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Research Article

PREDICTION OF BIOLOGICAL ACTIVITIES OF *A. SQUAMOSA* BIOACTIVE COMPOUNDS *BY-SILICO* DESIGN

Ravindra Madhukar Katole[1], Mukesh Kumar Sharma*[1, 2], Chetan Kumar Joshi[3]

[1]*Department of Biotechnology, Maharaj Vinayak Global University, Jaipur, Rajasthan, India*

[2]*Department of Botany, Vishwa Bharti PG College, Sikar, Rajasthan, India*

[3]*Department of Zoology, Government Science College, Sikar, Rajasthan, India*

**Corresponding author: mukeshsharma.dt@gmail.com*

ABSTRACT

Annona squamosa L. belongs to the Annonaceae family and is one of the basic dietary plants with edible fruits and is called "custard apple. The aim of our study was to carry out to PASS Predication investigate potential Prediction of Activity Spectra for phytoconstituents from Alpinia calcarata namely Acetogenins, Isoquinoline, Quercetin 3 Oglucoside, phenanthrene and Anoreticuin towards many deasease. Server based in silico pass prediction of the compounds was performed. Selected phytochemicals were also analyzed for ADME/T properties using the ADMET protocol. Among a wide range of predicting Acetogenins, Isoquinoline, Quercetin-3-O-glucoside, Phenanthrene and Annoreticuin are effective against fungal pathogens of CYP2H substrates and inhibitors of membrane permeability (0.66 <Pa> 0.90) activity and this can be supported by ADMET properties of these compounds. So Acetogenins have good absorbability, especially in human intestinal absorption. Isoquinoline and norepinephrine are kinase inhibitors, while the high molecular weight compounds phenanthrene and norepinephrine have a low GI absorption distribution across the blood-brain barrier (BBB) and central nervous system. Also the results from ADME/T properties ensured the compounds safe for human.

Keywords: ADMET, Antiviral, Custard apple, Metabolites.

1. INTRODUCTION

Annona squamosa L. belongs to the Annonaceae family There are about 119 species of Annonaceae. According to the Indian Council of Agricultural Research (ICAR) report, sugar apples are found in several states in India with a total planting area of 40,000 hectares [1]. *Annona squamosa* (*A. squamosa*) is famous for its edible fruit, the tree grows as a small shoot, rising from 3 m to 8 m, the large and randomly distributed branches have brown or light brown bark and thin leaves [2]. The sugar apple has been used as a natural medicine and several other food applications. For example, its pulp is used as a flavoring agent in ice cream, and 50-80% of the butter apple is edible and can be made into juice. It contains a considerable amount of vitamin C, 35-42 mg per 100g and the content of dietary fiber, vitamin B1 (thiamine) and potassium is also very high [3]. Recent articles indicate that various plant by-products, such as fruit or vegetable residues, bran/peel/seed coat, seeds, pericarp and leaves, are important sources of phytochemicals and can be used as innovative ingredients in foods [4-15]. Extracts from many parts of the *A. squamosa* plant, including the bark, roots, leaves, stems, fruits, shells, and seeds, have been used in traditional pharmaceutical applications in several nations to cure ailments like diarrhoea, epilepsy, bleeding, fever, and tumour [16]. *A. squamosa* seed powder is used to treat lice, leaf extract is used to treat boils and ulcers, and the fruit can be used as a relaxant for heart illness, vomiting, and tumour treatment [17]. Custard apples contain a variety of phenolic components, including proantho-cyanidins and 18 distinct secondary metabolites, mostly alkaloids or flavonoids, according to phytochemical research [18]. In addition to the fruit, a large number of leaves are produced during pruning, which brings complications related to leaf removal for farmers. Due to its wide range of pharmacological properties and biological activities, such as antioxidant, antibacterial, anti-diabetic, anti-viral, anti-cancer and hepatoprotective activities, These activities are caused by the presence of glycosides, phytosterols, sugars, oils, saponins, tannins, alkaloids, phenols, flavonoids, peptides, and other acetin chemicals

produce these activities [16, 19, 20]. The phytochemical evaluation emphasizes that many active compounds in *A. squamosa*, such as acetin and flavonoids, also have plant cytotoxicity, antimalarial, antidiabetic, and immunosuppressive activities. ASL extract helps maintain plasma insulin and lipid characteristics, and can significantly reduce blood sugar and lipid peroxidation [19]. The purpose of this research is to provide information describing the chemical composition of plants, primarily ACG, ALK, and EO, as well as the medicinal uses of various *A. squamosa* families.

