ANTIHYPERLIPIDEMIC ACTIVITY OF ETHANOLIC FRUIT EXTRACT OF SURATTENSE NIGHTSHADE

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Abstract:

Hyperlipoproteinemea and is considered as a key risk factor for cardio vascular disorders (CVD). The causes of hyperlipidemia are mainly life style changes (poor diet, smoking, alcohol). At least 3/4th of India's population has abnormal levels of cholesterol that increases the risk of cardio vascular diseases according to a study commissioned by the Indian Council of Medical Research (ICMR) HDL or good cholesterol is universally low across the country. Indigenous systems of medicine like Siddha, Ayurveda and Unani mainly use medicinal plants for treatment of various ailments of human beings and animals. With the development of these systems, herbal plants are being sought after, both by clinicians and patients in search for new cure of diseases. All the molecules possess good partition co-efficient except Carpesterol. Carpesterol and Diosgenin does not show desirable binding with human serum albumin whereas all other molecules have good effective binding with human serum albumin.[72] Absorption value less than 25% are, α-Solamargine, Solanine, Solasonine and more than 80% are Carpesterol, Diosgenin, Solasodine, Coumarin, Scopletin, Solanidine. Apigenin, Caffeic acid, Esculetin, Esculin, Methyl caffeate, Scopletin, Coumarin have the value as 0; Solasodine, Diosgenin, Solanidine, Tomotidenol have the value as 1; Carpesterol have the value as 2; α- Solamargine, Solanine, Solasonine have the value as 3.

Keywords: Hypercholestremia, Polypropylene cages, Atrovastatin, Silico toxicity, Docking

INTRODUCTION

The study group found hypercholestremia in 18.3% of Tamilnadu population[3]. The common treatment for hyperlipidemia is prescription of statins, bile acid sequestrants, fibric acid derivatives and nicotinic acid. Adverse effects associated with these drugs are headache, nausea, bowel upset, rashes, sleep disturbance, abnormal liver function, myositis, hyperuricemia, rise in serum transaminase, muscle tenderness and rise in Creatine Phosphokinase levels. To make it worse, 72.3% had low levels of HDL (good cholesterol), 11.8% had high levels of LDL (bad cholesterol). HDL or good cholesterol is universally low across the country[4].

Traditional treatment

Indigenous systems of medicine like Siddha, Ayurveda and Unani mainly use medicinal plants for treatment of various ailments of human beings and animals. With the development of these systems, herbal plants are being sought after, both by clinicians and patients in search for new cure of diseases[5].

HYPERLIPIDEMIA

Dyslipidemia refers to the alteration of one or many of the lipoproteins which may be an elevation of triglycerides or low density lipoprotein cholesterol, or decrease in high-density lipoprotein cholesterol. Elevation of lipid levels alone is termed as Hyperlipidemia.[6]

Hyperlipidemia- causes

Environmental factors[7]

Genetic factors

Secondary causes

Environmental factors[8]

Dietary factors and obesity.

Genetic factors[9]

Occur due to single gene or multiple gene defects.[10]

Secondary causes[11]

Diabetes mellitus

Hypothyroidism

Lipodystrophy

Alcoholism

Use of anti-hypertensive drugs, diuretics, Glucocorticoid, Protease inhibitor

Obstructive liver disease

Nephritic syndrome

Acute intermittent porphyria

Pathophysiology of hyperlipidemia

Exogenous pathway of lipids[12]

MATERIAL AND METHOD

Collection and identification of plant material

The fruits of *Surattense Nightshade*, were collected from the botanical garden Balaghat.

Preparation of plant extract

Chemicals

Analytical grade of 90% ethanol was bought from SPU chemical store Balaghat.

Extraction

The fruits were washed with tap water, shade dried at room temperature and then subjected to size reduction to a coarse powder by using wiley mill.[13] The powdered fruit material was packed in a Soxhlet apparatus and extracted with 90% ethanol. The extraction was continued until the color of the solvent in the siphon tube became colorless.[14] The ethanolic extract was concentrated in a rotary evaporator and this concentrated ethanolic extract of fruits of *Surattense Nightshade* was used for the *in vivo* studies[15].

