In-silico analysis of Gymnema sylvestreon in Diabetes

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Abstract:

Diabetes is a metabolic disorder characterized by higher than normal glucose in blood. Most of the oral hypoglycemic drugs available in the market produce adverse side effects which lead to continuous search in the alternative therapeutic drugs with little side effects. Herbal drugs are considered relatively safer alternatives and Gymnema Sylvestre is one of the most well known natural remedy for diabetes and it is traded under several brands world wide.

INTRODUCTION

The naturopathic treatment for diseases has been explored extensively since ancient times and gaining momentum in the present scenario. Indian flora accounts for about 45,000 plant species out of which several thousands have pharmacological significance Diabetes mellitus is a major endocrine disorder affecting nearly 10% of the population worldwide and a key issue of concern. The disease in its severe state affects major systems of the body, leading to multiorgan complications. Oral hypoglycemic agents like sulphonylureas and biguanides are the conventional drugs used for the treatment, but the adverse side effect associated with these drugs is a major limitation. The herbal medicines are becoming popular due to better results and safe use as compared to marketed drugs and more effective treatment of health problems . Plants possessing antidiabetic activities are of significant interest for ethnobotanical community as they are recognized to contain valuable medicinal properties in different parts and a number of them have shown varying degree of hypoglycemic and antihyperglycemic activity . The bioactive constituents found in many plant species are isolated for direct use as drugs, lead compounds, or pharmacological agents. These traditional approaches might offer a natural key to unlock diabetic complications . The chemical structures of a phytomolecule play a critical role in its antidiabetic activity. Several plant species being a major source of terpenoids, flavonoids, phenolics, coumarins, and other bioactive constituents have shown reduction in blood glucose levels .Various antidiabetic plant extracts like aloe (Aloe vera L), bitter Melon (Momordica charantia), fenugreek (Trigonella foenum-graecum), Asian ginseng (Panax ginseng C.A.Meyer) and American ginseng (Panax quinquefolius L), gymnema (Gymnema sylvestre), milk thistle (Silybum marianum), nopal (Opuntia streptacantha), salacia (Salacia oblonga; Salacia Reticulate), and formulations like those of chromium have been used and clinically tested for their activity as well as potential side effect .

The present review is a research update on Gymnema sylvestre, a rare herb with significant medicinal attributes with an overview of its ethnobotanical uses, phytochemistry dealing with an in-depth study of its phytochemicals, and their bioactivities. It also explores the facts and prospects of its development into a modern and efficient therapeutic, contemporary with the present trends of pharmacology and drug development. Furthermore, it holds significant prospects in major health problems like cardiovascular disorders, obesity, osteoporosis, and asthma besides being a popular medication for number of other health ailments. The herb finds significant application in various food preparations for control of obesity and blood cholesterol levels besides regulation of sugar homeostasis. The herbal preparations of G. sylvestre are presently used in tea bags, health tablets and supplements, beverages, and confectioneries.

Analysis of Gymnemagenin from Gymnema Sylvestre R.Br. with targets related to diabetes.

In the present study an attempt has been made to use in-silico techniques to understand and predict the drug likeliness of Gymnemagenin, one of the key constituents of G.sylvestre against 15 proteins having key role in carbohydrate metabolism.

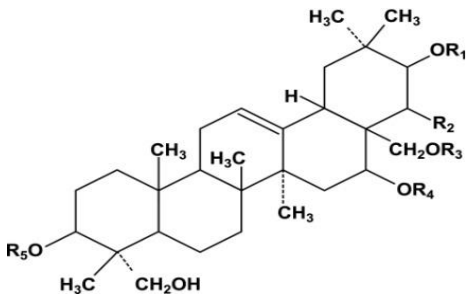
‘Gymnemagenin was found to dock well with crystallographic structures of 7 of the 15 selected targets and was found even better than the two known clinically used anti-diabetic compounds , repaglinide &sitaglipin taken in study for comparison. Gymnemagenin therefore can be considered further for development into a potent anti-diabetic drug'.

