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Unveiling the Pharmacological Potential and Drug-Likeness of Selected Phytocompounds with Anti-Diabetic Activity: A Comprehensive Evaluation of Nimbidin, 4-Hydroxyisoleucine, Eugenol, and β-Caryophyllene

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ABSTRACT

Traditional medicinal plant analysis has grown steadily in recent years due to the fact that plants enable them to supplement contemporary pharmacological methods. As computer mechanics advanced, in silico methods such as network analysis and screening were widely used to shed light on the pharmacological underpinnings of the traditional medicinal plants' functions. These methods, which include network pharmacology, in-silico screening, and pharmacokinetic screening, can identify the medicinal plants of *Azadirachta indica, Trigonella foenum-graecum and Ocimum sanctum* these and mechanism of action and increase the number of active compounds among this. The current study focuses on the pharmacological and pharmacogenetic profiling of these isolated compounds, using the Swiss ADME in-silico ADME tool. Researchers can use the findings of these studies to further explore *in-vitro* and *in-vivo* investigations to uncover the pharmacological underpinnings of traditional medicinal plants.

Keywords: Swiss ADME, Azadirachta indica, Trigonella foenum-graecum, Ocimum sanctum., in-vitro, in-vivo, in-silico, pharmacogenetic.

INTRODUCTION

The use of medicinal plants as herbal remedies is something that ancient humans were well aware of humans depend on herbs for their basic needs, including food, shelter, clothing, flavour, fragrance, and medicines, and over 80% of people in less developed nations worldwide rely on traditional medicine. [1].

For millennia, medicinal plant bioactive compounds have been used to treat distinguished diseases; their possible therapeutic properties make them attractive substitute therapy agents.[2]. Improved and necessary leads against several pharmacological targets including for diseases like cancer, malaria, cardiovascular diseases, diabetes and neurological disorders are provided by the drug discovery in medicinal plants. Ayurveda recommends number of medicinal plants for treatment of different disorders, one of them being *Azadirachta indica, Trigonella foenum-graecum and Ocimum sanctum*, frequently known as flame tree, belongs to family *Meliaceae, Fabaceae* and *Lamiaceae* distributed throughout India and south Asian peninsula (Shah GM, 1959). It has been used by traditional healers to treat pyrexia, inflammation, stomach-aches, and intermittent fevers. The entire plant has been used to treat respiratory infections, dyspepsia, influenza, dysentery, and malaria, as well as to counteract snakebite and some deadly insect stings. [3,4,5]. These include cytotoxic, immunological, anti-inflammatory, anti-oxidant, anti-diabetic, hormone-modulatory, and antimicrobial properties. It has been demonstrated that this plant contains biological activity, liver enzyme modulatory, anti-malaria, anti-angiogenic, and hepato-renal protective activity in a variety of formulations, extracts, and pure chemicals.Particularly for native trees, the main bioactive ingredients, associated

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diseases, and mode of action are not entirely understood. This restriction has limited their extensive application in drug development[6]. Finding bioactive substances that can be used to treat a range of illnesses is the goal of the drug development process. Furthermore, researchers are constantly searching for novel approaches to increase the efficacy of the drug discovery procedure [7]. In order to modernize the use of traditional medicinal plants, it is essential to analyze and predict the pharmacological basis of their therapeutic activity. This includes defining the specific chemical components in these plants and their primary biological functions, as well as taking into account their complex and varied phytoconstituents. Using computer-aided drug design (CADD), also known as the in-silico method, is one way to boost the effectiveness of creating new medications. Through molecular modeling, which essentially screens a large number of bioactive compounds for drug-like qualities and their interactions with pharmacological targets, CADD reduces the duration of the drug development process and the overall costs of research. [8]. One such website is Swiss ADME, which supports drug discovery by predicting ADME parameters, pharmacokinetic properties, drug-like nature, and medicinal chemistry friendliness of one or more small molecules in addition to computing physicochemical descriptors. The goal of the current study was to use the Swiss ADME website to submit the bioactive compounds found in Butea monospermic for *in-silico* ADMET screening in order to assess each ADME's unique behaviour and interpret the findings. [9].

