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Structures and Bioactive Properties of Plant Alkaloids

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ABSTRACT

Natural compounds called alkaloids, which contain nitrogen and have intricate and varied structures, can be found in bacteria, fungus, animals, and plants. Alkaloids are widely distributed, and their diverse range of structural variations make it challenging to classify them. Alkaloids can be categorised for research purposes based on their chemical makeup, biochemical provenance, and/or natural origin. A number of biosynthetic routes, including the terpenoid and polyketide pathway, the histidine and purine pathway, the ornithine, lysine, and nicotinic acid pathway, and the shikimate pathway, can produce alkaloids. Plant alkaloids have historically been used as purgatives, antitussives, sedatives, and remedies for a wide range of illnesses in traditional medicine. A number of alkaloids are currently employed in pharmacology, including codeine, brucine, morphine, ephedrine, and quinine. A number of alkaloids have also acted as models for contemporary medications. This work provides a thorough review of the most recent data on plant-derived alkaloids, their structural classification, and their bioactive qualities, taken from the Web of Knowledge and Scopus databases.

INTRODUCTION

Many metabolites with various physiological functions are found in plants. The phytochemicals, which are mostly secondary metabolites generated by plants and differ in structure, quantity, location, and action even among plants of the same cultivar, are among the most researched metabolites. According to Mazid et al. (2011) and Ncube et al. (2012), these metabolites can be divided into three main categories: phenolic chemicals, terpenes, and compounds that contain sulphur and nitrogen. The essential property of alkaloids, a widely diverse collection of naturally occurring substances formed through secondary metabolism, is the presence of a basic nitrogen atom in any position of the molecule (does not include nitrogen in an amide bond or peptide). They are commonly isolated from plants; however, they have also been found in animals, insects, marine invertebrates, and some microorganisms (Lu et al. 2012; Roberts

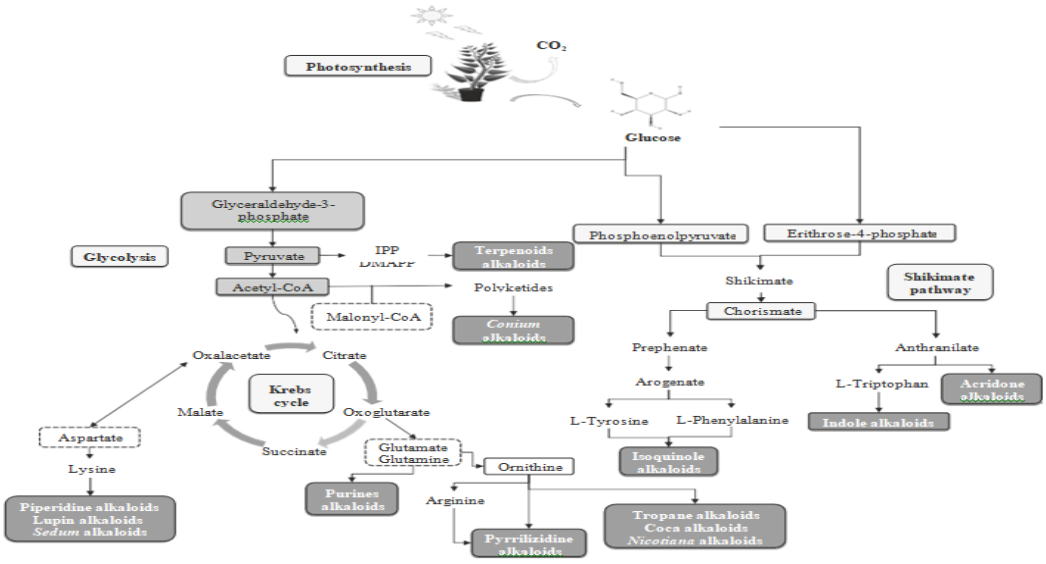
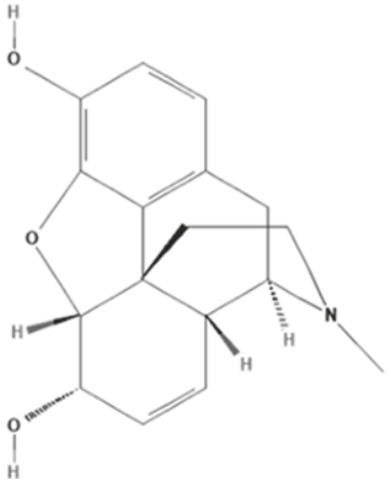


