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Research Article

In Silico study for better drug discovery

In Silico Prediction, Computational Physico Chemical Analysis in Gymnemic Acids

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Abstract: *Gymnema sylvestre* (Asclepiadaceae) also known as 'gurmar' or 'sugar destroyer' is a woody, climbing traditional medicinal herb which has many therapeutic applications in the Ayurvedic system of medicine. We present an overview of the most important databases with 2 gymnemic acid structural information about drugs and drug candidates, and of databases with relevant properties. Access to experimental data and numerical methods for selecting and utilizing these data is crucial for developing accurate predictive *in silico* models. Many interesting predictive methods for classifying the suitability of chemical compounds as potential drugs, as well as for predicting their physico-chemical and ADMET properties have been proposed in recent years. The gymnemic acids act as therapeutic agents and play vital roles in many therapeutic applications. Gymnemic acids are thought to be responsible for its anti-diabetic activity and are the major component of an extract shown to stimulate insulin release. It is also screened for bioavailability study, physicochemical study, drug likeness study, medicinal chemical analysis and target prediction. These methods are discussed, and some possible future directions in this rapidly developing field are also described. The commercial exploitation of this plant and its secondary metabolites are some of the major perspectives of this rare medicinal herb. The focus of the present study is to achieve the potential of therapeutic value of this herb its mechanism,and the action of their secondary metabolites.

Keywords: *G.sylvestre*, Gymnemic acids, bioavailability study, physicochemical study, Drug likeness study, medicinal chemical analysis, target prediction.

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1. INTRODUCTION

G.sylvestre (Asclepiadaceae) a vulnerable species is a slow growing, perennial, medicinal woody climber found in central and peninsular India. Its leaves, called "Gurmar " in India, are well known for their sweet taste suppressing activity and are used for the treatment of diabetes mellitus[1] for over 2000 year, hence the name "Gurmar " meaning 'sugar destroying'. It is used in food additives against obesity. *G.sylvestre* is a woody, climbing herb indigenous to the tropical forests of central and southern India. The plant belongs to Kingdom Plantae with Division Angiospermae and Class Dicotyledoneae. Gymnema is native to south-Indian forests. It is a large tropical liana native to central and western India and can be also found in tropical Africa and in Australia. It is used for lowering serum cholesterol, triglycerides and blood glucose level (hypoglycemic or antihyperglycemic), hypolipidemic, weight loss, stomach ailments, constipation, water retention and liver diseases, either high or low blood pressure, tachycardia or arrhythmias, it is alsoused as aperitifs, purgative, in eye troubles, anti-inflammatory, smooth muscle relaxant, prevention of dental caries, cataract and as anticancer-cytotoxic agent. Its flowers, leaves, and fruits contain alkaloids, flavones, saponins, sapogenins, anthraquinones, hentri-acontane, pentatriacontane, α and β-chlorophylls, phytin, resins, d-quercitol, tartaric acid, formic acid, butyric acid, lupeol, β-amyrin related glycosides and stigmasterol with its main principle bioactive compounds viz[2]. Gymnemic acids are isolated from the leaves of *G.sylvestre* (Asclepiadaceae), which is native to India and southern China. Gymnemic acids are glycosides of triterpene that suppress sweetness in humans[3]. After the leaves are chewed, the solutions that have been sweetened with sucrose taste like water. It is thought that gymnemic acid inhibits the binding of a sweet substance to the sweet receptor. Several gymnemic acid homologues with different acyl groups were purified from the leaves of *G.sylvestre* and their structures were determined. Interestingly, deletion of the acyl group diminishes the anti-sweet activity. It suppresses the sweetness of most of sweeteners, including intense artificial sweeteners such as aspartame and natural sweeteners such as thaumatin, a sweet protein. The herb is traditionally used for the treatment of diabetes in India and Gymnema extracts are sold in Japan for control of obesity[4]. It is a rich source of many bioactive compounds such as gymnemic acid (GA-I-X), quercitol, lupeol, stigmasterol, gymnemin, gymnemagenin, and gurmarin. which are mainly effective in the lowering of blood sugar. Gymnemic acid, the active ingredient of this plant, is extracted from leaves and is used widely as anti-diabetic[5], anti-sweetner[6] and anti-hypercholesterolemia[7]. It has stomachic, diuretic and cough suppressant property. The plant has been reported possessing antimicrobial[8] and ethno-veterinary medicinal properties[9]. In addition, it possesses antimicrobial, hepatoprotective, and anti-saccharine activities. Hence, because of these properties, *G.sylvestre* is the most important for plant prospecting. Protein-protein interactions (PPIs) represent an essentially untapped source of potential targets for therapeutic interventions. The modulation of PPIs by low molecular weight chemical compounds, particularly by orally bioavailable molecules (i.e., the most convenient, safest and least expensive way to deliver drugs), would be very valuable in numerous disease indications[10]. The analysis of thousands of PPI inhibitors (iPPIs) (hits or molecules that went through optimization cycles) reported in several databases [11] indicated that these compounds have in general a high lipophilicity (analysed via log P calculations) and a high molecular weight (MW), properties that are usually not favourable to the development of oral drugs (although there are numerous exceptions to these rules[12]. While the current state of the art investigations performed on iPPIs have essentially focused on physicochemical properties[13] in the present study, we move beyond these classical physicochemical properties (PC) to predict several Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) parameters using online servers and established commercial packages[14]. In order to outline iPPIs features, computations were carried out on eight datasets collected from several databases [15]. This study involves the *in silico* analysis of bioavailability , physicochemical , Drug likeness prediction , medicinal chemical analysis, target prediction in Gymnemic acids.

