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Study on Pharmacological properties and Medical Significance of extract of "*Solanum Viarum Dunal*" for Anti-inflammatory and Analgesic activity: A Concise Literature Review

Neda Anzar[1] , Manish Singh[1]

Narayana Institute of Pharmacy, (Gopal Narayan Singh University), Jamuhar , Bihar

Abstract:

In this literature review the medicinal use of the plant Solanum Viarum Dunal of the family Solanaceae was analysed. S. Viarum Dunal is observed to exhibit many pharmacological effects such as anti-inflammatory, analgesic, anti-cancer, anti-microbial, and so forth. Many phytoconstituents, including steroidal glycosides like solaviasides and glycoalkaloids like solasodine, solasonine, and solamargine, have anti-inflammatory properties., flavonoids and phenolic alkaloids, etc., present mainly in fruit seeds, roots, stem and leaves of the plant. S. Viarum Dunal, Anti-cancer activity is observed due to presence of solasodine and other glycoalkaloids. The presence of flavonoids and polyphenolic substances results in the observation of anti-microbial and anti-pyretic properties. Different methods are developed for the extraction of phytoconstituents with different, also different methods of cultivation and tissue culture techniques developed are discussed in this review. This review aims to cover the knowledge regarding the pharmacological activity and medicinal use, pharmacognosy and phytochemistry of different parts such as fruits leaf seeds and stems of plant Solanum Viarum Dunal belonging to family Solanaceae.

Keywords: -

Solanum Viarum Dunal, Anti-inflammatory, COX, 5-LOX, Glycoalkaloids, Solasodine, Polyphenolic compounds, Soxhlet Extraction techniques.

Introduction

In case of any injury the concomitant thing that exists along with it is pain and fever and inflammatory response which are relieved using drugs that reduce inflammatory responses and with drugs having analgesic action to relieve pain. Non-steroidal anti-inflammatory medicines, sometimes known as NSAIDs, work by limiting the production of prostaglandins by inhibiting the cyclooxygenase enzyme (COX).[(1)] However, NSAIDs are linked to a number of gastrointestinal issues, including perforation, blockages, peptic ulcers, and bleeding. however COX-2 inhibitors do not cause such problems but cardiovascular problems are associated with it and with other narcotic analgesic drugs used for chronic pain management reported various side effects related to CNS are there and due to its narcotic nature problem of social abuse is there due to its addictive nature and psychological dependency is also been observed along with it respiratory problems such as respiratory suppression along with constipation is observed. This opens an opportunity to search such molecules having potent Anti-inflammatory and analgesic activity and Solanum Viarum Dunal is observed to possess such pharmacological activity. Solanum viarum (Dunal) of family Solaneacae commonly called tropical soda apple and also synonymously known as S.viridifiorum S.chloranthum, S.Khasianum, etc. Solanum viarum has the characteristic feature of left herb, subshrub and shrub of one to two

meters prickly in nature and is much branched. This plant with Indian variety is the richest source of steroids. [2] Their height generally lies between 3-6 feet, their leaves varies between 2 to 8 inch long and up to 2 to 6 inch wide , their stem and leaves are alligned has prickles that are up to an inch long (2.5 cm in length). The inflorence lies between 1 to 3 flowered cyme, fruits globar berries are about 1 ± 0.2 inch in dimeter after they are fully grown, but in ripe fruits seeds develop as small up to 1cm in diameter. [3] Solanum Viarum (Dunal) chemically has a glycol alkaloid compound called soladosine (C27 cholestane skeleton) which is a nitrogen analogue of diosgenine has an intermediate compound 16-Di hydro pregnolone (16-DPA). It ultimately undergoes conversion into testosterone and a series of derivative substances like methyl testosterone as well as the production of corticosteroids like hydrocortisone and prednisolone. [4] In addition to treating Addison's illness and cancer, steroidal hormones are also used as contraceptives, to treat rheumatoid arthritis, and to treat Addison's disease. [5] The steroid compounds have observed to have action against inflammatory responses, with anabolic and anti-fertility activity. [6] Further, this plant has various other bio-actives components such as solanidine, α-solanine, solasonine, solamrgine, phenolics tannins, and flavonoids, etc. Poly Phenolic compounds is identified to have potentially active as antioxidant agent. The most prevalent polyphenols, flavonoids, are renowned for their strong therapeutic effects because of a variety of biological plant components. These substances have a key role in interactions with the plant environment, acting as the first line of defence against various biotic and abiotic stressors. [7] Caffeic acid, gallic acid, sinapic acid, rutin, ferulic acid, benzoic acid, querecitin, and kaempeferol are some of the significant flavonoids and polyphenolics found in the plant. They have anti-inflammatory, anti-cancer, antimicrobial, antimutagenic, and anti-fungal properties, among other properties. [8]

Due to its high importance of phytoconstituents and secondary metabolites and cost effectiveness it is making Industries deeply interested in production of these substances through plant tissue culture technology. [9]

Figure 1. Fruit of *S. Viarum Dunal (Solanaceae)*

Distribution and Habitat

In addition to Paraguay, south-eastern Brazil, and Uruguay, the Solanum Viarum Dunal, often known as the tropical soda apple, is widely distributed in north-eastern Argentina. It is also planted across Asian country such as India Nepal and many more countries due to its rich medicinal benefits. 700 m above sea level is the altitude at which tropical soda apples are produced.[10] Ripe fruits of Solanum Viarum Dunal traditionally identified to have the major active phytoconstituents. In INDIA for fruits having S. Viarum is cultivated extensively as it is the major source of most of the bioactive glycoalkaloids, steroids, alkaloids. The crop takes almost 7 months to 8 months to fully grown. Large agricultural cycle, non-synchronous evolution of fruit, the spike results in the management and harvesting of fruits expensive and process is complicated. [11] This attracted attention of many scientists toward the screening of vegetative parts of Solanum Viarum Dunal. Many studies have indicated the extracts of roots and leaves are the

origin of many steroidal glycosidic raw materials. In recent advances, plant cell culture is being recognised as another platform introduced for the formation of various phyto constituent. However, many researchers have explored various source for the production of bioactive phytoconstituents used available in the cosmetics and pharmaceutical sectors is Solanum sp. Production of alkaloids massively reported through Hairy roots and callus cultures.[12]

Figure 2. Leaves of *S. Viarum Dunal (Solanaceae*)

Common Names:

