

SECONDARY METABOLITES AND BIOLOGICAL PROFILES OF *DATURA* GENUSCAMILO CÉSPEDES-MÉNDEZ ^{a,c,*}, PATRICIO ITURRIAGA-VÁSQUEZ ^{b,c} AND EMILIO HORMAZÁBAL ^{b*}^aDoctorado en Ciencias de Recursos Naturales, Facultad de Ingeniería y Ciencias, Universidad de La Frontera, Temuco, Chile.^bCenter of Excellence in Biotechnology Research Applied to the Environment, Universidad de La Frontera, Temuco, Chile.^cLaboratorio de Síntesis Orgánica y Farmacología Molecular, Departamento de Ciencias Químicas y Recursos Naturales, Facultad de Ingeniería y Ciencias, Universidad de La Frontera, Temuco, Chile.

ABSTRACT

Solanaceae is an important family of plants where many species of this family are source for food, industrial products, ornamental and medicinal uses. Within the family of Solanaceae, the genus *Datura* is one of the most interesting, in principle for its known medicinal and psychotropic uses against different pathologies. Multiple biological activities of *Datura* species have been documented. The species of the genus are attributed with insecticide, fungicide, antioxidant, antimicrobial, hypoglycemic, and immune response enhancing activity against cancer cells. These activities are related to the presence of different secondary metabolites such us: terpenoids, flavonoids, withanolides, tannins, phenolic compounds and tropane alkaloids, the main secondary metabolite of the genus *Datura*, being the most abundant atropine and scopolamine. The propose of this review is to identify the main phytochemical compounds isolated from the genus *Datura* and describe their biological activities associated to different secondary metabolites.

Keywords: Solanaceae, phytochemical, metabolites, pharmacological potential, *Datura*.

INTRODUCTION

Solanaceae is an economically important plant family in the world. They are a monophyletic group containing approximately 100 genera and 2500 species [1]. It corresponds to a cosmopolitan family of flowering plants mainly distributed in the tropical and temperate regions, such as, Australia and Central and South America [2]. The family includes species used for food (potato, tomato), industry (tobacco), ornamental (angel's trumpet), and medicinal (belladonna) [3]. Solanaceae has a wide distribution in South America [4], and produce different secondary metabolites, such as: alkaloids, steroids, steroidal saponins, phenols, terpenoids, among others [5].

The genus *Datura* (solanacea) has always caused interest for its phytochemical and ethnopharmacological characteristics [6]. The genus is native to North America, India, Australia, and China, however, today it is possible to find the species worldwide [7].

The genus comprises 14 species (table 1) of annual herbs and perennial shrubs from 1 to 1.5 m tall, with straight stems, fruits full of thorns, leaves that emit an unpleasant odor, and very aromatic trumpet-shaped flowers that are born at the fork of the stems (figure 1) [6], [8]. Plants of the genus *Datura* develop mainly in nitrogen-rich soils and soils disturbed by human activity such as agricultural soils, roadsides, or animal pens [9].

In America, the use of species of the genus *Datura* has been documented in sanatory and religious rites even by pre-Columbian peoples. Its use in North America before the arrival of the Europeans has been reported as treatment for physical injuries, and, in low doses, as an aphrodisiac and in divine rituals [10]. Since the 16th century, the use of the genus *Datura* has been established in traditional medicine, associated with its psychotropic, anticholinergic, analgesic, or anti-inflammatory effects, among others [9]. In Chile, *Datura stramonium*, or "Miyaya" called by Mapuche people, has been used as a psychiatric narco-analysis by eating of ground seeds and under supervision of a Machi [11]. The psycho-active use of this plant is associated to narcosis and transitory delusions that produce a trance, however the mainly use of this species is as a "truth drug" where its use is the prediction of future behavior and personality, this prediction is made by the Machi [11]. *Datura metel* has been documented in treatments for mental disorders, fevers, tumors, or skin diseases in India [12].

