Solanum incanum, Solanum nigrum (Solanaceae)

In the plant family Solanaceae (night shadow plants) the genus Solanum is a very large group of about 1400 species found throughout in the temperate and tropical regions of the world like

Solanum aviculare (Europe, New Zealand), S. dulcamara (Europe), S. incanum (Africa), S. khasianum (Indian subcontinent), S. laciniatum (New Zealand, Australia), S. nigrum (cosmopolite), S. pseudocapsicum (an ornamental, cultivated in greenhouses), S. tuberosum (potatoe) and S. melongena (eggplant, aubergine).

These are the most prominent plants because they are growing or cultivated worldwide and/or are used commercially. Here we especially deal with following species being applied as medicines according to the new literature.

Solanum incanum: Bitter apple, Thorn apple

African vernacular names

Arabian: Ainal baqar, arsam Omar: mazi, helkem Yemen: nuquum
Chagga: Nduo Ndebele: Umdulukwa Shona: Djinsa, dungwiza, mudulukwa
Southern Soto: Thola Swahili: Tungujamito

Solanum nigrum: Engl.: Garden nightshade, hound`s berry, morel, Egyptian weed French: Creve chien, morelle noir, herbe a magicians, herbe a gale, raisin de loupe Spanish: Ballerina, ortense, solatro, yerba mora Portuguese: erba mora Ital.: Erba morella German: Schwarzer Nachtschatten Chinese: Long kui Tagalog (Philippines): Lubi-lubi

African vernacular names

Sudan: Gouta kaui Xhosa: Umsobo Swahili: Tungujamito Zulu: Isilalakule, ndoye, ugwabha, umaguqua, umsobo

Solanum melongena: Aubergine, eggplant, Jews apple, mad apple

Description of the plants

Solanum incanum: Herb or shrub up to 1.8 m heighth with spines on the stem, leaves, stalks and calyces, and with velvet hairs on the leaves. Leaves are alternate, flowers often borne in the leaf axilles, sometimes solitary or in few-flowered clusters. The calyx is united, corolla regular, bell- or wheel shaped. 5 stamens are inserted on its throat. Fruits are yellow at the beginning, later on black. They are mostly toxic.

Solanum nigrum: Annual herb, erect, 25-100 cm high, pubescent with simple hairs. Stems are often angular, sparsely-pubescent. The blades of the leaves are ovate, the bases are cuneate, 4-10 and 3-7 cm wide, pubescent, entire or coarsely dentate, the apex is obtuse. Inflorescences are extra-axillary umbels, the calyx cup-shaped, the corolla is white, 8-10 mm long , the lobes ovate-oblong, pubescent abaxially, ciliate spreading. Filaments are 1-1.5 mm long, anthers oblong, 2.5-3.5 mm. Fruiting

pedicels are strongly deflexed. The fruiting calyx is applied to the berry. The fruits are dull black, globose, 8-10 mm in diameter.
The fruits are toxic.
The name Solanum nigrum has become commonly used for many similar species, and more than one taxon may be presented in the material treated here under this name.

Plant parts used

The leaves, the whole plant, the fruits, the roots

Constituents

Steroid alkaloids

All **green and unripe parts** contain steroid glycosides, in form of glycoalkaloids. In the genus Solanum they are important, both ecologically and commercially. They are widely regarded as defensive allelochemicals of the plants against pathogens and predators. Economically they are used instead of the steroidal sapogenin diosgenin as raw material for the industrial production of corticoids.
The main steroid alkaloids are **Solanin** and **Solasonine**
Both consist of an aglycone and are connected mostly with 3 sugar parts like a chain. So they are called solatrioses.
The **total contents** of steroid alkaloids differ from 0.1 up to 0.5 % depending from the species and from the plant part investigated. The highest amounts are in the **fruits** and **seeds.** The content of solasodine in S. incanum **young leaves** is 0.42 % and in S.nigrum **young leaves** 0.17 % (15).

Solanin (aglycon solanidin): $C_{45}H_{73}N\,O_{15}$ MG 868, 04, mp 286 ^{0}C, white crystals, not soluble in water or aceton, soluble in MeOH and EtOH
Solanidin: $C_{27}H_{43}NO$, MG 397.65, mp 318 ^{0}C. It cannot be destroyed by cooking or heating.

Solasonine (aglycon solasodine) is a solatriose. It is connected with the 3 sugars galactose, rhamnose and glucose, in the same branched manner like solanin.

