Journal of Sustainability Science and Management
Volume 19 Number 12, December 2024: 155-167
eISSN: 2672-7226

PHARMACOLOGICAL PROPERTIES OF POLYHYDROXY ALKALOIDS: A MINI-REVIEW

ZURIAH ISMAIL AND AZIZ AHMAD*

Faculty of Science and Marine Environment, Universiti Malaysia Terengganu, 21030 Kuala Nerus, Terengganu, Malaysia.

**Corresponding author: aaziz@umt.edu.my*
http://doi.org/10.46754/jssm.2024.12.010
Received: 10 August 2023 *Accepted: 14 August 2024* *Published: 15 December 2024*

Abstract: Alkaloids are nitrogenous compounds within heterocyclic rings grouped into pyrrolidine, piperidine, pyrrolizidine, indolizidine, and nor-tropane alkaloids. Nevertheless, the origin and biological properties of polyhydroxy alkaloids remain limited. Therefore, this article aims to review polyhydroxy alkaloid' major source and pharmacological properties. Based on the literature, the major source of polyhydroxy alkaloids primarily originate from various plant families including Asteraceae, Araceae, Boraginaceae, Fabaceae, Convolvulaceae, Lamiaceae, Orchidaceae, Piperaceae, Poaceae, and Solanaceae. The pharmacological attributes of polyhydroxy alkaloids are highlighted as glycosidase enzyme inhibitors, antibacterial, anticancer, antifungal agents, and anti-inflammatory. The current review gives an overview of the pharmacological activity of polyhydroxy alkaloids, which may be useful for researchers to explore their hidden potential in developing new drugs to treat various diseases.

Keywords: Glucosidase inhibitors, anticancer, antibacterial, antifungal agents, skin-whitening.

Introduction

Polyhydroxy alkaloids comprise a nitrogen heterocyclic ring with several hydroxyl groups attached to the ring and are soluble in water (Trapero & Llebaria, 2012). Polyhydroxy alkaloids are also known as iminosugars, azasugars, and nitrogenous glycomimetics (Elbein & Molyneux, 1999). Polyhydroxy alkaloid comprises five different subclasses (Figure 1) which are pyrrolidines, piperidines, pyrrolizidines, indolizidines, and nor-tropane (Watson *et al*., 2001; Molyneux *et al*., 2002). This article described the biological activities of each group of alkaloids.

Pyrrolidine Alkaloids

Pyrrolidine is a saturated organic heteromonocyclic alkaloid consisting of five-membered rings that contain four carbon atoms and one nitrogen atom, also known as tetrahydropyrrole (Pant *et al*., 2000). This compound has a pyrrolidine C_4N skeleton nucleus and the structure α of these alkaloids is L-ornithine (in plants) and L-arginine (in animals) (Aniszewski, 2007). Pyrrolidine is the central structure of proline and hydroxyproline amino acids and a basis of racetam compounds. Pyrrolidine has an ammonia-like odour that appears colourless to pale yellow liquid. Pyrrolidine-type alkaloids are commonly found in tobacco leaves and carrots (Felpin *et al*., 2001). In bacteria, decarboxylation of L-proline could also produce pyrrolidine compounds (Verduyckt *et al*., 2016). Examples of natural compounds with a pyrrolidine ring structure are nicotine and hygrine (Gurusamy & Natarajan, 2013; Yu *et al*., 2015).

Piperidine Alkaloids

Piperidine alkaloid is a monocyclic six-membered rings alkaloid (Molyneux *et al*., 2002). This group of alkaloid compounds consists of five methylene units and one nitrogen atom with the properties of colourless liquid, pepper-like odour, and is less dense than water but miscible in water. Piperidine alkaloids contain the piperidine nucleus with

