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(REVIEW ARTICLE)

Plant toxins: alkaloids and their toxicities

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Abstract

Since ancient civilization, plants have been utilized in many aspects of life, especially in medicinal purposes due to the presence of distinctive secondary metabolites like alkaloids, phenolics and terpenoids. Among them, alkaloids represent a large group of secondary metabolites that have basic properties and comprise nitrogen atom within the heterocyclic ring. Plant synthesizes alkaloids to maintain their survivability under unfavorable conditions. Over 3000 years, indigenous people have been used alkaloid-containing plant extracts to treat several ailments such as fever, snakebite and insanity. However, despite significant benefits to humans and pharmaceutical industries, some of the plant alkaloids are categorized as main plant toxins due to their enormous structural diversity and various modes of actions. Humans and animals can be exposed to toxic alkaloids either through inhalation, swallowing or by direct contact, therefore leads to the specific mechanism that involves receptors, transporters, enzymes and genetic materials at specific cells and tissues, hence may cause hepatotoxic effects and musculoskeletal deformities. This review focuses on some of the plant alkaloids such as pyrrolizidine, tropane, piperidine and indolizidine, which can give various side effects on humans and animals such as itching, nausea, vomiting, mild gastrointestinal perturbation, psychosis, paralysis, teratogenicity, arrhythmias and sudden death.

Keywords: Plant toxins; Pyrrolizidine alkaloids; Tropane alkaloids; Piperidine alkaloids; Indolizidine alkaloids

1. Introduction

Alkaloids are a group of nitrogen-containing compounds present in plants, fungi, bacteria and animals [1]. The presence of nitrogen atom in the alkaloid structure makes the compound having drug properties. The lone pair electrons on the nitrogen can accept the protons while hydrogen in primary and secondary amine can act as a proton donor [2]. Alkaloids are mostly found in the higher plants, especially in plant root, fruit and stem, which about 31,000 compounds have been identified [3,4]. *Papaveraceae* (poppies), *Ranuncalaceae* (buttercups), *Solanaceae* (nightshades) and *Amaryllidaceae* (amaryllis) are among plant species that have been recognized to contain high alkaloid content. But, the concentration of alkaloids in these plants varies and always depends on the specific factors such as geographical region and climate [5,6]. Morphine is the first alkaloid isolated from the *Papaver somniferum* L. (Opium poppy) in 1804 [7]. Afterwards, discovering of several other alkaloids such benzylisoquinoline, papaverine and sanguinarine from *P. somniferum* makes this plant becomes a model system to investigate alkaloid biosynthesis [8].

Alkaloid-rich plants exhibit a wide range of pharmacological properties such as antibacterial, analgesic [9], antidepressant [10] and anticancer [11]. Also, some of them have been proven to possess neuroprotective properties, therefore they have been used to treat Alzheimer's disease [5, 12]. An interest to exploit alkaloids like pyrrolizidine, indolizidine, piperidine and tropane as pharmaceutical drugs has definitely drawn attention of toxicologists to further understand the alkaloid toxicity levels towards humans and animals. Most of the studies have shown that the structural diversity and various action modes of alkaloids are the main reasons of diverge toxicity effects of different alkaloid

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groups [13, 14]. Besides, the toxicity effects of alkaloids also depend on specific dosage, exposure time, sensitivity, site of action and developmental stage of organism [15]. Hence, this review focuses on some of the plant-derived alkaloids that give toxic effects on humans and animals.

2. Functions of alkaloids in plants and animals

In plants, alkaloids are nitrogen storage compounds that are involved to protect them from predators, and functioned as growth regulators and substitutes for minerals like potassium and calcium [16]. When predators attack plants, the alkaloids can interfere the predator's nervous system, membrane transport, protein synthesis and enzyme activity [17], while under abiotic or biotic stress alkaloids can enhance plant reproductive rates [15]. Some of the alkaloids may also act as herbicide by inhibiting the growth of competing plants [4, 18].