In English it commonly referred to as the Tropical soda apple. In Assamese this plant is known as Tit -bhekuri, Hati–bhekuri. In Malayalam this plant is known as Kandakarichunda in other language it is known as Tropical soda apple and Sondom Apple. [7]

Taxonomical Classifications: -

S. Viarum Dunal belongs to the Plantae kingdom, subkingdom of Embryophyta of genus Solanum L. of family Solanaceae belonging to Class Magnoliopsida and subclass Asteranae. [7]

Chemical Constituents:

Solanum viarum has a wide range of medicinal uses due to the occurrence of many bio active phyto-constituents such as steroidal glycosides, alkaloids and glycoalkaloids. These steroids have a large variety of pharmacological activity that supress inflammatory responses, anabolic properties, anti-fertility agents, anti-leprotic agents, antidiabetic, anthelmintic and insecticidal properties.[13] In S. Viarum the most commonly found chemical constituent are steroidal glyco alkaloids such as Solasodine, Solasonine, solamargine, diosgenin, khasianine, saponins - solakhasianine, natigenin, etc. however, majorly solasodine is present in the mature fruits are mainly used as a commercial source. [14] Compounds like steroids, flavonoids, glycosides, tannins, e.t.c. phenolic compounds also used in natural industries are also present in this plant.[15] Caffeoylqinic acid (CQA) derivatives is also identified to be present, as 5 - caffeoyl and 3 malonyl 5 caffeoyl [4-1beta-[6-(5-caffeoyl) quinate] glucopyranosyl] as quinic acidcompound [14] S. Viarum Dunal's fruit mostly contains the phenolic phytoconstituents Viarumacid A and Viarumacid B.[16] In addition to steroidal glycosides like Solaviaside A, B, and C. Solasodine a glycol-alkaloid compound is majorly present in seed part of the plant. [17]

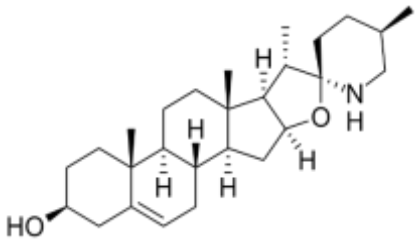


Figure 3. *Solasodine, a glycoalkaloid phytoconstituent present in the S. Viarum Dunal plant responsible for Anti-inflammatory activity*

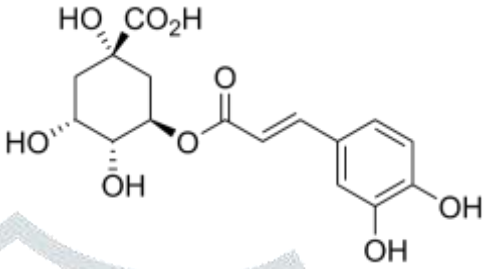


Figure 4. *Caffeoylqinic acid (CQA) a phytoconstituent present in the present in the S. Viarum Dunal plant responsible for Anti-inflammatory activity*

Medicinal Uses

Since however very little data is available for S. Viarum but after a thorough literature survey it is found that plant S. Viarum can be used as a painkiller and as a therapy for cancer and conditions like Addison's disease (a chronic disorder of the adrenal gland) also due to its anti-inflammatory effect can be used in the cure of rheumatic disorders, chronic Bronchial asthma, dermatological disease, obesity and leukaemia.[17] This plant can also be used to treat Plasy disease, a condition in which the facial muscles weaken and lose their capacity to move, eventually resulting in facial paralysis. Chemically components like solasodine and other glycoalkaloids are used for the production of various cortisone like compounds of steroids. [18]

Pharmacological Activity:

The S. viarum plant has different chemical constituents which eventually have different pharmacological activity like alkaloids show analgesic property, flavonoids have antioxidant property, steroids are used for the bronchitis and many other Anti-oxidant, anti-bacterial, anti-fungal, anti-insecticidal, antipyretic, and anti-cancer actions have been noticed. [19]

a) Anti-Inflammatory action: -

Activities including anti-oxidant, anti-bacterial, anti-fungal, anti-insecticidal, antipyretic, and anti-cancer have been noticed. When applied topically, solsodine is seen to reduce ear irritation brought on by repeated applications of tetradecanoyl phorbol 13-acetate.[20] Anti-inflammatory effect was also observed with the solasodine and tomatodine in a LPS-stimulated macrophages model. [21] In a complementary rat paw induced edema model Solasodine is observed that 75 mg/kg dose have anti-inflammatory effects through inhibiting the cyclooxygenase and 5-lipoxygenase pathways.

b) Anticancer activity: -

Solasodine was employed in an experiment to determine the role of the carbohydrate moiety in apoptosis. The C3 side chain of solasodine contains the 4'Rh-Glc-Rha2', 4'Rha-Glc, and H groups, respectively.[22] Solasodine also shown to have cytotoxic action against in vitro human PLC/PRF/5 cells. [23]

c) Analgesic and Anti pyretic activity: -

In an experiment on wistar rats conducted in 2018, Meena Kausar *et al.* used an ethanolic extract of the leaves of *S. Viarum Dunal* to assess the plant's analgesic and antipyretic activity. They discovered that *S. Viarum* has antipyretic activity at single dose levels of 100 mg/kg and 200 mg/kg in addition to its antipyretic activity, and that it also has analgesic activity. It also inhibits the production of prostaglandins. [24]

d) Anti-microbial activity: -

In 2013, V. Ramesh *et al*. carried out a leaf disc bioassay using fruit extract by n-hexane and benzene, as well as components like benzene and ethyl acetate extract, and in ethyl acetate and acetone explored about the potent activity as an insecticidal agent. They discovered that extract of water and acetone alone shows potent insecticidal effect but

no significant activity observed. [25] In 2013 S. Arivudainambi *et al*. performed Tropical bioassay and a poison and food bioassay where fruit extract with n-Hexane and benzene, along with benzene and ethyl acetate, and also with ethyl acetate and acetone individually in a ratio of equal proportion and in combination discovered insecticidal against Aphis gossypii (Glover) and 33% mortality shows.[25] In 2012 Jaishree V *et al.* performed in vitro model where methanolic extract of fruit was found to have anti-oxidant and anticancer properties Its antibacterial activity by two processes, the first of which is the microwave-assisted Soxhlet extraction method. They discovered that soxhelt extraction, as opposed to microwave assistance, exhibits antioxidant activity. [26]

e) Anti-oxidant activity: -

In 2012 Shi Biao Wu *et al.* performed in vitro model isolated a novel compound discovered to have antioxidant properties from the fruit Solanum viarum.[16] In 2009 Masateru Ono *et al.* Using the use of NMR spectroscopy and HPLC, the methanolic extract of S. viarum fruit was used to separate 10 compounds of steroidal glycosides. The fruit was then added to silica gel and Diaion HP20. However very few studies are available demonstrating anti-analgesic and anti-inflammatory effects. [27]

Phytoconstituents of Solanum Viarum Dunal with their Pharmacological Properties

Solasodine

Solanum viarum D, Solanum nigrum, S. khasianum, S. xanthocarpum, S. gracile, S. laciniatum, S. aculeastrum, and other Solanaceae plants contain the active ingredient solasodine.

