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REVIEW

Transition of Therapeutic to Toxicological Effects of Certain Plant Alkaloids: A Critical Review Based on their Forensic Perspective

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The secondary metabolites have a significant property of therapy as well as toxicity. One among the secondary metabolite that is enormously present in plants is alkaloids. The occurrence of the alkaloid is found to be about 20% in the plants. These compounds have a useful therapeutic application in health disorders. On the other hand, they also cause toxicity to humans as well as animals. Their toxicity levels in humans may tend to affect the gastrointestinal and nervous systems. In this review, occurrence, synthesis and the toxicity levels of non-heterocyclic alkaloids *viz. N*-methyl tyramine and colchicine as well as heterocyclic alkaloids, *viz.* derivatives of pyrrolizidine (seneciphylline, echimidine), purine (caffeine, theobromine), indole (ergotamine, brucine) and glycoalkaloids (solanine, tomatine) are discussed. The detection of these alkaloids by chromatographic techniques is also underlined.

Keywords: Plant alkaloids, Therapeutics, Toxicity, Detection, Forensic perspective.

INTRODUCTION

Plants consist of various compounds that aid their growth and development. The plant metabolites and extracts of the plant metabolites have an outburst commercial importance in recent trends. Upon the perception of the function the compounds present in the plants are classified into three groups such as primary metabolites, secondary metabolites and hormones [1]. A primary metabolite is a kind of metabolite that is directly involved in normal growth, development and reproduction. The *s*econdary metabolites specifically modulate health-maintaining processes, including excretion of waste and toxic products from the body and the hormones regulate organismal processes [2]. The primary metabolites are typically formed during the growth phase as a result of energy metabolism and are deemed essential for proper growth [3]. Prominently, the primary metabolism is being involved in the growth and development and reproduction of the cell [4]. The primary metabolites include the carbohydrates, proteins and lipids which have a definite role in the growth and development of a plant. When a plant recognizes the stress caused by any bacteria or viruses the primary metabolites trigger the signals for the defense response [5].

The name "secondary metabolites" was coined by A. Kossel in 1891; who described these organic compounds as incidentally occurring and not of vital significance to plant life [6]. Majority of these compounds indirectly participate in growth, development and reproduction of plants so it was named "secondary metabolites" [7]. These secondary metabolites exist vastly in plants and they play a vital role in the abiotic and biotic stresses caused to the plant. Though the secondary metabolites are familiar for their defense mechanism, they also involve in the integration of primary metabolism and regulation of hormones for the growth and development of plants along with the primary metabolites. These secondary metabolites include major groups of compounds that are specific in plants and aid plants to react with the biotic and abiotic environments [8].

The secondary metabolites are the major constituents of specific odour, colour and taste of plants and their parts. Earlier these compounds were considered to be biologically inconsequential and therefore a little attention was drawn to them. Later, when the chemical structures and properties were emp-

hasized during 1850s, these compounds received a unique method of study. Recent studies show prominently that secondary metabolites play a vital and key role in potential defense mechanisms, especially in the stress caused to the plant by the environmental factors that could be biotic or abiotic [9]. As the secondary metabolites are more prominent in the defense they produce various compounds that may cause toxic effects to the stress inducing factor, which is present in the different parts of plants. The role of secondary metabolites is shown in Fig. 1.

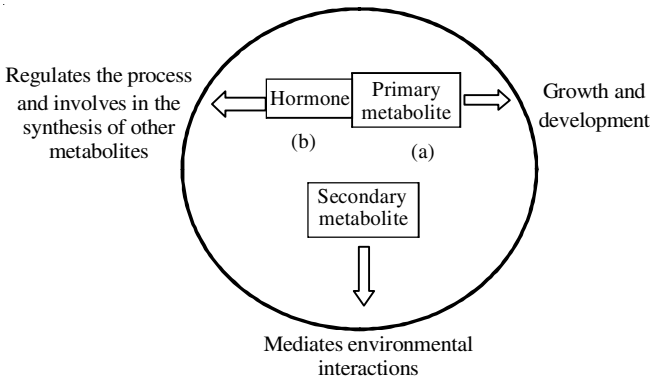

Fig. 1. (a) Secondary metabolites involve in the growth and development; (b) Secondary metabolites involve in the regulations of processes

It is said that more than 200,000 secondary metabolites are found to be in the plants [10]. Generally, the secondary metabolites are classified into (1) alkaloids, (2) terpenoids and (3) phenolic compounds [11]. Alkaloids are an assembly of naturally occurring chemical composites, which typically comprise basic nitrogen atoms. They may also contain some neutral or weakly acidic compounds [12]. Some synthetic compounds are also included in alkaloids [13]. Terpenoids are pervasive and they mainly contribute the flavour, aroma and shades in leaves, flowers and fruits [14]. Phenolic compounds are ubiquitary in all the parts of a plant and they play an integral part of the diet of humans [15]. Progressive studies suggest that few alkaloids are distinct in physiological function in plants, such as to protect them against certain pathogens, insects, or animals, to mediate signaling process in plants and to regulate the seed formation and ripeness [16]. Conjointly, the toxicity of alkaloids in plants is generally classified based on their dosage, exposure time, sensitivity, site of action, *etc.* [17]. This review article is mainly dealt with the properties of different alkaloids exist in plants. Further, their toxic effects on humans and animals are also discussed.

General description about alkaloids: Alkaloids are the group of organic compounds that contains nitrogen and widely found in plants, fungi, bacteria and animals [18]. In 1819, a German chemist, Carl F.W. Meissner coined the term "alkaloid" which originates from Arabic al-gali [6]. The alkaloids are derived from the amino acid tyrosine [19]. Because of the existence of nitrogen, these compounds have been used in pharmacological and medication fields [20]. As the nitrogen has one lone pair of electrons, it can accept the protons whereas the hydrogen in the primary and secondary amine can act as a proton donor [21].

The occurrence of the alkaloid is found to be about 20% in the plants [22]. Almost 12,000 alkaloids are extracted from different genera of the plants [23]. The alkaloids are common in the plants of the families of apocynaceae, annonaceae, amaryllidaceae, berberidaceae, boraginaceae, gnetaceae, liliaceae, leguminoceae, lauraceae, loganiaceae, magnoliaceae, rutaceae, menispermaceae, papaveraceae, piperaceae, ranunculaceae, rubiaceae, solanaceae, *etc.* [24].

