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Research Article

In-silico ADMET predicated Pharmacoinformatics of Quercetin-3-Galactoside, polyphenolic compound from *Azadirachta indica*, a sacred tree from Hill Temple in Alagarkovil Reserve Forest, Eastern Ghats, INDIA

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Abstract

Quercetin (3,3′,4′,5,7-Pentahydroxyflavone) is the one among the bioactive secondary metabolite (BASM) in neem seed of *Azadirachta indica* A. Juss. Quercetin (Que) and its derivatives hold promising pharmacological effects. Antidiabetic, anti-inflammatory, antioxidant, antimicrobial, anti-Alzheimer's, antiarthritic, cardiovascular, and wound-healing effects of Que have been extensively investigated, recently lot of work has been carried out on its anticancer activity against different cancer cell lines. Recently, *in silico/ in vitro* studies have demonstrated that Que interferes with different stages of coronavirus entry and replication cycle (PLpro, 3CLpro, and NTPase/helicase). Due to its pleiotropic effects in human health and disease and lack of systemic toxicity, Que and its derivatives could be tested for their efficacy on human target system in future clinical trials. In the present study, an attempt has been made to evaluate the physicochemical, druggable properties of Que from *A. indica* to prospect its ADMET properties.

Keywords: NEEM; *Azadirachta indica*; Quercetin; Pharmacoinformatics; ADMET; Drug-Likeness; Toxicology

INTRODUCTION

Azadirachta indica A. Juss commonly known as Neem belongs to the family Meliaceae[1-3]. Popular as natural store-house of phyto-drugs it has been exploited for its medicinal properties since the dawn of civilization[4,5]. Neem is a versatile plant across the country for its use in Indigenous/ Traditional Systems of Medicine. *A. indica* has its origin from India however, common in South East Asian (SEA) Region (Bangladesh, Srilanka, Bhutan, Myanmar, Pakistan, and Nepal)[6]. Recently, it has been disseminated world over, (tropical and sub-tropical regions)[7].

Neem, a perennial, medium-sized (10 - 15 m) fast-growing tree needs an optimum temperature of 40-50 °C, annual rainfall (400 – 800 mm/annum) and grows well in poor/ degraded/ mined soils. Being repository of bioactive secondary metabolites Neem tree remains as the ideal target for research. As most of the secondary metabolite are localised in leaves/ seeds, destruction of the plant is not warranted. Almost all of the bioactive secondary metabolites in Neem are therapeutic, eco-friendly and biodegradable in nature, therefore GRAS to man and environment[8-11]. The most active constituent is azadirachtin, besides others viz., nimbolinin, nimbin, nimbidin, nimbidol, sodium nimbinate, gedunin, salannin, and quercetin. Leaves contain BASM such as nimbin, nimbanene, 6-desacetylnimbinene, nimbandiol, nimbolide, ascorbic acid, n-hexacosanol, 7-desacetyl-7-benzoylazadiradione, 7-desacetyl-7-benzoylgedunin, 17-hydroxyazadiradione, and nimbiol[12-14]. Quercetin and β-sitosterol, polyphenolic flavonoids, obtained from fresh leaves have significant antibacterial and antifungal properties[14].

Since antiquity all parts of the plant, including root, stem, bark, leaves, fruits, and seeds are used to cure various ailments in humans and domestic animals therefore, Neem has been considered as multi-purposes village dispensary[15-

[25]. In fact, therapeutic applications attributed to Neem include abortive, analgesic, antibacterial, anticancer, antidiabetic, antifungal, anti-helminthic, anti-hyperglycemic, anti-inflammatory, antimalarial, antipyretic, antispasmodic, anti-spermatogenic, antiviral, diuretic, hyper-cholesteremic, immuno-modulatory, mouth-wash, contraception, dental plaque, head lice, heart disease, insect repellent, malaria, pesticide, psoriasis, skin diseases, wound healing, gastro-intestinal ailments, SARS-CoV-2 [26-59].