The use of alkaloids as a drug in human history has revealed the importance of these compounds in the pharmaceutical industry. For instance, the alkaloid derived from beta-carboline group such as harmine has been used as antimicrobial, anti-HIV and anti-parasitic [19]. The vinca alkaloid (vinblastine and vincristine) isolated from *Catharanthus roseus,* berberine isolated from *Coptis spp.* and taxol isolated from *Taxus bravifolia* have been employed as anticancer drugs for treating leukemias, lymphomas, testicular cancer, breast cancer, lung cancers and Kaposi's sarcoma [3,20-22].

3. Classification of alkaloids

Table 1 Classification of alkaloids based on chemical structure

Types of alkaloids		**Representative**
Non-heterocyclic alkaloids		Hordenine or N-Methyltyramine, Mescaline, Ephedrine, Colchicine, Erythromycin, Jurubin, Pachysandrine A, Taxol
Heterocyclic alkaloids	Pyrrole and pyrrolidine	Hygrines, Stachydrine
	Pyrrolizidine	Symphitine, Echimidine, Senecionine, Seneciphylline
	Pyridine and piperidine	Trigonelline, Coniine, Arecoline, Lobeline, Pelletierine, Nicotine, Anabasine, Piperine, Ricinine
	Tropane	Hyoscyamine, Atropine, Hyoscine, Meteloidine, Calystegines, Cocaine, Pseudo-pelletierine
	Quinoline	Quinine, Quinidine, Cinchonine, Cinchonidine, Cusparine
	Isoqunoline	Papaverine, Narceine, Narcotine, Corydaline, Hydrastine, Berberine, Emetine, Cephaeline, Tubocurarine, Morphine, Codeine, Erythraline, Galanthamine
	Aporphine	Boldine
	Quinolizidine	Sparteine, Cytisine, Lupanine, Laburnine
	Indole or benzopyrrole	Ergometrine, Ergotamine, Lysergic acid amide, Clavine Alkaloids, Physostigmine, Ajmaline, Serpentine, Reserpine, Yohimbine, Aspidospermine, Vinblastine, Vincristine, Strychnine, Brucine
	Indolizidine	Castanospermine, Swainsonine
	Imidazole or glyoxaline	Pilocarpine
	Purine (pyrimidine/imidazole)	Caffeine, Theobromine
	Steroidal (some combined as glycosides)	Solanidine, Veratrum alkamine esters and their glycosides, Conessine, Funtumine
	Terpenoid	Aconitine, Atisine, Lyctonine

The molecular complexities of alkaloid structures have caused difficulties in classifying these compounds [23]. However, previous reports have established the different approaches to classify alkaloids like pharmacological action, chemical structure, biochemical origin and taxonomical origin. Among these classification systems, the classification technique based on chemical structure and biochemical origin are the common methods used [1]. Table 1 shows alkaloid classification based on the chemical structure that is further categorized into two divisions, which are non-heterocyclic (protoalkaloids) and heterocyclic (typical alkaloids). The heterocyclic division is further subdivided into 14 groups depending on their ring structure [1].

4. Toxicity effects of plant alkaloids on animals and humans

Plants naturally synthesize alkaloid compounds based on their needs. Some of the synthesized alkaloids like hepatotoxic pyrrolizidine, indolizidine, piperidine and tropane have been documented to cause toxic effects on animals and humans [24-25]. These alkaloids may enter human body either through inhalation or swallowing. Further, the traditional medication that needs humans consume alkaloid-containing plants without proper medical prescription is a common way they get intoxicated by toxic alkaloids. For animals, grazing activity is a usual way they obtain these poisonous compounds [25].

The ingested plants containing toxic alkaloids can cause injury to the human body, even though the plant extract is taken in a relatively small amount. This indicates the intoxication response relies on the sensitivity of the target animal [13]. The toxic alkaloids may interfere normal functions of human body systems through specific mechanism that involves receptors, transporters, enzymes and genetic materials at specific cells and tissues [26]. The mild toxic effects of consuming toxic alkaloids are itching, nausea, vomiting and mild gastrointestinal perturbation while the chronic effects are psychosis, paralysis, teratogenicity, arrhythmias and sudden death [13, 24]. Hence, we further discuss the properties and toxic effects of some plant alkaloids that have been reported to display toxic effects on humans and animals.