Earlier, it was classified based on the similarity of the carbon skeleton [25]. Later the alkaloids were classified by their chemical structure and their biochemical origin. The structural classification is based on the presence of the ring and it was classified as non-heterocyclic alkaloid (proto-alkaloids) and heterocyclic alkaloid (typical alkaloids). The different types of alkaloids based on their chemical composition are presented in Table-1.

Non-heterocyclic alkaloids: The non-heterocyclic alkaloids (NHA) are commonly known as the proto-alkaloids. These are also derived from the amino acids, which do not contain a heterocyclic ring in their structure [26]. The main precursors of non-heterocyclic alkaloids are L-tryptophan and L-tyrosine. These non-heterocyclic alkaloids are the minor groups which are structurally composed of simple alkaloids. Yohimbine, mescaline and *N*-methyl tyramine and colchicine are the main alkaloids of non-heterocyclic alkaloids. These compounds have a useful therapeutic application in health disorders, including mental illness, pain and neuralgia [27-29]. On the other hand, they also cause toxicity to humans as well as animals.

***N*-Methyltyramine (NMT):** *N*-Methyltyramine (4-[2-(methylamino)ethyl]phenol; NMT, Fig. 2a) is a naturally occurring protoalkaloid that occurs in a variety of plants [30]. The

TABLE-1
IMPORTANT ALKALOIDS BASED ON THEIR CHEMICAL COMPOSITION

Type of alkaloid	Compounds		Occurrence
Non-heterocyclic alkaloid	*N*-Methyl tyramine		Acacia, citrus fruits, fermented foods, cheese (cheddar)
	Colchicine		*Colchium autumnale* L
Heterocyclic alkaloid	Pyrrolizidine	Seneciphylline	*Gynurajapoica*
		Echimidine	*Echiumplantaginum*
	Purine	Caffeine	*Coffeaarabica* and *C. canephora*
		Theobromine	*Theobroma cacao*
	Indole	Ergotamine	*Clavicepspurpurea*
		Brucine	*Strychnosnux-vomica*
	Glycoalkaloid	α-Solanine	*Solanum nigrum*
		α-Tomatine	*Lycopersiconesculentum*

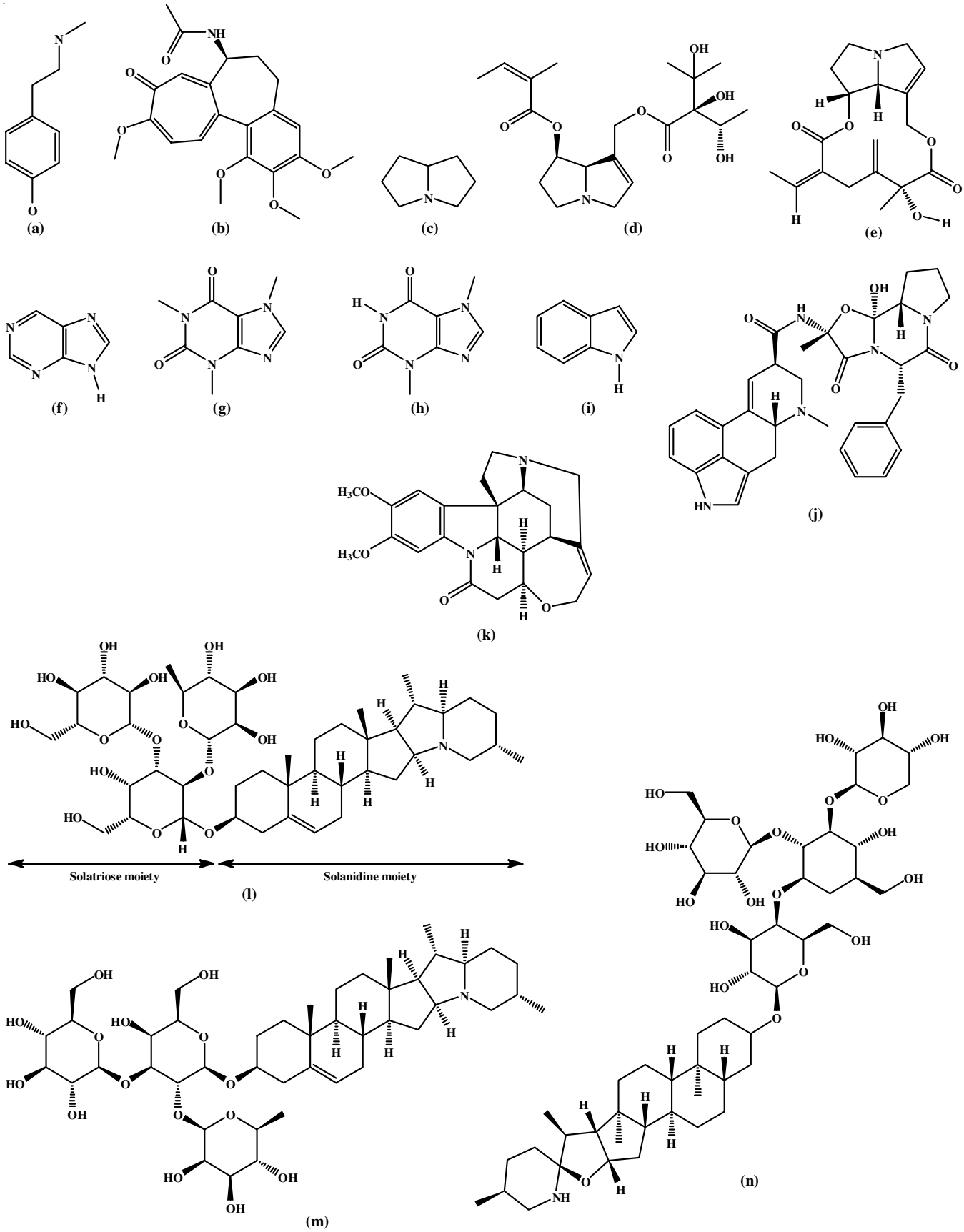

Fig. 2. Chemical structures of different types of alkaloids: (a) *N*-methyl tyramine, (b) colchicine, (c) pyrrolizidine, (d) seneciphylline, (e) echimidine, (f) purine, (g) caffeine, (h) theobromine, (i) indole, (j) ergotamine, (k) brucine, (l) glycoalkaloid, (m) α-solanine, (n) α-tomatine

properties of NMT are presented in Table-2. The NMT is a trace amine compound of amino acid tyramine. The tyramine is generally commonly degraded by monoamine oxidase. Also, the decarboxylase enzyme converts the tyrosine to tyramine [31]. The tyramine is found in the fermented foods, aged and pickled foods, *etc.* The first NMT from germinating roots of barley was isolated on 1950 and found to have 2 mg/g of malted barley [32]. A similar compound *N*,*N*-dimethyltyramine (hordenine) was also found to be present in various barley products. NMT was vastly present in beer as a result of the malted barley at a concentration of 2 mg/mL based on the amount and type of malted barley used [33]. Metabolic details are indicated in Fig. 3.