It can be seen from the structure-activity relationship (SAR) that *A. squamosa* and its biologically active compound have cytotoxic activity against several different cancer-causing cell lines [21]. In 2021, Acetogenins, Isoquinoline, Quercetin-3-O-glucoside, phenanthrene and annoreticuin were isolated from the three-fold antioxidant activity of *A. squamosa* having activity on breast cancer [22]. Considering all these promising results, several compounds have been isolated from commercially available quercetin 3 O glucoside. His previous research demonstrated that *A. Squamosa* has antioxidant, antibacterial, antidiabetic, antiviral, anticancer, and hepatoprotective activities, the pharmacological activity predicted by PASS, ADMET (absorption, distribution, metabolism, excretion, and toxicity), and drug similarity in this discussion.

2. MATERIAL AND METHODS

2.1. Collection of compounds

The bioactive compounds of *A. Squamosa* screened on the basis of previous research paper [23-25] and then collected from Pubchem (Fig.1) and converted to In ChI Key, isomeric SMILES (simplified molecular-input line-entry system).

2.2. PASS Predication

Computer simulation and prediction of drug biometrics provides a cheap and effortless way to find new drug candidates, and also reveals the potential for drug release [26]. Taking these aspects into consideration, we use a web-based PASS (Substance Activity Spectrum Prediction; http://www.way2drug.com/passonline/) to predict the biological activity of bioactive compounds synthesized by *A. squamosa* [7]. This is a well-known program that can predict/calculate the biological activity of compound with an accuracy of 90°. In this program, the calculation results show that Pa (probability from active compound) and Pi (probability from inactive compound) are in the range of 0.0 to 1.0, where $P_a + P_i \neq 1$. First, Geometry extracts appropriate compounds from Pubchem, such as Acetogenins, Isoquinoline, Quercetin-3-O-glucoside, Phenanthrene and Annoreticuin uses the isomer SMILES (for prediction Simplified input line system).

2.3. ADME/T parameter calculation

Pharmacokinetic (PK) properties such as absorption, distribution, metabolism, excretion, and toxicity (ADMET) aanlyses of the bioactive compounds of *A. squamosa* including Acetogenins, Isoquinoline, Quercetin-3-O-glucoside, Phenanthrene and Annoreticuin were determined using the ADMET protocol (http://biosig.unimelb.edu.au) [27]. In all the calculations, SMILES and SD file formats of the Acetogenins, Isoquinoline, Quercetin-3-O-glucoside, Phenanthrene and Annoreticuin were used. In addition, Swiss ADME based free web tools (http://www.swissadme.ch) was employed to calculate various drug-likeness related parameters [28].

3. RESULTS AND DISSCUSION

3.1. Structure uptake from pubchem

2D chemical structure of Acetogenins (PubChem id: CID 393472) , isoquinoline (PubChem id: CID 8405),Quercetin-3-O-glucoside (PubChem id: CID 5280804), phenanthrene (PubChem id: CID 995), Annoreticuin (PubChem id: CID 72778911) are shown in fig. 1.

3.2. PASS analyse the biological activities

Web-based PASS (Constituent Activity Spectrum Prediction; http://www.way2drug.com/passonline/) Predicted selectivity results are listed in table 1. Data indicate that these Acetogenins, Isoquinoline, Quercetin-3-O-glucoside, Phenanthrene and Annoreticuin are effective against fungal pathogens of CYP2H substrates and inhibitors of membrane permeability (0.66 <Pa> 0.90) activity. It should be noted that inhibition of mitochondrial membrane permeability is a putative drug target caused by downregulation of the ratio of Bcl2 (apoptosis regulator) and Bax (apoptosis induced by promoting mitochondrial cytochrome C release). Furthermore, the activation of Caspase3 stimulates the expression of many types of microRNAs that target Bcl2.