***In* vivo screening**

Experimental animals

Healthy wistar rats (150-200g) were procured from Animal Experimental Laboratory, Agrasen college of Pharmacy Dagania, Durg, C.G. The study was approved by Institutional Animal Ethics Committee which is certified by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India[16].

Maintenance of animals

The animals were kept in clean and dry polypropylene cages with stainless steel top grill having facilities for pelleted food and water[19]. The animals were maintained in a well-ventilated animal house in 12 hours and 12 hours dark cycle at a temperature of 28ºC ± 2ºC and they were acclimatized to laboratory conditions for 10 days prior to the commencement of the experiment. The animals were fed with standard pellet diet and water *ad libitum*.[18] All animal experiments were performed according to the ethical guidelines suggested by Institutional Animal Ethics Committee (IAEC). Paddy husk was used as bedding material and changed twice a week.[20]

Acute toxicity studies

Acute toxicity study has been already performed on the fruits of *Surattense Nightshade* Fruits of *Surattense Nightshade* were administered orally asa single dose to mice at different dose levels of 250, 500, 1000 and 2000mg/kg BW.[21] Animals were observed periodically for the symptoms of toxicity and death within 24h and then daily for 14 days. Fruits of *Surattense Nightshade* produced no mortality at 2000mg/kg. Hence 1/10th (200mg/kg) and 1/5th (400mg/kg) of this dose

was chosen for the antihyperlipidemic study.[22]

Evaluation of anti hyperlipidemic activity

The model used to evaluate the anti hyperlipidemic activity was Cholesterol diet induced hyperlipidemia in rats.[23]

Cholesterol diet induced hyperlipidemia in rats

Cholic acid and Cholesterol powder were bought from Agrasen college of pharmacy Dagania, Durg, C.G. All the chemicals used in the study were of analytical grade from SPU Balaghat.

Procedure

Hyperlipidemia was induced in rats by administration of cholesterol diet for 30 days. Cholesterol diet consists of Cholesterol 12%, Cholic acid 1%, Sucrose 40% and Coconut oil 10%. All the animals were weighed and divided into five groups, each group containing six animals. The details of the grouping are given in Table 1.

Table 1: Study design

S. No	Group (n=6)	Name of the group	Treatment schedule
1	I	Normal control	Rat chow diet for 30 days.
2	II	Hyperlipidemic control	Cholesterol diet for 30 days.
3	III	Standard	Cholesterol diet for 30 days + Atorvastatin 2mg/kg p.o from 16^{th} to 30^{th} day.
4	IV	Low dose	Cholesterol diet for 30 days + EEFSV 200mg/kg p.o from16^{th} to 30^{th} day.
5	V	High dose	Cholesterol diet for 30 days + EEFSV 400mg/kg p.o. from 16^{th} to 30^{th} day.

The blood samples were collected on 0, 15^{th} and 30^{th} day of the experiment from the retro orbital sinus using glass capillary. The blood was allowed to clot for 30 minutes at room temperature. The clear serum was separated by centrifugation at 2500 rpm for 10 minutes and used for the determination of biochemical parameters.

Parameters evaluated

Changes in body weight

The body weight of each animal in every group were recorded on, 15th and 30th day of study period and the changes in body weight were noted[24].

Biochemical analysis

The serum was subjected to the following evaluation

Total Cholesterol (TC)[25]

Triglycerides (TG)

High density lipoprotein (HDL)

Very Low density lipoprotein (VLDL)

Low density lipoprotein (LDL)

***IN SILICO* STUDIES**

Review of literature showed that fruits of *Surattense Nightshade* havethe phytochemicals like alkaloid, phenolic compounds, flavonoid, glycoalkaloid, sapogenin, coumarin, steroidal alkaloid, glycoside, carbohydrate, triterpenoid, steroids, fatty acids, amino acids, etc. Alkaloid, phenolic compounds, flavonoid, glycoalkaloid, sapogenin, coumarin, steroidal alkaloids were taken up for *in silico* toxicity, docking and drug likeness studies.[26]

