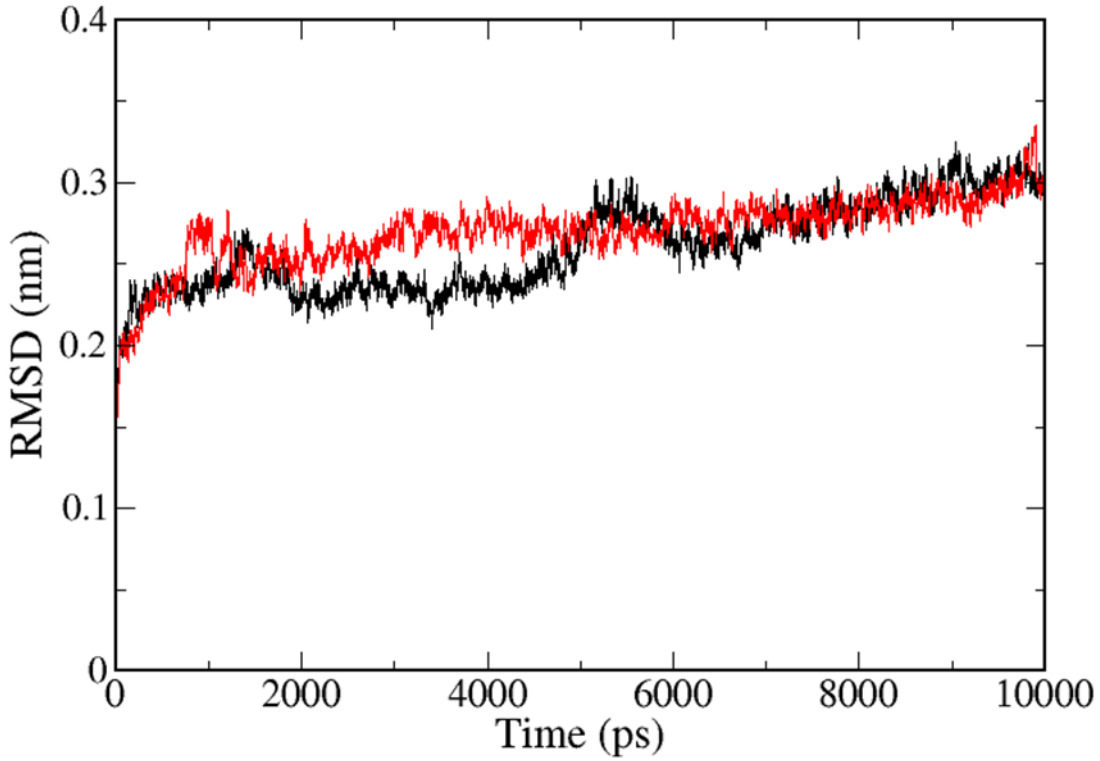

Figure 6. Root-mean-square deviation (RMSD) graphs of Maltase-Glucoamylase protein backbone alone and Luteolin-MGA complex at 10 ns. The graph lines with red and black represents luteolin-MGA complex and MGA alone, respectively. RMSD values in y-axis, atoms along the time frame in x-axis

Root mean square fluctuations (RMSFs) determination

In the entire simulation, RMSF gives the variation of each atom. In addition, RMSFs along the side chains of the MGA were monitored to monitor any changes related with the Luteolin binding (Fig. 7). The results revealed minimal variation of the residues of the binding site. The RMSF mean values were 0.27, 0.22 and 022 nm for the single protein and ligand. At the N-terminal ends of the protein, a high RMSF value was found because its unbound locations tend to vary further.

The findings of RMSDs and RMSFs have shown that a stable protein-ligand complex has been formed.

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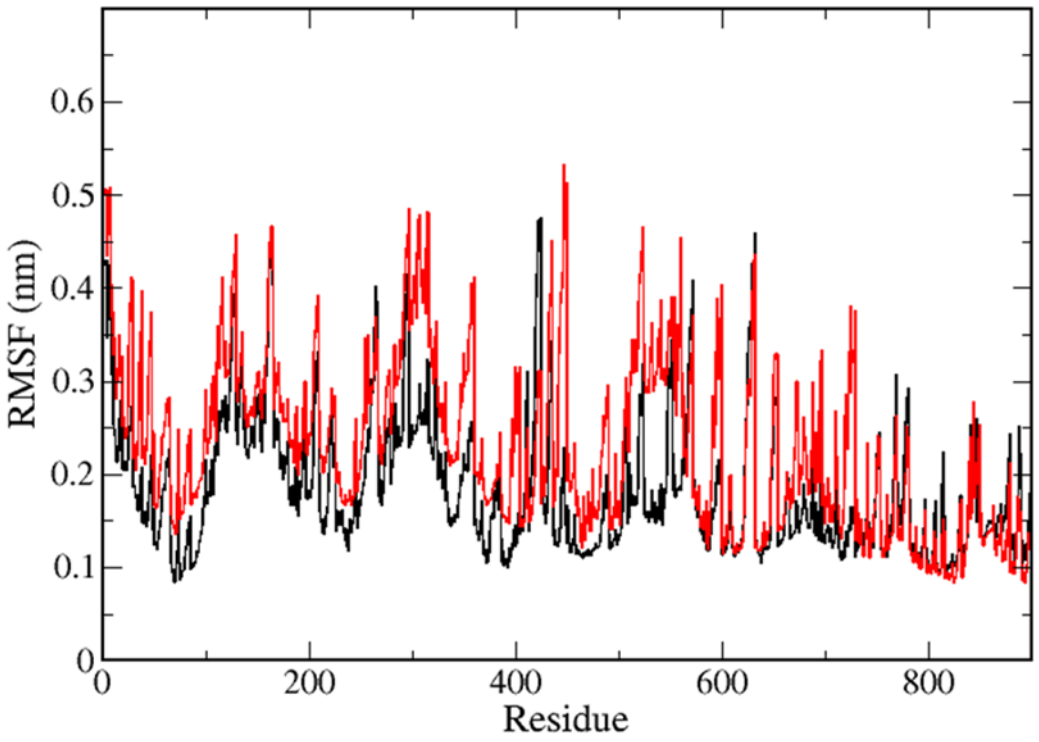