Furthermore, in the Chinese tradition, it has been documented its use for treatment against pustules, anal prolapse or nervous disorders [13], [14]. In the case of *Datura quercifolia*, it is also attributed activities against infections, cancer treatment and rheumatoid arthritis [15].

Currently, it has been documented that different extracts of the genus *Datura* not only have the described narcotic effects, also cover the treatment of other pathologies (antimicrobial, anti-inflammatory or cytotoxic activities), as well as potential agricultural uses (insecticide, herbicide), among others [13], [16]-[20].

The biological activities attributable to the genus *Datura* are related to the wide variety of secondary metabolites present in the plant. The mainly components are steroids, phenolic compounds, fatty acids, withanolides, and lactones, although the genus is mainly known for its production of tropane type alkaloids [6], [21]-[23].

Based on the ethnopharmacological uses and the diversity of chemical compounds presented by the genus, the objective of this article was to identify the main phytochemical components isolated from the genus *Datura* and describe their activity against different diseases and pathogens, with emphasis on the relevant literature of recent years.

Table 1. Geographical distribution of species belonging to the genus *Datura* and location within the three sections of the genus

Section	Species	Geographical distribution	Reference
Dutra	<i>Datura discolor</i>	Mexico	[24]
	<i>Datura innoxia</i>	Mexico, Botswana	[25], [26]
	<i>Datura kymatocarpa</i>	Mexico, Spain	[9]
	<i>Datura pruinosa</i>	Mexico	[27]
	<i>Datura reburra</i>	Mexico	[24]
	<i>Datura wrightii</i>	Australia	[28]
	<i>Datura leichardtii</i>	Australia	[28]
	<i>Datura velutinosa</i>	Cuba	[24]
	<i>Datura lanosa</i>	Mexico	[24]
	<i>Datura metel</i>	Mexico, Egypt	[29]
Ceratocaulis	<i>Datura ceratocaula</i>	Mexico	[30]
Datura	<i>Datura stramonium</i>	Mexico, France	[31]
	<i>Datura quercifolia</i>	USA, Mexico	[32]
	<i>Datura ferox</i>	Botswana	[29], [25]



Figure 1. Some of parts of individuals of the genus *Datura*. From left to right: leaves and flower of *Datura metel*; seeds of *Datura stramonium*; flowers and leaves of *Datura stramonium*

Phytochemistry of the genus

The biological activities attributed to the genus *Datura* are related to the chemical components (metabolites) presents. These compounds are produced in both primary and secondary metabolism of plants [33]. Primary metabolites are directly involved in the growth, development, and reproduction of plants, while secondary metabolites possess ecological functions [34].

In different species of the genus *Datura*, the presence of different groups of compounds has been described, such as terpenoids, flavonoids [35]-[37], steroids [22], [28], lectins [39]-[41] glycosides, fatty acids, saponins [12], tannins [42], phenolic compounds [12], [18], [43], withanolides [44]-[46] and different volatile terpenes [47], [48].

Terpenes

The genus *Datura* has different numbers and types of glandular and non-glandular trichomes and produce volatile compounds that emits against damage caused by herbivores [49]. Seventeen volatile compounds have been identified in *D. wrightii*, most of them are sesquiterpenes (Figure 2), such as limonene, linalool, (*E*)-3,8-dimethyl-1,4,7-nonatriene (DMNT), and (*E*)- β -caryophyllene where (*E*)- β -caryophyllene is the most abundant volatiles [48], [49].

