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A PHYTOCHEMICAL AND PHARMACOLOGICAL STUDY OF SOLANUM VILLOSUM.*[1]

BY EARL PETER GUTH.[2]

CHAPTER I.

INTRODUCTION.

The family *Solanaceæ* comprises about 75 genera and 1750 species (1), the majority of which contain either alkaloids or glucosides. Among this large number are two, *viz.*, *Solanum nigrum* L. and *Solanum villosum* Mill., that attracted attention because of conflicting reports relative to the poisonous effects on domestic animals when mixed with feed or when eaten while the animals were grazing. These two species are found growing as "weeds" in Washington fields and gardens.

According to Wehmer (2), *Solanum nigrum* contains the "Alkaloidal-Glucoside" solanine and traces of a not so well-defined mydriatic alkaloid. Schutte (3) reports finding an unidentified mydriatic alkaloid.

Pammel (4) reports a case of poisoning of a sheep by *Solanum nigrum* and concludes that the leaves were poisonous. The fruit he states is used in making jam and has little toxicity. At a later date (5) Pammel reports that the ripe fruit of *Solanum nigrum* is not poisonous but that the green or unripe fruit is toxic.

* Scientific Section, A. PH. A., New York meeting, 1937.

[1] An abstract of a thesis presented as a partial requirement for the degree of Doctor of Philosophy, College of Pharmacy. This Phytochemical work was supervised by Dr. H. A. Langenhan, Professor of Pharmacy.

[2] University of Washington, 1937.

A later report (6) states that nine ducks and six chickens died as a result of eating the fruit of *Solanum nigrum*. The same year Pammel (7) states that *Solanum nigrum* has been listed as a poisonous plant; that the ripe berries are probably not poisonous. In contradiction in part to the above reports, Stevens (8) states that *Solanum nigrum* does not seem to be poisonous to man or sheep.

Whereas no definite information was found in the available literature relative to the constituents of *Solanum villosum*, Wehmer (9) states that this specie is probably similar in composition as *Solanum nigrum* and locally the report prevails that *Solanum villosum* is poisonous to domestic animals, it was decided to attempt a phyto-chemical analysis and a pharmacological determination of the several parts of the plant.

Solanum villosum is an annual plant growing abundantly in cultivated fields in the Northwest. The plant is low, freely branching from the base, 30 to 60 cm. high, leaves ovate to broadly lanceolate, the blade 2 to 5 cm. long, coarsely sinuate-toothed, narrowed below to a more or less winged slender peticle; peduncles lateral 3–8 flowered, 3 to 6 cm. long; flowers white on pedicles 3–10 mm. long; calyx-lobes triangular-ovate half as long as the corolla; enlarging at length and embracing the fruit; corolla 4 to 10 mm. in diameter, the merely spreading lobes acute; filaments glabrous to the base; anthers oblong obtuse; berries globular, 4 to 8 mm. in diameter, yellow when ripe (10). The *Solanum villosum* growing in the Northwest, however, has green berries. This same species has been reported to grow in the vicinity of Philadelphia where it is supposed to have its origin in this country, it being transported in ballast from Europe. This plant grows most abundantly in loamy soils that have been heavily fertilized and where it is not too often disturbed by cultivation such as in tomato and in pea fields. The plant has become a very objectionable "weed" in that the green berries become mixed with the shelled peas causing them to be unfit for commerce and also that the plant becomes mixed with the pea vines, which are used as food for domestic animals.

Because the two species, *viz.*, *Solanum villosum*, Mill. and *Solanum nigrum* L. are very similar in physical appearance, a comprehensive description of both plants is inserted to enable those who may be interested to easily distinguish one plant from another.

