Available online on 15.09.2021 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

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Research Article

Physicochemical, Druggable, ADMET Pharmacoinformatics and Therapeutic Potentials of Azadirachtin - a Prenol Lipid (Triterpenoid) from Seed Oil Extracts of *Azadirachta indica* A. Juss.

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Article Info:

Article History:

Received 06 July 2021
Reviewed 09 August 2021
Accepted 16 August 2021
Published 15 Sep 2021

Cite this article as:

Loganathan T, Barathinivas A, Soorya C, Balamurugan S, Nagajothi TG, Ramya S, Jayakumararaj R, Physicochemical, Druggable, ADMET Pharmacoinformatics and Therapeutic Potentials of Azadirachtin - a Prenol Lipid (Triterpenoid) from Seed Oil Extracts of *Azadirachta indica* A. Juss., Journal of Drug Delivery and Therapeutics. 2021; 11(5):33-46

DOI: http://dx.doi.org/10.22270/jddt.v11i5.4981

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Abstract

Azadirachtin (AZA) is the most abundant bioactive secondary metabolite (BASM) in neem seed oil extract (NSOE) of *Azadirachta indica* A. Juss. AZA is localised in different parts of the plant (seeds, fruits, flowers, leaves, stem, bark and root) however, with varying degree of concentration. It has been documented that maximum concentration of AZA is present to the tune of 48000 μg g^{-1} in the seeds. It has been established that the environmental conditions determines the overall content and composition of BASM in different parts of the plant. Neem plant parts are most commonly used as therapeutic agents in remote villages in India for its ethnomedicinal therapeutic potentials; however, its physicochemical, druggable and pharmacological properties inadequately described. In the present study an attempt has been made to evaluate the physicochemical, druggable and pharmacological properties of Azadirachtin in NSOE of *A. indica* from ADMET perspectives.

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

INTRODUCTION

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

Neem is a perennial, small to medium-sized (10 - 15 m) and fast-growing tree and grows well in locations with temperature to a maximum of 48-50 °C, the plant needs low annual rainfall (400 – 800 mm/annum). Furthermore, the plant grows well in poor/ degraded/ mined soils. However, growth is affected by low temperature (poor growth below 14 °C) and frosts. Being the storehouse/ repository of wide array of BASM, Neem tree remains the ideal target of interest for research. As most of the BASM are localised in the leaves and seeds, destruction of whole plant is not required for the isolation/ extraction of bioactive principles. Furthermore, being perennial, annual replenishment of leaves and seeds prevents whole-plant harvest. BASM of Neem contains high proportion of water-soluble substances that favours DIY extraction and application in folklore medicine. Moreover, majority of these metabolites are eco-friendly bioactive compounds that are biodegradable in nature, adhere to GRAS standards, therefore harmless to man and environment[8].

A. indica shows therapeutics potential in healthcare and management due to rich source of BASM[9-11]. The most important active constituent is azadirachtin, while others include 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; while seeds are comparably rich in azadirachtin[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 a 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[26-55].

Neem is influenced by a myriad of factors, namely geographic area, climate, genetic variability, agronomic conditions, plant morphology and physiology, collection and storage of plant material which determines the therapeutic potential. Further, this variation affects the development processes as regulation of secondary metabolite synthesis is directly linked to gene expression. This boils down to the fact that growth of Neem plant and the biochemical composition of the active principle is significantly influenced by external parameters. Kaushik et al[56]. and Tomar et al[57]. independently, analysed trees from different regions of India and observed significant difference in the AZA content of seeds collected in different regions. Furthermore, Kaushik et al[56]. evaluated the effect of climatic conditions in the AZA content of seeds and indicated that AZA values of samples from semi-arid regions with mild winters were different from values observed in hot sub-humid, hot arid and hot semi-arid with cold winter regions. Similarly, Zheng et al.[58] pointed out that season and ecosystem properties significantly affect neem seed oil yield and, in a less extent, AZA content. In fact, AZA quantity obtained in seed was significantly influenced by precipitation, with lower values observed in rainy season. Likewise, the procedure and time of collection of the plant material also influences AZA concentration in the seeds. In the case of seeds, AZA concentration is maximized when clean and healthy seeds are collected[59,60].