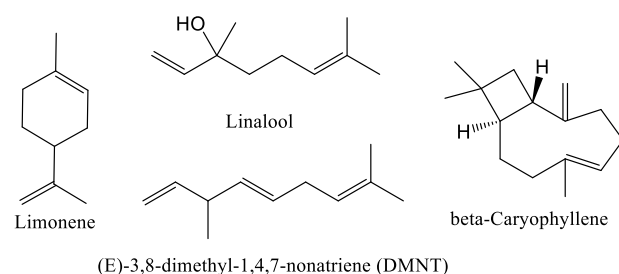


Figure 2. Structure of some isolated volatile compounds (terpenes) in the genus *Datura* in response to insect damage

From *D. metel* has been described sesquiterpenes and diterpenes, where 16 β ,17-dihydroxy-ent-kauran-19-oic acid, paniculose-IV and kaurane acid glycoside A, were isolated for the first time in Solanaceae, recently. (Figure 3) [50].

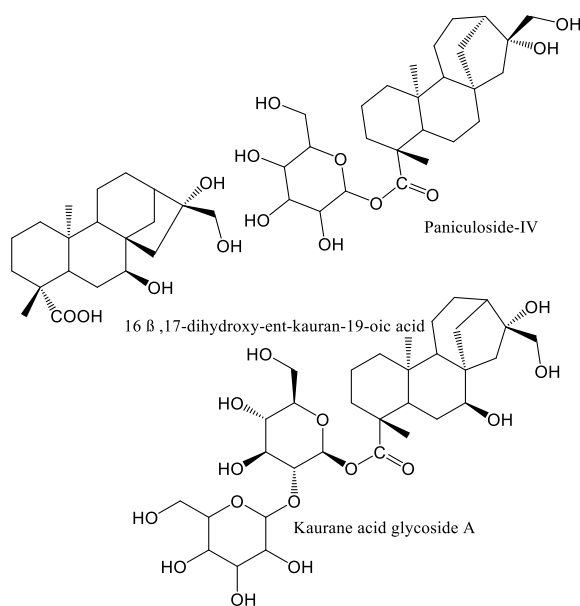


Figure 3. Structures of *D. metel* terpenes first identified in the Solanaceae family.

The identification of compounds from *D. metel* stems presented 6 sesquiterpenes, where two new compounds were isolated for the first time in the genus *Datura* (figure 4) [51]. On the other hand, nine new and three known sesquiterpenes were isolated from *D. metel* leaves displaying anti-inflammatory activity in nitric oxide production suppression assays [35].

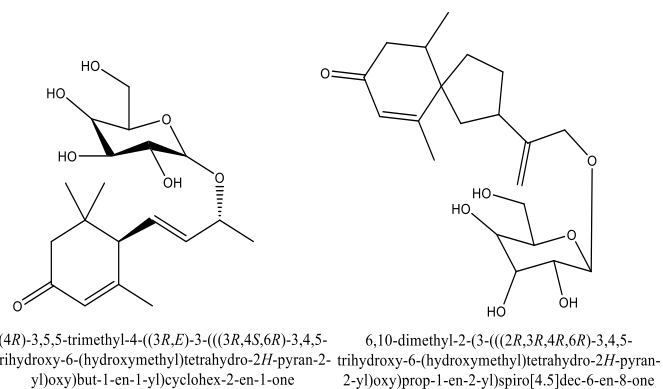


Figure 4. First identified sesquiterpenes in *D. metel* stems

Phenolic compounds

The presence of different groups of phenolic compounds in the genus *Datura* has been documented in methanolic and hydroalcoholic extracts. *D. metel* and *D. stramonium* present flavonoids, tannins, as well as glycosidic phenolic compounds [12].

Hossain et al [43] determined the presence of phenolic compounds in *D. metel* in different solvent fraction such as ethyl acetate, butanol, hexane, chloroform, and methanol. Analysis of methanolic extracts of roots and leaves of *D. metel* showed gallic acid, vanilic acid, quercetin and ferulic acid as the major phenolic compounds [23].

On the other hand, the composition analysis of the methanolic extract of the aerial organs of *D. innoxia* performed by means of LC-ESI-MS/MS showed the presence of 20 different phenolic compounds, where (-)-Epicatechin, (+)-Catechin, Hyperoside, *p*-Coumaric acid (Figure 4), are the most abundant metabolites isolated [52].

