



SOLANACEAE PLANTS OF ISRAEL AND PALESTINE - RICH SOURCE OF MEDICINALLY ACTIVE NATURAL PRODUCTS

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Solanaceae is one of the most studied among all plant families. Plants of this family are very rich with medicinally active natural products, some of them, with nutritional importance. Some of these compounds are psychoactive and mind altering. Alkaloids, physalins and withanolides are the major notable active natural products present in these plants. In this review article, we will present the vast majority of published research about these plants. This work will include biological and medicinal activities, extended presentation of natural products, their activities and in some cases, their synthesis, biosynthesis and production, along with other chemical aspects. Despite all the wideness of this article, we have introduced limited (but not ignored, presentations of two important aspects of this plant family, mainly due to the large size of this article. One, ethnobotany and ethnomedicine uses of these plants, and two, the influence of various cultivation conditions on these plants, and the results of these conditions.

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Finally, in the region between the Mediterranean sea and the Jordan river (Israel and Palestine), there are 24 species of *Solanaceae* wild plants.⁹ All of them were thoroughly studied except *Solanum cornutum* about which, as far as our knowledge could reach, there is not a single publication about its medicinal activities.

INTRODUCTION

The *Solanaceae* plants family is one of the most known and used by humans since the early dawn of humanity. It comprises 90 genera and 3000-4000 species, including some domesticated plants like potatoes (*Solanum tuberosum*), tomatoes (*S. lycopersicum*), eggplant (*S. melongena*) and chili pepper (*Capsicum annuum*).¹ These human cultivated species are among the most important for human nutrition and possess high economical value. Life forms of these plants are diverse and range from trees to annual grass.

They attracted the attentions of humans since antiquity. One of the earliest documented uses of these plants for medicinal uses can be found in the "Dioscorides Codex" (815 A.D).² All human civilizations utilized the plants of the *Solanaceae* family, while ancient people of the Americas (Maya) were the first to use the plants for food, ritual and religious matters.³ These civilizations used a wide variety of *Solanaceae* plants including the genera of *Capsicum* (some for war uses), *Solanum*, *Datura* and others. Shamanistic physicians of ancient Egypt used mandrake (*Mandragora autumnalis*) for several uses, including hypnosis, rituals and medications.⁴ Later studies showed that this type of use of *Solanaceae* plants was very common among all civilizations of the "Old World".⁵

Like other peoples of the world, ancient nations of the Middle East used the *Solanaceae* plants for many purposes, and these uses found their respectful rank in traditional medicines of civilizations of this region.⁶ They used and still use *Lycium europeum*, *Solanum nigrum*, *Hyoscyamus aureus*, *Hyoscyamus albus*, *Datura* spp., *Mandragora autumnalis* and *Wifhania somnifera*. Arab-Palestinian ethnomedicine used these plants with clear caution and only in limited cases.^{7,8}

PUBLISHED REVIEW ARTICLES: SOLANACEAE AND TROPANE ALKALOIDS

Expectedly, many review articles were published about this plant family that contains great numbers of biologically active natural products. In addition, some of the plants of this family are edible and highly nutritious (especially, the domesticated species), while some of the wild species, are highly toxic and psychoactive. In this part of our review, we will introduce some selected, previously published review articles, bearing in mind that many will not be presented here, since they contain almost the same information included in the articles that we will present. We will introduce these review articles as brief summaries rather than a table, since this presentation will include many figures and some notices. Each summary will present the reviewed species, major presented topics and references. The presentation is according to alphabetical order of the species names.

1. *Datura* ssp. focusing on *D. stramonium*. A comprehensive article that presents all ssp. of the genus of *Datura*. It introduces some botany, ethnomedicine, modern medical uses (detailed), toxicity and some important active compounds.¹⁰

2. *Datura* ssp. Systematic, clearly presented and comprehensive review, with good figures and tables of active alkaloids of *Datura*. Ethno uses in Mexico and Spain are presented.¹¹

3. *Datura* ssp., antibacterial activity. Partial scan of natural products of *Datura* with antibacterial activity. The review focuses on few compounds, extensively presenting one of them, with a strange error.^{12,a} See Figure 1.

Tandon *et al.* (ref. 12) attempted to review "most promising" natural products in *Datura* ssp. with antibacterial activity. The only structure that they chose to present is the structure of this steroidal alkaloid that was isolated from *Datura metel*.

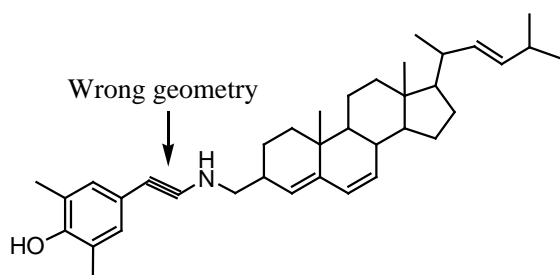


Figure 1. Wrong structure of steroidal alkaloid presented in reference 12

They cite: Okwu, D. E, Igara, E. C., Isolation, characterization and antibacterial activity of alkaloid from *Datura metel* Linn leaves, *Afr. J. Pharm. Pharmacol.*, **2009**, 3, 277-281. Oddly enough, authors of the original research and the review article presented the structure of the alkaloid containing alkyne functional group with *trans* (*E*) stereochemistry instead of linear. Nonlinear geometry of alkynes exists only in reactive intermediates. See: Sanz, R., Recent Applications of Aryne Chemistry to Organic Synthesis. A Review, *Org. Prep. Proced. Int.*, **2008**, 40, 215-291.

4. *Datura* ssp. Very detailed review of pharmacological activities of *Datura* ssp., with clear presentations of the structures of active natural products. Detailed tables also presented. Error in reference 12 is repeated here¹³ (see above).

5. *Datura* ssp. This very important review presents various *Datura* ssp. but focuses mainly on *D. stramonium*. The review introduces in great details its content of Tropane alkaloids (Figure 2), especially scopolamine and hyoscyamine, and the poisoning potential of the plants to animals.¹⁴

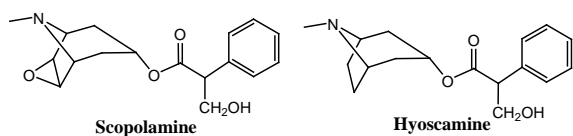


Figure 2. Tropane alkaloids, scopolamine and hyoscyamine

6. *Datura* ssp. This review focuses on *D. stramonium* and presents in very useful and detailed manner the different possibilities of *Datura* poisoning, its medical expressions and mechanisms, and most important, treatment of poisoning cases. It also presents some antidotes such as the natural alkaloid physostigmine (Figure 3).¹⁵⁻¹⁷

7. *Datura stramonium*. These comprehensive articles review the knowledge about this plant. Their major advantage is the detailed style but it lacks presentation of important natural products structures. *D. fastuosa* is also

reviewed (ref. 18. but this plant does not exist in the region of the interest of our article.^{18,19}

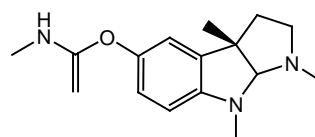


Figure 3. Physostigmine, natural alkaloid, antidote of *Datura* poisoning.

8. *Datura stramonium*. It is an important review with brief presentation of pharmacological activities of the plant, but with a wide scan of toxicity. It also includes an important, clear part of active natural products structures, alkaloids and many others.²⁰

9. *Datura stramonium*. A short document that presents active constituents.²¹

10. *Datura stramonium*. Another short document that presents in details active constituents, some structures, pharmacological activities, traditional uses (brief), with a list of amino acids present in the plant.²²

11. *Datura stramonium*. It is a very short documents with very few details. Useful short introductions of the plant.²³⁻²⁶

12. *Datura stramonium*. A short review that focuses on neurotoxicity of this plant, and provides a detailed list (no structures) of active compounds.²⁷

13. *Datura stramonium*. Despite the fact that the title of this short document gives the expression of presenting *Datura* ssp., it actually presents the toxicity history of *D. stramonium* in the 18-19th centuries in Europe.²⁸

14. *Hyoscyamus* ssp. This article reviews three plants of this genus namely *H. albus*, *H. niger* and *H. reticulatus*. It presents ethnobotanical uses, medicinal activities and list of some active natural products present in these species.²⁹

15. *Mandragora*. In one of the most comprehensive and useful review articles about this genus authors have presented in a very clear manner, with detailed structures, the interesting active natural products contained in the plants of these plants. In addition to tropane alkaloids, hydroxy acids, esters resulting from previous two families, N-oxides of tropane alkaloids, very interesting epoxy carotenoids, the structures of polyhydroxy tropane alkaloids, named Calystegines and of the alkaloid Coscohygrine, are presented.³⁰ In Figure 4 we present selected structures of three calystegines and of coscohygrine.

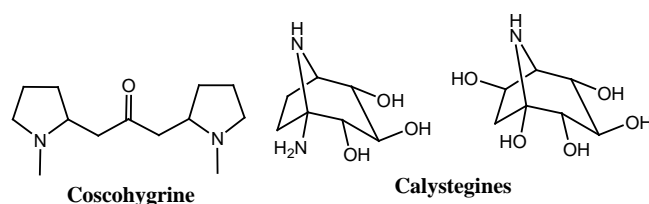


Figure 4. Structures of selected calystegines and coscohygrine (ref. 30).

16. *Nicandra physalodes*. The only published review about medicinal activities of this plant, and ethnomedicinal uses are also presented. It lacks introduction of active natural products.³¹

17. *Physalis angulata*. One of the most comprehensive reviews about this plant. Information about traditional applications and medicinal activities is provided. Active natural products are extensively shown, clear structures and family classifications.³² Some of these natural products are shown in Figure 5.

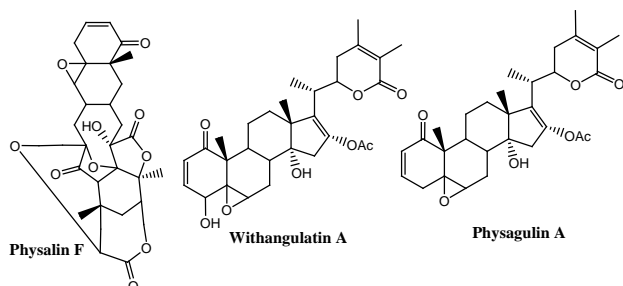


Figure 5. Selected natural products isolated from *Physalis angulata* (ref. 32).

18. *Physalis angulata*. A brief review that presents only medicinal activities.³³

19. *Physalis angulata*. This review presents medicinal activities and list some of the active compounds but does not provide structures.³⁴

20. *Physalis* spp. Wide scan of traditional uses as well as systematic review of active natural products and their structures (see Figure 6) are the two great advantages of these reviews. They also include some medicinal activities.^{35,36}

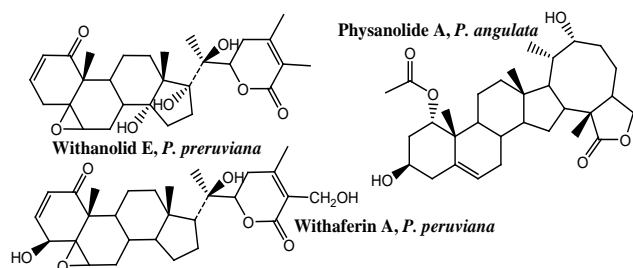


Figure 6. Structures of natural products isolated from *Physalis* spp. (35).

21. *Physalis peruviana*. The main focus of these reviews (by the same author. is highlighting the nutritional importance of this plant. Medicinal activities and natural products are presented.^{37,38}

22. *Physalis peruviana*. The morphology of the plant has been thoroughly discussed in this review, as well as its nutritional value. Limited chemical composition is presented.³⁹

23. *Physalis peruviana*. This short review presents the protective potential of this plant against intoxications by cigarette smoke, acetaminophen, cadmium and CCl₄.⁴⁰

24. *Solanum* spp. One of the most comprehensive and informative review articles about alkaloids of the *Solanum* genus and their structures. The article presents the glycoalkaloids and their free forms (aglycons, without the saccharide units).⁴¹ In Figure 7, the structure of α -Solanine is presented in both forms.

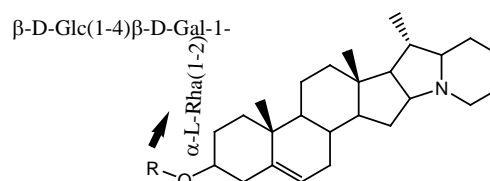


Figure 7. Glyco- α -solanine and its aglycon (ref. 41).

25. *Solanum* spp. This review focuses on the medicinal activities of *Solanum* alkaloids, without presenting their chemistry or structures. Instead, it presents the basic structures of active natural products. For example, it presents the bicyclic skeleton on tropane alkaloids, without examples. Some of the structures are poorly presented.⁴²

26. *Solanum* spp. This wide review focuses on two glycostreroidal-alkaloids found in *Solanum* plants: Solamargine and Solasonine (Figure 8). In addition to their structures and pharmacological activities, methods of their analysis are presented.⁴³

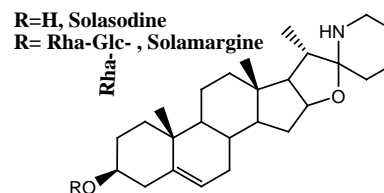


Figure 8. Solamargine and Solasonine (ref. 43).

27. *Solanaceae*. This vast, excellent review, presents the different active compounds groups in the *Solanaceae* plant family, their biological activities, toxicity and mechanisms of action. In Figure 9, we present some alkaloids from *Nicotiana glauca*.⁴⁴

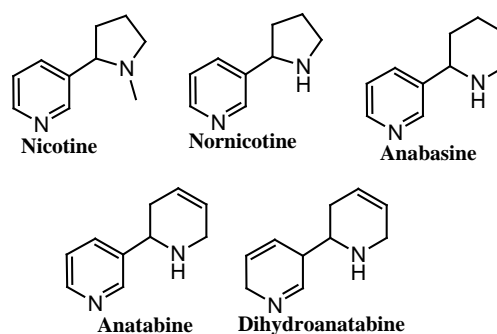


Figure 9. Selected alkaloids of *Nicotiana glauca* (ref. 44).

28. *Solanaceae*. In this large review, the focus is only on insecticidal activity of alkaloids of this plant family. It presents a brief introduction about the structures of these compounds, but provides a clear presentation of the mechanisms of action and structure activity relationship. It also provides very detailed (10 pages) table of plants, alkaloids and their bioinsecticidal activities.⁴⁵

29. *Solanum elaeagnifolium*. This article discusses the botany and biology of this plant, that few decades ago was almost rare, and now, it is spreading rapidly. In some areas of the Mediterranean basin, it became "monospecific". The article presents its negative effect on agricultural crops.⁴⁶

30. *Solanum incanum*. Two short reviews about the ethnopharmacology, medicinal activities and very short presentations of the chemical compositions. In both reviews, structures are not presented.^{47,48}

31. *Solanum nigrum*. Very colorful document, that presents the botany of the plant, very limited chemical composition (no structures, and some medicinal activities).⁴⁹

32. *Solanum nigrum*. A partial and brief presentation of chemical composition and medicinal activities of this plant.⁵⁰

33. *Solanum nigrum*. Despite the fact that the title of this article states that it discusses anticancer and antitumor activities of this plant, it also presents other activities.⁵¹

34. *Solanum nigrum*. A short review of the major active natural products.⁵²

35. *Solanum nigrum*. Presentation of botany, partial composition and some medicinal activities of this plant.⁵³

36. *Solanum nigrum*. An extended review that presents most topics related to this plant, including composition and medicinal activities. Special attention is drawn to the genetics of the plant, and some ethnobotanical aspects are presented.⁵⁴

37. *Solanum nigrum*. Very brief sections of traditional uses and chemical composition of the plant are presented, but a wider part of medicinal activities is provided.⁵⁵

38. *Solanum nigrum*. Very short document that presents culinary uses and anti-inflammatory activity of the plant.⁵⁶

39. *Solanum nigrum*. The capacity of this plant to hyperaccumulate heavy metals from contaminated soil or water is presented.⁵⁷

40. *Solanum villosum*. Short review of botany, ethnomedicine, medicinal activities and very partial composition of the plant.⁵⁸

41. *Withania somnifera*. In this comprehensive review about many medicinal activities of this plant, chemical composition is not presented.⁵⁹

42. *Withania somnifera*. This excellent review, that focuses on antibacterial and antifungal activities of the plant,

includes short chemical composition description, with structures of selected active compounds. The various medicinal activities of the plants are presented, and the selected activities are very detailed in a very helpful table.⁶⁰

43. *Withania somnifera*. This document summarizes the research of anticancer activity of this plant. Various types of cancer are reviewed, mechanisms of action are presented and partial chemical composition is listed, especially the natural products with anticancer activity.⁶¹

44. *Withania somnifera*. This excellent and very comprehensive review about this plant, presents very detailed structures of active natural products, their biosynthesis, and their medicinal activities. This review provides some explanations for understanding the structures of withanolides (Figure 10).⁶²

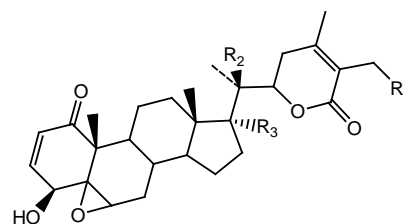


Figure 10. General structure of withanolides (ref. 62).

45. *Withania somnifera*. A minireview of medicinal activities of this plant with some information about withanolides. Structure of withanolide A is presented.⁶³

46. *Withania somnifera*. An extensive review of many medicinal activities of this plant, which includes almost every possible activity. Short chemical composition and ethnobotanical uses are presented.⁶⁴

47. *Withania somnifera*. Many medicinal activities are presented in these reviews, chemical structures and ethnobotanical uses are presented.⁶⁵⁻⁷²

48. *Withania somnifera*. A very good review that extensively presents the biosynthesis of withanolides. An excellent scheme is presented (page 5). The article presents an expanded review of enzymatic and genetic aspects, and builds future perspectives.⁷³

49. *Withania somnifera*. This review includes medicinal activities, partial chemical composition, genetic modifications, future perspective and molecular profiling. *W. coagulans* (that is not included in our review) is also discussed.⁷⁴

50. *Withania somnifera*. This is a very important and highly informative review. It presents extensive chemical composition part, along with some interesting modifications of natural products (an example is shown in Figure 11)^b. Many medicinal activities are presented, focusing on anticancer activity (an excellent figure on page 5) and neuroprotection activities (excellent figure page 6).⁷⁵

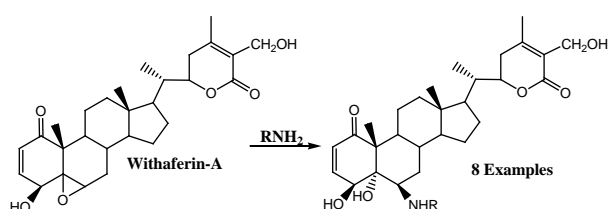


Figure 11. Aminolysis of Withaferin-A (ref. 75)^b b. Citation of Joshi, P. *et al.*, ref. 721.

51. *Withania somnifera*. This very extensive and excellent review presents various medicinal activities of the plant. Also, it includes a vast chemical composition section. But unlike all published reviews about this plant, this review specifies medicinal activity with single natural product. This information is summarized in clear, readable tables. In addition, it discusses the composition of the plant in two major habitats, India and Israel.⁷⁶

52. *Withania somnifera*. Anticancer activity specific review. It presents in details the anticancer activity of the plant products, its active compounds, as well as detailed mechanisms of action.⁷⁷

53. *Withania somnifera*. This review presents the beneficial effects of the plant products on human male fertility.⁷⁸

54. *Withania somnifera*. An excellent review of male fertility benefits of this plant and its products. The article presents general background of treating male infertility and sexual weakness with medicinal plants, partial chemical composition of this plant and some medicinal activities of it. It presents in clear and useful manner (very helpful tables and figures) the mechanism of action of the plant and its products in enhancing male reproductivity and sexual functioning.⁷⁹

55. Tropane alkaloids. This review is a followup of reference 14. It presents this family of natural products in clear link to *Solanaceae* plants, since these plants cause many cases of food contamination and poisoning, for humans and animals. The article provides chemical composition part, including general schemes of biosynthesis. But its main focus is toxicity of these compounds.⁸⁰

56. Tropane alkaloids. These three articles focus on biosynthesis and laboratory synthesis of tropane alkaloids. Biosynthetic and synthetic paths are presented in general scopes. To use these schemes for practical purposes, readers must use the original research papers cited by these review articles.⁸¹⁻⁸³

MEDICINAL, BIOLOGICAL AND OTHER ACTIVITIES OF SOLANACEAE WILD PLANTS

In this much extended section, we will present the published articles about the medicinal, biological and other activities of these plants. But it is important in our opinion to make it clear that some types of articles will not be presented here, for example, most publications of reported methods of enhancing the production of active natural

products by these plants, through genetic engineering or various agricultural conditions. We cited some of them in order to enable the interested readers to start exploring this information, and continue their search if they want to. Due to the great pharmacological importance of these active natural products, an enormous number of researches have been published about this very important issue, a number of carefully selected articles of this type will be also presented in the next section.

The chemistry of the natural products that were isolated from the *Solanaceae* plants is very important and extremely interesting. But the vast majority of these publications are not included in this article. We have very carefully selected a few of them, which in our humble opinion, have special importance. These will be presented in a separate section.

Finally, the information in this section will be presented in tables, each presenting the published data about a single species. In this way, it is easier for the interested readers to extract information about each plant. Publications are sorted by activity. All notes and figures related to a specific table will be shown right after it.

Datura ferox

This species is the less widespread among the three species that grow in our region (the others are *D. innoxia* and *D. stramonium*). But its natural habitat is very wide, including all continents. The activities of this plant are presented in Table 1.

Table 1. Medicinal, Biological and Other Activities of *Datura ferox*.