Solanum villosum, Mill.	*Solanum nigrum*, L.
Stem.	**Stem.**
More or less villous	Glabrous or nearly so
Freely branching from the base	Freely branching
30 to 60 cm. high	30 to 60 cm. high
Root.	**Root.**
Annual	Annual, usually larger than *Solanum villosum*
Leaves.	**Leaves.**
Villous	Glabrous or nearly so
Ovate to broadly lanceolate	Ovate petioled
2 to 5 cm. long	2 to 8 cm. long
Coarsely sinuate-toothed	Entire repand or sinuate-toothed
Narrowed below to a more or less winged	Acutish to acuminate at the apex
Slender petiole	Cunate to rounded at the base
Flowers.	**Flowers.**
White	Pedicles 5 to 12 mm. long
Pedicles 4 to 12 mm. long	Calyx-lobes ovate or oblong-ovate, obtuse
Calyx-lobes triangular, acute	Corolla 6 to 10 mm. in diameter, the spreading or reflexed lobes acute
Corolla 6 to 10 mm. in diameter the merely spreading lobes acute	Filaments pilose
Filaments glabrous	Anther oblong, obtuse, loosely connivent
Anther oblong obtuse	

Berries.	Berries.
Yellowish green when ripe	Black when ripe

CHAPTER II.

EXPERIMENTAL.

Forty pounds of fresh *Solanum villosum* were collected in October 1935, from a bulb farm near Seattle. The plants were fully matured. A few blossoms were still on some of the plants but most of them were abundant in berries.

The forty pounds were dried in a hot air drier at 90° C. The dried plants weighed five and one-half pounds indicating a loss of water content of 86–87 per cent.

The plants were then separated into their four major parts, *viz.*, berries, leaves, stem and root. The amount of each and the percentage of plant they constitute is tabulated below:

	Grams.	Per Cent.
Stem	715	30.6
Root	106	4.5
Leaves	785	33.6
Berries	730	31.3

Because the berries, leaves and stem comprised over 95 per cent of the plant and were the parts that were of immediate importance it was decided to investigate these only.

Ash.—The three parts of the plant were each assayed for ash and mineral content. The methods used were those described in the "Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists."

The following tabulation contains the result of the analysis and shows a very interesting distribution of the common plant mineral constituents.

	Berries. Per Cent.	Leaves. Per Cent.	Stem. Per Cent.
Total ash	9.49	26.84	15.81
Silica and sand	11.22	58.59	10.46
Fe_2O_3	1.20	1.33	1.07
Al_2O_3	2.27	6.22	1.65
CaO	3.13	8.94	7.83
MgO	2.89	2.68	1.88
Cl_2	1.55	0.87	2.80
SO_4	7.66	4.09	6.76
N	2.86	3.45	1.44
KCl, NaCl	51.40	20.10	58.10
P_2O_5	6.75	3.85	0.60

Extraction with Selective Solvents.—A process of selective extraction was carried out on each of the three parts of *Solanum villosum*, using ten-Gm. samples. The extraction was carried out with a Soxhlet apparatus using petroleum ether, ether, chloroform and alcohol as solvents and for a period of eighteen hours each. The extracts were allowed to evaporate spontaneously and dried in a desiccator over calcium chloride and weighed.

This experiment revealed the presence of a fixed oil in the berries, faintly positive tests for alkaloids in the leaves and a mixture of inorganic salts in the leaves.

Each extractive was examined carefully for crystalline substances and tested for alkaloids by the conventional methods of alkaloidal assay.

The following tabulation offers a comparison of the various amounts of extractive obtained from each part of the plant.

Solvent.	Berries. Per Cent.	Leaves. Per Cent.	Stem. Per Cent.
Petroleum ether	9.23	1.6	0.72
Ether	2.45	1.82	1.26
Chloroform	3.23	1.25	0.04
Alcohol	23.26	11.80	1.08

Moisture and Volatile Constituents of Plant.—The three parts of the plant were dried at 100° C. to determine moisture content and volatile constituents and again at 105° C.