Hyperglycaemia is a symptom of diabetes mellitus (DM), a chronic endocrine system disorder. Chronic long-term hyperglycaemia, which ultimately results in organ failure, is its defining feature. The majority of people on the planet now live with diabetes mellitus, which has become a global public health emergency. By 2045, DM is predicted to affect 783 million people worldwide, up from 537 million in 2021. According to the American Diabetes Association, it is still one of the deadliest diseases and one of the most serious health problems of the twenty-first century. Reduced glucose tolerance, insulin resistance, and oxidative stress brought on by the production of free radicals are some of the factors contributing to the rising incidence of diabetes. Two essential enzymes that help the body absorb carbohydrates in the intestines are amylase and glucosidase. By competing with other molecules that are essential for ROS oxidation, antioxidants are a class of molecules that protect living organisms from ROS species. As a preventive treatment, antioxidants may help mitigate the negative effects associated with oxidative stress. Since oxidative stress plays a major role in the development of diabetes mellitus, antioxidants are thought to be beneficial therapeutic alternatives. Furthermore, research has indicated that glucosidase inhibitors and antioxidants found in natural foods, such as fruits, may have anti-diabetic properties. As a result, scientists worldwide have been paying close attention to these natural substances. Nuts, fruits, vegetables, and plants are rich sources of phytosterols. Numerous *in-vitro* and *in-vivo* studies have demonstrated the diverse biological effects of sitosterol, the most prevalent phytosterol. Numerous scientific studies have demonstrated that sitosterol's antioxidant properties function as a membrane stabilizer and a chemical moderate radical scavenger. [10]

MATERIALS AND METHODS:-

Modelling platform:

The computational analysis, which included absorption, distribution, metabolism, and excretion (ADME) toxicity, was carried out using the Swiss ADME; the operating system was Windows 11 Home Single Language 64-bit, with an Intel ® Core TM i5-6200U CPU @ 2.30 GHz.

Swiss ADME:-

To estimate the individual ADME behaviours of the compounds from Butea monospermic, the Swiss Institute of Bioinformatics (http://www.sib.swiss)'s Swiss ADME software (www.swissadme.ch) was accessed on a web server that shows the Swiss ADME Submission page in Google. The simplified molecular input line entry system (SMILES) defines the list, which has multiple inputs with one input molecule per line. The results are displayed for each molecule in tables, graphs, and an Excel spreadsheet.[11]

Structure and Bioavailability radar:-

The first section displayed the two-dimensional chemical structure with canonical SMILES. Using six physicochemical properties—LIPO (lipophilicity), SIZE, POLAR (polarity), INSOLU (insolubility), INSATU (insaturation), and FLEX (flexibility)—the bioavailability radar provides an initial look at the drug likeness of the molecules of interest. Size: MW between 150 and 500 g/mol, polarity: TPSA between 20 and 130 0A2, solubility: log S not greater than 6, saturation: fraction of carbons in the sp3 hybridization not less than 0.25, flexibility: no more than nine rotatable bonds, and lipophilicity: XLOGP3 between -0.7 and +5.0 (Daina et al., 2017). [12]

