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Review

A review of the pharmacological aspects of *Solanum nigrum* Linn.

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This article reviews, bridges the gap between the folkloric use of *Solanum nigrum* linn. (Sn) and the results of evidence based experiments. Although Sn is a rich source of one of plants most dreaded toxins solanine, it has appreciably demonstrated its potential as a reservoir of antioxidants having hepatoprotective, anti-tumor, cytostatic, anti-convulsant, anti-ulcerogenic and anti-inflammatory effects. The review encompasses *in-vitro*, *in vivo* and clinical studies done on Sn, while examining whether or not correct scientific measures have been taken in generating experimental evidences for its traditional uses. This review would afford research scientist to know how much is known and what is left undone in the investigation of Sn.

Key words: *Solanum nigrum,* folklore medicine, anticancer, solanine.

INTRODUCTION

Solanum nigrum Linn. (Sn) commonly known as Black Nightshade is a dicot weed in the Solanaceae family. It is an African paediatric plant utilised for several ailments that are responsible for to infant mortality especially feverish convulsions. Sn is an Annual branched herb of up to 90 cm high, with dull dark green leaves, juicy, ovate or lanceolate, and toothless to slightly toothed on the margins. Flowers are small and white with a short pedicellate and five widely spread petals. Fruits are small, black when ripe (Cooper and Johnson, 1984). *S. nigrum* is found mainly around waste land, old fields, ditches, and roadsides, fence rows, or edges of woods and cultivated land. It is a common plant found in most parts of Europe and the African continent. Sn is a popular plant in part due to its toxic content of Solanine, a glyco-alkaloid found in most parts of the plant, with the highest concentrations in the unripened berries (Cooper and Johnson, 1984). Although it is considered a rich source of one of the most popular plant poisons, it has proven also to be a reservoir of phytochemicals with phamacological prospects (Lee and Lim, 2006). The aim of this review is to comprehensively put together the literatures consistent with the pharmacological potentials of Sn.

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CHEMICAL CONSTITUENTS

Several compounds have been isolated from different fractions of Sn which have shown pharmacological relevance to the observed effects of whole plant preparation of Sn. Sun et al. (2006) reported the variability of the concentration of organic acids between seedlings of Sn and the mature plants. Acetic acid, tartaric acid, malic acid and citric acid were identified as the major organic acids in Sn. Tartaric acid and citric acid however, were said to be most important in adaptive responses by Sn to environmental stresses. High concentrations of solanine, a glycoalkaloid is found in most parts of Sn, but highest levels are found in unripe berries of Sn. However, when ripe, the berries are the least toxic part of the plant and are sometimes eaten without ill effects. Similarly, the solanine increases in the leaves as the plant matures (Cooper and Johnson, 1984). Solanine presented in Figure 1 may be separated by chromatography into six components: Alpha, beta gamma chaconines, and alpha, beta gamma solanines (Merck, 1989). Solanidine (C_{27} H_{43} NO; MW = 397.62) is obtained after hydrolysis of solqnine, solanine and is less toxic. Bhat et al. (2008) also reported the salinity dependent production of a