3.3. *In silico* ADME/T parameter calculation

In this study, the ADMET properties (absorption, distribution, metabolism, excretion and toxicity) of the selected compounds were calculated from the online server molinspiration (https://www.molinspiration.com

/cgibin/properties). t should be noted that ADMET is the most important characteristic of pharmacokinetic profile (PK). As shown in table 3, Acetogenins have good absorbability, especially in human intestinal absorption. Isoquinoline and norepinephrine are kinase inhibitors (table 2), while the high molecular weight compounds phenanthrene and norepinephrine have a low GI absorption distribution across the blood-brain barrier (BBB) and central nervous system (CNS). However, these compounds are easily metabolized because they are substrates of the CYP3A4 enzyme. Its solubility in different solvents is excellent and better. They are not inhibitors of the human etheragogue-related gene (hERG); therefore, they can be used as safe drugs. Acetogenins are more active parameters than all activities. All compounds with a drug similarity score are the same 0.55. Compared to all selected compounds, only acetogenins have only hydrogen bond donating activity. The similar properties of other drugs are mentioned in table 2 calculated from Swiss ADME. Swiss ADME calculations show that all *A. squamosa* bioactive compounds have good hydrogen bond donors or acceptors, and water solubility is also very good.

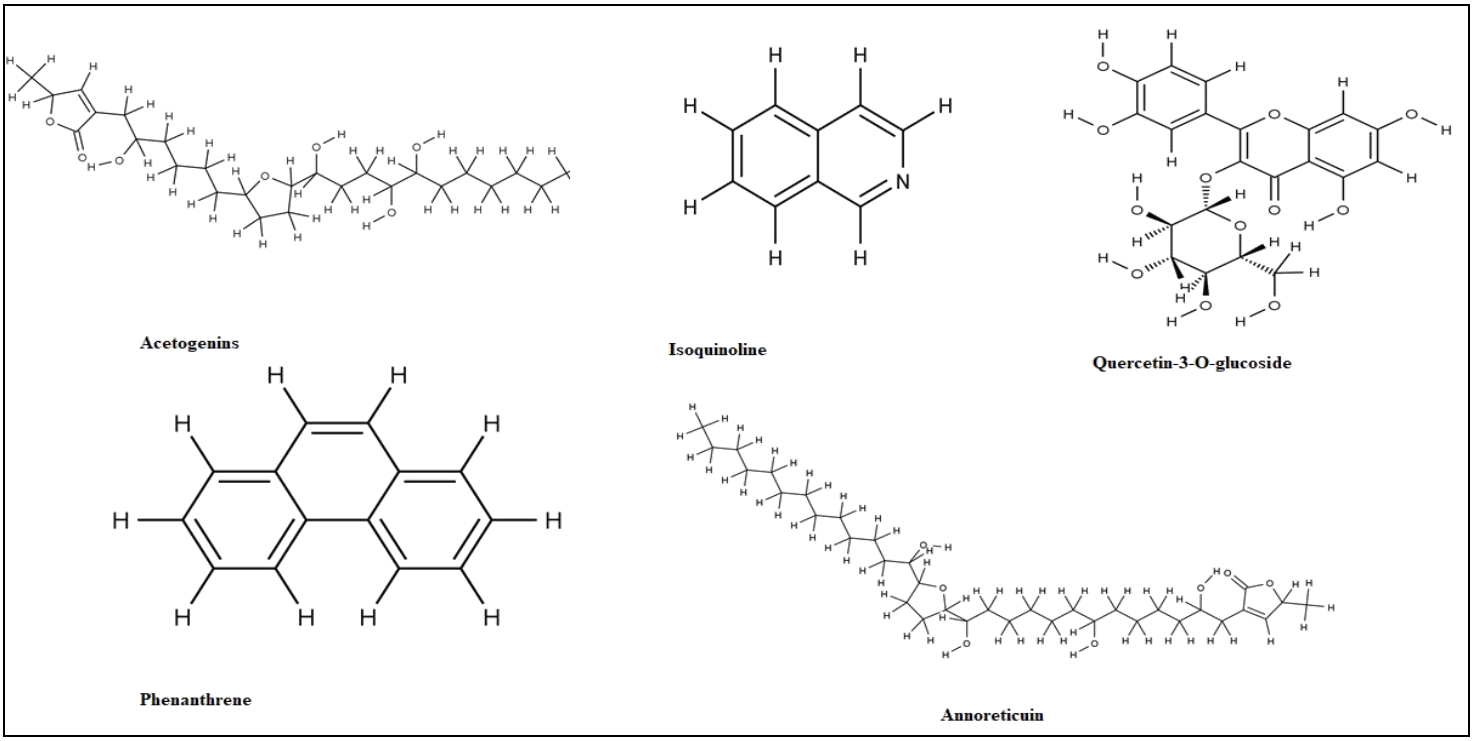

Fig. 1: 2D chemical structure of: Acetogenins (PubChem id: CID 393472), isoquinoline (PubChem id: CID 8405), Quercetin-3-O-glucoside (PubChem id: CID 5280804), phenanthrene (PubChem id: CID 995), Annoreticuin (PubChem id: CID 72778911)

Table 1: Predicted different biological activities of compounds using PASS online tool

Metabolites	Antibacterial		Anticancer		Antiviral		Antifungal	
	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi
Acetogenins	0.572	0.012	0.640	0.012	0.664	0.012	0.640	0.002
Isoquinoline	0.437	0.014	0.664	0.010	0.570	0.021	0.410	0.014
Quercetin-3-O-glucoside	0.546	0.014	0.600	0.012	0.419	0.026	0.314	0.022
Phenanthrene	0.546	0.012	0.800	0.012	0.448	0.026	0.314	0.022
Annoreticuin	0.547	0.016	0.600	0.012	0.450	0.026	0.314	0.024

Table 2: ADME bioactivity of *A. squamosa* bioactive compounds

Compound name	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
Acetogenins	0.21	0.03	0.18	-0.04	-0.28	0.69
Isoquinoline	-0.71	0.20	-0.37	-1.44	-0.87	-0.23
Quercetin-3-O-glucoside	-0.12	0.20	0.06	-0.22	-0.22	0.30
Phenanthrene	-0.12	0.20	0.06	-0.22	-0.22	0.30
Annoreticuin	-0.53	-0.10	-0.50	-0.64	-0.62	-0.20

The topological polar surface area (TPSA) data shows a good agreement with acceptable values (below 86 Å2), where the TPSA value should be less than 140 Å2 (Fig. 2). As the acyl chain length increases, their solubility in water decreases. The gastrointestinal absorption of acetogenins, isoquinoline, Acetogenins, Isoquinoline, Quercetin-3-O-glucoside, Phenanthrene and Annoreti-cuinrcetin-3-O-glucoside, phenanthrene and annoreticuin are low. More importantly, there are no compounds that violate Panassay Interfering Compounds (PAINS), and a positive PAINS value indicates an erroneous result in a high-throughput screening with many biological targets. Overall, all compounds using Molsoft chemical finger-prints have moderate drug similarity scores (Table 3).

Table 3: Calculation drug likeliness factor using SwissADME database

Compound name	HBA	HBD	Molar Refractivity	TPSA Å²	NRB	Water Solubility	GI absorption	PAINS alert	Drug likeness score
Acetogenins	7	4	129.41	116.45	17	Moderately soluble	High	0	0.55
Isoquinoline	1	0	41.74	12.89	0	Very soluble	High	0	0.55
Quercetin-3-O-glucoside	1	0	71.20	12.89	2	Moderately soluble	High	0	0.55
Phenanthrene	0	0	61.45	0.00	0	Moderately soluble	LOW	0	0.55
Annoreticuin	0	0	61.45	0.00	0	Moderately soluble	Low	0	0.55