TABLE-2
PROPERTIES OF *N*-METHYL TYRAMINE (NMT) [29]

IUPAC name	4-[2-(Methylamino)ethyl]phenol	
m.w.	151.21 g/mol	
m.f.	$C_9H_{13}NO$	
$T_{1/2}$	5.6 min	
Ld50 (mouse)	Intraperitoneal	780 mg/kg
	Intravenous	275 mg/kg

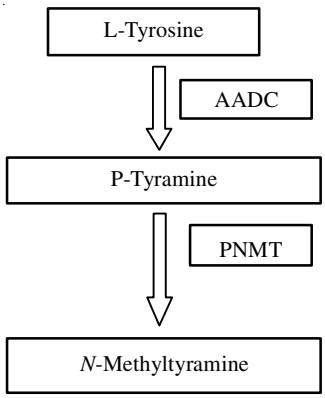

Fig. 3. Metabolic fate of tyrosine; AADC-l-amino acid decarboxylase; PNMT-phenylethanolamine *N*-methyltransferase

Toxicity of NMT: Tyramine functions as a substrate for monoamine oxidase, further limiting the breakdown of monoamine neurotransmitter [34]. In the absence of tyramine assimilation, tyramine is formed internally by the decarboxylation process of the amino acid tyrosine upon the action of enzyme aromatic L-amino acid decarboxylase (AADC) [35]. Followed by the enzyme phenylethanolamine, *N*-methyltransferase converts tyramine to form *N*-methyltyramine. The ingestion of tyramine supplants norepinephrine, epinephrine and dopamine from presynaptic storage vesicles [36]. This leads to the release of neurotransmitters, especially norepinephrine, which causes vasoconstriction, tachycardia and elevates blood pressure. Therefore, tyramine acts as an indirect sympathomimetic by releasing presynaptic endogenous neurotransmitters. Ingestion of high tyrosine content diet along with monoamine oxidase inhibitors produces headaches, blurry vision, chest pain and palpitations associated with hypertension, intracranial, hemorrhages and myocardial injury [37].

Colchicine: Colchicine is an alkaloid extracted from plants of the genus *Colchicum* (autumn crocus). It is often confused with autumn crocus (*Colchicum autumnale* L.) and Lily of the valley (*Convallaria majalis* L.) and they don't contain any significant toxins [38]. The structure of colchicine is shown in Fig. 2b. The properties of colchicine are presented in Table-3. The therapeutic use of colchicine has been well documented for the treatment of gout and familial Mediterranean fever (FMF) in humans. It has also been used in the treatment of other diseases including Behcet's disease (BD), pericarditis, coronary artery disease and other inflammatory and fibrotic conditions [39,40]. Their pharmacological characteristics are said to be beneficial for the treatment of gout (inflammatory arthritis) [41]. The biosynthesis of colchicines from dopamine is presented in Fig. 4.

TABLE-3
PROPERTIES OF COLCHICINE [38]

IUPAC name	*N*-[(7*S*)-1,2,3,10-Tetramethoxy-9-oxo-6,7-dihydro-5*H*-benzo[a]heptalen-7-yl]acetamide	
m.w.	399.4 g/mol	
m.f.	$C_{22}H_{25}NO_6$	
$T_{1/2}$	20-40 h	
Tdl_0	Man	510 µg/kg (0.51 mg/kg)
	Woman	400 µg/kg (0.4 mg/kg)

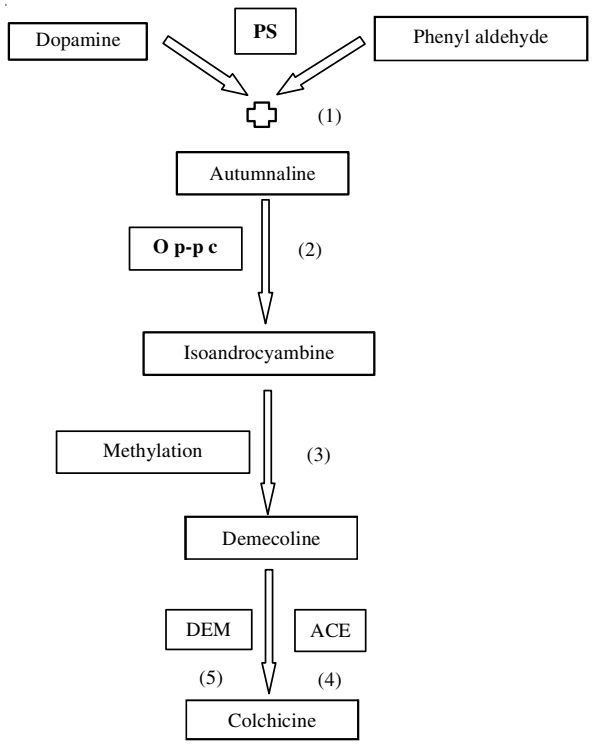

Fig. 4. Biosynthesis of colchicine from dopamine; (1) Dopamine and phenol aldehyde condenses to form autumnaline; (2) Autumanline undergoes oxidative phenol-phenol coupling and forms (S)-Isoandrocymbine; (3) (S)-isoandrocymbine underrgoes methylation to form the demecolcine; (4) Demecolcine further undergoes demethylation of the methyl group and then it acquires acetyl through acetylation and forms colchicine

Toxicity of colchicine: Colchicine's toxicity is an extension of its mechanism of action mainly based on its binding with tubulin which may disrupt the microtubular network [42]. Upon assimilation and absorption, colchicine tends to bind with the intracellular protein tubulin which in turn inhibits the

polymerization of microtubule. This effect may change the composition of a protein present in the Golgi apparatus, reduce endocytosis and change the structure and motility of a cell. It may lead to an inhibitory action over mitosis and affect the cell cycle [43]. Also, it may cause interrupted cardiac myocyte conduction and contractility which may lead to multi-organ dysfunction and failure [44,45]. Their mortality by the ingestion is found to be occasional, which can also cause adverse effects on humans.