Activity/Property	Major Findings/Reference
Defensive alkaloids	Production of defensive alkaloids in leaves of this plant, mainly atropine, hyoscyamine, scopolamine and solanine; is adaptive to cope with herbivores. ⁸⁴
Alkaloids content (Argentina)	The alkaloid content ranged from 0.02-0.52 g of total alkaloids in different parts of the plant, and 0.0029-0.32 g of scopolamine per 100 g of dried material. ⁸⁵
Alkaloids content (Algeria)	Qualitative study of alkaloid content revealed that hyoscyamine and scopolamine are major compounds. ⁸⁶
Alkaloids content (Argentina)	An extended qualitative study of alkaloids content (HPLC, GC-MS) found five additional alkaloids compared with previously published (ref. 85). ⁸⁷
Alkaloids content (Algeria)	Quantitative study of alkaloid content revealed that hyoscyamine is major compound. ⁸⁸
Alkaloid effect on hens and broilers	A mixture of scopolamine and hyoscyamine (98:2), was incorporated at different alkaloid levels, into a control diet fed to 100 egg-laying hens for 3 months. Various tests were performed to determine the effect of this treatment on different health aspects of the birds. Alkaloid dose as high as 75 mg kg ⁻¹ feed is safe. ^{89,90}

Chemical composition (partial)	Morphology and partial chemical composition, as well as general composition of the seeds were studied. ⁹¹
Poisoning of horses	Severe poisoning of horses by <i>D. ferox</i> contaminated hay, that resulted serious health problems that lead to euthanasia in some case. Analysis showed that hyscyamine was the major toxin. ⁹²
Human pisoning, special forensic method	A special method of forensic analysis was developed for detection an conformation of atropine and scopolamine, helped confirm the death cause of a man by this plant. ⁹³
Toxicity test for pigs	Alkaloid toxicity for pigs showed a limit of 1.5 mg kg ⁻¹ feed, for animals with 20-60 kg weight. ⁹⁴

Datura innoxia (or innoxia)

In our region, *D. innoxia* is widespread like *D. stramonium* and most people can not distinguish between both species. It has been thoroughly studied, and a summary of these studies is presented in Table 2.

Table 2. Medicinal, biological and other activities of *Datura innoxia*.

Activity/Property	Major Findings/Reference
Defensive alkaloids	Production of defensive alkaloids in leaves of this plant, mainly atropine, hyoscyamine, scopolamine and solanine; is adaptive to cope with herbivores. ⁸⁴
Alkaloid content	HPLC determination of total alkaloid content in different parts of the plant. Hyoscyamine and scopolamine were tested as well. ⁹⁵ Determination of alkaloids with various liquid chromatography techniques. ⁹⁶ Comprehensive analysis of 38 alkaloids, and comaprison between alkaloid content of the plants in Egypt and Bulgaria. ⁹⁷ Effect of various growing conditions on alkaloid content. ^{98,99} GC-MS determination of 53 alkaloids contained in the plant in Morocco. ¹⁰⁰ Influence of quantification methods on results of alkaloid determination. ¹⁰¹ Feeding plants with alkaloids with certain stereochemistry has no effect on the enantiomer composition and content. ¹⁰²
Analgesic	Aqueous leaves extract was tested and found active analgesic. It was analyzed for major active compounds. ¹⁰³
Antibacterial, antimicrobial, antifungal	Aerial parts were extracted with water and organic solvents. Extracts were tested against different bacteria. Methanolic extract was most active. ¹⁰⁴ Flowers were extracted with 90 % aqueous ethanol, followed by various organic solvents. Extract was active against different bacteria. ¹⁰⁵ Aqueous and methanolic extracts were prepared

	from seeds, leaves and roots of the plant. They were tested against some bacteria and the methanolic extract was more active. ¹⁰⁶ Leaves were extracted with 95 % aqueous ethanol and the extract had clear antibacterial activity. ¹⁰⁷ Lectin was isolated from seeds of the plant and found antibacterial and antifungal. ¹⁰⁸ Ethanolic and aqueous extracts of leaves were tested, and ethanolic extract was found more active. ¹⁰⁹ Leaves and seeds aqueous extracts, that were fractionized by organic solvents, found active against some bacteria and fungi. ¹¹⁰ Methanolic extract of aerial parts was found active against some bacteria strains. ¹⁴⁰
Anticancer and related activities	Leaves methanolic extract was found active against colon and breast cancer cells. ¹¹¹ Flowers methanolic extract was prepared and fractionized with other solvents. Extract and fractions showed clear cytotoxicity and anti-angiogenesis properties. ¹¹² Dinoxin B, was isolotared from the methanolic extract (and fractions) of leaves, and was found cytotoxic to cancer cells. ¹¹³
Anti-inflammatory	Aqueous leaves extract was tested and found active anti-inflammatory. ¹⁰³ Aqueous and methanolic extracts were prepared from seeds, leaves and roots of the plant. They were tested against <i>Aspergillus niger</i> fungus. Methanolic extract was more active. ¹⁰⁶
Antiparasitic, insecticide	Leaves and seeds were extracted with non-polar solvents. Extracts were active pediculocidal. ¹¹⁶ Leaves aqueous extract had high nematicidal activity. General chemical composition was also reported. ¹¹⁷ Leaves were extracted with water, methanol and hexane, and tested against <i>Agonoscelis pubescens</i> . Hexane extract had highest activity. ¹¹⁸ Fruits aqueous extract found active against <i>Holotrichia Serrata</i> (Fab). ¹¹⁹ Leaves aqueous had insecticidal activity against <i>Locusta migratoria</i> . ¹²⁰ Leaves were extracted with methanol and hexane. Both extracts found active against <i>Spodoptera Litura</i> (F.). ¹²¹ Leaves were extracted with ethanol and extract was found active against <i>Meloidogyne incognita</i> . General chemical composition of the extract was determine. ¹²²
Antioxidant	Leaves and seeds aqueous extracts were prepared and antioxidant capacity was determined (DPPH). ¹¹⁰ Leaves methanolic extract had high antioxidant capacity, determined with three methods. ¹¹⁴ Leaves and seeds ethanolic extracts had high antioxidant capacity, determined with three methods. ¹¹⁵ Seeds and roots were extracted with six

Chemical composition	solvents and antioxidant capacity was determined by two methods. General chemical composition was determined. ¹²³ Leaves and seeds aqueous extracts were prepared and total phenolic contents and total flavonoid content were determined. ¹¹⁰ Dinoxin B, a withanolide was isolated from the methanolic extract and characterized. ¹¹³ See Figure 12. General composition was determine for all parts of the plant, separately. ^{124,125} Quantitative analysis of Hyoscine (see Figure 12) in three extracts of seeds. ¹²⁶ Scopolamine and hyoscyamine content was determined in the seeds of diploid (2n) and induced autotetraploid (4n) forms. ¹²⁷ Total alkaloid content (1.75 %) and qualitative analysis of alkaloids was performed for leaves of Nigerian species. ¹²⁸ Roots and leaves were extracted with methanol and chloroform, successively, and phenylpropanoids and fatty acids were quantified. ¹²⁹
Enzyme inhibition	Leaves and seeds aqueous extracts were prepared and protein kinase inhibition was tested. ¹¹⁰
Phytoremediation	The plant was found good hyperaccumulator of Cd, Cu, Pb and Zn, for phytoremediation of contaminated soil. ¹³⁰
Toxicity	Leaves were extracted with 95 % aqueous ethanol and the extract had clear toxicity to rats. ¹⁰⁷ Leaves and seeds aqueous extracts were prepared and brine shrimp toxicity was determined. ¹¹⁰ Aqueous and methanolic leaves extracts were found toxic to rats. ¹³¹

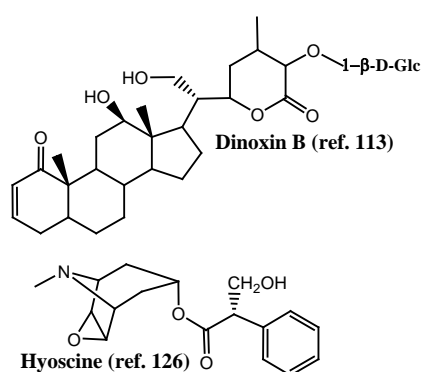


Figure 12. Selected active compounds isolated from *Datura innoxia* (Table 2).

Datura stramonium

D. stramonium is the most widespread of *Datura* species in the reviewed area. This is the main reason for the large number of published studies about it. This is also the reason of the high number of poisoning by it to humans and

animals. Summary of selected published activities of this plant is presented in Table 3.

Table 3. Medicinal, Biological and Other Activities of *Datura stramonium*

Activity/Property	Major Findings/Reference
Alkaloids	Production of defensive alkaloids in leaves of this plant, mainly atropine, hyoscyamine, scopolamine and solanine; is adaptive to cope with herbivores. ⁸⁴ Alkaloid analysis was done by GC-MS and the structures on new compounds were elucidated. Two of them are shown in Figure 13. ¹³² This is a followup, expanded study of previous one. ¹³³ Ammonia assisted, whole plant extraction yielded hyoscyamine and atropine as main alkaloids. ¹³⁴ The effect of nitrate fertilization on alkaloids production of the plant was tested. Results differ between young and mature plants. ¹³⁶ Effect of various hormones and fertilizers on alkaloid production is reported. ^{137,138,139}
Antibacterial, antimicrobial, antifungal	Ethanol and aqueous extracts of leaves were tested, and ethanolic extract was found more active. ¹⁰⁹ Methanolic extract of aerial parts was found active against some bacteria strains. ¹⁴⁰ Dry leaves were extracted with 95 % aqueous ethanol. Extract was active against some bacteria. General chemical composition was determined. ¹⁴¹ Methanolic and ethanolic leaves extracts were tested against 7 bacteria, and found active against 4. ¹⁴² Leaves were extracted with four organic solvents, and extracts were tested against some bacteria types. Chloroform extract was most active. ¹⁴³ Leaves were extracted with several organic solvents and extracts were tested against few bacteria. Hexane and ethyl acetate extracts were most active. ¹⁴⁴ Leaves were extracted with ethanol, and extract was found active against bacteria isolated from chicken. ¹⁴⁵ Leaves were extracted with 85 % aqueous ethanol, and extract was found active against <i>Staphylococcus aureus</i> isolated from sheep. ¹⁴⁶ Leaves were extracted with some organic solvents, and extracts were tested against several types of bacteria and found active. Against <i>E. coli</i> they had weak activity, but in combination with <i>Abutilon indicum</i> , synergism was observed. ¹⁴⁷ Aerial parts were extracted with ethanol, chloroform and benzene. All extracts showed antibacterial and antifungal activities. ¹⁵⁴ Methanol-Water (70 %) extract of aerial parts

had strong antifungal activity against *Fusarium* ssp.^{155,156} Leaves aqueous extract showed significant antibacterial activity against few types of bacteria. In this study, general chemical composition was also determined.¹⁵⁷ Silver nanoparticles were prepared with leaves aqueous extract, and they had antibacterial activity.¹⁵⁸ Ethanolic and aqueous extracts were prepared and found antibacterial. General chemical composition was determined in this study.¹⁵⁹ Alkaloids were extracted (ethanol, H₂SO₄) and found very active against some types of bacteria. Alkaloids were isolated and characterized.¹⁶⁰ Different parts of the plant were extracted separately with 4 organic solvents, and extracts were tested and found active against several types of bacteria. General chemical composition was also determined with special attention to glycoalkaloids.¹⁶¹ Ethanolic extract was found active antibacterial/ General chemical composition was determined.¹⁶² Leaves were extracted with 80% aqueous ethanol, and proteins were isolated and found active against several types of bacteria.¹⁶³ Different parts of the plant were extracted separately with cold methanol. All extracts showed antibacterial activity. General chemical composition was also determined.¹⁶⁴ Leaves were extracted with five organic solvents, and all extracts had antibacterial activity. Despite the article title, no chemical composition was reported.¹⁶⁵ Fresh whole plant was extracted with 90 % aqueous ethanol, and extract showed strong antibacterial activity. Total alkaloid content was also determined.¹⁶⁶ Leaves were extracted with Soxhlet assembly successively with petroleum ether, benzene, solvent ether, chloroform, acetone, ethanol and methanol, and all extracts showed antibacterial activity. General chemical composition was determined.¹⁶⁷ Seeds were extracted with methanol and extract had strong antibacterial activity. Total alkaloid content was determined.¹⁶⁸

Allelopathy

Alkaloid wash inhibited the growth of *Helianthus annuus*.¹⁴⁸ Leaf leachate (contained high concentration of alkaloids) inhibited the germination of *Linum usitatissimum*.¹⁴⁹ Extracts had no effect on *Sorghum halepense* germination but the inhibited its growth.¹⁵⁰ A wide range of extract concentrations was studied for its effect

on *Zea mays* L. and *Helianthus annuus*. Interesting results were found, from growth stimulation to inhibition.¹⁵¹ Aqueous leaf concentrations (2-8 %) inhibited the growth of *Vigna unguiculata* and *Triticum Aestivum*.¹⁵² Leaves aqueous extract was prepared in concentrations of 1-5 %, and found to have negative effect on the growth of *Phaseolus vulgaris*, *Vigna sinensis*, *Cajanus cajan* and *Medicago sativa*.¹⁵³ Essential oil was prepared and analyzed for chemical composition. The main components were phytosterols (see Figure 13). Saturated aqueous solution of this EO inhibited germination and growth of four crops.¹⁶⁹ Aqueous extract was used to prepare MgO-NPs which had antibacterial activity.^{175,c}

Anticancer and related activities

Flowers were extracted with several solvents, but only ethyl acetate extract had anticancer activity (liver). Unlike claimed in article, no pure compound was isolated.¹⁷⁰ Seeds were extracted with methanol and the extract showed cytotoxic activity against MCF7 cell line. Two active compounds were identified by TLC, but they were not isolated.¹⁷¹ Leaves methanolic extract had immunomodulatory and anticancer (lung, breast) activities.¹⁷² Leaves were extracted with methanol, and extract was analyzed for alkaloids, yielding three known compounds. This fraction showed anticancer activity.¹⁷³

Antidiabetic, antidiyslipidemic and related activities

Leaves aqueous extract showed significant α -amylase inhibition activity.¹⁵⁷ Roots were extracted with 70 % aqueous methanol. Extract was hypoglycemic (STZ-induced diabetic mice) and antidiyslipidemic.¹⁷⁴

Antioxidant, anti-inflammatory, anticoagulant, wound healing and related activities

Leaves were extracted with some organic solvents, and extracts had moderate antioxidant activity (DPPH).¹⁴⁷ Leaves were extracted with Soxhlet with ethanol and the antioxidant activity of the extract was determined (DPPH).¹⁶⁷ Seeds were extracted with methanol and extract had strong antioxidant activity (DPPH).¹⁶⁸ Seeds were extracted with methanol and the extract was tested for antioxidant activity (4 methods).¹⁷¹ Roots were extracted with 70 % aqueous methanol. Extract had significant antioxidant activity (DPPH).¹⁷⁴ Flowers were extracted with chloroform and methanol (5:7) and extract showed anticoagulant activity in poultry birds.¹⁷⁶ Seeds powder was washed with petroleum ether to remove fatty compounds, then extracted with 70 % aqueous methanol.

<p>Chemical composition</p> <p>Enzyme inhibition, brain influencing, fertility influencing and related activities</p>	<p>Extract showed anti-inflammatory activity in carrageenan induced paw edema in rats.^{177,d} Fresh leaves were extracted with methanol and extract had high antioxidant activity (DPPH).¹⁷⁸ Leaves were extracted with several solvents and tested for antioxidant activity (DPPH, NO/superoxide scavenging). Ethyl acetate had highest activity. General chemical composition was determined.^{179,180} Leaves were extracted with methanol and extract had high antioxidant activity (DPPH, ABTS).¹⁸¹ Essential oil was extracted from seeds by hydrodistillation and had anti-inflammatory activity.¹⁸² Leaves were extracted with petroleum ether and 50 % aq. EtOH. Extract showed analgesic activity in two tests in rats. General chemical composition was obtained.¹⁸³ Leaves were extracted with 70 % aq. EtOH and extract had wound healing effect on rats.¹⁹² Scopolamine and hyoscyamine content was determined in the seeds of diploid (2n) and induced autotetraploid (4n) forms.¹²⁷ Total alkaloid content (1.29 %) and qualitative analysis of alkaloids was performed for leaves of Nigerian species.¹²⁸ Roots and leaves were extracted with methanol and chloroform, successively, and phenylpropanoids and fatty acids were quantified.¹²⁹ Alkaloids were extracted (ethanol, H₂SO₄) and characterized by GC-MS (see Figure 13).¹⁶⁰ Essential oil was extracted from seeds by hydrodistillation and was analyzed by GC-MS. Terpenes were major compounds in this EO.¹⁸² Two studies of general chemical composition.^{184,185} Seeds were analyzed for chemical composition (GC-MS), yielding mainly alkaloids and terpenes.¹⁸⁶ Seeds were analyzed by column chromatography, and some compounds were isolated for the first time from the genus <i>Datura</i> or from the <i>Solanaceae</i> family. Two of them are shown in Figure 13.¹⁸⁷ Alkaloid extracts found as inhibitors of E-NTPDase, E-NTDase and ALP and stimulants of Na⁺/K⁺ ATPase.¹³⁵ Leaves were extracted with MeOH and extract inhibited serine protease.¹⁸¹ Leaves were extracted with 90 % aq. EtOH and extract showed clear inhibition of acetylcholinesterase.¹⁸⁸ Known alkaloids were extracted (hydroethanol) and analyzed by GC-MS. Extracts showed inhibitory activity of cholinesterase and monoamine oxidase.¹⁸⁹ Seeds cold aqueous extracts</p>	<p>Insecticidal, antiparasitic and related activities</p> <p>Metal chelating, accumulation and nanoparticles</p> <p>Toxicity, body changes after feeding</p> <p>had sedative activity on mice, showed by elongation of diazepam-induced sleeping periods.¹⁹⁰ Leaves were extracted with petroleum ether, ethanol and water. Ethanolic extract had clear antiovolatory activity.¹⁹¹ Leaves ethanolic extract showed high insecticidal activity against <i>Aedes Aegypti</i> and <i>Culex Quinquefasciatus</i>.¹⁹³ Ethanolic seeds and leaves extract had efficient insecticidal activity against <i>Tribolium castaneum</i>.¹⁹⁴ Acetone extract of aerial parts (excluding flowers) had lethal effect on <i>Callosobruchus maculatus</i>.¹⁹⁵ Leaves were extracted with several solvents and ethanolic extract showed highest activity against larvae of <i>Culex quinquefasciatus</i>.¹⁹⁶ Seeds were extracted with acetone, ethanol and chloroform, and acetone extract was most insecticidal against <i>Sitophilus oryzae</i> L.¹⁹⁷ Shoots were extracted with methanol and extract had nematocidal activity.¹⁹⁸ Alkaloid extracts had Fe²⁺ and Cu²⁺ chelating abilities.¹³⁵ Silver nanoparticles (AgNPs) were prepared by reduction of Ag⁺(aq) with leaves aqueous extract, and they had antibacterial activity.¹⁵⁸ Aqueous extract was used to prepare MgO-NPs.^{175,c} Methanol-Water (70 %) extract of aerial parts showed high toxicity in brine shrimp test.¹⁵⁶ Alkaloid leaves wash was found toxic to chicken when concentrations were higher than 1 %.¹⁹⁹ Alkaloid seed extract that was prepared by a multi-step method, was tested for toxicity in mice. This is a detailed study that tested different variables and results.²⁰⁰ Fatal case of dog poisoning was reported of an animal that ate leaves. Damage was found in most body organs.²⁰¹ Small dosages (0.02-0.08 mL kg⁻¹ of body mass) of seeds aqueous extract was administered to buck (Africa), increased white blood cells or spermatogenesis. Extract was not evaporized and material concentration was not reported.^{202,203,204} Alkaloid seed extract (1.5 mg kg⁻¹ of body mass) caused mild toxicity in pigs.²⁰⁵ Consuming aerial parts that were present in horse food, resulted in a poisoning outbreak.²⁰⁶ A case report of three horses that were poisoned by eating fresh leaves while grazing other plants.²⁰⁷ Many case reports of human poisoning after consumption of the plant, mistakenly or deliberately. Special attention is drawn to poisoning management in children.²⁰⁸⁻²¹¹</p>
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(c) This report (ref. 175) is unclear and even misleading. Authors claim that they used *D. stramonium* aqueous extract to prepare MgO-NPs. They report that the strating material was "magnesium nitrate, $Mg(NO_3)_3 \cdot 3H_2O$ ". To the best of our knowledge, $Mg(I)$ nitrate does not exist. Moreover, in all reports of NPs green synthesis, plants extracts either reduce the ions in starting materials or do not change their oxidation state. In this report, the Mg^+ ions were oxidized to Mg^{+2} (MgO). This contradicts all known published reports. In addition, we found no commercial suppliers of manesium nitrate trihydrate (only di- and hexahydrate are commercially available). See:

Imani, M. M., *et al.*, MgO-NPs, <https://doi.org/10.1155/2019/6063832>; Duong, T. H., *et al.*, MgO-NPs, <https://doi.org/10.1155/2019/4376429>; Ezealisiji, K.M., *et al.*, ZnO-NPs green synthesis, DOI: 10.1007/s40089-018-0263-1

(d) In the experimental section of ref. 177 there is a mistake in one of the plant mentions. It is mentioned as *Thevetia peruviana*.