Que - aglycone is able to conjugate with glucose, xylose, or rutinose attaching to one of the Que's hydroxyl groups with the consequent creation of various Que glycoside forms. Quercetin-3-O-glycoside is present as a pigment in flowers, vegetables, and fruits; as glycosides rather than as aglycones. Que exhibits higher bioavailability than other phytochemicals. Main sources of Que include grapes, berries, cherries, apples, citrus fruits, onions, buckwheat, kale, tomatoes, red wine, and black tea. However, the concentration of Que varies from one plant to another sometimes in different parts of the same plant even. Que, is powerful antioxidant than vitamins C and E. Que and its derivatives regulate cell cycle progression and cellular signal transduction pathway. Metabolic plasticity of Que is the key determinant in the plant adaptive reaction, Que aglycones are effective regulators of auxin transport, growth and development in plant systems. In animal system - anti-inflammatory and antioxidant effects of Que regulate oxidative, kinase, and cell cycle inhibitor activity, apoptosis-inducing effect holds anticancer potential. Furthermore, Que exerts a remarkable effect on cellular immunity and localised inflammations[60]. Recently, it has been reported that abundance of Que in different plant parts of *Artemisia annua* may be exploited for the treatment of coronavirus[61]. With this background information pharmacological characterization is expected to further validate Que as novel drug lead[62-68].

MATERIALS AND METHODS

Class	:	Equisetopsida C. Agardh
Subclass	:	Magnoliidae Novák Ex Takht.
Superorder	:	Rosanae Takht.
Order	:	Sapindales Juss. Ex Bercht.
Family	:	Meliaceae Juss.
Genus	:	*Azadirachta* A. Juss.
Species	:	*Azadirachta indica* A. Juss.
Common Name	:	Neem
Vernacular Name	:	Vempamaram (Tamil)

Botanical Description: Tree, up to 15 m tall. Branches glabrous; Leaves imparipinnate, pulvinus at the base; leaflets alternate to opposite, 2.5 - 7.0 cm long, 1.5 - 4.0 cm broad, ovate, subsessile, acuminate; Flowers white, sweet-scented; Sepals obovate, 1.5 mm long, puberulous, imbricate. Petals 6 mm long, obvoate to oblong, white, margin ciliate; Staminal tube 5 mm long, puberulous, 10-striate, 10-toothed; teeth 2-lobed; anthers oblong, basifixed; Ovary sub-globose; style linear 2.5 mm long; stigma trifid. Fruit: Drupe oblong, 1.3 - 2.0 cm long, greenish-yellow, Seed: 1-seeded. Plants were collected from the fields in the wild Alagar Hills, Eastern Ghats, INDIA as described previously[33].

GC-MS Analysis

Neem Seed Oil Extracts of *A. indica* was obtained from the seed samples collected from the foothills of Alagar Hills, Alagarkovil Reserve Forest, Dindigul District, Tamil Nadu, India. Phyto-components were identified using GC–MS detection system as described previously, however with modification, whereby portion of the extract was analysed directly by headspace sampling. GC–MS analysis was accomplished using an Agilent 7890A GC system set up with 5975C VL MSD (Agilent Technologies, CA, USA). Capillary column used was DB-5MS (30×0.25 mm, film thickness of 0.25 µm; J&W Scientific, CA, USA). Temperature program was set as follows: initial temperature 50°C held for 1 min, 5°C per min to 100°C, 9°C per min to 200°C held for 7.89 min, and the total run time was 40 min. The flow rate of helium as a carrier gas was 0.811851 mL/ min. MS system was performed in electron ionization (EI) mode with Selected Ion Monitoring (SIM). The ion source temperature and quadruple temperature were set at 230°C and 150°C, respectively. Identification of phyto-components was performed by comparison of their retention times and mass with those of authentic standards spectra using computer searches in NIST 08.L and Wiley 7n.l libraries[3,33].

ADMET Prediction

PubChem database was applied to get the smiles structures of the natural compounds, and was further used for the ADMET prediction. The qualitative assessment of pharmacokinetics viz; absorption, distribution, metabolism, excretion and toxicity (ADMET) profile of selected compounds were predicted computationally by using SwissADME and toxicity prediction using TOPKAT (Accelrys, Inc., USA). QikProp develops and employs QSAR/QSPR models using partial least squares, principal component analysis and multiple linear regression to predict physico-chemical significant descriptors[68-70].