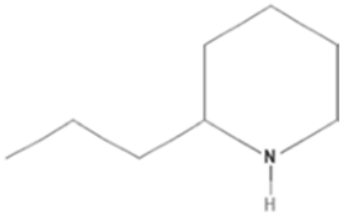
Fig. 1 Metabolic pathway of alkaloid biosynthesis. Abbreviations: IPP isopentenyl diphos- phate, DMAPP dimethylallyl diphosphate. Elaborated from data in Wink (2010)

2013; Bribi 2013). They may be found in a variety of cell organelles, including the mitochondria, vesicles, chloroplasts, and vacuoles. Its precursors, primarily amino acids, come from metabolic processes like glycolysis. The aromatic amino acids phenylalanine, tyrosine, and tryptophan are precursors of some alkaloids, such as indole and isoquinoline alkaloids, which are derived from the shikimate pathway, demonstrating how the biosynthetic pathways are as diverse as the group of alkaloids (Wink 2010; O'Connor 2010; Aniszewski 2012).

These substances are widespread in nature; at least 25% of plants contain them. Because they are allelopathic compounds—that is, they have the potential to be a natural herbicide—they are typically produced to aid in the survival of plants in the ecosystem (Jing et al. 2013). Animals, fungi, microbes, and plants all contain chemicals called alkaloids. Although their role in plants is not fully understood, it is closely related to seed formation and predator protection. Alkaloid activity is not unique to the organism that produces it, thus its pharmacological characteristics have received much research (Mazid et al. 2011). A base-type chemical with nitrogen that reacts with an acid to generate a salt was formerly referred to as an alkaloid.



Morphine structure. Adapted from PubChem (National Center for Biotechnology Information 2009b)



Coniine structure. Adapted from PubChem (National Center for Biotechnology Information 2009a)

Fig. 2 Chemical structure of morphine and coniine (National Center for Biotechnology Information 2009a, b)

Arabic origin for the word al-qali. When Sertürner isolated morphine from opium in 1806, the study of this class of metabolites got underway. Due to the alkaloid presence of many plant extracts, they have been utilised as drugs and poisons ever since. Chemically speaking, they are described as crystalline, colourless, bitter substances that, when combined with acids, can form salts; in plants, they can exist in the free state, resembling salts or N-oxides (Kutchan 1995; O'Connor 2010; Amirkia and Heinrich 2012; Encyclopaedia Britannica 2011; Bribi 2006).

History gives us examples of great people who consumed extracts containing alkaloids, such Socrates, whose death was caused by Conium maculatum extract, and Cleopatra, who is said to have consumed Hyoscyamus muticus to expand her pupils in order to appear more attractive. Women in mediaeval Europe frequently used Atropa belladonna, which contains the alkaloid coniine (Fig. 5.2), to mimic Cleopatra's effects. Its derivatives were first used to dilate pupils during medical exams later in history. Tropicanamide is another related example that has been used to identify Alzheimer's disease (Ncube et al. 2012). Thanks to research, we now know that over 4000 different plants contain a variety of alkaloids. Among other plant families, the Ranunculaceae, Papaveraceae, Solanaceae, and Amaryllidaceae are recognised for their abundance of species (Encyclopaedia Britannica, 2011).