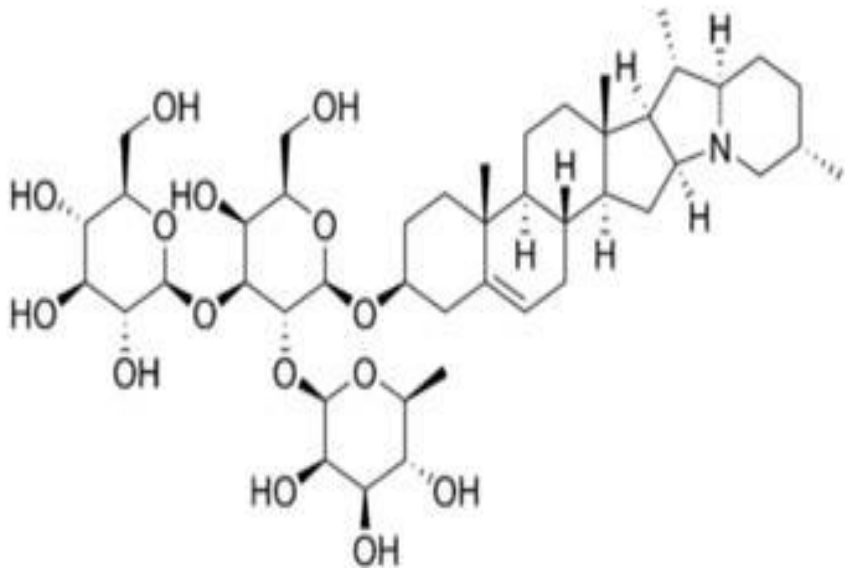

Figure 1. Solanine

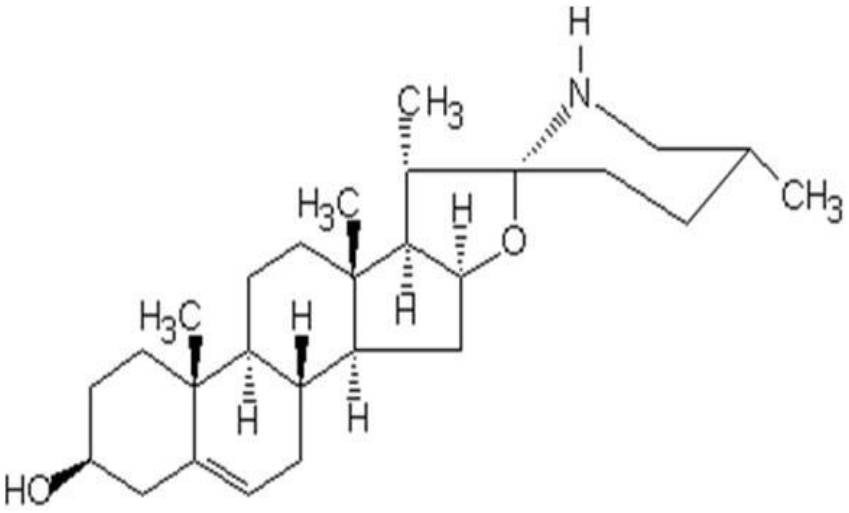

Figure 2. Solasodine

structurally similar steroidal alkaloid, solasodine (Figure 2). Eltayeb et al. (1997) demonstrated that the steroidal alkaloid solasodine was highest in the leaves. However, a somewhat contrasting report by some sources indicate the relative distribution of Solasodine as 9.93 mg g-1 (roots), 6.10 mg g-1 (stems), 4.06 mg g-1 (leaves) and 0.61 mg g-1 (fruits). The absolute amount of alkaloid per leaf increased during leaf development, whereas, the concentration declined. Small unripe fruits of *S. nigrum* had a high concentration of solasodine, but both the concentration and the absolute amount per fruit decreases with fruit maturation. Researches reveal that the alkaloidal content of plant parts changes during development of Sn. Nitrates and nitrites also occur in variable amounts in black nightshade and may contribute to its toxic effects (Cooper and Johnson, 1984). Hu et al. (1999) isolated three anti-neoplastic steroidal glycosides; beta 2-solamargine, solamargine and degalactotigonin.

Studies on Sn through spectroscopic analysis, chemical degradation and derivitisation led to the identification of six new steroidal saponins collectively called solanigrosides and a one known saponin degalactotigonin (Zhou et al., 2006). Similarly, any set of two steroidal saponin known as nigrumins I and II were characterised from Sn. Nigrumnin I was established as (25R)-5alpha-spirostan-3beta-ol 3-O-betaD-xylopyranosyl-(1-->3)-[alpha-L-arabinopyranosyl-(1 –>2)]- beta-D-glucopyranosyl-(1-->4)-[alpha-L-rhamnopyranosyl(1-->2)] -beta-D- galactopyranoside (1), and nigrumnin II was elucidated as (25R)-3beta, 17alpha-dihydroxy-5alpha-

spirostan-1 2-one 3-O-beta-D- xylopyranosyl-(1-->3)-[alpha-L-arabinopyranosyl-(1-->2)]-beta-D-glucopyranosyl-(1-->4)-[alpha-L-rhamnopyra-nosyl-(1-->2)l-beta-D-galac-topyranoside.

