THE EXPEDITIOUS OXIDATION OF ARYLBORONIC ACIDS TO PHENOLS BY TERTIARY BUTYL HYDROPEROXIDE IN GREEN AQUEOUS ETHANOL

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Keywords: arylboronic acids; tert-butyl hydroperoxide (TBPH); phenols; green method.

An efficient protocol for the synthesis of phenols from arylboronic acids has been developed by using t-butyl hydroperoxide (TBHP) as oxidant in water-ethanol as a binary reaction medium. The reaction is metal and additive free and does not require strong basic conditions. The developed protocol has a broad substrate scope and functional group compatibility. Notably the mild conditions, shorter reaction time, good to excellent yields and eco-friendly reaction medium are some important features of the developed method.

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INTRODUCTION

Phenols and their derivatives are found in numerous bioactive natural products and serve as well-known precursors for the synthesis of pharmaceuticals and natural product analogs of therapeutic importance.[1] Consequently, the synthesis of phenols has attracted a considerable impetus and numerous methods have been developed over the years. Among these, copper-catalyzed conversion of diazoarenes, benzynes and aromatic nucleophilic substitutions of aryl halides are the main routes for the synthesis of phenols.[2] Some other strategies utilize palladium-based catalysts using phosphine ligands and copper catalyst using non-phosphine ligands at elevated temperature for the conversion of aryl halides into phenols.[3,4] However, these methods involve prefunctionalization–defunctionalization strategies, rely upon the use of hazardous metal catalysts and harsh reaction conditions which limit their utility due to functional group compatibility problems.

An alternative easy accessible route utilizes arylboronic acids/esters for the synthesis of phenols. The harmless nature of arylboronic acids, their thermal, air and moisture stability make them useful and readily available precursors for the synthesis of phenols.[5,6] In this direction, numerous methods are known for arylboronic acid/ester hydroxylation which include $CuSO_4$-phenanthrolin,[7] H_2O_2-poly (N-vinylpyrrolidone),[8] NH_2OH,[9] potassium per-oxy sulfate,[10] H_2O/H_2O_2,[11] I_2/H_2O_2,[12] PEG400/H_2O_2,[13] Cu_2O NPs,[14] m-CPBA/KOH,[15] TBPH/KOH.[16] These strategies, however, have some demerits such as long reaction times.[9,11] use of strong basic conditions[7] and toxic chlorinated organic solvents.[8] Thus, development of more efficient and environmentally benign and mild synthetic procedure for the synthesis of phenols is still desirable. In our previous communication, we report ipso-hydroxylation of phenyl boronic acids.[17] therefore, in continuation of our previous research endeavors for the development of green and more efficient synthetic methods,[18-20] herein we wish to report a rapid, base-free *ipso*-hydroxylation of arylboronic acids to phenols at room temperature in a green binary reaction medium (water-ethanol) and TBHP as an oxidant/catalyst.

EXPERIMENTAL

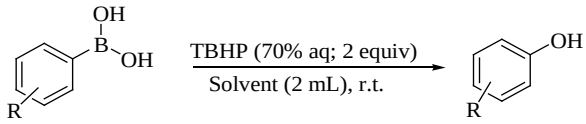
All the melting points were determined on a Kofler apparatus and are uncorrected. The IR spectra were recorded on KBr pellets with Perkin Elmer RXI Spectrophotometer and values are given in cm^{-1}. ^1H and ^{13}C NMR spectra were run in $CDCl_3$ on a JEOL Eclipse (400 MHz) instrument with TMS as internal standard and values are given in ppm (δ). Mass spectra were recorded on a JEOL SX 102/DA-6000 Mass Spectrometer. Thin layer chromatography (TLC) plates were coated with silica gel G and exposed to iodine vapours to check the homogeneity as well as the progress of reaction. Petroleum ether refers to a fraction of boiling point 60-80 °C. Sodium sulfate (anhydrous) was used as a drying agent. All the chemicals were purchased from Merck India and were used after distillation.

Procedure for ipso-hydroxylation of arylboronic Acid

A reaction flask was charged with 1.0 mmol of arylboronic acid and TBPH (2.0 mmol) in 2 mL of H_2O-C_2H_5OH solvent (1:1) and stirred at room temperature for 8-18 min. The reaction progress and completion was monitored by TLC. After completion, the crude reaction mixture was extracted with ethyl acetate and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by SiO_2 column chromatography (ethyl acetate: hexane) to afford the desired product. The prepared phenols were characterized by comparing the observed spectral data[17] and physical properties.

RESULTS AND DISCUSSION

The base-free *ipso*-hydroxylation of different arylboronic acids in a water-ethanol solvent system in presence of TBHP were completed within a short reaction time of 8-18 min and the phenols were produced in excellent yields. The reaction is shown below (Scheme 1).



Scheme 1. Synthesis of phenols from arylboronic acids.

Table 1. Effect of solvent systems on *ipso*-hydroxylation of arylboronic acid.

Entry	Solvent	Time, min	Yield,[a] %
1	Water	10	85
2	Ethanol	10	77
3	Methanol	12	70
4	EtOAc	15	53
5	DMF	15	67
6	CH_3CN	17	62
7	DMSO	12	62
8	Dioxane	18	55
9	DCM	18	60
10	water-ethanol	9	95
11	water-methanol	10	93
12	water-DMSO	15	88
13	water-CH_3CN	13	85
14	water-DMF	16	69
15	ethanol-DMSO	10	77
16	ethanol-DMF	12	70

[a] Isolated yields after purification using column chromatography.

To set up the optimum reaction conditions, phenylboronic acid (**1**) was chosen as a model substrate to evaluate the proposed hydroxylation of aryl boronic acids. The model reaction containing the mixture of (**1**) (1 mmol) and TBHP (70 % aq; 2.0 mmol) when stirred at room temperature in methanol furnished the corresponding phenol with 70% yield notably in a short reaction time of 12 min. We then began to evaluate a range of different solvents like water, ethanol, methanol, ethyl acetate (EtOAc), dimethylformamide (DMF), acetonitrile (ACN), dimethyl sulphoxide (DMSO) and dichloromethane (DCM) and noticed that the nature of the solvents have significant influence on rate and yield of the reaction (Table 1). Protic solvents such as water, methanol and ethanol proved to be better reaction medium than aprotic solvents with better yields (Table 1, entries 1-3) In aprotic solvents such as EtOAc, DMF, ACN, DMSO and DCM moderate yields were obtained with incomplete substrate conversion (Table 1, entries 4-9). Since protic medium particularly water proved to be a better solvent, we then evaluated different combination of water-organic solvents such as water-ethanol, water-methanol, water-ethanol, water-methanol, water-DMSO, Water-ACN and water-DMF to further improve the reaction conditions in terms of yield and reaction rate (Table 1, entries 10-16). It was observed that binary solvent system improved the reaction yield especially when water is one of the co-solvents (Table 1, entry 14). Finally water-ethanol combination was found to be the medium of choice for the proposed model reaction with 95 % yield of the phenol in a short reaction time of 9 min. Additionally this reaction medium offers to synthesize phenols under environmental friendly conditions due to biodegradable nature of ethanol.

Table 2. The *ipso*-hydroxylation reaction of substituted arylboronic acids.

Entry	Substituent	Time, min	Yield, %
1	R = H	8	94
2	R = *p*-F	10	90
3	R = *m*-CH_3	8	92
4	R = *m*-Br	10	88
5	R = *p*-OCH_3	14	95
6	R = *p*-Br	12	89
7	R = *p*-CF_3	13	91
8	R = 2-butyl	15	94
9	R = *p*-NO_2	10	82
10	R = *p*-C_6F_5	16	88
11	R = *o*-NO_2	18	60
12	R = *o*-Cl	10	89
13	R = *p*-F, *o*-CF_3	18	74
14	R = *o*-F	18	87
15	R = *p*-OCF_3	18	90

With the optimized reaction conditions, we evaluated a wide array of electronically and structurally diverse arylboronic acids to check the substrate scope of the developed protocol and found that a variety of functionalities were tolerated (Table 2). In general, arylboronic acid with either electron-withdrawing or electron-donating substituents like -OMe, -CH_3, -CF_3, -NO_2, OCF_3 and -OH underwent the *ipso*-hydroxylation reaction efficiently with excellent yields (Table 2, entries 2, 3, 5, 7, 9, 11 and 15). Ortho substituted arylboronic acids were found to be less reactive than para substituted arylboronic acids (Table 2, entries 2-6, 7, 9, 11, 12-15). Phenylboronic acids bearing bulky substituents, such as phenyl and butyl groups were also examined, and excellent yields of the phenols were obtained (Table 2, entries 8 and 10). Halogen substituted boronic acids like bromo, chloro and fluoro phenylboronic acids were also rapidly transformed into the corresponding products in excellent yield under the optimized conditions (Table 2, entries 2, 4, 6, 12, 13 and 14). Electron rich arylboronic acids (Table 2, entries 3, 5 and 8) gave satisfactory yields within 8-15 min. The optimized protocol was also found to be compatible with heteroaryl boronic acids furnishing good yields (Table 3).

Table 3. The *ipso*-hydroxylation of naphthyl and heteroaryl boronic acid.

No.	Substrate	Product	Time, min	Yield, %
1	1-Naphthyl boronic acid	1-Naphthol	8	93
2	2-Naphthyl boronic acid	2-Naphthol	15	93
3	2-Furyl boronic acid	2-Hydroxy furan	14	82

Mechanistically the reaction is actually a nucleophilic 1, 2-migration of the aryl group from boron to oxygen[21] which leads to the formation of phenols.

CONCLUSION

In conclusion, a mild and efficient prptpcol for the ipso-hydroxylation of arylboronic acids to the corresponding phenol using TBHP as oxidizing agent in water-ethanol solvent has been developed. The developed method has a broad substrate scope and functional group compatibility. Notably mild reaction conditions, shorter reaction time, metal free conditions, devoid of additives such as ligands or bases and finally a green reaction medium are some of the striking features of this protocol.

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Received: 29.04.2020.
Accepted: 30.05.2020

ONE-POT SYNTHESIS OF 1,2,4-TRIAZINE DERIVATIVES OF 2-SUBSTITUTED BENZAMIDES IN [BMIM][OH]

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Keywords: One-pot synthesis, Schiff bases, [BMIM][OH], 1, 2, 4-triazine.

One-pot three component synthesis of (Z)-N-5-(benzylidene/substituted benzylidene)-3-methyl-6-oxo-1,2,5,6-tetrahydro-1,2,4-triazine-2-substituted benzamide derivatives were described by one-pot reaction of (Z)-4-(benzylidene/substituted benzylidene)-2-methyl-oxazol-5(4H)-ones with hydrazine hydrate followed by PhCH=NPh in [BMIM][OH] as ionic liquid for 30 min at 80-85 ºC**.** The importance of this method includes shorter reaction time and high yield.

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INTRODUCTION

Nowadays ionic liquids (ILs) are being used widely as reaction medium for organic reactions. ILs have non-volatile nature at room temperature and are used to develop eco-friendly methods for organic synthesis.[2-4] Multi component reaction (MCR) is a one-pot reaction, which contains three to more components in single reaction vessel to give a final desired product containing substantial components of all the reactants.[5] One of great challenges in modern medicinal chemistry is design and discovery of pharmaceutical active molecules.

Nitrogen containing heterocyclic compounds abounds in nature and their application as pharmaceutical active compounds and agrochemicals are becoming increasingly important.[6] 1,2,4-Triazin-6-ones are a very important class of heterocyclic compounds that show a wide variety of applications in both pharmaceutical and agrochemical fields. 1,2,4-triazin-6-ones have exhibited anticancer, antitumor, antibacterial and antifungal activities, antimicrobial, biological activities of cell line cytotoxicity, antimalarials, antivirals and herbicides.[7-12]

Herein, we now wish to report synthesis of **(***Z***)**-N-5-(benzylidene/substituted benzylidene)-3-methyl-6-oxo-1,2,5,6-tetrahydro-1,2,4-triazine-2-substituted benzamide derivatives by one-pot three component reaction of (*Z*)-4-(benzylidene/substituted benzylidene)-2-methyl-oxazol-5(4H)-ones (**1a-f**) with hydrazine hydrate (**2**) followed by Schiff base (**3**) in the presence of [BMIM][OH], mediated at 80-85 ºC for 30 min with excellent yields.

EXPERIMENTAL

Melting points were measured in open capillary tubes in sulphuric acid bath and are uncorrected. TLC was run on silica gel-G and visualization was done using UV light. IR spectra were recorded using Perkin-Elmer 1000 instrument in KBr pellets. ^{1}H NMR spectra were recorded in DMSO-d_6 using TMS as internal standard with a 400 MHZ spectrometer. Mass spectra were recorded on Agilent-LCMS instrument under CI conditions and given by Q^{+1} value only.

Preparation of (*Z*)-5-(benzylidene/substitutedbenzylidene)-2-N-(benzamide/substituted benzamide)-3-methyl-6-oxo-1,2,5,6-tetrahydro-1,2,4-triazine derivatives (4 a-f).

Charged the (*Z*)-4-(benzylidene-2-methyl-oxazol-5(4H)-ones (**1 a-f**) (1 mmol) with hydrazine hydrate (**2**) (1 mmol) followed by Schiff base (**3**) (1 mmol) in 5 equiv. of [BMIM][OH]. The reaction mixture was heated at 80-85 ºC for 30-40 min. the reaction was monitored by TLC (solvent system 1:3 EtOAc:hexane). After completion the reaction mixture was cooled to room temperature and poured into ice-cold water (50 mL). A solid separated out which was collected, washed with water (10 mL) and dried. The product was recrystallised from ethanol to obtain (*Z*)5-(benzylidene/substituted benzylidene)-2-N-(benzamide / substituted benzamide)-3-methyl-6-oxo-1,2,5,6-tetrahydro-1,2,4-triazine derivatives (**4a-f**) (Scheme 1).

4a: M.P. >230 ºC. IR (KBr): 3360 (broad, -NH-N), 3313 (broad, -NH), 1680 (-C=O) cm^{-1}. ^{1}H NMR: δ = 2.9 (s, 3H, N-C**H**$_3$), 3.6 (s, 1H, -C**H**), 5.3 (s, 1H, -N**H**-CH) 7.2-8.8 (m, 16H, Ar-**H** and s, 1H, =C**H**-Ar)**,** 11.2 (s, 1H, **-NH**). MS: $M^{+\cdot}$+1 = 219.

4b: M.P. >230 ºC. IR (KBr): 3310 (broad, -NH-N), 3244 (broad, -NH) 1659 (-C=O) cm^{-1}. ^{1}H NMR: δ = 2.9 (s, 3H, N-C**H**$_3$), 3.5 (s, 1H, -C**H**), 3.9 (s, 3H, -C**H**$_3$), 5.3 (s, 1H, -N**H**-CH) 7.0-8.4 (m, 15H, Ar-**H** and s, 1H, =C**H**-Ar)**,** 11.1 (s, 1H, **-NH**). MS: $M^{+\cdot}$+1 = 249.

4c: M.P. >230 ºC. IR (KBr): 3440 (broad, -NH), 3250 (broad, -NH), 1710 (-C=O) cm^{-1}. ^{1}H NMR: δ = 2.8 (s, 3H, N-C**H**$_3$), 3.5 (s, 1H, -C**H**), 5.3 (s, 1H, -N**H**-CH) 7.0-8.4 (m, 15H, Ar-**H** and s, 1H, =C**H**-Ar)**,** 11.2 (s, 1H, **-NH**). MS: $M^{+\cdot}$+1 = 237.

4d: M.P. >230 ºC. IR (KBr): 3480 (broad, -NH), 3250 (broad, -NH), 1720 (-C=O) cm^{-1}. ^{1}H NMR: δ 2.9 (s, 3H, N-C**H**$_3$), 3.5 (s, 1H, -C**H**), 5.3 (s, 1H, -N**H**-CH) 7.0-8.4 (m, 15H, Ar-**H** and s, 1H, =C**H**-Ar)**,** 11.1 (s, 1H, **-NH**). MS: $M^{+\cdot}$+1 = 264.

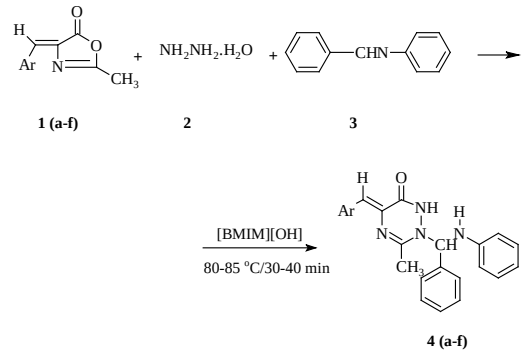
4e: M.P. 180-182 ºC. IR (KBr): 3322 (broad, -NH), 3304 (broad, -NH) 1720 (-C=O) cm^{-1}. ^{1}H- NMR: δ = 2.7 (s, 3H,

N-C**H**$_3$), 3.4 (s, 1H, -C**H**), 5.7 (s, 1H, -N**H**-CH) 7.0-8.4 (m, 15H, Ar-**H** and s, 1H, =C**H**-Ar)**,** 11.2 (s, 1H, **-NH**). MS: $M^{+\cdot}$+1 = 253.

4f: M.P. 170-172 ^{o}C. IR (KBr): 3334 (broad, -NH), 3283 (broad, -NH), 1712 (-C=O) cm^{-1}. ^{1}H- NMR: δ = 2.8 (s, 3H, N-C**H**$_3$), 3.5 (s, 1H, -C**H**), 5.5 (s, 1H, -N**H**-CH) 7.2-8.4 (m, 15H, Ar-**H** and s, 1H, =C**H**-Ar)**,** 11.2 (s, 1H, **-NH**). MS: $M^{+\cdot}$+1 = 253.

RESULTS AND DISCUSSION

Herein, the one-pot three component synthesis of (Z)-N-5-(benzylidene-3-(methyl/phenyl)-6-oxo-1,2,5,6-tetrahydro-1,2,4-triazine derivatives (**4**) has been described.



Scheme 1. One pot three-component synthesis of **4a-4f**.

To optimize the reaction conditions, **1a** (1 mmol) was treated with **2** (1 mmol) followed by Schiff base **3** (1 mmol) in the presence of 5 equiv. of different ionic liquid ([BMIM][OH], [BMIM]Br and [BMIM]BF$_6$) at different temperature (Table 1). However, compound **4a** has formed with excellent yield in [BMIM][OH] as ionic liquid mediated at 80-85 ^{o}C for 30 min with excellent yields 90% (Table 1, entry 4).

Table 1. Effect of Ionic liquid and temperature on the reaction.