***In silico* toxicity prediction**

Toxicity screening is done *in silico* using OSIRIS property explorer.[48] Itis a web based software available on the Organic Chemistry Portal. Using this prediction tool, mutagenicity, tumorogenicity, skin irritancy and reproductive effects can be calculated.[27] The prediction properties depends on a precompiled set of structure fragment that gives rises to toxicity alerts, if they are found in the structure currently drawn.[28] These fragment lists is created by rigorously shredding all compounds in the data base known to be active in a certain toxicity class. During the shredding any molecule is first cut at every rotatable bonds leading to a set of core fragments[29]. OSIRIS software is used to calculate various drug relevant properties of chemical structures. The results are color coded.[30] The green color represents that the compound is non-toxic. Yellow and red color indicates moderate and severe toxicity of the chemical respectively.[31]

Docking

In this study, Glide (Grid based Ligand Docking with Energetics) program was used for screening the isolated compounds. Glide automatically searches for favorable interactions between ligand molecule and the receptor in different conformations. Docking procedure using Glide includes the following steps.[32]

RESULTS AND DISCUSSION

In vivo anti hyperlipidemic activity

Effect of ethanolic extract of fruits of *Surattense Nightshade*on bodyweight of animals

The results are tabulated in table 3. Hyperlipidemic rats showed an increase in body weight whereas the weight of the control rats remained the same. Administration of Atrovastatin and ethanolic extract of fruit of *Surattense Nightshade* for 15 days significantly reduced the weight and brought back the BW towards normal.

Table 2: Effect of Cholesterol diet on body weight and the effect of Atorvastatin and EEFSV on the weight of hyperlipidemic rats

Group	Body Weight (g)		
	Induction period		Treatment period
	0 Day	15th Day	30th Day
I	181.5±0.957	181.5±1.258	182.16±1.067
II	179.83±1.343	200.33±0.942[a]	220.16±1.213[b]
III	180.83±1.34	199.83±1.863[a]	184.5±1.384[b]
IV	181.16±1.067	200.66±1.374[a]	186.83±1.674[b]
V	179.83±1.462	201.16±1.674[a]	184.66±1.247[b]

Values are as expressed as mean ± SD (n=6)a- P <0.001 compared with control

b- P<0.001 compared with disease control

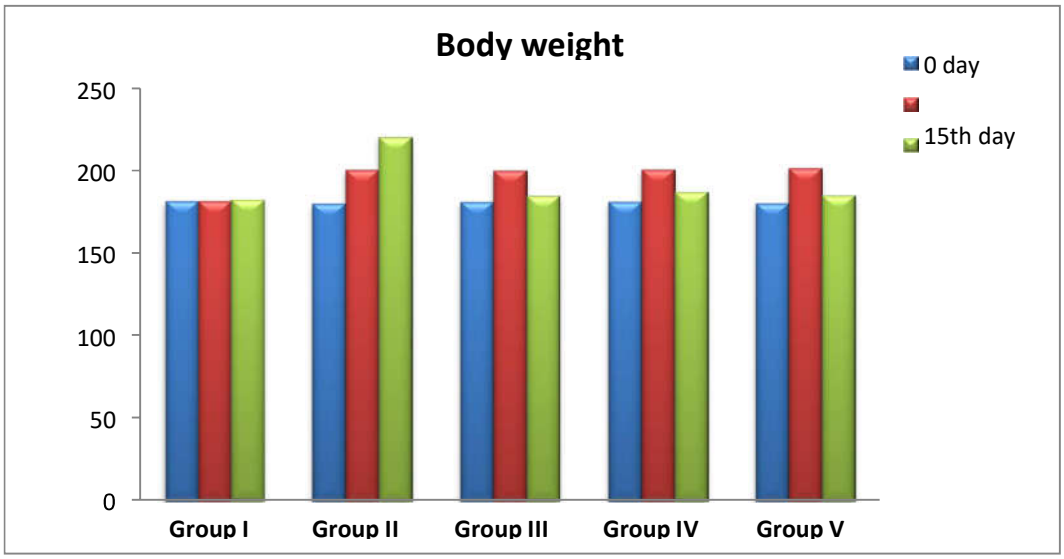

Figure 1: Effect of EEFSV on body weight

Biochemical analysis

Effect of ethanolic extract of fruits of Surattense Nightshade on Total Cholesterol level in hyperlipidemic rats. The results are tabulated in table 4. Hyperlipidemic rats showed an increase in Total Cholesterol whereas the Total Cholesterol of the control rats remained the same. Administration of Atrovastatin and ethanolic extract of fruit of *Surattense Nightshade* for 15 days significantly reduced the levels and brought back Total Cholesterol towards normal.