Indeed, it has been reported that mechanical damage, insect infestation and fungal infection of seeds significantly affect quantity and quality of AZA content. Since its isolation for the first time in 1968, AZA has been the subject of intense research, particularly of biological, synthetic and structural studies[61]. Azadirachtin - limonoid group of compound is a bioactive secondary metabolite present in neem seeds[12,13,26,27,60]. It is a highly oxidized tetranortriterpenoid that asserts a plethora of oxygen-bearing functional group which includes an enol-ether, acetal, hemiacetal, tetra-substituted epoxide structure with variety of carboxylic esters (Fig. 1). Increasing interest in AZA is mainly due to the unique biomolecular properties, including broad spectrum of activity even in trace amounts, no or low toxicity to mammals. Its complex structure makes its synthesis a daunting task. Biological activities attributed to AZA include application as a bioinsecticide, biopesticide, insect-pest repellent as it is non-toxicity to humans. Azadirachtin has been identified as potential inhibitor of SARS-CoV-2 main protease[62-64] and is expected to play a major role in the management of COVID-19. Furthermore, pharmacological characterization is expected to validate Azadirachtin as novel drug lead[65-68].

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	:	Vempu (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 Palani Hills, Western 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	:	**Lipids and lipid-like molecules**
Class	:	**Prenol lipids**
Subclass	:	**Triterpenoids**
PubChem Identifier	:	**102146586**
Synonyms	:	**Azadirachtanin**
Canonical SMILES	:	**CC(=O)O[C@@H]1OC[C@@]23C([C@@]1(C)[C@H](OC(=O)C)C[C@@H]2O)C[C@H]([C@@]1([C@@H]3C(=O)[C@H](OC(=O)C)[C@@]2(C1=CC[C@H]2c1ccoc1)C)C)O**
InChI Key	:	**YQSXXKRVYCLMRM-SIUABMRBSA-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. 2,3).

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[3,72,72].

CONCLUSION

The present study is an example to insights into the broad scope of pharmacoinformatics to plant based natural product research with an emphasis on 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 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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Table 1 Physicochemical, Medicinal Chemistry and ADMET properties of AZA

1. Physicochemical Property		
Property	**Value**	**Comment**
Molecular Weight	720.26	Contain hydrogen atoms. Optimal:100~600
Volume	670.289	Van der Waals volume
Density	1.075	Density = MW / Volume
nHA	16	Number of hydrogen bond acceptors. Optimal:0~12
nHD	3	Number of hydrogen bond donors. Optimal:0~7
nRot	10	Number of rotatable bonds. Optimal:0~11
nRing	8	Number of rings. Optimal:0~6
MaxRing	14	Number of atoms i The biggest ring. Optimal:0~18
nHet	16	Number of heteroatoms. Optimal:1~15
fChar	0	Formal charge. Optimal:-4 ~4
nRig	38	Number of rigid bonds. Optimal:0~30
Flexibility	0.263	Flexibility = nRot /nRig
Stereo Centers	16	Optimal: £ 2
TPSA	215.34	Topological Polar Surface Area. Optimal:0~140
logS	-3.837	Log of the aqueous solubility. Optimal: -4~0.5 log mol/L