2. MATERIALS AND METHODS

1.1. *Preparation of Extracts*

Crude Sample *G.sylvestre* extract was prepared by Soxhlet extraction method. About 20gm of powdered *G.sylvestre* sample material was uniformly packed into a thimble and had extracted with 250ml of different solvents (Distilled water). The process of extraction had to be continued for 24 hours or till the solvent in the siphon tube of the extractor became colourless. After that the extract was taken in a beaker and kept on a hot plate and heated at 30-40 °C till all the solvent evaporated. Dried extract was kept in the refrigerator at 4 °C till future use. *G.sylvestre (Retz.) R.Br.ex Sm.(Periploca sylvestris Retz.) ASCLEPIADACEAE*. Identification and authentication of *G.sylvestre* was done by Dr. M. Palanisamy, Scientist, Botanical Survey of India, Southern Regional Centre, Coimbatore, Tamilnadu and the voucher number is BSIS/RC/5/23/2017/ Tech/ 530[16].

2.1. *Drug-Likeness Prediction*

The OSIRIS Property Explorer uses chemical structures and calculates on-the-fly various drug-relevant properties whenever a structure is valid. Prediction results are valued and colour coded. Properties analysed are TPSA, calculation, molecular weight, fragment based drug-likeness, and drug score[17].

2.2. *ADMET Prediction*

ADMET properties of a compound deal with its absorption, distribution, metabolism, excretion, and toxicity in and through the human body. ADMET, which constitutes the pharmacokinetic profile of a drug molecule, is very essential to evaluate its pharmacodynamics activities. Today, a lot of online tools and offline software programs are available which helps us in predicting this behaviour of the drug candidate. In this study, we have used the ADMET SAR prediction tool[17].

3. RESULTS AND DISCUSSION

The interactions between protein ligands can be elucidated by molecular docking of ligands against the enzyme's active site[18]. In the area of drug discovery and development, this will pave the way for the discovery of novel phytomedicines. The GC-MS research compounds followed the Lipinski law of five. This law contains five sub-regulations, namely (1)

molecular weight (< 500), (2) log P (< +5.6), (3) hydrogen donor number (< 5), (4) hydrogen acceptor number (< 10) and (5) molar refractivity (40-130). The Lipinski rule of five is used to determine a compound's drug-likelihood; in other words, it is very important for a compound to fulfill this rule in order to be administered orally[19].