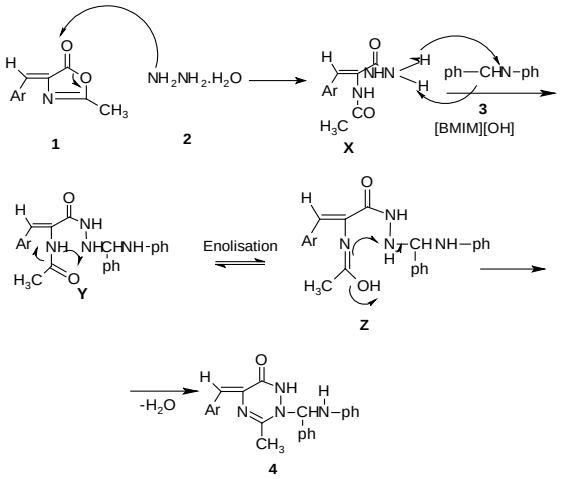
Entry	IL 5eq	Temp., ^{o}C	Time, min	4a, %
1	[BMIM][OH]	70-75	120	85
2	[BMIM] Br	70-75	450	83
3	[BMIM] BF$_6$	70-75	300	82
4	[BMIM][OH]	80-85	30	90
5	[BMIM] Br	80-85	300	85
6	[BMIM] BF$_6$	80-85	240	84
7	[BMIM][OH]	90-95	25	86
8	[BMIM] Br	90-95	120	82
9	[BMIM] BF$_6$	90-95	120	81

The structure of the compound has been confirmed by IR, ^{1}H and ^{13}C-NMR and MS (see in Electronic Supplementary Material). The IR spectrum of the compound **4a** confirms the formation of 1,2,4-triazine-6-one derivatives by the appearance of absorptions at 3360 cm^{-1} (NH), 2197 cm^{-1}(Ar) and 1681 cm^{-1}(C=O). The ^{1}H-NMR spectra showed the signals at δ 2.9 indicating methyl protons, along with trans olefinic proton observed at δ 11 and aromatic protons at δ7.1-8.8.Signals at δ 3.8 and δ 5.2 indicate two –NH protons which were D_2O exchangeable. ^{13}C NMR spectrum showed signals at δ20 (CH_3), δ115 (CH=C), δ127 (Ar C=C), δ130 (HC=C), δ137 (CH-Ar), δ139 (=CH-Ar), δ140(-C(CH3)), δ159(-CONH), δ164(N-C(Ar)-N). Further the mass spectrum of the compound **4a** showed the molecular ion peak at m/z 382 corresponding to molecular weight of the compound **4a**.

Based on the optimised condition and to test its generality the method, extended to six other derivatives and in the all cases the corresponding (*Z*)-N-5-(benzylidene/substituted benzylidene)-2-N-(benzamide/substituted benzamide)-3-(methyl/phenyl)-6-oxo-1,2,5,6-tetrahydro-1,2,4-triazine derivatives **(4a-4f)** were isolated in excellent yields. The synthesis of **4a-4f** in presence of [BMIM][OH] as ionic liquid at 80-85 ^{o}C for 30-40 min produced high yields, purities and short reaction time.

Mechanism

Though we have not investigated the mechanism, a plausible mechanism is suggested.



Scheme 2. A plausible mechanism of the formation of **4 a**

Initially, the compound (*Z*)-4-(benzylidene-2-methyl-oxazol-5(4H)-ones **1** was reacted with hydrazine hydrate by nucleophilic substitution to form the intermediate (Z)-N-(3-hydrazinyl-3-oxo-1-phenylprop-1-en-2-yl-acetamides **X** which was treated with the Schiff base which is a proton acceptor, accepts proton from NH_2 group of **X** to produce an unstable intermediate, which in presence of a base undergoes enolisation followed by cyclocondensation and eliminates water molecule to produce the title compounds (*Z*)-N-5-(benzylidene/substituted benzylidene)-2-N-(benzamide/ substituted benzamide)-3-methyl-6-oxo-1,2,5,6-tetrahydro-1,2,4-triazine (**4a)** (Scheme-2).

CONCLUSION

In summary, we developed the synthesis of (Z)-N-5-(benzylidene/substituted benzylidene)-3-methyl-6-oxo-1,2,5,6-tetrahydro-1,2,4-triazine-2-substituted benzamide derivatives (**4a-4f)** by one-pot reaction in [BMIM][OH] as

ionic. The importance of this method includes shorter reaction time and high yield.

ACKNOWLEDGEMENT

Authors are very thankful to the authorities of Department of Chemistry, Institute of Aeronautical Engineering, Dundigal, Hyderabad for providing laboratory facilities.

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Received: 29.04.2020.
Accepted: 31.05.2020.

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

Abdullatif Azab[a]*

Keywords: *Solanaceae;* alkaloids; physalins; withanolides; medicinal activity; psychoactive; poisoning.

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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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 potatos (*Solanum tuberosum*), tomatos (*S. lycopersicum*), eggplant (*S. melongena*) and chili pepper (*Capsicum annuum*).[1] These human cultivated species are among the most important for human nutrition and possees 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 europeaum*, *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]

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.

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*.

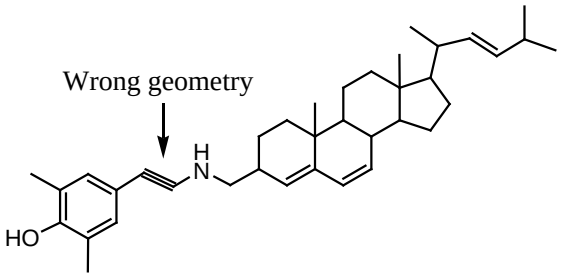


Figure 1. Wrong structure of steroidal alkaloid presented in reference 12

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 here[13] (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 hyocsyamine, and the poisoning potential of the plants to animals.[14]

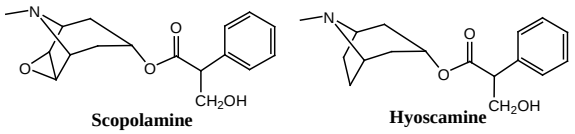


Figure 2. Tropane alkaloids, scopolamine and hyoscyamine

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 presentaion of important natural products structures. *D. fastuosa* is also reviewed (ref. 18. but this plant does not exist in the region of the inerest of our article.[18,19]

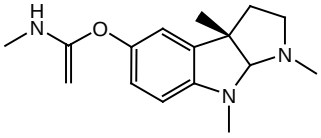


Figure 3. Physostigmine, natural alkaloid, antidote of *Datura* poisoning.

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 veryshort 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 structues 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.

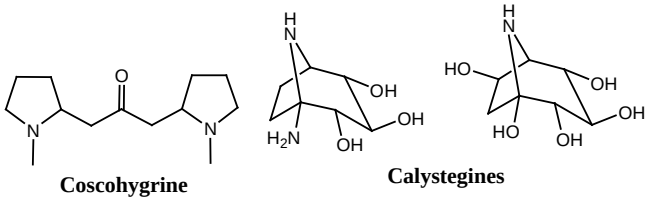


Figure 4. Structures of selected calystegines and coscohygrine (ref. 30).

16. *Nicandra physalodes*. The only published review about medicinal activities of this plant, and ethomedicinal 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.

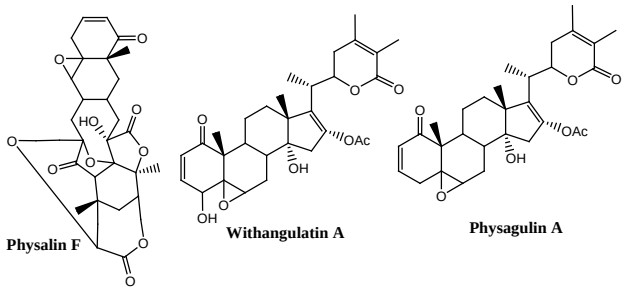


Figure 5. Selected natural products isolated from *Physalis angulata* (ref. 32).

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* ssp. Wide scan of traditional uses as well as systematic review of active natural pruducts and their structures (see Figure 6) are the two great adavantages of these reviews. They also include some medicinal activities.[35,36]

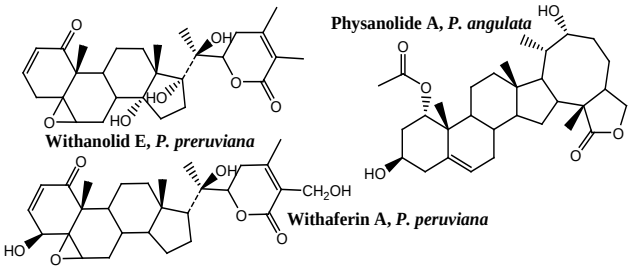


Figure 6. Structures of natural products isolated from *Physalis* ssp. (35).

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 CCl_4.[40]

24. *Solanum* ssp. 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.

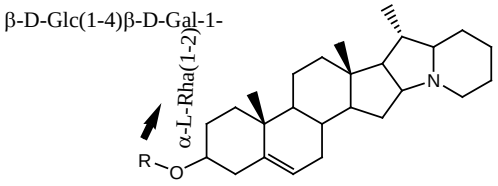


Figure 7. Glyco-α-solanine and its aglycon (ref. 41).

25. *Solanum* ssp. 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* ssp. This wide review focuses on two glyco-streroidal-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]

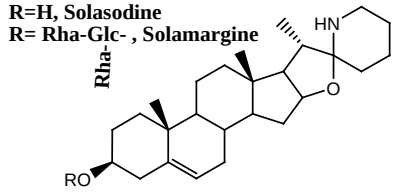


Figure 8. Solamargine and Solasonine (ref. 43).

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]

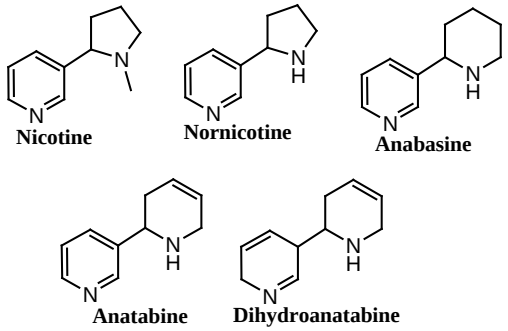


Figure 9. Selected alkaloids of *Nicotiana glauca* (ref. 44).

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 rapidlay. 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 ethobotanical 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 hyperaccommulate heavty 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 datailed 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]

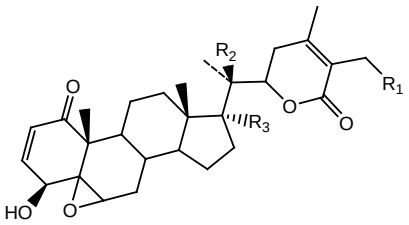


Figure 10. General structure of withanolides (ref. 62).

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 ezymatic 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 neuprotection activities (excellent figure page 6).[75]

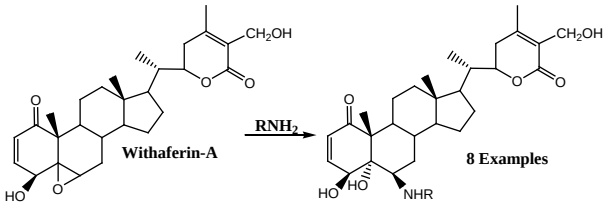


Figure 11. Aminolysis of Withaferin-A (ref. 75)[b] b. Citation of Joshi, P. *et al*., ref. 721.

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 phrmacological 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 fot 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 spcies 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 scopolamie are major compounds.[86]
Alkaloids content (Argentina)	An extended qualitative study of alkaloids content (HPLC, GC-MS) found five additional alkaloids compared with previously punlished (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 *D. ferox* 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 inoxia)

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, folllowed 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 *Aspergillus niger* 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 *Agonoscelis pubescens*. Hexane extract had highest activity.[118] Fruits aqueous extract found active against *Holotrichia Serrata* (Fab).[119] Leaves aqueous had insecticidal activity against *Locusta migratoria*.[120] Leaves were extracted with methanol and hexane. Both extracts found active against *Spodoptera Litura* (F.).[121] Leaves were extracted with ethanol and extract was found active against *Meloidogyne incognita*. 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

	solvents and antioxidant capacity was determined by two methods. General chemical composition was determined.[123]
Chemical composition	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]

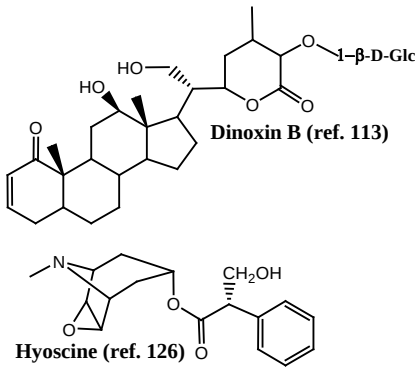


Figure 12. Selected active compounds isolated from *Datura innoxia* (Table 2).

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 assested, whole plant extraction yielded hyoscine 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	Ethanolic 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 ethnol, and extract was found active against *Staphylococcus aureus* isolated from sheep.[146] Leaves were extracted with some organic solvents, and extracts were tested against several types of bacteria and found active. Against *E. coli* they had weak activity, but in combination with *Abutilon indicum*, synergism was observed.[147] Aerial parts were extracted with ethanol, chloroform and benxene. 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 singnificant 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 antibaterial activity.[158] Ethanolic and aqueous extracts were prepared and found antibacterial. General chemical composition was determined in this study.[159] Alkaloids were extracted (ethanol, H_2SO_4) 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 aftive against several types of bacteria. General chemical composition was also determined with special attention to glycoalkaloids.[161] Ethanolic extract was found active antibaterial/ General chemical composition was determined.[162] Leaves were extracted with 80% aqueous ethanol, and protiens were isolated and found active against several types of bacteria.[163] Differenet 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 methaolic 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, antidyslipidemic and related activities	Leaves aqueous extract showed singnificant α-amylase inhibition activity.[157] Roots were extracted with 70 % aqueous methanol. Extract was hypoglycemic (STZ-induced diabetic mice) and antidyslipidemic.[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.

	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/super-oxide scavenging). Ethyl acetate had highest activity. General chemical composition was determined.[179,180] Leaves were extracted with methanol and extract had high anioxidant 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]
Chemical composition	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, H_2SO_4) 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 *Datura* or from the *Solanaceae* family. Two of them are shown in Figure 13.[187]
Enzyme inhibition, brain influencing, fertility influencing and related activities	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 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 antiovulatory activity.[191]
Insecticidal, antiparasitic and related activities	Leaves ethanolic extract showed high insecticidal activity against *Aedes Aegypti* and *Culex Quinquefaciatus*.[193] Ethanolic seeds and leaves extract had efficient inseticidal activity against *Tribolium castaneum*.[194] Acetone extract of aerial parts (excluding flowers) had lethal effect on *Callosobruchus maculatus*.[195] Leaves were extracted with several solvents and ethanolic extract showed highest activity against larvae of *Culex quinquefasciatus*.[196] Seeds were extracted with acetone, ethanol and chloroform, and acetone extract was most insecticidal against *Sitophilus oryzae* L.[197] Shoots were extracted with methanol and extract had nematicidal activity.[198]
Metal chelating, accummulation and nanoparticles	Alkaloid extracts had Fe^{2+} and Cu^{2+} chelating abilities.[135] Silver nanoparticles (AgNP's) were prepared by reduction of $Ag^+_{(aq)}$ with leaves aqueous extract, and they had antibaterial activity.[158] Aqueous extract was used to prepare MgO-NPs.[175,c]
Toxicity, body changes after feeding	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 toxicty in mice. This is a detailed study that tested different variables and results.[200] Fatal case of dog posoning 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), icreased 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, reasulted 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]

(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, $Mg(NO_3)\cdot 3H_2O$". 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*.

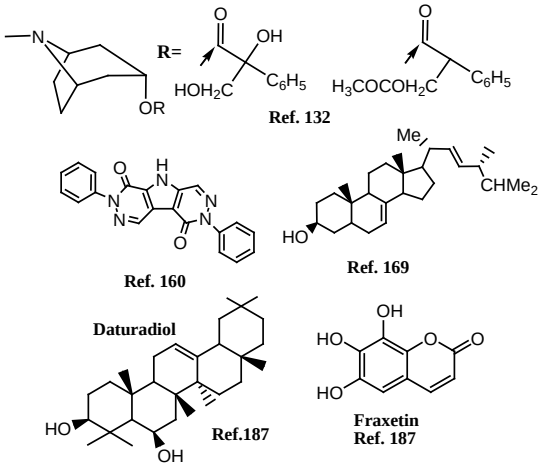


Figure 13. Selected active compounds in *D. stramonium.*

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 *Hyscoyamus 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] Leaves methanolic extract showed anlgesic (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]
Anticancer and related activities	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]
Antidiabetic, antidyslipidemic and related activities	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 $mgkg^{-1}$) and had significant antidiabetic activity (STZ-induced) in rats.[220]
Antioxidant, anti-inflammatory, anticoagulant, wound healing and related activities	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 actvity induced by ethanol.[223] Leaves were extracted as in ref. 218. General chemical composition was determined and extract had hepatoprotective actvity against CCl_4-induce toxicity.[224]
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] 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]

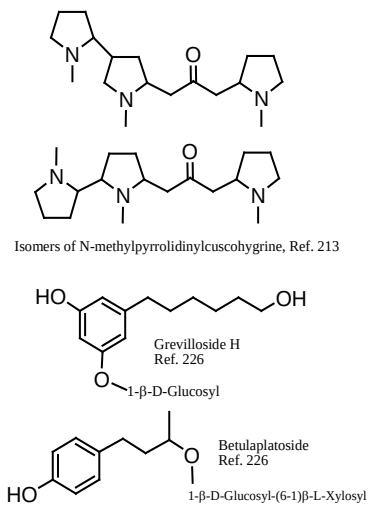


Figure 14. Selected compounds isolated from *H. albus.*

Hyoscyamus aureus

This plant is one of the least studied in the *Solanaceae* family and in the *Hyscyamus* 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 *Cichorium intybus* seeds germonation. Alkaloid fraction was analyzed and detailed compostion 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 (*iso*-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]

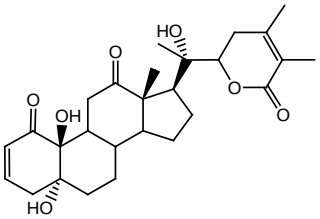


Figure 15. Structure of Muticin isolated from *Hyoscyamus muticus* (Ref. 236).

Hyoscyamus pusillus

The natural habital 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 know, including apohyoscine 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 *Hyoscyamus* in realtion 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 *Hyoscyamus* showed that *H. pusillus* 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]

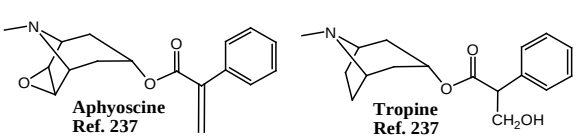


Figure 16. Active compounds isolated from *Hyoscyamus pusillus.*

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 *Hyoscyamus* in realtion 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 *Hyoscyamus* showed that *H. pusillus* 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 parially studied, and this one, is one of the least. Its chemical composition is completely unkown, and wether it contains alkaloids or not, is also unkown 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
Anticacer, cytotoxicity and related activities	Fruits were extracted with 80 % aqueous ethanol and extract had cutotoxic 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_2O_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_2O_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_2O_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]

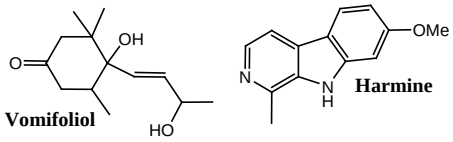


Figure 17. Selected compounds isolated from *L. europaeum* (Ref. 255).