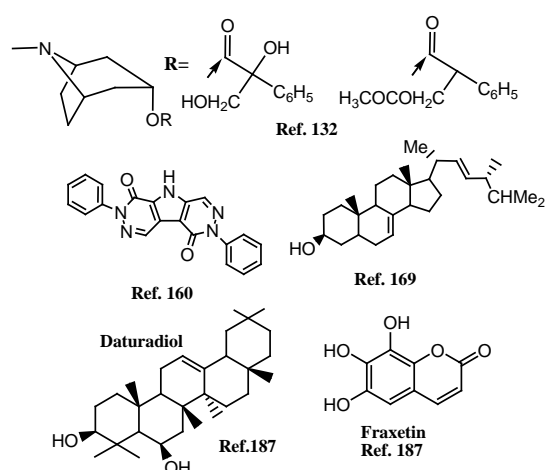


Figure 13. Selected active compounds in *D. stramonium*.

Hyoscyamus albus

Among the plants of the genus *Hyoscyamus*, this species, *H. albus* is the most studied so far. But it is important to mention that this genus is currently less investigated than some (not all) other genera of this family. Summary of selected published activities of this plant is presented in Table 4.

Table 4. Medicinal, biological and other activities of *Hyoscyamus albus*.

Activity/Property	Major Findings/Reference
Alkaloids	Auxin, an indole alkaloid plant hormone, increased the production of hyoscyamine and scopolamine (Figure 2) in roots. ²¹² Roots were analyzed for alkaloids, where some compounds were identified in this plant for the first time, along with some novel alkaloids. Two isomers are presented in Figure 14. ²¹³⁻²¹⁵
Antibacterial, antimicrobial, antifungal, analgesic and related activities	Aerial parts were extracted with aqueous methanol (70 %) and extract was found active antibacterial against some types of bacteria. Total alkaloid content and general chemical composition were determined. ²¹⁶

Anticancer and related activities

Antidiabetic, antidiabetic and related activities

Antioxidant, anti-inflammatory, anticoagulant, wound healing and related activities

Chemical composition

Leaves methanolic extract showed analgesic (acetic acid, formalin) and antipyretic (Brewer's yeast) activities. Extract had no toxicity for albino rats.²¹⁷ Leaves were extracted successively with petroleum ether, chloroform and methanol. General chemical composition was determined, and extract was active against few bacteria species.²¹⁸

Aerial parts were extracted with methanol, and extract had antitumor activity several cancer cell lines.²¹⁹ Atropine was isolated by HPLC and was active anticancer agent.²²²

Seeds were extracted by ion exchange column and total fraction of calystegines (polyhydroxylated aminosugars, see Figure 4) was isolated. The toxicity of this fraction was measured (non-toxic up to 2000 $mg\ kg^{-1}$) and had significant antidiabetic activity (STZ-induced) in rats.²²⁰

Leaves were extracted successively with petroleum ether, chloroform and methanol. General chemical composition was determined and antioxidant capacity was measured with two methods.²¹⁸ Seeds were extracted for calystegines-rich fraction, and its antioxidant (4 methods) and anti-inflammatory (carrageenan-induced paw edema) activities were tested.²²¹ Leaves were extracted as in ref. 218. General chemical composition was determined and extract had antiulcer activity induced by ethanol.²²³ Leaves were extracted as in ref. 218. General chemical composition was determined and extract had hepatoprotective activity against CCl_4 -induce toxicity.²²⁴

Aerial parts were extracted with several solvents successively, and total lipid content as well as fatty acid composition were determined by TLC and GC-MS. C16:0, C17:0 and C18:0 were detected with highest concentrations.²²⁵ Aerial parts were extracted with several solvents successively and fractions were analyzed by TLC. Along with known compounds, two new natural products were isolated and their structures were elucidated by NMR spectroscopy (see Figure 14).²²⁶ Roots of the plants were fed with auxin-free supplements and Putrescine N-Methyltransferase was isolated from them. Alkaloid composition was also determined.²²⁷

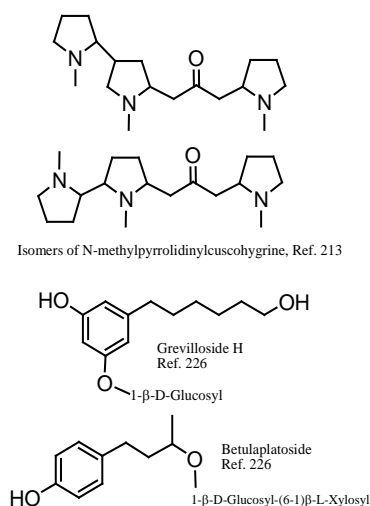


Figure 14. Selected compounds isolated from *H. albus*.

Hyoscyamus aureus

This plant is one of the least studied in the *Solanaceae* family and in the *Hyoscyamus* genus. Very few studies were published about its medicinal activities, and none about its complete chemical or alkaloid compositions. So, here in this part of this review, we will present the few published studies, and some will be presented in the Discussion section.

Composition: aerial parts were extracted with several solvents successively, and total lipid content as well as fatty acid composition were determined by TLC and GC-MS. C16:0, C18:0 and C17:0 were detected with highest concentrations.²²⁵

Alkaloid production: different growth promoters (mixtures) were used for cultivation of the plants, and total alkaloid content was measured.²²⁸

Insecticidal: leaves and flowers were extracted with 70 % aqueous ethanol, extract was dissolved in water, and the solution had insecticidal activity against three species of insect. Fatal concentration was 62.5 mgmL⁻¹.²²⁹

Hyoscyamus desertorum

This is a typical desert plant that can be easily found in Southern Israel, Egypt and some regions of North Africa. Despite this, very few studies were published about its composition and medicinal properties, all were done in Egypt. Alkaloid composition of plants in Egypt was analyzed by GC-MS detecting 39 different compounds.^{214,230}

Hyoscyamus muticus

On scanning the published literature about this plant, it is apparent that it has been very partially studied. Summary of these studies is presented in Table 5.

Table 5. Medicinal, biological and other activities of *Hyoscyamus muticus*.

Activity/Property	Major Findings/Reference
Alkaloids	Alkaloid composition of plants in Egypt was analyzed by GC-MS detecting 39 different compounds. ²¹⁴
Antibacterial, antimicrobial, antifungal	Aerial parts were extracted with aqueous methanol (70%) and extract was found active antibacterial against some types of bacteria. Total alkaloid content and general chemical composition were determined. ²¹⁶ Different species of fungi were exposed to hyoscyamine and scopolamine isolated from this plant. All fungi were tolerant to scopolamine but died when treated with hyoscyamine. ²³¹ Ethanolic, chloroform and hexane extracts of aerial parts were prepared by cold extraction. Each extract was dissolved in DMSO and tested against gram-positive and gram-negative bacteria. All extracts were active. General chemical composition was determined. ²³² Aerial parts were extracted with 80% aqueous ethanol and phenolic compounds were analyzed in extracts. No new compounds were reported. Extract was active against several types of bacteria. ²³³
Allelopathy	Aqueous extract and alkaloid fraction were prepared from the aerial parts. Both materials were tested and found active allelopathic against <i>Cichorium intybus</i> seeds germination. Alkaloid fraction was analyzed and detailed composition and structures are reported (all known compounds). ²³⁵
Antioxidant	Aerial parts were extracted with 80 % aqueous ethanol and phenolic compounds were analyzed in extracts. Antioxidant activity was determined with DPPH test. ²³³ Methanolic extract and essential oil of aerial parts were prepared and analyzed by GC-MS. No new compounds were reported. Both extract and EO were tested (DPPH) for antioxidant activity. ²³⁴
Chemical composition	Whole plant was extracted with various solvents, and each extract was analyzed by GC-MS. A detailed chemical composition is provided, including known compounds that were isolated for the first time from this plant (<i>iso</i> -fucosterol, scopoletin) and new withnolide, Muticin (Figure 15). ²³⁶
Insecticidal, antiparasitic and related activities	Aerial parts were extracted with 80 % aqueous ethanol and phenolic compounds were analyzed in extracts. Extract found active against larvae of

Spodoptera littoralis (Egyptian cotton leafworm).²³³ Whole plant was extracted with various solvents, and each extract was analyzed by GC-MS. Chloroform root alkaloid extract had high activity against *Teteranychus urticae*.²³⁶

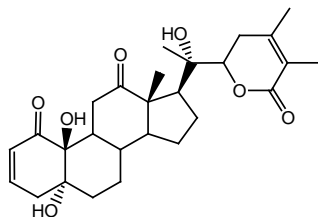


Figure 15. Structure of Muticin isolated from *Hyoscyamus muticus* (Ref. 236).

Hyoscyamus pusillus

The natural habitat of this plant in the reviewed region is desert and semi-arid soils. Despite this, it is not a rare plant, but was very limitedly studied and published. Findings are summarized in Table 6.

Table 6. Medicinal, biological and other activities of *Hyoscyamus pusillus*.

Activity/Property	Major Findings/Reference
Alkaloids	Alkaloid content of whole plant was extracted and fractionized by several solvents. All isolated alkaloids are known, including apophoscyne and tropine (Figure 16). ²³⁷ Alkaloid content was analyzed in whole plant effected by two variables: growth stage and fertilizers supply. Flowering stage had the highest content and fertilizers enhanced the production of alkaloids. Hyoscyamine and scopolamine were major compounds. ²³⁸ Genetic analysis of different species of <i>Hyoscyamus</i> in relation with alkaloid production in plants, showed that in genetically close species, similar alkaloids were produced, mainly hyoscyamine and scopolamine. ²³⁹ Comparison between different species of <i>Hyoscyamus</i> showed that <i>H. pusillus</i> contained mainly scopolamine. ²⁴⁰
Antibacterial	Ultrasound assisted extraction was done to whole plant with water and ethanol. Both extracts were active against several types of bacteria. ²⁴¹
Anti-inflammatory	Ultrasound assisted extraction was done to whole plant with water and ethanol. Both extracts had anti-inflammatory activity (COX1-inhibition). ²⁴¹

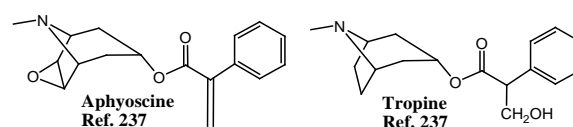


Figure 16. Active compounds isolated from *Hyoscyamus pusillus*.

Hyoscyamus reticulatus

This species was also, like most plants of the *Hyoscyamus* genus has been partially studied. But unlike most other species, studies of this plant are diverse. A summary is given in Table 7.

Table 7. Medicinal, biological and other activities of *Hyoscyamus reticulatus*.

Activity/Property	Major Findings/Reference
Alkaloids, chemical composition	Aerial parts were extracted with several solvents successively, and total lipid content as well as fatty acid composition were determined by TLC and GC-MS. C16:0, C17:0 and C18:0 were detected with highest concentrations. ²²⁵ Genetic analysis of different species of <i>Hyoscyamus</i> in relation with alkaloid production in plants, showed that in genetically close species, similar alkaloids were produced, mainly hyoscyamine and scopolamine. ²³⁹ Comparison between different species of <i>Hyoscyamus</i> showed that <i>H. pusillus</i> contained mainly hyoscyamine. ²⁴⁰ HPLC analysis of different aerial parts of the plant revealed that leaves contain the highest level of tropane alkaloids. ²⁴²
Antinociceptive	Aerial parts were extracted with methanol, and extract was active against pain in mice, induced by hot plate and acetic acid writhing. ²⁴³
Antihyperuricemia	Aqueous extract of aerial parts found active Antihyperuricemic in mice. ²⁴⁴
Antioxidant	Aqueous extract of aerial parts found active antioxidant (ABTS). ²⁴⁴
Enzyme inhibition	Aqueous extract of aerial parts found active xanthine oxidase inhibitor. ²⁴⁴
Toxicity	Case report of 19 children (Israel) poisoning that was treated with phytostigmine. ²⁴⁵ Six females (Turkey) were poisoned by consuming the plant and treated as mentioned before. ²⁴⁶

Lycium depressum

Plants of the *Lycium* (4 in our region) were partially studied, and this one, is one of the least. Its chemical composition is completely unknown, and whether it contains alkaloids or not, is also unknown until today. Leaves were extracted with water or 80 % aqueous ethanol, and both extracts showed notable antioxidant (several methods)

activity. Both extracts had no effect on four species of bacteria.²⁴⁷ In another study, leaves were extracted with methanol, and extract had significant wound healing activity in diabetic rats.²⁴⁸

Lycium europaeum

One of the notable properties of this plant is that its aerial parts are not toxic, and it is used as medicinal food, although it contains alkaloids and other cytotoxic natural products. But despite this, it has also been partially studied. Summary of the published data is presented in Table 8.

Table 8. Medicinal, biological and other activities of *Lycium europaeum*.

Activity/Property	Major Findings/Reference
Anticancer, cytotoxicity and related activities	Fruits were extracted with 80 % aqueous ethanol and extract had cytotoxic effect on A549 human lung cancer cells and PC12 rat adrenal medulla cancer cells. ²⁴⁹ Fruits were extracted with supercritical CO ₂ . Obtained oil inhibited Caco-2 cell growth. Oil was analyzed and its composition was determined (no new compounds). ²⁵²
Antidiabetic and related activities	Aqueous leaves extract was prepared and was found antihyperglycemic and antihyperlipidemic in diabetic (alloxan) rats. Total phenolic and flavonoid contents were also determined. ²⁵⁰
Antioxidant, anti-inflammatory, analgesic	Fruits were extracted with 80 % aqueous ethanol and extract had antioxidant activity (H ₂ O ₂). ²⁴⁹ Aqueous leaves extract was prepared and was found active antioxidant (DPPH). ²⁵⁰ Leaves were extracted with water and extract had antioxidant (DPPH, H ₂ O ₂) activity. ²⁵¹ Fruits were extracted with supercritical CO ₂ . Obtained oil had antioxidant activity (ABTS, DPPH). ²⁵² Whole plant methanolic extract was prepared and showed notable antioxidant (two methods) and analgesic (hot plate) activities. ²⁵³ Polysaccharide was isolated from the aqueous extract of fruits. It had antioxidant (DPPH, H ₂ O ₂) and anti-inflammatory (carrageenan-induced paw edema in rats) activities. ²⁵⁴ Roots were extracted with several solvents, and extracts were analyzed for chemical composition. Main isolated compounds were terpenes and an alkaloid (see Figure 17). All extracts and isolated natural products had antioxidant (DPPH) activity. ²⁵⁵
Internal organs protection, wound healing	Leaves were extracted with water and extract had kidney and liver protection activity against Cisplatin induced injuries. ²⁵¹ Whole plant methanolic extract was prepared and showed

	notable hepatoprotective and nephroprotective activities against CCl ₄ -induced injuries in mice. ²⁵³ Polysaccharide was isolated from the aqueous extract of fruits. It had hepato and renal protection against CCl ₄ -induced toxicity. ²⁵⁴
Enzyme inhibition	Roots were extracted with several solvents, and extracts were analyzed for chemical composition. All extracts and isolated natural products had acetylcholinesterase inhibition activity. ²⁵⁵
Food	Fruits are used in North Africa as food. ²⁵⁶

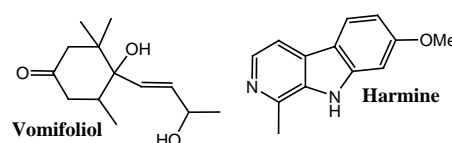


Figure 17. Selected compounds isolated from *L. europaeum* (Ref. 255).

Lycium chweinfurthii

As far as we could find in our published literature search, only two publications could be found. Different parts of the plant were extracted separately with several solvents. Each extract was analyzed and isolated compounds were characterized. No new compounds reported.²⁵⁷ A new glucoside (3-methoxy-4-O-β-D-glucopyranosyl-methyl benzoate) that was isolated from fruit aqueous extract, showed α-glucosidase inhibition activity.²⁵⁸

Lycium shawii

A thorny plant with red fruits, that its natural habitat is desert edge. It has been partially studied and a summary of published data is presented in Table 9.

Table 9. Medicinal, biological and other activities of *Lycium shawii*.

Activity/Property	Major Findings/Reference
Antibacterial, analgesic and related activities	Leaves were extracted with methanol and extract was active against some drug resistant pathogens. ²⁶⁰ Seeds were extracted with 70 % aqueous methanol and extract was very active against <i>Staphylococcus aureus</i> . ²⁶¹ Fruits were extracted successively with several solvents. Most extracts showed significant activity against bacteria strains. ²⁶²
Anticancer, cytotoxicity and related activities	Leaves methanolic extract was prepared and found active against HEK293 cancer cell line. ²⁵⁹ Aerial parts were defatted with <i>n</i> -hexane, suspended in aqueous ethanol (50 %) and extracted with several solvents.

Antioxidant, anti-inflammatory, wound healing	Most extracts showed anticancer activity. ²⁶³ Leaves were extracted with methanol and extract had notable antioxidant activity (DPPH, ABTS). Geral chemical composition, total phenolic and total flavonoid contents we also determined ²⁶⁰ Fruits were extracted successively with several solvents. Most extracts showed significant antioxidant activity. Total phenolic and total flavonoid contents were also determined. ²⁶² Aerial parts were defatted with <i>n</i> -hexane, suspended in aqueous ethanol (50 %) and extracted with several solvents. All extracts showed anticancer activity. ²⁶³
Chemical composition	Aerial parts were defatted with <i>n</i> -hexane, suspended in aqueous ethanol (50 %) and extracted with several solvents. Ethyl acetate fraction was analyzed and detailed list of compounds is provided. No new compounds. ²⁶³ Two new compounds were isolated and characterized (see Figure 18). ²⁶⁴ Detailed chemical compositions were determined effected by seasonal variations. The components that were reported are: general chemical composition, saccharides, fatty acids, hydrocarbons (including three sterols), total alkaloid, phenols, flavonols and tannins. ²⁶⁵ Chemotaxonomic significance study of the chemical composition. No new compounds. ²⁶⁶
Internal organs protection	Aerial parts were defatted with <i>n</i> -hexane, suspended in aqueous ethanol (50 %) and extracted with several solvents. Most extracts showed hepatoprotective activity. ²⁶³
Enzyme inhibition	Active urease inhibitors were scanned and a structure-activity relationship study was performed. ²⁶⁷

Mandragora autumnalis

M. autumnalis is a single species of the *Mandragora* genus, that grows in the reviewed area. Ripe fruits are edible and have pleasant smell, but all other parts of the plant are highly toxic, as can be seen in Table 10.

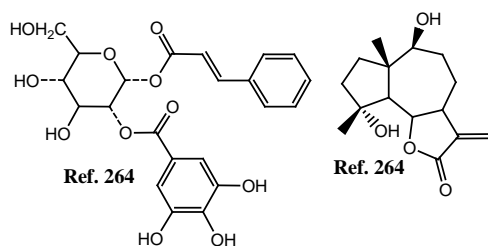


Figure 18. Selected natural products isolated from *L. Shawii*.

Table 10. Medicinal, biological and other activities of *Mandragora autumnalis*.

Activity/Property	Major Findings/Reference
Antioxidant	Aerial parts were extracted with acetone and methanol. Extracts showed high antioxidant capacity (4 methods) and metal chelating activity. Total phenolic and flavonoid contents were determined. ²⁶⁸
Chemical composition	Aerial parts were extracted with acetone and methanol. Extracts were analyzed for fatty acids: 11 saturated (C8:0-C22:0) and 11 unsaturated (C14:1 ω 5-C20:2 ω 6). ²⁶⁸ Roots were analyzed for alkaloids and some compounds were indentified for the first time in <i>Mandragora</i> plants. Two of these alkaloids are presented in Figure 18. ²⁶⁹ In these five publications, detailed compositions of volatile and odoriferous compounds are presented after analysis or extraction of essential oil. Alkaloids or withanolides are not included. ²⁷⁰⁻²⁷⁴ Composition and morphological characteristics are presented in order to avoid misidentification that leads to poisoning. ²⁷⁵
Enzyme inhibition	Aerial parts were extracted with acetone and methanol. Extracts had notable enzyme inhibition (cholinesterase, tyrosinase, α -amylase, α -glucosidase). ²⁶⁸
Toxicity	72 Y.O. Female was poisoned after eating fruits that she mistaked with edible <i>Borago Officinalis</i> . ²⁷⁶ Two Greek and 15 Brazilian adults (separately) were treated with phytostigmine after being hospitalized with fruits eating poisoning. ^{277,278}

Nicandra physalodes

N. physalodes, known also as "Apple of Peru", is the most widespread species of the three included in the *Nicandra* genus. It was partly investigated, and most published researches focus on its active ingredients (Table 11)

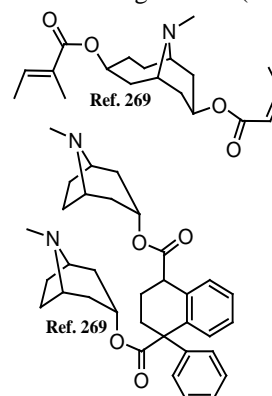


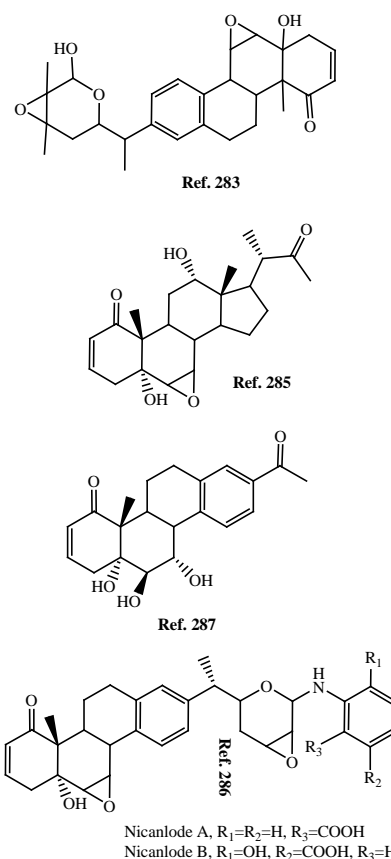
Figure 19. Natural products isolated from *M. autumnalis*.

Table 11. Medicinal, Biological and Other Activities of *Mandragora autumnalis*.