Lipophilicity:-

Because it enhances the most successful and instructive physicochemical property in medicinal chemistry (Testa et al., 2000), lipophilicity is a crucial parameter in drug discovery and design (Leeson & Springthorpe, 2007). It can be shown experimentally as distribution coefficients (log D) or partition coefficients (log P). The partition equilibrium of a unionized solute in the presence of water and an immiscible organic solvent is shown by log P. Greater lipophilicity is indicated by larger log P values (Arnott & Planey, 2012). Swiss ADME offers five freely available models—XLOGP3, WLOGP, MLOGP, SILICOS-IT, and iLOGP—to assess a compound's lipophilicity character. A purely atomistic method based on a fragmental system is applied in XLOGP3, an atomistic complement to WLOGP (Wildman and Crippen, 1999). WLOGP, a purely atomistic approach that is based on fragmental system (Wildman and Crippen, 1999) including corrective factors and knowledge-based library (Cheng, 2007) MLOGP is a topological method archetype that proposes a linear relationship with 13 molecular descriptors (Moriguchi et al., 1992 & Moriguchi et al., 1994). Consensus log P o/w is an arithmetic mean of the values predicted by the five suggested methods; SILICOS-IT, a mongrel method, relies on 27 fragments and 7 topological descriptors; iLOGP, a physics-based method, relies on free energies of solvation in n-octanol and water determined by the generalized-born and solvent accessible surface area (GB/SA) model (Daina et al, 2017). [13][14][15][16][17] [18].

Solubility:-

The solvent, ambient temperature, and pressure all have a significant impact on a compound's solubility. The saturation concentration is a measure of the breadth of solubility, meaning that adding more solute does not raise its concentration in the solution (Lachman et al., 1986 & Savjani et al., 2012) [19]. When a drug's maximum dose strength dissolves in 250 milliliters or less of aqueous media with a pH between 1 and 7.5, it is said to be highly soluble. Swiss ADME incorporates two topological methods for predicting water solubility: the first uses the ESOL model (Solubility class: Log S Scale: Insoluble<-10 poorly<-6, moderately<-4 soluble<-2 very<0<highly), and the second is based on an adaptation of Ali et al. (2012) (Solubility class: Log S Scale: Insoluble<-10 poorly<-6, moderately<-4 soluble<-2very<0<highly). According to Yalkowsky and Valvani (1980), both deviate from the basic general solubility equation [20]. Despite avoiding the melting point parameter, there was a strong linear correlation between the experimental and predicted values (R2=0.81 and 0.69, respectively). SILICOS-IT developed the third predictor of Swiss ADME (Solubility class: Log S Scale: Insoluble<-10 poorly<-6, Moderately<-4 Soluble<-2 Very<0<Highly), where the linear coefficient is corrected by molecular weight (R2=0.75). The decimal logarithm of the molar solubility in water (log S) is used for all predicted values. In addition to qualitative solubility classes, Swiss ADME offers solubility in mol/l and mg/ml.

Pharmacokinetics:

On a plot of two calculated descriptors, ALOGP and PSA, respectively, the delineation is located in an area of favourable characteristics for GI absorption. In order to evaluate the predictive power of the model for GI passive absorption and prediction for brain access by passive diffusion, the BOILED-Egg (Brain or Intestine L Estimate D permeation predictive model) is laid out using the Egan egg, an elliptical region that is most populated by well-absorbed molecules. For drug discovery and development, the BOILED-Egg model provides a quick, spontaneous, effective, but noisy way to predict passive GI absorption.[21]. The white region is the space of the molecules with greater extent of absorption by GI tract, the yellow region (yolk) is the space with