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 habital 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 *Staphylococcus aureus*.[261] Fruits were extracted successively with several solvents. Most extracts showed significant activity against bacteria strains.[262]
Anticacer, cytotoxicity and related activities	Leaves methanolic extract was prepared and found active against HEK293 cancer cell line.[259] Aerial parts were defatted with *n*-hexane, suspended in aqueous ethanol (50 %) and extracted with several solvents.

	Most extracts showed anticancer activity.[263]
Antioxidant, anti-inflammatory, wound healing	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 *n*-hexane, suspended in aqueous ethanol (50 %) and extracted with several solvents. All extracts showed anticancer activity.[263]
Chemical composition	Aerial parts were defatted with *n*-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 *n*-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.

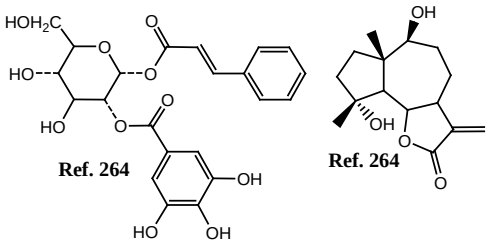


Figure 18. Selected natural products isolated from *L. Shawii.*

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 (C14:1ω5-C20:2ω6).[268] Roots were analyzed for alkaloids and some compounds were indentified for the first time in *Mandragora* 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 *Borago Officinalis*.[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)

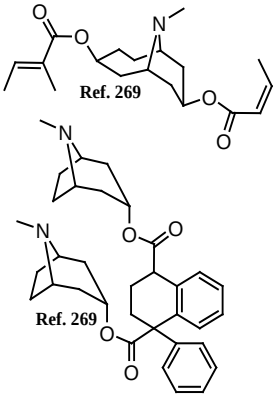


Figure 19. Natural products isolated from *M. atumnalis.*

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 prodution inhibition).[284]
Diuretic	Ethanolic 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 (*Tetranychus urticae*).[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 *Aedes aegypti*.[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.

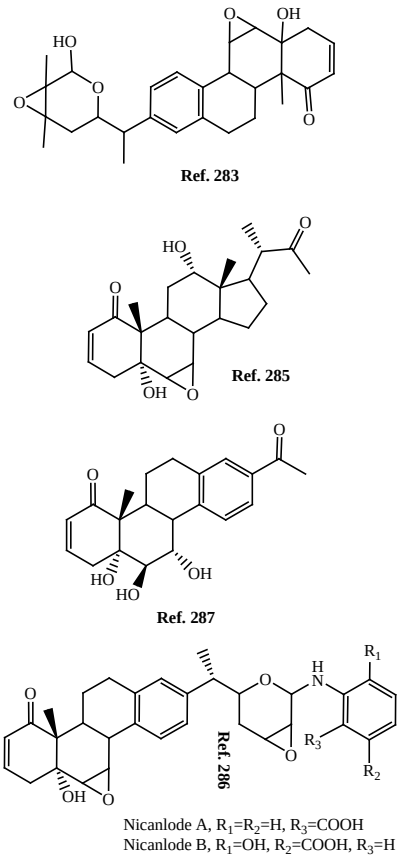


Figure 20. Natural products isolated from *N. physalodes.*

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 *Juniperus procera* was studied. Leaf extract promoted growth, while root extract supressed growth.[288]
Antibacterial	Aerial parts were extracted with water and *n*-hexane, several times over a time period of one year, and seasonal as well as location influemces were studied. Extracts had notable antibacterial activity.[289]
Anti-inflammatory, antioxidant	Aerial parts were extracted with water and *n*-hexane, several times over a time period of one year, and seasonal as well as location influemces were studied. Content of different antioxidant compound families, including enzymes was determined.[289] Who plant was defatted with *n*-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 (*Pieris rapae*).[291]
Chemical composition	Aerial parts were extracted with water and *n*-hexane, several times over a time period of one year, and seasonal as well as location influemces 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 accummu-lation	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 accummulation 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 *Staphylococcus aureus*.[305] Fruits ethanolic extract was against some bacteria species. Physalin B that was 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]
Anticancer and related activities	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 actvities 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 physlains, 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

	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-arthritic 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 anioxidant 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 compounds inhibited NO production induced by LPS.[342]
Chemical composition	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 CH_2Cl_2 and *n*-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]
Immune system and blood cells enhancing activities	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]
Enzyme inhibition and related activities	Whole plant was extracted with CH_2Cl_2 and *n*-BuOH. Three known compounds were isolated and characterized including physalin G which inhibited α-glucosidase.[336]
Insecticidal, anti-parasitic and related activities	Whole plant was extracted with dichloromethane and fractionized with several solvents. Physalin B and its 5,6-epoxide were isolated. Both compounds were antiplasmodial (*Plasmodium falciparum*).[334] Known Physalins were active antileishmanial in parasite infected mice.[352,353] Roots aqueous extract had notable activity against *Leishmania infantum*.[354]Whole plant and different parts were extracted and fractionized ethanol, methanol, ethyl acetate, dichoromethane, chloroform, and hexane. Each extract was analyzed to obtain pure physalins. These were tested and found active against *Biomphalaria tenagophila*.[355]
Nanoparticles synthesis	Leaves were extracted with water and extract was used to prepare nickel oxide nanoparticles (NiO-NPs). Extract was used as stabilizing agent

	not reductant.[356]
Toxicity	Administration of plant extract (parts, solvents, not indicated) along with Methylprednisolone (immunosupressor, anti-inflammatory) resulted no toxicity in mice.[357]

(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.

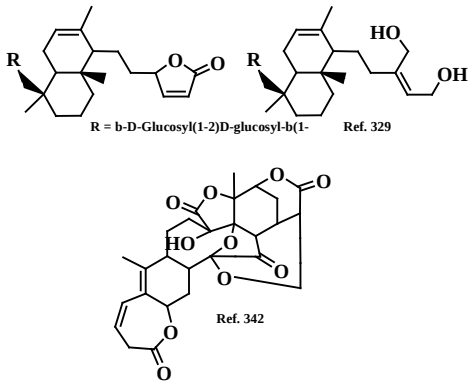


Figure 21. Selected natural products isolated from *Physalis angulata.*

Physalis peruviana

Even though *P. peruviana* is less widespread than *P. angulata*, locally and globally, it has ben 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 *Listeria* ssp. isolated from meat.[359] Leaves and fruits were extracted with ethanol, and extract was active against *Salmonella* ssp.[360] Fruits aqueous extract was prepared and found active againts 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 were active against several types of bacteria, where the fruit extract was most active. General chemical composition was determined.[363]
Anticancer and related activities	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 *n*-hexane and ethanol. Both extracts were tested and found active against two human breast cancer cell lines.[369] Fruits were extracted with ethanol and *iso*-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 farctions 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

	antioxidant activity (DPPH).[363] Fresh leaves were extracted separately with *n*-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 fruite 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 anhibited LPS-induced inflammation.[381] Aerial parts were extracted with water or different concentrantions of aqueous ethanol (20-95 %), and antioxidant capacity of all extracts was tested ($FeCl_2$-Ascorbic acid and lipid peroxidation). 95 % Aqueous ethanol extract had the highest activity.[382] Fresh fruit juice was added to rats food that had CCl_4-induced liver oxidative stress, and improvement was recorded compaired 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 culivated plants were tested for antioxidant capacity (DPPH), and cultivated fruits were more active.[385] Fruits were extracted with ethanol and *iso*-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]

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 fuits (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, triacylglyerols, 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 *Physalis* 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 fist 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]
Hepatoprotective	Roots were extracted with ethanol and 50 % aqueous methanol, successively. Extract had hepato-renal protective activity against CCl_4-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 CCl_4-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]
Insecticidal	Withanolide E was the major antifeedant against larvae of *Spodoptera littoralis*.[400]
Nutrition	Fresh fruits juice of wild and culivated plants were analyzed for nutritional value, and cultivated fruits contained more vitamin-C and β-carotene.[385]
Toxicity	Fresh fruit juice was administered to rats and a very detailed toxicity study

was performed. Results showed (entire body and organs) that it is not toxic.[401]

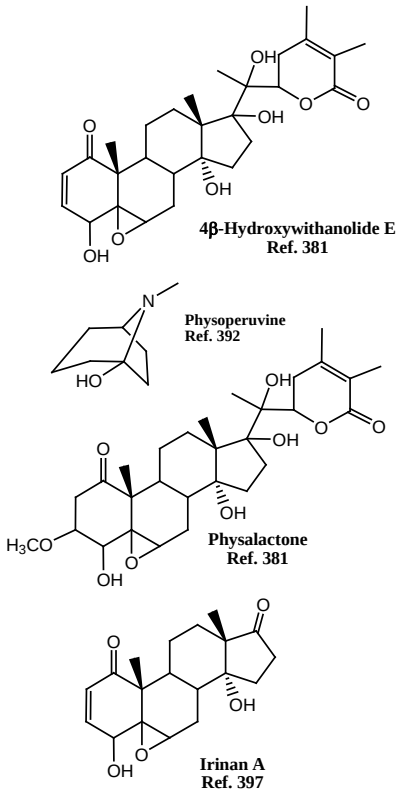


Figure 22. Selected natural products isolated from *Physalis peruviana.*

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 (*Zea mays*) 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 *Meloidogyne incognita* 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 analayzed, 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 (*Galba truncatula*). 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.

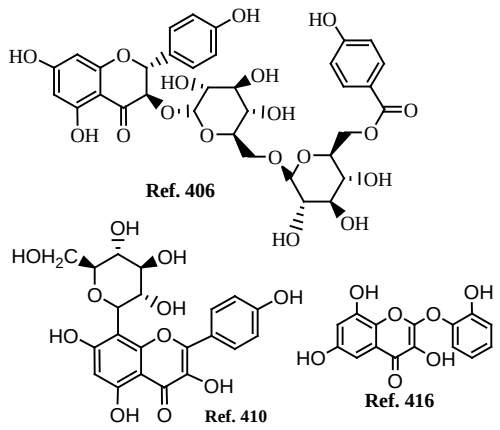


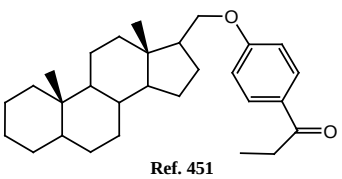
Figure 24. Selected natural products isolated from *Solanum elaeagnifolium.*

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 (*B. subtilis, S. aureus E. coli, K.pneumoniae, P. aeruginosa*).[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 bateria species.[420] A mixture of ripe and unripe fruit juice was prepared and diluted with water to prepare solutions with ten solutions, 10-100 μL/10 mL. 70 μL Was most effective against oral bacteria.[421] Fruits methanolic and aqueous extracts were prepared, diluted to a range of concentrations, and foud active against *S. aureus* 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 cholroform, each. All extracts were tested (10-20 %) against six microbial species. Methanolic extract of ripe fruit was most active and peroleum 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.

	Both nano particles found active against *P. erinaceus* and *E. coli*.[429]
Anticancer	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]
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]
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 deterined.[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 antinoceceptive activies, 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]
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 *Schistosoma mansoni*-infected mice.[441] Fresh fruits aqueous extract and found active against Chilli root knot nematodes (*Meloidogyne*).[442,f]
	Fresh fruit juice was diluted with water and was found active against cattle ticks larvae (*Rhipicephalus decoloratus*).[443] Fresh fruit juice was found active insecticidal against cabbage aphids (*Brevicoryne brassicae*).[444,f]
Nutrition	Nurtitional 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]
Toxicity	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, inappetance.[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]
Chemical composition	Analysis of 80 % aqueous methanolic extract of leaves and fruits, resulted the isolation and charcterization 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]

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.



Ref. 451

Figure 25. Struture 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 *S. typhi* and *S. aureus*.[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 activie 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 alklaloid 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 synergitically 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 gasrtic cancer by regulating lncNeat1_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, antihyperlipidimic, 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, H_2O_2).[467] Gold nanoparticles AuNP's were prepared using aqueous extract of leaves. AuNP's had strong antioxidant (DPPH, H_2O_2) 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] [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 galctose). 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 toxicated with ethanol resulting elavation 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-3β,12β-diol (Figure 26) along with other known natural products. Extract and isolated compounds inhibited LTC_4-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] Ethanoloc 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 acttivities.[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 componets. 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 CCl_4-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 nematicidal activity.[198] Plants were cultivated with growth promoters to produce high concentrantions 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 (*Dialerodus 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 accummulation, 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 ($HauCl_4$).[539] Growth of the plants and its production of different natural products, especially antioxidant enzymes, was tested under the effect of cadmium accummulation. The metal ions were accummulated 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 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]
Chemical composition and related activities	Changes in the concentration of glycoalkaloid solasonine according to growth steps.[459] Solanine A (Figure 26), a new natural product that was isolated from fruits along with other three new compounds: 7α-OH khasianine, 7α-OH solamargine and 7α-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-gycosides were isolated from fruits meathnolic extract.[563] Two new saponins, solanigroside Q and solanigroside 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]

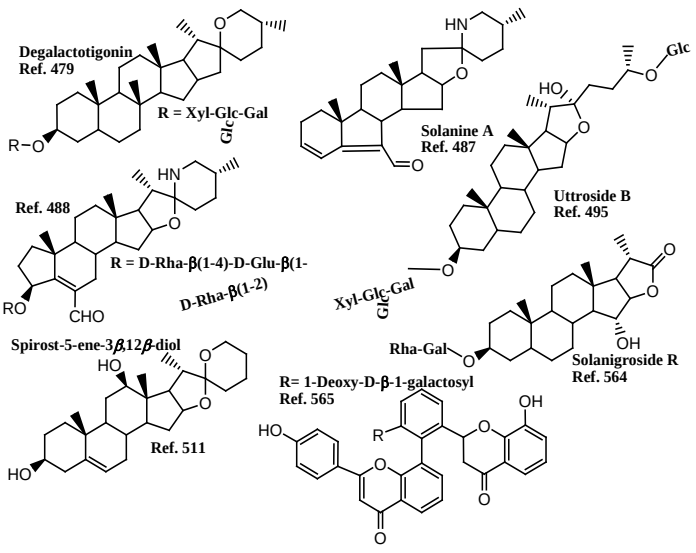


Figure 26. Structures of selected natural products isolated from *Solanum nigrum.*

Solanum villosum

Despite the very wide habitat of this plat, where it grows in the coldest and most rainiest areas (North) of the reviewed region, to the driest and most arid deserst 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, is very easy to distinguish both species: fruits of *S. villosum* are very red while fruits of *S. nigrum* are black. *S. villosum* was limitedy 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 frour 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 *n*-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 nanopartcles (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 actvity. 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, *Leptinotarsa decemlineata*, where methanol extract was most active. Among active compounds, *cis*-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 *Culex quinquefasciatus*. 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 *Stegomyia aegypti*. 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 *Anopheles subpictus*.[577]
Nanoparticles synthesis	Silver nanopartcles (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 nurtitional 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 *Cichorium intybus* seeds germonation. Alkaloid fraction was analyzed and detailed compostion and structures are reported (all known compounds).[235]

Antibacterial, antifunga, antiviral and related activities	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 *E. coli*.[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 Choornam) based of roots an leaves powder, was active gainst CHIKV virus in mice.[593]
Anticancer	Roots were extracted with water and extract was administered to patients with breast cancer with chemotherpay. 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 hepatocarcenoma 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 *in vitro* enhanced the activity of chemotherapy agent, cisplatin, in HT-29 colon cancer cells.[646]
Anticonvulsant	Stems and roots were extracted with ethanol and extracts showed positive results in treating seizures in duced 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]
Antidiabetic, anti-obesity and related activities	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 that 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]
Antioxidant, anti-inflammatory and related activities	Leaves aqueous extract was used to treat HepG2 hepatocarcenoma 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]
Brain related activities, aeging, addiction, stress, anxiety, memory, depression, neuroprotection,	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

Alzheimer, Parkinson, sleep	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 antiaxiety 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 antianxiety and antistress effects in healthy (physical and mental) humans.[608] Roots aqueous extract mixed with Ghee butter, was admistered 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 schezophrenia were treated with roots aqueous extract and positive antianxiety and antidepression results were recorded.[612] Commercial root extract (unkown solvent) was provided to patients with insomnia and anxiety, resulting 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 (*Drosophila melanogaster*) 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 hippo-campus through NO mediated modulation of corticosterone levels.[616] Whole plant (commerial powder) was extracted with water for proteins. Extract, along with scopolamine, were fed orally to rats resulting enhancement of learning and memory.[617] Commericial 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 inhiition of haloperidol-induced catalepsy in mice.[619] Root powder was orally fed to mice along with seed powder of *Mucuna pruriens*. 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 *Mucuna pruriens* were orally fed to mice. This resulted (several tests) in attenuation of paraquat (*N*,*N*′-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 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 [$(C_4H_6MnN_2S_4)_n$] 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 *in vitro* 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 acetylcholin-esterase 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 agaist

	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]
Cardioprotection, blood system, sport	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 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]
Enzyme inhibition activity	6-*n*-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 cholineesterase inhibition activity.[649]
Fertility, hormones, sexual functioning	Commercial leaves and roots was supplied to overweight male participants. No significat 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]
Nephroprotective	Root powder was supplemented to patients and it had significant diuretic activity.[647]
Antiparasitic	Whole plant aqueous extract was prepared and combined with whole plant extract of *Asparagus racemosus*. The combination was used to treat *Leishmania donovani*-infected mice. The results were positive and there was enhancement of the immune system of the animals.[655]
Nanoparticles, metal toxicity	Whole plant (or roots) was extracted with water (or MeOH) and extract redused $AgNO_3$ solution to prepare AgNP's.[583,584] Leaves aqueous extract had glioprotective effect *in vitro* (cells) and *in vivo* (rats) against Lead (lead

	nitrate) toxicity.[656]
Toxicity	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]
Chemical composition and related activities	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 plat. 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]

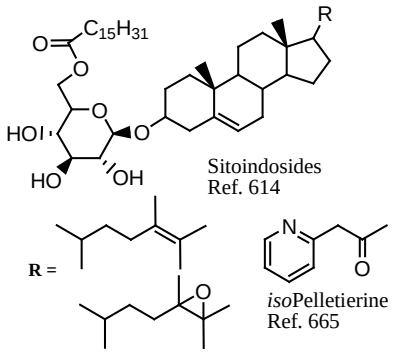


Figure 27. Strutures of selected natural products isolated from *Withania somnifera.*

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 direvatives 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 reprted 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 ($C_{15}H_{21}NO_4$), 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 intesting 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 resut, 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, repectively. 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, ptassium chloride, respectively).[676] In a closely related study, N. Panayotov and A. Popova investigated the effect of various culivation 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, $5Ca(NO_3)_2{\cdot}NH_4NO_3{\cdot}10H_2O$) 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.

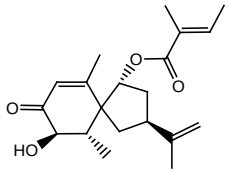
Table 20. Cultivation of *Solanaceae* plants for production of active compounds and/or properties.