logP	1.306	Log of the octanol/water partition coefficient. Optimal: 0~3
logD	1.493	logP at physiological pH 7.4. Optimal: 1~3
2. Medicinal Chemistry		
Property	**Value**	**Comment**
QED	0.14	A measure of drug-likeness based o The concept of desirability; Attractive: > 0.67; unattractive: 0.49~0.67; too complex: < 0.34
SAscore	7.579	Synthetic accessibility score is designed to estimate ease of synthesis of drug-like molecules. n SAscore ^{3} 6, difficult to synthesize; SAscore <6, easy to synthesize
Fsp3	0.771	The number of sp3 hybridized carbons / total carbon count, correlating with melting point and solubility. n Fsp3 ^{3}0.42 is considered a suitable value.
MCE-18	215.065	MCE-18 stands for medicinal chemistry evolution. n MCE-18^{3}45 is considered a suitable value.
NPscore	3.457	Natural product-likeness score. n This score is typically i The range from -5 to 5. The higher the score is, the higher the probability is that the molecule is a NP.
Lipinski Rule	Rejected	MW £ 500; logP £ 5; Hacc £ 10; Hdon £ 5 n If two properties are out of range, a poor absorption or permeability is possible, one is acceptable.
Pfizer Rule	Accepted	logP > 3; TPSA < 75 Compounds with a high log P (>3) and low TPSA (<75) are likely to be toxic.
GSK Rule	Rejected	MW £ 400; logP £ 4 n Compounds satisfying the GSK rule may have a more favourable ADMET profile
Golden Triangle	Rejected	200 £ MW £ 50; -2 £ logD £ 5 n Compounds satisfying the Golden Triangle rule may have a more favourable ADMET profile.
PAINS	0 alerts	Pan Assay Interference Compounds, frequent hitters, Alpha-screen artifacts and reactive compound.
ALARM NMR	1 alerts	Thiol reactive compounds.
BMS	0 alerts	Undesirable, reactive compounds.
Chelator Rule	0 alerts	Chelating compounds.
3. Absorption		
Property	**Value**	**Comment**
Caco-2 Permeability	-5.261	Optimal: higher than -5.15 Log unit
MDCK Permeability	0.000138	low permeability: < 2 × 10-6 cm/s n medium permeability: 2–20 × 10-6 cm/s n high passive permeability: > 20 × 10-6 cm/s
Pgp-inhibitor	1	Category 1: Inhibitor; Category 0: Non-inhibitor; The output value is the probability of being Pgp-inhibitor
Pgp-substrate	0.975	Category 1: substrate; Category 0: Non-substrate; The output value is the probability of being Pgp-substrate
HIA	0.66	Human Intestinal Absorption Category 1: HIA+(HIA < 30%); Category 0: HIA-(HIA < 30%); The output value is the probability of being HIA+
F20%	0.649	20% Bioavailability Category 1: F20%+ (bioavailability < 20%); Category 0: F20%- (bioavailability ^{3} 20%); The output value is the probability of being F20%+
F30%	0.985	30% Bioavailability Category 1: F30%+ (bioavailability < 30%); Category 0: F30%- (bioavailability ^{3} 30%); The output value is the probability of being F30%+
4. Distribution		
Property	Value	Comment
PPB	38.52%	Plasma Protein Binding n Optimal: < 90%. Drugs with high protein-bound may have a low therapeutic index.
VD	1.581	Volume Distribution n Optimal: 0.04-20L/kg