The classification of alkaloids, which will be discussed in more detail in this chapter, is based on a variety of factors, chief among them being their chemical makeup, taxonomy, and medicinal and botanical uses. The position of nitrogen and whether or not it is a ring component determine the most common classification; in this way, we may distinguish between heterocyclic alkaloids, also known as typical alkaloids, and non-heterocyclic or atypical alkaloids (Evans 2009). Alkaloids can also be divided into terpenoid indole alkaloids, benzylisoquinoline alkaloids, tropane alkaloids, and purine alkaloids depending on their metabolic process (Facchini 2001). To treat certain diseases or as poison, civilizations have employed plants (root, leaf, stem, fruit, and seeds) containing alkaloids from the dawn of time (Goyal 2013; Roberts 2013; Jing et al. 2012). Alkaloids' biological relevance relies on how strongly they are connected to positive health effects. Alkaloids are currently commonly used in medicine as anaesthetics, stimulants, antibacterials, antimalarials, analgesics, antihypertensive

agents, spasmolysis agents, anticancer medications, antiasthma therap- eutics, vasodilators, and other therapeutics. The study of these characteristics and their toxicity is still vital (Kuete 2013).

The Amaryllidaceae Family

Amaryllidaceae is a family of monocotyledonous plants with significant economic importance for its horticultural and ornamental appeal as well as its medicinal value. The family Amaryllidaceae is composed of about 1100 species in 75 genera that are distributed in warm tropical and subtropical zones around the world, including South America, the Mediterranean, and Southern Africa (Nair et al. 2013). The leaves are fleshy and two-ranked with parallel veins with linear, strap-like, oblong, elliptic, lan- ceolate, or filiform shape. The flowers are bisexuals and typically arranged in umbels, and the fruit is dry and capsule shaped or fleshy and berry-like. More than 100 alka- loids have been isolated from Amaryllidaceae plants, and some of them are shown in Table 5.2, which exert a wide range of interesting physiological effects.

Table 1: Plant alkaloids from the Amaryllidaceae family

Plant	Common name	Alkaloids	References
Crinumpowelli	Cape lily	Lycorine, 1-O-acetyl lycorineIsmine	Nino et al. (2007)
Hippeastrum puniceum	Easter lily	Didehydroanhydrolycorine, lycorine, narciclasine, pancratistain	Cortes et al. (2012) Santana et al. (2008)
Lycorisradiata	Hurricane lily	Dehydrodihydrolycorine, 6β-acetoxycrinamine, O-acetylhomolycorine, N-oxide, caranine, ungerine, homolycorine	Feng et al. (2011) Huang et al. (2013)
Hippeastrum vittatum	Bulb mavem	Montanine, lycorine, vittatine, vittacarboline, ismine, O-methylamine, pancracine,hippadine	Silva et al. (2008) Youssef (2001)

THE RUBIACEAE FAMILY

The Rubiaceae family is characterized with flowering plants known as bedstraw fam- ily. They are terrestrial trees, shrubs, lianas, or herbs. It is the fourth largest angio- sperm family that contains about 13,500 species in 611 genera, such as Acranthera, Aidia, Aidiopsis, Airosperma, Alberta, Anthorrhiza, Appunia, Badusa, Benkara, Bobea, Borojoa, Bouvardia, Breonadia, Capirona, Calycosia, Canthium, Ceriscoides, Chassalia, Chione, Cigarilla, Coffea, Coptosapelta, Cowiea, Cuviera, Cubanola, Danais, Dichilanthe, Deppea, Geophila, Gouldia, Greenea, Haldina, Hamelia, Phitopis, Pinckneya, Pimentelia, Pomax, Praravina, Pseudopyxis, Ramosmania, Rennellia, Rubia, Rustia, Sacosperma, Schachtia, Saldinia, Serissa, Simira, Sinoadina, Sommera, Stevensia, Stipularia, and Suberanthus, among others. Most of its species that are present in the subtropical regions belong to Cinchona (source of quinine) and have high commercial values (Table 5.9) (Nadkarni et al. 1995). Due to the increasing studies claiming potential human health promotion effects, alkaloids have been gaining popularity around the world and are currently being used as major therapeutic agents (Table 5.10).