Heterocyclic alkaloids: The heterocyclic compounds are also known as typical alkaloids as they contain a nitrogen atom in the ring. The heterocyclic alkaloids were further divided into 14 groups with respect to the ring structure, *viz.* pyrrole and pyrrolidine, pyrrolizidine, pyridine and piperidine, tropane, quinoline, isoqunoline, aporphine, quinolizidine, indole or benzopyrrole, indolizidine, imidazole or glyoxaline, purine (pyrimidine/imidazole) and glycoalkaloids [37]. Among them, few important types are discussed below:

Pyrrolizidine alkaloids: Pyrrolizidine alkaloids are group of ester alkaloids that contain the necine bases and necic acid moiety as illustrated in Fig. 2c. These are commonly found in the plants that they come under the family asteraceae, boraginaceae and fabaceae [46,47]. Most of the pyrrolizidine alkaloids present as *N*-oxides in the plants [48]. They remain toxic due to the presence of the 1,2-double bond at the necic moiety. This is converted into the reactive pyrroles by the oxidase, which then reacts with the nucleic acid and the proteins [49]. The ingestion of grains contaminated by pyrrolizidine alkaloids may cause acute or chronic liver toxicity. Manifestation of the pyrrolizidine alkaloid toxicity involves the abdominal pain, ascites, nausea, vomiting, diarrhea, dropsy, jaundice and fever [50]. The pyrrolizidine alkaloids such as seneciphylline and echimidine are discussed further.

Seneciphylline: Seneciphylline (Fig. 2d), consists of 12-membered diester compound, which forms a macrocycle derived from retronecinepyrrolozidine [51,52]. The properties of seneciphylline are presented in Table-4. The necine base is obtained from the amino acids L-arginine or L-ornithine along with the similar intermediates such as putrescine and homospemidine [53] and the necine moiety derived from the precursor L-isoleucine [54]. Initially, it was determined to have the pharma-ceutical properties and used in the treatment for blood stasis [55]. The synthesis of seneciphylline is shown in Fig. 5.

Toxicity of seneciphylline: Seneciphylline, the derivatives of pyrrolizidine alkaloids tend to be metabolically active in the liver and they are capable of alkylating the proteins and the DNA molecules [56,57]. Earlier in 1954, it was found that

TABLE-4
PROPERTIES OF SENECIPHYLLINE [51]

IUPAC name	(1*R*,4*Z*,7*R*,17*R*)-4-Ethylidene-7-hydroxy-7-methyl-6-methylidene-2,9-dioxa-14-azatricyclo-[9.5.1.$0^{14,17}$]heptadec-11-ene-3,8-dione	
m.w.	333.4 g/mol	
m.f.	$C_{18}H_{23}NO_5$	
$T_{1/2}$	0.631 h	
Ld50 (mouse)	Intraperitoneal	77 mg/kg (77 mg/kg)
	Intravenous	80 mg/kg (80 mg/kg)

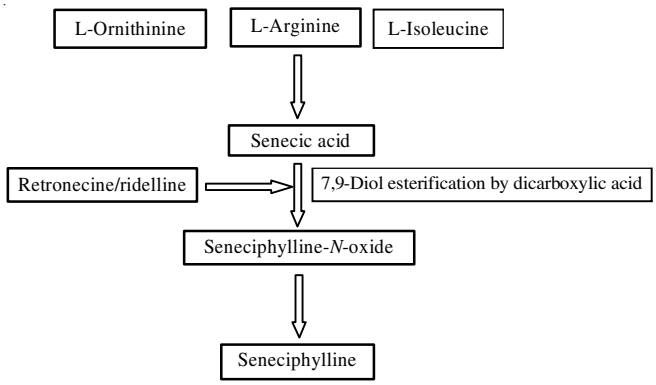

Fig. 5. Synthesis of seneciphylline from the amino acid moiety of necine and necic acid

the retronecine and its derivatives are capable of inducing tumor upon experiment [58]. Later, the mechanism was studied and found to be formation of DNA adducts by the riddelline in the form of DHPA [59]. These molecules are remarked as hepatotoxic which can cause acute to chronic toxicity effects. Depending on the intoxication, the toxic effects can be of three classes, *viz.*, acute, sub-acute and chronic. Acute toxicity leads to hemorrhagic necrosis, hepatomegaly and ascites. Whereas the sub-acute toxicity forms blockage in the hepatic veins which causes the hepatic sinusoidal obstruction syndrome (HSOS) [60]. The chronic toxicity leads to the fibrosis, necrosis, cirrhosis and the proliferation of the bile ducts [61].

Echimidine: Plant genera-producing pyrrolizidine alkaloids are the major constituents of honey production. The bees forage mainly on the echium species for the making of honey, which constitutes echimidine as the major alkaloid [62,63]. A species of boraginacaea family, *Echium plantagineum* produces echimidine (Fig. 2e), in the roots along with naphthoquinones. The properties of echimidine are presented in Table-5. The metabolism of the echimidine takes place in the hepatic system by hepatic microsomal enzymes which convert this compound into pyrrole derivative. The toxicity is indicated by weakness, weight loss, lethargy, yawning, photosensitivity and depression. The synthesis of echimidine is presented in Fig. 6.

TABLE-5
PROPERTIES OF ECHIMIDINE [62]

IUPAC name	[(7*R*,8*R*)-7-[(*Z*)-2-Methylbut-2-enoyl]oxy-4-oxido-5,6,7,8-tetrahydro-3*H*-pyrrolizin-4-ium-1-yl]methyl(2*R*)-2,3-dihydroxy-2-[(1*S*)-1-hydroxyethyl]-3-methylbutanoate	
m.w.	413.5 g/mol	
m.f.	$C_{20}H_{31}NO_8$	
$T_{1/2}$	0.721 h	
Ld50 (mouse)	Intraperitoneal	518 (228.9-654.3) mg/kg

Toxicity of echimidine: After the ingestion of echimidine, it is absorbed from the gastrointestinal tract and transferred to the hepatic system [64]. The echimidine metabolized the hepatic enzymes into the pyrrole derivatives, which are very toxic derivatives [65]. Pyrrolizidine alkaloids are oxidized by cytochrome P450 enzymes (CYP), which converts them to the reactive and toxic pyrrole derivatives. They are capable of reacting with the nucleophiles, nucleosides and proteins. This may cause modi-

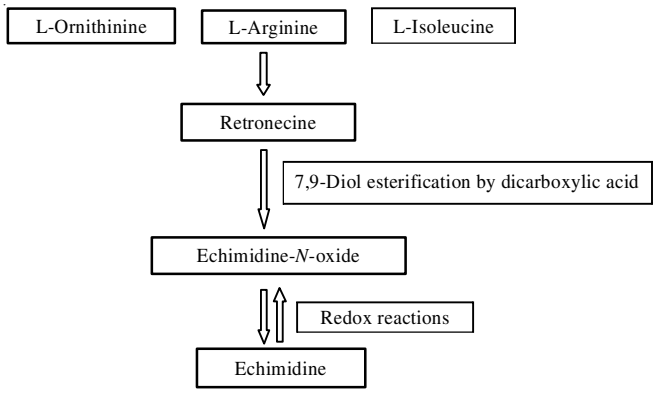

Fig. 6. Synthesis of the echimidine from the amino acids

fications in the DNA and lead to adverse toxic effects [66]. This compound may also cause necrosis and apoptosis in humans [67].