	Per Cent Lost at 100° C.	Per Cent Lost at 105° C.
Berries	6.6	6.9
Leaves	8.3	8.3
Stem	7.3	7.4

Fixed Oil of Solanum villosum (Berries).—In the first petroleum-ether extraction of the berries it was noted that a fixed oil was present. Two hundred and fifty grams of powdered dried berries were percolated with ether and 24 Gm. of oil were obtained. This oil was a dark green due to the chlorophyll. An attempt was made to remove the chlorophyll by using various solvents and mixtures of solvents but was unsuccessful. The oil was then assayed for its general characteristics. All methods used were those outlined in the "Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists."

Odor—plant or hay-like
Taste—bland
Color—dark green
Solubility—miscible with petroleum ether, chloroform, acetone, carbon tetrachloride, methyl alcohol and ethyl alcohol.

Density	0.8861	25° C.
Refractive index	1.4818	25° C.
Saponification number	192.15	
Reichert Meisel Number	1.6711	
Iodine number	126.00	
Polensky number	0.3763	

Tannins.—Each of the three parts of the plant, *viz.*, berries, leaves and stems were assayed for tannins as directed in the "Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists" for tannin in tea.

The concentrated extracts from large quantities of the plant gave a qualitative test for bloom tannin.

On assay, however, comparatively small amounts of tannin were found. The berries contained the most with 0.95 per cent, the leaves and stem only traces.

Carbohydrate Analysis.—The plant was assayed for reducing sugars, non-reducing sugars and starch by the method indicated in the "Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists" for plants using the gravimetric determination and hydrochloric acid for hydrolysis. Ten-gram samples were used for sugars and 4–5-Gm. samples for starch. The reducing sugars were calculated to dextrose and the non-reducing sugars to sucrose. Pentosans were assayed for by the method described in the "Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists."

	Per Cent of Dextrose.	Per Cent of Sucrose.	Per Cent of Starch.	Per Cent of Pentosan.
Berries	3.65	6.60	7.75	5.96
Leaves	1.90	0.00	10.1	5.92
Stem	1.90	5.90	13.2	8.60

Glucosides.—One hundred grams of berries were extracted with boiling water made alkaline with $CaCO_3$. The extract was filtered while hot and treated with neutral lead acetate to precipitate the plant extractive. The excess lead was removed with Na_3PO_4 and filtered. The filtrate was washed with chloroform. The chloroform washings were dried over anhydrous sodium sulfate, filtered and evaporated (11). The slight residue obtained was of a gummy nature with a very decided aromatic odor. This residue was treated with 10 per cent HCl. The acid solution was stratified with alcoholic solution of phloroglucinol. A red zone formed at the junction. This red zone formation and aromatic odor might be due to the presence of vanillin (12).

Preparation of Solanine.—Some solanine (?) was prepared from potato sprouts by the following method: Fresh young potato sprouts were finely ground and macerated for 24 hours with

a two per cent acetic acid solution. The liquid was strained and the pulp expressed to obtain the maximum amount of extractive. To this strained liquid ammonia was added until distinctly alkaline. The precipitate formed was filtered off and treated with boiling 95 per cent alcohol. On cooling beautiful long white needles separated from the alcoholic solution. These needles after drying in a desiccator had a m. p. of 240 ° C. On further purification the m. p. was 249° C. Pure solanine is difficult to obtain inasmuch as it decomposes into solanidine and a mixture of sugars including dextrose, rhamnose and galactose. Also various imperical formulæ have been assigned to solanine, all having different melting points.

(Firbas) $C_{52}H_{93}O_{4.5}H_2O$ m. p. 250° C. (13)
(Cazeneuve & Breteau) $C_{25}H_{47}O_{11}N.2H_2O$ m. p. 235° C. (13)
Davis $C_{42}H_{75}O_{12}N$ (13)
Colombano $C_{32}H_{51}O_{11}N$ m. p. 244° C. (13)

It was therefore assumed that the solanine (?) prepared from potato sprouts was pure enough for color test comparisons. The color tests conformed only partially with the color tests given by other workers for solanine.