Plant species	Cultivation conditions, results, reference
Datura innoxia	Hairy roots were infected with *A. rhizogenes* 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 miskae 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, $C_{14}H_{16}ClN_3O_2$). Total indole alkaloid, antioxidant phenolics and antioxidant enzymes contents, all were significantly increased.[684]
Datura stramonium	Hairy roots were infected with *A. rhizogenes* 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

	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 iirigation 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 $CaCl_2$,1:1 w/w), and supplied with nutrients $Ca(NO3)_2$, KCl, KH_2PO_4 and $MgSO_4$. Concent-rations 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 concentratios of material supply was needed and T= 25-30 °C, to achieve maximum yield of the alkaloid.[688]
Hyoscyamus albus	Plants were cultivated under Fe-ddeficiency 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 $CuSO_4$ and methyl jasmonate enhanced the production of three known phytoalexines and four new, which were isolated and characterized. One of them is presented in Figure 28.[690]
Hyoscyamus aureus	Twenty seven nutrients were used to cultivate plants for tropane alkaloids. Results were comapired with wild plant yiels, 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]
Hyoscyamus muticus	Seeds were collected from wild plants, sterilized and cultured with gibberellic acid, in 25 °C and high concentrations of NaCl. Contents of alkaloids, antioxidant 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]
Hyoscyamus reticulatus	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 *h6h* gene were increased.[695] Hairy roots were genetically modified *Agrobacterium rhizogenes* and supplied with iron oxide nanoparticles (FeO-NPs). Antioxidant enzyme activity and hyoscyamine and scopolamine production were significantly increased.[696]
Physalis angulata	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]
Physalis peruviana	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]
Solanum nigrum	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]
Solanum villosum	Plants were cultivated under 100 mM

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 unlear 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. Strutures 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-hysoscyamine 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*.

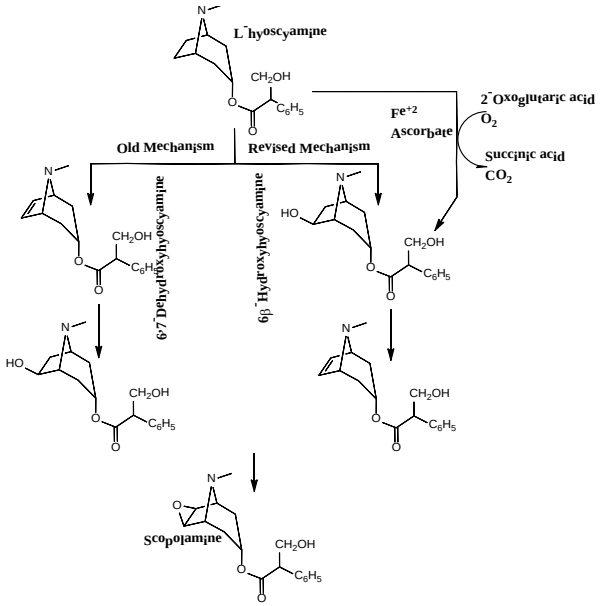


Figure 29. Mechanism of biosynthesis of scopolamine from L-hyoscyamine (Ref. 706).

They argue with older proposed mechanisms which state that L-hyoscaymine is dehydrogenated to 6,7-dehydrohyoscyamine, which is converted to scopolamine (see Figure 29). But by chemoenzymatic study, they prove that between L-hyoscaymine and 6,7-dehydrohyoscyamine, there is an intermediate: 6β-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-$^{13}C_2$]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 ^{13}C-NMR spectra of the three compounds was almost the same, 55 Hz.

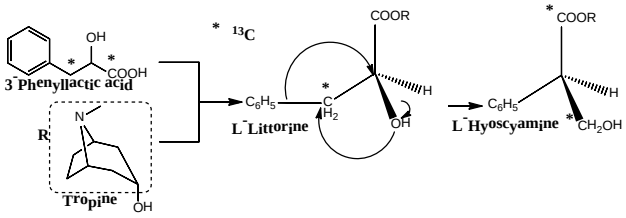


Figure 30. Part of the biosynthesis of Scopolamine (Ref. 707).

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 labled strating materials with ^{14}C and ^{13}C, 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 occurres 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.

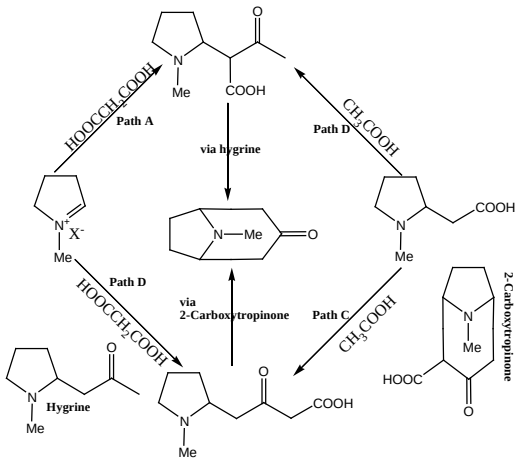


Figure 31. Proposed biosynthesis paths of tropinone (Ref. 708).

Researchers used a special method named protin-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 conclutions 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] The managed to achieve this by using asymmetric phase-transfer catalytic alkylation, as shown in figure 32.

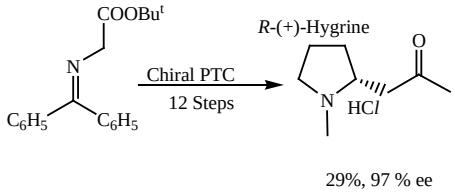


Figure 32. Synthesis of hygrine by J-H. Lee *et al*. (ref. 709).

The earliest synthesis of atropine was published by A. Landenburg in 1879.[710] Since then, this synthesis was published in several atricles. 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 (hyoscine) was published by P-A. Nocquet and T. Opatz.[712] But since it included many starting materials preperation reactions, and since the synthesis itself is of a very multiple step type, it will be very partial presentation if were introduce it here with one scheme figure. In our humble opinion, interested readers should use the original publication (ref. 712).

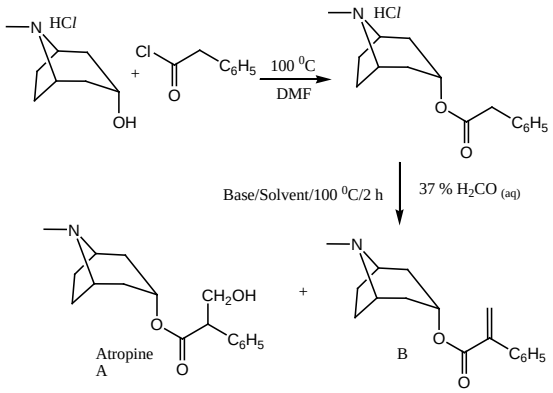


Figure 33. Continuous flow synthesis of atropine (ref. 711).

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 nueroprotection. 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.

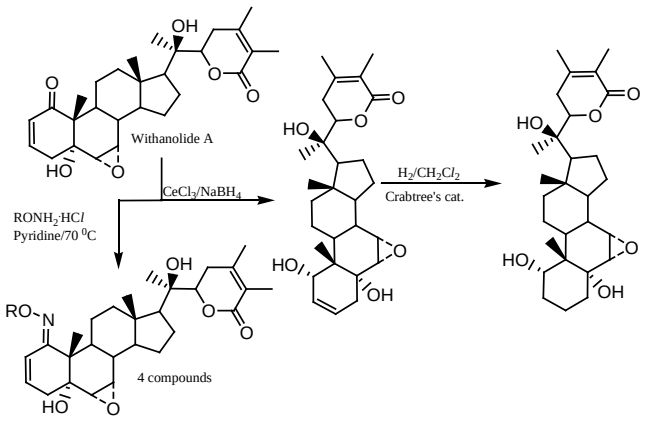


Figure 34. Withanolide A derivatives (ref. 719)

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

Since the biosynthesis of in hairy roots of *Solanaceae* plants involves also 6β-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).

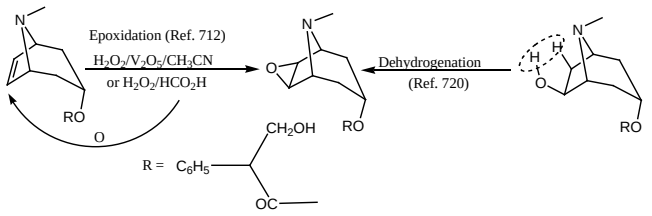


Figure 35. Biosynthesis vs. synthesis of scopolamine (ref. 720 and 712).

DISCUSSION

Finally, interested thiiranes (epoxide-like three membered ring of CSC) were prepared from epoxide moiety (C5-C6) of witholides.[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 reviewd 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 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 devide 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 concerened, 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 and 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 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 *Salanaceae* 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 wost types of this poisoning, is that can be caused by herbal teas (page 3 in article). Another dangerous poisoning

caused by these contamination, occurres 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 icludes, 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, toxicty, 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 trure, scopolamine or other alkaloid content in cultivated plats, 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. iinoxia* 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 endopythic 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 matabolites, 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 gainst 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 vermixocin 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 difficuly 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 CO_2 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 tese 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 have 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 fuits (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 *Solanaeae* 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 reviewd 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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Received: 29.04.2020.
Accepted: 04.06.2020.

ECO-FRIENDLY SYNTHESIS OF 1,2,4-TRIAZINE DERIVATIVES

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Keywords: Eco-friendly synthesis; 1,2,4-triazines; 1,8-diazabicyclo[5.4.0]undec-7-ene.

Eco-friendly synthesis of (*Z*)-3-alkyl-5-(benzylidene/substituted benzylidene)-2N-(carbothioamido)-6-oxo-1,2,5,6-tetrahydro-1-NH-1,2,4-triazine derivatives have been developed in 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as solvent without catalyst for 20-30 min at 60-65 ^{o}C with good yields.

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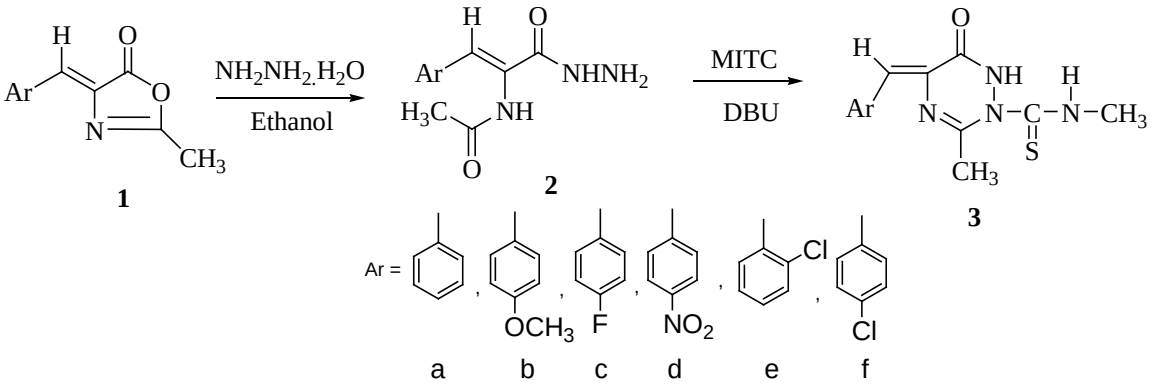
INTRODUCTION

1,2,4-Triazines are well known compounds. A large number of 1,2,4-triazine derivatives including 1,2,4-triazin-6-ones were reported in the literature discussing their special aspects in chemistry and medicine.[1-7] Interest in the biochemical properties of 1,2,4-triazines is high because some 3,5–disubstituted 1,2,4-triazines represent analogues of pyridine nucleobases and a number of antibiotics belong to pyrimido[5,4-*e*]1,2,4-triazine family. 1,2,4-Triazines are reported as both uncondensed and condensed systems. As reported in the literature, there are a large number of 1,2,4-triazines of uncondensed systems having substituent to the carbon atom or nitrogen atom exhibiting profound biological activities. 1,2,4-Triazin-6-ones have exhibited anticancer, antitumor, antibacterial and antifungal, antimicrobial, biological activities of cell lines cytotoxicity, antimalarials, antivirals and herbicides. 1,2,4-Triazine ring system is very significant for its applications as corrosion inhibitors, additives to photographic development baths, UV absorbers for textiles, plastic resins and papers and indicators for volumetric analysis of NH-acids in acetonitriles. The foregoing survey reveals that 1,2,4-triazin-6-ones are characterized by multifarious physiological activities and a scant information regarding synthetic methods is observed. In view of the importance associated with the structural motif, an attempt was made to develop a simple and facile synthesis of substituted 1,2,4-triazin-6-oxo derivatives with high yields, purities and simple processing methods from easily available ecofriendly chemicals. This investigation deals with simple and facile synthesis of (*Z*)-3-alkyl/aryl-5-(benzylidene/substituted benzylidene)-2-N-(carbothioamido)-6-oxo-1,2,5,6-tetrahyd-ro-1(NH)-1,2,4-triazine derivatives possessing different functional groups attached to triazine ring with a sole view to arrive a new heterocyclic system of high antibacterial activity.

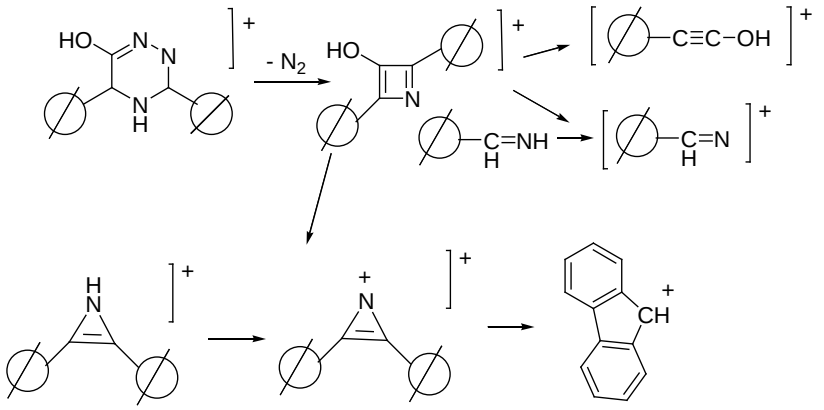
RESULTS AND DISCUSSION

The starting materials, 2-oxazolin-5-one derivatives (**1**) were synthesized from acetylglycine and different aromatic aldehydes in the presence of acetic anhydride and sodium acetate (Erlenmeyer's synthesis). The acetyl glycine is prepared from glycine and acetyl chloride. The corresponding 2-oxazolin-5-ones (**1**) were subjected to ring opening reaction with hydrazine hydrate in ethanol at room temperature to produce (*Z*)-N-[3-hydrazinyl-3-oxo-1-phenylprop-1-en-2-yl]acetamide **(2)**. The title compounds, (*Z*)-3-alkyl/phenyl-5-(benzylidene/substituted benzylidene)-2N-(carbothioamido)-6-oxo-1,2,5,6-tetrahydro-1-NH-1,2,4-triazine derivatives (**3a-f**) have been synthesized in a one pot reaction by cyclocondensation of (*Z*)-N-[3-hydrazinyl-3-oxo-1-phenylprop-1-en-2-yl]acetamides (**2a-f**) in the presence of methyl isothiocyanate (MITC) in DBU for 20-30 min at 60-65 ^{o}C followed by neutralization with CH_3COOH solution in good yields within a short time (Scheme 1).

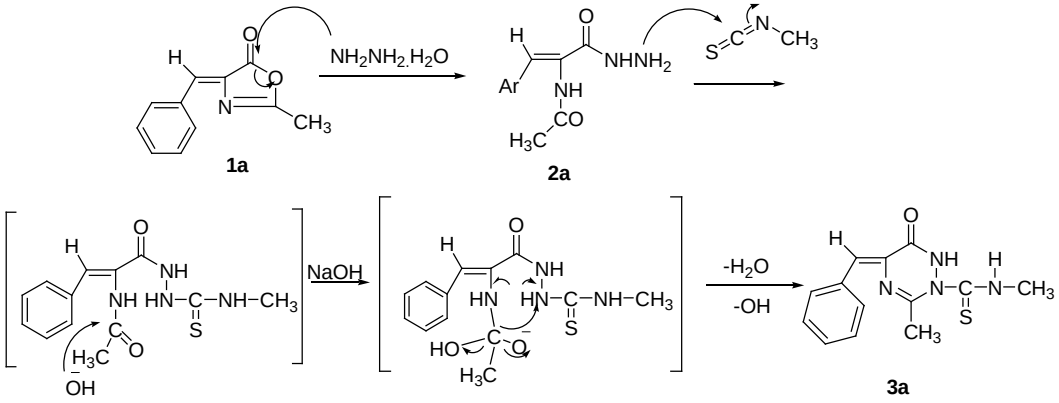
All isolated 1,2,4-triazin-6-one derivatives (**3a-3f)** are stable crystalline solids with high melting points whose structure has been established on the basis of spectral and analytical data. The appearance of NH absorptions at 3471 cm^{-1}, absence of stretching absorption peak for NH_2 at 3248 cm^{-1}, appearance of C=O absorption at 1714 cm^{-1} and C=S absorption at 1270 cm^{-1} in the IR spectrum of the compounds **3a** confirmed cyclocondensation of **2a** to produce 1,2,4-triazine-6-one derivative **3a**. The all 1,2,4-triazin-6-oxo derivatives were synthesized in moderate to good yields. The ^{1}H NMR spectra showed the appearance of signal at δ 2.1 and 2.6 indicate methyl protons of (C-CH_3) and (N-CH_3) groups, two trans olefinic protons were observed at 10.4 along with the signals for aromatic hydrogens at 7.8 and 8.4, signal at 6.8 and 7.4 indicate two –NH group which are D_2O exchangeable. ^{13}C NMR confirms the presence C=S group at δ = 177 and C-N linkage at 164 ppm for the title compound **3a**. The fragmentation of all the compounds follows the pattern as given in Scheme 2. It shows that the fragmentation starts with the loss of nitrogen. The IR, NMR and Mass spectral data of the compounds confirm the proposed structure of all the compounds as per the Scheme 2.



Scheme 1. Synthesis of **3a-3f.**



Scheme 2. Fragmentation pattern of compounds **3**.



Scheme 3. A plausible mechanism for the synthesis of **3a**.

Supposed mechanism

Though we have not done any investigation regarding the mechanism of the reaction, a speculative mechanism of the formation of 1,2,4-triazin-6-oxo-derivatives **3a-3f** has been postulated. Initially, nucleophilic addition of hydrazine hydrate to 4-(benzylidene-2-methyloxazolin-5-one (**1a)** produced (*Z*)-N-[3-hydrazinyl-3-oxo-1-phenylprop-1-en-2-yl]acetamide (**2a).** Treatment of **(2a)** with methyl isothiocyanate (MITC) yielded an unstable intermediate (Z)-N-[N^2–[thiouredo-3-hydrazinyl-3-oxo-1-phenylprop-1-en-2-yl]acetamide, which base hydrolysis produces the title compound (Z)-3-alkyl/phenyl-5-(benzylidene/substituted benzylidene)-2N-(carbothioamido)-6-oxo-1,2,5,6-tetrahydro-1-NH-1,2,4-triazine derivative **(3a)**. The hydroxyl ion of the base is nucleophilic and attacks the carbonyl carbon. The electron rich oxygen abstracts the protons from acidic amide groups resulting in elimination of water, followed by cyclisation as depicted in the Scheme 3.