This special branched connection is said to be responsible for the activity against skin cancer.
There is a difference concerning the connection in the sugar chains, too.
In chacotrioses like chaconin the aglycon of the alkaloid is connected directly with glucose, which itself is connected with two portions rhamnose in a branched mode.
In solatrioses like solanine the alkaloid aglycon is connected with galactose, which itself is connected with glucose and rhamnose in a branched mode.
Chacotrioses are said to have a higher activity than solatrioses with regard to their membrane disruptive activity. (41).
In many species “paired"glycoalkaloids are present. It means two glycoalkaloids have a common aglycon, but differ in their carbohydrate moiety (41).

Content of glycoalkaloids

In extracts of Solanum sodomaeum: (10)

ripe fruits	0.83 +/- 0.11	unripe fruits 0.45 +/- 0.08
leaves	0.14 +/- 0.01	stem < 0.04
		(g/100 g/fresh weight)

In green parts of Solanum tuberosum

0.6 - 1.3 % during flowering	
0.3 – 1.0 %	(% of dry weight)

Analytical determination of glycoalkaloids:

By TLC: Eluent EtAc, pyridin, water (30/30/10) upper phase for Silicagel plates, detection by the steroid reagent anisaldehy-H_2SO_4 or Dragendorff solution after heating the plates

By HPLC: Eluent acetonitril and pentasulfonic acid (83+17), pH adjusted to 2,8 with phosphoric acid (conc), prepacked column 30.0 cm x3,9 mm, particle size10 µ, alkamine material from Waters, detection wavelength 205 nm (10). According to the reaction between alkaloids and Dragendorff reagent a simple spectrophotometric method can be exerted for commercial samples and pharmaceutical products (45).

Practical application of glycoalkaloid analysis

Nightshade berries containing glycoalkaloids can be contaminants of green peas. A HPLC method can detect this contamination, mainly caused by solasodine:

Extraction of the green peas by 1 % acetic acid, C18 cartridge, UV-detection at 200 nm. The method was evaluated in a 2-year study with 60 samples of frozen green peas from Ontario, Canada (8).

Steroidal saponines

In most species steroid saponines were found, additionally. Their sapogenines are diosgenin, hispigenin, neochlorogenin, solagenin, tigogenin, yamogenin.

From S. nigrum whole plants six new steroid saponines, solanigrosides 2-7 and one known saponine, degalactotigonin were isolated. Their chemical structures were analysed. On human tumour cell line their cytotoxicity was tested. Only degalactogonin was toxic with IC 50 values 0.25 – 4.49 µM (48).

From the **whole plant** of S. nigrum two new steroidal oligoglycosides, together with two known saponines were isolated and named nigrumnin I and II. According to the structure analysis they are both spirostan derivatives (21).

Further compounds

In some other Solanum species, like S. malacoxylon and S. verbascifolium glycosides of dihydrocalciferol could be detected. If cattle take up these substances they can become ill.

In the **whole fruit** and in the **peel** of S. melongena the flavonoid delphinidine was detected (36).

In fresh **berries** of S. incanum an additional steroid alkaloid glycoside could be found. It was named incunamine and characterised as a further compound of solasodine (32).

Traditional uses

In historical times Solanaceous plants like Datura spec, Mandragora autumnalis, and Withania somnifera were used as narcotics. Because of the extensive distribution of modern, safe narcotics and anaesthetics now, the use of these plants has been abandoned. Only some local healers employ them, mostly externally and not as narcotics. In a recent survey of the Haifa University in Israel local healers, belonging to various religious and ethnic communities apply only the four species Lycium europaeum, Solanum nigrum, Hyoscyamus aureus, Hyoscyamus albus (13).

In the Ayurvedic system of traditional medicine in India S. nigrum is applied against enteric diseases. But in an antibacterial screening of such plants methanolic and

aqueous extracts showed only moderate activity with multidrug-resistant Salmonella typhi. Other Ayurvedic plants had a stronger activity (39).
In the Guruve District of Zimbabwe 15 plant species are used against sexually transmitted diseases. The informations gathered from traditional healers mention Solanum incanum of which the roots are applied orally as extracts (23).
In the traditional Chinese medicine Solanum nigrum has been used for centuries because of its diuretic and antipyretic effects (29).
In Kenya the fruits of S. incanum are applied against cutaneous mycotic infections and other pathological conditions (7).

