SUMMARY

Computational drug design of potential α-amylase inhibitors using some commercially available flavonoids

Introduction

Diabetes has become a leading killer disease in recent years. According to WHO, it is estimated that 3% of the world's population have diabetes and the prevalence is expected to double by the year 2025 to 6.3%. Alpha-amylases are endoglucanases that can hydrolyze internal α-1,4glucosidic bonds of starch.

Objective

Auto Dock Tools (ADT) is a program package of automated docking tools and designed to predict how small molecules bind to a target protein of known 3D-structure. The objective of the present work is to study the *in silico* α-amylase inhibitory activity of commercially available flavonoids.

Experimental Methods

The preparation of the target protein 1HNY (α-amylase) was done with the AutoDock Tools software. Gasteiger charges are calculated for each atom of the macromolecule in AutoDock 4.2. The druglikeness scores of the compounds were evaluated with the help of Lipinski's rule of 5. Rapid energy evaluation was achieved by precalculating atomic affinity potentials for each atom in the ligand molecule. In the AutoGrid procedure, the target enzyme was embedded on a three dimensional grid point[1]. The energy of interaction of each atom in the ligand was encountered. Important docking parameters selected for the LGA as follows: population size of 150 individuals, 2.5 million energy evaluations, maximum of 27000 generations, and number of top individuals to automatically survive to next generation of 1, mutation rate of 0.02, crossover rate of 0.8, 10 docking runs, and random initial positions and conformations. The probability of performing local search on an individual in the population was set to 0.06. AutoDock was run several times to get various docked conformations, and used to analyze the predicted docking energy. The binding sites for these molecules were selected based on the ligand-binding pocket of the templates. AutoDock Tools provide various methods to analyze the results of docking simulations such as, conformational similarity, visualizing the binding site and its energy and other parameters like intermolecular energy and inhibition constant. For each ligand, ten best poses were generated and scored using AutoDock 4.2 scoring functions[2].

Results and Discussion

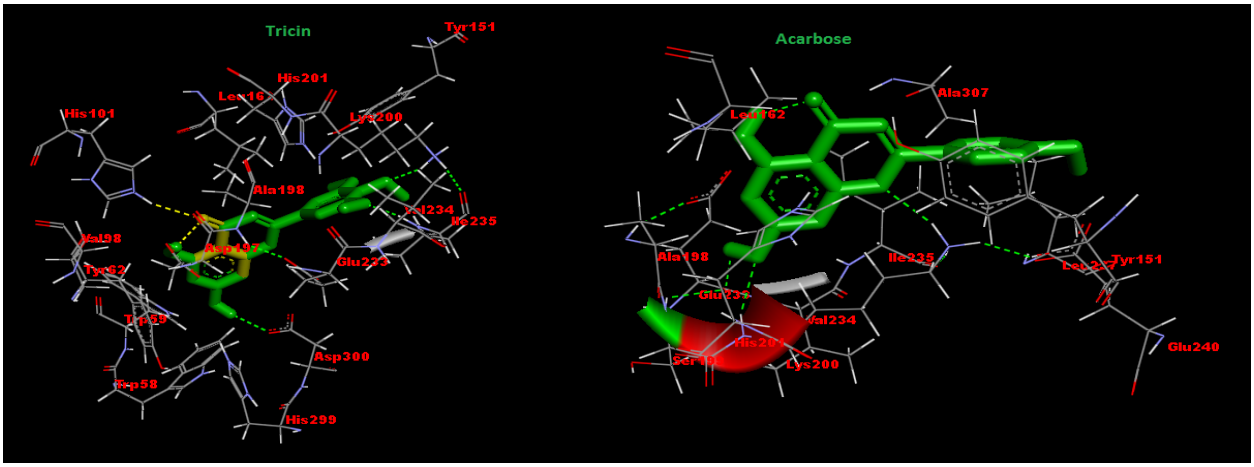

Fig. 1 Docked pose of α-amylase enzyme (1HNY) with tricin and acarbose

The docking poses were ranked according to their docking scores and both the ranked list of docked ligands and their corresponding binding poses. This ranking of the compounds were based on their binding energy with the enzyme. If the binding energy of the compound is less, then the particular compound has more active in nature. In Fig. 1, docked pose of α-amylase enzyme with the ligands tricin and acarbose clearly demonstrated the binding positions of the ligand with the enzyme.

The binding sites of the acarbose was found to be Tyr 151, Leu 162, Ala 198, Ser 199, Lys 200, His 201, Glu 233, Val 234, Ile 235, Leu 237, Glu 240, Ala 307. The potential binding sites of the tricin was found that, Trp 58, Trp 59, Tyr 62, Val 98, His 101, Tyr 151, Leu 162, Asp 197, Ala 198, Lys 200, His 201, Glu 233, Val 234, Ile 235, His 299, Asp 300. This proves that the effective binding sites are present in the selected flavonoid tricin when compared with the standard acarbose.

Table 1. Docking parameters of the selected Flavonoids

COMPOUNDS	Binding energy (kcal/mol)	Inhibition Constant (μM, mM*)	Intermolecular energy (kcal/mol)
Biochanin	-6.21	27.89	-7.41
Chrysin	-6.36	21.86	-7.25
Hesperitin	-7.19	5.35	-8.68
Morin	-6.35	21.99	-8.14
Tricin	-7.20	5.31	-8.99
Vitexycarpin	-6.56	15.61	-8.65
Acarbose	-2.94	6.98*	-9.50

Based on the docking studies, the α-amylase inhibitory activity of the selected compounds was found to be decreased in the order of tricin, hesperitin, vitexycarpin, chrysin, morin and biochanin (Table 1).

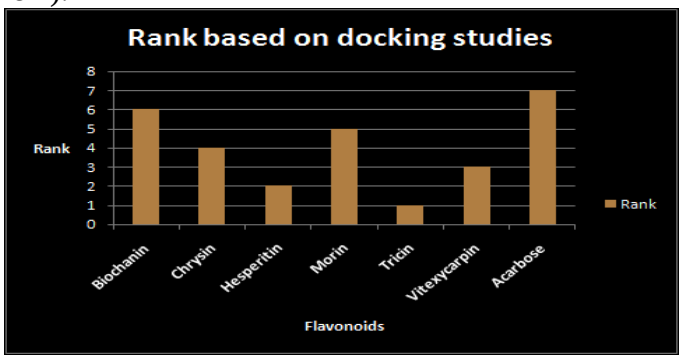

Fig.2 **α-amylase inhibitory activity of flavonoids based on docking studies**

On the basis of the above study, tricin and hesperitin possess potential α-amylase inhibitory binding sites similar to that of the standard (Fig. 2). This may be attributed due to the differences in the position of the functional groups in the compounds.

Conclusion

These results clearly indicate that from the selected flavonoids, tricin and hesperitin have better binding sites and interactions with α-amylase enzyme and further investigations are necessary to develop potential chemical entity for the prevention and treatment of diabetes.

Bibliography

1. Madeswaran, A., *et al.*, IJBPS, Vol. 7 (1), pg 7, 2013.
2. Morris, G. M., *et al.*, J Comput Chem, Vol. 19(14), pg 2785, 2009.