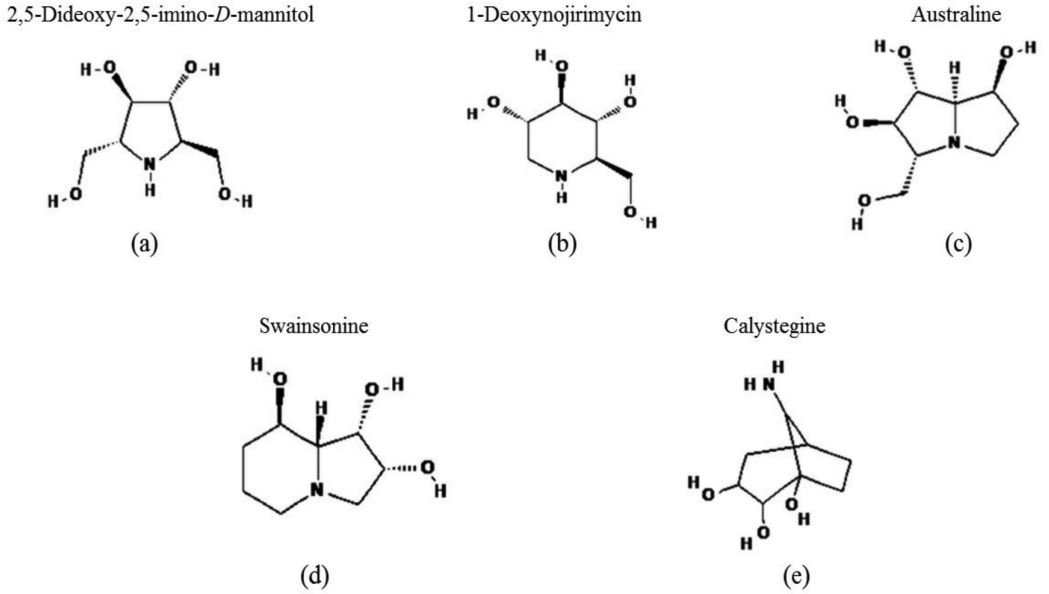

Figure 1: Examples of polyhydroxy alkaloid compounds based on their group: (a) Pyrrolidine, (b) piperidine, (c) pyrrolizidine, (d) indolizidine, and (e) nor-tropane, respectively
Source: Molyneux *et al*. (2002)

structural α being L-lysine and β cadaverine (Aniszewski, 2007). Nojirimycin and fagomine are the general structure of piperidine. N-butyl-deoxy-nojirimycin (NB-DNJ) and N-nonyldeoxynojirimycin (NN-DNJ) is an analogue of deoxynojirimycin, DNJ (Andersson *et al*., 2004). Piperidine alkaloids can be found naturally in Piperaceae plants such as *Piper nigrum* and *Piper longum* (Reshmi *et al*., 2010). Due to their moiety which can be found in an enormous number of bioactive natural products, piperidine is widely used as a building block and chemical reagent, especially in pharmaceuticals (Yang, 2015; Bathula *et al*., 2016; Luescher & Bode, 2016).

Pyrrolizidine Alkaloids

Pyrrolizidine alkaloids are a bicyclic organonitrogen heterocyclic compound that resulted from the ortho-fusion of two pyrrolidine ring systems with a common nitrogen atom at the bridgehead (Molyneux *et al*., 2002). The nucleus of this alkaloid group α is either L-arginine or L-ornithine while β is a biogenic amine, the putrescine (Aniszewski, 2007). Pyrrolizidine alkaloids are widely distributed in plants frequently found in the Boraginaceae, Asteraceae, Orchidaceae, and Fabaceae families and less frequently in the Convolvulaceae, Poaceae, and Lamiaceae families (Haas *et al*., 2023; Jayawickreme *et al*., 2023). The flower is the most predominant part of plants containing pyrrolizidine alkaloids (Johnson *et al*., 1985); therefore, these alkaloids species are widely found in raw honey and bee pollen (Dübecke *et al*., 2011; Kowalczyk & Kwiatek, 2018). Their natural occurrence in plants is used as a defence mechanism against insect herbivores. In recent years, pyrrolizidine alkaloids have accumulated attention due to their occurrence in some species related to human and animal nutrition, as well as their toxicological and pharmacological properties (Moreira *et al*., 2018; Wei *et al*., 2021; Haas *et al*., 2023; Jayawickreme *et al*., 2023).

Indolizidine Alkaloids

A fusion of pyrrolidine-piperidine ring, yielding a bicyclic five or six-ring system is known as indolizidine alkaloids, e.g., swainsonine and castanospermine (Molyneux *et al*., 2002). The structural development of α is L-lysine while β is α-aminoapidic acid δ-semialdehyde (Aniszewski, 2007) for this alkaloid group. Indolizidine alkaloid occurs in diverse natural sources such as bacteria, fungi, higher plants, invertebrates, and vertebrates including terrestrial and marine sources (Michael, 2007). Swainsonine, a widely known indolizidine alkaloid is a potent inhibitor of a mannosidase that alters glycoprotein processing (Kang & Elbein, 1983; Tulsiani & Touster, 1983; Cook *et al*., 2014), an immunomodulator (Hino *et al*., 1985; Mohla *et al*., 1989), and potential chemotherapy drug (Oredipe *et al*., 2003).