On testing the solanine for solubility in various solvents it was found to be insoluble in cold alcohol, ether, chloroform and carbon tetrachloride but that a jell was formed if the solanine was warmed with amyl alcohol, amyl acetate and benzol. These jells were very permanent as they did not break or change on standing for several months. Twenty milligrams of solanine made a very stiff jell with 5 cc. of solvent. This phenomenon was later noticed in the jelling of benzol by an unidentified compound extracted from the berries of *Solanum villosum*.

Examination of Young Plants for Solanine.—It was thought that inasmuch as young potato sprouts contained more solanine than in the mature plant that perhaps solanine may be present in very young plants of *Solanum villosum*. Fifteen hundred grams of small plant were collected in May 1936. These plants were not over 3–4 inches in height and contained no blossoms. They were ground to a pulp while still fresh and immediately treated with a 2 per cent aqueous acetic acid solution. This mixture was allowed to macerate for 24 hours, filtered and the pulp expressed to obtain all the extractive. This extractive was treated with NH_4OH until alkaline and allowed to stand. On standing there was no precipitation. The extractive was then evaporated on a water-bath to dryness and the residue tested for the presence of solanine by taking up in hot alcohol, from which there was no precipitation on cooling. On evaporation of the alcohol solution and treating the residue with acetic acid and sulfuric acid followed with diluted formaldehyde there was no color reaction. It is, therefore, assumed that there is no solanine present in the very young plants.

Extraction of an Active Substance.—Solanine is classified a glucosidal alkaloid because it readily hydrolyzes to give solanodine and sugars. It hydrolyzes more readily with mineral acids, less so with organic acids (14). Therefore believing that the alkaloid most likely to be present in *Solanum villosum* would be solanine the extractions were carried on by means of a 2 per cent acetic acid. Two hundred-gram samples of ground berries were allowed to macerate for 24 hours with 2000 cc. of 2 per cent acetic acid. The liquid was removed by straining through a muslin cloth and the berries finally expressed to obtain the maximum amount of extractive. This acetic extractive was treated with NH_4OH until alkaline. The alkaline solution deposits a heavy magma which was filtered off and allowed to drain. This magma was then treated with boiling 95 per cent alcohol and the alcohol filtered and evaporated on a water-bath. The residue was then taken up with 10 per cent acetic acid and filtered. The filtrate again precipitated with ammonia and the magma collected and digested with hot alcohol (95 per cent). The process was again repeated giving, as final residue, a light amber, varnish-like substance.

This residue was subjected to several color tests for solanine. For comparison the same color tests were run on some solanine prepared from young potato sprouts.

The tests are as follows:

(*a*) When solanine is dissolved in glacial acetic acid, followed by one or two drops of sulfuric acid and then treated with a drop of 1 per cent formaldehyde a deep purple color develops (14).

(*b*) Solanine with nitric acid gives a yellow to orange color (15).

(*c*) Solanine with alcoholic sulfuric acid gives a green tint (15).

(*d*) Solanine with sodium sulfate dissolved in sulfuric acid gives a red color (15).

The following tabulation gives the results of the color tests as run on solanine from potato sprouts, the residue from *Solanum villosum* compared with the colors solanine should give.

Test.	Solanine.	Solanine from Potato Sprouts.	Residue from *Solanum villosum*.
(*a*)	Purple	Purple	Purple
(*b*)	Yellow-red	Yellow-orange	Yellow-orange-yellow
(*c*)	Green tint	Reddish orange	Reddish orange
(*d*)	Red	Deep orange	Deep orange

This tabulation shows a very striking resemblance between the solanine from potato sprouts and the residue obtained from *Solanum villosum* but differs from the colors that solanine is supposed to give, according to the tests referred to.

Numerous experiments were carried out in an attempt to obtain this compound with a crystalline structure and a definite melting point. These experiments became limited due to the fact that only a very small amount of concentrated material was obtained by extraction. This unidentified compound is present in the dried berries in the amount of 0.1 of 1 per cent.