Activity/Property	Major Findings/Reference
Antibacterial	Leaves were extracted with acetone and crude extract was fractionized with several solvents. Extract and fractions had various levels of antibacterial activity. ²⁸⁷
Anti-inflammatory	Fruits were extracted with 70 % aqueous ethanol and 18 glycosides were isolated, 3 of them new. Extract and pure compounds showed anti-inflammatory activity (NO production inhibition). ²⁸⁴
Diuretic	Ethanol and aqueous extracts of whole plant found diuretic in Wistar rats. ²⁷⁹
Insecticidal	Petroleum ether extract was prepared (plan part is not indicated) and was chromatographed for general composition: triterpenes, hydrocarbons and sterols. The crude extract and fraction had insecticidal activity against Spotted Spider Mites (<i>Tetranychus urticae</i>). ²⁸⁰ Nicandrenone, a natural product with insecticidal activity was isolated from leaves. ²⁸³ Leaves were extracted with acetone and crude extract was fractionized with several solvents. Extract and fractions had various levels of insecticidal activity against <i>Aedes aegypti</i> . ²⁸⁷
Chemical composition	General chemical composition was determined in fresh fruits tissue, and detailed composition of vitamins, antioxidants and minerals. ²⁸² Nicandrenone was isolated and characterized (Figure 20). ²⁸³ Three new glycosides were isolated from fruits, one of them is shown in Figure 20. ²⁸⁴ Three new withanolides were isolated from the flowers and characterized. One of them (nicphysatone B) is shown in Figure 20. ²⁸⁵ Nicanlodes A and B were isolated from the aerial parts (Figure 20). ²⁸⁶ Five new withanolides were isolated from leaves acetone extract. One of them is presented in Figure 20. ²⁸⁷
Nanoparticles and their applications	Leaves aqueous extract was prepared and used to reduce Ag ⁺ (aq) ions, to prepare AgNP's, that had anti-mosquito activity. ²⁸¹

Nicotiana glauca

N. glauca is the only wild species of the *Nicotiana* genus (21), that grows in the reviewed area. Domesticated varieties of *N. tabacum* are cultivated and both species include many common natural products. *N. glauca* is toxic, as can be seen in Table 12.

**Figure 20.** Natural products isolated from *N. physalodes*.**Table 12.** Medicinal, biological and other activities of *Nicotiana glauca*.

Activity/Property	Major Findings/Reference
Allelopathic	Aqueous extracts of different parts of the plant were prepared and their effect on the growth of <i>Juniperus procera</i> was studied. Leaf extract promoted growth, while root extract suppressed growth. ²⁸⁸
Antibacterial	Aerial parts were extracted with water and <i>n</i> -hexane, several times over a time period of one year, and seasonal as well as location influences were studied. Extracts had notable antibacterial activity. ²⁸⁹
Anti-inflammatory, antioxidant	Aerial parts were extracted with water and <i>n</i> -hexane, several times over a time period of one year, and seasonal as well as location influences were studied. Content of different antioxidant compound families, including enzymes was determined. ²⁸⁹ Who plant was defatted with <i>n</i> -hexane and extracted with methanol and for alkaloids. Each part of the plant was treated similarly, and all extracts were tested for anti-inflammatory (ear edema) and antioxidant (DPPH, ABTS) activities. General chemical composition is also reported. ²⁹⁰

Insecticidal	Leaves were extracted for alkaloids and extract was analyzed by HPLC to obtain pure anabasine (Figure 9). Both alkaloid and anabasine showed high activity against cabbage white caterpillars (<i>Pieris rapae</i>). ²⁹¹
Chemical composition	Aerial parts were extracted with water and <i>n</i> -hexane, several times over a time period of one year, and seasonal as well as location influences were studied. General chemical composition, fatty acids composition and enzyme composition, were recorded. ²⁸⁹ First isolation and characterization of anabasine. ²⁹² High hydrocarbons (C29-C33) were analyzed in leaves by GC-MS. ²⁹³ Leaves essential oil was prepared by water distillation and analyzed by GC-MS. ²⁹⁴
Corrosion inhibition, metal accumulation	Leaves aqueous extract was prepared and found efficient corrosion inhibitor of steel, under different conditions of acidity and salinity. Detailed potentiodynamic polarization curves are presented. ²⁹⁵ General chemical composition was determined after extraction of leaves and flowers with several solvents. Metal accumulation in these plants parts (that grew in polluted habitat) was low. ²⁹⁶
Toxicity	Two cows died after eating leaves. Postmortem analysis detected nicotine and anabasine in corpses. ²⁹⁷ Seven ostriches that ate leaves died and anabasine was the major toxicant. ²⁹⁸ Five reports of human poisoning by leaves of the plant, with some fatal cases. ²⁹⁹⁻³⁰³

Physalis angulata

P. angulata is one of two species of the *Physalis* genus, that grow in our area. Both of them, were sufficiently studied until now. In addition, research included many areas and topics, as can be seen in Table 13.

Table 13. Medicinal, biological and other Activities of *Physalis angulata*.

Activity/Property	Major Findings/Reference
Antibacterial, antimicrobial, antifungal	Fruits ethanolic extract found active against some bacteria, separately or with ZnO in an formulation. ³⁰⁴ Essential oils of aerial parts and roots were separately prepared by hydrodistillation. EO of aerial parts was more active against tested bacteria, and both EO's did not affect <i>Staphylococcus aureus</i> . ³⁰⁵ Fruits ethanolic extract was against some bacteria species. Physalin B that was

Anticancer and related activities	isolated from this extract was proposed as the natural product responsible for this activity. ³⁰⁶ Known physalins (B, D, F) were found active against several types of bacteria, while physalin D was most active. Some NMR results for physalin D are reported for the first time. ³⁴³ Fruits were extracted with several solvents and all extracts were active against human breast cancer MAD-MB 231 and MCF-7 cell lines. ³⁰⁷ Leaves were extracted with 70 % aqueous ethanol, and extract was active against human ovary cancer cell lines (SKOV3) and human blood cancer cell lines (HL60). ³⁰⁸ Whole plant was extracted with 96 % aqueous ethanol and extract was active against myeloma cell line. ³⁰⁹ Ethanol and aqueous extracts of fresh leaves were prepared. Both extracts inhibited lymphocyte cell proliferation. ³¹⁰ Nine studies that present similar researches: anticancer activities of natural products isolated from this plant (physalines and withanolides, see Figures 5, 6, 10). It is important to mention that many of these compounds are new. ³¹¹⁻³¹⁹ Stems and leaves were extracted with ethanol and methanol. Extracts had antitumor activity. ³²⁴ Whole plant was extracted with dichloromethane and fractionized with several solvents. Physalin B and its 5,6-epoxide were isolated. Both compounds were cytotoxic (WI-38 cells). ³³⁴ Physalin F was isolated (no plant part or solvent indicated) and proved antiproliferative against HTLV-1-infected cells. ³⁴¹ Leaves were extracted with ethanol and 15 physalins were isolated, five of them were new. All compounds had high anticancer activity against different human cancer cell lines. ³⁴² Cytotoxic compounds search using various methods and techniques, revealed many active natural products, some are new physalins, withanolides and physagulides. ³⁴⁵⁻³⁴⁹
Antioxidant, anti-inflammatory and related activities	Ethanol and aqueous extracts of fresh leaves were prepared. Total phenolic content was determined for both extracts, and their antioxidant capacities were measured. ³¹⁰ Leaves methanolic extract was found analgesic (acetic acid induced writhing test) and anti-inflammatory (carrageenan induced paw edema) in mice. ³²⁰ Aerial parts were extracted with super critical CO ₂ and extract had anti-inflammatory activity against TNBS-induced colitis in rats. ³²¹ Whole

<p>plant aqueous extract was prepared and found anti-inflammatory (carrageenan induced paw edema) in rats. General chemical composition was determined in this study.³²² Leaves were extracted with water, ethanol and methanol. Extracts had anti-inflammatory and anti-arthritis activities. Aqueous extract was most active. General chemical composition was determined.³²³ Roots aqueous extract had antinociceptive activity against formalin induced pain in rats.³²⁵ Leaves were extracted with methanol and extract had antioxidant (DPPH) activity.³²⁶ Leaves were extracted with water and extract was found active against oxidative stress in cell, induced by 2,4-dichlorophenoxyacetic acid.³²⁷ Physalin E was isolated from aerial parts and tested for anti-inflammatory (12-O-tetradecanoyl-phorbol-13-acetate-induced) activity in rats.³²⁸ Twelve new labdane-type diterpenoids were isolated from leaves and tested for anti-inflammatory activity (LPS-induced NO production). Ten of them found active, and structures of two of them are shown in Figure 21.³²⁹ Physalin B was isolated from whole plant ethanol extract and was active against LPS-induced inflammation.³³⁰ Different parts of the plant, which was collected in different locations and seasons, were extracted separately with 80 % aqueous ethanol. Each extract was tested for antioxidant capacity (3 methods), analyzed for total phenolic content, total flavonoid content, total phenolic acids content and analyzed with HPLC for phenolic compounds. New compounds were not reported.³³¹ Fruits were separately extracted with 70 % aqueous ethanol and water. Each extract was tested for antioxidant capacity (ABTS, FRAP, DPPH), analyzed for total phenolic content and general chemical composition, including use of NMR.³³² Leaves were extracted with methanol and general chemical composition was determined. Extract found active against ethanol-induced ulcer in rats.³³³ Methanolic extracts from leaves, roots, stems, and fruits were prepared, general chemical composition of each part was determined, and antioxidant capacity of these extracts were determined (DPPH).³³⁸ Leaves were extracted with ethanol and 15 physalins were isolated, five of them were new. most</p>	<p>compounds inhibited NO production induced by LPS.³⁴² Whole plant was extracted with dichloromethane and fractionized with several solvents. Physalin B and its 5,6-epoxide were isolated.^{334,e} Essential oil was extracted from leaves by hydrodistillation. No new compounds reported.³³⁵ Whole plant was extracted with CH₂Cl₂ and <i>n</i>-BuOH. Three known compounds were isolated and characterized: physalin B, physalin G and quercetin 3-O-rutinoside.³³⁶ Precise and comprehensive analysis of the chemical compositions of plant parts. All reported compounds are known.³³⁷ Leaves (dried or fresh) were extracted and fractionized with several solvents and total contents of alkaloids, phenolics flavonoids and saponins were determined.^{339,340} Leaves were extracted with ethanol and 15 physalins were isolated, five of them were new. One of them is shown in Figure 21.³⁴² Three new withanolides (physagulins A, B, C, see Figure 5) were isolated and characterized, from methanolic of fresh leaves.³⁴⁴</p> <p>Leaves aqueous extract was prepared and had antisickling activity (blood cells).³⁵⁰ Leaves aqueous extract was prepared and fractionized. Fractions tested and found active in enhancing blastogenesis and stimulatory activity on B cells and less effect on T cells.³⁵¹</p> <p>Whole plant was extracted with CH₂Cl₂ and <i>n</i>-BuOH. Three known compounds were isolated and characterized including physalin G which inhibited α-glucosidase.³³⁶</p> <p>Whole plant was extracted with dichloromethane and fractionized with several solvents. Physalin B and its 5,6-epoxide were isolated. Both compounds were antiplasmodial (<i>Plasmodium falciparum</i>).³³⁴ Known Physalins were active antileishmanial in parasite infected mice.^{352,353} Roots aqueous extract had notable activity against <i>Leishmania infantum</i>.³⁵⁴ Whole plant and different parts were extracted and fractionized ethanol, methanol, ethyl acetate, dichloromethane, chloroform, and hexane. Each extract was analyzed to obtain pure physalins. These were tested and found active against <i>Biomphalaria tenagophila</i>.³⁵⁵</p> <p>Leaves were extracted with water and extract was used to prepare nickel oxide nanoparticles (NiO-NPs). Extract was used as stabilizing agent</p>
Chemical composition	
Immune system and blood cells enhancing activities	
Enzyme inhibition and related activities	
Insecticidal, anti-parasitic and related activities	
Nanoparticles synthesis	

Toxicity	not reductant. ³⁵⁶ Administration of plant extract (parts, solvents, not indicated) along with Methylprednisolone (immunosuppressor, anti-inflammatory) resulted no toxicity in mice. ³⁵⁷
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(e) Physalin B that was reported by P.M. Kimpende and his colleagues (ref. 334) is not a new compound. Its reported epoxide was also mentioned in the past, but both epoxides differ in the stereochemistry of the epoxide group. See: Kawai, M., *et al.*, *Bull. Chem. Soc. Jpn.*, **1994**, 67, 222–226.

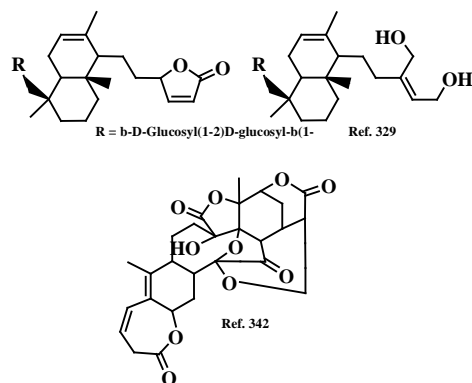


Figure 21. Selected natural products isolated from *Physalis angulata*.

Physalis peruviana

Even though *P. peruviana* is less widespread than *P. angulata*, locally and globally, it has been reasonably studied. The amount of published research is sufficient and properties that were studied are diverse. Summary of research findings is presented in Table 14.

Table 14. Medicinal, biological and other activities of *Physalis peruviana*.

Activity/Property	Major Findings/Reference
Antibacterial, antimicrobial, antifungal	Fruits were extracted (solvent not indicated) and the resulting extract/s was/were active against 9 (out of 11 tested) species of bacteria. ³⁵⁸ Leaves and fruits were extracted with 95 % aqueous ethanol, and extract was active against <i>Listeria</i> ssp. isolated from meat. ³⁵⁹ Leaves and fruits were extracted with ethanol, and extract was active against <i>Salmonella</i> ssp. ³⁶⁰ Fruits aqueous extract was prepared and found active against six bacteria species. General chemical composition was determined in this study. ³⁶¹ Flowers were extracted with 80 % aqueous methanol and extract was active against four bacteria species. Detailed chemical composition was reported but all compounds are previously known. ³⁶² Ethanolic extracts of different plant parts (fruit, seed, root, stem and leaf) were prepared separately. All extracts

Anticancer and related activities	were active against several types of bacteria, where the fruit extract was most active. General chemical composition was determined. ³⁶³ Fruits aqueous extract was prepared and found active against two types of human cancer cells. ³⁶¹ Flowers were extracted with 80 % aqueous methanol and extract was active against three types of human cancer cells. ³⁶² Whole plant was extracted with 95 % aqueous ethanol and extract was active against nicotine-derived-nitroamine-ketone-induced cancer in rats. ³⁶⁴ Active natural product 4β-hydroxy-withanolide E was isolated from different parts of the plants with different solvents and fractionation steps and found active against various human cancer cells. ³⁶⁵⁻³⁶⁸ Fresh leaves were extracted separately with <i>n</i> -hexane and ethanol. Both extracts were tested and found active against two human breast cancer cell lines. ³⁶⁹ Fruits were extracted with ethanol and <i>iso</i> -propanol. Both extracts had anticancer and immunomodulatory activities. ³⁹⁵
Antidiabetic, antiobesity and related activities	Fruits were defatted with petroleum ether then extracted with 95 % aqueous ethanol. The extract showed antidiabetic (STZ-induced) high-fat fed rats. ³⁷⁰ Fruits aqueous extract was added to drinking of STZ-induced diabetic rats, resulting improvement of biochemical parameters in their brains. ³⁷¹ Flowers were extracted and fractionized with several solvents. Butanol and 80 % aqueous ethanolic fractions had antidiabetic activity. ³⁷² Fruits ethanolic extract had α-amylase inhibition activity. ³⁷³ Obese diabetic (alloxan-induced) rats were treated with fruits ethanolic extracts, resulting improvement of both tested parameters. General chemical composition was determined in this study. ³⁷⁴ Fruits fresh juice had high antidiabetic activity in STZ-induced diabetic rats. ³⁷⁵ Dried fruit pomace was fed to high-cholesterol diet-induced hypercholesterolemia in rats resulting in body weight control. ³⁷⁶ Fresh fruits were crushed and processed as pulp, which promoted insulin-dependent skeletal muscle glucose uptake. ⁷⁵²
Antioxidant, anti-inflammatory and related activities	Fruits aqueous extract was prepared and tested for antioxidant capacity (DPPH). ³⁶¹ Ethanolic extracts of different plant parts (fruit, seed, root, stem and leaf) were prepared separately. All extracts had notable

<p>antioxidant activity (DPPH).³⁶³ Fresh leaves were extracted separately with <i>n</i>-hexane and ethanol. Both extracts had antioxidant capacity (DPPH). General chemical composition and detailed volatile compounds content were determined.³⁶⁹ Fruits fresh juice had high antioxidant (DPPH) activity.³⁷⁵ Filtered fresh fruit juice ameliorated rabbit eye inflammation.³⁷⁷ Flowers petroleum ether extract was prepared, and its anti-inflammatory activity was tested by two methods: TNBS-induced colitis in rats and inhibition of NO production induced by LPS. Antioxidant capacity of extract was determined (DPPH, ABTS).³⁷⁸ Leaves methanolic extract inhibited ovalbumin-induced airway inflammation by attenuating the activation of NF-κB and inflammatory molecules.³⁷⁹ Flowers were extracted with methanol and 4β-Hydroxywithanolide E was isolated. It had anti-inflammatory activity by inhibiting the NF-κB signaling in diabetic mouse adipose tissue.³⁸⁰ 4β-Hydroxywithanolide E and physalactone (Figure 22) were isolated from flowers and had inhibited LPS-induced inflammation.³⁸¹ Aerial parts were extracted with water or different concentrations of aqueous ethanol (20-95 %), and antioxidant capacity of all extracts was tested (FeCl₂-Ascorbic acid and lipid peroxidation). 95 % Aqueous ethanol extract had the highest activity.³⁸² Fresh fruit juice was added to rats food that had CCl₄-induced liver oxidative stress, and improvement was recorded compared with control animals.³⁸³ Fruits were extracted with ethanol and fractionized with several solvents. Extract and fractions were tested against rotenone-induced oxidative stress in astrocytic cells. Extract and acetone fraction were most active.³⁸⁴ Fresh fruits juice of wild and cultivated plants were tested for antioxidant capacity (DPPH), and cultivated fruits were more active.³⁸⁵ Fruits were extracted with ethanol and <i>iso</i>-propanol. Both extracts were analyzed for general chemical composition, total phenolic and β-carotene contents, and antioxidant capacity was determined (DPPH, FRAP).³⁹⁵ Fresh fruits were crushed and processed as pulp, which prevented inflammation and lipoperoxidation in the liver of diet-induced obese mice.⁷⁵²</p>	<p>Chemical composition First report of isolation and characterization of 4β-Hydroxywithanolide E.³⁸⁶ First report of isolation and characterization of perulactone.³⁸⁷ Different protection compounds (mainly withanolides and their derivatives) were isolated from leaves and flowers (aqueous extract) and fresh fruits (juice) in various maturity steps. New compounds are not reported.³⁸⁸ Fresh berries juice; seeds, and pulp/peel (extracts); were analyzed by HPLC, GC-MS and FT-IR for fatty acids, lipid classes, triacylglycerols, phytosterols, fat-soluble vitamins, phenolics and β-carotene.³⁸⁹⁻³⁹¹ New alkaloids, such as physoperuvine (Figure 22) were isolated and characterized.³⁹² Comprehensive alkaloid analysis revealed eight compound, three of them reported first time in <i>Physalis</i> genus.³⁹³ Whole plant was analyzed using various techniques, resulting the determination of 18 odor compounds. Aroma recombination and sensory evaluations tests were also performed.³⁹⁴ Flowers of cultivated plants were analyzed with various methods, revealing high concentrations (compared with wild plants) of phytoprostanes (phenolics), some detected for the first time in this plant.³⁹⁶ A group of irinans (one is shown in Figure 22), androstane-type withanolides, were isolated for the first time and characterized.³⁹⁷</p> <p>Hepatoprotective Roots were extracted with ethanol and 50 % aqueous methanol, successively. Extract had hepato-renal protective activity against CCl₄-induced toxicity in rats. Further analysis of extract revealed that the major active natural product responsible for this activity is cuscohygrine (Figure 4).³⁹⁸ Fresh fruits juice had hepatoprotective activity against CCl₄-induced toxicity in rats. Analysis of extract revealed that the major active natural product responsible for this activity is kaempferol. In this study, general chemical composition and antioxidant capacity (TBARS, NO radical inhibition) were determined.³⁹⁹</p> <p>Insecticidal Withanolide E was the major antifeedant against larvae of <i>Spodoptera littoralis</i>.⁴⁰⁰</p> <p>Nutrition Fresh fruits juice of wild and cultivated plants were analyzed for nutritional value, and cultivated fruits contained more vitamin-C and β-carotene.³⁸⁵</p> <p>Toxicity Fresh fruit juice was administered to rats and a very detailed toxicity study</p>
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was performed. Results showed (entire body and organs) that it is not toxic.⁴⁰¹

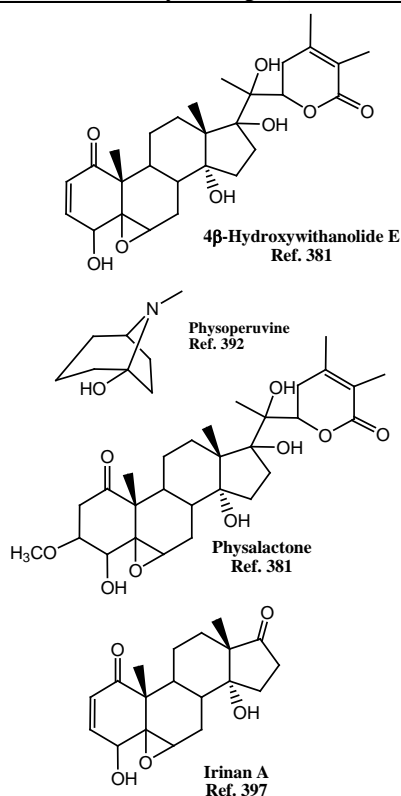


Figure 22. Selected natural products isolated from *Physalis peruviana*.