Table 2: Alkaloids from Rutaceae family

Plant	Common name	Alkaloids	Reference	Alkaloids	References
Aegle marmelos	Bael tree	Aegeline, marmeline, shahidine, skimmianine, ethyl cinnamamide	Sugenget al. (2001) Yadav and Chanotia (2009)	Aegeline, marmeline, shahidine, skimmianine, ethyl cinnamamide	Sugeng Riyantoet al. (2001); Yadav and Chanotia (2009)
Casimiroa edulis	White sapote	Edulein, scopoletin, zapoterin, casimiroedine	Awaad et al. (2012)	Edulein, scopoletin, zapoterin, casimiroedine	Awaad et al. (2012)
Evodia rutaecarpa	Wu ZhuYu or Evodia fruit	Evodiamine, rutaecarpine, evocarpine, 1-methy-2-[(6Z,9Z)]-6,9-pentadecadienyl-4-(1H)-quinolone (IV), 1-methyl-2-dodecyl-4-(1H)-quinolone (V)	Jiang and Hu (2009)	Evodiamine, rutaecarpine, evocarpine, 1-methy-2-[(6Z,9Z)]-6,9-pentadecadienyl-4-(1H)-quinolone (IV), 1-methyl-2-dodecyl-4-(1H)-quinolone (V)	Jiang and Hu (2009)

Skimmia japonica	Japanese *skimmia*	Skimmianine	Sackett et al. (2007)	Skimmianine	Sackett, Towers, and Isman (2007)
Toddalia asiatica	Orangetree	8-Methoxynorchelerythrine, 11-demethylrhoifoline B, 8-methoxynitidine,8-acetylnorchelerythrine, 8,9,10,12-tetramethoxynorchelerythrine, isointegriamide, 1-demethyl dicentrinone, 11-hydroxy-10-methoxy-(2,3),methylenedioxytet rahydroprotoberberine, nitidine, magnoflorine, 8-methoxynitidine	Hu et al. (2013)	8-Methoxynorchelerythrine, 11-demethylrhoifoline B, 8-methoxynitidine,8-acetylnorchelerythrine, 8,9,10,12-tetramethoxynorchelerythrine, isointegriamide, 1-demethyl dicentrinone, 11-hydroxy-10-methoxy-(2,3),methylenedioxytet rahydroprotoberberine, nitidine, magnoflorine, 8-methoxynitidine	Hu et al. (2013)

Table 3: Alkaloids from Fabaceae family

Plant	Common name	Alkaloids	References
Albizia gummifera	Peacockflower	Budmunchiamine K Budmunchiamine G Normethylbudmunchiamine K	Rukunga and Waterman (1996) Mahlangu et al. (2010)
Erythrina variegata	Tiger claw	Spirocyclic (6/5/6/6) erythrivarine A (1), spiro-fused (6/5/7/6) rings erythrivarine B	Suryawanshi and Patel (2011) Zhang et al. (2013)
Sophora flavescens	Shrubby sophora	12α-Hydroxysophocarpine, oxymatrine, matrine, 9α-hydroxymatrine, allomatrine, oxysophocarpine, sophocarpine, anagyrine,9α-hydroxysophocarpine, lehmannine, 13,14-dehydrosophoridine	Ding et al. (2006)

Table 4: Important alkaloids from Rubiaceae family

Plant	Common name	Alkaloids	References
Cinchona officinalis	Cinchona bark	Quinine, quinidine, cinchonine, cinchonidine	Song (2009)
Mitragyna speciosa	Tang	Corynoxine, mitragynine, speciogynine, paynantheine, corynoxine B	Poklis and Peace (2010)
Nauclea orientalis	Bur tree	Naucleficine; naucleactonine; naucleaorals	Sichaem et al. (2012) Zhang et al. (2001)
Psychotria colorata		Calycanthine, isocalycanthine, chimonanthine, hodgkinsine, quadrigemine C	Verotta et al. (1998)
Uncaria tomentosa	Cat's claw	Pteridine, speciophylline, isomitraphylline, uncarine F, mitraphylline, isopteropodine	Sandoval et al. (2002)