The conversation of 4-(benzylidene-2-methyloxazolin-5-ones to the corresponding acetamides **2** is confirmed by spectral data. The IR spectra of **2a** showed the presence of NH-stretching absorptions for NH_2 and NH at 3574 and 3249 cm^{-1} and absence of stretching absorptions of lactone ring at 3444 $cm^{-1.}$ The ^1H NMR data showed doublet signal for NH_2 at δ 4.0, a singlet at δ 7.0 for NHCO, a triplet for NH-NH_2 at δ 8.4, and a singlet for NH-CO at δ 8.4 ppm

which are D_2O exchangeable. The mass spectrum of the compound confirms the molecular weight by appearance of M+ peak at *m/z* 119.

The cyclocondensation of **2** to **3** is confirmed by IR spectra showing the absence of N-H stretching absorptions of the amino group of hydrazine and presence of N-H stretching of amide group. The ^{1}H NMR spectra showed the disappearance of signals for NH_2 protons and appearance of D_2O exchangeable signals for NH-CH_3 and NH-N at δ 6.8 and 7.2 ppm, respectively. The ^{13}C NMR spectra of the compound **3a** showed signals for the presence of Ar, C=O, C=C, C-N, C=S and O-C at δ 24, 42, 149, 164 and 177 ppm, respectively. Finally, the mass spectrum of the compound **3a** confirms the molecular weight of the compound and the mass fragmentation pattern supports the structure of the title compound. All the 1,2,4-triazin-6-ones were synthesized with good yields and the structure was confirmed by elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and MS data.

Table 1. Synthesis of **2a-2f** from **1a** and hydrazine hydrate.

No.	Starting material	Product obtained	Time, min	Yield, %*	M.P., ^{0}C
1	**1a**	**2a**	60	80	154-156
2	**1b**	**2b**	60	80	175-179
3	**1c**	**2c**	65	78	208-210
4	**1d**	**2d**	60	80	220-222
5	**1e**	**2e**	70	75	212-214
6	**1f**	**2f**	60	80	> 220

***** Refers to yields of crude products only.

Table 2. Synthesis of **3a-3f** from **2a-2f** and MITC in DBU.

No.	Starting material	Product obtained	Time, min	Yield %,*	M.P., ^{0}C
1	**2a**	**3a**	20	84	> 220
2	**2b**	**3b**	25	84	> 220
3	**2c**	**3c**	23	80	> 220
4	**2d**	**3d**	24	84	212-214
5	**2e**	**3e**	25	79	> 220
6	**2f**	**3f**	30	85	191-193

EXPERIMENTAL

Melting points are uncorrected and taken in open capillary tubes in sulphuric acid bath. TLC was run on silica gel-G and visualization was done using UV light. IR spectra were recorded using Perkin – Elmer 1000 instrument in KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent using TMS as an internal standard with Bruker AM-400 spectrometer at 400 and 100 MHz respectively. Mass spectra were recorded on Agilent-LCMS instrument under CI conditions and given by Q+1 values only.

Preparation of 2a-2f

Starting compound **(1a-1l,** 10 mM) was added to hydrazine hydrate (15 mM) in EOH and stirred at room temperature for 30 min. The deep yellow colour of the solution changed to light yellow. Solid was separated, washed with H_2O (10 mL), dried and recrystallised from EtOH to afford **2a-2f.**

Preparation of 3a-3f

Equimolar quantities of **2a-2f** (10mM) and MITC (10mM) were mixed together in DBU (20 mL). The mixture was heated at 60-65 ^{o}C for 20-30 min. The completion of the reaction was checked by TLC. Om completion the reaction mixture was cooled to 20-30 ^{o}C and poured into ice-cold water (50 mL). A solid separated out, which was collected, washed with water (10 mL) and dried. The product was recrystallised from ethanol to obtain **3a-3f**.

(*Z*)-3-alkyl-5-(benzylidene/substituted benzylidene)-2N-(carbothioamido)-6-oxo-1,2,5,6-tetrahydro-1-NH-1,2,4-triazine derivatives (3a-3f)

3a: IR (KBr): 3471 (broad, -NH-N), 3084 (broad, -NH), 1714 (-C=O), 1270 (C=S) cm^{-1}. ^{1}H NMR (400 MHz, CDCl3/TMS) δ = 2.1 (s, 3H, C-CH_3), δ 2.6 (s, 3H, N-CH_3), δ 6.8 (s, 1H, -NH-CH_3) 7.4-8.4 (m, 6H, Ar-H and s, 2H, =CH-Ar), 10.6 (s, 1H, -NH). ^{13}C NMR ($CDCl_3$) δ = 24.66 (C-CH_3), 42.94 (N-CH_3), 116.79 (Ar-C=C), 120.14-137.69 (Ar), 147.79 (N-C-CH_3), 149.96 (Ar-C=C), 164.01 (C=S), 177. 70 (O=C-N). MS: *m/z* 239 (20 %), 260 (10 %), $M^{+\cdot}1$ = 275.

3b: IR (KBr): 3313 (broad, -NH-N), 3249 (broad, -NH) 1656 (-C=O), 1263 (C=S) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ = 2.2 (s, 3H, C-CH_3), δ 2.6 (s, 3H, N-CH_3), δ 3.0 (s, 3H, -CH_3), δ 6.8 (s, 1H, -NH) 7.2-8.3 (m, 5H, Ar-H and s, 2H, =CH-Ar), 10.6 (s, 1H, -NH). ^{13}C NMR ($CDCl_3$) δ = 23.62 (C-CH_3), 43.93 (N-CH_3), 53.93 (-OCH_3), 114.29 (Ar-C=C), 124.13-133.65 (Ar), 146.73 (N-C-CH_3), 149.94 (Ar-C=C), 163.31 (C=S), 176. 30 (O=C-N). MS: *m/z* 273 (10 %), $M^{+\cdot}1$ = 305.

3c: IR (KBr): 3445 (broad, -NH), 3051 (broad, -NH), 1724 (-C=O), 1280 (C=S) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ = 2.4 (s, 3H, C-CH_3), δ 2.8 (s, 3H, N-CH_3), δ 6.6 (s, 1H, -NH) 7.4-8.4 (m, 5H, Ar-H and s, 2H, =CH-Ar), 10.4 (s, 1H, -NH). ^{13}C NMR ($CDCl_3$) δ = 23.26 (C-CH_3), 42.24 (N-CH_3), 116.59 (Ar-C=C), 123.15-136. 69 (Ar), 144.49 (N-C-CH_3), 148.96 (Ar-C=C), 163.04 (C=S), 174. 60 (O=C-N). MS: *m/z* 239 (20 %), $M^{+\cdot}1$ = 293.

3d: IR (KBr): 3283 (broad, -NH), 3251 (broad, -NH), 1726 (-C=O), 1257 (C=S) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ = 1.8 (s, 3H, C-CH_3), δ 2.3 (s, 3H, N-CH_3), δ 6.6 (s, 1H, -NH) 7.4-8.4 (m, 5H, Ar-H and s, 2H, =CH-Ar), 10.2 (s, 1H, -NH). ^{13}C NMR ($CDCl_3$) δ = 23.63 (C-CH_3), 41.93 (N-CH_3), 115.39 (Ar-C=C), 121.13-136.62 (Ar), 146.74 (N-C-CH_3), 148.93 (Ar-C=C), 163.04 (C=S), 179.78 (O=C-N). MS: *m/z* 273 (10 %), $M^{+\cdot}1$ = 320

3e: IR (KBr): 3307 (broad, -NH), 3198 (broad, -NH) 1729 (-C=O), 1255 (C=S) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ = 1.8 (s, 3H, C-CH_3), δ 2.4 (s, 3H, N-CH_3), δ 6.6 (s, 1H, -NH) 7.4-8.4 (m, 5H, Ar-H and s, 2H, =CH-Ar), 10.2 (s, 1H, -NH). ^{13}C NMR ($CDCl_3$) δ = 23.26 (C-CH_3), 41.93 (N-CH_3), 113.29 (Ar-C=C), 121.24-135.66 (Ar), 146.76 (N-C-CH_3), 148.94 (Ar-C=C), 163.05 (C=S), 174. 60 (O=C-N). MS: $M^{+\cdot}1$ = 309

3f: IR (KBr): 3300 (broad, -NH), 3280 (broad, -NH), 1710 (-C=O), 1280 (C=S) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$/TMS) δ = 2.4 (s, 3H, C-CH_3), δ 2.6 (s, 3H, N-CH_3), δ 6.8 (s, 1H, -NH) 7.4-8.4 (m, 6H, Ar-H and s, 2H, =CH-Ar), 10.6 (s, 1H, -NH). ^{13}C NMR (CDCl3) δ = 23.56 (C-CH_3), 41.54 (N-CH_3), 114.69 (Ar-C=C), 122.24-137.65 (Ar), 146.69 (N-C-CH_3), 148.76 (Ar-C=C), 163.21 (C=S), 176. 40 (O=C-N). MS: $M^{+\cdot}1$ = 309.

CONCLUSION

Eco-friendly synthesis of compounds **3a-3f** has been developed with excellent yields, short time and easy work up process in 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as solvent without catalyst for 20-30 min at 60-65 ºC.

ACKNOWLEDGEMENT

Authors are very thankful to the authorities of Department of Chemistry, Institute of Aeronautical Engineering, Dundigal, Hyderabad for providing laboratory.

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Received: 17.05.2020.
Accepted: 08.06.2020

COVID-19: A GLOBAL PANDEMIC

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Keywords: COVID-19; global pandemic; corona; virus

The novel corona virus-2 (n-CoV-2) identified in the December 2019 which then spread worldwide has become pandemic in the form of Corona virus disease 2019 (COVID-19) and affected the health, economy and the medical system to a significant extent. As on date, around 8.20 million confirmed cases including death of around 443,815 have been reported. The present review deals with the history and origin of the COVID-19, its worldwide pandemic spread, symptoms and preventive measures as an attempt to create awareness of the fatal disease.

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INTRODUCTION

Corona viruses belong to a large family of viruses. Several types of corona viruses are known to cause respiratory infections like Severe Acute Respiratory Syndrome (SARS). Some of them cause the common cold in people; others infect animals, including bats, camels, and cattle. The past few decades have seen endemic outbreaks in the form of respiratory syndrome coronavirus (MERSCoV) and severe acute respiratory syndrome related coronavirus (SARS-CoV)[1,2] and now another the outbreak comes due to a new strain called the SARS-CoV-2 virus. The virus was firstly detected in Wuhan city of China, in December 2019 and has set off a global pandemic.[3]

The most recently discovered coronavirus causes coronavirus disease COVID-19 which is affecting people in different ways. Most of the infected people can develop mild to moderate illness and recover without hospitalization. The disease was named as COVID-19 after recommended by the World Health Organization (WHO). Crowded conditions can let viruses an easy spread. Sometimes the virus changes much faster and can start to infect and spread among people. As SARS-CoV-2 has spread both inside and outside China, it has infected people who had no direct contact with animals i.e. the virus is transmitted from human to human contact. It is now spreading worst in the U.S. and around the globe.

As on 16th June 2020, more than 8.20 million confirmed cases resulting in more than 443,815 deaths worldwide have been reported including at least 213 countries. The WHO has declared it a global health emergency at the end of January 2020.

The medical science, public health, economics and infrastructure of whole world have been challenged by the novel corona virus-2 (n-CoV or (COVID-19) pandemic outbreak. The International Committee on Taxonomy of Viruses renamed the virus SARS-CoV-2.[4] Coronavirus disease COVID-19 is an ongoing global health emergency.

SARS-CoV-2 is a rapid pandemic due to its highly contagious nature. As the number of cases continues to rise, there is no confirmed medication or vaccine available as on today. Hence the virus poses a threat to the public health. The COVID-19 pandemic is spreading across the globe at an alarming rate. It is more infectious and severe; hence the number of deaths as compared with SARS or MERS is very high.[5] Only isolation protocols to prevent further transmission can reduce its impact.

HISTORY AND ORIGIN

Corona viruses were firstly discovered in the 1930s when an acute respiratory infection of chickens caused by infectious bronchitis virus (IBV) was observed.[6] Arthur Schalk and M.C. Hawn described a new respiratory infection of chickens in 1931. In 1940s mouse hepatitis virus (MHV) and transmissible gastroenteritis virus (TGEV) were isolated.[7] Common cold virus B814 was discovered in the 1960s as Human corona viruses,[8-11] as it caused a common cold.

Later on, researchers found a group of similar human and animal viruses and named them after their crown-like appearance. The name "corona virus" was derived from Latin word *"corona"*, meaning "crown" by June Almeida and David Tyrrell who firstly observed and studied human coronaviruses.[12-15] In the same year research group at the National Institute of Health was able to isolate another member of this group of viruses using organ culture which was named as virus strain C43[16] and observed distinctive club-like spikes such as B814, 229E, and IBV with the electron microscope.[17,18] A new group of IBV-like viruses came to be known as corona viruses after its distinctive morphological appearance related to the mouse hepatitis virus.[19] A large number of animal corona viruses were identified since 1960s.[20]

Till 2002; corona virus was treated as simple non-fatal virus. Several cases of SARS caused by corona and their mortally found to be more than 1000 patient as reported in 2003. Four corona viruses namely HKU1, NL63, 229E and

OC43 have been in circulation in humans, and generally cause mild respiratory disease. In 2002-2003 when a β genera new corona virus origin in bats crossed over to humans *via* the intermediary host of palm civet cats in China. This β-genera new corona virus affected 8422 people mostly in China and Hong Kong as SARS and caused 916 deaths. World health organization (WHO) and centers for disease control and prevention declared as state emergency in 2004. In 2012, several infected patients and deaths were found in Saudi Arabian reports.[21-25] In 2012, due to the Middle East respiratory syndrome coronavirus (MERS-CoV), which was also of bat origin emerged with dromedary camels as the intermediate host; affected 2494 people and caused 858 deaths. A novel SARS coronaviruses in 2003[26] resulting in the detection of number of novel corona viruses in humans, animals and wildlife.[27-29]

Chu DK *et. al* described that animals are the natural reservoirs of the viruses as corona viruses found in bat and avian species.[30,31] Other human corona viruses have since been identified, including SARS-CoV in 2003, HCoV NL63 in 2004, HCoV HKU1 in 2005, MERS-CoV in 2012, and SARS-CoV-2 in 2019.[32,33] COVID-19 was first identified and isolated from pneumonia patent in the Wuhan city of China.[34,35]

Experts say SARS-CoV-2 originated in bats like that the corona viruses behind MERS and SARS started through animals. The epicenter of this ongoing outbreak is in the city of Wuhan in Hubei Province of central China and the Huanan seafood wholesale market was thought to be at least one of the places where SARS-CoV-2 from an unknown animal source might have crossed the species barrier to infect human. In the Wuhan's wet seafood market, a few customers buying fresh meat and fish, including animals were killed on the spot. The first concrete evidence for human-to-human transmission of SARS-CoV-2 was reported by a group of clinicians and scientists from the University of Hong Kong.[36]

MICROBIOLOGY OF SARS-COV-2

Coronaviruses (family *Coronaviridae*, subfamily *Coronavirinae*) are important pathogens of bird and mammal origin. Corona viruses are positive-sense RNA viruses and are currently classified into four genera:[37]

1) α-coronavirus

2) β-coronavirus

3) γ-coronavirus and

4) δ-coronavirus

α-coronaviruses and β-coronaviruses are found exclusively in mammals, whereas γ-coronaviruses and δ-corona viruses primarily infect the birds.

SARS-CoV-2 is a spherical or pleomorphic enveloped particles containing single-stranded positive-sense. Virus of zoonotic origin is ranging from 60 to 140 nm in diameter associated with a nucleoprotein within a capsid comprised of matrix protein. Spike like projections on its surface afford it a crown like appearance under the electron microscope; hence named as corona-virus. SARS CoV-2 contains four structural proteins, namely envelope (E), spike (S), membrane (M), and nucleocapsid (N). S, M, and E proteins together form the envelope of the virus and are involved in replication of genetic material. N proteins remain associated with the RNA forming a nucleocapsid inside the envelope. Polymers of S proteins remain embedded in the envelope giving it a crown-like appearance.[38-41]

These viruses are intracellular parasites with lack of their own metabolism and require a host to replicate i.e it is not living. Viruses are nanostructures, typically comprised of proteins, genetic material, and often lipid membrane. Their outer lipid membranes are stable and comprised of fatty acids with hydrophobic interactions between chains.

SPREAD OF COVID-19

In December 2019, adults in Wuhan, capital city of Hubei province local hospitals with sevier pneumonia of unknown cause emerged. On December 31st 2019, China notified the outbreak to the WHO and the virus was identified as a Corona-virus.

However, there is no evidence so far that the origin of SARS-CoV-2 was from the seafood market or anywhere else. Rather, bats are the natural reservoirs of a wide variety of CoVs, including SARS-CoV-like and MERS CoV viruses.[42-44] Environmental samples from the Huanan sea food market were also tested positive, signifying that the virus originated from this place.[45] The number of cases started increasing exponentially, that human-to-human transmission was occurring and the disease went on spreading.[46,47]

COVID-19 was analyzed by virus genome sequencing throughout the genome to Bat CoV RaTG13 and showed 96.2 % overall genome sequence identity,[48] suggesting that bat SARS-CoV-2 might share the same ancestor. Similar residues of receptor were observed in many species by phylogenetic analysis[49] suggesting the possibility of alternative intermediate hosts, such as turtles, pangolin and snakes.

Large droplets generated during coughing and sneezing by symptomatic patients are transmitted rapidly from person to person. It becomes more dangerous as in the form of transmission through asymptomatic people before onset of symptoms.[50] The virus can remain viable on surfaces for several days in favorable atmospheric conditions. Infection is acquired either by inhalation of these droplets or touching surfaces contaminated by them or then touching the nose, mouth and eyes. Transmission of SARS-CoV-2 occurs mainly between family members, relatives and friends who comes in contact with patients or incubation carriers.

SYMPTOMS, TRANSMISSION AND PREVENTATION

Close contact between individuals can also result in transmission.[51] This also indicates possible transmission in closed spaces due to elevated aerosol concentrations has a basic multiplying number of SARS-CoV-2 is 2.2. This

suggests that a patient can transmit the infection to two other individuals. Current data suggests that the virus has an incubation period of three to seven days.[52] COVID-19 virus can survive for up to 72 hours on plastic and stainless steel, less than 4 hours on copper and less than 24 hours on cardboard.

