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COMPUTER-AIDED PREDICTION OF BIOLOGICAL ACTIVITIES AND TOXICOLOGICAL PROPERTIES OF THE CONSTITUENTS OF *SOLANUM TRILOBATUM*

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ABSTRACT
Solanum trilobatum Linn., belongs to the family of Solanaceae and is commonly used as traditional medicine for the treatment of respiratory illness by the peoples of Indian subcontinent. This plant contains steroidal alkaloid and glycosides. The medicinal use of plant constituents remain unclear, hence the present study was planned to predict the biological activities and toxicological properties of constituents of *S. trilobatum* using online prediction tools. The biological activities and toxicological properties of the constituents of*S. trilobatum* were predicted using PASS and lazar online tools, respectively.The predicted biological activities of plant constitutes showed presence of various activities which includes anti-inflammatory, antineoplastic, respiratory analeptic, hepatoprotectant, hypolipidemic, mucomembranous protective and hypercholesterolemic activities. Toxicity prediction of the constituents of *S. trilobatum* did not show any major toxicity. Computer aided prediction tools were found useful for initial prediction of the activities of the constituents of *S. trilobatum* which could lead to further exploration.

Keywords: Computer-aided prediction, biological activity, *Solanum trilobatum*.

INTRODUCTION
Solanum trilobatum Linn., (Thuthuvalai in tamil; Climbing Brinjal in English) belongs to the family of Solanaceae and this plant parts such as berries and flowers are used for the treatment of respiratory illness which includes cough and chronic bronchitis. The fruit and leaves of *S. trilobatum* contains steroidal alkaloid, solasodine and beta-solamarine.[1,2] The biological activity of the compound is depends on physio-chemical properties of the compound. The biological screening of the any compound is a time taking process, which can be narrow down by *in silico* screening methods or computer-aided predictions. The computer-aided prediction may narrow down the research and minimize the biological wastage.
The bioinformatics tool such as Prediction of activity spectra for substances (PASS) prediction, lazar predication, etc. will help to understand the biological activities of any compounds.

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PASS prediction tool is constructed using 20000 principal compounds from MDDR database and contains over 180000 biologically relevant compounds and is constantly updated.[3] Lazar predication is an open source predictive toxicology software developed by Machine Learning Lab (University Freiburg) in 2004. Prediction of biological activities of any compound may reduce the pre-clinical exercise and minimize the cost of the experiment. Hence the present study was planned to predict the biological activities and toxicological properties of the constituents of *S. trilobatum* using *in silico* tools.

METHODS
Plant profile: Solanum trilobatum Linn., (Solanaceae) prickly diffuse, bright green perennial herb, woody at the base, 2-3 m height grown in dry places of Indian sub-continent. Leaves are deltoid/ triangular, irregularly lobed and flowers are in purple in color. *S. trilobatum* is reported to have hepatoprotective, antimicrobial, larvicidal and anticancer activity.[4] Govindan *et al.,* was studied the clinical efficacy of the whole plant powered against bronchial asthma and conformed its traditional climb.[5]

Table – 1: Canonical SMILES format of constituents of *S. trilobatum*

Phytoconstituents	Molecular formula	Canonical SMILES
Soladunalinidine	$C_{27}H_{46}N_2O$	CC1CCC2(C(C3C(O2)CC4C3(CCC5C4CCC6C5(CCC(C6)N)C)C)C)NC1
Tomatidine	$C_{27}H_{45}NO_2$	CC1CCC2(C(C3C(O2)CC4C3(CCC5C4CCC6C5(CCC(C6)O)C)C)C)NC1
Solasodine	$C_{27}H_{43}NO_2$	CC1CCC2(C(C3C(O2)CC4C3(CCC5C4CC=C6C5(CCC(C6)O)C)C)C)NC1
Beta-solamarine	$C_{45}H_{73}NO_{15}$	CC1CCC2(C(C3C(O2)CC4C3(CCC5C4CC=C6C5(CCC(C6)OC7C(C(C(C(O7)CO)OC8C(C(C(C(O8)C)O)O)O)O)OC9C(C(C(C(O9)C)O)O)O)C)C)C)NC1
Sobatum/ Clionasterol	$C_{29}H_{50}O$	CCC(CCC(C)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)O)C)C)C(C)C
Solaine	$C_{45}H_{73}NO_{15}$	CC1CCC2C(C3C(N2C1)CC4C3(CCC5C4CC=C6C5(CCC(C6)OC7C(C(C(C(O7)CO)O)OC8C(C(C(C(O8)CO)O)O)O)O)OC9C(C(C(C(O9)C)O)O)O)C)C)C
Diosogenin	$C_{27}H_{42}O_3$	CC1CCC2(C(C3C(O2)CC4C3(CCC5C4CC=C6C5(CCC(C6)O)C)C)C)OC1