Results of experimental studies

Solanum incanum

Common effects on the metabolism of animals:

In South Africa rats given herbal extracts were monitored about metabolic affects. The daily dose was 20 mg/kg bodyweight.
In the group of S. incanum the root extract given for 5 weeks increased the food consumption. The blood glucose concentration was reduced. Similar results were obtained in the group of diabetic rats treated with metformin or glibenclamid.
The authors conclude that the examined herbal extracts cause glycaemia, probably by interfering with either food uptake or gastrointestinal glucose absorption (35).
In contrast the leaves of S. nigrum were tested in mice using the oral glucose tolerance test. There was no significant lowering in the levels of blood glucose after administration of leaves (46).
In rats the powder and the methanolic extract of aerial parts from S.nigrum lowered the ulcer index significantly (4).
S. nigrum fruit extract was applied in ulcerated rats. After treatment of 7 days the fruit extract (200 and 400 mg/kg) accelerated the healing of acetic acid induced ulcers. It significantly inhibits H^+ and K^+ ATPase activity and lowered the gastrin secretion in ethanol-induced ulcer model (22).

Cytotoxicity and anticancer effects

Different extracts from S. incanum berries were tested in vitro for antimicrobial activity against three Gram-positive two Gram-negative, and five human fungal pathogens. S. incanum methanol extract of fruits showed a very strong inhibition (5).
Solamargine, purified from Chinese S. incanum possessed a potent cytotoxicity to human hepatocytes and normal skin fibroblasts leading to cell apoptosis by changes of cell morphology and DNA content (19,24). In similar mode, solamargine from S. incanum herb displays a superior cytotoxicity in four human lung cancer cell lines with IC50 values of 3 – 5.8 µmol (33).
In Taiwan crude drug extracts of entire S. incanum plants were administered to rats as doses of 1.0 g/kg i.p. injection. It was shown, that these injections possessed a marked hepatic protective effect. The hepatic fatty metamorphosis and necrosis of central lobules were obviously improved by S. incanum (12).
The ethanol extract of ripe berries was tested for its growth inhibiting effect with breast cancer cells (MCF-7). The proliferative capacity of the cells was strongly suppressed in the presence of the extract. They became apoptotic, based on the appearance of DNA laddering and the increase of DNA fragmentation (44).

Tick control

In Western Ethiopia plants and plant products are used for tick control of rural livestocks, here in the indigenous Bos indicus cattle infected with ticks. Between

others the fruit juice of S. incanum was tested in vitro. Preparations of S. incanum applied against female Boophilus decoloratus resulted in 30-70 % killing of the parasites (40).

Solanum nigrum

Cytotoxicity and anticancer effects

In mouse macrophage cells (MCF-7) S. incanum purified glycoprotein was toxic in low doses. It induced apoptosis through modulation of PKC alpha and NF kappa B activity. It interfered with the PKC alpha membrane translocation and inhibited the NF kappa protein activity in MCF-7 cells stimulated with TPA (61.68 ng/mL =100 nM), dose dependently. These data may show that S. nigrum glycoprotein is a potential natural anticancer agent (18).

In mouse peritoneal macrophage cells a study about NO production was performed. With S. nigrum (no information about the preparation) together with 20 U/ml recombinant interferon gamma there was a marked induction of NO production, an important anticancer agent. (6).

The radical scavenging activity of S. nigrum protein of superoxide anion and hydroxyl radicals is optimal in acidic pH and at a temperature up to $6o^{0}$ C. It is not depending on M^{2+} ions like Ca^{2+*} and Mn^{2+}. In the presence of EDTA it is minimal (18).

A glycoprotein isolated from S. nigrum (150 kDa) consisted of 69.74 % carbohydrate and 30.26 % protein. In HTC-116 cells it showed a remarkable cytotoxic and apoptotic effect at 40 μg/ml in 4 h. It had a stimulatory effect on caspase-3 and PARP cleavage in HCT-116 cells. It blocked the nuclear factor kappa B activation and reduced inducible the nitric oxide production. The apoptosis in HCT-cells resulted in more than 50 % cell deaths (28,30).

The same glycoprotein lowered the cell number of viable HT-29 cells at the low concentration of 60 μg/ml during 4 h. The apoptotic effects and the amount of DNA fragmentation increased in a dose dependant manner after the treatment with the protein. Authors believe this glycoprotein as a natural anticancer agent due to its potential to induce apoptosis in the HTC-29 cells (30).

In the presence of the glycoprotein the lipid levels in mice were tested. In mice treated with either Triton WR-1339 or corn oil the contents of plasma lipids, triglycerides, cholesterol, and low density lipoproteins increased. In the presence of glycoprotein these levels were significantly reduced.