4.1. Pyrrolizidine alkaloids

Pyrrolizidine alkaloids (PAs) are ester alkaloids composed of necine and necic acid moieties as illustrated in Figure 1. These alkaloids can be found in families Asteraceae, Boraginaceae and Fabaceae [25, 27]. They are classified as toxic alkaloids owing to the presence of 1,2 double bond at necine moiety. The toxic effects of PAs are generally associated with the exposure time, dosage amount, susceptibility of organisms and the conversion rate of PAs by oxidases. In biological system, the oxidases can covert PAs to reactive pyrroles, which later the product of catalytic reaction can react with nucleic acids and proteins [15, 28]. Examples of PAs are riddelliine, retrosine, monocrotaline, symphytine, lasiocarpine, heliotrine, senkirkine and petasitenine [29-31].

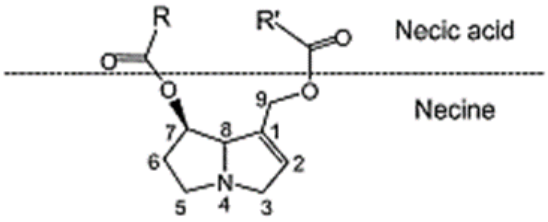

Figure 1 Schematic structure of pyrrolidizine alkaloid [29]

Other than oxidases, liver esterases also take part in the detoxification of PAs. Detoxification failure can cause liver damage (hepatotoxic), which can be indicated by abdominal pain, nausea, vomiting, diarrhea and edema in animals and humans [15, 27]. The esterases can break down PAs ester bond and produce necine and necic acid moieties [32]. Previous researches on rats and guinea pigs further proved the importance of esterases in PAs detoxification process. The rats were reported susceptible to PAs due to lack of esterase activity in liver while guinea pigs showed apparent resistance to PAs due to high liver esterase activity [29]. Table 2 shows the type of PAs that is available in plants and their toxicity effects on humans.

Table 2 Toxicity effect of pyrrolizidine alkaloids

Plants	Pyrrolizidine alkaloids	Toxicity effects	References
Cynoglossum officinale	7-Angelylheliotridine, Echinatine, Acetylheliosupine and Heliosupine	Anorexia, depression, diarrhea, photosensitivity, icterus, constipation, ascites and aberrant behavior	[33-34]
Senecio spp.	Seneciphylline, Senecionine, Jacidine, Jacobine, Jacoline, Jaconine, Jacozine and Retrorsine	Hepatic insufficiency, secondary photosensitization and central nervous system derangement due to elevated blood ammonia	[34-35]
Senecio formosus	Retrorsine	Severe veno-occlusive liver disease in humans	[25]
Symphytum officinale	Lycopsamine, Echimidine and Lasiocarpine	Produce irreversible hepatic damage if ingested chronically as an herbal tea	[36]

4.2. Tropane alkaloids

Tropane alkaloids (TAs) (as listed in Table 3) are the common alkaloids found in all plant parts, but the highest contents are determined in roots and seeds of families Brassicaceae, Solanaceae and Erythroxylacea [37]. The TAs production in plants varies depending on plant species and growth location. Over 200 of TAs have been identified, and further subdivided into subgroup according to the number of carbons in the tropane skeleton and stereochemical features [38-40]. The most common TAs that can be found in plants are atropine, hyoscyamine and scopolamine (Figure 2) [41].