BBB Penetration	0.246	Blood-Brain Barrier Penetration Category 1: BBB+; Category 0: BBB-; The output value is the probability of being BBB+
Fu	37.25%	The fraction unbound in plasms n Low: <5%; Middle: 5~20%; High: > 20%
5. Metabolism		
Property	**Value**	**Comment**
CYP1A2 inhibitor	0	Category 1: Inhibitor; Category 0: Non-inhibitor; The output value is the probability of being inhibitor.
CYP1A2 substrate	0.993	Category 1: Substrate; Category 0: Non-substrate; The output value is the probability of being substrate.
CYP2C19 inhibitor	0.017	Category 1: Inhibitor; Category 0: Non-inhibitor; The output value is the probability of being inhibitor.
CYP2C19 substrate	0.724	Category 1: Substrate; Category 0: Non-substrate; The output value is the probability of being substrate.
CYP2C9 inhibitor	0.014	Category 1: Inhibitor; Category 0: Non-inhibitor; The output value is the probability of being inhibitor.
CYP2C9 substrate	0.005	Category 1: Substrate; Category 0: Non-substrate; The output value is the probability of being substrate.
CYP2D6 inhibitor	0.003	Category 1: Inhibitor; Category 0: Non-inhibitor; The output value is the probability of being inhibitor.
CYP2D6 substrate	0.107	Category 1: Substrate; Category 0: Non-substrate; The output value is the probability of being substrate.
CYP3A4 inhibitor	0.719	Category 1: Inhibitor; Category 0: Non-inhibitor; The output value is the probability of being inhibitor.
CYP3A4 substrate	0.857	Category 1: Substrate; Category 0: Non-substrate; The output value is the probability of being substrate.
6. Excretion		
Property	**Value**	**Comment**
CL	1.748	Clearance n High: >15 mL/min/kg; moderate: 5-15 mL/min/kg; low: <5 mL/min/kg
T1/2	0.016	Category 1: long half-life; Category 0: short half-life; long half-life: >3h; short half-life: <3h The output value is the probability of having long half-life.
7. Toxicity		
Property	**Value**	**Comment**
hERG Blockers	0.03	Category 1: active; Category 0: inactive; The output value is the probability of being active.
H-HT	0.342	Human Hepatotoxicity Category 1: H-HT positive (+); Category 0: H-HT negative (-); The output value is the probability of being toxic.
DILI	0.32	Drug Induced Liver Injury. Category 1: drugs with a high risk of DILI; Category 0: drugs with no risk of DILI. The output value is the probability of being toxic.
AMES Toxicity	0.844	Category 1: Ames positive (+); Category 0: Ames negative (-); The output value is the probability of being toxic.
Rat Oral Acute Toxicity	0.978	Category 0: low-toxicity; Category 1: high-toxicity; The output value is the probability of being highly toxic.
FDAMDD	0.961	Maximum Recommended Daily Dose Category 1: FDAMDD (+); Category 0: FDAMDD (-) The output value is the probability of being positive
Skin Sensiti zation	0.005	Category 1: Sensitizer; Category 0: Non-sensitizer; The output value is the probability of being sensitizer.

Carcinogen city	0.976	Category 1: carcinogens; Category 0: non-carcinogens; The output value is the probability of being toxic.
Eye Corrosion	0.003	Category 1: corrosives; Category 0: non-corrosives The output value is the probability of being corrosives.
Eye Irritation	0.01	Category 1: irritants; Category 0: non-irritant The output value is the probability of being irritants.
Respiratory Toxicity	0.963	Category 1: respiratory toxicants; Category 0: respiratory non-toxicants The output value is the probability of being toxic.
8. Environmental toxicity		
Property	**Value**	**Comment**
Bioconcentration Factors	0.985	Bioconcentration factors are used for considering secondary poisoning potential and assessing risks to human health via the food chain. The unit is -log10[(mg/L)/(1000*MW)]
IGC_{50}	3.752	*Tetrahymena pyriformis* 50 percent growth inhibition concentration The unit is -log10[(mg/L)/(1000*MW)]
LC50FM	5.88	96-hour fathead minnow 50 percent lethal concentration The unit is -log10[(mg/L)/(1000*MW)]
LC50DM	5.549	48-hour daphnia magna 50 percent lethal concentration The unit is -log10[(mg/L)/(1000*MW)]
9. Tox21 pathway		
Property	**Value**	**Comment**
NR-AR	0.022	Androgen receptor Category 1: actives; Category 0: inactives; The output value is the probability of being active.
NR-AR-LBD	0.816	Androgen receptor ligand-binding domain Category 1: actives; Category 0: inactives; Output value is probability of being active.
NR-AhR	0.014	Aryl hydrocarbon receptor Category 1: actives; Category 0: inactives; The output value is the probability of being active.
NR-Aromatase	0.773	Category 1: actives; Category 0: inactives; The output value is the probability of being active.
NR-ER	0.209	Estrogen receptor Category 1: actives; Category 0: inactives; The output value is the probability of being active.
NR-ER-LBD	0.778	Estrogen receptor ligand-binding domain Category 1: actives; Category 0: inactives; The output value is the probability of being active.
NR-PPAR-gamma	0.923	Peroxisome proliferator-activated receptor gamma Category 1: actives; Category 0: inactives; The output value is the probability of being active.
SR-ARE	0.711	Antioxidant response element Category 1: actives; Category 0: inactives; The output value is the probability of being active.
SR-ATAD5	0.976	ATPase family AAA domain-containing protein 5 Category 1: actives; Category 0: inactives; The output value is the probability of being active.
SR-HSE	0.769	Heat shock factor response element Category 1: actives; Category 0: inactives; The output value is the probability of being active.
SR-MMP	0.968	Mitochondrial membrane potential Category 1: actives; Category 0: inactives; The output value is the probability of being active.
SR-p53	0.999	Category 1: actives; Category 0: inactives; The output value is the probability of being active.
10. Toxicophore Rules		
Property	**Value**	**Comment**
Acute Toxicity Rule	0 alerts	20 substructures; acute toxicity - oral administration
Genotoxic Carcinogenicity Rule	8 alerts	117 substructures; carcinogenicity or mutagenicity
Non-Genotoxic Carcinogenicity Rule	1 alerts	23 substructures; carcinogenicity through non-genotoxic mechanisms
Skin Sensitization Rule	5 alerts	155 substructures; skin irritation