3.1 Gymnemic acid

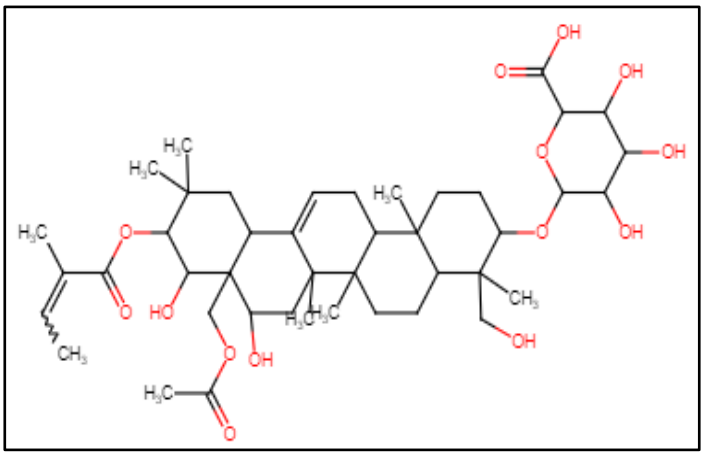

Fig 1: Chemical Bond of Gymnemic acid

3.2 Bioavailability Study

The coloured zone is the suitable physicochemical space for oral bioavailability
LPO (Lipophilicity): -0.7 < XLOGP3 < +5.0
SIZE: 150g/ mol <MV <500g / mol
POLAR (Polarity): 20 A^2 <TPSA < 130 A^2
INSOLU (Insolubility): 0 < Log S (ESCOL) < 6
INSATU (Insaturation): 0.25 < Fraction Csp3 < 1
FLEX (Flexibility): 0 < Num. rotatable bonds < 9