The surge in demand for pharmacologically active steroids and the difficulty acquiring diosgenin have led to searches for alternate source materials. The diosgenin N-analogue solasodine can also be converted to 16-dehydropregnenolone, which shares many characteristics with diosgenin and is employed as a steroidal precursor in the steroid pharmaceutical industry for the creation of corticosteroids, antifertility drugs, anabolic steroids, and other steroids, among others. [28]

Solasodine (aglycone) can be created by hydrolyzing solamargine glycosides chemically or microbiologically. The glycosides of plant sources of energy can also be extracted with aqueous or alcoholic acids to make solasodine. Hydrolysis of the glycol-alkaloids occurs concurrently with or following extraction, separating the sugar moiety. () Many times, solasodine is thought of as an allelochemical that defends against many illnesses and predators. Aglycone solasodine derivatives are highly cytotoxic to a variety of cancer cell types. Numerous pharmacological effects of solasodine on the central nervous system include anticonvulsant, antinociceptive, antiinflammatory, cardio-tonic, cytotoxic, hepatoprotective, anti-atherosclerotic, antifungal, immune-modulatory, and antipyretic characteristics. [29]

Chemical Structure:

Solasodine is an oxaspiro compound and steroid alkaloid sapogenin belonging to the Solanum (nightshade) family with the formula C27H43NO2. It acts as a starting point for the production of complex steroidal compounds, such as those included in birth control pills. It has teratogenic, diuretic, antifungal, cardiotonic, immunomodulatory, antipyretic, apoptosis-inducing, antioxidant, antiinfective, anticonvulsant, central nervous system depressant, and antispermatogenic properties. It is an antibacterial steroid alkaloid, an azaspiro compound, an oxaspiro compound, a hemiaminal ether, and a sapogenin. It is a conjugate base of solasodine(1+). [30]

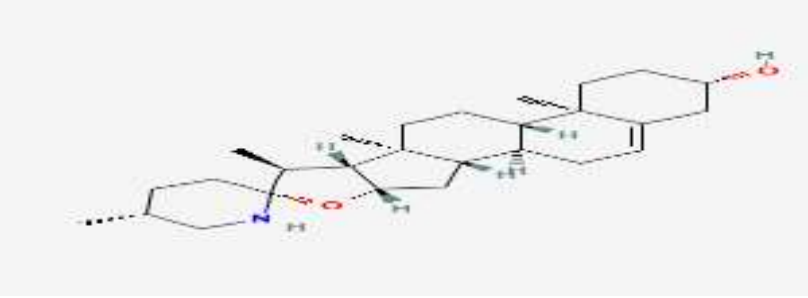


Fig 8 : Stucture of Solasodine

Molecular Formula: $C_{27}H_{43}NO_2$

IUPAC Name: (1*S*,2*S*,4*S*,5'*R*,6*R*,7*S*,8*R*,9*S*,12*S*,13*R*,16*S*)-5',7,9,13-tetramethylspiro[5-oxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icos-18-ene-6,2'-piperidine]-16-ol

Neuroprotective effect of Solasodine:

Experimental evidence of solasodine's neuroprotective properties in a rat ischemia model. Solasodine therapy dramatically decreased lipid peroxide (LPO) and nitric oxide (NO) levels in a dose-dependent manner and elevated antioxidant enzyme levels, including glutathione (GSH), catalase (CAT), and thiols. The cerebral infarction in the solasodine-treated rat brains was dramatically reduced, according to histopathological examinations.[31] These results suggest that the antioxidant (free radical scavenging) properties of solasodine may contribute to some of its protective effects. In addition to its neuroprotective properties, solasodine has been experimentally shown to exhibit substantial neurogenesis features in rats. It is possible that solasodine has synaptogenesis and neurogenetic properties given its capacity to differentiate teratocarcinoma P19 cells into neurons and promote the expression of synaptophysin. [32]

Anti-inflammatory and anti-nociceptive effects of Solasodine

Solasodine from Solanum trilobatum was characterised as an anti-inflammatory drug in a dose-dependent manner using a model of carrageenan-induced rat paw oedema. Solasodine considerably decreased the ear inflammation that tetradecanoylphorbol 13-acetate-induced in rats when applied topically. [33] Additionally, there was evidence of a decrease in exudate volume, leucocyte total, and neutrophil migration in rats given solasodine. In order to test its anti-inflammatory activity, carrageen-induced rat paw edoema and skin irritation test investigations were used to develop transdermal patches of isolated solasodine.[34] Transdermal patches containing Solasodine demonstrated a stronger anti-inflammatory impact as compared to generic indomethacin. The antiinflammatory effects of solasodine and tomatidine were also investigated using lipopolysaccharide (LPS)-induced macrophages as a model of inflammation. In this study, solasodine had a less-inhibitory effect than tomatidine. The analgesic efficacy of Solasodine, produced from Solanum trilobatum, has also been examined in rodents using a variety of experimental techniques, including acetic acid, formalin, and hot plate tests. The writhing and licking responses brought on by formalin and acetic acid, respectively, were greatly diminished by solasodine pretreatment. Solasodine overestimated the analgesic effect in the hot plate test. [35]

Anti-atherosclerotic effect of Solasodine:

The effects of solasodine on lipidemia and atherosclerosis were studied in rabbits fed an atherogenic diet. Solasodine therapy reduced blood cholesterol, LDL cholesterol, and VLDL cholesterol in groups fed an atherogenic diet. (36) The ratio of HDL increased whereas the ratio of cholesterol to phospholipids significantly decreased after Solasodine therapy. Solasodine therapy resulted in a nearly normalised aorta lumen since it also reduced aortic triglycerides and plaque size. The liver and aorta of the atherogenic food fed group likewise had decreased cholesterol levels following Solasodine therapy. [36]