Also, five non-saponin namely 6-methoy-hydroxycoumarin, syringaresinol-4-O-beta-D-glucopyran-oside, pinoresinol-4-O-beta-D-glucopyranoside, 3, 4-dihy-droxhbenzoic acid (IV), p-hydroxybenzoic acid and 3-methoxy-4-hydroxyienzoic acid were isolated for studies by Wang et al. (2007)

It was discovered by Schmidt and Baldwin (2007) that Sn produces Sysytemin, an 18 amino acid polypeptide similar to systemic wound response protein produced by tomato. Recently, the isolation of a 910 bp cDNA encoding osmotin-like protein with an open reading frame of 744 bp encoding a protein of 247 amino acids (26.8 kDa) was cloned from *S. nigrum* (SniOLP) (Jami et al., 2007). Phylogenetic analysis revealed the evolutionary conservation of this protein among diverse taxa belonging to a small multigene family and it showed organ-specific expression. The expression of this protein has been discovered to be upregulated by osmotic and oxidative stress inducers.

One spirostanol glycoside and two furostanol glycosides have been isolated from a methanol extract of the stems and roots of *S. nigrum* (Sharma et al., 1983). Quercitin represents one of the most potent natural antioxidants. Sn contains two quercetin glycosides namely, quercetin 3-O-(2^{Gal}-α-rhamnosyl)-β-glucosyl (1→6)-β-galactoside and quercetin 3-O-α-rhamnosyl(l→2)-β-galactoside. Also, previously known quercetin 3-glucosyl(l→6)galactoside, 3-gentiobioside, 3-galactoside and 3-glucoside, were also found (Nawwar et al., 1989). The most recent phytochemical analysis of *S. nigrum* has resulted in the isolation of two novel disaccharides. Their structures were determined as ethyl β-d-thevetopyranosyl-(1→4)-β-d-oleandropyranoside and ethyl β-d-thevetopyranosyl-(1→4)-α-d-oleandropyrano-side, respectively, by chemical and spectroscopic methods (Chen et al., 2009).

The berries of *S. nigrum* have been found to contain a saturated steroidal genin, which has been identified as tigogenin by mixed melting point and i.r. spectroscopy (Varshney and Sharma, 1965). 150-kDa glycoprotein was isolated from *S. nigrum*, which has been used as an antipyretic and anticancer agent in folk medicine. The SNL glycoprotein consists of carbohydrate content (69.74%) and protein content (30.26%), which contains more than 50% hydrophobic amino acids such as glycine and proline (Lee and Lim, 2006).

Although toxic constituents are present in most part of the plants, studies on the nutritional potential of the leaves and seeds revealed that Sn is nutritive despite the presence of some anti-nutritive components like oxalate. Protein content of the leaves and seed was found to be24.90 and 17.63%, respectively. Other findings are ash 10.18 and 8.05%, crude fibre, 6.81 and 6.29% and carbohydrate, 53.51 and 55.85% for the leaves and seed respectively. Mineral analysis revealed the magnitude of presence in the order Mg>K>Ca>Fe>Na>Mn>Zn in the leaves and Mg>K>Fe>Ca>Na>Mn>Zn in the seeds.

Phosphorus and sulphur levels were 75.22 and 8.55 mg/100 g in the leaves and 62.50 and 14.48, g/100g in the seeds. Vitamin content indicate the order of magnitude as Vit C>Vit B,>Folic acid>Vit E>Vit A in both the leaves and seeds. Phytochemical analysis revealed high oxalate, phenol, but low sterol content in the studied plant materials. Cyanide levels were higher in the leaves compared to the seeds.