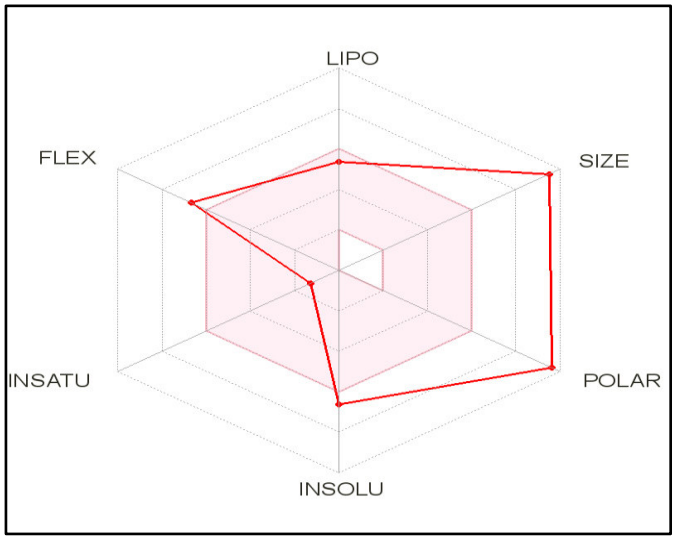

Fig 2: Bioavailability Study for Gymnemic acids

To test the durability of a drug molecule, the Lipinski 's rule of five is also used[19]. Therefore, for a bioactive compound to be considered an oral drug, this law is important[20]. The basic information on bioactive compounds with their respective properties is provided in Fig: 2. The molecular docking *in silico* analysis revealed the significance of the structure-based drug design strategy for the production of novel drugs against the inhibition of the potential drug target. The enzyme's active site was docked with bioactive compounds (Oleic Acid) from methanolic leaf extract of Gymnemic acids (Figure 1).Physicochemical Properties for Gymnemic acids formula is $C_{43}H_{66}O_{14}$,(Fig :1) Molecular weight is 806.98 g/mol, Number of heavy atoms is 57, Number of atoms in heavy atoms is 0, Fraction Csp3 is 0.84, Num. rotatable bonds are 10, Num. H-bond acceptors are 14, Num. H-bond donors are 7, Molar Refractivity is 207.11 and TPSA is 229.74 Å². The Lipophilicity Log Po/w (iLOGP) is 2.28, Log Po/w (XLOGP3) is 0.86, Log Po/w (WLOGP) is 3.0311, Log Po/w (MLOGP) is 1.25, Log Po/w (SILICOS-IT) is 2.55 and Consensus Log Po/w is 2.59. The water Solubility for Log S (ESOL) is -6.62,

Solubility 1.96e-04 mg/ml; 2.43e-07 mol/l, Class is Poorly soluble, Log S (Ali) is -8.38, Solubility is 3.35e-06 mg/ml; 4.16e-09 mol/l, Class is poorly soluble, Log S (SILICOS-IT) is -2.85, Solubility is 1.15e+00 mg/ml; 1.43e-03 mol/l and Class is soluble. Toxicity of drugs is another extremely important problem, leading to a significant number of drug failures. Author[20] published a review paper about a number of commercial prediction systems, including DEREK[21], OncoLogic[22], Hazard Expert, COMPACT[23], CASE/Multi-CASE[24] and TOPKAT[25] have developed QSAR models for the prediction of toxicity (Figure 2).