Anticonvulsant and CNS depressant activity of Solasodine:

Solasodine, a compound derived from S. sisymbriifolium, has been shown to have anticonvulsant and CNS depressant properties in rats' tests. Solasodine administration showed a dose-dependent anticonvulsant efficacy in the model of maximal electric shock (MES)-induced convulsions by reducing the latency of the hind leg tonic extensor (HLTE) phase. [37] Additionally, the picrotoxin (PCT) model's HLTE phase's latency was significantly lowered after solasodine administration. In contrast, there were no anti-seizure effects of solasodine in the pentylenetetrazole (PTZ) model. Solasodine is a neurosedative medicine, as evidenced by the fact that it prolongs sleep duration when thiopental is taken. [38]

Anticancer activity of Solasodine:

Numerous cancer cell lines have been proven to be resistant to the anti-neoplastic effects of solasodine and its glycosides. In earlier studies, a variety of cancer cell lines (MCF-7, KB, K562, and PC3 cells) were synthesised and evaluated for their cytotoxicity against solasodine and its glycoside with different sugar moieties. These studies have shown that solasodine, which also has a rhamnose sugar component, has potent anticancer effects. Solasodine has been demonstrated to exhibit dose-dependent anti-proliferation in breast cancer cell lines MCF-7. [39] Solasodine increased the expression of Bax and Bak, two

pro-apoptotic proteins, while decreasing the expression of Bcl-2 and Bcl-xL, two anti-apoptotic proteins, in MCF-7 cells. It has the capacity to kill cancer cells by inducing apoptosis brought about by antilysosomal and antimitochondrial action. Solasodine rhamnosyl glycosides, which are substances derived from solanum plants, have also shown strong anti-neoplastic action. A topical cream formulation (CuradermR) containing solasodine glycosides can be used to treat skin cancer without harming healthy skin cells. Curaderm cream has completed testing (and received a licence in 1991) in Australia for the treatment of solar keratosis. Investigations on the cytotoxic properties of solasodine were conducted using the HT29, MCF7, and HeLa cancer cell lines. Solasodine showed the most inhibitory effects on HeLa cells. Furthermore, Solanum xanthocarpum unripe fruit solasodine has demonstrated anti-cancer activities against the cancer cell lines HeLa and U937. A variety of Solasodine compounds have also been developed and tested for their potency against the PC-3 cell line's capacity to multiply prostate cancer cells. [(40)]

Hepatoprotective effect of Solasodine:

It has been demonstrated that the solasodine isolated from S. incanum exhibits hepatoprotective properties against CCl4-induced hepatotoxicity in rats. Rats that had received solasodine treatment had lower levels of transaminase enzymes including glutamic-oxalacetic transaminase (SGOT) and glutamic-pyruvic transaminase (SGPT), which may have shielded the liver against CCl4 poisoning. Additionally, Solasodine protected rat liver tissues from CCl4-induced DNA damage. Solasodine may have hepatoprotective qualities due to its capacity to repair liver cells and inhibit COX-2 and TNF-α. [(41)]

Solasonine

The glycoalkaloid known as solasonine is found in Solanum plants, which belong to the Solanaceae family. Solasonine is a chemical compound that is hazardous when used in large quantities. Solasodine glycoside is what it is. Solasonine is one of many glycoalkaloids that have use in pharmacology, cancer treatment, and even pest management. [(42)]

Glycoalkaloids are toxic to humans in high doses due to their ability to damage cell-membrane function. There is a breakdown of membrane integrity because each material that comes into contact with the cell has the potential to cause apoptosis, or cell death. [(43)]

There are more than 1700 species in the genus Solanum (family: Solanaceae), which is widespread in both temperate and tropical areas. It stands out for its ability to produce SGAs, which are highly beneficial from both an ecological and health perspective. Seven of the twenty recognised Solanum species—Solanum cordatum, Solanum incanum, Solanum melongena, Solanum nigrum, Solanum surattense, Solanum tuberosum, and Solanum villosum—can be found in Oman. [(44)] S. incanum, popularly known as thorn apple, is an important medicinal plant. Its stem, fruits (berries), and roots are employed in traditional medicine in Oman to treat dyspepsia, earaches, and wounded fingers. Glycoalkaloids are amphiphilic because they have two structural components. The 27-carbon hydrophobic cholestane skeleton that makes up the aglycone unit has nitrogen introduced into the F ring. The second unit consists of a hydrophilic carbohydrate side chain linked to the 3-OH position. [(45)] According on the quantity of sugars in the side chain, the number of cleavages (by acid or enzymatic hydrolysis) of the glycoside's constituent sugars leads in the formation of -, -, or -compounds. Glycoalkaloids are commonly referred to as -compounds. Solasodine is the main aglycone in probably many plants that possess glycoalkaloids. About 200 species of Solanum contain the water-soluble triglycosides solasonine (SN) and solamargine (SM). Both simply differ in the types of trioses they contain while sharing the same aglycone, solasodine.[(46)] Solamargine and solasonine are used as a crucial source for the development of steroidal anti-inflammatory drugs and contraceptives because of their chemical similarities to steroidal hormones. The most research has been done on the anticancer, antifungal, antiparasitic, antibiotic, antimicrobial, and antiviral properties of these glycoalkaloids. Numerous human cancer cell lines, including cutaneous tumours, have shown significant cytotoxicity.[(47)]

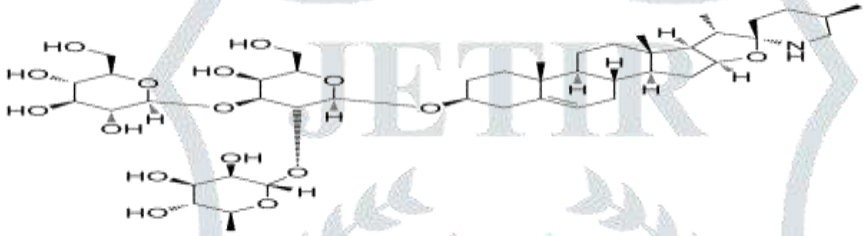
The glycoalkaloids discovered in Solanum species are referred to as solanum glycoalkaloids. All plant organs generally contain these, although the levels are highest in the metabolically active parts of the plant, such as the flowers, sprouts, unripe berries, young stem, and shoots. [(48)] They are referred to as allelochemicals because of their defence mechanisms against different

pathogens and predators such fungi, viruses, bacteria, insects, and worms. The antibacterial, antifungal, antiviral, and antibiotic properties of glycoalkaloids have been established. [49]

Chemical Structrue: [50]

Solasonine is a steroidal glycoalkaloid isolated from *Solanum viarum D*. Solasonine has cytotoxicity to human gastric cancer cells.