highest probability to permeate to the brain [22]. More than 50–90% of therapeutic compounds from CYP's five main isoforms—CYP1A2, CYP3A4, CYP2C9, CYP2C19, and CYP2D6—are biotransformed by CYP isoenzymes. P-gp is widely distributed in intestinal epithelium, which pumps xenobiotics back into the intestinal lumen and from the brain's capillary endothelial cells back into the capillaries. For binary classification, Swiss ADME uses the support vector machine algorithm (SVM) on datasets of known substrates and non-substratum or inhibitors and non-inhibitors. "Yes" will be returned by the resulting molecule. or "No" if the molecule under investigation expected to be substrate for both P-gp and CYP respectively. The SVM model for P-gp substrate was built on 1033 molecules (training set) and tested on 415 molecules (test set), 10 fold CV: ACC=0.72/AUC=0.77, External: ACC=0.88/AUC=0.94 respectively. The SVM model for Cytochrome P-450 1A2 inhibitor molecule was built on 9145 molecule (training set) and tested on 3000 molecules (test set), 10 fold CV: ACC=0.83/AUC=0.90, External: ACC=0.84/AUC=0.91. The SVM model for Cytochrome P-450 2C19 inhibitor molecule was built on 9272 molecule (training set) and tested on 3000 molecules (test set), 10 fold CV: ACC=0.80/AUC=0.86, External: ACC=0.80/AUC=0.87. With a 10 fold CV of ACC=0.78/AUC=0.85 and an external ACC=0.71/AUC=0.81, the SVM model for the Cytochrome P-450 2C9 inhibitor molecule was constructed on 5940 molecules (training set) and evaluated on 2075 molecules (test set). With a 10 fold CV of ACC=0.79/AUC=0.85 and an external ACC=0.81/AUC=0.87, the SVM model for the Cytochrome P-450 2D6 inhibitor molecule was constructed using 3664 molecules (training set) and evaluated on 1068 molecules (test set). With a 10 fold CV of ACC=0.77/AUC=0.85 and an external ACC=0.78/AUC=0.86, the SVM model for the Cytochrome P-450 3A4 inhibitor molecule was constructed on 7518 molecules (training set) and evaluated on 2579 molecules (test set).[23]

Drug Likness:-

Swiss ADME performs filtering of chemical libraries to exclude molecules with peculiarities incompatible with an acceptable pharmacokinetics profile with five disparate ruled based filters elemental from considerable Pharma companies intended to improve the condition of proprietary chemical collections (Daina *et al*., 2017) [24]. The Lipinski filter (Pfizer) is the pioneer rule of five that characterize small molecules based on physicochemical property profiles which includes Molecular Weight (MW) less than 500, MLOGP ≤ 4.15, N or O ≤ 10, NH or OH ≤ 5. Lipinski considers stringently that all nitrogen and oxygen as H-bond acceptor and all nitrogen and oxygens with at least one hydrogen as H-bond donors. Besides, aliphatic fluorine's are acceptors and alanine nitrogen are neither donors nor acceptors (Lipinski *et al*., 2001). The Ghose filter (Amgen) describes small molecules stationed on physicochemical property, existence of functional groups and substructures. The qualifying range includes of molecular weight is between 160 and 480 Da, WlogP is between -0.4 to 5.6, molar refractivity (MR) is between 40 to 130 for total number of atom; the qualifying range is between 20 and 70 atoms in a small molecule (Ghose *et al*., 1998 & Ghose *et al*., 1999). [25][26]. Veber filter (GSK filter) model symbolize molecules as drug like if they have ≤ 10 rotatable bonds and a TPSA equal to or less than 140 Å2 with 12 or fewer H-bond donors and acceptors. Compounds with these properties will have good oral bioavailability, reduced TPSA correlates increased permeation rate, increased rotatable bonds counts has a negative effect on the permeation rate (Veber *et al*., 2002) [27]. Egan filter (Pharmacia filter) anticipates drug absorption depend on processes involved in membrane permeability of a small molecule. These model symbolizes molecule as a drug like if they have WLOGP ≤ 5.88 and TPSA ≤ 131.6 respectively. The Egan computational model for human passive intestinal absorption (HIA) of small molecule accounts for active transport and efflux mechanisms and is therefore robust in predicting absorption of drugs (Egan *et al*., 2000)[28]. Muegge filter (Bayer filter) is a self-reliant Pharmacophore point filter that segregates drug like and non-drug like molecules. This model symbolizes molecule as a drug like if they have molecular weight between 200 to 600 Da, XLOGP between -2 and 5, TPSA ≤ 150, Number of rings ≤ 7, Number of carbon atoms > 4, number of heteroatoms > 1, number of rotatable bonds ≤ 15, H-bond acceptor ≤ 10, H-bond donor ≤ 5 respectively. Abbott bioavailability score

seeks to predicts the probability of a compound to have at least 10% oral bioavailability in rat or measurable Caco-2 permeability which predicts probability of a compound to have F>10% based on the predominant charge at biological pH in a rat model. It focusses on fast screening of chemical libraries to select best molecules to be synthesized (Martin, 2005) [29]