ANTICANCER PROPERTIES

The effect of crude polysaccharide isolated from *S. nigrum* linn. (SNL-P) was examined both *in vivo* and *in vitro* on U14 cervical cancer cells. Though exposure to SNL-P had no antiprolifreative effect *in vitro* at doses up to 1 mg/ml, it decreased the number of ascites tumor cells and survival time of U14 cervical cancer bearing mice which received between 90 - 360mg/kg bw. P.o. FACScan flow cytometer analysis showed that most of the ascites tumor cells were arrested in G2/M phase of cell cycle. This can be considered as the basis for its use as an anticancer agent (Jian et al., 2009). Similarly, in an earlier work by Jian et al. (2007) on the *in vivo* effect of a 12-day oral administration of SNL-P, showed a significant growth inhibition effect on cervical cancer (U14) of tumor-bearing mice with increased expression of Bax and a decreased expression of Bcl-2 and mutant p53 which had a positive correlation with the number of apoptosising tumor cells. Moreover, SNL-P treatment decreased the level of blood serum TNF-α, this corresponds to triggerring of apoptosis in tumor cells. These findings demonstrated that the SNL-P is a potential antitumor agent (Jian et al., 2007). The review by An Lei et al. (2006) suggests that the anticancer potential of Sn was based on its capacity to interfere with the structure and function of tumor cell membrane, disturb the synthesis of DNA and RNA, change the cell cycle distribution, blocking the anti-apoptotic pathway of NF-kappaB, activating caspase cascades reaction and increasing the production of nitric oxide. The contribution of autophagic cell death in the anticancer pathways of Sn was carefully elucidated through studies utilising LC3-I and LC3-II proteins in Hep G2 cells. Results show a concentration dependent mechanism of Sn in cell autophagy and vacuolisation. This may provide a leverage to treat liver specific cancer.

A case-control study of dietary and social factors was performed for 130 patient/control pairs matched for age, gender, and educational level. Staple diet, consumption of wild vegetables, use of tobacco, and traditional beer consumption were compared between the two groups. *S. nigrum* contains protease inhibitors capable of oesophagic proliferative and oncogenic drive (Sammon, 1998).

The anti-tumor activity of solanine, a steroid alkaloid isolated from the nightshade has been evaluated by the MTT assay on the three digestive system tumor cell lines namely, HepG(2), SGC-7901, and LS-174. Solanine had a concentration specific IC (50) score for HepG (2), SGC-7901, and LS-174 cell lines (14.47, > 50, and > 50 microg/ml, respectively) and signs for apoptosis were found. These effects are obtainable, although much less, in other cancer cell line, for example, the Chang liver and WRL-68 cells (Lin et al., 2007). Cells in the G(2)/M phases disappeared, while the number of cells in the S phase increased significantly for treated groups, which decreased the expression of Bcl-2 protein. Therefore, the target of solanine in inducing apoptosis in HepG (2) cells seems to be mediated by the inhibition in the expression of Bcl-2 protein (Ji et al., 2008). There seems to be a differential response of exposure to either high or low concentrations SNE on the nature of cell death. While high doses elicited apoptotic cell death with corresponding mitochondria release of cytochrome c, and caspase activation at low concentrations SNE (50-1000 µg/ml), revealed morphological and ultrastructural changes of autophagocytic death. Furthermore, these cells showed increased levels of autophagic vacuoles and LC3-I and LC3-II proteins, and specific markers of autophagy. Taken together, these findings indicate that SNE induced cell death in hepatoma cells via two distinct antineoplastic activities of SNE- the ability to induce apoptosis and autophagocytosis, therefore, suggesting that it may provide leverage to treat liver cancer (Lin et al., 2007).

Also, the aqueous fraction of Sn was tested for its antitumor activity *in vivo*. This closely mimics the preparation of plant in folklore medicine. Aqueous extract of *S. nigrum* (SNL-AE) inhibited U14 cervical carcinoma growth and increased the number of CD4+ T lymphocyte subsets as well as the ratio of CD4+/CD8+ T lymphocyte, decreased the number of CD8+ T lymphocyte subsets of tumor-bearing mice and PCNA positive cells. Furthermore, SNL-AE caused cell cycle arrest in G0/G1 phase and induced apoptosis of more transplanted tumor cells in a dose-dependent manner, suggesting that the anti-tumor activity of SNL-AE is embedded in its immune-modulatory effects (Jian et al., 2008). Results of some studies show that Sn achieves antitumor activity by beefing up the oxidative stress threshold of the neoplastic cell.