Nor-tropane Alkaloids

The nor-tropane alkaloid is a fused bicyclic system, a combination of a five-membered pyrrolidine ring with a six-membered piperidine ring at positions α- to the nitrogen atom of each monocyclic system (Pant *et al*., 2000; Molyneux *et al*., 2002). Calystegines, a nor-tropane alkaloid has been isolated from many plants mainly Convolvulaceae, Solanaceae, and Moraceae families (Dräger *et al*., 1995; Asano *et al*., 1996; Asano *et al*., 2001; Schimming *et al*., 2005).

Pharmacological Properties

Glycosidase Enzyme Inhibitors

In the past two decades, the discovery of polyhydroxy alkaloids has progressively occurred due to their natural properties as glycosidase inhibitors (Molyneux *et al*., 2002). Sugars have been found to play a key factor in the selective inhibition of various enzymatic functions. Therefore, their contribution is beneficial in the pharmacology field, specifically in the treatment of metabolic disorders (Major *et al*., 2011). Polyhydroxy alkaloids are also helpful in therapeutic and biochemical applications as anticancer agents, chemotherapeutic agents, anti diabetic agents, anti viral agents, treatment for Glycosphingolipid Lysosomal Storage (GLS) diseases, treatment of infectious agents, and treatment of autoimmune diseases (Watson *et al*., 2001).

Several plants and parts were reported to contain various polyhydroxy alkaloids with glycosidase enzyme inhibition properties, as shown in Table 1. These include α-glucosidases (Nash *et al*., 1990; Molyneux *et al*., 1990; 1991; Asano *et al*., 1997; 2001; Katavic *et al*., 2006; Niger *et al*., 2018), β-glucosidase (Nash *et al*., 1990; Molyneux *et al*., 1991; 1993c; Kato *et al*., 1997; Asano *et al*., 1997; 1998), myloglucosidase (Nash *et al*., 1990; Pastuzak *et al*., 1990; Molyneux *et al*., 1991), α-galactosidase (Molyneux *et al*., 1993a; 1993c), β-galactosidase (Nash *et al*., 1990; Molyneux *et al*., 1993a; 1993c; Kato *et al*., 1997; Asano *et al*., 1998), α-mannosidase (Dorling *et al*., 1980; Asano *et al*., 1997; Kato *et al*., 1997), β-mannosidase (Molyneux *et al*., 1993b), isomaltase (Molyneux *et al*., 1993a; Asano *et al*., 1998), α-L-fucosidase (Asano *et al*., 1998), and trehalase (Asano *et al*., 1998).

Anticancer, Antimicrobial, Anti-inflammatory and Other Properties

Other than glycosidase enzyme inhibitors, each group of polyhydroxy alkaloids also exhibit various pharmacological properties such as anticancer, anti-inflammatory, antimicrobial, antiviral, antidiabetics, and skin-whitening agents. Table 2 lists the biological activities of polyhydroxy alkaloids from the respective group. Additionally, a compound from the indolizidine group known as phenanthroindolizidine isolated from the whole plant of *Tylophora atrofolliculata* possesses the hypoxia-inducible factor-1 inhibitor (Chen *et al*., 2016).

Table 1: A list of various polyhydroxy alkaloids based on their group obtained from different part of plant species and glycosidase enzyme inhibition activity