Table 3: Effect of Cholesterol diet on TC and the effect of Atorvastatin and EEFSV on TC of hyperlipidemic rats

Group	Total Cholesterol (mg/dL)		
	Induction period		Treatmentperiod
	0 Day	15th Day	30th Day
I	91.33±5.15	90±3.87	91±5.09
II	89.33±5.79	170±5.80 [a]	252.83±4.37 [b]
III	87.16±6.09	170.5±5.64[a]	100.66±3.29[b]
IV	86.66±5.67	168±5.62[a]	115.33±3.63[b]
V	89.66±6.47	169.66±5.21[a]	103.83±2.26[b]

Values are as expressed as mean ± SD (n=6)

P<0.001 compared with control

P<0.001 compared with disease control

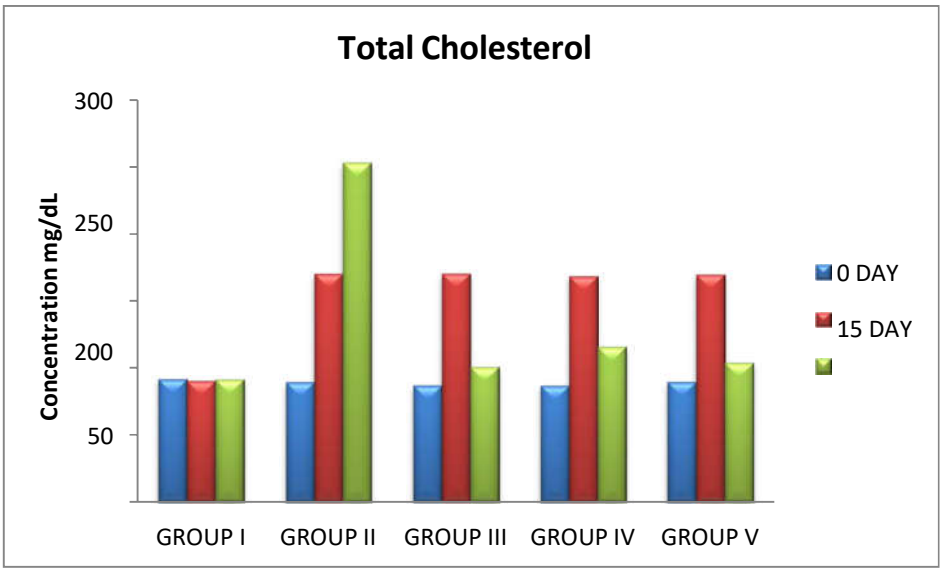

Figure 2: Effect of EEFSV on Total Cholesterol

Effect of ethanolic extract of fruits of *Surattense Nightshade* on Triglyceride level in hyperlipidemic rats

The results are tabulated in table 5. Hyperlipidemic rats showed an increase in Triglycerides whereas the Triglycerides of the control rats remained the same. Administration of Atrovastatin and ethanolic extract of fruit of *Surattense Nightshade* for 15 days significantly reduced the levels and brought back Triglycerides towards normal.

Table 4: Effect of Cholesterol diet on TG and the effect of Atorvastatinand EEFSV on TG of hyperlipidemic rats

Group	Triglycerides (mg/dL)		
	Induction period		Treatment period
	0 Day	15th Day	30th Day
I	69±4.50	68.66±3.94	68.5±3.59
II	70±3.05	150.66±4.74[a]	211.13±7.01[b]
III	69.83±2.54	149.66±6.15[a]	74.66±2.92[b]
IV	67.66±5.52	148.66±5.59[a]	96.66±3.72[b]
V	69.33±4.81	149.83±5.11[a]	84±2.23[b]

Values are as expressed as mean ± SD (n=6)