Table – 2: Predicted biological activity of constituents of *S. trilobatum*

Phytoconstituents	Predicted activities
Soladunalinidine	• Prediction of biological activities of soladunalinidine shows presence of spasmolytic, anti-inflammatory and antineoplastic activities. • Soladunalinidine predicted for inhibitory activity for the enzyme glyceryl-ether monooxygenase.
Tomatidine	• Prediction of biological activities of tomatidine shows presence of anti-inflammatory, spasmolytic, antineoplastic, diuretic inhibitor and contraceptive activities. • Tomatidine predicted for inhibitory activity for the enzymes such as acylcarnitine hydrolase, alkylacetylglycerophosphatase, glyceryl-ether monooxygenase, alkenylglycerophosphocholine, testosterone 17 beta-dehydrogenase (NADP+) and dolichyl-diphosphooligosaccharide-protein glycotransferase.
Solasodine	• Prediction of biological activities of solasodine shows presence of predicted anti-inflammatory, antineoplastic, contraceptive and diuretic inhibitor activities. • Solasodine predicted for inhibitory activity for the enzymes such as testosterone 17beta-dehydrogenase (NADP+), glyceryl-ether monooxygenase, oxidoreductase. • Solasodine predicted for cholesterol antagonist property.
Beta-solamarine	• Prediction of biological activities of beta-solamarine shows presence of cholesterol antagonist, antineoplastic, respiratory analeptic, anti-inflammatory, anticarcinogenic, antiprotozoal (leishmania), antifungal, immunosuppressant, diuretic inhibitor, analeptic, hepatoprotective and chemopreventive activities. • Beta-solamarine indicated (predicted) for the treatment of proliferative diseases, dementia and vascular dementia. • Beta-solamarine predicted for inhibitory activity for the enzymes such as

	glyceryl-ether monooxygenase, CDP-glycerol glycerophosphotransferase, dolichyl-diphosphooligosaccharide-protein glycotransferase, alkenylglycerophosphocholine hydrolase, bilirubin oxidase and oxidoreductase.
Sobatum/ Clionasterol	• Prediction of biological activities of sobatum shows presence of anti-hypercholesterolemic, cholesterol antagonist, hypolipemic, anesthetic general, chemopreventive, respiratory analeptic, hepatoprotectant, proliferative diseases treatment, antihyperlipoproteinemic, antieczematic, antipruritic, dermatologic, mucomembranous protective, antiosteoporotic and immunosuppressant activities. • Sobatum indicated (predicted) for the treatment of adenomatous polyposis, bone diseases and prostate disorders. • Sobatum predicted for inhibitory activity for the enzymes such as DELTA14-sterol reductase, prostaglandin-E2 9-reductase, alkenylglycerophosphocholine hydrolase, alkylacetylglycerophosphatase, acylcarnitine hydrolase, testosterone 17beta-dehydrogenase (NADP+) inhibitor, oxidoreductase, dextranase, linoleatediol synthase inhibitor, cholestanetriol 26-monooxygenase, alkenylglycerophosphoethanolamine hydrolase, 27-hydroxycholesterol 7alpha-monooxygenase, cholesterol oxidase, protein-disulfide reductase (glutathione), N-(long-chain-acyl)ethanolamine deacylase, glucan endo-1,3-beta-D-glucosidase, cholesterol synthesis, peptidoglycan glycosyltransferase, trans-1,2-dihydrobenzene-1,2-diol dehydrogenase, glyceryl-ether monooxygenase, alcohol O-acetyltransferase, cycloartenol synthase, plasmanylethanolaminedesaturase, and lipoprotein lipase.
Solaine	• Prediction of biological activities of solaine shows presence of respiratory analeptic, analeptic, cholesterol antagonist, antiprotozoal (leishmania), hepatoprotective and immunosuppressant activities. • Solaine indicated (predicted) for the treatment of Dementia. • Solaine predicted for inhibitory activity for the enzymes such as CDP-glycerol glycerophosphotransferase, beta-adrenergic receptor kinase, G-protein-coupled receptor kinase, glyceryl-ether monooxygenase, dolichyl-diphosphooligosaccharide-protein glycotransferase, alkenylglycerophosphocholine hydrolase, glucan endo-1,3-beta-D-glucosidase, oxidoreductase and benzoate-CoA. • Solaine predicted for transcription factor NF kappa B stimulant.
Diosogenin	• Prediction of biological activities of diosogenin shows presence of cholesterol antagonist, hypolipemic, nootropic, chemopreventive, apoptosis agonist, antineoplastic, anticarcinogenic, anti-inflammatory, immunosuppressant, antiprotozoal (leishmania), antineoplastic (pancreatic cancer) and antifungal activities. • Diosogenin indicated (predicted) for the treatment of proliferative diseases. • Diosogenin predicted for inhibitory activity for the enzymes such as glyceryl-ether monooxygenase, bilirubin oxidase, beta-adrenergic receptor kinase inhibitor, G-protein-coupled receptor kinase, dolichyl-diphosphooligosaccharide-protein glycotransferase, 27-Hydroxycholesterol 7alpha-monooxygenase, phosphatase, testosterone 17 beta-dehydrogenase (NADP+) inhibitor, alkenylglycerophosphocholine hydrolase, oxidoreductase, galactolipase, alkylacetylglycerophosphatase and DELTA14-sterol reductase.