Solanum cornutum

No publications.

Solanum elaeagnifolium

This plant is one of the most known of the *Solanaceae* family and the *Solanum* genus in the reviewed region of Israel and Palestine. It can be easily confused with *S. incanum*, especially in terms of flowers shapes and colors. But leaves of both species are slightly different, where leaves of *S. elaeagnifolium* have smooth-shaped edges, while leaves of *S. incanum* have gulf-like edges.



Figure 23. *Solanum elaeagnifolium*

Even though *S. elaeagnifolium* was always a well known plant, it grew with low densities over a very wide range of natural habitats, excluding only very arid, desert areas. In recent years, this plant is spreading very rapidly, and now, in habitats of heavy soils, it is one of the most common plants. Its medicinal properties are presented in Table 15.

Table 15. Medicinal, biological and other activities of *Solanum elaeagnifolium*.

Activity/Property	Major Findings/Reference
Allelopathy	Seeds were extracted with water and several organic solvents or mixtures. All extracts were tested for allelopathic activity against for plants growing in Corn (<i>Zea mays</i>) fields. Active extracts and fractions were analyzed (GC-MS), and ethanolic extract was most active, containing chlorogenic acid. ⁴⁰² Leaves aqueous extract had pesticidal activity against nematode <i>Meloidogyne incognita</i> and three weed species. Active ingredients were known phenolics. ⁴⁰³
Antibacterial	Leafy branches were extracted with water and several organic solvents. Each extract was tested against bacteria strains and analyzed, mainly for lipids and fatty acids. Detailed data is provided. New compounds were not reported. ⁴⁰⁴
Anticancer	Seeds were extracted with 30 % aqueous ethanol and chloroform-methanol (2:1, v/v), separately. Extracts found active in anti-proliferation test (MMT). ⁴⁰⁵ Whole plant was extracted with 90 % aqueous methanol and extract was chromatographed and analyzed, leading to isolation of two compounds (one new, see Figure 24) that had activity against several human cancer cell lines. ⁴⁰⁶ Fruits were extracted with 10 % aqueous methanol, and extract was active against several breast cancer cell lines. Extract was analyzed and approximate composition is provided, presenting mainly known active phenolics. ⁴⁰⁷
Antidiabetic	Fruits were extracted successively with cyclohexane, dichloromethane, ethyl acetate and methanol. Each extract was tested for antidiabetic activity with Anti-AGEs assay. ⁴⁰⁸
Antioxidant, anti-inflammatory and related activities	Seeds were extracted with 30 % aqueous ethanol and chloroform-methanol (2:1, v/v), separately. Extracts anti-inflammatory activity (LPS-induced NO production inhibition) and antioxidant capacity (4 methods). ⁴⁰⁵ Fruits were extracted successively with cyclohexane, dichloromethane, ethyl acetate and methanol. Each extract was tested for

	antioxidant capacity (4 methods) and metal chelating activity. ⁴⁰⁸ Five organic solvents and water used to extract seeds. For each extract, general chemical composition was determined and antioxidant capacity (TAOC, DPPH) was measured. ⁴⁰⁹
Hepatoprotective	Methanolic extract of aerial parts was prepared and found hepatoprotective against paracetamol-induced liver injury. In this study, a new compound was isolated and characterized (Figure 24). ⁴¹⁰
Insecticidal, molluscicidal	Seeds methanolic extract had moderate insecticidal effect on three pest species, and strong effect inhibiting their oviposition. Leaf extract had lower efficiency. ^{411,412} Seeds were extracted with several solvents successively. Methanolic extract was most active against snails (<i>Galba truncatula</i>). Analysis of this extract revealed active compound β -solamarine, which was isolated for the first time from this plant. Total alkaloid and saponin contents of this extract were also determined. ⁴¹³
Toxicity	Alkaloid extract caused congenital craniofacial malformations in rats and high ratio of deformed litter incidence. It is reported that solasodine (Figure 8) is the major cause of these effects. ⁴¹⁴
Chemical composition	Detailed seed oil chemical composition is presented. ⁴¹⁵ Leaves were extracted and analyzed with standard multi-step isolation procedure, yielded a new compound (Figure 24) along with known others. ⁴¹⁶

Solanum incanum

S. incanum has a close appearance to *S. elaeagnifolium*, but the former grows in drier areas and it is less widespread in eastern part of the Mediterranean basin.

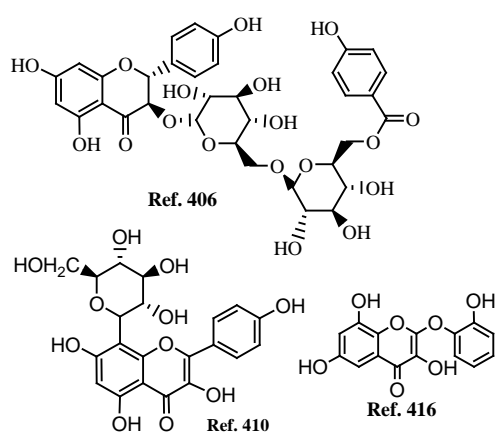


Figure 24. Selected natural products isolated from *Solanum elaeagnifolium*.

Table 16. Medicinal, biological and other activities of *Solanum incanum*.

Activity/Property	Major Findings/Reference
Antibacterial and related activities	Aqueous and methanolic leaves extracts found active against several bacteria species. ⁴¹⁷ Aerial parts were extracted with several organic solvents and all extracts were found weak antibacterial (<i>B. subtilis</i> , <i>S. aureus</i> , <i>E. coli</i> , <i>K. pneumoniae</i> , <i>P. aeruginosa</i>). ⁴¹⁸ Ethanolic fruits extract was analyzed for general chemical composition, and it had notable antibacterial activity. ⁴¹⁹ Unripe fruits methanolic extract found active against some bacteria species. ⁴²⁰ A mixture of ripe and unripe fruit juice was prepared and diluted with water to prepare solutions with ten solutions, 10-100 μ L/10 mL. 70 μ L was most effective against oral bacteria. ⁴²¹ Fruits methanolic and aqueous extracts were prepared, diluted to a range of concentrations, and found active against <i>S. aureus</i> and/or other bacteria species. General chemical composition was determined in these studies. ^{422,423} Aerial parts were extracted with 80 % aqueous ethanol. Extract was analyzed for general chemical composition and found active against several bacteria types. ⁴²⁴ Fruits juice was filtered on silica gel and fractionized with several solvents. Some fractions had notable antibacterial activity, but it is reported that a compound that had "purine-like in structure and probably phosphorylated" had high activity. Compound was isolated by TLC but structure is not reported. ⁴²⁵ All parts of the plant, including ripe and unripe fruits were extracted separately with methanol, petroleum ether and chloroform, each. All extracts were tested (10-20 %) against six microbial species. Methanolic extract of ripe fruit was most active and petroleum ether extracts were inactive. General chemical composition is reported. ⁴²⁶ Fruits were extracted with 70 % aqueous ethanol. Extract was analyzed for qualitative composition and found active against several bacteria species. ⁴²⁷ Fruity aerial parts were extracted with methanol and extract was analyzed for general chemical composition. It was found active against two bacteria species. ⁴²⁸ Nano particles were prepared by mechanical procedure from dry fruits powder and from dry methanolic extract of this powder.

Anticancer	Both nano particles found active against <i>P. erinaceus</i> and <i>E. coli</i> . ⁴²⁹ Extract "SR-T100" (no preparation method) which contains mainly alkaloid fraction (solamargine), had anti-ovarian-cancer activity. Mechanism of action is also investigated. ⁴³⁰ Extract "SR-T100" (partial preparation method) found active against lung melanoma cells. ⁴³¹ Aqueous fruit extract found active against human colorectal carcinoma cell line (HCT 116). ⁴³² First isolation and characterization of incanumine (fruits, methanolic extract), structure elucidation, which revealed a glycoside of solasodine (Figure 8). It was found active against human hepatoma cancer cells. ⁴³³	Fresh fruit juice was diluted with water and was found active against cattle ticks larvae (<i>Rhipicephalus decoloratus</i>). ⁴⁴³ Fresh fruit juice was found active insecticidal against cabbage aphids (<i>Brevicoryne brassicae</i>). ^{444,f}
Antidiabetic	Aqueous fruit extract modulated glucose uptake by yeast cells inhibited the enzymes α -glucosidase and α -amylase. ⁴³⁴ Fruits aqueous extract had clear antihyperlipidemic activity in alloxan-induced diabetic rats. ⁴³⁵	Nutritional values and general chemical composition are reported. ^{445,446} Fresh fruit juice added to milk resulting milk clotting for the purpose of cheese manufacturing. ⁴⁴⁷ Unripe fruits were found toxic to goats. ⁴⁴⁸ Unripe fruits and seed are reported as causing poisoning cases of livestock. Results are: diarrhea, lacrimation incoordination, inappetence. ⁴⁴⁹ Fruits ethanolic extract was added to healthy female Swiss mice, in a single dose of 100, 250, 500, 750, 1000 and 2000 mgkg ⁻¹ body weight. Signs of toxicity and mortality were noted after 1, 4 and 24h of administration of the extract for 14 days. ⁴⁵⁰
Antioxidant, anti-inflammatory and related activities	Roots were extracted with dichloromethane and extract was found active antinociceptive (formalin-induced) and anti-inflammatory (carrageenan-induced). ⁴³⁶ Leaves were extracted with 80% aqueous methanol and extract had analgesic activity in hot plate test and acetic-acid induced writhing test in mice. Very general chemical composition was determined. ⁴³⁷ Roots were defatted with petroleum ether and extracted in a standard procedure to obtain flavonoid-rich extract, and it was analyzed for general chemical composition. This extract had anti-inflammatory and antinociceptive activities, after inducing these health disorders (both) in mice with formalin. ⁴³⁸ Methanolic extract of aerial parts was prepared, and its antioxidant (DPPH) capacity was measured. ⁴³⁹ Leaves methanolic extract was prepared and an ointment was made containing 1% of this extract. Ointment found active against burn wound induced by hot metal rod. ⁴⁴⁰	Toxicity Chemical composition Analysis of 80 % aqueous methanolic extract of leaves and fruits, resulted the isolation and characterization of a new steroid shown in Figure 25. ⁴⁵¹ Whole plant was extracted with petroleum ether, chloroform, methanol, and ethanol, separately. Each extract was analyzed with GC-MS. Detailed chemical compositions and spectra are presented. New compounds are not reported. ⁴⁵² General chemical composition is presented. ⁴⁵³⁻⁴⁵⁶ Using two countercurrent chromatographic techniques resulted the isolation of solasonine and solamargine (Figure 8). ⁴⁵⁷ Changes in the concentration of glycoalkaloids solasonine and solamargine according to growth steps. ^{458,459}
Insecticidal, molluscicidal, antiparasitic	Methanolic extract of aerial parts was prepared and was found active against four parasite species. ⁴³⁹ Roots were extracted with 98% aqueous ethanol and extract was active against <i>Schistosoma mansoni</i> -infected mice. ⁴⁴¹ Fresh fruits aqueous extract and found active against Chilli root knot nematodes (<i>Meloidogyne</i>). ^{442,f}	

Despite this, it was more investigated as can be concluded according to published studies about both plants. Summary of these studies is presented in Table 16.

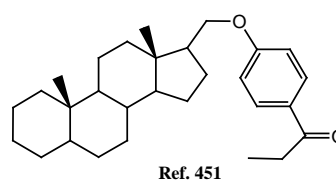


Figure 25. Structure of a steroid isolated from *Solanum incanum*.

Solanum nigrum

This species is the most studied among the plants of the *Solanum* genus. In the reviewed region, it is unmistakable with other plants, since most people can identify it very easily. It has been very extensively studied and published for almost every possible activity and property. Summary of these published studies is presented in Table 17.

Table 17. Medicinal, biological and other activities of *Solanum nigrum*.

Activity/Property	Major Findings/Reference
Allelopathy	Shoots and roots were extracted separately with water. Both extracts had allelopathic effect on seed germination of cabbage, spinach and tomato. Roots essential oil was prepared and analyzed by GC-MS. A detailed composition is presented but new compounds are not reported. ⁴⁶⁰
Antibacterial, antifungal, antiviral and related activities	Various parts of the plants were extracted with methanol and extracts were tested against four bacteria species. Extract of whole plant had highest activity. ⁴⁶¹ Fruits were extracted with seven solvents and extracts were tested against some bacteria species. Methanolic and aqueous extracts had highest activities. ⁴⁶² Leaves were extracted with 95% aqueous ethanol and extract was found active against pathogenic bacteria. ^{463,464} Acetone whole plant extract was prepared and found active antibacterial. General chemical composition was determined in this study. ⁴⁶⁵ Leaves aqueous extract was used to prepare silver nanoparticles (AgNP's), that had activity against <i>S. typhi</i> and <i>S. aureus</i> . ⁴⁶⁶ Solanine was isolated from leaves and found active against several bacteria species. ⁴⁶⁷ Aerial parts were ultrasonic-assisted-extracted with ethanol. Extract had activity against several bacteria species, with rutin as the major active compound. A mechanism of action is presented. ⁴⁶⁸ Aqueous and methanolic extracts were prepared and both were active against bacteria and fungi. General chemical composition was determined. ^{469,470} Gold nanoparticles AuNP's were prepared using aqueous extract of leaves. AuNP's had strong antibacterial activity. ⁴⁷¹ Ethanolic extract was prepared after defatting the "plant materials" (no parts indicated) with petroleum benzene and its antibacterial properties were tested. General chemical composition was determined and functional groups (in extract) were detected by IR spectroscopy. ⁴⁷² Leaves were

extracted with five solvents and for each extract, antibacterial activity and general chemical composition were determined.⁴⁷³ Leaves methanolic extract was prepared and found active antibacterial. General chemical composition and detailed analysis by GC-MS is provided, with structures and chromatograms. Some interesting siloxans are shown.⁴⁷⁴ Whole plant was extracted with water, acetone and ethanol, separately. Each extract was tested for antibacterial activity and analyzed for flavonoids.⁴⁷⁵ Leaves were extracted with water, chloroform and *n*-butanol, separately. For each extract, general chemical composition and antibacterial activity were determined.⁴⁷⁶ Leaves aqueous extract was prepared and found active against different fungi species. General chemical composition is presented.^{477,478} Whole plant was extracted with 70 % aqueous ethanol, and extract was active against Cabbage Black Leaf Spot Disease (*Alternaria brassicicola*). Analysis (LC-MS, NMR) of extract lead to the natural product responsible for this activity: degalactotigonin (Figure 26).⁴⁷⁹ Different parts of the plant were extracted with methanol and extract was fractionized with acetone, *n*-hexane and chloroform. Extract and fractions had antiviral activity (hepatitis C), where seed extract was most active.⁴⁸⁰

Anticancer

Solanine was isolated from leaves and found active against HEP-2 and AGS cell lines.⁴⁶⁷ Aerial parts were ultrasonic-assisted-extracted with ethanol. Extract had activity against several cancer cell lines, with rutin as the major active compound. A mechanism of action is presented.⁴⁶⁸ Ethanolic, methanolic and aqueous extracts of fruits were prepared. All had anticancer activity against HL-60 human leukemia cell lines.⁴⁸¹ Leaves were extracted with chloroform and 80 % aqueous methanol. The combined extracts were active against PC3 and Hela-a cancer cells.⁴⁸² Leaves aqueous extract had anticancer activity against human breast cancer cells. Detailed mechanism of action is presented.⁴⁸³ Unripe fruits were extracted with hexane and chloroform, then with methanol. Extract was treated for alkaloid extraction and HPLC analysis showed high concentration of α -solanine. This extract had high activity against

Adriamycin (commercial name, active compound: doxorubicin) resistant cancers.⁴⁸⁴ Fruits ethanolic extract was active against breast cancer cells.⁴⁸⁵ Aqueous whole plant extract had activity against human breast cancer cells MCF7 cells. Mechanism of action is presented.⁴⁸⁶ Solanine A, a new natural product that was isolated from the fruits, showed activity against MGC803, HepG2 and SW480.⁴⁸⁷ A new nor-spirosolane (unnamed) type steroidal alkaloid was isolated from unripe fruits, exhibited anticancer activity against HL-60, U-937, Jurkat, K562, and HepG2 cell lines.⁴⁸⁸ Leaves were extracted with ethanol and water, separately. Both extracts were analyzed for active compounds and a detailed list and structures are presented. New compounds are not reported. Both extracts and active compounds had anticancer activity (HepG2).⁴⁸⁹ Solamargine (commercially purchased) was found active against human cholangiocarcinoma QBC939 cancer cells.⁴⁹⁰ Ten (purchased) known alkaloids were tested for anticancer activity through SAR study.⁴⁹¹ Leaves aqueous extract was found active against AU565 breast cancer cells. It was analyzed (HPLC) for phenolics and a detailed composition is presented.⁴⁹² Six known glycoalkaloids were tested and found active against MGC-803 cancer cells.⁴⁹³ Stems were defatted with petroleum ether and extracted with 80% aqueous methanol, to obtain a polysaccharide (glucose and galctose). This polysaccharide was found active against RAW 264.7 cancer cells.⁴⁹⁴ Leaves were extracted and fractionized with several solvent, yielding the isolation of a new saponin. Uttroside B. It was characterized (Figure 26) and found active against liver cancer cell line, HepG2.⁴⁹⁵ Polysaccharide was isolated (plant part not indicated) by extraction with ethanol. Extract had activity against H22 cancer cells. Monosaccharide composition is not reported.⁴⁹⁶ Six new steroidal saponins were isolated from whole plant ethanolic extract, along with degalactotigonin, and all had activity against four types of cancer cell lines.⁴⁹⁷ Degalactotigonin was isolated from leaves and commercially purchased, and found active osteosarcoma cells.⁴⁹⁸ Leaves aqueous

extract acted synergistically with known anticancer synthetic drugs (Cisplatin, Doxorubicin, Docetaxel, and 5-Fluorouracil) against human colorectal carcinoma cells.⁴⁹⁹ Leaves extraction with methanol yielded seven known compounds. Five of them had anticancer activity (inhibition of GLI1-DNA complex formation), where phisalin H was most active.⁵⁰⁰ Commercial solamargine inhibited the progression of gastric cancer by regulating IncNeat1_2 via the MAPK pathway.⁵⁰¹ Alkaloid fraction was extracted with *n*-butanol, and it was active against LIM-1863 human colon carcinoma cell line.⁵⁶²

Anticonvulsant

Leaves were extracted with *n*-hexane, benzene, chloroform, ethanol and water. All extracts were analyzed for flavonoid composition, and tested for anticonvulsant activity (electric shock in rats). Ethanolic extract was most active.⁵⁰²

Antidiabetic, anti-obesity and related activities

Low concentrations of fruits aqueous extract, have vasodilatory effect in diabetic (STZ-induced) and non-diabetic rats. Higher concentrations produced counter effect.⁵⁰³ Fruits aqueous extract had nephropathy prevention effect in diabetic (STZ-induced) rats.⁵⁰⁴ Fruits aqueous extract had blood glucose lowering, antihyperlipidemic, and sensitivity lowering of the vascular mesenteric bed to phenylephrine effects, in diabetic (STZ-induced) rats.⁵⁰⁵ Leaves were extracted with 50 % aqueous ethanol, and extract had α -amylase inhibition activity in STZ-induced diabetic rats. Phenolic composition was determined.⁵⁰⁶ Rats were toxicated with ethanol resulting elavation blood lipid levels. Animals were treated with fruits aqueous extract, which showed strong antihyperlipidemic activity.⁵⁰⁷ Phenolic (aqueous) whole plant extract was found to have anti-obesity activity in high-fat-diet mice.⁵⁰⁸ Leaves aqueous extract was active in diabetic (STZ-induced) rats.⁵⁶⁹