P<0.001 compared with control

P<0.001 compared with disease control

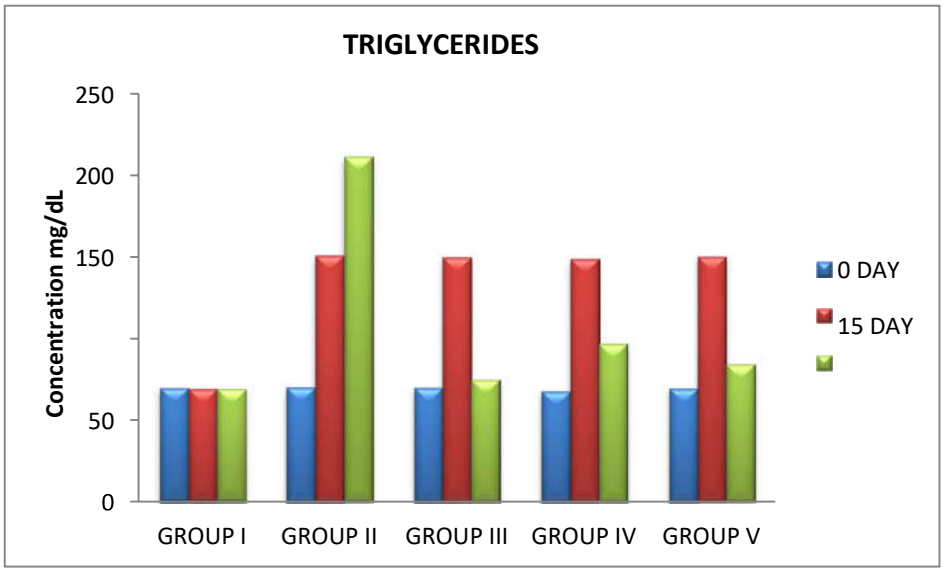

Figure 3: Effect of EEFSV on Triglycerides

Effect of ethanolic extract of fruits of *Surattense Nightshade*on HDL level in hyperlipidemic rats

The results are tabulated in **Table 7**. Hyperlipidemic rats showed decrease in HDL whereas the HDL of the control rats remained the same. Administration of Atrovastatin and ethanolic extract of fruit of *Surattense Nightshade* for 15 days significantly increase the levels of HDL and brought back HDL towards normal.

Table 5: Effect of Cholesterol diet on HDL and the effect of Atorvastatin and EEFSV on HDL of hyperlipidemic rats

Group	HDL (mg/dL)		
	Induction period		Treatmentperiod
	0 Day	15thDay	30th Day
I	25.83±2.26	25.16±2.11	25.5±1.97
II	25.5±2.98^{a}	19.5±2.81^{a}	13.66±1.49^{b}
III	25±1.91^{b}	19.16±1.77^{a}	26.16±1.95^{b}

IV	25±3.26[b]	19.83±1.77[a]	22±1.29[b]
V	24.33±3.09[b]	19±2.01[a]	25.83±1.34[b]

Values are as expressed as mean ± SD (n=6)

P<0.001 compared with control

P<0.001 compared with disease control

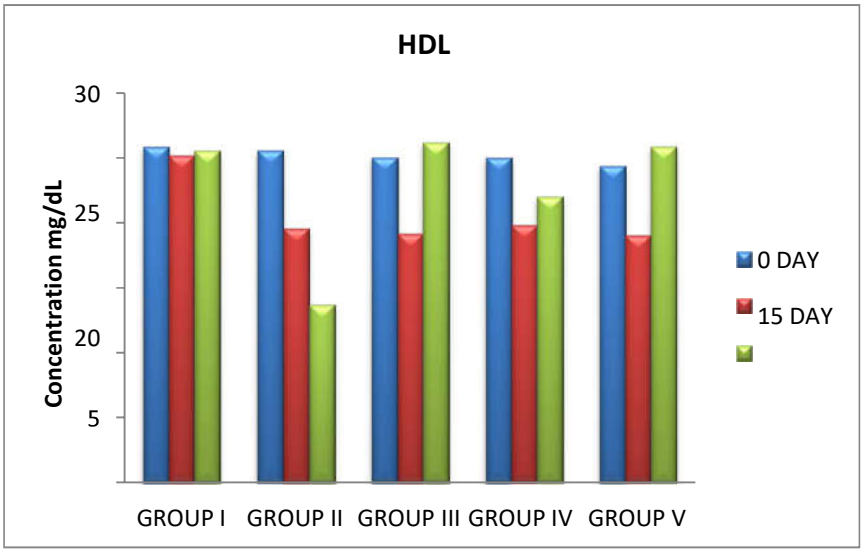

Figure 4: Effect of EEFSV on HDL

Effect of ethanolic extract of fruits of *Surattense Nightshade* on VLDL level in hyperlipidemic rats