Table – 3: Predicted toxicological properties of constituents of *S. trilobatum*

Compound	Prediction					
	DSSTox Carcinogenic Potency DBS Mutagenicity	Kazius-Bursi Salmonella mutagenicity	DSSTox Carcinogen-ic Potency DBS Rat	DSSTox Carcinogenic Potency DBS Mouse	FDA v3b Maximum Recommended Daily Dose mmol	EPA v4b Fathead Minnow Acute Toxicity LC50_mmol
Soladunalinidine	Non-Mutagenic	Non-Mutagenic	Non-Carcinogen	Non-Carcinogen	0.00296	Not predicted
Tomatidine	Non-Mutagenic	Non-Mutagenic	Non-Carcinogen	Non-Carcinogen	0.00292	Not predicted
Solasodine	Non-Mutagenic	Non-Mutagenic	Non-Carcinogen	Carcinogen (Confidence 0.718)	0.00226	0.0037
Beta-solamarine	Non-Mutagenic	Non-Mutagenic	Non-Carcinogen	Carcinogen (Confidence 0.671)	0.00794	0.0037
Sobatum/ Clionasterol	Non-Mutagenic	Non-Mutagenic	Non-Carcinogen	Carcinogen (Confidence 0.723)	0.00746	0.0037
Solaine	Non-Mutagenic	Non-Mutagenic	Non-Carcinogen	Carcinogen (Confidence 0.645)	0.00820	0.0037
Diosogenin	Non-Mutagenic	Non-Mutagenic	Non-Carcinogen	Carcinogen (Confidence 0.728)	0.00292	0.0037

In various studies, plant showed the presence of carbohydrates, reducing sugar, saponins, phytosterols, tannins, flavonoids, anthroquinone, amino acid and glycosides. The identified constituents of *S. trilobatum* is soladunalinidine, tomatidine, solasodine, beta-solamarine, sobatum, beta-solamarine, solaine, glycoalkaloid and diosogenin.[1]

Prediction of biological activities of constituents of S. trilobatum:

Soladunalinidine, tomatidine, solasodine, beta-solamarine, sobatum, solaine and diosogenin are the compound present in the leaves *S. trilobatum*. The canonical SMILES format of phytoconstituents of *S. trilobatum* were obtained from PubChem [https://pubchem.ncbi.nlm.nih.gov/] and used for biological activity prediction.

Prediction of biological activity spectra and toxicity profile were carried out with online PASS prediction tools (www.way2drug.com; www.way2drug.com/PASSOnline/index.php), and lazar toxicity prediction tools (http://lazar.in-silico.de/) respectively in the period between June andJuly 2015. The input canonical SMILES format of solasodine, beta-solamarine, sobatum, solaine, and diosogenin were used for prediction of biological activity spectra and toxicity properties [Table – 1].

RESULTS AND DISCUSSION

The predicted biological activitiesof constituents of *S. trilobatum* at 70% levels showed various biological actions which were summarized in Table – 2. Most of the *S. trilobatum* constituents showed the presence of anti-inflammatory, antineoplastic, respiratory analeptic, hepatoprotectant, hypolipemic, hypercholesterolemic and mucomembranous protective activities at various *Pa: Pi* levels. Toxicity prediction of the constituents of *S. trilobatum* didn't showed any major toxicity, carcinogenicity and mutagenicity [Table – 3].

The predicted activates of soladunalinidine, tomatidine, solasodine, beta-solamarine, sobatum, solaine and diosogenin were summarized in the Tables 2 and 3. In that few of the activities were already proven in various pre-clinical experiments. Tomatidine, solasodine and sobatum has significant acetylcholinesterase and anti-inflammatory activities.[6,7] In *in vitro* experiment tomatidine inhibited the lipopolysaccharide (LPS) liberated nitric oxide synthase and cyclooxygenase-2 expression in mouse macrophage cells.[7] The predicted activity for the same also showed anti-inflammatory at *Pa: Pi* level of 0.886: 0.005. Tomatidine also has anti-cancer and anti-hyperlipidemic activities which also predicted at *Pa: Pi* level of 0.725: 0.005 and 0.696: 0.009respectively.[8-10] In DPPH method, two steroid glycoside (solasodine, tomatidine) of *S. trilobatum* showed antioxidant activity which was not detected at 70% *Pa: Pi* level.[11] The anticancer activity of beta-solamarine was predicted 0:886: 0.005 and same was reported by Kupchan *et al*.[12]

The extract and constituents of *S. trilobatum* known to have analgesics, anti-inflammatory and anti-allergic activities and other predicted activities are remaining unclear. From this study the predicted activities of constituents of *S. trilobatum* may give lead to the further studies.

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