Antioxidant, anti-inflammatory and related activities

Solanine was isolated from leaves and found active antioxidant (DPPH, H₂O₂).⁴⁶⁷ Gold nanoparticles AuNP's were prepared using aqueous extract of leaves. AuNP's had strong antioxidant (DPPH, H₂O₂) activity.⁴⁷¹ Solanine A, a new natural product that was isolated from the fruits, showed anti-inflammatory activity through inhibition of LPS-induced NO

production.⁴⁸⁷ A new nor-spirosolane (unnamed) type steroidal alkaloid was isolated from unripe fruits, exhibited anti-inflammatory activity through inhibition of LPS-induced NO production.⁴⁸⁸ Leaves were extracted with ethanol and water, separately, and extracts were analyzed for active compounds. Both extracts and active compounds had antioxidant activity (DPPH).⁴⁸⁹ Stems were defatted with petroleum ether and extracted with 80 % aqueous methanol, to obtain a polysaccharide (glucose and galactose). This polysaccharide inhibited LPS-induced NO production.⁴⁹⁴ Leaves were extracted with *n*-hexane, benzene, chloroform, ethanol and water. All extracts were analyzed for flavonoid composition, and tested for anti-inflammatory activity (carrageenan-induced paw edema in rats). Ethanolic extract was most active.⁵⁰² Rats were intoxicated with ethanol resulting elevation of oxidant thiobarbituric acid reactive substances. Animals were treated with fruits aqueous extract, which showed strong antioxidant activity.⁵⁰⁷ Whole plant was extracted with 95 % aqueous methanol, and extract showed significant dose dependent anti-inflammatory activity in carrageenin and egg white induced paw edema in rats.⁵⁰⁹ Leaves chloroform extract was found to have antinociceptive (hot plate and formalin tests), anti-inflammatory (carrageenan-induced paw edema) and antipyretic (Brewer's yeast-induced pyrexia test) in mice.⁵¹⁰ Fresh fruits were extracted with 50 % aqueous ethanol to obtain a new compound, Spirost-5-ene-3 β ,12 β -diol (Figure 26) along with other known natural products. Extract and isolated compounds inhibited LTC₄-release (anti-inflammatory activity).⁵¹¹ Oral inflammation was induced in rats by methotrexate and radiation. Leaves aqueous extract was found active against this inflammation.⁵¹² Ethanolic extracts of aerial parts (excluding flowers) were tested for antioxidant activity (Mo-VI, DPPH), and their general chemical compositions were determined.⁵¹³ Leaves or fruits were extracted with several solvents and antioxidant capacity (DPPH) of extracts was determined.^{514-517,522} Leaves were extracted with several solvents and antioxidant capacity of extracts was

determined by stabilization of Sun flower oil. Polar extracts were more active than nonpolar ones. General chemical compositions were determined in this study.⁵¹⁸ Aerial parts were extracted with 95 % aqueous ethanol. Extract was analyzed for general chemical composition, and had antioxidant, anti-inflammatory and anti-ulcer activities.⁵¹⁹ Leaves were extracted with water, and extract was fractionized for alkaloid content. Both crude extract and alkaloid fraction had significant antioxidant activity.⁵²⁰ Fruits were extracted with several aqueous-organic mixed solvents, and extracts were tested for antioxidant capacity (DPPH) and general chemical compositions were determined.⁵²¹ Frozen fruits were extracted for anthocyanins fraction, and it was analyzed for its components. Its antioxidant capacity was determined by ABTS test.⁵²³ Leaves aqueous extract had notable activity of healing second degree burn wounds in rats.⁵²⁴

Anti-stress

Stress was induced in rats by cycles of light-dark and immobilization. These animals were treated with leaves aqueous extract, resulting improvement in several physiological parameters (brain enzymes) compared with control.⁵²⁵

Hepatoprotective

Leaves were extracted with water, and extract was fractionized for alkaloid content. Both crude extract and alkaloid fraction inhibited formation of thiobarbituric acid reactive substances in rats liver.⁵²⁰ Fruits were extracted with 95 % aqueous ethanol and extract was active against CCl₄-induce damage of liver rats.⁵²⁶⁻⁵²⁹ Leaves aqueous extract had protective effect in rats liver against oxidative damages of thymus DNA.⁵³⁰ Aqueous extract (plant part not indicated) had ameliorative effect on high-fat/ethanol damages of rat liver. Extract had also antidiabetic effect.⁵³¹

Insecticidal,
molluscicidal,
antiparasitic

Seeds were extracted with methanol and extract had nematocidal activity.¹⁹⁸ Plants were cultivated with growth promoters to produce high concentrations of glycoalkaloids, which were extracted with 95 % aqueous methanol. These extracts were highly active against bilharziasis.⁵³² Aerial parts were extracted successively with dichloromethane, methanol and 80 % aqueous methanol. Extracts were active against *Galba truncatula*

(snail).⁵³³ Leaves were extracted with methanol, and extract had antileishmanial activity in mice. Extract antibacterial activity was also investigated.⁵³⁴ Eight extracts were prepared from leaves using water and organic solvents. All extracts were tested for molluscicidal (*Lymnaea acuminata*) and insecticidal (*Culex vishnui*) activities. General chemical composition is also presented.⁵³⁵ Several fruits extracts were found active mosquitocidal (*Culex quinquefasciatus*).⁵³⁶ Alkaloid fraction extracted from leaves was active against citrus whitefly (*Dialeurodes citri*).⁵³⁷ Leaves were extracted with 1:1 methanol:chloroform (v:v). Extract had strong activity against two mosquito species (*Culex vishnui* and *Anopheles subpictus*).⁵³⁸ Green leaves were extracted with several solvents, and extracts were found active against Colorado potato beetle, *Leptinotarsa decemlineata*, where methanol extract was most active. Among active compounds, *cis*-hex-3-enyl acetate, was highly active.⁵⁴⁵

Metal accumulation, corrosion inhibition, nanoparticles

Leaves aqueous extract was used to prepare silver nanoparticles (AgNP's) by reduction of silver nitrate solution.⁴⁶⁶ Gold nanoparticles AuNP's were prepared using aqueous extract (reductant) of leaves and AuCl.⁴⁷¹ Leaves methanolic extract was prepared and used for steel corrosion inhibition and preparation of gold nanoparticles (AuNP's) by reduction of chloroauric acid (HauCl₄).⁵³⁹ Growth of the plants and its production of different natural products, especially antioxidant enzymes, was tested under the effect of cadmium accumulation. The metal ions were accumulated in highest concentration in leaves, and over all tested properties and activities of the plant were not affected.⁵⁴⁰ Plant was found as a good phytoremediator for cadmium removal from contaminated soils, without or with biochar.^{541,542}

Nutrition

Comprehensive analysis of seed with special focus of nutritional potential. Presented parameters are: protein content, ash and mineral contents, dry matter, fatty acids composition, iodine value, saponification value, peroxide value, energy value, viscosity and triglyceride composition.⁵⁴³ Ripe fruits were extracted and fractionized with various solvents, including obtaining alkaloid fraction. All products were

Chemical composition and related activities

analyzed for general chemical composition and some medicinal activities (such as antioxidant) to determine the toxicity/safety of these fruits. The aim of this study was to consider the possible use of these fruits as food source. The results indicate that the fruits are not toxic.⁵⁴⁴ Changes in the concentration of glycoalkaloid solanone according to growth steps.⁴⁵⁹ Solanine A (Figure 26), a new natural product that was isolated from fruits along with other three new compounds: 7 α -OH khasianine, 7 α -OH solamargine and 7 α -OH solasonine.⁴⁸⁷ A new nor-spirosolane (Figure 26 unnamed) type steroidal alkaloid was isolated from unripe fruits, with two novel spirosolane type steroidal alkaloid glycosides.⁴⁸⁸ In the following reports, chemical compositions and some activities were reported but new compounds were not isolated. In some cases, known natural products were isolated for the first time from this species or the *Solanum* genus. Some reports are very detailed.⁵⁴⁶⁻⁵⁶¹ Two new quercetin-3-glycosides were isolated from fruits methanolic extract.⁵⁶³ Two new saponins, solanigraside Q and solanigraside R (Figure 26) were isolated from whole plant methanolic extract.⁵⁶⁴ Whole plant was extracted with several solvents and extracts were fractionized. Extracts had anticholinesterase and anti-tyrosinase activities. Two new phenolic glycosides were isolated, one of them is shown in Figure 26.⁵⁶⁵

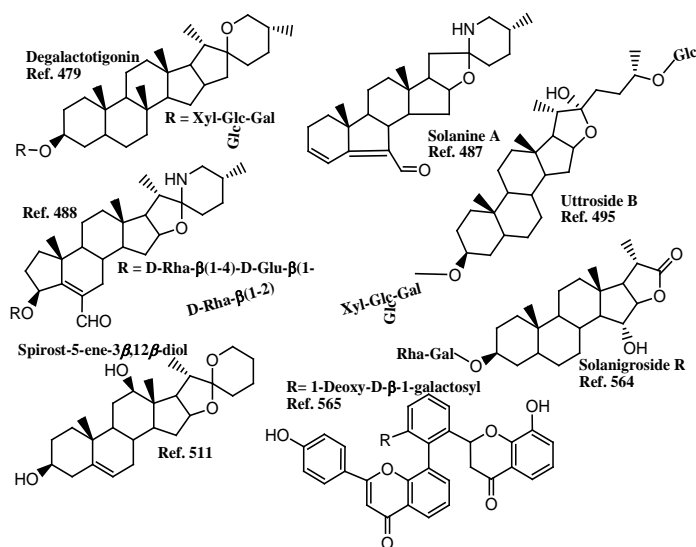


Figure 26. Structures of selected natural products isolated from *Solanum nigrum*.

Solanum villosum

Despite the very wide habitat of this plant, where it grows in the coldest and most rainiest areas (North) of the reviewed region, to the driest and most arid desert areas in the South. It is very easy to confuse it with *S. nigrum*. Out of fruit ripening season, the major visible difference is that stems (and to less extent, leaves) of *S. nigrum* are smooth while these of *S. villosum* are hairy. After fruits ripening, it is very easy to distinguish both species: fruits of *S. villosum* are very red while fruits of *S. nigrum* are black. *S. villosum* was limitedly studied, and a summary of selected published studies about it are presented in Table 18.

Table 18. Medicinal, biological and other activities of *Solanum villosum*.

Activity/Property	Major findings/Reference
Antibacterial	Leaves aqueous extract was found active against four bacteria species. ⁵⁷² Oils from leaves and fruits were extracted using petroleum ether. Both oils had activity against four bacteria species. ⁵⁷³
Anticancer	Alkaloid fraction was extracted with <i>n</i> -butanol, and it was active against LIM-1863 human colon carcinoma cell line. ⁵⁶² Leaves ethanolic extract was found active against diethylnitrosamine-induced hepatocellular carcinoma in experimental rats. ⁵⁶⁶ Silver nanoparticles (AgNP's) were prepared using leave aqueous/ethanolic extract to reduce AgNO ₃ solution. Extracts and AgNP's had anticancer activity (diethylnitrosamine-induced). ^{567,568,578}
Antidiabetic	Leaves aqueous extract was active in diabetic (STZ-induced) rats. ⁵⁶⁹
Antioxidant	Leaves were extracted with ethanol, and antioxidant capacity (DPPH) of extract was determined. General chemical composition is reported. ⁵⁷⁰ Ethanolic extract of leaves enhanced the production of antioxidant enzymes in goat liver. ⁵⁷¹
Hepatoprotective	Hepatotoxicity in rat was induced by carbon tetrachloride, and was treated 95 % aqueous whole plant extract, which had also antifibrotic activity. Comprehensive chemical composition is presented with detailed GC-MS data. ⁵⁷⁴
Insecticidal	Green leaves were extracted with several solvents, and extracts were found active against Colorado potato beetle, <i>Leptinotarsa decemlineata</i> , where methanol extract was most active. Among active compounds, <i>cis</i> -hex-3-enyl acetate, was highly active. ⁵⁴⁵ Leaves aqueous extract was found active against three mosquito species. ⁵⁷² Leaves were extracted with

	six organic solvents and each extract was tested against larvae of <i>Culex quinquefasciatus</i> . Methanol:chloroform (1:1) extract had the strongest activity. ⁵⁷⁵ Fruits were extracted with six organic solvents and each extract was tested against larvae of <i>Stegomyia aegypti</i> . Methanol:chloroform (1:1) extract had the strongest activity. ⁵⁷⁶ Leaves were extracted with methanol:chloroform (1:1) and extract was active against larvae of <i>Anopheles subpictus</i> . ⁵⁷⁷
Nanoparticles synthesis	Silver nanoparticles (AgNP's) were prepared using leave aqueous/ethanolic extract to reduce AgNO ₃ solution. ^{567,568,578}
Nutrition	Ripe fruits were extracted and fractionized with various solvents, including obtaining alkaloid fraction. All products were analyzed for general chemical composition and some medicinal activities (such as antioxidant) to determine the toxicity/safety of these fruits. The aim of this study was to consider the possible use of these fruits as food source. The results indicate that the fruits are not toxic. ⁵⁴⁴ Oils from leaves and fruits were extracted using petroleum ether, and their fatty acid compositions were determined, in purpose of testing their nutritional potential. ⁵⁷³
Toxicity	Leaves ethanolic extract was orally fed to rats and found non-toxic. ⁵⁷⁹
Chemical composition	Leaves were extracted with ethanol and extract was analyzed by GC-MS. A detailed composition is presented but new compounds are not reported. ⁵⁸⁰

Withania somnifera

There is only a single species of the *Withania* genus in the reviewed region. Globally, this genus includes 12 species, and another one, *W. obtusifolia*, grows on Eastern side of the Jordan valley. *W. somnifera* was extensively studied, and published researches about it are summarized in Table 19.

Table 19. Medicinal, biological and other activities of *Withania somnifera*.

Activity/Property	Major findings/Reference
Allelopathy	Aqueous extract and alkaloid fraction were prepared from the aerial parts. Both materials were tested and found active allelopathic against <i>Cichorium intybus</i> seeds germination. Alkaloid fraction was analyzed and detailed composition and structures are reported (all known compounds). ²³⁵

Antibacterial, antifunga, antiviral and related activities	<p>Leaves were extracted with ethanol, and extract was found active against bacteria isolated from chicken.¹⁴⁵ Leaves were extracted with 95 % aqueous ethanol and extract was found active against pathogenic bacteria.⁴⁶³ Whole plant was extracted with three solvents and tested against four bacteria species. Activity order of extracts was ethyl-acetate > ethanol > dichloromethane.⁵⁸¹ Fresh leaves were extracted with 95 % aqueous ethanol and extract was active against <i>E. coli</i>.⁵⁸² Whole plant was extracted with water and extract was used to prepare silver nanoparticles (AgNP's), which had antibacterial activity.⁵⁸³ Roots were extracted with methanol and extract was used to prepare silver nanoparticles (AgNP's), which had antibacterial activity.⁵⁸⁴ Plant parts were extracted and fractionized separately with several solvents. Each fraction was extracted for flavonoids, and these extracts were active against five bacteria species.⁵⁸⁵ Indian traditional antiviral formulation (Amukkara Chooram) based of roots an leaves powder, was active gainst CHIKV virus in mice.⁵⁹³</p>	<p>results in treating seizures induced in rats by electrical and chemical (pentylenetetrazol, PTZ) shocks.⁵⁹² Ethanolic root extract was active against PTZ-induced seizures in mice. A mechanism of action is proposed.⁵⁹⁴ Leaves ethanolic extract had lowering effect of collagen glycation and cross-linking in rats.⁵⁹⁵ Diabetes was induced in rats by STZ, and they were treated with formalin to induce pain in paws. When fed with roots, pain sensation in test group was lower than in control.⁵⁹⁶ Diabetes was induced in rats by STZ, and they were fed with aqueous roots extract. Compared with control groups, test group had lower blood glucose, lower hyperlipidemia and less oxidative stress.⁵⁹⁷ Root powder was supplemented to patients and it had significant hypoglycemic and hypocholesterolemic activities.⁶⁴⁷</p>
Anticancer	<p>Roots were extracted with water and extract was administered to patients with breast cancer with chemotherapy. Control group was treated only with chemotherapy. Test group showed positive results.⁵⁸⁶ Rats/mice with cancer were treated with 70-75 % aqueous ethanol root extract. Positive results were recorded in test group compared with control.^{587,588} Leaves aqueous extract was used to treat HepG2 hepatocarcinoma cells. Molecular modeling and a mechanism of action are presented.⁵⁸⁹ Roots ethanolic extract was prepared as Viwithan, and it was active against B16F1 murine melanoma cells. Analysis showed that it contained mainly: withaferin A, withanoloids A, B.⁵⁹⁰ Roots methanolic extract analysis yielded six new withanolides named withasilolides A-F (structures very close to compounds in Figures 5, 6, 10, 15, 20, 22). The compounds had cytotoxic effect on four cancer cell lines.⁵⁹¹ Roots were treated with dilute ammonia, methanol and then extracted with water. Extract <i>in vitro</i> enhanced the activity of chemotherapy agent, cisplatin, in HT-29 colon cancer cells.⁶⁴⁶</p>	<p>Antidiabetic, anti-obesity and related activities</p>
Anticonvulsant	<p>Stems and roots were extracted with ethanol and extracts showed positive</p>	<p>Antioxidant, anti-inflammatory and related activities</p> <p>Leaves aqueous extract was used to treat HepG2 hepatocarcinoma cells. Results indicated more production of natural antioxidant enzymes (glutathione S-transferase and glutathione reductase) in treated cells compared with control.⁵⁸⁹ Arthritic (collagen-induced) rats were treated with powder or roots aqueous extract of the plant compared with methotrexate treatment, and proved effective.^{598,599} Different parts of the plant were extracted separately with 80 % aqueous methanol, and antioxidant capacity of extracts was determined (DPPH). Mature roots had the highest activity.⁶⁰⁰ Roots aqueous extract was administered to humans with type II diabetes. Results showed improvement in lowering oxidative stress biomarkers (malondialdehyde, nitric oxide and glutathione).⁶⁰¹ Chronic footshock in rats induced stress that resulted an increase in superoxide dismutase and lipid peroxidation activity, with concomitant decrease in catalase and glutathione peroxidase activities in the brain. Treating animals with glycowithanolides extracted from the plant, altered the oxidative stress.⁶⁰² Rats were dehydrated to result kidney oxidative stress, then they were treated with roots aqueous extract that had significant antioxidant activity.⁶⁰³ Chronic footshock in rats induced stress mainly due to oxidative processes in the brain of rats, that were altered after treating animals with glycowithanolides extracted from the plant.⁶⁰² Withanamides A and C that</p> <p>Brain related activities, aeging, addiction, stress, anxiety, memory, depression, neuroprotection,</p>