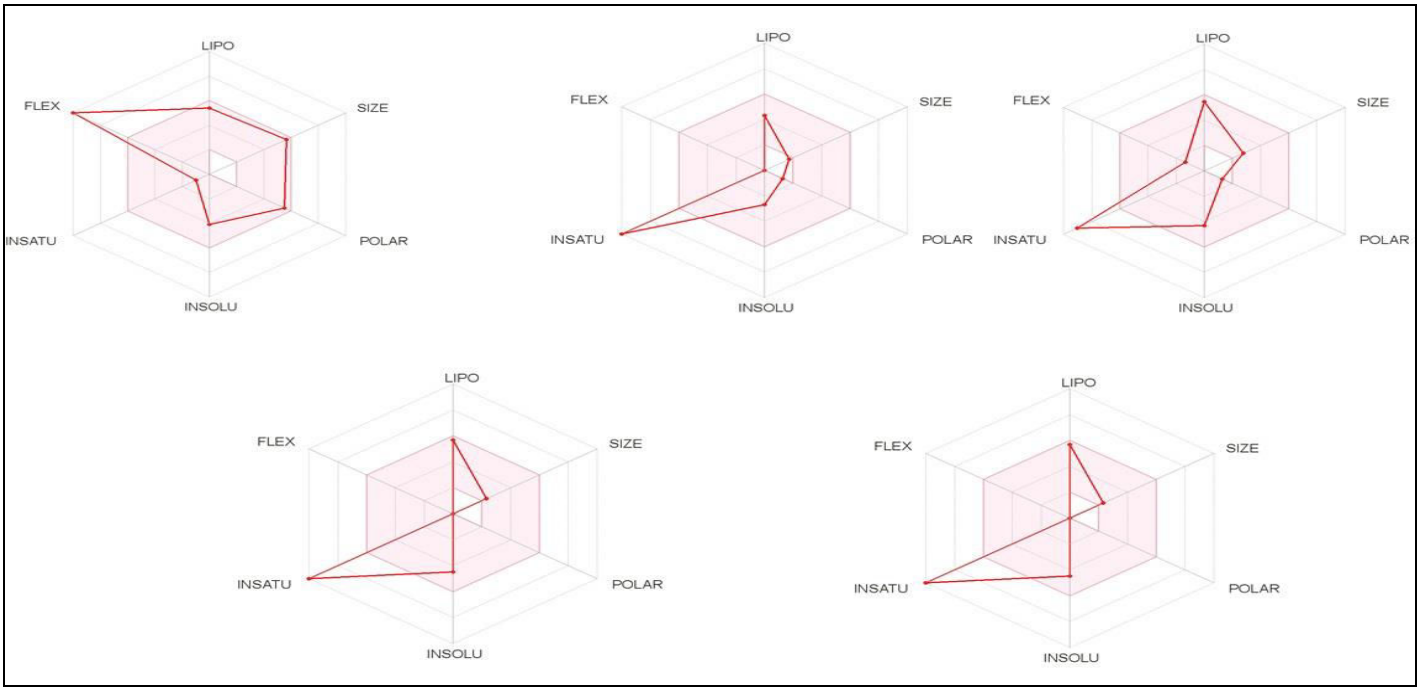

Fig. 2: Topological polar surface area of Acetogenins, Isoquinoline, Acetogenins, Isoquinoline, Quercetin-3-O-glucoside, Phenanthrene and Annoreticuin

4. CONCLUSION

Modern drug discovery programs involve searches for clues of small molecules with attractive pharmacokinetic characteristics. The existence of this type in library PASS and ADME/T properties is very important, so makes the database attractive, in addition to known properties: "similar to a drug", "similar to lead", "similar to a segment "and diversification. PASS predictions result indicate that they are more effective as antifungal agents than as antibacterial agents with other promising biological characteristics. In this context, the pharmacokinetic characteristics of ADMET and the characteristics of similar drugs were predicted and discussed and it safe for human being.

Conflict of interest:

Authors have declared that no conflict of interest exists.

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