Medicinal Chemistry:-

These sections are intended to support medicinal chemists in their ongoing efforts to discover new drugs. Regardless of the protein targets, PAINS (Pan Assay Interference Compounds, also known as frequent hitters or promiscuous compounds) are molecules that exhibit strong assay responses. Notably, these compounds have been shown to be active in a wide range of assays, which may serve as promising avenues for future research. If such moieties are detected in the molecule being evaluated, Swiss ADME returns warnings (Baell & Holloway, 2010).[30]. In order to expand lead optimization opportunities, Brenk takes into account compounds that are smaller, less hydrophobic, and not those that fall under "Lipinski's rule of five" in another model. This came after substances with potentially mutagenic, reactive, and un favourable groups—such as nitro groups, sulphates, phosphates, 2-halopyridines, and thiols—were eliminated. The Brenk model limits the number of heavy atoms to between 10 and 27, the ClogP/ClogD to between 0 and 4, and the number of hydrogen-bond donors and acceptors to less than 4 and 7, respectively. Furthermore, according to Brenk et al. (2008), only compounds with limited complexity—defined as having fewer than eight rotatable bonds, fewer than five ring systems, and no ring systems with more than two fused rings—are deemed medicinal. In high throughput screening (HTS), the lead likeness concept is intended to yield leads with exceptional affinity that promise to exploit additional interactions during the lead optimization stage. Chemical changes to leads are likely to reduce their size and increase their lipophilicity, making them less hydrophobic than molecules that resemble drugs. Using a rule-based approach, lead optimization has been carried out using molecules with molecular weights between 100 and 350 Da and ClogP between 1 and 3.0. These molecules are widely regarded as being superior to those of drug-like compounds and, thus, lead-like (Teague et al., 1999; Hann & Keseru, 2012).[31], [32]

RESULT:-

TABLE:-1, General Characteristics of Phytoconstituents

Sr. No.	Name of Molecule	PUB CHEM ID	Molecular Formula	SMILES	Molecular Weight (g/mol)
1	Nimbidin	101306757	C26H34O6	OC1CC (O) C2 (C3C1(C)C1CC(=O) C4 (C(=CCC4c4ccoc4) C1 (C) C (C3OC2)O)C) C	442.54
2	4-Hydroxy-isoleucine	6918732	C6H13NO3	C [C@H] ([C@H] ([C@@H] (C(=O)O) N) C) O	147.17
3	Eugenol	3314	C10H12O2	C=CCc1ccc (c(c1)OC) O	164.20
4.	Caryophyllene	5281515	C15H24	C/C/1 = C\CCC (=C) [C@@H] 2 [C@@H] (CC1) C(C2) (C)C	204.35

TABLE:-2, Lipophilicity of the Phytoconstituents

Sr. No.	Molecule Name	ilogP	XlogP3	WlogP	Mlog P	Silico IT	Consensus Log Po/w
1	Nimbidin	2.69	1.46	2.82	1.50	2.74	2.24
2	4-Hydroxy isoleucine	0.83	-2.82	-0.58	-2.67	-0.82	-1.21
3	Eugenol	2.37	2.27	2.13	2.01	2.48	2.25
4	Caryophyllene	3.25	4.38	4.73	4.63	4.19	4.24

TABLE:-3, Water solubility of the Phytoconstituents

Sr. No.	Mol. Name	ESOL				Ali				SILICOS-IT			
		Log S	Solubility		Class	Log S	Solubility		Class	Log S	Solubility		Class
			Mg/ ml	Mol/ l			Mg/ ml	Mol/ l			Mg/ ml	Mol/ l	
1	Nimbidin	-3.55	1.24 e-01	2.80 e-04	Soluble	-3.17	3.00 e-01	6.78 e-04	Solubility	-4.03	4.17 e-02	9.42e -05	Moderately Soluble
2	4-Hydroxy-isoleucine	1.22	2.45e +03	1.67e +01	Highly Soluble	1.62	6.14e +03	4.17 e+01	Highly Soluble	0.78	8.89e+ 02	6.04e +00	Soluble
3	Eugenol	2.46	5.69 e-01	3.47 e-03	Soluble	2.53	4.90 e-01	2.98 e-03	Soluble	-2.79	2.65 e-01	1.61e -03	Soluble
4.	Caryophyllene	3.87	2.78 e-02	1.36 e-04	Soluble	-4.10	1.64 e-02	8.01 e-05	Moderatel y Soluble	-3.77	3.49 e-02	1.71e -04	Soluble