<p>Alzheimer, Parkinson, sleep</p>	<p>were isolated from the fruits, protected PC-12 cells, rat neuronal cells, from β-amyloid induced cell death, supposedly by prevention of fibril formation.⁶⁰⁴ Roots were extracted with methanol:chloroform (1:1) and extract was orally (in ethanol) administered to mice. The result was lowering in low density lipoprotein in the liver and β-amyloid in the brain.⁶⁰⁵ Anxiety was induced in rats by ethanol, and ethanolic root extract (contained mainly withanolides) had positive effect on these animals.⁶⁰⁶ Ethanolic root extract had anti-anxiety and antidepressant activities, compared with control groups which were not treated or were treated with standard drugs (benzodiazepine lorazepam and imipramine).⁶⁰⁷ Ethanolic root extract had anti-anxiety and antistress effects in healthy (physical and mental) humans.⁶⁰⁸ Roots aqueous extract mixed with Ghee butter, was administered to mice that went through three depression methods: forced swimming, tail suspension and anti-resperine test. In all cases, the extract had positive effect on animals.⁶⁰⁹ Roots ethanolic extract nicotine-induced addiction in mice.⁶¹⁰ Healthy humans were treated with roots extract (70 % aqueous ethanol) and showed antidepressant results.⁶¹¹ Patients with schizophrenia were treated with roots aqueous extract and positive anti-anxiety and antidepressant results were recorded.⁶¹² Commercial root extract (unknown solvent) was provided to patients with insomnia and anxiety, resulting in improvement in both parameters.⁶¹³ Roots were extracted with 50 % aqueous methanol, and extract was administered to rats that were exposed to various stress inductors. Improvement was indicated in all tests.⁶¹⁴ Commercial, standardized root extract (Withaferin A, 2.38 %) was administered to Common fruit fly (<i>Drosophila melanogaster</i>) to test effect on brain disorders induced by rotenone. The result was lowering of the following parameters: locomotor deficits, oxidative impairments and neurotoxicity.⁶¹⁵ Aqueous root extract was administered to rats, and resulted in amelioration of memory impairment and neurodegeneration in hippocampus through NO mediated modulation of corticosterone levels.⁶¹⁶ Whole plant (commercial powder) was extracted with water for proteins.</p>	<p>Extract, along with scopolamine, were fed orally to rats resulting in enhancement of learning and memory.⁶¹⁷ Commercial roots aqueous extract (containing 5 % withanolides) was administered to human patients, resulting in immediate and general memory, as well as improving executive function, attention, and information processing speed.⁶¹⁸ Commercial ethanolic root extract was administered to mice with L-dopa, which resulted in inhibition of haloperidol-induced catalepsy in mice.⁶¹⁹ Root powder was orally fed to mice along with seed powder of <i>Mucuna pruriens</i>. This, attenuated the neurotoxicity due to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride) in mice.⁶²⁰ Ethanolic root extracts of the plant and seed of <i>Mucuna pruriens</i> were orally fed to mice. This resulted (several tests) in attenuation of paraquat (<i>N,N'</i>-dimethyl-4,4'-bipyridinium dichloride) induced parkinsonian.⁶²¹ Commercial roots ethanolic extract attenuated 6-hydroxydopamine-induced parkinsonism in rats.⁶²² Fresh roots were extracted with methanol and extract was fractionized with several organic solvents, yielding the isolation of 18 known compounds. These were tested for axon or dendrite growth. It was found that withanolide A enhanced axons while withanosides IV and VI enhanced dendrites.⁶²³ Roots ethanolic extract was prepared and administered to mice that were treated with paraquat and maneb [(C₄H₆MnN₂S₄)_n] to induce parkinson. Results showed protection against nigrostriatal dopaminergic neurodegeneration and marked improvement in the behavioral, anatomical and the biochemical deformities.⁶²⁴ Commercial extract (plant part and solvent not indicated) was active <i>in vitro</i> against Aβ peptide- and acrolein-induced toxicity and acetylcholinesterase inhibitor.⁶²⁵ Root ethanolic extract had protective antioxidant and anti-inflammatory effects against aluminum neurotoxicity, and could prevent the decline in cholinergic activity by maintaining normal acetylcholinesterase activity.⁶²⁶ Leaves aqueous extract was found protective against LPS-induced oxidative stress and inflammation that produce neurodegeneration.⁶²⁷ Commercial roots extract (solvent not indicated) had neuroprotective activity against</p>
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<p>Cardioprotection, blood system, sport</p> <p>MPTP toxicity in mice.⁶²⁸ Ethanolic root extract had neuroprotective activity by reducing oxidative stress (iNOS) and significantly improved the maneb-and-paraquat mediated induction of a pro-apoptotic state.⁶²⁹ Commercial standardized extract (plant part and solvent not indicated) was administered to patients with exacerbation of schizophrenia, which resulted in amelioration of their mental health.⁶³⁰ Whole plant powder was orally fed to rats resulting in attenuation of neuropathic pain arises due to chronic constriction injury.⁶³¹ Roots ethanolic extract was given to patients with obsessive-compulsive disorder, which reduced their food addiction.⁶³² Leaves aqueous extract had neuroprotective effect against stress in sleep-deprived rats.⁶³³ Standardized root extract (70 % aqueous ethanol) had positive effects on patients with nonrestorative sleep disorder.⁶³⁴ Roots were extracted with 50 % aqueous ethanol was administered orally to rats, and had significant antistress (that was induced by several methods) adaptogenic activity.⁶³⁵ Roots ethanolic extract was supplemented to rats (100 mgkg⁻¹ of body weight). As a result, behavioral deficits induced by Bisphenol A were alleviated, and treatment reinstated the number of NMDA receptors in hippocampus region in the brain.⁶⁶⁰ Methanolic roots extract was prepared and analyzed by HPLC. It was supplemented to rats resulting prevention of morphine withdrawal-induced decrease in spine density in nucleus accumbens shell of rats.⁶⁶⁶ Commercial roots hydroalcoholic (ratio is not indicated) extract was prepared and was found cardioprotective against isoprenaline-induced myocardial necrosis in rats. Control animals were fed with Vitamin E.⁶³⁶⁻⁶³⁹ Commercial leaves extract (solvent not indicated) was orally fed to rats that were toxicated with doxorubicin. Extract had cardioprotective activity measured by several tests.⁶⁴⁰ Water root extract was supplied to athletes and they were tested for their endurance, by measuring peak oxygen consumption. Positive results were recorded.⁶⁴¹ Root powder was supplied to stress-oriented hypertensive subjects, and improvement was recorded when powder was supplied with milk.⁶⁴² Commercial root extract was supplied</p>	<p>to healthy people who practice sports on regular basis. Several parameters were measured to test the effect of the supplement, and it was found positive in all tested parameters, especially muscle mass, strength and distribution.^{643,644} Roots aqueous extract was prepared and supplemented to mice. Tests of endurance and stamina were conducted compared to control. Test group showed clear improvement.⁶⁴⁵ 6-<i>n</i>-Propyl-2-thio-uracil (PTU) induced hypothyroid in rats, and they were treated with leaves EtOH extract along with eltroxin for 60 days. Results showed recovery of thyroid hormone secretion as compared to control.⁶⁴⁸ Whole plant was extracted with methanol and extract was fractionized with several solvents, yielding two new compounds (withanolides, see Figure 10). These compounds and other known had cholinesterase inhibition activity.⁶⁴⁹ Commercial leaves and roots was supplied to overweight male participants. No significant difference was recorded between test group and control in cortisol, estradiol, fatigue, vigor, or sexual well-being.⁶⁵⁰ Root powder was supplied to infertile men (in stress or normal, 5 g day⁻¹) orally for 3 months with milk. Positive indication of fertility increase (pregnancy of female mates) and stress reduction were recorded.^{651,652} High concentration methanolic roots extract was supplied to healthy women, who reported increase of sexual function.⁶⁵³ Roots were extracted with 70 % aq. EtOH and extract ameliorated diet-induced obesity by enhancing energy expenditure via improving mitochondrial activity in skeletal muscle and adipose tissue.⁶⁵⁴ Root powder was supplemented to patients and it had significant diuretic activity.⁶⁴⁷ Whole plant aqueous extract was prepared and combined with whole plant extract of <i>Asparagus racemosus</i>. The combination was used to treat <i>Leishmania donovani</i>-infected mice. The results were positive and there was enhancement of the immune system of the animals.⁶⁵⁵ Whole plant (or roots) was extracted with water (or MeOH) and extract reduced AgNO₃ solution to prepare AgNP's.^{583,584} Leaves aqueous extract had glioprotective effect <i>in vitro</i> (cells) and <i>in vivo</i> (rats) against Lead (lead</p>
<p>Enzyme inhibition activity</p>	<p>6-<i>n</i>-Propyl-2-thio-uracil (PTU) induced hypothyroid in rats, and they were treated with leaves EtOH extract along with eltroxin for 60 days. Results showed recovery of thyroid hormone secretion as compared to control.⁶⁴⁸ Whole plant was extracted with methanol and extract was fractionized with several solvents, yielding two new compounds (withanolides, see Figure 10). These compounds and other known had cholinesterase inhibition activity.⁶⁴⁹</p>
<p>Fertility, hormones, sexual functioning</p>	<p>Commercial leaves and roots was supplied to overweight male participants. No significant difference was recorded between test group and control in cortisol, estradiol, fatigue, vigor, or sexual well-being.⁶⁵⁰ Root powder was supplied to infertile men (in stress or normal, 5 g day⁻¹) orally for 3 months with milk. Positive indication of fertility increase (pregnancy of female mates) and stress reduction were recorded.^{651,652} High concentration methanolic roots extract was supplied to healthy women, who reported increase of sexual function.⁶⁵³ Roots were extracted with 70 % aq. EtOH and extract ameliorated diet-induced obesity by enhancing energy expenditure via improving mitochondrial activity in skeletal muscle and adipose tissue.⁶⁵⁴</p>
<p>Nephroprotective</p>	<p>Root powder was supplemented to patients and it had significant diuretic activity.⁶⁴⁷</p>
<p>Antiparasitic</p>	<p>Whole plant aqueous extract was prepared and combined with whole plant extract of <i>Asparagus racemosus</i>. The combination was used to treat <i>Leishmania donovani</i>-infected mice. The results were positive and there was enhancement of the immune system of the animals.⁶⁵⁵</p>
<p>Nanoparticles, metal toxicity</p>	<p>Whole plant (or roots) was extracted with water (or MeOH) and extract reduced AgNO₃ solution to prepare AgNP's.^{583,584} Leaves aqueous extract had glioprotective effect <i>in vitro</i> (cells) and <i>in vivo</i> (rats) against Lead (lead</p>

Toxicity	<p>nitrate) toxicity.⁶⁵⁶ Roots ethanolic extract was found toxic to rats when supplemented in very high dosage (1100 mg kg⁻¹ of body weight) and safe in lower doses (100 mg kg⁻¹) in rats and mice.⁶⁵⁷ Methanolic roots extract standardized for withaferin A, was found safe in rats up to 2000 mg kg⁻¹ of body weight, which was the highest tested dose.⁶⁵⁸ "Purified extract", solvent and plant part were not indicated, contained 35 % glycowithanolides and less than 1 % alkaloids, was commercially prepared. It was found safe to rats up to 2000 mg kg⁻¹ of body weight, which is the highest tested dose.⁶⁵⁹</p>
Chemical composition and related activities	<p>Roots were extracted with 50 % aq. MeOH, and two new compounds were isolated and characterized, acylsterylglucosides, sitoindoside VII and sitoindoside VIII (see Figure 27). Known withaferin A was also isolated.⁶¹⁴ HPLC analysis was conducted for 10 commercial products that contain ingredients of the plant. Most of the contained withanolides.⁶⁶¹ General chemical composition of roots of plants that were harvested in five different locations, was determined.⁶⁶² Three known compounds (withaferin A, 12-deoxywithastramonolide, withanolide A) were determined in different parts of the plant by LC-ESI-MS-MS (MRM) method.⁶⁶³ General chemical composition of roots was determined.⁶⁶⁴ First isolation and characterization of isopelletierine (Figure 27).⁶⁶⁵ Seven new withanolide glycosides were isolated from the methnolic root extract. They were characterized along with identification of other known compounds. The withanolides aglycons are not new. Some of these compounds had inhibitory activity against tachyphylaxis to clonidine (high blood pressure drug) in isolated guinea-pig ileum.⁶⁶⁷ Seven withanolides (commercially purchased) were tested for bioavailability to cancer cells. Detailed structures and chromatograms are provided.⁶⁶⁸ Quantitative HPLC analysis of withanolides was developed, including the determination of withaferin A and withanolide D.⁶⁶⁹ 28 Commercial products were analyzed, mainly by HPLC to determine their compositions and genuineness.⁶⁷⁰</p>

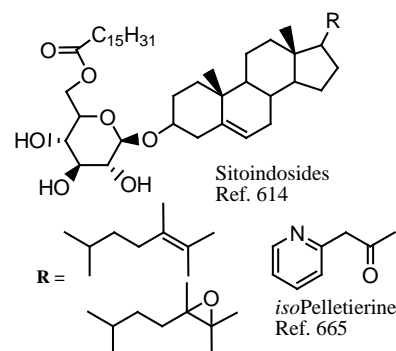


Figure 27. Structures of selected natural products isolated from *Withania somnifera*.

CULTIVATION OF SOLANACEAE PLANTS AND PRODUCTION OF ACTIVE INGREDIENTS

One of the remarkable traits that can be observed immediately when searching literature about wild *Solanaceae* plants is the numerous number of published articles about the cultivation of these plants. This is a huge mass of articles and obviously, the main reason in the interest production of very important, active or potentially active natural product, especially alkaloids and withanolides and their derivatives and analogues. Laboratory syntheses of these compounds is possible (see next section, Synthesis, Biosynthesis and Selected Chemistry of *Solanaceae* Natural Products). But in the vast majority of cases, production of these compounds by cultivation of their plant source, is way easier. So, we reported very few of these cultivation/production researches in the previous section and we are reporting here some more articles. Among the vast number of publications, these represent the notion of the entire literature in this subject.

Among the wild plants of the *Solanaceae* family plants, *Solanum nigrum* is the most cultivated and most important source of active natural products. A. de Sousa and her colleagues grew doubly sterilized (70 % aqueous ethanol, 0.02 % aq. NaClO) seeds that were harvested from wild plants.⁶⁷¹ They treated young plants fungicide chemical metalaxy (C₁₅H₂₁NO₄), which inhibited growth by reduction of photosynthesis and induced photorespiration. As a result, plants produced higher amounts of defense antioxidants and less sugars.

Tropane alkaloids, steroidal alkaloids and their glycons, are among the most active and interesting natural products in the plants of the *Solanaceae* family. They are the major defence compounds. Y. Sun *et al.* cultivated *S. nigrum* in a greenhouse with leaves infection with *Fusarium oxysporum* infectious fungus. As a result, plants produced more of the enzyme squalene synthase, which has a key role in the biosynthesis of defence steroidal alycoalkaloids (solasodine and γ -solamargine, detected by HPLC-DAD-MS).⁶⁷²

Cultivation of *S. nigrum* under heavy metals stress was published by many research groups. R. Li *et al.* incorporated cultivation of *S. nigrum* with two domesticated, major food plants, tomato (*S. lycopersicum*) and eggplant (*S.*

melongena). The three plant species were planted together and stressed with cadmium contamination (CdCl_2).⁶⁷³ Researchers measured potassium content, and they found that this incorporated cultivation, increases the content in tomato and eggplant, aerial parts and roots, respectively. This means that the domesticated and the wild plant are more resistant to heavy metal stress. Another study was published by J. Xu *et al.* where they cultivated the plant under the stress of zinc contamination (ZnCl_2). While it was known that such stress results in programmed cell death (PCD), it was not clear what is the role of nitric oxide (NO) in this process. Researchers found out that zinc stress elevate the concentration of NO that causes, and if treated with either 2-phenyl-4,4,5,5-tetramethyl-imidazoline-1-oxyl-3-oxide (NO scavenger) or N^G -nitro-L-arginine-methyl ester (NO synthase inhibitor); PCD process decreases.⁶⁷⁴ Incorporated cultivation was also used by W. Huo *et al.*, where they cultivated maize (*Zea mays*) with *S. nigrum*, under cadmium (CdCl_2) stress. They studied the effect of N-fertilizers (ammonium sulfate and calcium nitrate) on the hyperaccumulation of the contaminating metal in the plants. Their finding indicated clearly that this incorporated cultivation accumulated the metal in *S. nigrum*, resulting in safety to grow maize in Cd-contaminated soils.⁶⁷⁵

As in agricultural crops, C. de Matos and his colleagues, reported that cultivation of *Nicandra physalodes*, was enhanced by chemical fertilizers (NPK, ammonium sulfate, monocalciumphosphate, potassium chloride, respectively).⁶⁷⁶ In a closely related study, N. Panayotov and A. Popova investigated the effect of various cultivation conditions on the productivity and the storability of *Physalis peruviana*.⁶⁷⁷ They found that the productivity under cultivation by non pricking seedlings or by direct outdoor sowing was higher. Fruits from plants grown by direct outdoor sowing, were characterized with the highest storability, and with the weaker one were those grown by pricking out. Similarly, the effect of nitrogen supply (Calcium ammonium nitrate, $5\text{Ca}(\text{NO}_3)_2 \cdot \text{NH}_4\text{NO}_3 \cdot 10\text{H}_2\text{O}$) on plant growth and leaf N content of *Solanum villosum*, was studied by P. Masinde and his colleagues of a multinational research group.⁶⁷⁸ Expectedly, with N supply, plant growth was enhanced, leaf area was increased and total nitrogen content on a dry weight basis was significantly higher.

Nicotine is one of the major defence natural products in the plant kingdom. So, a very interesting study was carried out by I. Baldwin and P. Callahan. They supplied two some *Solanaceae* plants, two of them of our concern, *Nicotiana glauca*, a nicotine producer, and *Datura stramonium*, that does not produce nicotine.⁶⁷⁹ They tested the accumulation and tolerance of the plants towards this supply. They discovered that *N. glauca* accumulated nicotine but its photosynthesis process was not decreased, despite the fact that nicotine is known for its photosynthesis suppression capacity. As for *D. stramonium*, nicotine was not accumulated and physiological damages were not observed.

When we presented the literature about *Solanum elaeagnifolium* above (see information and Figure 23), we mentioned the fact that until approximately two decades ago, this plant was not very widespread or even common. But in recent years, it is spreading very rapidly, and now it threatens agricultural fields and farmlands, and it also invading areas outside of its usual habitat. This problem exists also in Australia, and H. Wu and his colleagues,

considered the plant "as one of the worst weeds of crop and pasture systems".⁶⁸⁰ They studied the herbicidal effect of different combinations of chemicals in growth inhibition of the plant, as well as the optimal timing for performing this activity. They concluded that using two combinations was most effective, and application at early flowering followed by a late application in autumn is necessary to effectively control the seedset (seedbank) and the root regrowth (rootbank).

The main objective of most cultivation researches of *Solanaceae* plants, is as mentioned earlier, production of active natural products and/or enhancement of important medicinal activities. A summary of some carefully selected (out of the vast number) publications is presented in **Table 20**, but some of them will be presented in details (as text and figures) since they include additional value of information such as synthesis, biosynthesis or corrections of previous knowledge. It is important to emphasize that the presentation of this very important literature as a table, will not be enough for the interested readers and researchers who wish to apply this information into their practical work. It is highly recommended for these to follow the citations. Another important note that should be made, is that some of these articles mention some *Solanaceae* plants and other families and genera that are not included in this review, and consequently, they will not be mentioned in **Table 20**. So, it is highly recommended to interested researchers to follow the cited literature.

Table 20. Cultivation of *Solanaceae* plants for production of active compounds and/or properties.

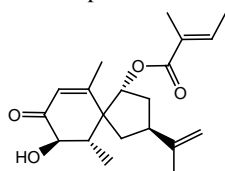
Plant species	Cultivation conditions, results, reference
<i>Datura innoxia</i>	Hairy roots were infected with <i>A. rhizogenes</i> and treated with elicitors salicylic acid and acetyl salicylic acid. Hyoscyamine content increased. ⁶⁸¹ AlCl_3 enhanced the production of hyoscyamine and scopolamine and antioxidant enzyme superoxide dismutase. ⁶⁸² Total alkaloid content increased in young leaves when plants were cultivated under salt stress (with a molar amount of NaCl amount in abstract, 153.8 mol/m^{-3} that should be 153.8 mg). ⁶⁸³ Plants were cultivated with supply of triadimefon (fungicidal, $\text{C}_{14}\text{H}_{16}\text{ClN}_3\text{O}_2$). Total indole alkaloid, antioxidant phenolics and antioxidant enzymes contents, all were significantly increased. ⁶⁸⁴
<i>Datura stramonium</i>	Hairy roots were infected with <i>A. rhizogenes</i> and treated with elicitors salicylic acid and acetyl salicylic acid. Hyoscyamine content increased. ⁶⁸¹ Plants were grown in Mexico, original habitate of them, and in Spain, in which they were introduced, under the same conditions. The plants in Mexico produced about 36 times more atropine and around 21 times more scopolamine, in leaves, than in Spain. In their natural habitate (Mexico), plants have natural enemies (herbivores) that do not exist in

	<p>Spain.⁶⁸⁵ A very comprehensive research that studied the relation between irrigation and production of tropane alkaloids in the plant. The study measured the quantitative (direct proportion), and very broad presentation of the qualitative relation. Researchers present very detailed analysis of tropane content, including changes of isomers ratios as a result of different irrigation conditions. They also present quantitative and qualitative analysis of different plant parts. Moreover, a mechanism of isomers ratio is proposed.⁶⁸⁶ Plants were grown under salt stress (NaCl and CaCl₂ ,1:1 w/w), and supplied with nutrients Ca(NO₃)₂, KCl, KH₂PO₄ and MgSO₄. Concentrations of insoluble and total carbohydrate, insoluble protein. Free amino acids (not)proline and total alkaloid increased significantly, while soluble carbohydrate, soluble and total protein, and proline contents decreased.⁶⁸⁷ The effect of three parameters was tested, on plant growth but mainly on hyoscyamine production: Gamborg's B5 salts (mixture of 14 compounds) supply, nutrition with sucrose and temperature. Results indicated that high concentrations of material supply was needed and T= 25-30 °C, to achieve maximum yield of the alkaloid.⁶⁸⁸</p>	
<i>Hyoscyamus albus</i>	<p>Plants were cultivated under Fe-deficiency condition, and as result, the production of hyoscyamine and scopolamine was reduced. The mechanism of this reduction was studied, and researchers discovered gene expression changes, that led to reduction of key enzyme for tropane alkaloids biosynthesis, such as hyoscyamine 6β-hydroxylase, that involves iron in the conversion of hyoscyamine to scopolamine.⁶⁸⁹ Treatment of hairy roots with CuSO₄ and methyl jasmonate enhanced the production of three known phytoalexins and four new, which were isolated and characterized. One of them is presented in Figure 28.⁶⁹⁰</p>	<p><i>Hyoscyamus reticulatus</i></p> <p>enzymes and pigments, were increased.⁶⁹² The same research group reports the effect of UV-C radiation (253.7 nm) on the growth, total alkaloid and hyscyamine contents. The optimal time period they found is 2 h of exposure.⁶⁹³</p> <p>The effect of ammonium nitrate fertilization on the following variables was studied: plant height, stem diameter, number of branch per plant, number of capsules per plant, capsule length, capsule width, number seed per capsule, seed yield per plant, thousand seed weight and alkaloid content. Fertilizer supplementation was done in various courses, and alkaloid content was increased.⁶⁹⁴ Hairy roots were treated with Zinc oxide nanoparticles (ZnO-NPs). Growth was decreased but antioxidant activity of the enzymes catalase, guaiacol peroxidase and ascorbate peroxidase was significantly higher. Contents of hyoscyamine, scopolamine and biosynthetic <i>h6h</i> gene were increased.⁶⁹⁵ Hairy roots were genetically modified <i>Agrobacterium rhizogenes</i> and supplied with iron oxide nanoparticles (FeO-NPs). Antioxidant enzyme activity and hyoscyamine and scopolamine production were significantly increased.⁶⁹⁶</p> <p><i>Physalis angulata</i></p> <p>Methyl jasmonate was supplemented to hairy roots, resulting increase of the production of physalins D and H. Researchers propose that this supplement increases in the levels of a number of terpenoid backbone biosynthesis and steroid biosynthesis related enzymes.⁶⁹⁷ Cultivation season has major effect on phenolic compounds content, antioxidant capacity and many agricultural qualities of the plant. April is the best cultivation time period.⁶⁹⁸</p>
<i>Hyoscyamus aureus</i>	<p>Twenty seven nutrients were used to cultivate plants for tropane alkaloids. Results were compared with wild plant yields, to reveal higher production of hyscyamine in cultivated plants and higher production of scopolamine in wild plants. Genetic variation were also observed in cultivated plants.⁶⁹¹</p>	<p><i>Physalis peruviana</i></p> <p>Plants were supplied with commercial fertilizer (Torped®, N,P,K and 9 other elements), which increased the number, average mass and total productivity of fruits. It also promoted antioxidant activity (DPPH).⁶⁹⁹</p>
<i>Hyoscyamus muticus</i>	<p>Seeds were collected from wild plants, sterilized and cultured with gibberellic acid, in 25 °C and high concentrations of NaCl. Contents of alkaloids, antioxidant</p>	<p><i>Solanum nigrum</i></p> <p>Leaves slices were grown in nutritive medium (general description). Production of glycoalkaloids (solasodine and solanidine) was increased by 2-5 folds. They were also tested for biological activities and found active: antiviral, cytotoxic anti-inflammatory and antiparasitic.⁷⁰⁰ Contents of proline and solasodine were increased in plants under salt (NaCl, 150 mM).^{701,g} Production of solasodine was increased by 5 folds under NaCl stress, 150 mM.⁷⁰²</p> <p><i>Solanum villosum</i></p> <p>Plants were cultivated under 100 mM</p>

Withania somnifera

NaCl stress. Leaf caffeic acid, lutein, and beta-carotene contents were considerably increased, along with the up regulation of some related enzymes and genes. The leaf contents of β -solamargine and α -solasonine also increased significantly.⁷⁰³ Accumulation of withaferin A and withanone was increased in leaves when plants were supplemented with saccharides or their combinations. The highest increase recorded when 4 % sucrose and glucose (2:1) was supplied. No control was mentioned.⁷⁰⁴ Enhanced production of withanolide A was recorded when plants were supplied with 4 % mixture of sucrose and glucose (3:4) and with optimal pH of 5.8.⁷⁰⁵

(g) The increase of solasodine in *S. nigrum* that was reported by J. Sutkovic *et al.*, is not clear. They present an unclear bar graph (page 45 in reference 701). They also direct readers to "table 1" for these results (page 46), but "table one" does not exist in the publication, supporting materials are not provided.