After the treatment with glycoprotein the activities of the detoxicant enzymes superoxide dismutase, catalase, glutathione peroxidase remarkably raised. Authors speculate that this glycoprotein can be used as a cholesterol lowering agent (28).

Molluscicidal activity

The molluscicidal properties of S. nigrum plants collected in Fayium and Giza (Egypt) were tested against three Egyptian snail species (Biomphalaria alexandrina, Bulinus truncates, Lymnaea natalensis), each an intermediate host of parasites causing schistosomiasis and fascioliasis.

The snails were exposed to the dried powdered fruits and leaves or to water extracts. The mortality was recorded. The water extract of the material from Fayium had the highest molluscicidal activity with a LC 50 value of 14.5 - 18.6 mg/l. Biomphalaria alexandrina infested with Schistosoma mansoni and exposed to the Fayium extract shed significantly fewer cercarias than unexposed snails. The cercaricidal activity after 30 min exposure was observed directly. It had a LC 100 value of 30 mg/L for

both Schistosoma haematobium and Schistosoma mansoni, and of 40 mg/L for Fasciola gigantica. (3).
An ethanolic extract, made by soaking leave powder from S. nigrum overnight has the highest activity, LC 50 3.37 mg/L within 24 h. This extract also showed larvicidal activity against the larvae of the mosquito species Aedes caspius and Culex pipiens (LC 50 51.29 and 125.89 mg/L within 24 h and 21.38 and 38.11 mg/L within 48 h). The concentrated extract (1000mg/L) can be stored at room temperature for six month without any change in its activity. But diluted solutions lost their activity after four weeks (2).
A crude water extract of S. nigrum leaves was used to attenuate Schistosoma mansoni cercaria prior to infection of Swiss female mice. The observed reduction of cercarial penetration was significant at concentrations of 7.5 and 10 mg/L ($p<0.001$). The mean number of he worm burden declined from 28.5 worms/mouse (untreated) to 4.4 worms/mouse (treated with 7.5 mg/L) ($P<0.01$). Mice treated with 10 mg/L had no adult worms. The number of schistosome eggs in hepatic tissue decreased in the treated mice (1).
Aspartate (AST) and alanine amino transferase (ALT), and lactate dehydrogenase (LDH) of Biomphalaria arabica, the intermediate host of Schistosoma mansoni in Saudi Arabia was measured. The enzymes of Schistosoma, treated with sublethal doses of S. nigrum were altered. AST and ALT were slightly affected, but LDH was significantly altered (14).

Effects of other Solanum species

Solanum aculeatum:
In Kenya aqueous suspensions of powdered S. aculeatum berries were tested for activity against the snails Biomphalaria pfeifferi, Bulinus globosus and Lymnaea natalensis under laboratory conditions.
100 or 50 mg powder of sun- or freeze dried berries killed over 60 % of the tested organisms; whereas 25 mg of the sun dried material killed less than 60 %.The freeze dried plant material was more potent than the freeze dried berries. The powdered material retained molluscicidal activity, even after several months` storage at room temperature. Authors recommend S. incanum as a potent molluscicide in Kenya (34).

Solanum melongena

Protective effects Looking for protective effects of vegetables for human health an investigation was performed about the properties of the eggplant (S. melongena), especially against cancer. Here the inhibitory effect of delphinidin, a flavonoid compound of the whole eggplant and of the peel was analysed. The extract and delphinidin did not affect tumour cell adhesion of human fibrosarcoma HT-1080 cell invasion on reconstituted basement membrane matrigel. Delphinidin slightly inhibited the activity of matrix metalloproteinases-2 and -9. This may be responsible, in part for the inhibition of tumour cell invasiveness (36).

Solanum sodomaeum

Antitumour effects: Glycoalkaloid extracts (33 % solasonine and 33 % solamargine, remainder mixture of mono-and diglycoside with solasodine) of S. sodomaeum showed an antineoplastic activity against Sarcoma 180 in mice: In single dose studies ED50 was 9 mg/kg and LD50 was 30 mg/kg. Single doses of 8 mg/kg, given on two consecutive days inhibited the tumour progression with greater than 40 % survival. The same doses given on 3 or 4 consecutive days resulted in a survival more than 90 %of the animals (10).

Results of clinical studies

Anticancer activity

The naturally occurring solasodine glycosides ("BEC") have an anticancer activity in cell cultures of animals and in humans. Specific endogenous lectins in membranes of cancer cells recognise and bind the sugar moiety of BEC. BEC is subsequently internalised and causes cell death by destroying the lysosomes. This mechanism is different from other anticancer drugs working on the nuclear contents of DNA and RNA in the cells, destroying normal cells as well (9).