BIOACTIVE PROPERTIES OF PLANT ALKALOIDS

Plant alkaloids have been used as medicines, since ancient times, and their use is widespread around the world. The ethnobotanical use of alkaloid-rich plants led the way to elucidate, isolate, and evaluate the pharmacological properties of these com- pounds that have ended in the production of several drugs, which are being used at present. Alkaloids have been described with many uses; nowadays they are used as chemotherapy agents, and also are being studied for their antidiabetic and neuropro- tective capacity.

Table 5: Anticancer properties of plant alkaloids

Alkaloid type	Alkaloids	Anticancer effect	References

Vinca alkaloids	Vinblastine, vincristine, vindesine,and vinorelbine	Antitumor activity against MCF-7, MDA-MB-231, HepG2, HepG2/ ADM, and K562 cells	Zheng et al. (2013)
Mitragyna speciosa	Tang	Corynoxine, mitragynine, speciogynine, paynantheine,corynoxine B	Poklis and Peace (2010)
Nauclea orientalis	Bur tree	Naucleficine; naucleactonine; naucleaorals	Sichaem et al. (2012) Zhang et al. (2001)
Psychotria colorata		Calycanthine, isocalycanthine, chimonanthine, hodgkinsine, quadrigemine C	Verotta et al. (1998)
Uncaria tomentosa	Cat's claw	Pteridine, speciophylline, isomitraphylline, uncarine F, mitraphylline, isopteropodine	Sandoval et al. (2002)

ANTIDIABETIC PROPERTIES OF PLANT ALKALOIDS

Several reports have shown promising studies on the antidiabetic properties of alka- loids from different plants, such as Rhizoma coptidis, Trigonella foenum-graecum, Berberis vulgaris, and Ervatamia microphylla, which have been reported to exert their antidiabetic potential through several mechanisms such as diminishing insulin resistance, promoting insulin secretion, and ameliorating gut microbiota structures, among others (Zhou et al. 2012; Pirillo and Catapano 2012; Mirhadi et al. 2008; Umezawa et al. 2008; Ma et al. 2009).

For instance, Coptis chinensis alkaloids like berberine, epiberberine, coptisine, palmitine, and magnoflorine have been related with anti-obesity effects. Choi et al. (2013) showed that C. chinensis alkaloids inhibit adipogenesis in 3 T3-L1 cells; alkaloid action was dose dependent without any apparent cytotoxic effect. The authors suggest that the potential obesity-ameliorating effect of Coptis alkaloids is through the downregulation of major adipogenic transcription activators such as PPAR-γ and C/EBP-α proteins. Further, in vivo research and clinical trials are needed to clarify the efficacy, safety, and precise molecular mechanisms of the anti- obesity effects of these alkaloids.

Plant alkaloids can also be potential antidiabetic agents by their potent α-glucosidase inhibitory activity. Choudhary et al. (2011) showed that nummularine-R, nummularin- C, and hemsine-A cyclopeptide alkaloids isolated from Ziziphus oxyphylla Edgw are potent α-glucosidase inhibitor with IC50 values of 212.1, 215.1, and 394.0 μM, respec- tively and that the alkaloids nummularine-R and hemsine-A are also anti-glycation agents. Moreover, Choi et al. (2012) reported that alkaloids from rhizome of Coptis chinensis, identified as berberine, epiberberine, magnoflorine, and coptisine, possess antidiabetic effect mediated by their inhibitory potential against protein tyrosine phos- phatase 1B, a non-transmembrane protein tyrosine phosphatase, an enzyme in which its overproduction is involved in the onset of non-insulin-dependent diabetes mellitus. The authors reported that the evaluated alkaloids had inhibitory activities against PTP1B with IC50 vales of 16.3, 24.19, 28.14, and 51.04 μM, respectively, and that this inhibition was mixed-type for berberine and epiberberine and noncompetitive for mag- noflorine and coptisine. Furthermore, a docking simulation analysis showed that the