A proline and glycine rich glycoprotein (150kDa) isolate of Sn had modulatory effects on transcriptional factors (NF-kappa B and AP-1) and iNO production which in turn enhanced NO production in MCF-7 cells (Heo et al., 2004; Son et al., 2003; Lim, 2005). It is evident that this glycoprotein stimulates the mitochondrial release of cytochrome C, which culminates in caspase activation and the eventual death of tumor cells. Another 43 amino acid, 4.8 kDa peptide Lunasin originally found in soybean was identified in Sn. It elicits anticancer and cell-cycle arrest by inhibiting phosphorylation of retinoblastoma protein (Rb) and acetylation of core histone H3 and H4 (Jeong et al., 2008). Anti-angiogenesis is an established antineoplastic mechanism of many chemotherapeutic agents. Sn displayed anti-angiogenic activity on chick chorioalliantoic membrane (Xu et al., 2008).

IMMUNOMODULATORY EFFECTS

In vivo experiments showed that the ratio of CD4+/CD8+ peripheral blood T-lymphocyte subpopulations were restored following the treatment of SNL-P. Furthermore, treatment with SNL-P also caused a significant increased in IFN-α ($p < 0.01$, 90, 180 and 360 mg/kg bw) and a remarkable decrease in IL-α ($p < 0.01$, 90, 180 mg/kg b.w.; $p < 0.05$, 360 mg/kg b.w.) measured by the method of ELISA.

These data showed that SNL-P possess potent antitumor activity and SNL-P might exert antitumor activity via activation of different immune responses in the host rather than by directly attacking cancer cells on the U14 cervical cancer bearing mice. Thus, SNL-P could be used as an immunomodulator (Jian et al., 2009).

ANTIMICROBIAL, NEMATICIDAL AND MOLLUSCICIDAL PROPERTIES

Root extracts of black nightshade (*S. nigrum*) were analyzed for its activity against isolates ABA-31 and ABA-104 of *Alternaria brassicicola*, the causal agent of black leaf spot of Chinese cabbage (*Brassica pekinensis*). Methanolic extracts of dried root tissues of black nightshade contained antifungal properties wchich act against *A. brassicicola*. Further fractionation and anti-microbial screening of ethyl acetate, n-butanol and water fractions of root extracts showed that n-butanol extracts was the most potent. Saponins were identified as the active principles conferring antimicrobial effects on Sn (Muto et al., 2006). Afaf s' and Soads' (2007) investi-gation on the effect of sub-lethal (LC25) concentration of leaves of Sn on Saudi Arabian mollusc *Biomphalria arabica* revealed that AST, ALT and LDH activities were affected in them and may suggest the mechanism for its molluscicidal activities. Similarly, binary combination of Sn and *Iris pseudacorus* by Amer and Manal (2005) had molluscicidal and cercaricidal efficacy against *Biomphalaria alexandrina* and *Schistosoma mansoni cercariae*, respectively (Ahmed and Ramzy, 1998). The effect of a 30 min pre-treatment of mice with varied concentration (2.5 – 10 mg/ml) of crude water extract of Sn on penetration and infectivity of *S. mansoni cercariae* showed a significant reduction in penetration ($p < 0.001$) and infectivity ($p < 0.01$) (Amer and Manal, 2005). Also, a recent work done by Raghavendra et al. (2009) and Ahmed et al., (2002) appraised Sn extracts as a larvicidal agent against five laboratory colonised strains of mosquito species.

ANTIOXIDANT PROPERTIES

Many pathological states encompassing both communicable and non-communicable diseases have been shown to have association with oxidative stress.

Consequently, the need for potent antioxidants in our diet and drug supplements becomes very necessary. A study which utilises six pretreatment methods before cooking on the peroxidase activity, chlorophyll and antioxidant status of *S. nigrum* L., showed that pretreatment methods have significant effects ($p < 0.05$) on the parameters measured. A sharp difference in the carotenoids, phenolics, flavonoids and tannins contents has been reported, indicating the fragility of this antioxidant present in Sn (Adebooye et al., 2008). SNL glycoprotein showed a dose-dependent radical scavenging activity on radicals, including 1, 1-diphenyl-2-picrylhydrazyl (DPPH) radicals, hydroxyl radical (OH), and superoxide anion (O_2^-).