Table:-4, Pharmacokinetics

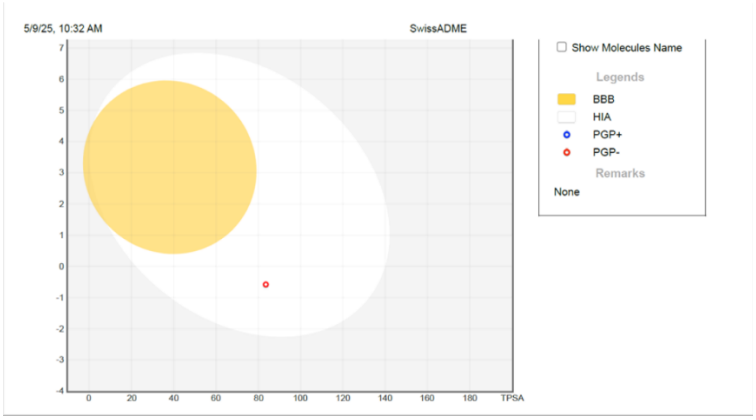
Sr. No.	Molecule Name	BBB Permanent	P-gp Substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Log Kp (cm/s)
1	Nimbidin	No	Yes	No	No	No	Yes	No	-7.96
2	4-Hydroxy-isoleucine	No	No	No	No	No	No	No	-9.20
3	Eugenol	Yes	No	Yes	No	No	No	No	-5.69
4	Caryophyllene	No	No	No	Yes	Yes	No	No	-4.44

Table:- 5 Drug Likness

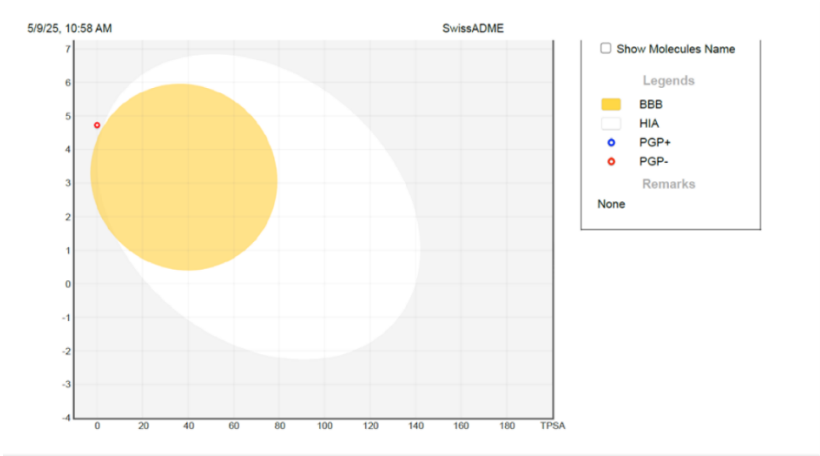
Sr. No.	Molecule Name	Lipinski's Rule	Veber	Egan	Muegge	Bioavailability score
1	Nimbidin	Yes	Yes	Yes	Yes	0.55
2	4-Hydroxy-isoleucine	Yes	Yes	Yes	Yes	0.55
3	Eugenol	Yes	Yes	Yes	No, 1 violation MW<200	0.55
4	Caryophyllene	Yes, 1 Violation MLOGP>4.15	Yes	Yes	No. 1 Violation Heteroatoms<2	0.55