RESULTS AND DISCUSSION

Chemical kingdom	:	Organic compounds
Super class	:	Phenylpropanoids and polyketides
Class	:	Flavonoids
Subclass	:	Flavonoid glycosides
PubChem Identifier	:	10813969
Synonyms	:	ISOQUERCITIN; QUERCETIN-3-GALACTOSIDE
Canonical SMILES	:	OC[C@@H]1O[C@H](Oc2c(oc3c(c2=O)c(O)cc(c3)O)c2ccc(c(c2)O)O)[C@H]([C@@H]([C@H]1O)O)O
InChI Key	:	OVSQVDMCBVZWGM-LQSBFMDOSA-N

Physicochemical Properties

The molecular weight of AZA was 720.72 (g/mol); the calculated LogP value was -0.20; LogD - 0.14; LogSw - -4.34. The total number of stereo-centers in the molecule was 16; the stereo-chemical complexity of the molecule was 0.457; the calculated Fsp3 value of AZA was 0.771; The overall calculated Topological polar surface area of AZA was 215.34(Å2). Likewise the calculated number of hydrogen bond donors in the molecule was 3; whereas the number of hydrogen bond acceptors was 16; the number of smallest set of smallest rings (SSSR) in the molecule analyzed was 2; the size of the biggest system ring in the molecule was 15; similarly, the total number of rotatable bonds in the molecule was 6; the number of rigid bonds was 38; the number of charged groups was 0; similarly the total charge of the compound was 0; the number of carbon atoms in the molecule was 35; whereas the number of heteroatoms in AZA was calculated as 16; the number of heavy atoms in the molecule was calculated as 51; the ratio between the number of non-carbon atoms and the number of carbon atoms in the compound was 0.46 (Fig. 1).

Druggability Properties

Lipinski's rule of 5 violations of the molecule was 2; Veber rule was Low for the molecule; similarly Egan rule for the molecule was also Low; the Oral PhysChem score (Traffic Lights) for the molecule was recorded as 5; GSK's 4/400 score for the molecule was Good; Pfizer's 3/75 score for the molecule was Good; Weighted quantitative estimate of drug-likeness (QEDw) score for the molecule was 0.164; Solubility Forecast Index was Good and the solubility score was 9441.49;

ADMET Properties

Only when the ADME/Tox properties of a drug like compound are of high quality, and when the target has been validated, the compound could be developed into a pharma-drug. *In silico* drug-likeness evaluation of Azadirachtin for Human Intestinal Absorption (HIA+) value had a probability of 0.890; Blood Brain Barrier (BBB-) value for the molecule had a probability of 0.773; Caco-2 permeable (Caco2-) value for the molecule had a probability of 0.711 (Fig. 4); P-glycoprotein substrate (Substrate) value for the molecule had a probability of 0.835; P-glycoprotein inhibitor I (Inhibitor) value for the molecule had a probability of 0.672; P-glycoprotein inhibitor II (Non-inhibitor) value for the molecule had a probability of 0.534. CYP450 2C9 substrate (Non-substrate) value for the molecule had a probability of 0.857; CYP450 2D6 substrate (Non-substrate) - 0.872; CYP450 3A4 substrate (Substrate) - 0.714; CYP450 1A2 inhibitor (Non-inhibitor) - 0.887; CYP450 2C9 inhibitor (Non-inhibitor) - 0.845; CYP450 2D6 inhibitor (Non-inhibitor) - 0.944; CYP450 2C19 inhibitor (Non-inhibitor) - 0.833; CYP450 3A4 inhibitor (Non-inhibitor) - 0.770; CYP450 inhibitory promiscuity (Low CYP Inhibitory Promiscuity) - 0.886; Ames test (Non AMES toxic) - 0.756; Carcinogenicity (Non-carcinogens) - 0.946; Biodegradation (Not ready biodegradable) - 1.000; Rat acute toxicity (4.348 LD50, mol/kg) - PNA; hERG inhibition (predictor I) (Weak inhibitor) - 0.992; hERG inhibition (predictor II) (Non-inhibitor) - 0.569 respectively. Computational methods for analysing and estimating the toxicity of natural bioactive compounds are considered as useful tool for validation as it provides in-depth understanding of toxicogenomics. Therefore, determining the toxicity of BASM *in-silico* is warranted to identify their potential harmful effects on humans, animals, plants, besides the environment as in-vivo animal tests are constrained by time, ethical considerations, and financial burden. Data pertaining to the descriptors viz., Toxicity, Environmental toxicity, Tox21 pathway and Toxicophore Rules for Azadirachtin are summarized in Table 2. Furthermore, GPCR ligand, ion channel modulator, kinase inhibitor, nuclear receptor ligand, protease inhibitor, enzyme inhibitor score for AZA were calculated as -0.71; -1.51; -1.46; -0.67; -0.35 and -0.71 respectively (Fig. 3). Swiss Target Prediction towards Macrophage migration inhibitory factor, Heat shock protein (HSP 90-alpha), Kappa Opioid receptor, Mu opioid receptor, Delta opioid receptor, Thrombin, Squalene synthetase, Glycogen synthase kinase-3 beta, Glycogen synthase kinase-3 alpha, Protein kinase C alpha, Apoptosis regulator Bcl-X, HMG-CoA reductase, Zinc finger protein GLI1, Proto-oncogene c-JUN, Vanilloid receptor for the compound has been provided in Table 4. Chemical and biological investigations on *Azadirachta indica* bioactive compounds indicates that the compound is safe for use as a drug molecule[3,72-74].