The results are tabulated in table 7. Hyperlipidemic rats showed an increase in VLDL whereas the VLDL of the control rats remained the same. Administration of Atrovastatin and ethanolic extract of fruit of *Surattense Nightshade*for 15 days significantly reduced the levels and brought back VLDL towards normal.

Table 6: Effect of Cholesterol diet on VLDL and the effect of Atorvastatinand EEFSV on VLDL of hyperlipidemic rats

Group	VLDL (mg/dL)		
	Induction period		Treatmentperiod
	0 Day	15th Day	30th Day
I	13.8±0.90	13.73±0.78	13.7±0.71
II	14±0.61	30.13±0.94[a]	42.26±1.40[b]
III	13.96±0.50	29.93±1.23[a]	14.9±0.58[b]
IV	11.21±4.50	29.73±1.19[a]	19.33±0.74[b]
V	13.86±0.96	29.96±1.02[a]	16.8±0.44[b]

Values are as expressed as mean ± SD (n=6)

P<0.001 compared with control

P<0.001 compared with disease control

Effect of ethanolic extract of fruits of *Surattense Nightshade* on LDLlevel in hyperlipidemic rats

The results are tabulated in Table . Hyperlipidemic rats showed an increase in LDL whereas the LDL of the control rats remained the same. Administration of Atrovastatin and ethanolic extract of fruit of *Surattense Nightshade* for 15 days significantly reduced the levels and brought back LDL towards normal.

Table 7: Effect of Cholesterol diet on LDL and the effect of Atorvastatin and EEFSV on LDL of hyperlipidemic rats

Group	LDL (mg/dL)		
	Induction period		Treatment period
	0 Day	15th Day	30th Day
I	53.6±5.89	51.1±5.05	51.5±6.80
II	49.5±7.58[a]	120.36±7.51[a]	196.9±4.67[a]
III	48.2±7.08[b]	125.9±8.92[b]	59.56±5.42[b]
IV	48.11±7.76[b]	118.43±6.20[b]	74±4.25[b]
V	51.46±8.50[b]	120.7±5.89[b]	61.2±3.39[b]