In different hospitals of London (The Royal London Hospital, The Mary`s Hospital, The Thomas`Hospital), in Leicester and in Liverpool multi-centre Phase III clinical trials were done against non-melanoma skin cancers. The medicament was a so called **Curaderm-BEC-5**, a cream formulation with 0.005 %. BEC-5 is a standardised mixture of triglycosides from solasonine, solamargin and their corresponding di- and monoglycosides. All glycosides contain the same aglycon solasodine.

In an open study with 72 patients the treatment resulted in the regression of all treated lesions, 56 actinic keratoses, 39 basal cell carcinomas (BCC), and 29 superficial cell carcinomas (SCC). The result was 100 % after a treatment of 1-13 weeks. In this study the application of the cream with 10 % Curaderm BEC-5 resulted in swelling of the BCC and SCC lesions with reddening of the surrounding skin, then ulceration in about 2 days, followed over the next weeks by healing, and with healthy new cell growth. The only reported adverse events were mild itching and burning feelings of the lesion with few patients. Lesions treated appropriately with Curaderm BEC-5 resulted in no recurrence, the cosmetic result was excellent.

The authors recommend Curaderm BEC-5 as an ideal therapy for skin cancers, if these are treated for long enough time, therefore.

This recommendation is not valid for melanoma cancers.

In another clinical trial with Curaderm BEC-5 cream the remission was 78 % within 8 weeks. A longer therapy than that of 8 weeks would have resulted in higher success rates.

In a subsequent study with 41 patients, carried out at the Dermatologic Department of the Royal London Hospital, it was also shown that Curaderm BEC-5 was effective on morpheoic BCC lesions, a type of invasive BCC.

Success was defined as zero presence of BCC in the histological examination after the punch biopsy.

The dermatologists at the Royal London Hospital conclude that the topical Curaderm BEC-5 therapy is safe and effective, cost effective and an ideal therapy for outdoor patients. It is a much needed alternative to surgery for BCC, the most common cancer worldwide with an increasing ageing population (9).

The amount of BEC in Curaderm is very small. One average sized egg plant fruit (300g) contains the same amount of BEC as 60 tubes of Curaderm. Thus, Curaderm-BEC is safe as shown by the many published studies, according to the meaning of the authors.

Toxicology

Complaints of an intoxication are burning of the throat, headache, dizziness, nausea, vomiting, abdominal pain, diarrhoea. With one exemption from older literature of the year 1940, never any illness was reported with fatal result.

Steroidal alkaloids for humans per os
2 – 5 mg /kg: toxic effects
3 – 6 mg/kg: possibly lethal
400 mg dosis lethalis (16)

LD 50 values

Solanin:	Mice i.p.	32 – 42 mg/kg	1000 mg/kg per os not toxic
	Rats i.p.	67 – 75 mg/kg	
	Rats per os	590 mg/kg	
	Sheep i.v.	50 mg/kg lethal, up to 225 mg/kg per os not lethal	
	per os	500 mg/kg lethal	
	Rabbits i.p.	10 - 30 mg/kg lethal	
	Rhesus i.p.	20 mg/kg lethal	
Solanidine:			
	Mice i.p.	500 mg/kg (16)	

Glycoalkaloids of Solanum sodomaeum (extracted with DMSO)

Mice	i.p.		
	lethal	150 mg/kg	
	LD50	30 mg/kg	
	LD50	550mg/kg, single dose with gastric intubation	
Rats	i.p.		
	LD50	41 mg/kg	(10,16)

Evaluation

Solanaceous plants are biologically active because of two groups of their compounds, glycoalkaloids and steroid alkaloids. Glycoalkaloids interfere with membranes of the cells. They disrupt the integrity of cells up to apoptosis, especially in cancer cells. Steroidal saponines are active concerning solubility in cells. They support the activity of glycoalkaloids, additionally. In intact organisms acetylcholinesterase, important for nerve impulse transmission is inhibited.

Although the concentration of these compounds is very low all green parts, the roots and the green berries of Solanaceous plants are toxic. They can not be eaten by men or animals.
Green herbs of potatoes are burned after harvesting, therefore.

With exception of the application against skin cancers the use of these plants with men must argued against.

Solanum spec. (different species, green parts)

internal use with men	**- - -**
against skin cancers	*******
against parasites of live stocks	******
against snails	*******

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