Fig 9 : Showing structure of Solasonine



IUPAC: (2*S*,3*R*,4*R*,5*R*,6*S*)-2-[(2*R*,3*R*,4*S*,5*S*,6*R*)-5-hydroxy-6-(hydroxymethyl)-2-[(1*S*,2*S*,4*S*,5'*R*,6*R*,7*S*,8*R*,9*S*,12*S*,13*R*,16*S*)-5',7,9,13-tetramethylspiro[5-oxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icos-18-ene-6,2'-piperidine]-16-yl]oxy-4-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxyoxan-3-yl]oxy-6-methyloxane-3,4,5-triol

Anticancer properties of Solasodine Glycosides

Numerous cancer research studies using traditional medicinal herbs (biochemical agents) have been conducted to discover new therapeutic agents that target cancer cells and avoid the ineffectiveness linked to current chemotherapy therapies. However, chemotherapy also influences fast growing non-cancer cells. Chemotherapy predominantly affects rapidly proliferating cells, such as cancer cells. Traditional anticancer drugs lack selectivity since they primarily penetrate the cells by diffusion. [51] It can take some time, call for hospitalisation, and involve several therapies. Additionally, the development of medication resistance in some cancers considerably increases the difficulty of chemotherapy. The negative effects of chemotherapy are well known. Because of their DNA reactivity, anticancer drugs can induce a second tumour that is distinct from the one that was initially treated. [52]

Solanum species extracts have demonstrated anticancer properties.

Several active substances, including solamargine, solasodine, and solasonine, inhibit the proliferation of cancer cells both in vitro and in vivo. These anticancer active compounds have been attempted to be extracted from Solanum plants on several occasions. Different Solanum plants contain these compounds in varied levels. Solamargine, a glycoalkaloid found in at least 100 Solanum species, including S. incanum, is present. Similar to other steroidal substances, solamargine can permeate cell membranes and function through simple diffusion. Solasodine has been demonstrated to inhibit a variety of human tumour cell lines, including the colon (HT-29), prostate (LNCap and PC-3), breast (T47D, MDA-MB-231), lung (A549, H441, H520, H661 and H69), human ileocecal carcinoma (HCT-8), and hepatoma (SMMC-7721, Hep3B). [53]

On the other hand, more research is still needed to determine the underlying mechanisms of solamargine's anticancer activity. Solamargine induced morphological changes of chromatin condensation, DNA fragmentation, and sub-G1 peak in a DNA histogram in human hepatoma cells (Hep3B), human lung cancer cells (H441, H520, H661 and H69), and human lung cancer cells (A549), indicating cell death via apoptosis. [54]

Biologically active components of Solasodine Glycosides

Previous studies showed that the carbohydrate residues connected to the 3-OH position of the aglycone have a considerable impact on the biological activities of glycoalkaloids. After the sugar chains in glycoalkaloids were modified, the effectiveness of glycoalkaloids and their derivatives was investigated. [55] Aglycone solasodine appears to have significantly less biological activity when compared to its glycosidic analogue. Solasodine, an alkaloid that lacks a sugar side chain, has not been found to

be effective in treating cancer. Despite being given in rather high dosages, solasodine was unable to kill cancer cells. [56] HeLa (cervical cancer), HT29 (colonic adenocarcinoma), and MCF-7 (breast adenocarcinoma) cells did not exhibit apoptosis even at much greater solasodine concentrations of 500 M. Cancer cells are specifically killed by solasodine glycosides. [57]

The importance of the sugar moiety in the cytotoxic activity of the glycoalkaloid solasonine is shown by the fact that solasonine has a larger cytotoxic effect than the aglycone solasodine does against K562 leukaemia cells. Solasonine was shown to be cytotoxic to human K562 leukaemia cells only at doses higher than solamargine (IC50 = 76.92 M).[58] Solasonine is the only chemical that contains rhamnose, while solamargine contains two of them. It has been found that the rhamnose moiety of -solamargine is crucial for inducing apoptosis, which kills cells. [59]

Solamargine

Previously it was discovered that the active component of Solanum nigrum, solamargine, inhibits the growth of cancer cells. Solamargine's impact on human cholangiocarcinoma cells and the underlying molecular mechanism, however, are still unknown. [60]

The Solanum nigrum plant is the principal source of the alkaloid solamargine. Traditional Chinese medicine holds that S. nigrum may have cooling and detoxifying benefits on the body. In particular, human hepatocellular carcinoma cells may be susceptible to the growth-suppressing and apoptosis-inducing effects of solamargine, a powerful component of S. nigrum. [61]

Solamargine may also increase the sensitivity of human breast and lung tumours to chemotherapy drugs. Chacotriose and the steroidal aglycone solasodine, an oxaza-spiro, are the two primary structural elements of solamargine.Solamargine, the active ingredient of Solanum nigrum, has previously been found to stop the growth of cancer cells. However, the effects of solamargine on human cholangiocarcinoma cells and the underlying molecular mechanism are not yet understood.[62]

Solasodine's 3-hydroxy group (2,4-bis-a-Lrhamnopyranosyl-b-D-glucopyranose) was connected to it. Solamargine is now produced in chemical laboratories in 13 steps starting with the naturally occurring diosgenin. [63]

The Solanum nigrum plant is the principal source of the alkaloid solamargine. Traditional Chinese medicine holds that S. nigrum may have cooling and detoxifying benefits on the body. In particular, human hepatocellular carcinoma cells may be susceptible to the growth-suppressing and apoptosis-inducing effects of solamargine, a powerful component of S. nigrum. Furthermore, solamargine may increase the sensitivity of human lung cancer and breast cancer to chemotherapy drugs. [64]

The two main structural components of solamargine are chacotriose and solasodine, an oxaza-spiro steroidal aglycone. [65]