The substance was taken up with hot 95 per cent ethyl alcohol and allowed to evaporate spontaneously and also in vacuum. The residue obtained in both cases was an amber varnish substance with no definite melting point. The melting point varied from 125° to 178° C. depending on the particular extraction. By taking the substance up with hot methyl alcohol and allowing this solution to evaporate a similar amorphous residue was obtained. The residue was then washed with ether to remove any possible fat and after recovering from alcohol it had a melting point of 192° to 195° C. The substance was then taken up with alcohol and a quantity of acetone added. A gelatinous precipitate formed which was filtered off, dried and had a melting point of 205° to 215° C. The alcoholic-acetone solution was then treated with benzol which caused a separation of an amber-colored layer which on evaporation deposited microscopic rosettes, m. p. 215° to 230° C. Each of these fractions gave similar color tests to that of the original residue. This substance emulsified mercury, slowly hemolyzes red blood cells in isotonic solution and foams when shaken with water.

Inorganic Salts from Leaves and Stems.—In the selective extraction experiment under leaves and stems with alcohol as the solvent it was noted that inorganic crystals were formed. These crystals on assay were found to be a mixture of potassium and sodium chlorides and nitrates. From 4600 Gm. of dried stem and leaf 15 Gm. of crystals were obtained. This constitutes 0.32 per cent. Quantitative analysis of crystals.

	Per Cent.		Per Cent.
Chlorides	21.5	Potassium	23.00
Nitrates	41.55	Sodium	20.00

The nitrates were assayed for taking 0.4507 Gm. of crystals and heating them on a water-bath with 10 cc. of hydrochloric acid until dry. Ten cubic centimeters of hydrochloric acid were again added and heated until an aqueous solution of the crystals was neutral to litmus. This converted all the nitrates to chlorides. The total chlorides were assayed for by the Volhard Method. The difference between the original chlorides present and those formed by treatment with hydrochloric acid was computed to nitrates. An approximate assay of potassium was run by precipitating the potassium by adding tartaric acid and igniting to obtain potassium carbonate. Sodium was taken by difference.

PHARMACOLOGY.[1]

Toxicological studies were made on extracts of the leaf, stem and berries by administering the extracts to rabbits by stomach tube. An extract of the stems equivalent to 400 Gm. of the fresh material per Kg. showed no immediate effects but death occurred after nine hours. A dose of the leaf extract equivalent to 400 Gm. of the fresh material per Kg. caused death in one hour and fifteen minutes. A similar dose of the berry extract produced death in one hour and five

[1] This work was supervised by Dr. James M. Dille, Associate Professor, Department of Pharmacology.

minutes. In the last two instances respiratory failure occurred first. Autopsy indicated a great deal of the material unabsorbed. Thus the actual toxic dose is probably less. Indications of gastric and intestinal irritations were observed.

The oil secured from the berry was without effect after a similar administration of 8 cc. per Kg., an amount equivalent to about 400 Gm. of fresh berries.

The toxic dose was determined on rats by injecting 1 mg. of the substance obtained from the berries by chemical methods described by the injection of a graded series of doses beginning at 1 mg. per Kg. and extending to 70 mg. per Kg. All doses were made by intraperitoneal injection. Doses below 10 mg. per Kg. showed no effect. Doses between 10 mg. and 20 mg. per Kg. produced some depression but the animal recovered within a few hours. Higher doses up to 30 mg. showed more pronounced depression and evidence of gastro-intestinal irritation as indicated by diarrhea. A dose of 50 mg. per Kg. produced death in 2 out of 4 rats and with 70 mg. all rats receiving this dose died. Evidence of intestinal irritation was found in each case.

The cause of death was further investigated by means of kymograph records in which the substance obtained from the berries and extract made from the leaf were injected intravenously in rabbits anesthetized with sodium phenobarbital. In each case respiration failed before the heart stopped or the blood pressure fell below critical levels. Artificial respiration was effective in prolonging the animal's life for only about eight minutes after which the blood pressure fell and death occurred.