Symptoms of COVID-19 may appear in few days i.e. in 2 days or as long as 14 days. The most common symptoms of COVID-19 are fever or chills, dry cough, shortness of breath or difficulty in breathing, loss of taste or smell, sore throat and tiredness. Other symptoms those are less common and may affect some patients include nasal congestion, headache, conjunctivitis, diarrhea, nausea or vomiting, rashes on skin or discoloration of fingers or toes. People associated with difficulty in breathing/shortness of breath, chest pain/pressure, or loss of speech or movement should seek medical attention immediately and self-isolation and monitoring of their symptoms.

Two kinds of tests are available for COVID-19:

A viral test for current infection: It includes analysis of swabs of the inside of the nose to check the possible infection with SARS-CoV-2, or not that causes COVID-19.

An antibody test for previous infection: It includes blood check by looking for antibodies, which indicate that, is there was a past infection with the virus. For current infection, antibody test was not be used because it can take 1-3 weeks after infection to make antibodies.

The disease spreads primarily from person to person through small droplets from the nose or mouth, which are expelled when a person with COVID-19 coughs, sneezes, or speaks. These droplets are relatively heavy, do not travel far and quickly sink to the ground. People can catch COVID-19 if they breathe in these droplets from a person infected with the virus. This is why it is important to stay at least 1 meter away from others. These droplets can land on objects and surfaces around the person such as tables, doorknobs and handrails. People can become infected by touching these objects or surfaces, followed by touching their eyes, nose or mouth. Thus it is important to wash your hands regularly with soap and water or clean with alcohol-based hand rub. When we wash our hands with soap these hydrophobic interactions are disrupted and the lipid membrane is dissolved, destroying or deactivating the virus. It is not possible to use soap as an internal treatment because it also destroy our own cells. Following precautions have been suggested for protection from COVID-19……

Clean your hands regularly and thoroughly with soap and water for at least 30 seconds. Use a hand sanitizer that contains at least 70 % ethyl or isopropyl alcohol which kills viruses ($\log_{10}$ is ~4.0 for various corona virus strains)[60,61] Various household or medical disinfectant/cleaning agents including povidone iodide, dimethyldidecylammonium salts, and polyhexanide and their combinations or oxidative/lipid-dissolving agents like hydrogen peroxide, sodium hypochlorite or household washing up agents containing alkyldimethylamine N-oxides and other surfactants were found to effective against enveloped viruses, but the resistivity of various types of corona viruses are different and the contact time needs for reaching completeness of the disinfection process varies in a wide range, the details can be found in the refs.[60,61]

Practicing hand and respiratory hygiene is important at all times. Maintain at least a two meter (2 m) distance between yourself and others, so as to prevent from small liquid droplets from nose or mouth which may contain virus. Avoid touching your eyes, nose, and mouth with unwashed hands because contaminated hands can transfer the virus to your eyes, nose or mouth.

Cover your mouth and nose with a cloth face cover, wear a mask if possible. Cover your mouth and nose with a tissue paper when you cough or sneeze.

Avoid going to crowded places. Stay home and self-isolate.

Clean and disinfect frequently touched surfaces daily**.**

Avoid public transportation.

Take your temperature if symptoms develop. Be in touch with your doctors.

STATISTICS OF COVID-19

The **COVID-19** a worldwide pandemic of corona virus disease 2019 caused by the SARS-CoV-2 virus. The Epidemic Diseases Act, 1897 invoked in many countries declared it an epidemic due to significant outbreak of COVID-19. Educational institutions and many commercial establishments have been shut down worldwide. As on 16th Jun 2020, more than **8,207,780** confirmed cases including more than **443,815** deaths have been reported worldwide, affecting at least 213 countries (Figure 1 and 2). The WHO has declared this a global health emergency at the end of January 2020.

India currently has the fourth largest number of confirmed cases in Asia with the number of cases 354,161 on 16th June 2020 including more than 11,921 deaths. India observed a 24-hour voluntary public curfew on 22 March 2020 at the instance of the Prime Minister Narendra Modi. Further, the government ordered a nationwide lockdown for 21 days, extended the ongoing nationwide lockdown till 3 May. 1 May, lockdown across the country was further extended till 30 May and afterward till 30 June 2020 with some conditions. Oxford COVID-19 Government Response Tracker (OxCGRT), in its report based on data from 73 countries, reports that the Indian Government has responded more stringently than other countries in tackling the pandemic.The death rate is highest in US and that of India is 2.80% is quit less than other countries.

VACCINE AND TREATMENT

Currently, no vaccine is available to prevent COVID-19. Antibiotics only work on bacterial infections and do not work against viruses.

Use of antibiotics only prevents or treats secondary bacterial infections in severely ill COVID-19 patients. Current treatment strategies are aimed at symptomatic care and oxygen therapy. Prophylactic vaccination is required for the future prevention of CoV-related epidemic or pandemic.[53,54]

Intense global R&D activity has been forced to develop a vaccine against the disease after the genetic sequence of SARS- CoV-2. COVID-19 pandemic is driving evaluation of next generation vaccine. The humanitarian and economic impact of the COVID-19 accelerates the development of vaccine. The first COVID-19 vaccine entered human clinical testing on 16th March 2020 and multiple platforms are under development. Vaccine development is a lengthy and expensive process. Attrition is high, and it typically takes multiple candidates and many years to produce a licensed vaccine. Coronavirus vaccine developed by Oxford University began human safety trials and at the same time an Indian company Serum Institute of India has started to work on making the vaccine locally so as to be ready in case the trial succeeds. This is the sixth coronavirus vaccine to enter the first phase of clinical trials. In this vaccine a gene may be inserted for an important protein of the virus which can lead to build immunity in patients.

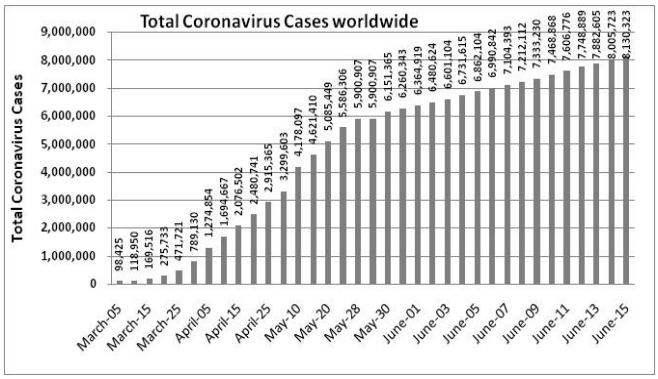

Figure 1. Total coronavirus cases in worldwide

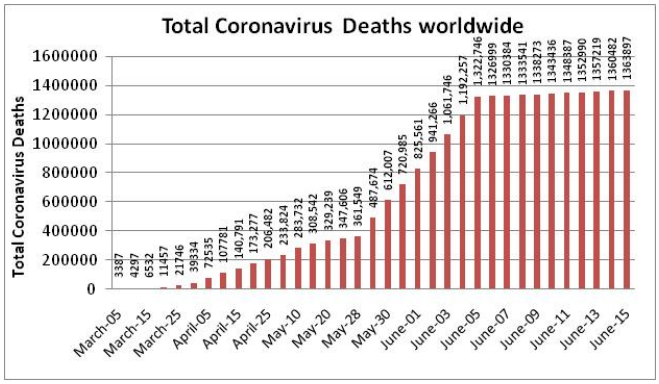

Figure-2. Total coronavirus death in worldwide

Chen from the Beijing Institute of Biotechnology describes that virus which infects human cells delivers genetic material those codes for the SARS-CoV-2 spike protein into the cells. These cells then produce the spike protein and travel to the lymph nodes where they create antibodies by immune system. Antibodies recognize the spike protein and fight off the coronavirus. Vaccine produces virus-specific antibodies and T cells within 14 days.[55]

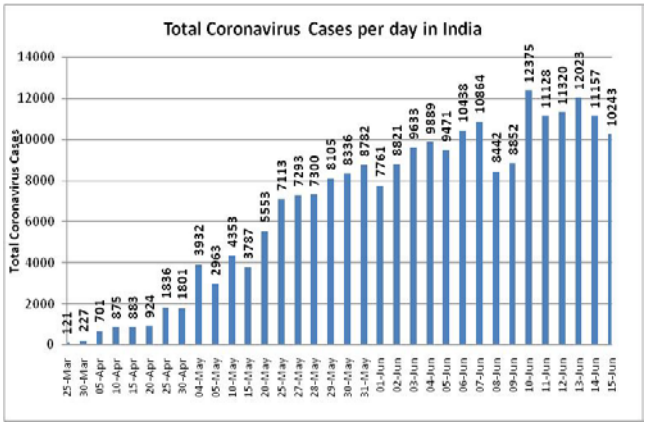

Figure 3. Total coronavirus cases in India /day

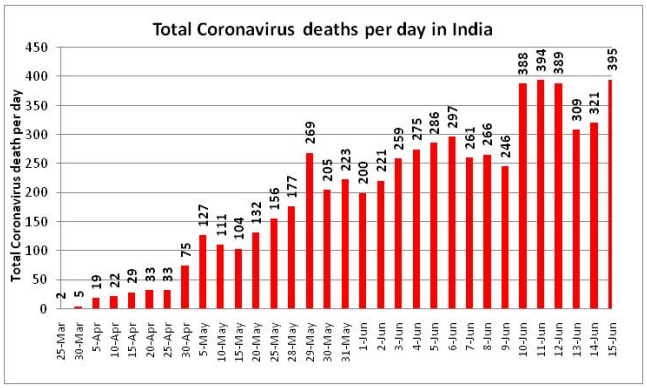

Figure 4. Total coronavirus death in India/day

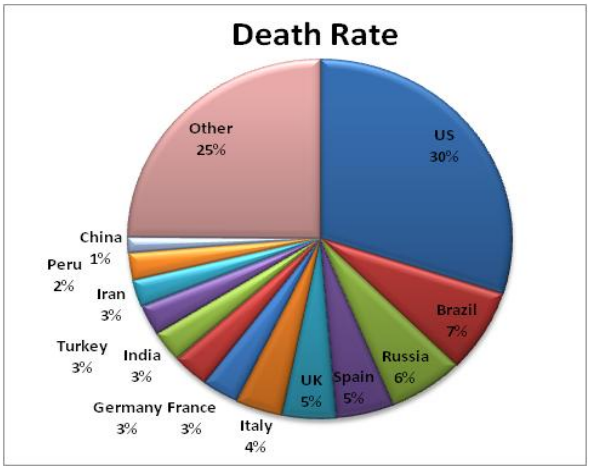

Figure 5. Death rate due to COVID-19

Vaccine of Moderna has already entered clinical trials in the US with mRNA platform. A similar technology is being used for vaccination of other infectious diseases. Promising immune response to the coronavirus in animals, clinical trials for its anti-COVID-19 vaccine by US-based vaccine maker Inovio is also under progress. US drug giant Pfizer has made a funding to vaccine maker BioNTech for developing its mRNA vaccine, expected to go on human trials.

Drug maker J&J, and USA's Biomedical Advanced Research and Development Authority (BARDA) are also started to develop the vaccine, will work on the same platform and technology which was used for developing the vaccine for Ebola.

The Department of Biotechnology, Council of Scientific and Industrial Research and ICMR are working on developing a vaccine for COVID-19. The vaccine development is being supported by three Indian industries. Research on therapeutic and drug development has started. Rising Pharma, the US partner of Hyderabad-based Laurus Labs, in collaborative agreement with the Division of Infectious Disease and International Medicine at the University of Minnesota on a clinical trial exploring hydroxychloroquine as a preventive treatment. France is expecting preliminary results in two weeks from a clinical test of hydroxychloroquine and three other drugs remdesivir, lopinavir and ritonavir in combination.

A broad-spectrum antiviral, similar to broadspectrum antibiotics, would rapidly treat newly emerging viral outbreaks [56]. There are two main approaches for treatment of viruses to antivirals, intracellular and extracellular. Intracellular antivirals are drugs which designed to inhibit the intracellular replication of viruses. Remdesivir is a promising candidate for treating SARS-CoV-2, which was originally developed for Ebola[57] and for HIV[58,59] in ritonavir and lopinavir combination.

CONCLUSION

In summary, COVID-19 has turned a fatal disease worldwide. The number of active cases and deaths due to the disease are continuously increasing day by day across the entire world. To face the pandemic, the world has utilized a range of measures and although each country has their own approach, included periods of self-isolation or quarantine and lockdown for control the spread of virus. Many crossovers with chemistry and materials are ready to be exploited problem of viruses, but no perfect drug or vaccine exists as on today. Taking own precaution seems to be a better solution in the present scenario.

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Received: 07.06. 2020
Accepted: 17.06. 2020.

ABRAHAM SOLVATION PARAMETER MODEL: PREDICTION OF ENTHALPIES OF VAPORIZATION AND SUBLIMATION OF MONO-METHYL BRANCHED ALKANES USING MEASURED GAS CHROMATOGRAPHIC DATA

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Keywords: Chromatographic retention indices; Abraham model; solute descriptors; enthalpy of vaporization; enthalpy of sublimation.

Abraham model L solute descriptors have been determined for 174 additional mono-methyl branched alkanes based on published linear-programmed gas chromatographic retention indices. Standard molar enthalpies of vaporization and sublimation at 298 K are calculated for the 174 mono-methylated alkanes using the reported solute descriptors and our recently published Abraham model correlations. Calculated vaporization and sublimation enthalpies derived from the Abraham model compare very favourably with values based on a popular atom-group additivity model. Unlike the additivity model the Abraham model gives different predicted values for each mono-methyl alkane having a given C_nH_{2n+2} molecular formula.

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INTRODUCTION

Gas-liquid chromatographic measurements[1-10] have been used in the indirect determination of both standard molar enthalpies of vaporization, $\Delta H_{vap,298K}$, and standard molar enthalpies of sublimation, $\Delta H_{sub,298K}$, of organic compounds at 298 K. For example, Hamilton[1] determined the $\Delta H_{vap,298K}$ of eleven herbicide esters based on experimental gas chromatographic retention volumes, V_g, measured on a nonpolar SE-30 stationary phase. The method assumed that the ratio of the enthalpy of vaporization of each herbicide ester to that of the reference compound (which in this case was dibutyl phthalate) was independent of temperature. The $\Delta H_{vap,298K}$ of each individual ester herbicide was calculated from the slope of the graph of $ln(V_{g,ester}/V_{g,reference})$ versus the natural logarithm of the vapor pressure of the reference compound at the column temperature T, $ln\ P_{reference,T}$, in accordance to Eqn. (1).

$$ln\left(\frac{V_{g,ester}}{V_{g,reference}}\right) = \left[1 - \frac{\Delta H_{vap,ester,298K}}{\Delta H_{vap,reference,298K}}\right] ln\ P_{reference,T} + C \quad (1)$$

Peacock and Fuchs[2-4] developed a method for determining $\Delta H_{vap,298K}$ based on solution calorimetric measurements of liquid organic compounds being dissolved in the stationary phase solvent. The enthalpy of vaporization was calculated as the difference in the measured enthalpy of solution of the organic liquid, $\Delta H_{soln,298K}$, minus the chromatographically-measured enthalpy of solution of the gaseous compound in the stationary phase liquid. The later value was determined from the variation in the compound's retention volumes with temperature, and then corrected back to 298 K using liquid-phase and gas-phase heat capacities.

Chickos and coworkers[5] proposed a method for determination of $\Delta H_{vap,298K}$ based on linear plots of the chromatographically-measured ΔH_{soln} values of gaseous reference compounds in the liquid stationary phase versus the compounds' known $\Delta H_{vap,298K}$ values. Enthalpies of vaporization of additional compounds can then be calculated from the linear mathematical relationship established by the reference compounds. The authors demonstrated the applicability of their method using 102 hydrocarbon and mono-functional hydrocarbon derivatives. Enthalpies of vaporization based on the authors' method differed from published literature values by a standard deviation of 1.27 kJ mol^{-1}. The method was later extended to the determination of $\Delta H_{sub,298K}$ by combining $\Delta H_{vap,298K}$ values measured by correlation gas chromatography with calorimetric enthalpy of fusion, $\Delta H_{fus,298K}$, adjusted to 298 K.[6] Numerical values of $\Delta H_{vap,298K}$ and $\Delta H_{sub,298K}$ determined in this fashion depend on the reference compounds used in establishing the ΔH_{soln} versus $\Delta H_{vap,298K}$ mathematical correlation.

Our method of obtaining $\Delta H_{vap,298K}$ and $\Delta H_{sub,298K}$ values is more of a computational method that uses gas chromatographic retention data to calculate Abraham model solute descriptors. Once calculated, the numerical values of the solute descriptors are then used in conjugation with our published Abraham model correlations[11,12] to calculate the desired $\Delta H_{vap,298K}$ and $\Delta H_{sub,298K}$ values of organic, organometallic and inorganic compounds. The Abraham solvation parameter model is among the most widely used linear free energy relationship in the prediction of solute properties having chemical and biological significance. To

date predictive mathematical correlations have been reported for describing solute transfer into more than 130 different organic nonelectrolyte mono-solvents[13-19] and into more than 100 different ionic liquid solvents.[20-29] Mathematical correlations have also been developed for predicting enthalpies of solvation of organic vapors and inorganic gases into water and 35 common organic solvents[30-40] blood-to-body tissues/fluids partition coefficients,[41-45] lethal median concentrations of organic compounds towards fish and other aquatic organisms,[46-49] nasal pungency,[50-53] eye irritation thresholds and Draize eye scores,[53-55] and many other solute properties.[56-61] More recently the Abraham model has been extended to predicting enthalpies of vaporization[11] and sublimation[12] and the vapor pressure of organic and organometallic compounds.[62]

In the present communication we illustrate the application of the Abraham solvation parameter model in predicting $\Delta H_{vap,298K}$ and $\Delta H_{sub,298K}$ values. First, we calculate the Abraham model solute descriptors of mono-methyl branched alkanes from published gas chromatographic retention indices of Krkosova and co-workers.[63] Once calculated, the solute descriptors will be substituted into our previously published Abraham model correlations.[11,12]

$$\Delta H_{vap,298K}\ (\text{kJ mol}^{-1}) = 6.100 - 7.363\ \boldsymbol{E} + 9.733\ \boldsymbol{S} + 4.025\ \boldsymbol{A} + 2.123\ \boldsymbol{B} + 9.537\ \boldsymbol{L} - 1.180\ \boldsymbol{S \cdot S} + 77.871\ \boldsymbol{A \cdot B} - 5.781\ \boldsymbol{I}_{\text{amine}} - 14.783\ \boldsymbol{I}_{\text{non-}\alpha,\omega\text{-diol}} - 17.873\ \boldsymbol{I}_{\alpha,\omega\text{-diol}} \quad (2)$$

(N = 703, SD = 2.09, R^2 = 0.986, F = 4925.6) and

$$\Delta H_{sub,298K}\ (\text{kJ mol}^{-1}) = 13.93 - 16.90\ \boldsymbol{E} + 9.66\ \boldsymbol{S} + 10.02\ \boldsymbol{A} + 1.82\ \boldsymbol{B} + 13.57\ \boldsymbol{L} - 0.30\ \boldsymbol{S \cdot S} + 35.43\ \boldsymbol{A \cdot B} - 0.05\ \boldsymbol{L \cdot L} - 9.09\ \boldsymbol{I}_{\text{OH,adj}} + 17.26\ \boldsymbol{I}_{\text{OH,non}} + 7.37\ \boldsymbol{I}_{\text{NH}} \quad (3)$$

(N = 864, SD = 9.94, R^2 = 0.867, F = 503.2)

Thus enabling the estimation of $\Delta H_{vap,298K}$ and $\Delta H_{sub,298K}$ values for those compounds for which solute descriptors are known. Solute descriptors are identified in Eqns. 2 and 3 by the capitalized alphabetical characters, and are defined as follows: the solute excess molar refractivity expressed in units of (cm^3 mol^{-1}) / 10(***E***); the solute dipolarity/polarizability (***S***); the overall or summation hydrogen-bond acidity and basicity (***A*** and ***B***, respectively); and the logarithm of the gas-to-hexadecane partition coefficient at 298 K (***L***). Both Abraham model correlations use indicator variables ($\boldsymbol{I}_{\text{amine}}$, $\boldsymbol{I}_{\text{NH}}$, $\boldsymbol{I}_{\text{non-}\alpha\omega\text{-diol}}$, $\boldsymbol{I}_{\alpha\omega\text{-diol}}$, $\boldsymbol{I}_{\text{OH,adj}}$, $\boldsymbol{I}_{\text{OH,non}}$) to improve the predictions or organic compounds having amino- and more than one hydroxy-functional group. Mono-methylalkanes do not contain either of these functional groups, so no further discussion of indicator variables is needed. The two mathematical correlations were developed based on $\Delta H_{vap,298K}$ and $\Delta H_{sub,298K}$ values for N = 703 and N = 864 compounds, respectively. As indicated by the standard deviation (SD), squared correlations coefficient (R^2), and Fisher F-statistic (F), both Abraham model correlations provide reasonably accurate mathematical correlations of the $\Delta H_{vap,298K}$ and $\Delta H_{sub,298K}$ data for wide range of organic compounds.