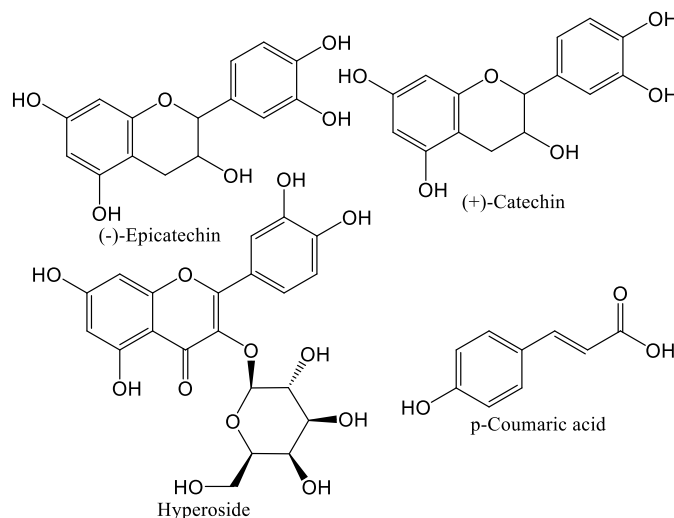


Figure 5. Structure of most abundant polyphenols identified in *D. innoxia*

Withanolides

Withanolides are a group of steroidal lactones that have been isolated from different genera of Solanaceae [54]. These compounds have been reported to exhibit biological activities such as anti-inflammatory, antioxidant, antitumor, insecticide, antifungal, and immunosuppressive properties [53], [54]. Different withanolides have been isolated and characterized within the genus *Datura* (daturalactones), differentiating themselves by possessing an epoxy in the lactone ring [15].

Five withanolides were identified from the aerial parts (flowers, leaves and stems) of *D. quercifolia* Kunth (Figure 6) which showed weak cytotoxic and pro-oxidant activities, as well as a relevant inhibitory activity against acetylcholinesterase [44].

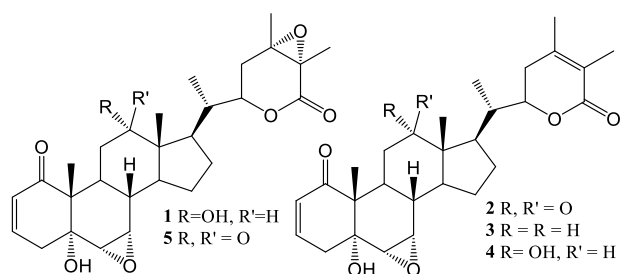


Figure 6 Withanolides active against acetylcholinesterase isolated from *D. quercifolia*

Many new undescribed withanolides were isolated from leaves of *D. metel* and two of them has showed anti-inflammatory activity [35].

In addition, thirteen other withanolides were isolated from flowers of *D. metel* and has showed immunosuppressive properties against splenocyte proliferation in mice, as well as activity against human gastric adenocarcinoma cell proliferation (SGC-7901), human hepatoma (HepG2) and human breast cancer (MCF-7) in vitro [51].

Lectins

Lectins are a group of carbohydrate-specific binding proteins that have been isolated from *D. stramonium* and other Solanaceae [55]. There are controversies regarding the biological role of lectins, although a defensive role for plants has been proposed due to the toxicity of lectins in both mammals and insects [41], [56]-[59].

D. stramonium agglutinin (DSA) is a chitin-binding lectin that has been extracted and purified from *D. stramonium* seeds [60]. The use of *D. stramonium* agglutinin in lectin microarrays has been used in the identification of renal pathologies in diabetic patients. Results of lectin microarrays revealed that N-acetyl-D-glucosamine (GlcNAc) linked to (β-1,4)-linked N-acetyl-D-glucosamine recognized by lectin *D. stramonium* agglutinin (DSA) was significantly higher in patients with diabetic nephropathy [50].