Values are as expressed as mean ± SD (n=6)a- P<0.001 compared with control

b- P<0.001 compared with disease control

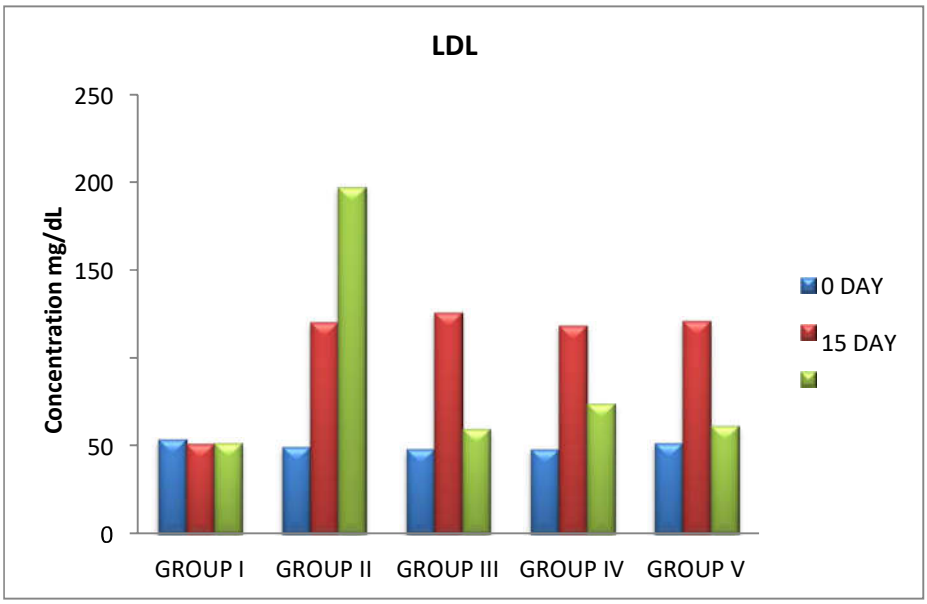

Figure 5: Effect of EEFSV on LDL

***In silico* studies**

Toxicity studies

Toxicity is one of the major criteria to be considered for a molecule to shine as a successful clinical candidate in the pharmaceutical research. So the toxicity studies of some of the already isolated molecules of Surattense Nightshade were performed. Toxicity was predicted by the Property Explorer, the online software of Thomas Sander, Acetelion Pharmaceuticals Ltd., Gewerbestrasse 16 and 4123 Allschwil, Switzerland. Prediction results were valued and color coded. Properties with high risks like mutagenicity, reproductive effect, tumorigenicity and skin irritantcy are shown in red color whereas a green and orange color indicates non- toxic behavior of the drug. Toxicity parameters are tabulated in Table and Figure.

Table 8: Prediction of toxicity

S. No	Molecules	Mutagenicity	Tumerogenicity	Irritant	Reproductive effect
1	Apigenin	-	-	-	+
2	Caffeic acid	+	+	-	+
3	Carpesterol	-	-	-	-
4	Coumarin	+	+	-	+
5	Diosgenin	-	-	-	-
6	Esculetin	-	+	-	-
7	Esculin	-	-	-	-
8	Methyl caffeate	-	-	-	-
9	Scopletin	-	-	-	-
10	α-Solamargine	-	-	-	-
11	Solanidine	-	-	-	-
12	Solanine	-	-	-	-
13	Solasodine	-	-	-	-

14	Solasonine	-	-	-	-
15	Carpesterol	-	-	-	-

indicates as safe; + indicates as toxic

Docking

The same 15 compounds were docked against the target 3GCX after the activesite on the protein was selected using Sitemap function. For perfect docking of the ligand into the cavity of the protein having active site, extra precision mode molecular docking was executed. During the docking procedure different poses of the ligand were generated. The ligands were docked in different poses.[70] The best docked posewas selected based on the G Score and the interactions between the protein and the ligand. G score values are tabulated in **Table 11 and Figure 10**.

Table 9: Compounds docked against 3GCX

S. No	Ligands	G score	D Score	Lipophilic EvdW	H Bond	Electro
1	Solanine	-11.32	-11.32	-2.53	-7.96	-1.74
2	Esculin	-7.51	-7.51	-2.87	-3.16	-1.08
3	Solasonine	-6.66	-6.64	-3.26	-4.09	-1.05
4	Esculetin	-6.51	-6.5	-2.87	-2.47	-0.67
5	α-Solamargine	-6.24	-4.29	-1.87	-4.16	-0.75
6	Apigenin	-5.84	-5.82	-3.28	-1.47	-0.69
7	Scopletin	-5.5	-5.49	-2.83	-1.62	-0.55
8	Caffeic acid	-5.3	-5.3	-1.26	-1.66	-0.74
9	Methyl caffeate	-4.6	-4.64	-1.98	-1.53	-0.76
10	Coumarin	-4.06	-4.06	-2.71	-0.7	-0.15
11	Solanidine	-3.52	-3.52	-2.14	-0.98	-0.57
12	Diosgenin	-1.18	-1.18	-1.56	0	-0.01
13	Solasodine	-0.88	-0.86	-0.79	0	-0.35
14	Carpesterol	0.12	0.12	-1.76	-0.44	-0.18

15	Tomatidenol	0.79	0.81	-1.39	0	-0.24
16	Atorvastatin	-5.38	-5.38	-3.95	-2.26	-0.94

It is considered that lesser the G score value greater is the binding of the ligand with the protein. From the G score values, it is observed that Solanine, Esculin, Solasonine, Esculetin, α-Solamargine, Apigenin, Scopletin and Caffeic acid showed a G score value ranging between -11.32 to -5.3 indicating a good score. It is also seen that Methyl caffeate, Coumarin, Solanidine, Diosgenin and Solasodine had a G score value ranging between -4.6 to – 0.88 3 indicating a moderate score as compared to Atorvastatin.