Purine alkaloids: Purine (Fig. 2f), a nucleotide that contains nitrogenous base, which is the building blocks of DNA and RNA. The nucleotides consist of purine ring and a ribose sugar and have a pyrimidine base. Some of the common purine alkaloids are caffeine, theophylline, theobromine and theacurine. These compounds act as a pollinator's attraction compound and also as the insecticides. Their toxic effects generally include anxiety, insomnia and nausea and increase in the blood pressure [68,69].

Caffeine: The genera of *coffea* have more than 100 species commonly distributed in the tropical and subtropical areas. The economically habitual species is found to be *C. arabica* and *canephora.* Hitherto *C. arabica* is analyzed vastly since it has thetetraploidic chromosomes. It is also contemplated to be a segmental polyploid for the presence of disomic inheritance and meiotic etiquette [70,71]. It is the best known as a CNS stimulant and also recently reported for the anti-inflammatory and antioxidant properties were reported [72]. The properties of caffeine are presented in Table-6. Caffeine (Fig. 2g) can increase the metabolic action activity therefore which can induce cell proliferation by producing higher energy levels to the cells [73]. The synthetic fate of caffeine is shown in Fig. 7.

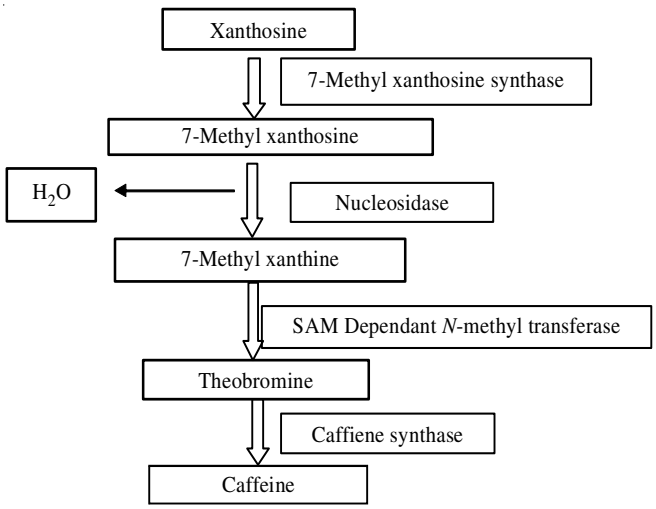

Fig. 7. Synthetic fate of caffeine

TABLE-6
PROPERTIES OF CAFFEINE [70,71]

IUPAC name	1,3,7-Trimethylpurine-2,6-dione	
m.w.	194.19 g/mol	
m.f.	$C_8H_{10}N_4O_2$	
$T_{1/2}$	About 5 h	
Ld50 (albino rats)	Oral administration	367/mg/kg

Toxicity of caffeine: The structure of caffeine is similar to purine base adenine, which modulates the nervous signal transmission [74]. The caffeine competes to bind at the adenosine receptor and delays the sleepiness, which is activated by the adenosine [75,76]. It also triggers seizures with A1 antagonism and cerebral and coronary vasoconstriction with A2. The caffeine inhibits the enzyme phosphodiesterase, which leads to the elevation of intracellular cyclic AMP and calcium levels. It also creates an induction for the release of catecholamines specifically noradreanline with β1 antagonism. This may lead to tachycardia, peripheral vasodilation and hypotension with β2 antagonism [77].

Theobromine: Theobromine (Fig. 2h) is predominant alkaloid in the seeds of *Theobroma cacoa.* This compound constitutes about 1.5-3% in the cacoa beans. It is commonly found in the chocolate, tea and cocoa products. It is the precursor for the caffeine production. Earlier, theobromine and its derivatives, *viz.* theophylline and paraxanthine used as diuretics, myocardial inducers, vasodilators and muscle relaxants. The salts such as calcium salicylate, sodium salicylate and acetate are used to dilate the coronary arteries [78,79]. The properties of theobromine are presented in Table-7. Synthesis of theobromine from xanthosine is presented in Fig. 8.

TABLE-7
PROPERTIES OF THEOBROMINE [79]

IUPAC name	3,7-Dimethylpurine-2,6-dione	
m.w.	180.16 g/mol	
m.f.	$C_7H_8N_4O_2$	
$T_{1/2}$	2.5-5 h	
LD50 (Albino Rats)	Oral administration	950 mg/kg

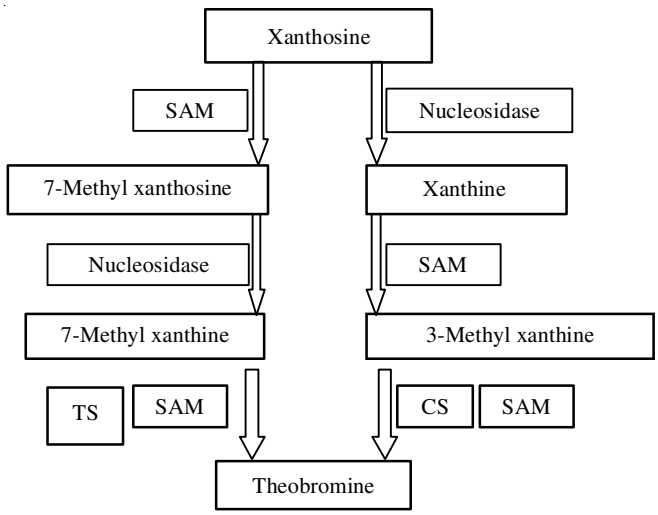

Fig. 8. Synthesis of theobromine from xanthosine; SAM = S-adenosylmethyl transferase; TS = theobromine synthase; CS = caffeine synthase

Toxicity of theobromine: Theobromine metabolized into caffeine and paraxanthine in the hepatic system. The theobromine is capable of widening blood vessels and the ingestion beyond 0.8-1.5 g daily is found to be affected. The toxicity is indicated by sweating, trembling and severe headaches and anorexia. It is reported that the higher ingestion of the theobromine induces sister chromatid exchanges indirectly [80].