evaluated alkaloids have high proximity to PTP1B residues, including Phe182 and Asp181 in the WPD loop, Cys215 in the active sites, and Tyr46, Arg47, Asp48, Val49, Ser216, Ala217, Gly218, Ile219, Gly220, Arg221, and Gln262 in the pocket site, which indicates a higher affinity and tighter binding capacity of these alkaloids for the active site of the enzyme. Another study by Hulcova et al. (2008) showed that Amaryllidaceae alkaloids are potential glycogen synthase kinase 3β inhibitors. Twenty-eight alkaloids of seven structural types (1) belladine, (2–6) haemanthamine, (7–10) crinine, (11–13) galanthamine, (14–19) lycorine, (20) tazettine, and (21–28) homoycorine were reported by the authors. Only caranine, 9-O-demethylhomolycorine, and masonine showed gly- cogen synthase kinase 3β inhibitory activity above 50%. Interestingly, the two homoly- corine-type Amaryllidaceae alkaloids, masonine and 9-O-demethylhomolycorine, and one lycorine-type alkaloid caranine showed the highest IC50 values with 27.81, 30, and 30.75 μM, respectively. Interestingly, the authors described a detailed structure-activity relationship where the presence of hydroxyl substitution at position 2, as in hip-peastrine, is connected with a distinct reduction of GSK-3β inhibitory activity com- pared with masonine, 9-O-demethylhomolycorine, oduline, and O-ethyllycorenine, where no substituent in position C-2 is present.

The opening of the tetrahydropyrane ring in tetrahydromasonine also reduces the GSK-3β inhibitory potency of homolyco-rine-type alkaloids. However, further structure-activity relationship studies are needed. Moreover, Ullah et al. (2008) reported that streptozotocin-induced diabetic rats treated with steroidal alkaloids from Sarcococca saligna at a subcutaneous

dose of 5 mg/kg reduced the glucose level in blood. This effect was attributed to the alkaloids sarcovag- ine-D and holaphylline, and also these alkaloids were related with the good improve- ment in blood lipids. It is important to mention that abnormal lipid levels in diabetic patients may produce hypertriglyceridemia and high cholesterol in blood. A 4-week study by Zhang et al. (2008) showed that alkaloids from Litsea glutinosa barks in ob/ ob mice at doses of 50, 100, and 200 mg/kg decreased body and fat weights without reducing average food intake in treated mice; the efficiency of the treatment was simi- lar to that of metformin. The identified alkaloids in the extracts used in the treatment were laurelliptine, 6-isoquinolinol, laurolitsine, isoboldine, N-methyl laurolitsine, lau- rolitsine, boldine, and litseglutine. Furthermore, the L. glutinosa alkaloid extracts at concentrations ranging from 100 to 200 mg/kg significantly reduced the serum levels of fasting glucose, glycosylated hemoglobin, and glycosylated serum protein. The authors also showed that the alkaloid extract from L. glutinosa significantly enhanced the activity of liver glucokinase, a key enzyme in glycogen synthesis, and increased the content of hepatic glycogen. Moreover, a chronic inflammation is a common character- istic of diabetes, which may lead to insulin resistance; in this regard, the alkaloid treat- ment significantly decreased the inflammation markers such as MCP-1, TNF-α, and IL-6. The vindoline, vindolidine, vindolicine, and vindolinine, alkaloids from the dichloromethane extract of C. roseus, induced high glucose uptake in pancreatic β-T6 cells at a concentration of 25 μg/ml. Furthermore, the alkaloids vindolidine, vindoli- cine, and vindolinine demonstrated inhibitory activity against tyrosine phosphatase 1B. Also, C. roseus alkaloids showed a higher antioxidant activity than quercetin, which may be involved in controlling oxidative stress damage caused by ROS produc- tion, and is related with the onset of diabetes comorbidities such as cardiovascular