Alkaloids

The genus *Datura* shows a varied phytochemical composition of tropane-type alkaloids and correspond to the most active compounds in the plant [37], [38], [61], [63].

In particular, tropane alkaloids are a group of about 200 alkaloids with a tropane ring (N-methyl-8-azabicyclo[3.2.1]octane) (Figure 6) in their chemical structure, where the main precursor of this group is L-ornithine [64].

The most abundant alkaloids present in the genus *Datura* are Atropine (hyoscyamine) and Scopolamine (hyoscyne) [65], [66].

The alkaloid analysis in *D. ceratocaula* showed 36 compounds in the alkaloid fraction that shows a characteristic mass fragmentation spectrum, being Atropine the most abundant alkaloid in seed, and Scopolamine the most abundant in flowers [67]. Similar abundances of Atropine and scopolamine have been observed in *D. ferox*, reaching 0.32 g of scopolamine per 100 g of dry plant material [68], [69]. In *D. innoxia* the presence of Scopolamine and Atropine was observed in aerial parts, and 3a-6b-Ditigloyloxytropane and Atropine in roots [70].

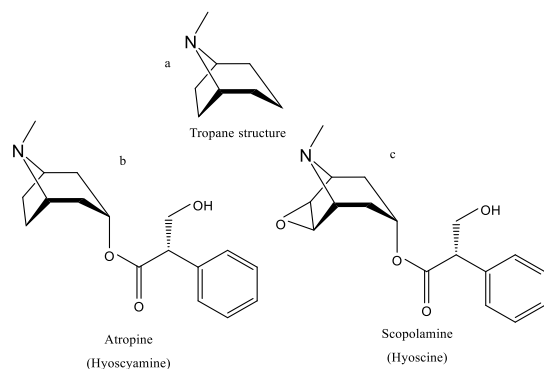


Figure 7 a) Base structure of the tropane alkaloids. b) and c) Hyoscyamine and Hyoscyne, the two most abundant alkaloids present in the genus *Datura*

The main alkaloids were Scopolamine and Atropine, varying their concentrations depending on the part of the plant [14]. Tropinone, Tropine, Pseudotropine, Atropine, and Scopolamine are the most abundant alkaloids in *D. quercifolia* [32].

In particular, at least 67 tropane alkaloids (table 2) have been identified in different parts of the plant in the species *D. stramonium* [64], [65]. Of which, in addition to atropine and scopolamine, the most abundant have been identified as Tropine, 3-Tigloyloxy-6-propionyloxy-7-hydroxytropane, 3,6-Ditigloyloxy-7-hydroxytropane [71].

Table 2 Most abundant tropane alkaloids identified in the genus *Datura* [32], [65], [71].

Alkaloid	Specie	Organ
Scopolamine	All	Roots, leaves, flowers, and seeds
Atropine	All	Roots, leaves, flowers, and seeds
3-Tigloyloxy-6,7-dihydroxytropane	<i>Datura stramonium</i>	Roots
Apoatropine	<i>Datura stramonium</i>	Roots, leaves, flowers, and seeds
3-Tigloyloxy-6-hydroxytropane	<i>Datura stramonium</i>	Roots
Hyoscyamine	<i>Datura stramonium</i> , <i>Datura quercifolia</i>	Roots, leaves, flowers, and seeds
3α-Tigloyloxy-6-isovaleroyloxy-7-hydroxytropane	<i>Datura stramonium</i>	Roots
3,6-Ditigloyloxy-7-hydroxytropane	<i>Datura stramonium</i>	Roots
Scopolamine	<i>Datura stramonium</i>	Roots, leaves, flowers, and seeds
Tropine	All	Roots, leaves, flowers, and seeds
3-acetoxynortropane	<i>Datura quercifolia</i>	Roots

On the other hand, Okwu and Igara [72] identified one steroidal alkaloid in *D. metel* (figure 8) with significant antibacterial activity.