Indole alkaloids (IA): Indole alkaloids (Fig. 2i) are the vast group of alkaloids and are derived from tryptophan. These are bicyclic compounds that resemble the purine structure with an aromatic ring and a pyrrole ring. In indole alkaloids, the nitrogenous base is present in the pyrrole ring and found in the plants, *viz. Loganiaceae*, *Nyssaceae*, *Apocynaceae* and *Rubiaceae.* The neurotransmitter serotonin and the amino acid tryptamine are derivatives of indole alkaloids within brain [81,82]. These molecules feature polyhalogenation frequently. Further classification of the indole alkaloids are shown in Table-8.

TABLE-8
CLASSIFICATION OF INDOLE ALKALOIDS [28]

Type of alkaloid	Example
Simple alkaloids	Aplysinopsin, gramine
Bisindoles	Indirubin, 6,60-dibromoindigotin
Simple tryptamine alkaloids	Tryptamine
Cyclotryptamine alkaloids	Physostigmine
Quinazolinocarbazole alkaloids	Rutaecarpine
β-Carboline alkaloids	Harman
Ergot alkaloids	Ergotamine
Carbazole alkaloids	Ekeberginine
Indolonaphthyridine alkaloids	Canthin-6-one

Ergotamine: Ergot alkaloids are predominantly produced by *Claviceps purpurea* a fungal pathogen [83]. The properties of ergotamine (Fig. 2j) are presented in Table-9. It mainly presents in the plants of *Poaceae* family, *viz.* rye, triticale, wheat, barley and sorghum. Ergotamine is a compound with tetracyclic ring of ergoline. It has a remarkable pharmaceutical property where it was used in post-partum hemorrhage during child birth. Later, it was used to treat migrane attacks [84]. The synthesis of ergotamine from agroclavine is presented in Fig. 9.

Toxicity of ergotamine: Ergotamine is also an antagonist of adreno receptor and also a potent vasoconstrictor. These molecules, are closely related to serotonin and this is capable of recognizing and binding to 5-HT-1d receptors, which reduce the blood flow in the cerebral arteries leading to vascular headaches [85,86]. Prominently ergotamine stimulates bradycardia even in normal blood pressure. This also elevates vagal activity and causes myocardial depression. As ergotamine is a vasoconstrictor, it causes ischemic changes and anginal pain in a coronary artery. Also vascular stasis, thrombosis and gangrene are prominent in ergot poisoning [84].

TABLE-9
PROPERTIES OF ERGOTAMINE [83]

IUPAC name	3,7-Dimethylpurine-2,6-dione	
m.w.	581.7 G/Mol	
m.f.	$C_{33}H_{35}N_5O_5$	
$T_{1/2}$	2 h	
Tdl0 (Human)	Subcutaneous	171 µg/Kg

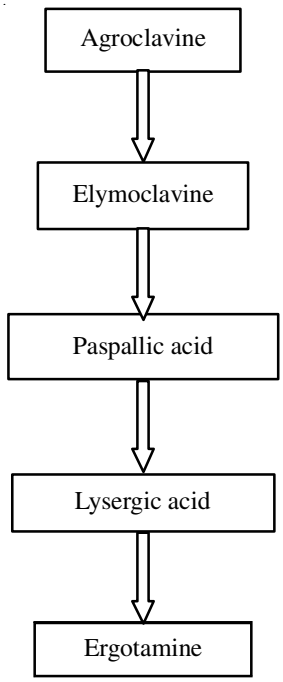

Fig. 9. Synthesis of ergotamine from agroclavine [85]

Brucine: 2,3-Dimethoxystrychnidin-10-one, known as brucine (Fig. 2k), which is the dimethoxy form of strychnine and is found in *Strychnosnux-vomica*. The properties of ergotamine are presented in Table-10. Brucine seeds constitute the highest alkaloid content which is used in the chemical industry. It is used as an additional agent in the paints and oils. It is used for the study of glycine receptors. It mainly involves in the inhibition of angiogenesis. It was also used to alleviate physical and emotional distress and it acts as an antioxidant [86,87]. The synthesis of brucine is presented in Fig. 10.

TABLE-10
PROPERTIES OF BRUCINE [86]

IUPAC name	2,3-Dimethoxystrychnidin-10-one
m.w.	394.5 g/mol
m.f.	$C_{23}H_{26}N_2O_4$
$T_{1/2}$	9 h
Tdl_0 (1 g)	Oral

Toxicity of brucine: Featured concentrations lie in between toxic to therapeutic action of brucine. This toxicity mainly affects the nervous system followed by immune, urinary and digestive systems. Though it is less toxic than strychnine, it causes stiff neck, anxiety, convulsions, euphoria, rhabdomyolysis and renal failures. The mechanism of toxication is found that brucine acts as an antagonist of glycine receptors which paralyzes the peripheral nerve endings leading to convulsions [88].

Glycoalkaloids: Plants from the *Solanaceae* family are prominent for the presence of glycoalkaloids. These compounds retain nitrogenous base in their structure along with the sugar molecules. Depending on the removal of sugar molecules, they are classified as α, β, γ and δ. The removal one sugar molecule is known as α-glycoalkaloids and two molecules known as β-glycoalkaloids, γ-alkaloids and δ-alkaloids are