Several earlier publications have illustrated the calculation of Abraham model solute descriptors from either liquid-liquid partition coefficients,[64] or high-performance liquid chromatographic retention data,[65] or in the case of crystalline nonelectrolyte compounds from saturation solubilities.[66-70] The latter papers primarily focused on using the calculated solute descriptors to select organic solvents for recrystallization and/or biphasic partitioning systems for liquid extraction. The intended audience of the solubility studies were chemical engineers and industrial working in the chemical manufacturing sector. Recrystallizations and liquid extractions are commonly used purification methods in chemical syntheses. A more recent publication[71] reported Abraham solute descriptors of terpene esters determined from gas-liquid chromatographic retention data of solutes eluted on several stationary phase liquids. Here the application was to predict the human odor thresholds of the terpene esters. Solute descriptors of terpene hydrocarbons[72] had been reported previously. There was very little information in the afore-mentioned studies that would attract the attention of chemical thermodynamic experts or computation chemists, which is the intended audience of the current communication. The calculated solute descriptors of mono-methyl branched alkanes will be used to predict thermodynamic properties, namely $\Delta H_{vap,298K}$ and $\Delta H_{sub,298K}$ values. These thermodynamic quantities are required in the calculation of gas-phase standard molar enthalpies of formation from measured enthalpies of combustion, and in describing how the vapour pressure of a compound varies with temperature. Such information is also needed by individuals working in the chemical manufacturing sector.

CALCULATION OF ABRHAM MODEL SOLUTE DESCRIPTORS

Determination of solute descriptors generally involves constructing a series of Abraham model correlations that involve solute transfer between two condensed phases (Eqn. 4) or solute transfer from the gas phase into a condensed phase (Eqn. 5).

$$\text{Solute property} = c_p + e_p \cdot \boldsymbol{E} + s_p \cdot \boldsymbol{S} + a_p \cdot \boldsymbol{A} + b_p \cdot \boldsymbol{B} + v_p \cdot \boldsymbol{V} \quad (4)$$

$$\text{Solute property} = c_k + e_k \cdot \boldsymbol{E} + s_k \cdot \boldsymbol{S} + a_k \cdot \boldsymbol{A} + b_k \cdot \boldsymbol{B} + l_k \cdot \boldsymbol{L} \quad (5)$$

Solute properties used in these computations have included the logarithms of partition coefficients, logarithms of molar solubility ratios, logarithms of chromatographic retention factors, and chromatographic retention indices. Two of the solute descriptors, ***E*** and ***V*** (McGowan volume), can be reasonably estimated from the solute's molecular structure. For solutes that lack an acidic hydrogen capable of hydrogen-bond formation, the ***A*** solute descriptor can be set equal to zero. This leaves either four solute descriptors (***S, A, B*** and ***L***) or three solute descriptors (***S, B*** and ***L***) to be determined from the Abraham model correlations from the measured solute properties.

The numerical values of c_p, e_p, s_p, a_p, b_p, v_p, c_k, e_k, s_k, a_k, b_k, and l_k in Eqns. 4 and 5 are known as the solute properties are measured in systems having known values of solvent/process coefficients. The set of Abraham model equations are then solved simultaneously to yield numerical descriptor values for the given solute molecule.

In the case of mono-methyl branched alkane solutes the computation is greatly simplified as $\boldsymbol{E} = 0$, $\boldsymbol{S} = 0$, $\boldsymbol{A} = 0$ and $\boldsymbol{B} = 0$. Mono-methyl branched alkane solutes possess no excess molar refraction ($\boldsymbol{E} = 0$) or polarity/polarizability ($\boldsymbol{S} = 0$), and are not capable of hydrogen-bond formation ($\boldsymbol{A} = 0$ and $\boldsymbol{B} = 0$) with surrounding solvent molecules. Only the $\boldsymbol{L}$ solute descriptor remains to be calculated. We calculate the $\boldsymbol{L}$ solute descriptor of the mono-methyl branched alkanes by first establishing a linear relationship between the measured temperature-programmed linear retention indices, *RI*, and the $\boldsymbol{L}$ solute descriptor based on the values for the n-alkanes and 22 of the 196 compounds studied by Krkosova and coworkers[63] for which we have a known $\boldsymbol{L}$ solute descriptor.

$$\boldsymbol{L} = 0.505(0.000)\ (RI/100) - 0.381(0.007) \qquad (6)$$

($N = 49$, $SD = 0.022$, $R^2 = 1.000$, $F = 1323009$)

Standard errors in the equation coefficients are given in parenthesis immediately following the respective coefficient. Numerical values for the 49 compounds used in constructing Eqn. (6) are tabulated in Table 1. The derived mathematical relationship then allows us to calculate the L-solute descriptors of the remaining 174 mono-methyl branched alkanes. These calculations are summarized in the last column of Table 1. Examination of the numerical entries reveals that eqn. (6) provides reasonably accurate back-calculation of the known **L** descriptor values as one might expect from the correlation's small standard deviation, SD = 0.022, and near unity value for the squared correlation coefficient, $R^2 = 1.000$.

Table 1. Retention Indices, *RI*, and Abraham Model $\boldsymbol{L}$ Solute Descriptors for n-Alkanes and Mono-methyl Branched Alkanes.

Compound	*RI*	*L* value (database)	*L* value Eqn. 6
Butane	400.00	1.615	1.643
2-Methylpropane	354.77	1.409	1.414
Pentane	500.00	2.162	2.149
2-Methylbutane	466.23	2.013	1.978
Hexane	600.00	2.668	2.655
2-Methylpentane	561.31	2.503	2.459
3-Methylpentane	578.05	2.581	2.544
Heptane	700.00	3.173	3.161
2-Methylhexane	662.48	3.001	2.971
3-Methylhexane	672.19	3.044	3.020
Octane	800.00	3.677	3.667
2-Methylheptane	764.32	3.480	3.486
4-Methylheptane	765.88	3.483	3.494
3-Methylheptane	772.17	3.510	3.526
Nonane	900.00	4.182	4.173
4-Methyloctane	864.06	3.961	3.991
2-Methyloctane	865.00	3.966	3.996
3-Methyloctane	871.89	3.998	4.031
Decane	1000.00	4.686	4.679
5-Methylnonane	961.09	4.432	4.482
4-Methylnonane	962.83	4.441	4.491
2-Methylnonane	965.39	4.453	4.504
3-Methylnonane	972.06	4.486	4.538
Undecane	1100.00	5.191	5.185
5-Methyldecane	1058.94	4.963	4.977
4-Methyldecane	1062.04	4.963	4.993
2-Methyldecane	1065.62	4.981	5.011
3-Methyldecane	1072.06	5.037	5.044
Dodecane	1200.00	5.696	5.691
6-Methylundecane	1156.16		5.469
5-Methylundecane	1157.36		5.475
4-Methylundecane	1161.21		5.495
2-Methylundecane	1165.48		5.516
3-Methylundecane	1172.15		5.550
Tridecane	1300.00	6.200	6.197
6-Methyldodecane	1254.15		5.965
5-Methyldodecane	1256.18		5.975
4-Methyldodecane	1260.75		5.998
2-Methyldodecane	1265.36		6.022
3-Methyldodecane	1272.12		6.056
Tetradecane	1400.00	6.705	6.703
7-Methyltridecane	1351.94		6.460
6-Methyltridecane	1352.60		6.463
5-Methyltridecane	1355.43		6.477
4-Methyltridecane	1360.35		6.502
2-Methyltridecane	1365.35		6.528
3-Methyltridecane	1372.33		6.563
Pentadecane	1500.00	7.209	7.209
7-Methyltetradecane	1450.13		6.957
6-Methyltetradecane	1451.63		6.964
5-Methyltetradecane	1454.71		6.980
4-Methyltetradecane	1460.18		7.008
2-Methyltetradecane	1465.37		7.034
3-Methyltetradecane	1472.51		7.070
Hexadecane	1600.00	7.714	7.715
8-Methylpentadecane	1548.19		7.453
7-Methylpentadecane	1548.85		7.456
6-Methylpentadecane	1550.66		7.465
5-Methylpentadecane	1554.24		7.483
4-Methylpentadecane	1559.97		7.512
2-Methylpentadecane	1565.24		7.539
3-Methylpentadecane	1572.67		7.577
Heptadecane	1700.00	8.218	8.221
8-Methylhexadecane	1646.96		7.953
7-Methylhexadecane	1647.63		7.956
6-Methylhexadecane	1650.07		7.968
5-Methylhexadecane	1653.97		7.988
4-Methylhexadecane	1659.91		8.018
2-Methylhexadecane	1665.35		8.046
3-Methylhexadecane	1672.99	8.073	8.084
Octadecane	1800.00	8.722	8.727
9-Methylheptadecane	1745.40		8.451
8-Methylheptadecane	1745.55		8.451
7-Methylheptadecane	1746.93		8.458
6-Methylheptadecane	1749.71		8.473
5-Methylheptadecane	1753.65		8.492
4-Methylheptadecane	1759.94		8.524

2-Methylheptadecane	1765.29		8.551
3-Methylheptadecane	1773.21	8.573	8.591
Nonadecane	1900.00	9.226	9.233
9-Methyloctadecane	1844.03		8.950
8-Methyloctadecane	1844.56		8.952
7-Methyloctadecane	1846.51		8.962
6-Methyloctadecane	1849.34		8.977
5-Methyloctadecane	1853.61		8.998
4-Methyloctadecane	1859.97		9.030
2-Methyloctadecane	1865.28		9.057
3-Methyloctadecane	1873.44		9.099
Eicosane	2000.00	9.731	9.739
10-Methylnonadecane	1942.61		9.449
9-Methylnonadecane	1943.01		9.451
8-Methylnonadecane	1943.74		9.454
7-Methylnonadecane	1945.79		9.465
6-Methylnonadecane	1948.99		9.481
5-Methylnonadecane	1953.45		9.503
4-Methylnonadecane	1959.94		9.536
2-Methylnonadecane	1965.23		9.563
3-Methylnonadecane	1973.84		9.607
Heneicosane	2100.00	10.236	10.245
10-Methyleicosane	2041.65		9.950
9-Methyleicosane	2042.17		9.952
8-Methyleicosane	2043.28		9.958
7-Methyleicosane	2045.45		9.969
6-Methyleicosane	2048.79		9.986
5-Methyleicosane	2053.39		10.009
4-Methyleicosane	2060.16		10.043
2-Methyleicosane	2065.34		10.070
3-Methyleicosane	2074.15		10.114
Docosane	2200.00	10.740	10.751
11-Methylheneicosane	2140.37		10.449
10-Methylheneicosane	2140.48		10.450
9-Methylheneicosane	2141.20		10.453
8-Methylheneicosane	2142.57		10.460
7-Methylheneicosane	2144.97		10.473
6-Methylheneicosane	2148.36		10.490
5-Methylheneicosane	2153.24		10.514
4-Methylheneicosane	2160.05		10.549
2-Methylheneicosane	2165.23		10.575
3-Methylheneicosane	2174.30		10.621
Tricosane	2300.00	11.252	11.257
11-Methyldocosane	2239.26		10.950
10-Methyldocosane	2239.65		10.952
9-Methyldocosane	2240.71		10.957
8-Methyldocosane	2242.27		10.965
7-Methyldocosane	2244.66		10.977
6-Methyldocosane	2248.15		10.995
5-Methyldocosane	2253.04		11.019
4-Methyldocosane	2260.03		11.055
2-Methyldocosane	2265.06		11.080
3-Methyldocosane	2274.34		11.127
Tetracosane	2400.00	11.758	11.763
12-Methyltricosane	2338.03		11.449
11-Methyltricosane	2338.15		11.450
10-Methyltricosane	2338.69		11.453
9-Methyltricosane	2340.01		11.459
8-Methyltricosane	2341.69		11.468
7-Methyltricosane	2344.25		11.481
6-Methyltricosane	2347.92		11.499
5-Methyltricosane	2352.88		11.525
4-Methyltricosane	2360.07		11.561
2-Methyltricosane	2365.04		11.586
3-Methyltricosane	2374.70		11.635
Pentacosane	2500.00	12.264	12.269
12-Methyltetracosane	2437.35		11.952
11-Methyltetracosane	2437.61		11.953
10-Methyltetracosane	2438.25		11.957
9-Methyltetracosane	2439.74		11.964
8-Methyltetracosane	2441.52		11.973
7-Methyltetracosane	2444.20		11.987
6-Methyltetracosane	2447.95		12.006
5-Methyltetracosane	2452.97		12.031
4-Methyltetracosane	2460.14		12.067
2-Methyltetracosane	2465.07		12.092
3-Methyltetracosane	2474.86		12.142
Hexacosane	2600.00	12.770	12.775
13-Methylpentacosane	2536.47		12.454
12-Methylpentacosane	2536.54		12.454
11-Methylpentacosane	2536.98		12.456
10-Methylpentacosane	2537.74		12.460
9-Methylpentacosane	2539.36		12.468
8-Methylpentacosane	2541.32		12.478
7-Methylpentacosane	2543.98		12.492
6-Methylpentacosane	2547.85		12.511
5-Methylpentacosane	2553.15		12.538
4-Methylpentacosane	2560.60		12.576
2-Methylpentacosane	2565.29		12.599
3-Methylpentacosane	2575.45		12.651
Heptacosane	2700.00	13.276	13.281
13-Methylhexacosane	2635.44		12.954
12-Methylhexacosane	2635.87		12.957
11-Methylhexacosane	2636.31		12.959
10-Methylhexacosane	2637.35		12.964
9-Methylhexacosane	2639.09		12.973
8-Methylhexacosane	2641.09		12.983
7-Methylhexacosane	2643.84		12.997
6-Methylhexacosane	2647.91		13.017
5-Methylhexacosane	2653.06		13.043
4-Methylhexacosane	2660.71		13.082
2-Methylhexacosane	2665.30		13.105
3-Methylhexacosane	2675.72		13.158
Octacosane	2800.00	13.780	13.787
14-Methylheptacosane	2734.93		13.458
13-Methylheptacosane	2735.00		13.458
12-Methylheptacosane	2735.45		13.460
11-Methylheptacosane	2736.16		13.464
10-Methylheptacosane	2737.21		13.469
9-Methylheptacosane	2739.14		13.479
8-Methylheptacosane	2741.07		13.489
7-Methylheptacosane	2743.87		13.503
6-Methylheptacosane	2747.82		13.523
5-Methylheptacosane	2753.22		13.550
4-Methylheptacosane	2760.86		13.589
2-Methylheptacosane	2765.26		13.611
3-Methylheptacosane	2776.09		13.666
Nonacosane	2900.00	14.291	14.293

14-Methyloctacosane	2834.42		13.961
13-Methyloctacosane	2834.57		13.962
12-Methyloctacosane	2835.14		13.965
11-Methyloctacosane	2835.88		13.969
10-Methyloctacosane	2837.14		13.975
9-Methyloctacosane	2839.07		13.985
8-Methyloctacosane	2841.19		13.995
7-Methyloctacosane	2843.96		14.009
6-Methyloctacosane	2848.04		14.030
5-Methyloctacosane	2853.40		14.057
4-Methyloctacosane	2861.18		14.097
2-Methyloctacosane	2865.70		14.119
3-Methyloctacosane	2876.38		14.173
Triacontane	3000.00	14.794	14.799
15-Methylnonacosane	2933.77		14.464
14-Methylnonacosane	2933.82		14.464
13-Methylnonacosane	2934.26		14.466
12-Methylnonacosane	2934.85		14.469
11-Methylnonacosane	2935.54		14.473
10-Methylnonacosane	2937.00		14.480
9-Methylnonacosane	2938.90		14.490
8-Methylnonacosane	2941.11		14.501
7-Methylnonacosane	2943.93		14.515
6-Methylnonacosane	2948.14		14.537
5-Methylnonacosane	2953.43		14.563
4-Methylnonacosane	2961.56		14.604
2-Methylnonacosane	2965.72		14.626
3-Methylnonacosane	2976.43		14.680

PREDICTION OF STANDARD MOLAR ENTHALPIES OF VAPORIZATION AND SUBLIMATION

The chromatographic retention measurements performed by Krkosova and coworkers[63] allowed us to have a complete set of solute descriptors for an additional 180 saturated hydrocarbons. Previously we had only the five solute descriptors (***E, S, A, B***, and ***V***) needed for Eqn. (4). Published studies have shown, however, that Eqn. (5) of the Abraham model provides the better set of predicted values for several thermodynamic properties such as enthalpies of vaporization[11] and enthalpies of solvation of organic vapours and inorganic gases dissolved both in water and in organic solvents.[30-40] Having a complete set of solute descriptors will provide better applicability for these important thermodynamic quantities.