Hyoscyamus albus
Ref. 690

Figure 28. Structures of a new compound isolated from cultivated *Hyoscyamus albus*.

T. Hashimoto and Y. Yamada, performed a thorough research to reveal the mechanism of the biosynthetic path from L-hyoscyamine to scopolamine.⁷⁰⁶ They chose to study cultured root of *Hyoscyamus niger* which is not one of the plants included in this review, but they indicate that this mechanism is common for many *Solanaceae* plants of the genera *Atropa*, *Datura*, *Duboisia*, *Hyoscyamus*, and *Nicotiana*.

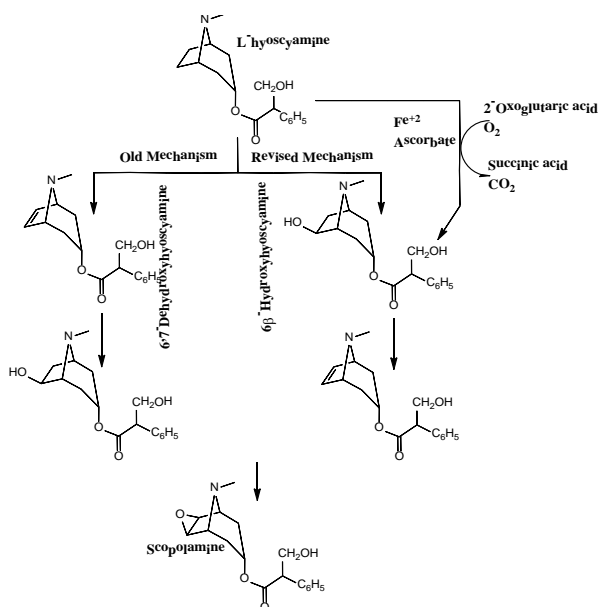


Figure 29. Mechanism of biosynthesis of scopolamine from L-hyoscyamine (Ref. 706).

They argue with older proposed mechanisms which state that L-hyoscyamine is dehydrogenated to 6,7-dehydrohyoscyamine, which is converted to scopolamine (see Figure 29). But by chemoenzymatic study, they prove that between L-hyoscyamine and 6,7-dehydrohyoscyamine, there is an intermediate: 6 β -hydroxyhyoscyamine.

Swiss group of A. Lanoue and his colleagues studied the rearrangement of L-littorine to L-hyoscyamine in the biosynthesis of scopolamine.⁷⁰⁷ For this purpose, they cultured hairy roots of *Datura innoxia* that were genetically modified by *Agrobacterium rhizogenes*. The supplemented the roots with labeled (*RS*)-phenyl[1,3-¹³C₂]lactic acid. This molecule reacted (in roots) with tropine yielding L-littorine, which rearranged to L-hyoscyamine (Figure 30). The carbon-carbon coupling constant that was calculated from ¹³C-NMR spectra of the three compounds was almost the same, 55 Hz.

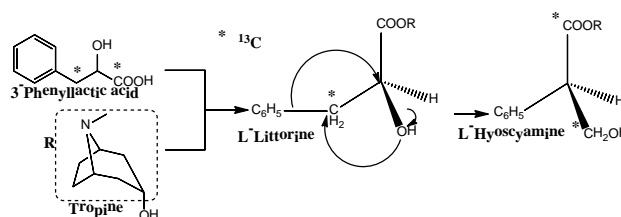


Figure 30. Part of the biosynthesis of Scopolamine (Ref. 707).

The last research that we will cite in this section was published by R.J. Robins and his colleagues.⁷⁰⁸ They studied the biosynthetic path of tropane alkaloids in cultured roots of *Datura stramonium*. For this objective, they have labeled starting materials with ¹⁴C and ¹³C, in order to decide which of the proposed biosynthesis paths in literature is/are true. Their work provided an evidence that hygrine is not a direct precursor of tropane alkaloids, while cyclization occurs to give 2-carboxytropinone, that forms tropinone decarboxylation. This is shown path B in a scheme that they present in their publication, which we present here as Figure 31.

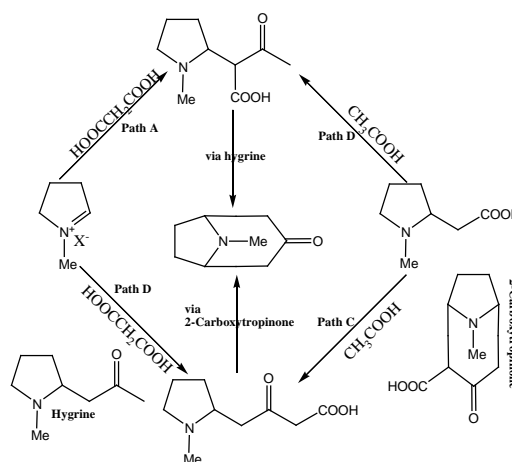


Figure 31. Proposed biosynthesis paths of tropinone (Ref. 708).

Researchers used a special method named proton-noise decoupled ^{13}C -NMR, where coupling and splitting of peaks of ^{13}C atoms is clear, but peaks heights are not proportional to the number of atoms that produced this peak. They present ^{13}C -NMR spectra of hyoscyamine that was produced in the roots of *D. stramonium*, and derive their conclusions from this outstanding work.

SELECTED PUBLICATIONS OF SYNTHESIS AND CHEMISTRY OF SOLANACEAE NATURAL PRODUCTS

Active natural products found in plants of *Solanaceae* family have drawn notable attention for their medicinal and other properties. Attempts of their large scale production were and are done continuously. In the previous section, we presented a brief summary of carefully selected articles of the biogeneses of these compounds in plants (or plant parts) of this family.

Naturally, there are many attempts to prepare these compounds through pure synthetic work. Many of these synthetic works focused on few compounds such as atropine, scopolamine and withanolide A. The laboratory syntheses of some of these compounds, such as hyoscyamine, were published.

Many synthetic works have limited value since the final product of the synthesis is racemic modification, while in most plants, the synthesis target is pure enantiomer, in the vast majority of cases. So, in this sense, the work of J-H. Lee *et al.* has additional importance because they prepared 97 % enantiopure hygrine.⁷⁰⁹ They managed to achieve this by using asymmetric phase-transfer catalytic alkylation, as shown in figure 32.

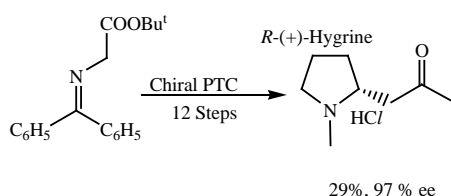


Figure 32. Synthesis of hygrine by J-H. Lee *et al.* (ref. 709).

The earliest synthesis of atropine was published by A. Landenburg in 1879.⁷¹⁰ Since then, this synthesis was published in several articles. One of the latest describe semi-industrial, continuous flow synthesis and purification (Figure 33).⁷¹¹

Researchers (ref. 711) report that the best reaction conditions were: DMA, buffer (pH=10) in a ratio of 5:1, isolated yield of atropine was 79 % and A:B ratio was 16:1.

An outstanding synthesis of scopolamine (hyoscyine) was published by P-A. Nocquet and T. Opatz.⁷¹² But since it included many starting materials preparation reactions, and since the synthesis itself is of a very multiple step type, it will be very partial presentation if we introduce it here with one scheme figure. In our humble opinion, interested readers should use the original publication (ref. 712).

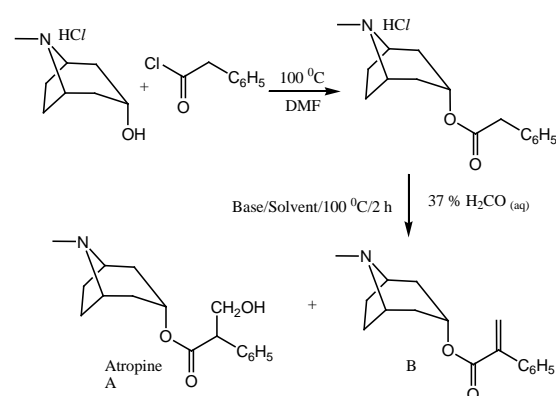


Figure 33. Continuous flow synthesis of atropine (ref. 711).

Withanolides and structurally related natural products are among the most medicinally active compounds and they are major ingredients of *Withania somnifera*. Withanolide A, was isolated among the first compounds of this unique compound family. It is also one of the most studied. It had significant activity against several bacteria species,⁷¹³ and has antioxidant activity (DPPH).⁷¹⁴ But according to published literature about withanolide A, it is clear that neuroprotection is its most important activity. It prevents neurodegeneration by modulating hippocampal glutathione biosynthesis during hypoxia,⁷¹⁵ attenuation of glutamate-induced excitotoxicity in neuron-like cells,⁷¹⁶ and by induction of neurite outgrowth.⁷¹⁷

Several syntheses of withanolide A have been reported so far. One of the best reports was published by C. K. Jana *et al.*⁷¹⁸ In addition to synthesis, some biological activities of the compound were tested, especially neuroprotection. But the work that we chose to present was published by R. Liffert and his colleagues.⁷¹⁹ It is a very comprehensive work of synthesis of withanolide A, preparation of 28 of its derivatives, out of which we will present three of them in Figure 34.

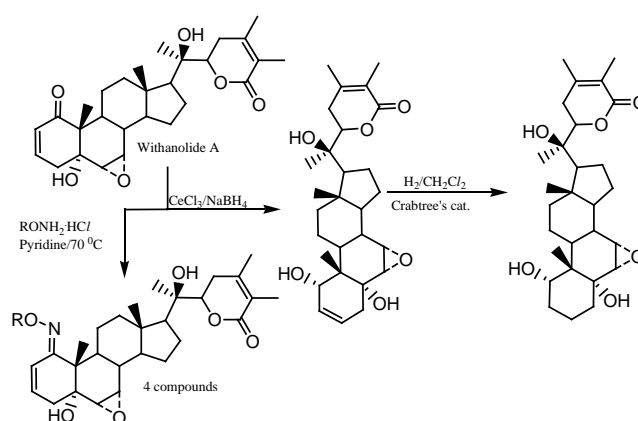


Figure 34. Withanolide A derivatives (ref. 719)

In the work of P-A. Nocquet and T. Opatz that we cited above (ref. 712), they prepared scopolamine by epoxidation of 6,7-dehydrohyoscyamine (see Figure 35).

Since the biosynthesis of in hairy roots of *Solanaceae* plants involves also 6 β -hydroxyhyoscyamine, T. Hashimoto and his colleagues, investigated the mechanism of the epoxide (scopolamine) biosynthesis, using ^{18}O labeling.⁷²⁰ They discovered that the epoxide biosynthesis is a result of a very unique step of dehydrogenation of the hydroxy compound and not epoxidation of the alkene (Figure 35).

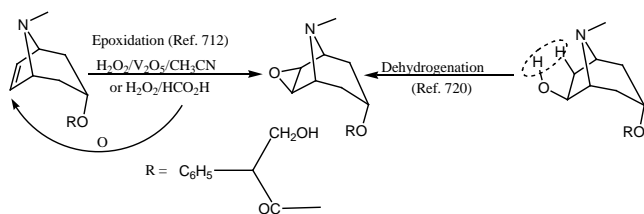


Figure 35. Biosynthesis vs. synthesis of scopolamine (ref. 720 and 712).

DISCUSSION

Finally, interested thiiranes (epoxide-like three membered ring of CSC) were prepared from epoxide moiety (C5-C6) of withanolides.⁷²¹ P. Joshi and his colleagues prepared four different thiiranes from four different starting withanolides.

One of the major aspects that we noticed very clearly while scanning the published article about *Solanaceae* plants of the reviewed region, is the large number of review articles. As we have already mentioned, some of them were not cited. Those were of two classes. First, those focus on ethnomedicine and ethobotany of these plants. Despite being very interesting topic that sparked many of modern studies, in this review we decided to focus on medicinal activities. Second, those reviews that in our humble opinion had no additional value and/or knowledge compared to the review articles that we presented.

But there were eight review articles that we chose to present in this section because we think that they deserve special attention, in terms of their contents. A very recently published review by A. Kerchner and A. Farkas, analyzes the poisons of the plants of *Datura* and *Brugmansia* genera.⁷²² Even though *Brugmansia* is not one of the plants reviewed in our article, it is closely related to *Datura* plants, and in most cases, it is grown as an ornamental plant. They present statistics of 25 years as tables and graphs. They divide their analysis to continents but present detailed information about Hungary, their homeland. They conclude that data of poison information centers from all over the world indicate that most exposures to *Brugmansia* and *Datura* are related to abuse, in connection with their hallucinogenic property, mostly in the age group of adolescents. Anticholinergic intoxication may also result from the improper use of traditional herbal medicines containing *Datura*. More recently, the use of *Brugmansia* and *Datura* as incapacitating drug in sexual crimes and robberies has caught the attention of authorities.

Psychoactivity of *Datura* plants has drawn the attention and use by humans since early times (ref. 4 and 5) and as mentioned in the previous citation. The review article published by T. Debnath and R. Chakraverty, focuses

mainly on this aspect of biological and medicinal activities of *Datura stramonium*.⁷²³ This is a very short document that very briefly presents traditional uses, phytochemistry and medicinal activities of this plant. But right in the beginning in this article, we found a taxonomic mistake, that might easily mislead readers: in addition to using scientific name (*D. stramonium*), authors mistakenly use a common name of another plant: Angels' trumpet. We have already expressed our opinion on this issue (see note f), and as far as we are concerned, these names should not be used in scientific publications. This common name is for *Brugmansia* and not *Datura* plants.⁷²⁴

F. Elisante and P.A. Ndakidemi published an interesting review article about the allelopathic effects of *D. stramonium* on plants of Tanzania.⁷²⁵ Allelopathy of this plant has been widely studied (see ref. 148-153), but the special interest of this review article is that it focuses on allelopathic effects of this plant on legumes, that are major nutrient plants for wild and domestic animals in natural reserves.

Review articles of chemical compositions of plants are very common literature. But some of them possess special importance. One of these unique review articles was published by D. Qian *et al.*⁷²⁶ It is one of the most comprehensive reviews that were published about plant chemical composition in general and about the *Lycium* genus in particular. It presents 355 natural products of different compound family, with structure, tables and graphs. This article is a very important resource for readers and researchers who are interested in this genus. Similar but way smaller review article was published by Y-J. Zhang *et al.* about the chemical composition of *Physalis peruviana*.⁷²⁷ Along with using its common name (Cape Gooseberry), they use the scientific name, and their work consists of two major issues, chemical composition and some medicinal activities of the plant. Their special contribution is listing the systematic (IUPAC) names of major natural products. Since they did not present structures of these compounds, scholars can easily convert these names to structures.

Withanolides were reviewed in several publications, but very few of them were reviewed as single compounds. On this basis, the review article of M. Dom and his colleagues has special importance.⁷²⁸ It presents broad perspective of antitumor activities of withaferin A (Figure 6). The article presents excellent figures of mechanism of action and pharmacokinetics against different types of tumors.

Poisoning of humans and animals by *Solanaceae* plants, their products and pure natural products, was extensively studied and reviewed as we cited earlier. But the review article of T.Y. Chan has very special relevance and importance.⁷²⁹ It presents an issue of health concern, poisoning of humans by tropane alkaloids that are found as contaminations in herbal medicines. These medicines are supposed to help cure health disorders, and these contaminations make these products life threatening. One of the worst types of this poisoning, is that can be caused by herbal teas (page 3 in article). Another dangerous poisoning

caused by these contamination, occurs after use of different slimming pills, which is becoming more and more a global trend, in the course of combating overweight and obesity, as well as fashion and modeling goals. Even prescribed herbal products are listed among these contaminated commercially used medications.

Last review article that we found as having special value, was published by F. Albouchi and her colleagues.⁷³⁰ Its importance emerges from the fact that includes, in brief, all aspects that are needed about *Solanum nigrum*. The article presents taxonomy and morphology, ecology (including cultivation under different stress conditions), distribution and habitat (including introduction in different regions), reproduction, traditional and ethnobotanical uses, toxicity, chemical composition (major active compounds), essential oils and their uses; and medicinal activities (detailed).

In addition to the selected review articles there are some research articles that in our opinion possess the same attribute and deserve special attention. One of the earliest publications of production of alkaloids in cultivated *Solanaceae* plants, was published by G.H. Gerlach in 1948.⁷³¹ It discusses the production of scopolamine in cultivated *Datura innoxia*. One of the major claims in this article is that scopolamine accumulation in cultivated *D. innoxia*, an originally "new world" plant, is higher than in cultivated *Datura metel*, the similar plant of the "old world". In fact, this is not only not true, scopolamine or other alkaloid content in cultivated plants, may vary over a wide range and is mainly a result of cultivation conditions.⁷³²

A. H. El-Said and his colleagues prepared the chloroform extract of cultivated endophytic fungi that was growing on *Datura innoxia* and *Hyoscyamus muticus*.⁷³³ They report that this extract had clear activity against several types of bacteria, as well as L-asparaginase inhibition. Interestingly, the chloroform extract of the *D. innoxia* itself or parts of it, were not tested for antibacterial activity (see Table 2) and it could be interesting to compare the plant extracts with those of endophytic fungi that grow on the plant. Contrary to that, the chloroform extract of *H. muticus* was prepared and tested for antibacterial activity (ref. 232) and it is less active than the fungi extract.

The role of alkaloids as defense metabolites, extensively studied in alkaloid-containing plants in general,⁷³⁴ in *Solanaceae* plants,^{44,45,735} and specifically in *Datura stramonium*,⁸⁴ are well known and published. But I. Shonle and J. Bergelson published an interesting research, which actually proposes that *D. stramonium* alkaloids have another opposite role.⁷³⁶ When insects feed on *D. stramonium* leaves that have low content of scopolamine and hyscyamine, they practically help plants in the natural selection and evolution, by extermination of defenseless "weak" plants. Further, it is evident that endophytic fungi can tolerate these toxic alkaloids and live on *D. stramonium* as a host plant. So, K. I. Tapfuma *et al.*, have investigated the anticancer activity of the fungi extracts against two cancer cell lines.⁷³⁷ They performed LC-QTOF-MS/MS analysis of the active extracts, and the major natural products that they found were: 1,8-dihydroxynaphthalene, anserinone B, phelligridin B, metacytofilin, phomopsidin and vermioxocin A. Interestingly, none of these compounds is an alkaloid.

Chlorophyll a or b, are two of the most challenging natural products for every researcher who desires to extract them. The major reason for this difficulty is their instability. Not only the classical extraction sequence (collection of plant or plant parts, drying, powdering and then extraction with a solvent, cold or hot) but even modern methods such as ultrasound-assisted or use of supercritical CO₂ extractions, are destructive and modifying the sensitive pigments. For this reason, there was a need for two important tools. First, an adjustment of a solvent/s for the pigment extraction of plants and second, developing methods and technologies for field conditions extraction/determination of pigments in plants, in order to minimize the time that these natural products are exposed to external effects, that can lead to their decomposition or modification.⁷³⁸⁻⁷⁴² On this basis, T.T. Tanan and her colleagues described the methods used to determine the pigment content of *Physalis angulata*.⁷⁴³ They concluded that the use of the 80 % aqueous acetone tissue maceration protocol followed by filtration was the most efficient for use in the laboratory, while in field conditions, the immersion technique of foliar disks in 95 % aqueous ethanol and 24 h incubation is best method.

B. Bibhuti and A. K. Yadav discuss the production and use of digestive pills from *Solanum nigrum*.⁷⁴⁴ In our view, their article has two disadvantages. The minor one is language mistakes ("and Makoi are the common name for it"). But the major one is their statement, "fruits of black colour are not used as they possess toxicity, therefore they are not used for medicinal purposes. Reddish-brown coloured fruits are used for edible purpose". Ripe fruits are black, and from this very fact, emerges the name of this plant. This statement completely contradicts other reports that unripe fruits (green or other colors but black) are toxic and not edible, while black, ripe fruits are.^{56,544,745} Another strange fact about this article is that it was published (exactly same article, with only a different title) in another journal in the same year.⁷⁴⁶

Solasodine, a steroidal alkaloid, is one of the most active natural products found in the *Solanaceae* plants (see figure 8). In addition to the publications that we have already cited about this important compound (ref. 414, 433, 459, 560, 672, 700-702), numerous articles have been published about it.^{747,748} Because of their importance, several methods (and many publications) were developed for the separation, extraction, quantification and validation of this compound.⁷⁴⁹⁻⁷⁵¹

CONCLUSIONS

1. Plants of the *Solanaceae* family, in the reviewed region, are very rich with active natural products.
2. Some of these 24 plants are extensively studied but some of them are moderately studied.
3. There very few published studies about some of the plants. More research of these plants is needed.
4. There are no publications about medicinal, biological and other activities of *Solanum cornutum*. There is an immediate need for comprehensive study of this species.

5. Some of the natural products isolated from these plants were reasonably investigated for their medicinal activities, while others were either not or very partially studied. So, these studies should be expanded.

6. The cultivation of some of these plants for the purpose of active natural products accumulation was done under various conditions, while other plants were very limitedly or not studied. It is important to expand this research.

7. It is very highly recommended to avoid using common name of plants in scientific publications. This use is inaccurate and misleading.

8. Global climate changes are seemingly responsible for the rapid habitat expansion of some of these plants. Careful approach is needed to understand this phenomenon, and to try to utilize the results for combating the plants weed spreading.

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