Table 3 Tropane alkaloids in plants [40, 41]

Plants	Tropane alkaloids
Atropa belladonna	Atropine, Scopolamine, Hyoscyamine
Datura stramonium	Atropine, Scopolamine, Hyoscyamine
Datura suaveolens	Scopolamine, Hyoscyamine
Datura tatula, *metel*	Atropine
Duboisia myoporoides	Atropine, Scopolamine
Erycibe henryi	Tropane
Hyoscyamus muticus	Scopolamine, Hyoscyamine
Hyoscyamus niger	Atropine, Scopolamine, Hyoscyamine
Latua pubiflora	Scopolamine, Hyoscyamine
Lycium barbarum	Atropine
Nicotiana tabacum	Scopolamine, Hyoscyamine
Mandragora officinarum	Scopolamine, Hyoscyamine, Atropine
Scopolia carniolica Jacq.	Scopolamine, Hyoscyamine, Atropine
Hyoscyamus muticus	Scopolamine, Hyoscyamine
Nicotiana tabacum	Scopolamine, Hyoscyamine
Calystegia sepium	Calystegine
Convolvulus arvensis	Calystegine
Physalis alkekengi	Calystegine
Physalis peruviana	Tigloidine, Secotropane
Erythroxylum coca	Many alkaloids including cocaine

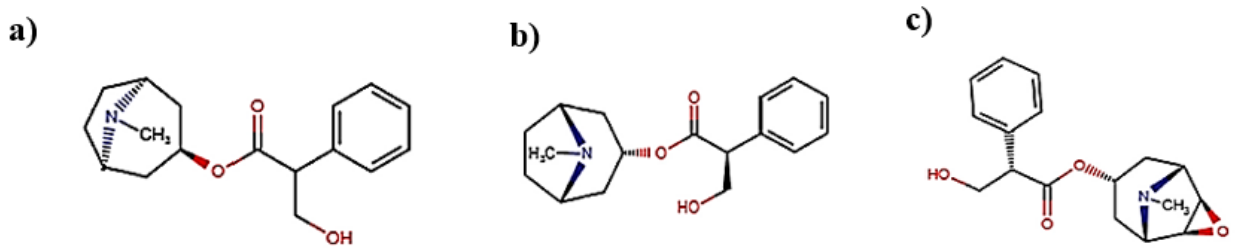

Figure 2 The structure of common tropane alkaloids (TAs) (a) Atropine (b) Hyoscyamine (c) Scopolamine [42]

According to [15], the TA-containing plants have been used by old folks for folkloric and medicinal purposes due to their anticholinergic properties and hallucinogenic effects, which can cause constipation, photophobia, pupil dilatation, vision disturbance, and dryness of upper digestive and respiratory tract mucosa. Exposure to TAs can happen either through direct ingestion of *Datura* species for their psychoactive properties or indirect ingestion of TA-contaminated foods. The presence of *D. stramonium* in freshly cut hay or maize is usually the source of TAs that causes poisoning incident in horses and cattle [43-45]. But, in low dosage the TAs can be absorbed by gastrointestinal tract and extensively distributed to animal or human tissues, and later excreted from body through urine [40, 42].

The pupillary dilation and neurobehavioral consequences are the common toxicological effects occur in experimental animals [46]. In humans, TAs prevent the interaction of acetylcholine to its receptor. This reaction may affect the heart rate, respiration and functions of central nervous system. For example, scopolamine is a competitive antagonist of acetylcholine at both peripheral and central muscarinic receptors [41]. This reaction may lead to the toxicological effects on humans and animals, which for severe cases may lead to the death of both organisms due to respiratory failure [25, 47].

4.3. Piperidine alkaloids

Piperidine alkaloids are characterized by a six-membered nitrogen heterocyclic ring [48]. Their toxicity is recognized based on the ability of these compounds to desensitize nicotinic acetylcholine receptors (nAChRs) by targeting the ligand-gated cation channels that mediate the activity of acetylcholine in excitatory neurotransmission [49]. *Conium maculatum* (Poison Hemlock) is a well-known plant that consists several piperidine alkaloids such as coniine (Figure 3a) and γ-coniceine (Figure 3b) [24]. According to Diaz [25], coniine was the first alkaloid that chemically synthesized in 1886.