Aquatic Toxicity Rule	7 alerts	99 substructures ; toxicity to liquid(water)
Non-Biodegradable Rule	2 alerts	19 substructures; non-biodegradable
SureChEMBL Rule	2 alerts	164 substructures; Med-Chem unfriendly status

Table 2 Summary of Physicochemical, Druggability, ADMET of AZA

PROPERTY		**VALUE**
Physicochemical Properties		
Molecular weight		**720.72 g/mol**
LogP		**-0.20**
LogD		**0.14**
LogSw		**-4.34**
Number of stereo-centers		**16**
Stereochemical complexity		**0.457**
Fsp3		**0.771**
Topological polar surface area		**215.34 Å²**
Number of hydrogen bond donors		**3**
Number of hydrogen bond acceptors		**16**
Number of smallest set of smallest rings (SSSR)		**2**
Size of the biggest system ring		**15**
Number of rotatable bonds		**6**
Number of rigid bonds		**38**
Number of charged groups		**0**
Total charge of the compound		**0**
Number of carbon atoms		**35**
Number of heteroatoms		**16**
Number of heavy atoms		**51**
Ratio between The number of non-carbon atoms and the number of carbon atoms		**0.46**
Druggability Properties		
Lipinski's rule of 5 violations		**2**
Veber rule		**Low**
Egan rule		**Low**
Oral PhysChem score (Traffic Lights)		**5**
GSK's 4/400 score		**Good**
Pfizer's 3/75 score		**Good**
Weighted quantitative estimate of drug-likeness (QEDw) score		**0.164**
Solubility		**9441.49**
Solubility Forecast Index		**Good**
ADMET Properties		
Property	**Value**	**Probability**
Human Intestinal Absorption	HIA+	**0.890**
Blood Brain Barrier	BBB-	**0.773**

Caco-2 permeable	Caco2-	**0.711**
P-glycoprotein substrate	Substrate	**0.835**
P-glycoprotein inhibitor I	Inhibitor	**0.672**
P-glycoprotein inhibitor II	Non-inhibitor	**0.534**
CYP450 2C9 substrate	Non-substrate	**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**

The 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.