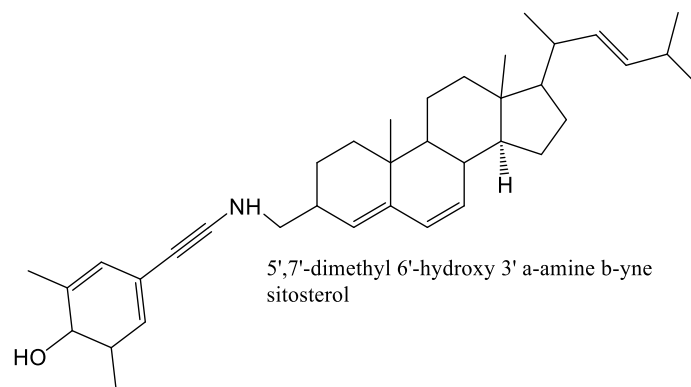


Figure 8 Alkaloid with antibiotic activity isolated by Okwu and Igara [72].

Biological activities of the genus *Datura*

Different biological activities in the genus *Datura* associated with the different metabolites described have been studied. These properties are beneficial both in

Insecticide activity

The insecticidal and repellent activity of *Datura* species has been addressed by different authors [5]. Leaf extracts of *D. metel* (acetone, water, and petroleum ether) have been documented to display insecticidal and insect repellent activity against different insect species in contact and spray application assays. EC₅₀ results showed values of 12,000 ppm for grasshoppers and 11,600 ppm for red ants in organic extracts of *D. metel* [38], [61], [62], [73]. In the case of *D. stramonium*, insecticide activity has been evaluated in non-polar extracts, both by contact and by diet, in adult individuals and larvae of different insects [56], [74], [75].

The larvicidal effect of the aqueous root extract of *D. stramonium* was measured against two species of mosquitoes, reaching between 50% and 100% larval mortality at 100% concentration of the extracts at 24 h after the treatment was applied [76]. On the other hand, the effect of *D. wrightii*'s trichome exudates against *Manduca sexta* larvae reached 20% mortality [77].

Different concentrations of an aqueous extract of leaves and seeds of *D. stramonium* was presented as an effective treatment against flea beetles which is a major pest of maize [78].

The effect of acetone extracts from *Datura innoxia* was evaluated against *Tribolium castaneum*, *Trogoderma granarium* and *Sitophilus granarius* where the toxic effect of the plant extracts was observed in addition to the inhibition of enzymes acetylcholinesterase (AChE), α -carboxylesterase (α -CE), β -carboxylesterase (β -CE), acid phosphatases (ACP) and alkaline phosphatases (ALP) in toxicity test survivors showing lethal effects against three stored grain insect species by up to 15% lethality associated to a significant effects on AChE inhibition, α -EC, β -EC, ACP and ALP at different concentrations [78].

Herbicidal

D. metel has reported potential herbicidal activity against "noxious weed parthenium" in aqueous and methanolic extracts, where the root presents outstanding effects compared to the stems, with both extracts inhibiting weed germination, as well as the development of the stems in individuals of a couple of weeks [6]. Similarly, the herbicide activity of *D. metel* has been evaluated against *Phalaris minor* where germination inhibition occurred in methanolic and hexane root extracts [79].

Sakadzo, et al. [80] reported the significative effect of aqueous extract of *D. stramonium* in inhibiting root development, plumule length, and dry matter amount against *Amaranthus hybridus* and *Tegetes minuta* with pre- and post-emergence herbicidal effects.

Acaricide activity

The methanolic extracts of leaves and seeds of *D. stramonium* showed acaricidal effects reaching 98% mortality of adult individuals of *Tetranychus urticae* Koch (spider mites) in the leaf extract, and 25% mortality for the seed extract, where a direct relationship between concentration and mortality rate was observed for the leaf extracts, without the relationship in the seed extracts [37].