CONCLUSION

The present study is an example to insights into the broad scope of pharmacoinformatics of Quercetin-3-Galactoside, a polyphenolic compound from *Azadirachta indica* (Neem), with an emphasis on plant based natural product drug discovery. The study indicates that plant based natural products still possess an extraordinary challenge that has to be solved before taken for drug development. However, it is anticipated that as more quality data on natural product research, such as bio-activity, biomolecularinformatics, cheminformatics, toxicoinformatics integrated together with new IoT data mining, algorithms and machine learning techniques to accelerate natural product based drug discovery. Furthermore, online databases serve as attractive sources for identifying novel natural product scaffolds with promising drug-like

properties in NPs which is expected to accelerate the pace of Drug Discovery.

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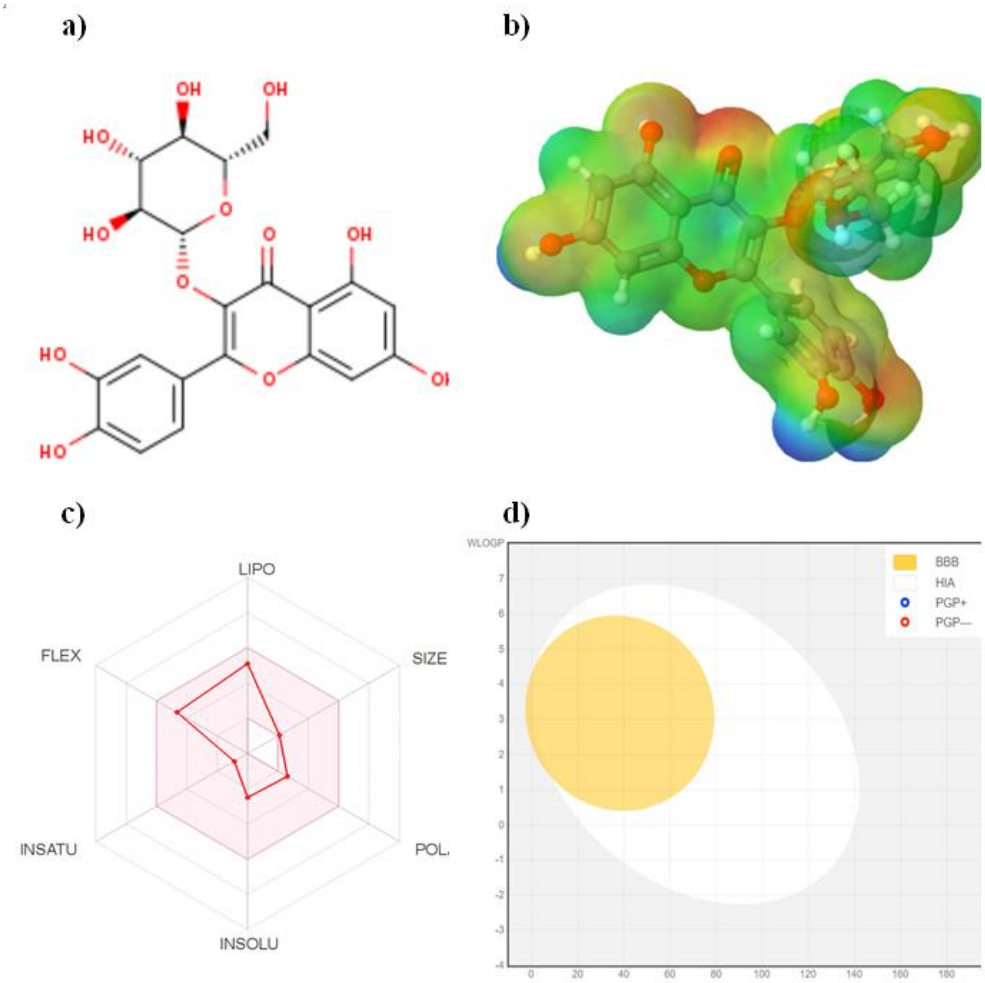