Table 3 Molecular Properties and of Bioactivity Score of AZA

Property	**Score**
miLogP	1.42
TPSA	215
n-atoms	51
MW	721
n-ON	16
n-OHNH	3
n-violations	2
n-rotb	10
Volume	612
Bioactivity	**Score**
GPCR ligand	-0.71
Ion channel modulator	-1.51
Kinase inhibitor	-1.46
Nuclear receptor ligand	-0.67
Protease inhibitor	-0.35
Enzyme inhibitor	-0.71

Table 4 Swiss Target Prediction

Target	Common name	Uniprot ID	ChEMBL ID	Target Class	Probability*	Known actives (3D/2D)
Macrophage migration inhibitory factor	MIF	P14174	CHEMBL 2085	Enzyme	0.06613	0 / 1
Heat shock protein HSP 90-alpha	HSP90AA1	P07900	CHEMBL 3880	Other cytosolic protein	0.06613	0 / 2
Kappa Opioid receptor	OPRK1	P41145	CHEMBL 237	Family A G protein-coupled receptor	0.00	0 / 128
Mu opioid receptor	OPRM1	P35372	CHEMBL 233	Family A G protein-coupled receptor	0.00	0 / 35
Delta opioid receptor	OPRD1	P41143	CHEMBL 236	Family A G protein-coupled receptor	0.00	0 / 21
Thrombin	F2	P00734	CHEMBL 204	Protease	0.00	0 / 2
Squalene synthetase (by homology)	FDFT1	P37268	CHEMBL 3338	Enzyme	0.00	0 / 28
Glycogen synthase kinase-3 beta	GSK3B	P49841	CHEMBL 262	Kinase	0.00	0 / 1
Glycogen synthase kinase-3 alpha	GSK3A	P49840	CHEMBL 2850	Kinase	0.00	0 / 1
Protein kinase C alpha	PRKCA	P17252	CHEMBL 299	Kinase	0.00	0 / 1
Apoptosis regulator Bcl-X	BCL2L1	Q07817	CHEMBL 4625	Other ion channel	0.00	0 / 1
HMG-CoA reductase	HMGCR	P04035	CHEMBL 402	Oxidoreductase	0.00	0 / 1
Zinc finger protein GLI1	GLI1	P08151	CHEMBL 5461	Transcription factor	0.00	0 / 1
Proto-oncogene c-JUN	JUN	P05412	CHEMBL 4977	Transcription factor	0.00	0 / 2
Vanilloid receptor (by homology)	TRPV1	Q8NER1	CHEMBL 4794	Voltage-gated ion channel	0.00	0 / 1