Ethanol extract from *Datura stramonium* leaves achieved 20% mortality against *Rhipicephalus microplus* (Asian blue tick) in adult mite immersion trials [81]. Similarly, the methanolic extract of *D. stramonium* reached a 77% inhibition in the oviposition of *Rhipicephalus (Boophilus) microplus* in vitro assays [82].

Antifungal activity

The antifungal activity has been evaluated in 3 species of the genus: *D. discolor*, *D. metel* and *D. stramonium*. Ethanol and methanolic extracts from stems and leaves of *D. discolor* were mixed with the culture medium where, *Aspergillus flavus*, *Aspergillus niger*, *Penicillium chrysogenum*, *Penicillium expansum*, *Fusarium moniliforme* and *Fusarium poae* were grown, resulting in a significant inhibition of *A. flavus* growth of 66.2% and up to 60% inhibition against *P. chrysogenum* [12].

Aqueous and methanolic extracts of *D. metel* leaves had antifungal activity against *Rhizoctonia solani*. Methanolic extract of *D. metel* exhibited up to 35% more toxicity than other 15 species studied, inhibiting mycelial growth and

the agricultural field (herbicide, acaricide, insecticide) and in the medicinal field (antibacterial, cytotoxic, or antioxidant).

sclerotium production [46]. Moreover, extracts of all parts of *D. metel* with different solvents (hexane, chloroform, acetone, and methanol) showed antifungal activity against three *Aspergillus* species: *A. fumigatus*, *A. niger* and *A. flavus*, where the minimum inhibitory concentration (MIC) of chloroform fraction was 625.0 μ g/mL [83].

The antifungal activity of methanol extracts from the leaves, seeds, stems and roots of *D. innoxia* was evaluated by determining the growth inhibition of five fungal species: *A. flavus*, *A. niger*, *Alternaria solani*, *Fusarium solani* and *Helianthus sporium* [84].

The antifungal activity of *D. stramonium* extracts on *Candida albicans* showed higher growth inhibition rates in aqueous extracts (74%), although with good inhibitory activities of methanol and chloroform extracts (69% and 65%, respectively) [19].

Antibacterial activity

Leaf and fruit extracts of *D. stramonium* with solvents of different polarity were evaluated against 5 pathogenic microorganisms where the extracted methanol and chloroform fractions from both leaves and fruits showed growth inhibition of all tested microorganisms at different concentrations. Growth of *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* was effectively reduced by all extracted fractions from the fruits. The maximum growth reduction (77%) was presented by the chloroform extract of leaves against *K. pneumoniae* [19].

Antibiotic activity of methanolic extracts (80%) of *Datura innoxia* against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* by paper disk diffusion method using ampicillin as a positive control. The results indicated activity against all bacteria at the highest concentration of the extracts except *E. coli*. (2.5 μ g/mL) [85]. Similarly, ethanolic and methanolic extracts from leaves and fruits of *Datura metel*, respectively, were tested as antibiotics against *S. aureus*, *P. aeruginosa*, *P. mirabilis*, *E. coli*, *K. pneumoniae*, resulting in growth inhibition against all bacteria species except *E. coli* [43], [62], [73].

On the other hand, methanolic, ethanolic and aqueous extracts of *D. stramonium* have shown antibacterial activities against gram-positive and gram-negative bacterial in paper disk diffusion method [64]. Ethanolic extract of leaves inhibited the growth of bacteria for *P. aeruginosa*, *K. pneumoniae* and *E. coli* with 25% w/v as the minimum inhibitory concentration [86]. The methanolic leaf extract demonstrated antibacterial activity against gram-positive bacteria *Staphylococcus haemolyticus*, *S. aureus*, *Shigella dysenteriae*, *Bacillus cereus*, and against gram-negative bacteria, such as: *P. aeruginosa*, *K. pneumoniae* and *E. coli* at 2.5, 1.25 and 0.75 mg/mL [42], [64], [85], [87], [88].