Although Sn acts as an anti-tumor, the SNL glycoprotein may induce apoptosis through the inhibition of NF-κB activation, induced by oxidative stress in HT-29 cells (Heo et al., 2004). A 50% ethanol extract of the whole plant of *S. nigrum* also possess hydroxyl radical scavenging potential which is suggested as cytoprotective mechanism (Kumar et al., 2001; Mohamed et al., 2007). Evaluation of the antioxidant potential of Sn leaves on the modulation of a 6 h restraint induced oxidative stress, which suggest that Sn was better as an antioxidant with post-restraint treatment than with pre-restraint administration.

ANTI-CONVULSANT ACTIVITY

Central nervous system-depressant action of Sn was ascertained by measuring the effects of intraperitoneal injection of Sn on various neuropharmacological parameters. Fruit extracts of Sn significantly prolonged pentobarbital-induced sleeping time, produced alteration in the general behaviour pattern, reduced exploratory behaviour pattern, suppressed the aggressive behaviour, affected locomotor activity and reduced spontaneous motility. This buttresses its usage as an anti-convulsant and may concur with its acetylcholine-like activity (Perez et al., 1998). The potency of Sn in combating infant convulsion is widely accepted in African paediatric medicine. Wannang et al. (2008) tested the anti-convulsant effects of leaves of *S. nigrum* in chicks, mice and rats.

A 30 min pretreatment by intraperitoneal injection of Sn leaf extract protected the animal subjects against different types of proconvulsants. The aqueous leaf extract produced a significantly ($p < 0.05$) dose dependent protection against electrically-induced seizure in chicks and rats, pentylenetetrazole-induced seizure in mice and rats and picrotoxin-induced seizure in mice and rats (Wannang et al., 2008). De Melo et al. (1978) were the first to present experimental data supporting the claims of the acetylcholine-like activity of Sn. They based their conclusion on the basis of the observation of the following effects: Isotonic contraction of the isolated toad rectus abdominis; 2) Negative chronotropic and inotropic action on the isolated toad heart; 3) Isotonic contraction of the isolated guinea pig's ileum; 4) Isotonic contraction of the rat's isolated jejunum; 5) Decrease on the cat's arterial blood pressure; 6) Secretory effects on the rat's submaxillary gland. Fruits of Sn were also found to contain acetylcholine-activity compounds up to 250 micrograms/g of fruit (de Melo et al., 1978).

HEPATOPROTECTIVE EFFECTS

S. nigrum L. (SN) is an herbal plant that has been used as hepatoprotective and anti-inflammatory agent in Chinese medicine. Sprague-Dawley (SD) rats orally fed with SNE (0.2, 0.5, and 1.0 g kg^{-1} bw) along with the administration of CCl_4 (20% CCl_4/corn oil; 0.5 mL kg^{-1} bw) for 6 weeks displayed that Sn had hepatoprotective effects against CCl_4. The test drug significantly lowered the CCl_4-induced elevation of hepatic enzyme markers (GOT, GPT, ALP, and total bilirubin) and decreased superoxide and hydroxyl radical generation (Raju et al., 2003) in comparison with the CCl_4 treatment group. Liver histology showed that SNE reduced the incidence of liver lesions including hepatic cells cloudy swelling, lymphocytes infiltration, hepatic necrosis, and fibrous connective tissue proliferation induced by CCl_4 in rats (Lin et al., 2008). Other studies using other hepatotoxic challenges such as thioacetamide (TAA), a liver fibrosis inducer was attenuated by a 12 days administration of SNE (0.2 or 1.0 g/kg) via gastrogavage throughout the experimental period. SNE reduced the hepatic hydroxyproline and α-smooth muscle actin protein levels of TAA-treated mice. SNE inhibited TAA-induced collagen (α1) (I) and transforming growth factor-β1 (TGF-β1) mRNA levels in the liver (Hsieh et al., 2008; Sultana et al., 1995).

Another study by Hsu et al. (2009) utilised 2-acetylaminoflorene as an inducer of hepatocarcino-genesis. Sn inhibited hepatocarcinogenesis which is consistent with increased expression of glutathione S-transferase-alpha and -mu, the level of transcription factor Nrf2, glutathione peroxidase, superoxide dismutase-1, and catalase (Hsu et al., 2009).