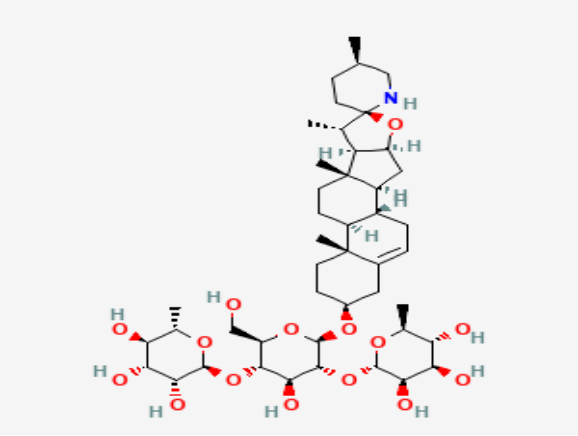


Fig 10: Showing structure of Solmarginine

Molecular Formula: $C_{45}H_{73}NO_{15}$

IUPAC : (2*S*,3*R*,4*R*,5*R*,6*S*)-2-[(2*R*,3*S*,4*S*,5*R*,6*R*)-4-hydroxy-2-(hydroxymethyl)-6-[(1*S*,2*S*,4*S*,5'*R*,6*R*,7*S*,8*R*,9*S*,12*S*,13*R*,16*S*)-5',7,9,13-tetramethylspiro[5-oxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icos-18-ene-6,2'-piperidine]-16-yl]oxy-5-[(2*S*,3*R*,4*R*,5*R*,6*S*)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxyoxan-3-yl]oxy-6-methyloxane-3,4,5-triol

In vitro cytotoxicity studies of solamargine on cancer cells

The Solanum nigrum plant is the principal source of the alkaloid solamargine. Traditional Chinese medicine holds that S. nigrum may have cooling and detoxifying benefits on the body. In particular, human hepatocellular carcinoma cells may be susceptible to the growth-suppressing and apoptosis-inducing effects of solamargine, a powerful component of S. nigrum. Solamargine may also increase the sensitivity of human breast and lung tumours to chemotherapy drugs.[66]

Human retinal pigment epithelium (RPE1), Chinese hamster lung fibroblasts (V79), human lung fibroblasts (GM07492A), human liver (HL-7702 cells), and human lung fibroblasts (GM07492A). These investigations' findings suggested that solamargine's cytotoxic effects are time- and dose-dependent.[67] Solamargine's IC50 value, or the concentration at which 50% of cell proliferation is inhibited, ranged from 0.91 to 26.66 M for various cell types. Solamargine's cytotoxic effects have also been compared to those of a number of traditional chemotherapy drugs, such as paclitaxel, cisplatin, etoposide, and gemcitabine, in human lung cancer cell lines (H441, H520, H661, and H69). Approximately 6.7, 21, >250, >250, and >250 M for H520, 7.2, 23.4, 136, >250, and >250 M for H661, and 3, 45, >250, >250, and >250 M for H520, respectively, were the IC50s of solamargine, paclitaxel, cisplatin, etoposide, and gemcitabine. [68] In all lung cancer cell lines, solamargine is the most sensitive drug when compared to paclitaxel, cisplatin, etoposide, and gemcitabine. Solamargine's acute or long-term toxicity, however, is not well understood (Sun et al., 2011) .[69]

Anticancer medications frequently cause harm to both healthy and cancerous cells, which is known as an unfavourable impact and can influence the treatment approach. The best anticancer medications should have little to no negative effects on healthy cells while having the greatest capacity to kill cancer cells (Nawab et al., 2012).[70] Because cancer cells grow and divide far more quickly than healthy cells do, oncology therapy procedures place a high priority on medicines that can immediately limit cancer cell proliferation.Al Sinani et al. (2016) showed for the first time the selective effects of solamargine in producing cytotoxicity on human cancer cells (primary bovine aortic endothelial cells, primary human melanoma cell line WM35 (radial growth phase), primary human melanoma cell line WM115, and metastatic human melanoma cell line WM239 (vertical growth phase), in comparison with normal cell lines).[71] Because it selectively and quickly caused necrosis in the high proliferative melanoma cells (WM115 and WM239) while having minimal necrotic effects on the benign radial growth phase melanoma (WM35) and normal cells, the results indicated that solamargine has potential features as a promising anticancer agent (Al Sinani et al., 2016).[72] The previous evidence indicated higher cytotoxicity of solamargine in all lung cancer cell lines with minimal effect on normal cells.

Diosgenin

Diosgenin (25R-spirost-5-en-3-ol), a dioscin hydrolysate, is found in the rootstock of the yam (Dioscorea) and is extensively dispersed in natural plants as a glucoside. Numerous plants, including Trigonella foenum graecum, Solanum incanum, Solanum xanthocarpum, Smilax china Linn, and Dioscorea nipponoca Makino, contain this steroidal sapogenin. [73] It is a phytochemical with physiological activity that affects plants in a number of ways, including the creation of useful meals.1 It serves as a typical first step in the creation of steroid and contraceptive medications. It is also used as medicine to treat diseases like leukaemia, hypercholesterolemia, climacteric syndrome, and colon cancer. [74] It is the basis for the development of sex hormones, oral contraceptives, and many steroidal compounds.1 It takes on steroid saponins in plants. Due to its high steroidal saponin content, China uses Dioscorea zingiberensis (C.H. Wright) to make diosgenin. The traditional method of making diosgenin requires acid hydrolysis of the raw herb, which hydrolyzes the sugar chains of the plant's steroidal saponins to

produce diosgenin.[75] Both the preservation of healthy blood cholesterol levels and the creation of dehydroepiandrosterone have been shown to be advantages of diosgenin. Long-term diosgenin administration significantly reduces bone loss. A literature search revealed that diosgenin may be used as an alternative treatment for a variety of ailments and disorders due to its impressive pharmacological profile. The information gathered in this review will therefore be useful for researchers looking at natural goods. [76]

Diosgenin is a steroidal sapogenin that has been studied extensively to determine whether it can be useful in treating a wide range of Medicinal disorders due to its intriguing bioactivity that has been known for many years.[77] This substance is actually known to have anti-inflammatory and antioxidant properties and can be helpful, for example, in blood and cerebral disorders, allergic diseases, diabetes and obesity, menopausal symptoms, and skin ageing; it can also play a protective role in cardiovascular diseases (like thrombosis and atherosclerosis), but more importantly, in cancer.[78]