Antioxidant activity

Aqueous extracts of *D. metel* stems, roots and leaves presented between 23.8 and 49.3 % antioxidant activity [62]. Methanolic extract of *D. stramonium* presented values of IC₅₀ for radical DPPH, superoxide, and radical cation ABTS of 35.3, 10.5 and 49.36 μ g/mL, respectively [20]. In *D. innoxia* the antioxidant capacity and concentration of phenolic compounds and flavonoids in addition to the higher antioxidant capacity (221.25 \pm 1.06 mg EPA/g) was evaluated in comparison to *D. metel* reaching significantly higher values than the latter in all determinations [89]. *D. metel* leaf methanol extract showed the highest antioxidant capacity in a DPPH purification test against other solvents and plant organs mainly due to the presence of the highest number of phenolic compounds, including flavonoids and tannins [90].

Hypoglycemic activity

The hypoglycemic activity of *D. metel* seeds were studied by adding ground seeds to the diet of rats with induced diabetes finding a significant reduction in blood glucose levels after 8 hours of its administration [91]. Hydromethanolic extract of *D. stramonium* root was evaluated in diabetic mice not showing significant hypoglycemic activity in the mice, although at relatively high doses (100, 200 and 400 mg/kg), the extract significantly reduced blood glucose levels in diabetic by orally loaded mice [92]. *D. innoxia* methanolic leaf extract showed inhibitory effect on α -glucosidase, α -amylase, lipase, and urease indicating antihyperglycemic effects [93].

Cytotoxic activity

The ethyl acetate fraction of the ethanolic extract of *D. metel* flowers was studied against cancer cell lines, showing cytotoxicity activity against A549 was observed, reaching 66.84% at 599 µg/mL [20]. These results were like those exposed by Gupta et al. [95] where the cytotoxic effects of methanolic extracts of *D. stramonium* leaves against A549 and MCF7 were evaluated, presenting a significant immunostimulation [94]. *D. innoxia* methanolic leaf extract showed a potential cytotoxic effect on MCF-7 cell lines of human breast cancer with an IC₅₀ of 93.73 µg/ml [94].

A phytosterol was identified and isolated from *D. innoxia* leaf extracts, Rhinoxia B, which showed antiproliferative activity against human colon adenocarcinoma cells, HCT 15 with an IC50 value of 4 µM [95].

OTHER ACTIVITIES

The presence of tropane alkaloids gives to the genus *Datura* anticholinergic (mydriatic, antispasmodic), anesthetic, analgesic, sedative-hypnotic, anti-parkinsonian, and aphrodisiac properties [13]. This activities in tropane alkaloids are associated to a competitive antagonist of muscarinic receptors [66]. however, some tropane alkaloids and their derivatives have shown different affinities to nicotinic acetylcholine receptor, although to a lesser extent, being in some cases a partial agonist [96]-[99].

The effects of tropane alkaloids on the nervous system are also related to the activity of monoaminergic neurotransmitters, where tropane alkaloids have different levels of affinity with monoaminergic transporters [100]-[102].

CONCLUSION

Species of the genus *Datura* are one of the oldest plants known used in traditional medicine. Its psychotropic effects have made it a source of important cultural traditions. Based on this cultural knowledge, the effects of plants of the genus have been evaluated in different general biological activities, such as: insecticide, fungicide and antibacterial, among others. Moreover, the study of plant components has led to studies on more important biological activities such as cytotoxicity in cancer cells. The importance of studies of secondary metabolites of the genus *Datura* has led to important discoveries regarding its biological activities. However, new studies continue to discover new metabolites with potential biological activity at different systems that made the genus as an important source of compounds with interesting pharmacological applications.

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(tongue), BGC-823 (gastric) and K562 (leukemia) [53]. Likewise, cytotoxicity of methanolic extracts of *Datura stramonium* seed against MCF7 (breast cancer)

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