problems like atherosclerosis (Tiong et al. 2013; Halliwell and Gutteridge 2012). Alkaloids also have the potential to be antidiabetic agents due to their modulation of blood glucose and lipid content. For example, Capparis decidua alkaloids attenuated the activity of glucose 6-phosphatase by 44% in streptozotocin-induced diabetic mice. Moreover, liver and muscle glycogen content also improved by 33 and 28%, respec- tively, with alkaloid treatment. In this regard, the lipid profile of alkaloid-treated mice as well as their level of total cholesterol, low-density lipoprotein, and triglyceride decreased around 25, 32, and 27%, respectively. On the other hand, the level of high- density lipoprotein improved by 28% with alkaloid treatment (Sharma et al. 2010). The authors also evaluated the mechanism of action by evaluating the expression profiles of genes involved in glucose homeostasis from alkaloid-treated mice. Expression of glu- cose regulatory genes, G6Pase and PEPCK, reduced clearly in the treated group. On the other hand, hepatic GK and Glut-4 expression improved significantly in compari- son to the diabetic untreated group. Also, streptozotocin-induced upregulation of TNF-α in adipose tissue was significantly downregulated by the alkaloid treatment. Moreover, transcription of PPAR-α gene also increased in the adipocytes of the treated diabetic mice; there was almost no change in the level of PPAR-α. Interestingly, alka- loids managed to reduce renal aldose reductase expression in treated animals as com- pared to untreated mice.

PLANT ALKALOIDS AND ALZHEIMER'S DISEASE

Several plant alkaloids are of interest due to their potential to be used as drugs to treat neurodegenerative disorders such as Huntington disease, Parkinson's disease, epilepsy, schizophrenia, and Alzheimer's disease (Hussain et al. 2008). Alzheimer's disease is one of the major neurodegenerative diseases and is characterized by pro- gressive deterioration of memory, learning, and other cognitive functions. The main hallmarks of Alzheimer's disease are the accumulation of amyloid plaques contain- ing extracellular deposits of β-amyloid peptide and intraneuronal neurofibrillary tangles, which lead to neuronal cell loss in the nucleus basalis of Meynert and in the hippocampus (Konrath et al. 2013; Hussain et al. 2008). Furthermore, normal cells have a neuronal microtubule-associated protein called tau protein to stabilize the axonal microtubules; however, in Alzheimer's disease, this protein becomes hyper- phosphorylated by kinases disassociating it, thus destabilizing the microtubule net- work, cytoskeletal collapse, loss of viability and neuronal cell death. Interestingly, the β-amyloid peptide accelerates tau protein aggregation, and reduction of the β-amyloid peptide expression may block the amyloid-induced neuronal dysfunction (Ng et al. 2012). In this regard, alkaloids may have a role in Alzheimer's disease, since they have the potential to be good inhibitors of acetylcholinesterase, a key enzyme in the breakdown of acetylcholine, involved in Alzheimer's disease (Konrath et al. 2013).

As it has been established, the chemical structure of compounds with bioactive properties on health promotion influences heavily on their activity. In this regard, a study by McNulty et al. (2010) showed that the inhibition of alkaloid-1-acetyllycorine, a potent Amaryllidaceae alkaloid with acetylcholinesterase inhibition capacity, func- tions through their ability to act as hydrogen bond acceptor, analogous to the –OH group of galanthamine, and also the introduction of lipophilic substituents at C-1 and C-2 plays a pivotal role on their acetylcholinesterase inhibitory potential. Also, the distribution of alkaloids in each plant source heavily influences their potential bioac- tive effect, which may be the result of a synergistic effect or by a single compound. On this subject, Cardoso-Lopes et al. (2010) reported that the solvent of choice to extract alkaloids from plants has a significant effect on their inhibitory rate on the acetylcholinesterase enzyme, which, as aforementioned, may be related to the alka- loid composition in each solvent fraction. The authors used ethanol,