In Africa, Aflatoxin B1 induced liver cancer is a common cause of hepatocarcinogenesis. Activation of several cytochrome p450 systems and depression in the expression of phase II enzymes responsible for AFB1 metabolism precludes its toxicity. Sn increased the activity of uridine diphosphate glucuronyltransferase (UDPGT) and glutathione S-transferase in female rats toxicated with AFB1 (0.2 or 0.4 mg/kg bw) (Moundipa and Domngang, 1991).

ANTIULCEROGENIC AND ANTI-INFLAMMATORY EFFECTS

Sn is recommended in ayurveda for the management of gastric ulcers, it is therefore, essential to find out what the mechanism of anti-ulcerogenic effect is. Rats were exposed to various types of stress (cold restraint stress, indomethacin, pyloric ligation, ethanol and acetic acid) to induce stress ulcers. Sn fruits extract significantly inhibited the gastric lesions induced by 76.6, 73.8, 80.1 and 70.6%, respectively, with equal or higher potency than omeprazole. Sn extracts showed concomitant attenuation of gastric secretory volume, acidity and pepsin secretion in ulcerated rats (Akhtar and Munir, 1989). In addition, SNE (200 and 400 mg/kg b.w.) accelerated the healing of acetic acid induced ulcers after treatment for 7 days. Enzymatic studies on H^+K^+ATPase activity to ascertain the antisecretory action showed that SNE significantly inhibits H^+K^+ATPase activity and decreases the gastrin secretion in EtOH-induced ulcer model. Histological studies revealed a reduction of ulcer size by SNE (Jainu et al., 2006). Data suggesting the anti-inflammatory and analgesic potential of Sn is provided by Zainul et al. (2006). Quite recently, the potency of the 150 kDa glycoprotein of Sn in preventing dextran sodium sulfate-induced colitis in A/J mouse was determined. It was observed that Sn had suppressive effects on the concentrations of nitric oxide production, lactate dehydrogenase release and thiobarbituric acid reactive substances. This is achieved through the regulation of transcription factors such as NF-kappaB (p50) and AP-1 (c-Jun). Also, Sn regulates the expression of iNOS and COX-2, which are principal enzymes in inflammatory response pathways.

HYPOLIDEAMIC, ANTI-HYPERGLYCEMIC AND HYPOTENSIVE POTENTIALS

Hyperlipidemia is a major risk factor in cardiovascular pathologies. Atherosclerosis and other forms of cardiovascular dysfunction are promoted by excessive agitation of the cation pumps on the cell membranes. It is therefore, conceivable that since Sn had inhibitory effects on the H+K+ATPase, it could serve as cardioprotective regimen. Hypolipidemic agents are the first defence against lipid associated pathologies, therefore, the investigation of the effects of 150 kDa glycoprotein isolated from *S. nigrum* Linn. (SNL), which has been used as a hepatoprotective and anticancer agent in folk medicine is necessary. Mice treated with Sn had decreased levels of the plasma lipoprotein levels (TG, TC and LDL). In addition, SNL glycoprotein inhibits the activity of cholestyramine-induced hepatic HMG-CoA reductase at 40 µg/g head body weight (Lee et al., 2005). Validation of the ethnobotanical use of the leaves of *S. nigrum* Linn. (Solanaceae), *Vitex negundo* Linn. (Verbenaceae) and stems of *Nopalea cochinellifera* (Linn.) as anti-diabetic agents using the oral glucose tolerance test showed that there was no significant lowering in BGLs by *S. nigrum* (Villaseñor and Lamadrid, 2006).

Sn which has been used as an antipyretic and anticancer in folk medicine was investigated for its anti-hypertensive properties. A 150 kDa glycoprotein isolated from Sn is made up of carbohydrates (69.74%) and protein (30.26%), which contains more than 50% hydrophobic amino acids such as glycine and proline blocked nuclear factor-kappa B (NF-κB) activation, and reduced inducible nitric oxide (iNO) production *in vitro* at a concentration of 40 µg/ml (Lee and Lim, 2006).

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