We illustrate the application of the Abraham model by calculating the enthalpies of vaporization (Eqn. 7) and enthalpies of solvation (Eqn. 8) of the 174 mono-methyl branched alkanes for which we have just determined the ***L*** descriptor. For the convenience of the reader we have simplified the predictive expressions to contain only the non-zero terms.

$$\Delta H_{vap,298K}\ (\text{kJ mol}^{-1}) = 6.100 + 9.537\ \boldsymbol{L} \qquad (7)$$

$$\Delta H_{sub,298K}\ (\text{kJ mol}^{-1}) = 13.93 + 13.57\ \boldsymbol{L} - 0.05\ \boldsymbol{L}\cdot\boldsymbol{L} \qquad (8)$$

Enthalpy of sublimation predictions given in Table 2, start with the C_{20}-compounds as most of the smaller compounds is liquid at 298 K. Predicted values of $\Delta H_{vap,298K}$ are given in Table 3 for all compounds as vaporization enthalpies of compounds that are crystalline at 298 K can be easily determined using the method of correlation gas chromatography.[5]

Table 2. Comparison of the Enthalpies of Sublimation, $\Delta H_{sub,298K}$ (kJ mol^{-1}), Predicted by the Abraham Model Eqn. (6) and the Group-Additivity Method of Naef and Acree (Eqn. 11).

Compound	$\Delta H_{sub,298K}$ **Eqn. 8**	$\Delta H_{sub,298K}$ **Eqn. 11**
10-Methylnonadecane	137.68	140.76
9-Methylnonadecane	137.71	140.76
8-Methylnonadecane	137.76	140.76
7-Methylnonadecane	137.89	140.76
6-Methylnonadecane	138.09	140.76
5-Methylnonadecane	138.38	140.76
4-Methylnonadecane	138.79	140.76
2-Methylnonadecane	139.13	140.76
3-Methylnonadecane	139.68	140.76
10-Methyleicosane	144.00	147.11
9-Methyleicosane	144.03	147.11
8-Methyleicosane	144.10	147.11
7-Methyleicosane	144.24	147.11
6-Methyleicosane	144.45	147.11
5-Methyleicosane	144.75	147.11
4-Methyleicosane	145.18	147.11
2-Methyleicosane	145.50	147.11
3-Methyleicosane	146.06	147.11
11-Methylheneicosane	150.27	153.46
10-Methylheneicosane	150.27	153.46
9-Methylheneicosane	150.32	153.46
8-Methylheneicosane	150.41	153.46
7-Methylheneicosane	150.56	153.46
6-Methylheneicosane	150.77	153.46
5-Methylheneicosane	151.08	153.46
4-Methylheneicosane	151.51	153.46
2-Methylheneicosane	151.84	153.46
3-Methylheneicosane	152.42	153.46
11-Methyldocosane	156.52	159.81
10-Methyldocosane	156.55	159.81
9-Methyldocosane	156.61	159.81
8-Methyldocosane	156.71	159.81
7-Methyldocosane	156.86	159.81
6-Methyldocosane	157.08	159.81
5-Methyldocosane	157.39	159.81
4-Methyldocosane	157.83	159.81
2-Methyldocosane	158.15	159.81
3-Methyldocosane	158.73	159.81
12-Methyltricosane	162.74	166.16
11-Methyltricosane	162.75	166.16
10-Methyltricosane	162.79	166.16
9-Methyltricosane	162.87	166.16

8-Methyltricosane	162.97	166.16
7-Methyltricosane	163.14	166.16
6-Methyltricosane	163.37	166.16
5-Methyltricosane	163.68	166.16
4-Methyltricosane	164.13	166.16
2-Methyltricosane	164.44	166.16
3-Methyltricosane	165.05	166.16
12-Methyltetracosane	168.98	172.51
11-Methyltetracosane	168.99	172.51
10-Methyltetracosane	169.03	172.51
9-Methyltetracosane	169.13	172.51
8-Methyltetracosane	169.24	172.51
7-Methyltetracosane	169.40	172.51
6-Methyltetracosane	169.64	172.51
5-Methyltetracosane	169.95	172.51
4-Methyltetracosane	170.40	172.51
2-Methyltetracosane	170.71	172.51
3-Methyltetracosane	171.32	172.51
13-Methylpentacosane	175.17	178.86
12-Methylpentacosane	175.17	178.86
11-Methylpentacosane	175.20	178.86
10-Methylpentacosane	175.25	178.86
9-Methylpentacosane	175.35	178.86
8-Methylpentacosane	175.47	178.86
7-Methylpentacosane	175.64	178.86
6-Methylpentacosane	175.88	178.86
5-Methylpentacosane	176.21	178.86
4-Methylpentacosane	176.67	178.86
2-Methylpentacosane	176.97	178.86
3-Methylpentacosane	177.60	178.86
13-Methylhexacosane	181.33	185.21
12-Methylhexacosane	181.36	185.21
11-Methylhexacosane	181.38	185.21
10-Methylhexacosane	181.45	185.21
9-Methylhexacosane	181.56	185.21
8-Methylhexacosane	181.68	185.21
7-Methylhexacosane	181.85	185.21
6-Methylhexacosane	182.10	185.21
5-Methylhexacosane	182.42	185.21
4-Methylhexacosane	182.90	185.21
2-Methylhexacosane	183.18	185.21
3-Methylhexacosane	183.83	185.21
14-Methylheptacosane	187.50	191.56
13-Methylheptacosane	187.50	191.56
12-Methylheptacosane	187.53	191.56
11-Methylheptacosane	187.57	191.56
10-Methylheptacosane	187.64	191.56
9-Methylheptacosane	187.76	191.56
8-Methylheptacosane	187.88	191.56
7-Methylheptacosane	188.05	191.56
6-Methylheptacosane	188.29	191.56
5-Methylheptacosane	188.63	191.56
4-Methylheptacosane	189.10	191.56
2-Methylheptacosane	189.37	191.56
3-Methylheptacosane	190.04	191.56
14-Methyloctacosane	193.64	197.91
13-Methyloctacosane	193.65	197.91
12-Methyloctacosane	193.68	197.91
11-Methyloctacosane	193.73	197.91
10-Methyloctacosane	193.80	197.91
9-Methyloctacosane	193.92	197.91
8-Methyloctacosane	194.05	197.91
7-Methyloctacosane	194.22	197.91
6-Methyloctacosane	194.48	197.91
5-Methyloctacosane	194.81	197.91
4-Methyloctacosane	195.28	197.91
2-Methyloctacosane	195.56	197.91
3-Methyloctacosane	196.22	197.91
15-Methylnonacosane	199.74	204.26
14-Methylnonacosane	199.75	204.26
13-Methylnonacosane	199.77	204.26
12-Methylnonacosane	199.81	204.26
11-Methylnonacosane	199.85	204.26
10-Methylnonacosane	199.94	204.26
9-Methylnonacosane	200.06	204.26
8-Methylnonacosane	200.19	204.26
7-Methylnonacosane	200.37	204.26
6-Methylnonacosane	200.63	204.26
5-Methylnonacosane	200.95	204.26
4-Methylnonacosane	201.45	204.26
2-Methylnonacosane	201.70	204.26
3-Methylnonacosane	202.36	204.26

Table 3. Comparison of the Enthalpies of Vapoiization, $\Delta H_{vap,298K}$ (kJ mol^{-1}), Predicted by the Abraham Model, Eqn. 7, and the Group-Additivity Method of Naef and Acree, Eqn. 10

Compound	$\Delta H_{vap,298K}$ **Eqn. 7**	$\Delta H_{vap,298K}$ **Eqn. 10**
6-Methylundecane	58.26	59.83
5-Methylundecane	58.32	59.83
4-Methylundecane	58.50	59.83
2-Methylundecane	58.71	59.83
3-Methylundecane	59.03	59.83
6-Methyldodecane	62.99	64.59
5-Methyldodecane	63.09	64.59
4-Methyldodecane	63.31	64.59
2-Methyldodecane	63.53	64.59
3-Methyldodecane	63.86	64.59
7-Methyltridecane	67.71	69.35
6-Methyltridecane	67.74	69.35
5-Methyltridecane	67.88	69.35
4-Methyltridecane	68.11	69.35
2-Methyltridecane	68.35	69.35
3-Methyltridecane	68.69	69.35
7-Methyltetradecane	72.45	74.11

6-Methyltetradecane	72.52	74.11
5-Methyltetradecane	72.67	74.11
4-Methyltetradecane	72.93	74.11
2-Methyltetradecane	73.18	74.11
3-Methyltetradecane	73.53	74.11
8-Methylpentadecane	77.18	78.87
7-Methylpentadecane	77.21	78.87
6-Methylpentadecane	77.30	78.87
5-Methylpentadecane	77.47	78.87
4-Methylpentadecane	77.75	78.87
2-Methylpentadecane	78.00	78.87
3-Methylpentadecane	78.36	78.87
8-Methylhexadecane	81.94	83.63
7-Methylhexadecane	81.98	83.63
6-Methylhexadecane	82.09	83.63
5-Methylhexadecane	82.28	83.63
4-Methylhexadecane	82.57	83.63
2-Methylhexadecane	82.83	83.63
9-Methylheptadecane	86.69	88.39
8-Methylheptadecane	86.70	88.39
7-Methylheptadecane	86.77	88.39
6-Methylheptadecane	86.90	88.39
5-Methylheptadecane	87.09	88.39
4-Methylheptadecane	87.40	88.39
2-Methylheptadecane	87.65	88.39
9-Methyloctadecane	91.45	93.15
8-Methyloctadecane	91.48	93.15
7-Methyloctadecane	91.57	93.15
6-Methyloctadecane	91.71	93.15
5-Methyloctadecane	91.92	93.15
4-Methyloctadecane	92.22	93.15
2-Methyloctadecane	92.48	93.15
3-Methyloctadecane	92.87	93.15
10-Methylnonadecane	96.21	97.91
9-Methylnonadecane	96.23	97.91
8-Methylnonadecane	96.27	97.91
7-Methylnonadecane	96.36	97.91
6-Methylnonadecane	96.52	97.91
5-Methylnonadecane	96.73	97.91
4-Methylnonadecane	97.05	97.91
2-Methylnonadecane	97.30	97.91
3-Methylnonadecane	97.72	97.91
10-Methyleicosane	100.99	102.67
9-Methyleicosane	101.02	102.67
8-Methyleicosane	101.07	102.67
7-Methyleicosane	101.17	102.67
6-Methyleicosane	101.34	102.67
5-Methyleicosane	101.56	102.67
4-Methyleicosane	101.88	102.67
2-Methyleicosane	102.13	102.67
3-Methyleicosane	102.56	102.67
11-Methylheneicosane	105.75	107.43
10-Methylheneicosane	105.76	107.43
9-Methylheneicosane	105.79	107.43
8-Methylheneicosane	105.86	107.43
7-Methylheneicosane	105.98	107.43
6-Methylheneicosane	106.14	107.43
5-Methylheneicosane	106.38	107.43
4-Methylheneicosane	106.70	107.43
2-Methylheneicosane	106.95	107.43
3-Methylheneicosane	107.39	107.43
11-Methyldocosane	110.53	112.19
10-Methyldocosane	110.55	112.19
9-Methyldocosane	110.60	112.19
8-Methyldocosane	110.67	112.19
7-Methyldocosane	110.79	112.19
6-Methyldocosane	110.96	112.19
5-Methyldocosane	111.19	112.19
4-Methyldocosane	111.53	112.19
2-Methyldocosane	111.77	112.19
3-Methyldocosane	112.22	112.19
12-Methyltricosane	115.29	116.95
11-Methyltricosane	115.30	116.95
10-Methyltricosane	115.33	116.95
9-Methyltricosane	115.39	116.95
8-Methyltricosane	115.47	116.95
7-Methyltricosane	115.59	116.95
6-Methyltricosane	115.77	116.95
5-Methyltricosane	116.01	116.95
4-Methyltricosane	116.36	116.95
2-Methyltricosane	116.60	116.95
3-Methyltricosane	117.06	116.95
12-Methyltetracosane	120.09	121.71
11-Methyltetracosane	120.10	121.71
10-Methyltetracosane	120.13	121.71
9-Methyltetracosane	120.20	121.71
8-Methyltetracosane	120.29	121.71
7-Methyltetracosane	120.42	121.71
6-Methyltetracosane	120.60	121.71
5-Methyltetracosane	120.84	121.71
4-Methyltetracosane	121.19	121.71
2-Methyltetracosane	121.42	121.71
3-Methyltetracosane	121.90	121.71
13-Methylpentacosane	124.87	126.47
12-Methylpentacosane	124.87	126.47
11-Methylpentacosane	124.89	126.47
10-Methylpentacosane	124.93	126.47
9-Methylpentacosane	125.01	126.47
8-Methylpentacosane	125.10	126.47
7-Methylpentacosane	125.23	126.47

6-Methylpentacosane	125.42	126.47
5-Methylpentacosane	125.67	126.47
4-Methylpentacosane	126.03	126.47
2-Methylpentacosane	126.26	126.47
3-Methylpentacosane	126.75	126.47
13-Methylhexacosane	129.65	131.23
12-Methylhexacosane	129.67	131.23
11-Methylhexacosane	129.69	131.23
10-Methylhexacosane	129.74	131.23
9-Methylhexacosane	129.82	131.23
8-Methylhexacosane	129.92	131.23
7-Methylhexacosane	130.05	131.23
6-Methylhexacosane	130.25	131.23
5-Methylhexacosane	130.50	131.23
4-Methylhexacosane	130.86	131.23
2-Methylhexacosane	131.09	131.23
3-Methylhexacosane	131.59	131.23
14-Methylheptacosane	134.45	135.99
13-Methylheptacosane	134.45	135.99
12-Methylheptacosane	134.47	135.99
11-Methylheptacosane	134.51	135.99
10-Methylheptacosane	134.56	135.99
9-Methylheptacosane	134.65	135.99
8-Methylheptacosane	134.74	135.99
7-Methylheptacosane	134.88	135.99
6-Methylheptacosane	135.07	135.99
5-Methylheptacosane	135.33	135.99
4-Methylheptacosane	135.70	135.99
2-Methylheptacosane	135.91	135.99
3-Methylheptacosane	136.43	135.99
14-Methyloctacosane	139.25	140.75
13-Methyloctacosane	139.25	140.75
12-Methyloctacosane	139.28	140.75
11-Methyloctacosane	139.32	140.75
10-Methyloctacosane	139.38	140.75
9-Methyloctacosane	139.47	140.75
8-Methyloctacosane	139.57	140.75
7-Methyloctacosane	139.71	140.75
6-Methyloctacosane	139.90	140.75
5-Methyloctacosane	140.16	140.75
4-Methyloctacosane	140.54	140.75
2-Methyloctacosane	140.76	140.75
3-Methyloctacosane	141.27	140.75
15-Methylnonacosane	144.04	145.51
14-Methylnonacosane	144.04	145.51
13-Methylnonacosane	144.07	145.51
12-Methylnonacosane	144.09	145.51
11-Methylnonacosane	144.13	145.51
10-Methylnonacosane	144.20	145.51
9-Methylnonacosane	144.29	145.51
8-Methylnonacosane	144.40	145.51
7-Methylnonacosane	144.53	145.51
6-Methylnonacosane	144.74	145.51
5-Methylnonacosane	144.99	145.51
4-Methylnonacosane	145.38	145.51
2-Methylnonacosane	145.58	145.51
3-Methylnonacosane	146.10	145.51

We are unable to find experimental $\Delta H_{vap,298K}$ and $\Delta H_{sub,298K}$ data in the published chemical literature to compare our calculated values against. What we offer in the way of a comparison is to compare our calculated values against the calculated values of a popular group-additivity method[73] that has been shown to predict $\Delta H_{vap,298K}$ and $\Delta H_{sub,298K}$ values for a wide range of organic and organometallic compounds to within standard deviations of SD = 4.30 kJ mol^{-1} (N = 3460 compounds) and SD = 10.33 kJ mol^{-1} (N = 1866 compounds), respectively. The basic method (Eqn. 9) sums the contributions that each atomic group makes to the given thermodynamic or physical property,

$$Property = \sum_i A_i a_i + \sum_j B_j b_j + C \qquad (9)$$

where A_i is the number of occurrences of the ith atom group, B_j is the number of times each special group occurs, a_i and b_j are the numerical values of each atom group and special group, and C is a constant. For both the $\Delta H_{vap,298K}$ and $\Delta H_{sub,298K}$ computations a C_nH_{2n+2} mono-methyl branched alkane would be fragmented into 3 sp^3 carbons (with an environment of 3 hydrogen atoms and 1 carbon), 1 sp^3 carbon atom (with an environment of 1 hydrogen atom and 3 carbon atoms), n-4 sp^3 carbon atoms (with an environment of 2 hydrogen atoms and 2 carbon atoms), and one special alkane group that is multiplied by the number of carbon atoms in the molecule. Numerical values of the groups values and constant are different for each property. In Eqns. (10) and (11) below we have filled in the numerical group values and constants for predicting $\Delta H_{vap,298K}$ (kJ mol^{-1}) and $\Delta H_{sub,298K}$(kJ mol^{-1}) of C_nH_{2n+2} mono-methyl branched alkanes:

$$\Delta H_{vap,298K} = 3\ x\ 3.07 + (n\text{-}4)\ x\ 4.67 + 3.57 + n\ x\ 0.09 + 8.61 \qquad (10)$$

$$\Delta H_{sub,298K} = 3\ x\ 5.99 + (n\text{-}4)\ x\ 6.88 + 2.28 - n\ x\ 0.53 + 21.03 \qquad (11)$$

Examination of the numerical entries in Tables 2 and 3 reveals that the predictions based on the Abraham model are similar to predictions based on the group-additivity model of Naef and Acree.[73] The group-additivity method though is not able to distinguish between the placement of the methyl group within the molecule, and gives the same predicted values for a given molecular formula. In other words, the predicted values of all methylheneicosane molecules are the same. This limitation is a common feature of most group-addivity and group contribution methods. The Abraham model, on the other hand, does provide different predicted values for a given molecular formula, and does not require

fragmentation of the molecule into atom groups or functional groups. Fragmentation of molecules into functional groups can be difficult at times, particularly in the case of more complex molecules having many different functional groups. Moreover, the solute descriptors for a given molecule can be used to predict many other properties of chemical and biological importance, such as vapour pressure, water-to-organic solvent partition coefficients, gas-to-water partition coefficients, solubility ratios and the infinite dilution activity coefficients of the compound in water.[74,75]

CONCLUSION

Numerical values of the Abraham model ***L*** solute descriptor have been reported for the first time for 174 different C_{12}-C_{30} mono-methyl branched alkanes. The numerical values were determined by regression analysis of published linear-programmed gas chromatographic retention indices versus known ***L*** solute descriptors of linear alkanes and smaller mono-methylated alkane molecules. Calculated ***L*** solute descriptors were used to predict the standard molar enthalpies of vaporization and standard molar enthalpies of sublimation of 174 mono-methyl alkanes at 298 K based on recently published Abraham model correlations.[11,12] The predicted values compare very favorably with calculated values based on an atom-group additivity model.[73] Unlike the additivity model the Abraham model gives different predicted values of $\Delta H_{vap,298K}$ and $\Delta H_{sub,298K}$ for each mono-methyl alkane having a given C_nH_{2n+2} molecular formula.

ACKNOWLEDGEMENTS

Shrika Eddula, Carina Jiang, Jennifer Huang, Priya Tirumala, and Angelina Xu thank the University of North Texas's Texas Academy of Math & Science (TAMS) Program for providing them with a TAMS summer research scholarship award.

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Received: 01.06.2020.
Accepted: 17.06.2020.