Table:-6 Medicinal Chemistry Properties of Phytoconstitutents

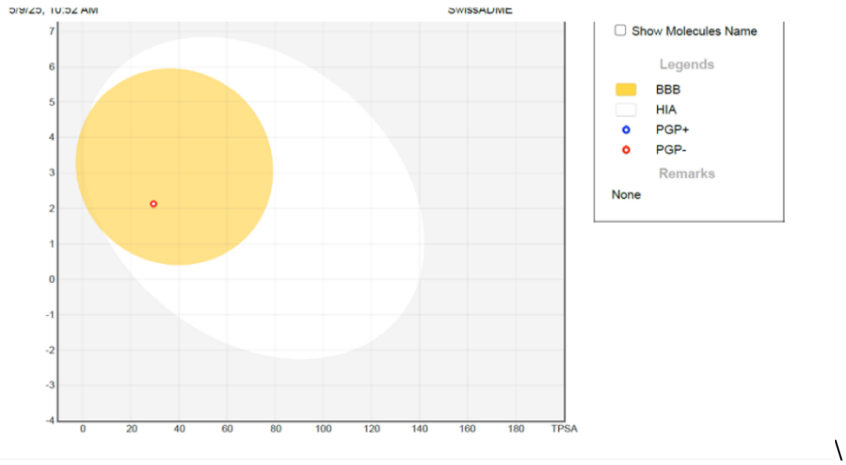
Sr. No.	Molecule Name	Pains	Brenk	Leadlikeness	Synthetic accessibility
1	Nimbidin	0 alert	1 alert	No. 1 violation, MW>350	6.18
2	4-Hydroxy-isoleucine	0 alert	0 alert	No, 1 Violation MW>250	2.31
3	Eugenol	0 alert	1 alert	No, 1 Violation MW<250	1.58
4	Caryophyllene	0 alert	1 alert	No.2 Violations, MW<250 XLOGP3>3.5	4.51



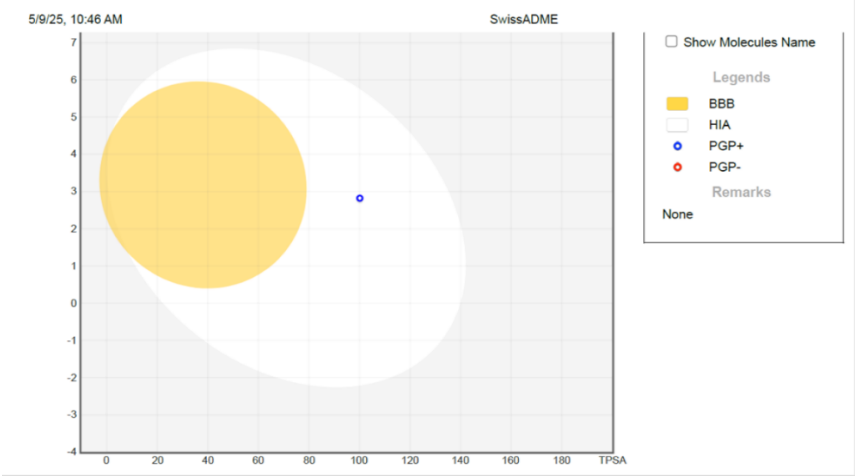
Pic:- 4-hydroxy isoleucine Swiss ADME with boiled egg



Pic:- Caryophyllene Swiss ADME with boiled egg



Pic:- Eugenol Swiss ADME with boiled egg



Pic:- Nimbidin Swiss ADME with boiled egg

CONCLUSION: -

With the rapid increase in biological and chemical information, Computational technology has been dramatically reshaping research and development pathways in drug candidate identification. Use of different software in drug discovery and development process is widely appreciated in terms of implementation, time and money. A freely available Swiss ADME, a web-based tool is presented for these studies to evaluate the ADME properties of phytoconstituents present in *Azadirachta indica, Trigonella foenum-graecum, Ocimum sanctum* plant. This information can be used as a primary tool for further evaluating the biological and pharmacological properties of the plant.

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