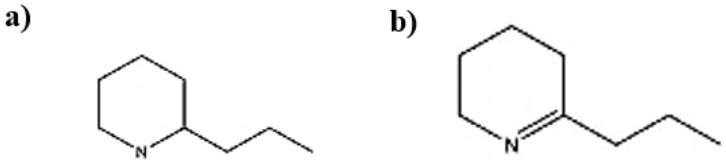

Figure 3 The structure of piperidine alkaloids (a) Coniine (b) γ-Coniceine [49]

Piperidine alkaloids can give an acute toxic response to the adult livestock animals by causing musculoskeletal deformities. This acute response can be seen through the symptoms of frequent urination and defecation, muscle weakness, tachycardia, ataxia, muscular weakness, collapse and death due to respiratory failure [15]. Green *et al.* [49] further stated that the teratogenic effects of piperidine alkaloids can lead to multiple congenital contracture deformities and cleft palate in pigs, goats, cattle and sheep. In humans, an accidental consumption of alkaloid containing plants may induce the toxicity symptoms. Herbal medication is a common source of these alkaloids if the medicines are incorrectly prepared or the herb plants are incorrectly used due to misidentification [48]. Table 4 shows the toxicity effects of piperidine alkaloid from different plant species on humans and animals.

Table 4 Toxicity effects of piperidine alkaloids

Plants	Piperidine compounds	Toxicity effects	References
Conium maculatum	Coniine, γ-coniceine	Associated with accidental and deliberate deaths in humans Paralysis of the musculature due to the blockade of the neuromuscular junctions	[50]
	Conium	Congenital malformations in calves including cleft palate and musculoskeletal contractures	[24]
Equisetum palustre	Palustrines, Palustridienes	Unpalatable to cattle due to its high silicate content Lack of appetite, emaciation, decrease in milk yield and diarrhea	[51]
Prosopis juliflora	Juliprosopine, Juliprosine	Neurotoxic damage in the central nervous system of cattle and goats	[52]

4.4. Indolizidine alkaloids

Swainsonine (Figure 4) is an indolizidine alkaloid isolated from *Swainsona* plants [25]. The swainsonine can inhibit lysosomal hydroxylases such as α-mannosidase and Golgi α-mannosidase, hence leads to the cellular alteration that can be indicated by lysosomal storage disease due to excessive carbohydrate accumulation in lysosomes [53]. Most of the swainsonine poisoning cases are caused by locoweeds species such as *Astragalus spp.* and *Oxytropis spp.* [24].

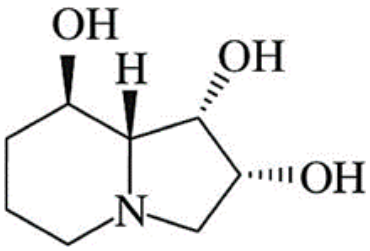

Figure 4 The structure of swainsonine [54]

According to Chenchen *et al.* [55], ingestion of locoweeds by cattle, sheep and horses can cause the neurological condition called locoism. Apart from that, the swainsonine toxicity may also cause intention tremors, depression, nervousness, proprioceptive deficits, aberrant behavior, emaciation, reproductive dysfunction and death [53, 55]. There are cases of swainsonine poisoning on animals such as a horse where the animal shows a symptom of excitement, exaggerated fright reaction, trembling and mild ataxia [56].

Apart from locoweeds, *Ipomoea carnea* (batatilla) is one of the plants that accumulates swainsonine, and widely used for hedging [25, 57]. The plant has been reported to contain toxic alkaloids that can inhibit mannosidase and glycosidase, hence causes lysosomal storage disease in animals. Goats that consumed this plant showed poisoning symptoms such as ataxia, head tremor and nystagmus [57].

5. Conclusion

Even though the plant alkaloids have been widely used in the pharmacological especially in the drug discovery, some of these alkaloids show toxicity effects on humans and animals. The precise identification of alkaloid containing plants needs to be done to reduce the poisoning cases. Profiling and identification of toxic alkaloids in plants can definitely help in reducing the risk of taking poisonous plants. Also, the toxicity studies can precisely determine the toxicity level of these alkaloids as well as understand their mode of action in humans and animals.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that there is no conflict of interest.

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