Chemical Compounds	Plant	Plant Part	Inhibition of Enzyme Activity	Reference
Pyrrolidine group				
2R,5R-dihydroxy-methyl-3R,4R-dihydroxy pyrrolidine (DMDP)	*Aglaonema treubii*	Whole plant part	Inhibit α-glucosidases	Asano *et al.* (1997)
2-hydroxymethyl-3,4-dihydroxy-6-methyl pyrrolidine (6-deoxy DMDP)	*Angylocalyx pynaertii*	Seeds and pods	Inhibit β-mannosidase	Molyneux *et al.* (1993b)
2,5-imino-2,5,6-trideoxy-D-manno-heptitol (6-deoxy homo DMDP)	*Hyacinthus orientalis*	Bulb	Suppressed activity toward β-glucosidase, β-galactosidase, and trehalase	Asano *et al.* (1998)
2,5-imino-2,5,6-trideoxy-D-gulo-haptitol	*Hyacinthus orientalis*	Bulb	Inhibits α-L-fucosidase	Asano *et al.* (1998)
Piperidine group				
3-epi-fagomine	*Xanthocercis zambesiaca*	Leaves	Inhibits isomaltase and β-galactosidase	Asano *et al.* (1998)
1,2,5-trideoxy-1,5-imino-D-arabinohexitol (fagomine)	*Angylocalyx pynaertii*	Roots	Inhibits isomaltase, α, and β galactosidase	Molyneux *et al.* (1993a)
1,5-dideoxy-1,5-imino-D-glucitol (1-deoxynojirimycin)	*Morus alba L.*	Root bark	Inhibit α-glucosidase	Asano *et al.* (2001)
β-homonojirimycin & β-homomanno jirimycin	*Aglaonema treubii*	Whole plant	Weak inhibitors for β-glucosidase	Asano *et al.* (1997)
α-homomanno jirimycin	*Aglaonema treubii*	Whole plant	Very weak inhibitor of human liver α-mannosidase	Asano *et al.* (1997)
Pyrrolizidine group				
(1S,2R,3R,7S, 7aR)-3-hydroxy methyl-1,2,7-trihydroxy-pyrrolizidine (1-epi-australine)	*Castanospermum australe*	Leaves	Inhibits amyloglucosidase and α-glucosidase	Nash *et al.* (1990)
(1R,2R,3R,7S, 8R)-3-hydroxy methyl-1,2,7-trihydroxy-pyrrolizidine (3,7a-diepi-alexine)	*Castanospermum australe*	Seeds	Poor inhibitor of glucosidase	Nash *et al.* (1990)
(1R,2R,3R,7S, 8S)-3-hydroxy methyl-1,2,7-trihydroxy-pyrrolizidine (alexine)	*Castanospermum australe*	Dried pod	Poor inhibitor of mammalian digestive β-glucosidase and β-galactosidase	Nash *et al.* (1990)

(1S,2R,3R,7R, 7aR)-3-hydroxy methyl-1,2,7-trihydroxy-pyrrolizidine (1,7a-diepi-alexine)	*Castanospermum australe*	Seeds	Potent inhibitor against α-glucosidase	Nash *et al.* (1990)
Indolizidine group				
(1S,2S,8aS)-1,2-dihydroxy indolizidine (2-epi-lentiginosine)	*Astragalus lentiginosus*	Leaves	Inactive against amyloglucosidase and another glucosidase	Pastuzak *et al.* (1990)
(1S,2R,8R,8aR)-1,2,8-trihydroxyoctahydro-indolizidine (swainsonine)	*Swainsona canescens*	Whole plant	Potent against α-mannosidase	Dorling *et al.* (1980)
6,7-diepicastano spermine	*Castanospermum australe*	Seeds	Good inhibitor for fungal α-glucosidase, amyloglucosidase, and weak inhibitor for β-glucosidase	Molyneux *et al.* (1991)
7-deoxy-6-epi-castanospermine	*Castanospermum austral*	Seeds	Inhibits amyloglucosidase and yeast α-glucosidase	Molyneux *et al.* (1990)
(1R,2S,3R,5R,8aR)-3-(hydroxymethyl)-5-methyloctahydro-Indolizidine-1,2-diol (steviamine)	*Stevia rebaudiana*	Leaf	Selective inhibitor of α-galactosidase	Michalik *et al.* (2010)
Isoelaeocarpiline	*Elaeocarpus grandis*	Leaves	Potent inhibitor for yeast α-glucosidase	Katavic *et al.* (2006); Niger *et al.* (2018)
Nor-tropane group				
Calystegin A_3	*Convolvulus arvensis*	Roots	Moderately good inhibitor of β-glucosidase and a weak inhibitor of α-galactosidase	Molyneux *et al.* (1993c)
Calystegin B	*Convolvulus arvensis*	Roots	Potent inhibitors of β-glucosidase and α-galactosidase	Molyneux *et al.* (1993c)
Calystegin C_2	*Duboisia leichhardtii*	Leaves	Active against α-mannosidase	Kato *et al.* (1997)
Calystegin C_1	*Duboisia leichhardtii*	Leaves	Potent inhibitor of β-glucosidase and β-galactosidase	Kato *et al.* (1997)

Table 2: A list of polyhydroxy alkaloids from each group with therapeutic activities