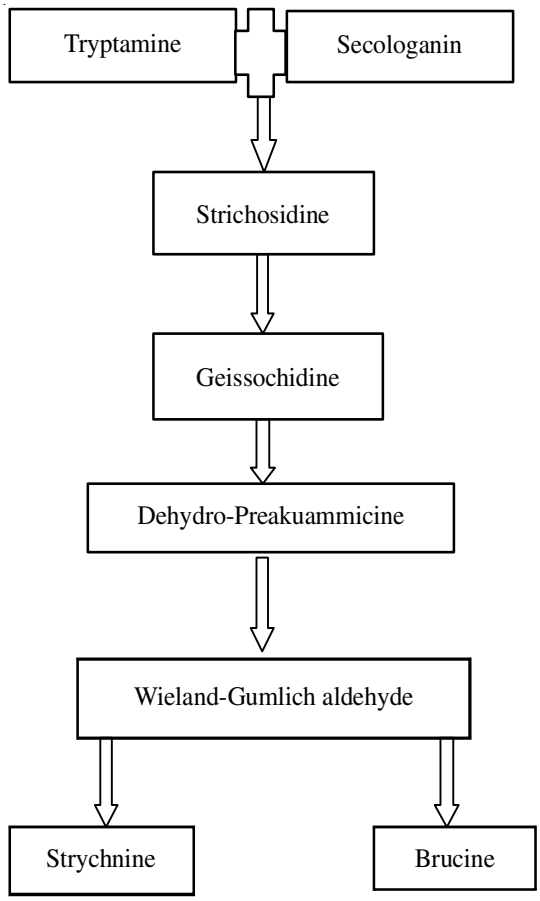

Fig. 10. Synthesis of brucine [88]

based on removal of more two sugar molecules. Some of the common glycoalkaloids are α-solanine and α- tomatine, α-chaconine [89,90]. The structure of glycoalkaloid with solatriose and solanidine moieties is presented in Fig. 2l.

α-Solanine: α-Solanine (Fig. 2m), a glycoalkaloid found in the *Solanum tuberosum* (potatoes). The properties of α-solanine are presented in Table-11. It is a derivative of solanidine. It is reported that it has an apoptotic inducing capability and it involves in the antineoplastism [91-93]. It has a longest half-life of 21 h. When potatoes are exposed in the cold temperature for a prolonged time, the chlorophyll is formed along with the solanine, which are accumulated in the periderm and in the cortical parenchyma [94]. It is reported that α-solanine tends to inhibit the proliferation and induce apoptosis [95,96]. The synthesis of solanine is presented in Fig. 11.

TABLE-11
PROPERTIES OF α-SOLANINE [92]

IUPAC name	(2*S*,3*R*,4*R*,5*R*,6*S*)-2-[(2*R*,3*R*,4*S*,5*S*,6*R*)-5-Hydroxy-6-(hydroxymethyl)-2-[[(1*S*,2*S*,7*S*,10*R*,11*S*,14*S*,15*R*,16*S*,17*R*,20*S*,23*S*)-10,14,16,20-tetramethyl-22-azahexacyclo[12.10.0.0^{2,11}.0^{5,10}.0^{15,23}.0^{17,22}]tetracos-4-en-7-yl]oxy]-4-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxyoxan-3-yl]oxy-6-methyloxane-3,4,5-triol
m.w.	868.1 g/mol
m.f.	$C_{45}H_{73}NO_{15}$
$T_{1/2}$	21 h
Ld50	42 mg/kg

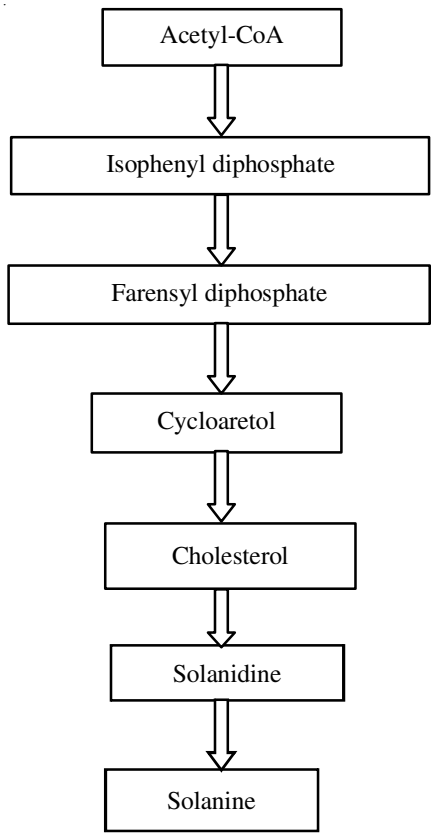

Fig. 11. Synthesis of solanine [96]

Toxicity of solanine: The derivative of glycoalkaloids possesses anticholinesterase activity, where it affects the nervous system and regulates the acetylcholine. This may cause adverse effects in the transmission of nerve impulses. The solanine also disrupts the cell membranes causing gastrointestinal damage indicated by vomiting, abdominal pains, diarrhea, headache and fatigue. The higher the concentration, higher the complications, *viz.* neurological disorders, rapid pulse, low blood pressure. Sometimes, this may lead to adverse effects causing comatose and death [93].

α-Tomatine: α-Tomatine (Fig. 2n), an glycoalkaloid with tetra-carbohydrate residues bound to the 3-OH group of tomatidine without glycol residues [97,98]. It was first isolated by fontaine that consist of tomatine and dehydrotomatine. The tomatine has the tetrasaccharide side chain as the hydrophilic and steroidal moiety as the hydrophobic part along with nitrogenous base as polar molecule. It is vastly active against invasion of pathogens causing their cell disruption. It is reported that they can exhibit antimicrobial and antioxidant properties [99]. The properties of α-tomatine are presented in Table-12. The synthesis of α-tomatine is shown in Fig. 12.

Toxicity of α-tomatine: α-Tomatine generally binds with the cholesterol and forms an insoluble complexes causing compromized cell membranes. The tomatine binds specifically with 3β-hydroxy sterols [99]. The alkaloid part of tomatine reacts with sterols and leaves the sugar residual part outside the membrane. This causes the loss of barrier function increasing matrix. This leads to disruption of the cells which may contain

TABLE-12
PROPERTIES OF α-TOMATINE [97]

IUPAC name	(2*S*,3*R*,4*S*,5*S*,6*R*)-2-[(2*S*,3*R*,4*S*,5*R*,6*R*)-2-[(2*R*,3*R*,4*R*,5*R*,6*R*)-4,5-Dihydroxy-2-(hydroxymethyl)-6-[(1*R*,2*S*,4*S*,5'*S*,6*S*,7*S*,8*R*,9*S*,12*S*,13*S*,16*S*,18*S*)-5',7,9,13-tetramethylspiro[5-oxapentacyclo-[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icosane-6,2'-piperidine]-16-yl]oxyoxan-3-yl]oxy-5-hydroxy-6-(hydroxymethyl)-4-[(2*S*,3*R*,4*S*,5*R*)-3,4,5-trihydroxyoxan-2-yl]oxyoxan-3-yl]oxy-6-(hydroxymethyl)oxane-3,4,5-triol	
m.w.	1034.2 g/mol	
m.f.	$C_{50}H_{83}NO_{21}$	
$T_{1/2}$	21 h	
Ld50	Oral	500 mg/kg
	Sub-cutaneous	25 mg/kg