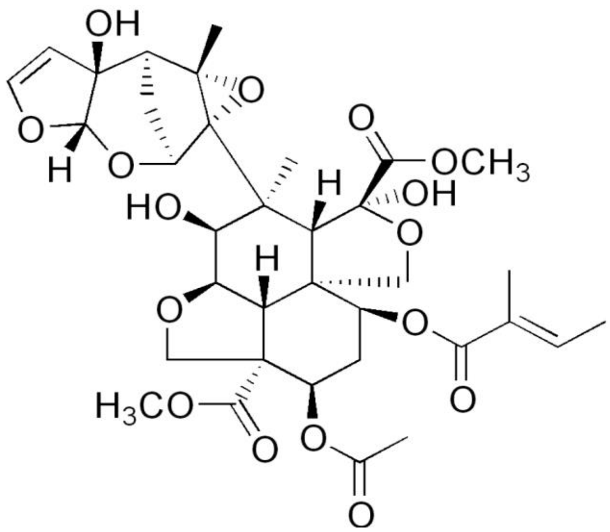

Figure 1: Structure of Azadirachtin (AZA) molecule

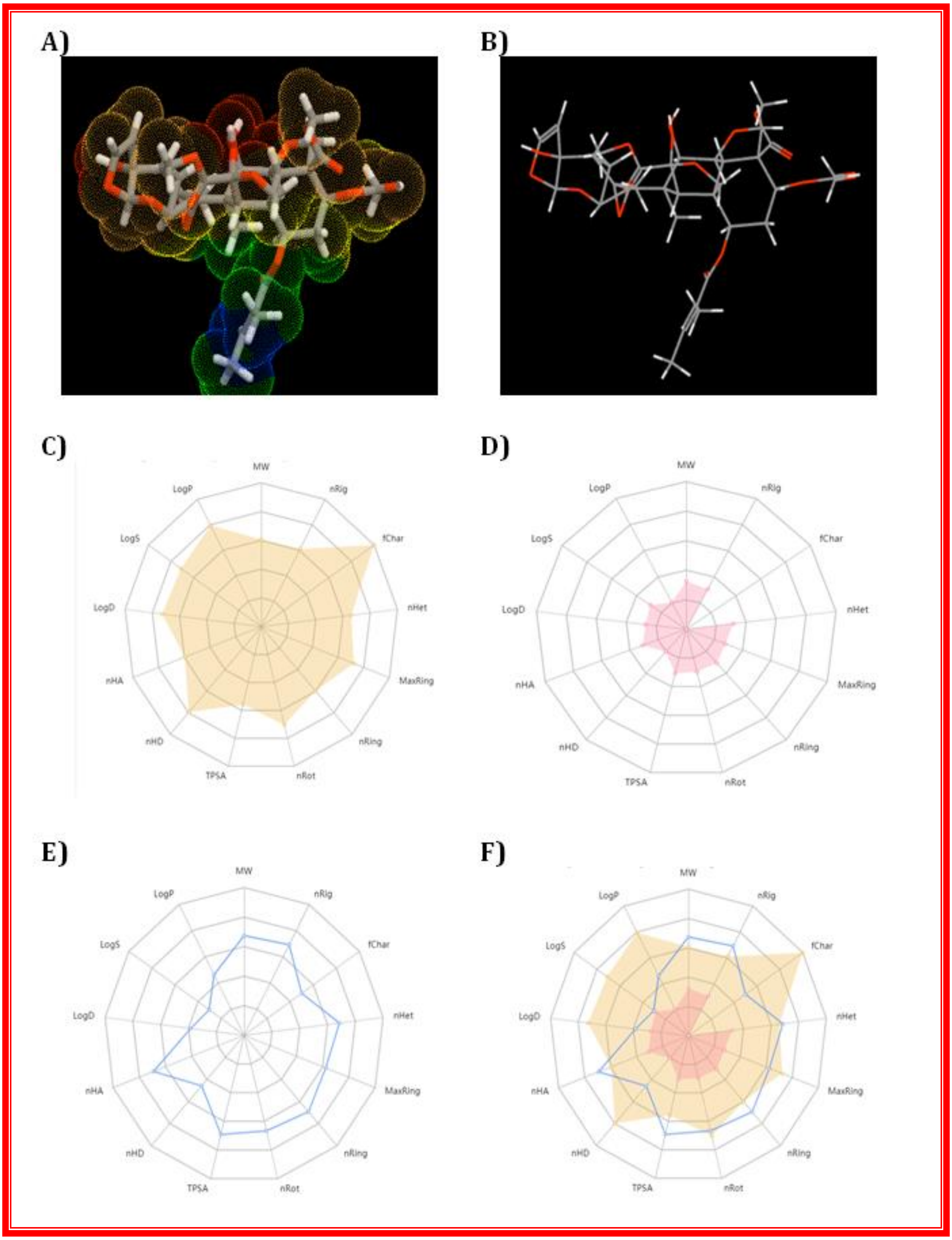

Figure 2: Phytocompound physiochemical properties of Azadirachtin; a) 3D; b) 2D; c) Upper Limit Radar Map; d) Lower Limit Radar Map; e) Compound Properties Radar Map; f) Cumulative Radar Map.