Since many alkaloids of the solanaceous plants behave like parasympatholytic substances, experiments were made on turtles to test the effect of this substance on the vagus mechanism. Marked paralysis of the vagus occurred from which it was impossible to secure recovery by washing the heart with Ringer's solution. Pilocarpine applied after the substance had no effect but similar administration of atropine produced a marked increase in the rate of the heart. The effect therefore appears to be central to the parasympathetic endings.

DISCUSSION.

At the beginning of this investigation of *Solanum villosum* it was hoped that a definite principle such as an alkaloid or glucoside could be extracted that had toxic properties as the plant was generally believed to be toxic to stock. Repeated attempts to isolate a definite principle from the plant were unsuccessful. However, a substance or compound was isolated that gave promise of being composed at least in part of a toxic principle as indicated in the toxicity experiments. The plant as a whole was also found to be toxic when taken in large amounts. This was proven definitely when rabbits were fed the extract from the stem, leaves and berries in amounts equivalent to 400 Gm. of fresh material per Kg. body weight.

The question as to what causes death has not been completely answered. However, every indication is that the primary cause is a failure of the respiration. In the toxicity experiments it was noted that respiration had ceased long before the heart had stopped beating. This same respiratory failure was found in the administration of the concentrated substance from the berries on rats and rabbits.

This substance obtained from the berries has many of the properties attributed to sapo-toxins. It slowly hemolyzes red blood corpuscles in isotonic solution, emulsifies mercury and foams when shaken with water. Sapo-toxins are also said to paralyze the respiratory center when injected intravenously (16). Sapo-toxins in general are soluble in water and not precipitated by moderate amounts of alcohol but are not soluble in pure alcohol or fat solvents.

The pharmacological action of the substance from the berries closely resembles the pharmacological action of saponins when injected intravenously but the solubility of this product differs greatly in that it is not water soluble and is soluble in pure alcohol and fat solvents.

It must also be pointed out here that the poisonous principle of *Solanum villosum* is probably distributed throughout the plant and is absorbed from the intestinal tract, the latter property placing the compound in the class of saponins (?) that are absorbed, thereby separating it from the large class of unabsorbed saponins.

It is believed that the toxic principle of *Solanum villosum* is probably closely related to solanine and sapo-toxins and that the compound isolated from the berries contains a large share of the toxic principle. This work will be continued in an attempt to definitely establish the identity of the toxic principle. The work done so far points out that caution should be observed by those who are in daily contract with the plant and that the practice of jelly making with the berries and the feeding of live stock with the plant should be discouraged.

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DUTIES OF THE HOSPITAL PHARMACISTS.

T. C. Daniels, states in *Hospitals*, quoted in part, that

"The pharmacist must make certain that all unstable preparations are dated as to their expiration date. There should be a routine check of all products subject to rapid deterioration and where there is evidence of decomposition the product should be discarded and replaced with a fresh supply. The importance of this is sometimes overlooked.

"All medication in the emergency ward should be under the pharmacist's control. An approved antidote list should be available and the medicinals required for such emergency kept in good condition, ready for use. This requires regular inspection.

"Laboratory reagents and stains should logically be under the control of the pharmacist and they require routine inspection to determine if they are in good order.

"The storage and complete control of all biological preparations should be one of the pharmacist's responsibilities. Proper refrigeration facilities must be available for this and products that are "out-dated" should be promptly returned to the manufacturer.

"The pharmacist should be responsible for and at least supervise the preparation and sterilization of all solutions intended for parenteral use. If possible a small room with filtered air should be provided for the purpose. Labels should clearly show the lot number and expiration date of the solution. All injectable solutions should be tested for sterility, pyrogenic properties and where the hydrogen-ion concentration of the solution differs markedly from that of the tissues or environment where it is to be employed it should be buffered at the desired hydrogen-ion level. There are several exceptions to this but in general such a procedure should be adopted. Furthermore unless a hypertonic or hypotonic solution is desired the concentration should be adjusted to make it isotonic."