Figure 1: 2D, 3D, Physicochemical and Boiled-Egg Prediction of Quercetin-3 Galactoside

Table 1 Physicochemical, Druggability, ADMET properties of Quercetin-3 Galactoside

PHYSICOCHEMICAL PROPERTIES		**VALUE**
Molecular weight		464.38 g/mol
LogP		-0.54
LogD		-1.16
LogSw		-2.91
Number of stereo enters		5
Stereo-chemical complexity		0.238
Fsp3		0.286
Topological polar surface area		210.51 Å^2
Number of hydrogen bond donors		8
Number of hydrogen bond acceptors		12
Number of smallest set of smallest rings (SSSR)		3
Size of the biggest system ring		10
Number of rotatable bonds		4
Number of rigid bonds		24
Number of charged groups		0
Total charge of the compound		0
Number of carbon atoms		21
Number of heteroatoms		12
Number of heavy atoms		33
Ratio between the number of non-carbon atoms and the number of carbon atoms		0.57
DRUGGABILITY PROPERTIES		**VALUE**
Lipinski's rule of 5 violations		2
Veber rule		Good
Egan rule		Good
Oral PhysChem score (Traffic Lights)		3
GSK's 4/400 score		Good
Pfizer's 3/75 score		Good
Weighted quantitative estimate of drug-likeness (QEDw) score		0.288
Solubility		25415.67
Solubility Forecast Index		Good Solubility
ADMET PROPERTIES	**VALUE**	**PROBABILITY**
Human Intestinal Absorption	HIA+	0.786
Blood Brain Barrier	BBB-	0.698
Caco-2 permeable	Caco2-	0.940
P-glycoprotein substrate	Substrate	0.591
P-glycoprotein inhibitor I	Non-inhibitor	0.878
P-glycoprotein inhibitor II	Non-inhibitor	0.797
CYP450 2C9 substrate	Non-substrate	0.812
CYP450 2D6 substrate	Non-substrate	0.892

CYP450 3A4 substrate	Non-substrate	0.604
CYP450 1A2 inhibitor	Non-inhibitor	0.908
CYP450 2C9 inhibitor	Non-inhibitor	0.930
CYP450 2D6 inhibitor	Non-inhibitor	0.951
CYP450 2C19 inhibitor	Non-inhibitor	0.929
CYP450 3A4 inhibitor	Non-inhibitor	0.919
CYP450 inhibitory promiscuity	Low CYP Inhibitory Promiscuity	0.773
Ames test	AMES toxic	0.578
Carcinogenicity	Non-carcinogens	0.959
Biodegradation	Not ready biodegradable	0.626
Rat acute toxicity	2.387 LD50, mol/kg	Not applicable
hERG inhibition (predictor I)	Weak inhibitor	0.981
hERG inhibition (predictor II)	Non-inhibitor	0.687

Physicochemical properties were computed using FAF-Drugs4 (28961788) and RDKit open-source cheminformatics platform. The druggabiity scoring schemes were computed using FAF-Drugs4 (28961788) and FAF-QED (28961788) open-source cheminformatics platform. ADMET features were predicted using admetSAR (23092397) open-source tool.