Drug likeness

All the 15 molecules were subjected to *in silico* evaluation using Molinspiration Cheminformatics Software to evaluate drug likeness. It can be accessed online for calculation of important molecular properties such as partition co- efficient, binding with human serum albumin, percentage human oral absorption, number of hydrogen bond donors and acceptors for the most important drug targets like GPCR ligands, kinase inhibitors, ion channel modulators and nuclear receptors. Drug likeness parameters are tabulated in table 10.

Table 10: Prediction of drug likeness

S.No	Molecule	QPlogP_o/W	QPlogkhsa	% oral human absorption	Rule of five
1	Carpesterol	8.44	2.305	100	2
2	Solasodine	5.83	1.304	100	1
3	Apigenin	1.92	0.05	75.23	0
4	Caffeic acid	0.558	-0.798	54.28	0
5	Coumarin	1.39	-0.554	94.30	0
6	Diosgenin	6.124	1.642	100	1
7	Esculetin	0.118	-0.593	69.66	0
8	Esculin	-1.596	-1.012	39.72	0
9	Methyl caffeate	1.008	-0.407	75.97	0
10	Scopletin	0.968	-0.492	85.73	0
11	Solanidine	5.118	1.435	95.89	1

12	α-Solamargine	0.473	-0.943	9.92	3
13	Solanine	-0.791	-1.045	0	3
14	Solasonine	-1.14	-1.046	0	3
15	Tomatidenol	5.325	1.143	100	1
16	Atorvastatin	6.812	1.124	70.53	2

From the table,

QPlogP_o/W - It is used to predict the Partition co-efficient of the molecules. The values are normally in the range between -2.0 to 6.5. QPlogkhsa - It is used to predict the binding with human serum albumin.[71] The values are normally ranges between -1.5 to 1.5. Percent human oral absorption - It is used to predict the human oralabsorption on 0 to 100% scale. Absorption values normally ranges between 25-80%. Rule of 5 - Lipinski's rule said that molecules should possess MW<500, donor HB≤5, accept HB≤10, QPlogP_o/W<5. Molecules that statisfy this rule are considered drug-like.

Results indicates that

All the molecules possess good partition co-efficient except Carpesterol. Carpesterol and Diosgenin does not show desirable binding with human serum albumin whereas all other molecules have good effective binding with human serum albumin.[72] Absorption value less than 25% are, α-Solamargine, Solanine, Solasonine and more than 80% are Carpesterol, Diosgenin, Solasodine, Coumarin, Scopletin, Solanidine. Apigenin, Caffeic acid, Esculetin, Esculin, Methyl caffeate, Scopletin, Coumarin have the value as 0; Solasodine, Diosgenin, Solanidine, Tomotidenol have the value as 1; Carpesterol have the value as 2; α- Solamargine, Solanine, Solasonine have the value as 3.

CONCLUSION

Extract of fruits of *Surattense Nightshade* have significant antihyperlipidemic activity. In the phytochemicals study such as alkaloids, flavonoids, coumarins, phenolic compounds and glycosides are responsible for antihyperlipidemic activity. It is also concluded from *in silico* studies of already isolated compounds of *Surattense Nightshade*, against 3GCX confirming the activity through its G score.

SUMMARY

Hyperlipidemia can be treated bu using herbal medicines which are found to be most effective in the treatment of various ailments. The present work was selected plant named as *Surattense Nightshade.* It belong to Family Solanaceae, is claimed to be useful for reducing the fats but the claim has not been scientifically validated. Antihyperlipidemic activity of the ethanolic extract of fruits of *Surattense Nightshade* using the Cholesterol diet induced model of hyperlipidemia. The parameters evaluated were body weight changes and serum lipid profile. Administration of standard (Atorvastatin 2mg/kg b.w), ethanolic extract of fruits of *Solanum virginianum* Linn., at 200mg/kg and 400mg/kg significantly ($P<0.001$) reduced the body weight and normalized the serum lipid profile. This confirms the antihyperlipidemic activity of fruits of *Surattense Nightshade. In silico* studies like toxicity, docking and drug likeness were performed for establishing safety and identifying the mechanism of action of some of the selected molecules which have already been isolated from *Surattense Nightshade.*

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