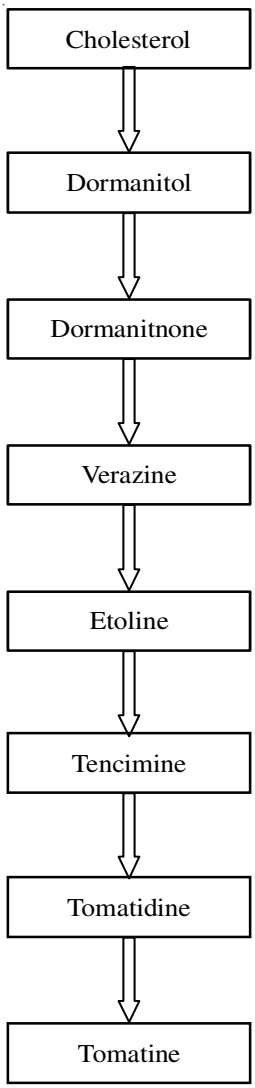

Fig. 12. Synthesis of α-tomatine [98]

the repairing molecules [100]. Disruption of the membrane is prominent in the toxicity of tomatine. It also opens pores of the membranes causing leakage of extracellular fluids and eventually causing cell death [101]. Though the absence of 3β-hydroxy sterols, it exhibits toxic effects. It was reported that it induces the production of reactive oxygen species through mitochondria and causes cell damage [102]. The toxicity is indicated by neurological symptoms, *viz.* depression, confusion, drowsiness and other symptoms, *viz.* vomiting, abdominal pain and weakness [103].

Detection of alkaloids by chromatographic techniques: There is a wide range of active compounds present in the alkaloids derived from plant extracts. Depending on their polarity index, separation techniques are used for their identification and characterization. Various analytical techniques are used for this purpose. The chromatographic analysis of few non-heterocyclic and heterocyclic alkaloids are presented in Table-13.

Conclusion

As Paracelsus states that "*there is none that is not poison, the right proportion differentiates remedy to toxic*", the alkaloids are utile in the therapeutics and pharmacological aspects up to certain concentration levels but they become toxic at high concentration levels. The alkaloids discussed in this review were formerly used in therapeutics and later found to have toxic effects. These alkaloids generally affect the gastro-intestinal and neurological systems. These alkaloids were well known for their defense against many parasite, invasion of pathogens, *etc.* Direct toxication caused by the exposure to the alkaloids literally resulting in the damage of important cells. Indirect toxication can be caused due to the ingestion or exposure to the contaminated or affected hosts. The alkaloid toxicity ranges from acute to chronic based on certain factors, *viz.* type of toxic chemical, its concentration, its effect on the body and its mode of ingestion. Though the alkaloids have pharmacological importance, they are recently focused for their toxic effects. Even though their mortality level is comparatively minimal, they may cause adverse effects in animals and humans because of certain unwanted reactions. Their mechanism of toxicity is to be focused and studied intensely.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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TABLE-13
CHROMATOGRAPHIC ANALYSIS OF NON-HETEROCYCLIC AND HETEROCYCLIC ALKALOIDS

	Alkaloid		Detection technique		LOD	Ref.
Non- heterocyclic alkaloids	*N*-Methyl tryptamine	HPLC	Column Particle size Flow rate Inj. vol. Column temp. Mobile phase	C_{18} (100 × 1.0 mm) 5 µm 40 µL/min 10 µL 40 °C A 50% methanol and 0.2% formic acid B 50% water and 0.2% formic acid	0.05 µg/L	[104]
	Colchicine	LC	Column Particle size Flow rate Inj. vol. Mobile phase (pH 3.5 adjusted with formic acid)	C_{12} (150 mm × 2 mm) 4 µm 200 µL/min 10 µL A Water:acetonitrile (5 mM ammonium formate) (90:10) B Acetonitrile:water (5 mM ammonium formate) (90:10)	3.5 ng/mL	[105]
Pyrrolizidine alkaloids	Seneciphylline	LC	Column Particle size Flow rate Inj. vol. Mobile phase	C_{18} (100 × 2.1 mm) 1.7 µm 400 µL/min 5 µL 0.1% Formic acid-water (v/v): Acetonitrile	1.3 µg/mL	[106]
	Echimidine	LC	Column Particle size Flow rate Inj. vol. Mobile phase	C_{18} (100 × 3.0 mm) 3.5 µm 500 µL/min 5 µL A Water: 0.1% formic acid B Acetonitrile: 0.1% formic acid	0.1 µg/mL	[107]
Purine alkaloids	Caffiene	LC	Column Particle size Flow rate Inj. vol. Mobile phase	C_{18} (100 × 2.1 mm) 3 µm 100 µL/min 10 µL A 95% 10 mmol/L ammonium formate: 5% methanol B 95% methanol: 5% 10 mmol/L ammonium formate	0.05 µg/mL	[108]
	Theobromine	UPLC	Column Particle size Flow rate Inj. vol. Mobile phase	C_{18} (50 × 2.1mm) 1.7 µm 600 µL/min 70 µL A 0.1% Formic acid in double distilled water B 0.1% Formic acid in acetonitrile	1.25 µmol/L	[109]
Indole alkaloids	Ergotamine	Reverse phase LC	Column Particle size Flow rate Inj. vol. Mobile phase	C_{18} (150 × 2.1 mm) 5 µm 500 µL/min 50 µL A 0.1% formic acid in double distilled water B 0.1% formic acid in acetonitrile	1 nM	[110]
	Brucine	LC	Column Particle size Flow rate Inj. vol. Mobile phase	C_{18} (100 × 2.1 mm) 3.5 µm 200 µL/min 10 µL A Water: 10 mM ammonium acetate pH4.0 with formic acid B Acetonitrile: 10 mM ammonium Acetate pH4.0 with formic acid	0.008 µg/mL	[111]
Glycoalkaloids	α-Solanine	UHPLC	Column Particle size Flow rate Inj. vol. Mobile phase	C_{18} (100 × 2.1 mm) 2.6 µm 400 µL/min 5 µL A 10nm Ammonium formate with 0.1 formic: water B 10nm Ammonium formate with 0.1 formic: methanol	1 µg/mL	[112]
	α-Tomatine	LC	Column Particle size Flow rate Inj. vol. Mobile phase	C_{16} (250 mm × 4.6 mm) 5 µm 800 µL/min 10 µL A 0.1% formic Acid: water B 0.1% formic Acid: methanol	0.94 µg/mL	[113]

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