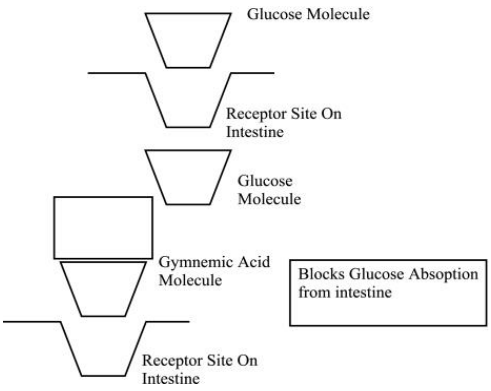
Phytochemical profiling

The leaves of *G. sylvestre* contain triterpene saponins belonging to oleanane and dammarane classes. The major constituents like gymnemic acids and gymnemasaponins are members of oleanane type of saponins while gymnemasides are dammarane ssaponin. Other phytoconstituents include anthraquinones, flavones, hentriacontane, pentatriacontane, phytin, resins, tartaric acid, formic acid, butyric acid, lupeol, *β*-amyrin related glycosides, stigmasterol, and calcium oxalate. The presence of alkaloids had been detected in plant extracts. Leaves of *G. sylvestre* have acidic glycosides and anthraquinones and their derivatives.The major secondary metabolites in *Gymnema* includes a group of nine closely related acidic glycosides, the main are gymnemic acid A–D and found in all parts of the plant. The maximum content of gymnemic acid is found in shoot tips (54.29 mg-g^{-1} DW) and least in seeds (1.31 mg-g^{-1} DW). Antisaccharin property of gymnemic acid A_1 was greatly reduced on conversion into A_2, while no activity was observed in case of A_3 suggesting that the ester group in the genin portion of gymnemic acid imparts the antisweet property to the triterpene saponins, the gymnemic acids. Gymnemic acids A_2 and A_3 possessed both glucuronic acid and galactose in their molecular structures while glucuronic acid was found to be the only moiety in gymnemic acid A_1 . Further, a series of gymnemic acids (gymnemic acid I, II, III, IV, V, VI, and VII) were isolated and characterized from the hot water extract of dry leaves of *G. sylvestre* . The Gymnemic acids comprise of several members designated as gymnemic acids I–VII, gymnemosides A–F, and gymnemasaponins. The derivatives of gymnemic acids are several acylated tigloyl, methylbutyryl group substituted members, derived from deacylgymnemic acid (DAGA) which is a 3-O-*β*-glucuronide of gymnemagenin (3*β*, 16*β*, 21*β*, 22*α*, 23, 28-hexahydroxy-olean-12-ene). Gymnemic acid A comprises of gymnemic acids A_1, A_2, A_3, and A_4 and named gymnemagenin. This constituent is a D-glucuronide of hexahydroxy-triterpene that esterifies with acids . Other five gymnemic acids, namely, VIII, IX, X, XI, and XII, were isolated and characterized later. Gymnemasaponins III, another antisweet compound, isolated from *G. sylvestre* was found to consist of 23 hydroxylongispinogenin as the aglycone moiety glycosylated with either one or two glucose molecules at both the 23 or 28 hydroxyl groups. These compounds exhibited lesser antisweet effect than those of gymnemic acids.

Diabetes mellitus can be defined as a group of syndromes characterized by hyperglycemia, altered metabolism of lipids, carbohydrates and proteins along with an increased risk of complications from vascular disease. It is characterized by polydipsia (chronic excessive thirst and fluid intake), polyphagia excessive eating), glycosuria (excessive glucose in the blood) and “acetone breath” i.e. the breath of the patient smells of acetone due to an abnormal increase of ketone bodies in the blood. The classification of diabetes can be done in two types as: Type-1 (insulin-dependent diabetes mellitus, IDDM) and Type-2 (non-insulin-dependent diabetes mellitus, NIDDM).

Fig: Basic molecular structure of Gymnemic acid& Inhibition of receptor site on intestine by Gymnemic acid.





Docking:

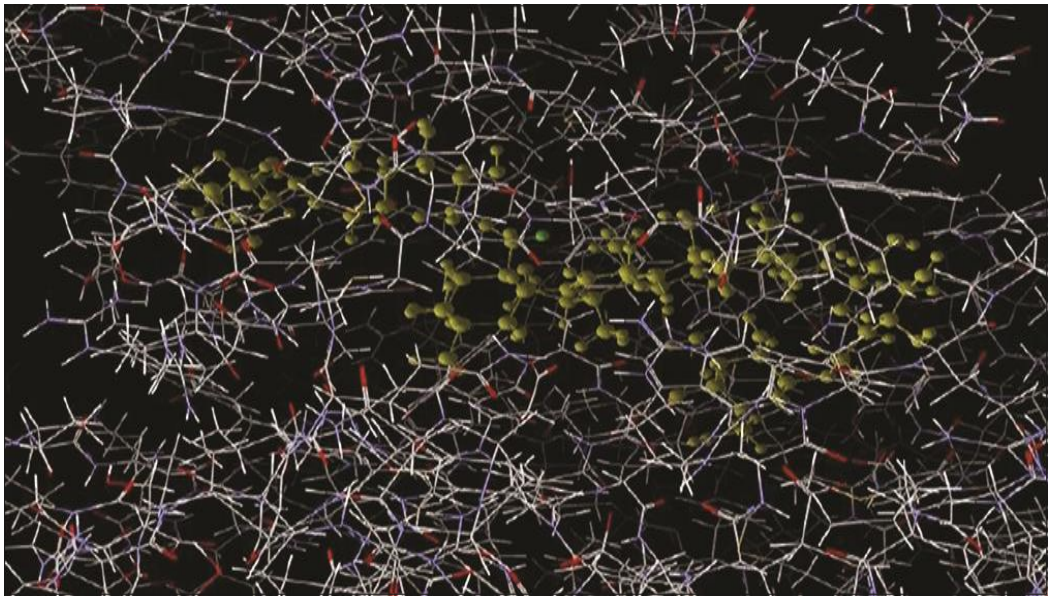


Fig: Target and energy values after docking with Gymnemagenin with endothelial nitric oxic synthase.

Conclusion

Although there are many phytoconstituents that could combat diabetes and obesity, a single phytoconstituent that could be used in the treatment of both the diseases simultaneously would be a welcome addition. Gymnemic acid fulfills this criterion. The common masses do not avail of the fact that obesity can also be caused due to over-accumulation of sugar molecules specially sucrose, along with fat molecules. The common man layman needs to be made aware of these facts, since they are posing a big threat after cardiac problems and cancer. This review paper aimed at putting forth a molecular perspective of the medicinal aspect of gymnemic acids, and also a possible linkage between obesity and diabetes via a potential common medicine.

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