Figure 7. Root-mean-square fluctuation (RMSF) graph of MGA protein alone and Luteolin-MGA complex at 10 ns. The graph lines with black and red represents MGA protein alone and Luteolin-MGA complex, respectively. RMSF values in y-axis, number of residues/atoms along the time frame in x-axis.

Determination Radius of Gyration (Rg)

Protein compactness is assessed using gyration radius (Rg). In terms of simulatory time (10 ns) the Rg of maltase-glucoamylase and the complex Luteolin was identified (Fig. 8). The Rg values were found to range between 2.92 A0 and 2.9 A0 for protein-only and protein-ligan complexes respectively. The findings of Rg show that throughout the simulation period 0-10,000 ps (0.10 ns), the values have changed within the permissible ranges, which indicates a stable conformation.

Insight into stable of leteolin-MGA's complex, which was conducted via MD pathways, thus increases the effectiveness of the docking findings.

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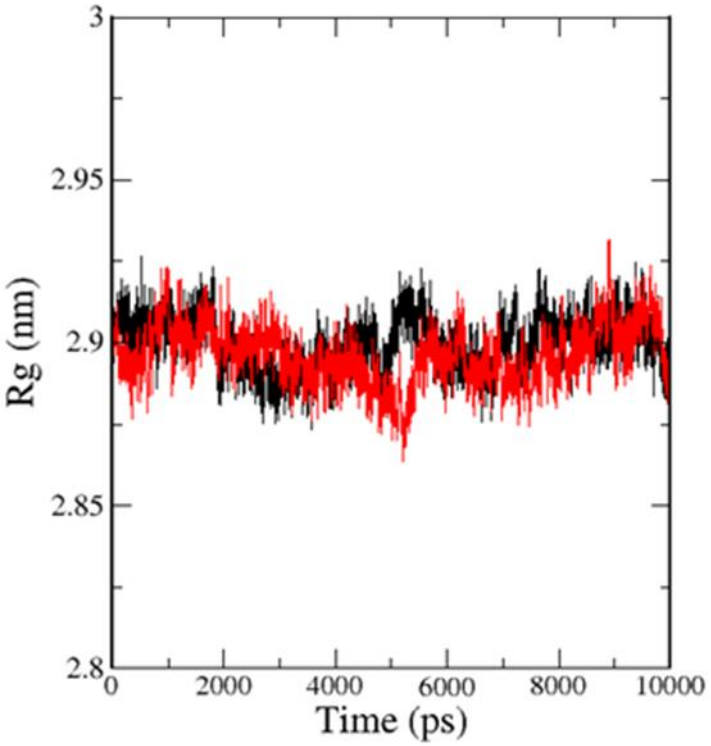

Figure- 8. Radius of gyration (Rg) graph of MGA alone and Luteolin-MGA complex at 10 ns. The graph lines with black and red represents MGA protein alone and Luteolin-MGA complex, respectively. Rg values in y-axis, atoms along the time frame in x-axis.

This research has for the first time documented the docking of discovered molecules. Although no literature on the docking study of such compounds is available, the binding energy of Luteolin and Apigenin compounds with the MGA is extremely promising. The development of these molecules into a novel maltasis glucoamylases inhibitor would be an opportunity if the compounds discovered maintain an effective binding affinity with mallasis glucoamylase enzyme comparable to our research.

Quassinoids and other compounds such as kaempferol, amarolid, saponin etc. were identified and reported for a variety of biological actions in various families including antidiabetic properties (Noor Shahida et al, 2009). But, with limited research on Quassia amara (Ceriello A et al, 2016) and Brucea javanica plants (Xiao J B et al, 2015), there is no comprehensive investigation of antidiabetical characteristics of such chemicals from R. vesicarius. In this research, the luteolin activity against MGA was analysed with other phytochemicals by means of both in-silico and molecular dynamic simulations. This discovery would inspire future research into these two substances as new natural MGA inhibitors. Overall findings show that the phytochemicals of luteoline and apigenine may also be regarded to be MGA inhibitors to develop further into active commercial anti-T2DM medicines.

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Conclusion

The emphasis of this research was on the finding for MGA inhibitors to treat Type-2 diabetes mellitus (T2DM) using in silico-based techniques. The interaction between phytochemicals and our target enzyme was investigated. The molecular docking research shows that luteolin and apigenin have excellent docking results and binding manner and thus have shown medicinal promise for suppression of MGA. In comparison with the conventional medication, all the plant compounds in *Rumex vesicarius* had the lowest binding energy. In comparison with all compounds tested and demonstrated significant interactions with active residues in sites, Luteolin demonstrated the greatest energy binding and could thus be the best candidates for in-vitro and in-vitro effectiveness, safety and clinical studies to discover a new MGA inhibitor. The study of MD simulation for a selective docking complex has also verified the stability of protein ligand complexes. Finally, our study has shown that MGA is successfully inhibited by all substances, and MGA's phytochemicals may serve as inhibitors of MGA. Further in vitro and in vivo research may be done to verify the physiological significance of such findings.

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Conflicts of Interest: None

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