hexane, and alkaloid fractions of Esenbeckia leiocarpa, which showed acetylcholinesterase inhibitory rates with IC50 values of 50.7, 6.0, and 1.6 μg/mL, respectively. This inhib- itory activity was related with the presence of alkaloids such as leiokinine A, lep- tomerine, kokusaginine, skimmianine, masculine, and flindersiamine. Furthermore, Zhan et al. (2010) isolated indole alkaloids from Ervatamia hainanensis to identify the compound responsible for the acetylcholinesterase inhibitory activity.

They reported that the alkaloids coronaridine and voacangine have the same level of ace- tylcholinesterase inhibitory potency as galantamine, a known inhibitor, with IC50 val- ues of 8.6 and 4.4 μM for coronaridine and voacangine, respectively. Interestingly, voacangine is an analog of coronaridine, with a methoxyl at phenyl group displayed nearly twofold improvement in acetylcholinesterase potency compared to coronari- dine. Neuroinflammation is a pathological hallmark of Alzheimer's disease. In this sense, microglial cells (specialized macrophages found in the nervous central sys- tem) are activated by amyloid β peptide to produce increased amounts of proinflam- matory molecules such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, nitric oxide (NO), and reactive oxygen species. Furthermore, Ligusticum chuanxiong is ethnobotanically used in oriental medicine to treat cardiovascular and cerebrovas- cular diseases, and some studies have shown antioxidant and anti-inflammatory effects, and these properties have been linked to the alkaloid tetramethylpyrazine. On this subject, the alkaloids tetramethylpyrazine have been able to suppress the activity of Aβ1–42-induced proinflammatory mediators and neurotoxicity; thus tetramethyl- pyrazine is a potential alkaloid that can be used as treatment for neurodegenerative diseases like Alzheimer's disease (Kim et al. 2013). An in vivo study by Chonpathompikunlert et al. (2010) reported that the oral administration of piperine at doses from 5 to 20 mg/kg BW during 2 weeks to Wistar rats, showed that piperine, at all doses, had a neuroprotective effect by measuring mice neuron density in regions of the hippocampus, which resulted in improved memory impairment, decreased escape latency, and increased retention time. However, due to the potential cytotoxic- ity of piperine, further pre-clinical studies are needed before piperine is used in humans.

Conversely, the use of alkaloids must be cautionary, since they may show toxic- ity, and toxicity and pre-clinical studies are needed before they are used in humans. For instance, it has been reported that Areca nut has been associated with oral and pharyngeal cancers, which is associated with its arecoline content, an alkaloid that has shown to be genotoxic and cytotoxic (Shih et al. 2010). Thus, Shih et al. (2010)

evaluated the mechanism of action of the cytotoxic effect of arecoline in rat primary cortical neurons. They showed that arecoline at concentrations ranging from 50 to 200 μM induced neuronal cell death and increased the production of reactive oxy- gen species and mRNA levels of NADPH oxidase 2, and also arecoline enhanced the expression of proapoptotic proteins, such as cytochrome C, Bax, caspase-9, and caspase-3. Moreover, the authors also reported that antioxidant enzymes can attenu- ate the redox disruption caused by arecoline.

CONCLUSION AND FUTURE PERSPECTIVES

Alkaloids are a widespread group of compounds with extended use as medicinal agents throughout the world, since ancient times. The chemical structural diversity, distribution, and functional properties of alkaloids are very complex, as well as their study. However, the importance of alkaloids as potential biopharmaceuticals relies on the fact that nowadays, they are used as chemotherapeutic agents to treat dis- eases, including cancer, diabetes, and neurological disorders. The search for new alkaloids to treat chemotherapy-resistant cancers still continues. However, due to the wide chemo-diversity of alkaloids, the work to describe their structures and pharmacological properties are still needed alongside pre-clinical and clinical stud- ies to test their safe use in humans.

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