3.3 *Boiled – Egg*

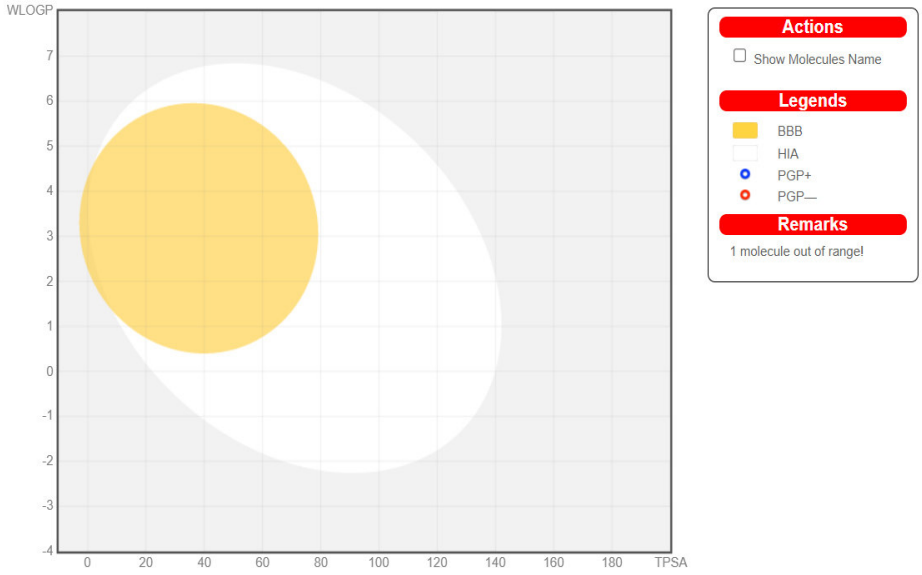

Fig 3 Boiled – Egg plot of bioavailability of GYMNEMIC ACIDS

In Pharmacokinetics the GI absorption is Low, BBB permeate is No, P-gp substrate is Yes, CYP1A2 inhibitor is No, CYP2C19 inhibitor is No, CYP2C9 inhibitor is No, CYP2D6 inhibitor is No, CYP3A4 inhibitor is No and Log Kp (skin permeation) is -8.48 cm/s (Figure 3). In Drug likeness studies the Lipinski is No; 3 violations: MW>500, NorO>10, NHorOH>5, Ghose is No; 3 violations: MW>480, MR>130, #atoms>70, Veber is No; 1 violation: TPSA>140, Egan is No; 1 violation: TPSA>131.6, Muegge is No; 4 violations: MW>600, TPSA>150, H-acc>10, H-don>5 and Bioavailability Score is 0.11. In Medicinal Chemistry the PAINS is 0 alert, Brenk is 4 alerts: isolated_alkene, michael_acceptor_1, more_than_2_esters, saponine_derivative, Lead likeness is No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5 and Synthetic accessibility is 8.81. The OSIRIS tool measures the value (logarithm of compound's partition coefficient between -octanol and water) which is a well-established measure of the compound's hydrophilicity[26,27,28,29,30].

3.4 *Target Classes – Top 15*

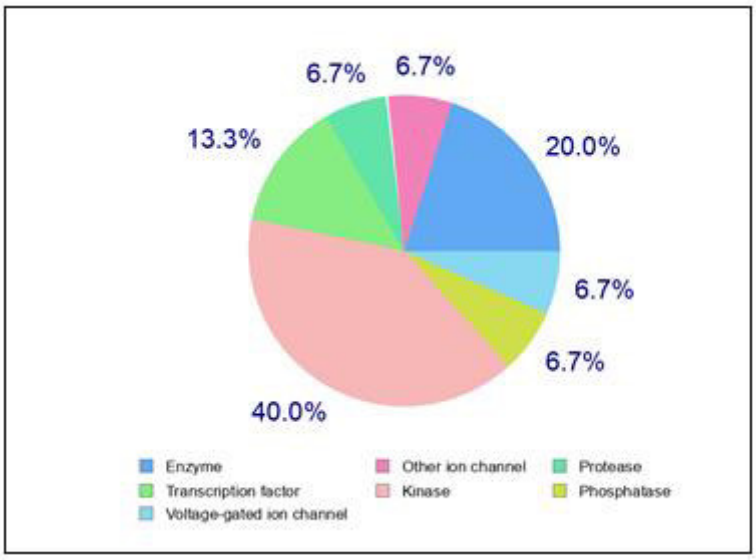

Fig 4 Target Classes – Top 15

Higher value indicates lower hydrophilicity and, thus, poor absorption and permeation. A value indicates solubility; the lesser the value, the higher the solubility which would enhance the absorption[31,32,33]. A lower molecular weight would again enhance the absorption rate and thus most of the drugs are tried to be kept at the lowest possible molecular weight. TPSA or *Topological Polar Surface Area* indicates the surface belonging to polar atoms in the compound (Figure 4). An increased TPSA is associated with diminished membrane permeability and the compounds with higher TPSA are better substrates for p-glycoprotein (responsible for drug efflux from cell). Thus comparing the compounds, lower TPSA is favourable for drug-like properties. It is also predicted that a molecule with better CNS penetration should have lower TPSA value[34,35,36].

4. CONCLUSION

Though *in silico* prediction of chemical toxicity has made a good progress in recent years, there are still some challenges and limitations to be improved. At first, data quality is still a big issue. Currently many toxicity data are obtained from high-throughput *in vitro* assays or *in vivo* tests on animals. The current study revealed the bioactive compounds (Gymnemic acid) for the inhibition of the enzyme leading to new discoveries of medicinal drugs based on plants. Computational analysis may be used for the drug development process as an efficient supporting tool. Computational simulations often give us, with high precision, a detailed performance. Therefore, in order to grow the drug discovery and development business, their participation is important.

5. AUTHOR CONTRIBUTION STATEMENT

Dr. Ramasamy Sujatha and Mrs.Dhanapal Indumathi conceptualized and discussed the methodology and results in the final manuscript and gathered the data with regard to this work., Dr. Palanisamy Shanmuga Sundaram analysed all the given data gathered. All authors discussed the methodology and results and contributed to the final manuscript.

6. CONFLICT OF INTEREST

Conflict of interest declared none

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