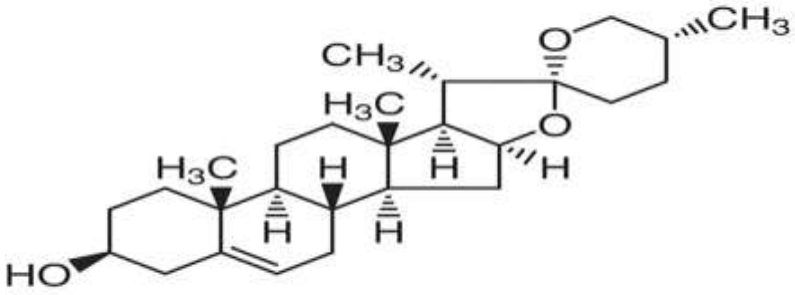


Fig 11: Showing structure of Diosgenin

4.4.1. Molecular Formula: $C_{27}H_{42}O_3$

IUPAC : 2S,4aR,4bS,5'R,6aS,6bR,7S,8R,9aS,10aS,10bS)-4a,5',6a,7-Tetramethyl-1,2,3,3',4,4',4a,4b,5,5',6,6',6a,6b,7,9a,10,10a,10b,11-icosahydrospiro[naphtho[2',1':4,5]indeno[2,1-b]furan-8,2'-pyran]-2-ol

Pharmacological Properties of Diosgenin:

Neuroprotective:

Reactive oxygen stress causes oxidative stress, which in turn causes a number of diseases include cancer, cardiovascular disease, and neurological disorders. Diosgenin is a neuroprotective drug that has been shown to have health advantages in the treatment of multiple sclerosis, multiple sclerosis-related neuroinflammation, spinal cord injury, stroke, thrombosis, and neuropathic pain. (79) A few recent studies based on diosgenin and associated topics have been examined using in vitro, in vivo, and in silico methods and are discussed here. To determine the solubility of the substance diosgenin, a new structure of the neural network has been created. Due to its logical design idea, conventional neural network modelling was utilised to increase calculation accuracy and predict the solubility of diosgenin in nalkanols with more carbon atoms. [80] In a different study, the protective effects of diosgenin against cerebral ischemia-reperfusion injury were assessed in vitro, in vivo, and in silico (proteome dynamic approach). From the brain samples, the authors examined 5043 regulatory proteins and several signalling pathways. Aaron and the team screened small compounds for their ability to target the fungal virulence factors without affecting viability. [81] They showed that blocking Mpr 1's proteolytic activity while keeping Cryptococcus neoformans (Cn) viable prevented Cn from crossing the blood-brai216n barrier. To put it another way, diosgenin greatly decreased Mpr 1 proteolytic activity when combined with two other chemicals (IC50: p; DD10: D-galactose +10 of diosgenin; and DD50: D-galactose +50 mg/kg/day of diosgenin orally). This treatment lasted up to 8 weeks. The overall findings of this study demonstrated that diosgenin has neuroprotective effects against D-galactose-induced ageing brain by suppressing (D-

galactose-induced neuronal Fas-dependent and mitochondria-dependent apoptotic pathways) and enhancing (Bcl-2 family-associated prosurvival and IGF-1- PI3K-AKT survival pathways). [82] Leng and the team further examined the neuroprotective properties of diosgenin in the diabetic rat model. [80] Streptozotocin (dose: 100 mg/kg for 2 days) was administered intraperitoneally to all rats (male C57) and fed to them for up to 8 weeks (high fat diet). The four groups of eligible rats were control (n = 6), diabetic (n = 6), low-dose (n = 6, 50 mg/kg), and high-dose (n = 6, 100 mg/kg) diosgenin groups. The major finding of this study is that diosgenin greatly boosted body weight and decreased blood glucose levels in diabetic rats. MDA levels were reduced by diosgenin (in a dose-dependent manner), although antioxidant enzyme activities (such as glutathione peroxidase (GPx) and superoxide dismutase (SOD)) and expression of heme oxygenase (HO), NAD(P)H dehydrogenase [quinone] (NQO)-1, and nuclear factor-erythroid factor 2-related factor (Nrf2) in diabetic rats. These signalling mechanisms contributed to its neuroprotective effects. [83]

Anticancer:

Cancer is the most dangerous disease that affects people around the globe, with one in every six deaths due to cancer. [84] Different therapeutic tactics, including radiotherapy, chemotherapy, and laser-based therapy, are currently under practice. [84] The cytotoxicity properties of diosgenin have been the subject of numerous tests by scientists all over the world. In a recent study, the cytotoxic effects of Trigonella foenum-graecum's standardised extracts, fractions, and compounds were assessed against human cancer cells (SKOV-3, HeLa, and MOLT-4 cells). Strongest cytotoxic effects on cancer cells were demonstrated by the steroid saponins fraction (C) (IC50: 3.94 (HaCaT), 3.91 (HeLa), 3.97 (SKOV-3), and 7.75 (MOLT-4)). The percentage markedly boosted the cells' generation of reactive oxygen species and caspase activity.[84]

A total of 28 diosgenin amino acid ester derivatives (3a3g and 7a-7g) were designed and synthesized by Ma et al. and evaluated for their cytotoxicity against six human cancer cells including K562, T24, MNK45, HepG2, A549, and MCF-7. [85] The bulk of the derivatives can kill these six tumour cells. Out of 28 derivatives, compound 7g significantly outperformed diosgenin in terms of cytotoxicity against K562 cells (IC50: 4.41 M vs. 30.04 M). Additionally, compound 7 induced apoptosis in K562 cells via mitochondria-related mechanisms. Two distinct Paris polyphylla rhizome extracts (ethanol extract and diosgenin-rich extract) were tested for their cytotoxicity against Hep-2, MCF-7, and MDA-MB-231 human breast cancer cell lines. The highest activity was seen in MCF-7 cells, and the diosgenin-rich extract considerably inhibited the multiplication of all malignant cells. [85]

By suppressing the S-phase kinase-associated protein Skp-2 in breast cancer cells, diosgenin dramatically reduced the cell viability and motility of breast cancer cells and induced death. Although NF-B encourages the onset and progression of cancer, certain studies show that it also plays a function in tumour suppression. [86]

Antiatherosclerosis.