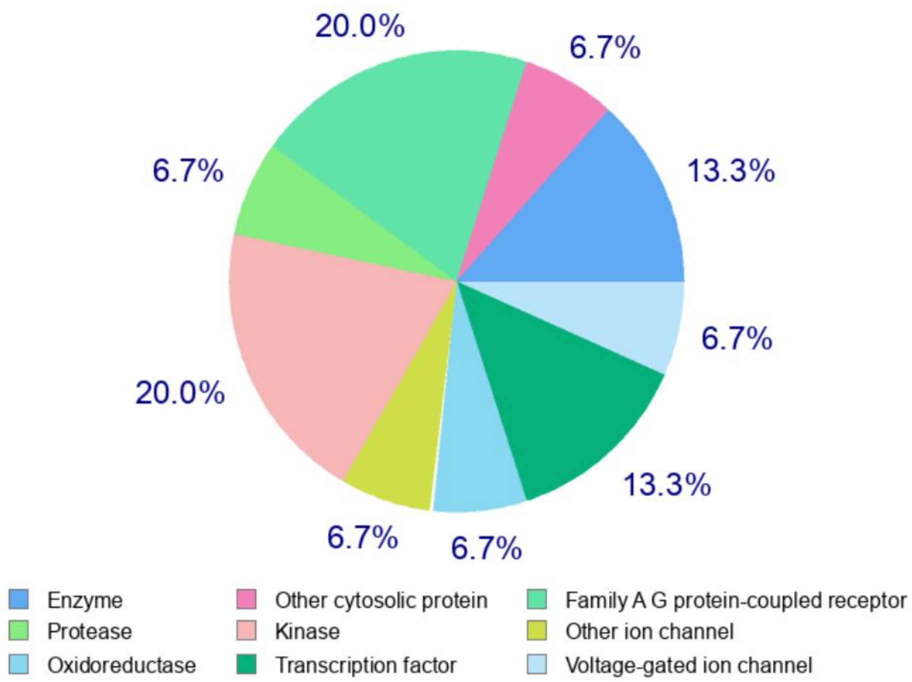

Figure 3: Bioactivity properties and percentage distribution chart for Azadirachtin

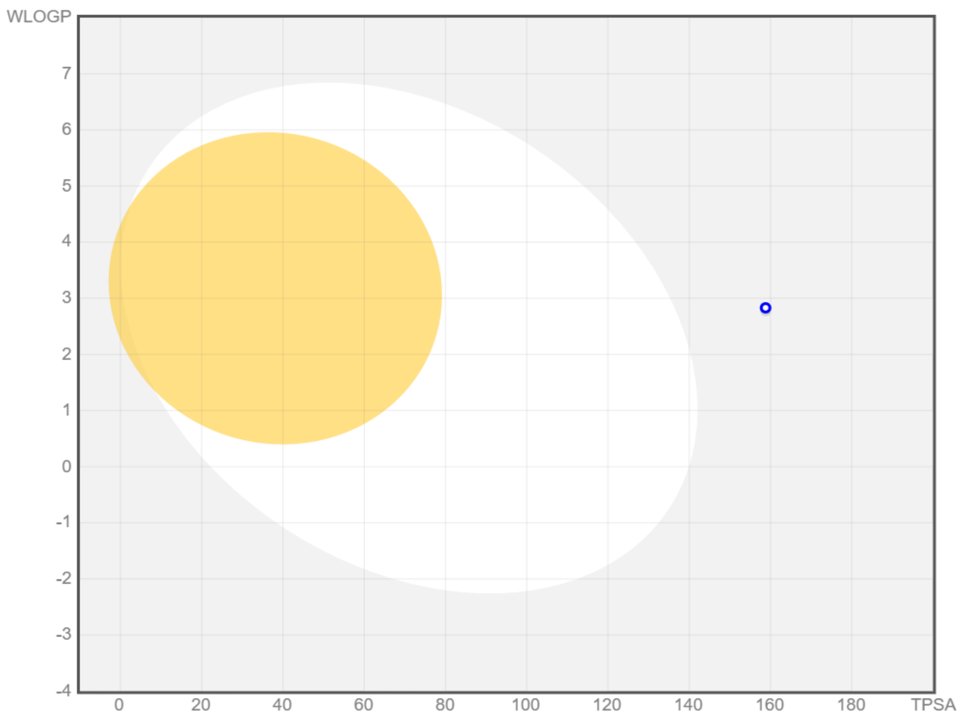

Figure 4: Boiled Egg Model for Azadirachtin as drug candidate