Atherosclerosis is a disease of the middle and large arteries characterized by the formation in the inner tunic and middle deposits of atheromatous plaques, which contain accumulations of LDL-cholesterol, lipophage, and sometimes calcifications on former lesions that prevent normal blood flow through the vessel. [87] It is a condition in which artery plaque builds up and can lead to significant issues like heart failure, stroke, or even death. The numerous pathogenic pathways that contribute to ageing and degenerative brain damage include lipid peroxidation, oxidative stress, inflammation, and altered immunological response.[88] Few researchers have investigated the antiatherosclerotic properties of diosgenin and its derivatives. Lv and the group investigated the therapeutic effects of diosgenin on macrophage cholesterol metabolism and its mechanism in this setting. The liver X receptor levels were unaffected by the diosgenin therapy, but it greatly increased the expression of the ATP-binding cassette transporter A1 (ABCA1) protein. Additionally, diosgenin therapy prevents the evolution of aortic atherosclerosis by downregulating miR-19b proteins in foam cells produced from THP-1 macrophages and MPM. Binesh and colleagues conducted an in vivo investigation of the diosgenin compound and its effects on Wistar rats fed an atherogenic diet. In this study, the atherogenic diet increased the levels of the inflammatory mediators COX-2, TNF, and NFkBp65 in the rats' hearts, livers, and brains, while diosgenin treatment decreased these levels and prevented the onset of atherosclerosis. The same research group reported the downregulation of NF-κB expression and polarization of macrophages by diosgenin treatment. In another study, compound dioscin was evaluated for its inhibitory activity against atherosclerosis and postmenopausal atherosclerosis in ovariectomized LDLR-/-rats.[88]

Different Methods of Extractions:

a) Methanol Extract:

In experiment performed by Naidu Mahadev *et al.* 2014 All tissues of leaf, stem, root, and fruits are allowed to dry firstly and powdered and was allowed to soaked overnight in methanol approx. 30 ml in a beaker for overnight and then the samples were sonified on room temperature for about half hour and the process was carried out three times in all yield followed by metabolites and methanolic extracts was gathered. After collection the extract was was concentrated in rota vapours while being filtered using Whatman filter paper grade 1. The final extract was passed through 0.22µm membrane filter, followed by examination using gas chromatography-mass spectrometry (GC-MS) and High-Performance Liquid Chromatography (HPLC). [28]

b) Soxhlet extraction method:

The fruits should be cut and packed as 50 gm packets using Whatman No, 40 filter paper and extracted by solvents like n-hexane, and acetone, benzene and ethyl acetate, as well as n-hexane and benzene in equal proportion, benzene and ethyl acetate are combined in an equal amount and acetone equally (HPLC grades) for 3 days, in a Soxhlet apparatus individually. Then extracts should be passed through NaOH in anhydrous form to absorb water particles and drying was done under decreased pressure with the help of vacuum pump. Then store the extract it in deep freezer of temperature up to -10^{o}C. [25]

c) Cold Extraction Method (Room temperature extraction method):

For cold extraction fruits are packed in 250 gm packets using Whatman No. 40 filter paper and then it should be placed in a round bottom stopper flask (5 litre capacity) and respective solvent of benzene, n-hexane, acetone, and ethyl acetate are all present in equal amounts and acetone equally (HPLC grades). After allowing it to rest for 72 hrs remove the paper packets and pass by anhydrous sodium hydroxide to absorb water particles and drying was done under decreased pressure using vacuum pump. Then label the extract store in deep freezer (-10^{o}C). [25]

d) Aqueous extraction method:

Pieces of berries to be packed as 250 gm packet using Whatman NO. 40 filter paper will be extracted with HPLC grade water at room temperature in round bottom stopper flask. Wait for 72 hrs after that remove the extract and label the store in a refrigerator. [25]

e) Poison food bioassay (Leaf disc bioassay):

Bioassay is conducted to select the effect accessions and effective extract.

Leaf disc of around 2 cm diameter needs to be cut and the extract need to be smeared on both the ad axial and ab axial surfaces of leaf disc @ 100µ/slide with blunt glass rod. The concentration should be 1 %. Consider Untreated leaf disc as control. Treated leaf after drying with air is placed in petri plates. Then larvae of causative bacilli to be introduced separately in to each Petri plate and covered. All these Petri plates should be kept in the controlled conditions of 23^{o}C to 27^{o}C temperature and 65 to 75 % Relative humidity. Leaves will be gathered from the container when the control leaf disc was fed completely and the leaf area unfed should be identified in each treatment with the help of leaf area meter. Percentage of leaf area over control should be computed and anti feedency needs to be rated as per formula and scale mentioned below. [25]

leaf area protection percent over control can be calculated by =

$$\frac{\text{Percent of protected leaf area in treatment} - \text{Percent of protected leaf area in absolute control} \times 100}{100 - \text{leaf area in protection in control (Percent)}}$$

Tissue Culture Techniques: -

In experiment performed by *S.Viarum* was inoculated and germinated via in vitro seeds in about four week through Young nodal explant of 1.0 to 2.0 cm on MS medium is supplemented with several carbon sources, such as sugars and glucose derivatives, and is solidified with 0.8% (w/v) agar with 2.0 mg/ml of the cytokine BAP. and this was

cultured at 26 ±2° C and Relative humidity between 60 to 70% light intensity was measured between 3000 lux over16–18 hours of daylight and 5–6 hours of night time. [28, 29]

Conclusion: -

Solanum Viarum Dunal has been observed to have a potent anti-inflammatory effect due to the presence of steroidal glycosides such as Solaviaside A, Solaviaside B, Solaviaside C majorly present in fruit part of plant and also due to glycoalkaloids such as Solasodine mainly extracted from roots of plants of S. Viarum Dunal which ultimately act through. S. Viarum Dunal is observed to have very potent anti-bacterial and anti-fungal activity and also Anti-Cancer activity is reported due to solasodine and some antiandrogenic activities are also observed with solasodine, which is chemically present in it. There are various methods of extraction of different steroidal glycosides, glycoalkaloids and Poly phenolic compounds can be extracted through different methods like Methanolic extraction, Soxhlet extraction, Cold extraction method are very useful and can be used for the extraction of different phytoconstituents. It can be grown through different tissue culture methods with temp in 26±2° C and at relative humidity between 60 to 70%. Solanum Viarum Dunal has a very effective role in different inflammatory disease, bacterial infections, which can be explored and used as it has very rich source of phytoconstituents and its potency needs to be identified and explore different prospects of medicinal uses.

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Conflict of Interest: -

There was no conflict interest while performing this study.

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