Compounds	Activity	Description	Reference
Pyrrolidine alkaloid			
3,4-dihydroxy pyrrolidinone derivative	Anti-cancer	A 100 to 300 uM of the compounds were tested on human glioblastoma LN18 and brain-derived endothelial LNZ308 cell cultures. The growth of both cancer cells was inhibited with IC_{50} at 100 uM.	Fiaux *et al*. (2008)
Nicotine or 3-(1-methyl-2-pyrrolidinyl) pyridine and analogues	Anti-inflammatory	The effects of nicotine vary depending on the types of administered and animal models. For instance, in ulcerative colitis-induced mice with dextran sodium sulphate (DSS), 0.1 mg/mL nicotine administrated in drinking water suppressed the mucosal vascular in cell adhesion molecule-1 (MAdCAM-1). Nicotine at 10 ug/kg/day reduced the histologic inflammation in colon tissue in DSS-induced adult mice. Oral administration of 0.1 to 1.0 mg/kg nicotine effectively in habiting hyperalgesia in mice.	Han and Lau (2014); Zhang *et al*. (2022)
	Anti-fungal	The 3-(5-(4-fluorophenyl) nicotinoyl)-1-methylpyrrolidin-2-one at a concentration of 5 ug/mL strongly inhibits the growth of *Candida albicans.*	Gandhi and Athmaram (2016)
	Anti-bacterial	The 3-(5-(5-acetyl thiophene-2-yl) nicotinoyl)-1-methyl pyrrolidine-2-one at a concentration of 100 ug/mL moderately inhibit the growth of *Staphylococcus aureus* and *Escherichia coli.*	Gandhi and Athmaram (2016)
Piperidine alkaloid			
1-Deoxynojirimycin (DNJ)	Antioxidants and anti-inflammatory	DNJ at concentrations of 5 μM and 10 μM (50 mg/kg) improve oxidative stress and inflammation responses in the chicken by increasing the malondialdehyde, total superoxide dismutase, catalase, glutathione peroxidase, and inflammatory cytokines (IL-6, IL-1β, and TNF-α) in plasma and intestinal tissues. DNJ treatment was associated with significant changes in the expression of genes of inflammatory cytokines. DNJ at 5 μmol/L mitigated oxidative DNA damage and cell senescence in human umbilical vein endothelial cells (HUVEC) cultured in a medium containing 50 mmol/L glucose. DNJ treatment also stimulates the expression of an anti oxidative response regulator, Nuclear factor (erythroid-derived 2)-like 2 (NRF2) by around 50% in cells cultured with high glucose.	Wang *et al.* (2023); Chen and Wang *et al.* (2024)

	Anti-cancer	DNJ at concentrations of 0.02% (w/v) inhibits the growth of colorectal cancer by inducing apoptosis in an induced cancer model in mice using azoxymethane dextran sodium sulphate.	Shuang *et al*. (2017)
	Anti-diabetic	Diabetic mice treated with DNJ at 150 mg/ kg body weight for 90 days and continued without DNJ for an additional 30 days exhibited a decrease in blood glucose levels.	Li *et al.* (2013)
Pyrrolizidine alkaloid			
Madhumidine A, Lindelofidine Benzoic acid ester, Minalobine (Isolated from leaves of *Madhuca pasquieri*)	Anti-inflammatory	Potent and moderate inhibitors on lipopolysaccharide-induced nitric oxide production in macrophage RAW264.7 cells with 50 % cell viability (IC_{50}) at concentrations higher than 30 µg/ mL.	Hoang *et al*. (2015); Wei *et al.* (2021)
Subulacine -N-oxide, 7- angeloyl heliotrine, retronecine, heliotrine (Isolated from aerial plant of *Heliotropium subulatum*)	Anti-microbial	At 2 mg/ mL significantly inhibits the growth of *Escherichia coli, Streptococcus pneumoniae*, *Bacillus subtillis*, *Bacillus anthracis*, *Staphylococcus aureus, Aspergillus fumigatus*, *Aspergillus niger*, *Rhizoctonia phaseoli*, and *Penicillium chrysogenum.*	Singh *et al*. (2002)
Heliotrine, lasiocarpine, monocrotaline, seneciphyline europine	Anti-cancer	Europine and monocrotaline had EC_{50} values ranging from 200 to 500 µM after 72 hours on in vivo model of cancer cells (adenocarcinoma 755, lymphoid leukaemia L1210, sarcoma 180, walker 256, and plasma cystoma 1). Lasiocarpine and seneciphylline reduced cell viability to 21% at 40 µM and 24% at 100 µM, respectively. Monocrotaline has mild cytotoxicity (77%) at 500 µM against the Walker 256 (intramuscular) system and strongly inhibited Adenocarcinoma 755. Heliotrine at 125 mg/kg dosage inhibited the tumour walker 256.	Culvenor (1968); Haas *et al.* (2023); Jayawickreme *et al*. (2023)
Indolizidine alkaloid			
Swainsonine	Anti-cancer	The 0.06-0.96 µg/mL concentration inhibits the viability and growth of HepG2, SMCC7721, Huh7, and MHCC97-H human hepatoma cells.	You *et al*. (2012)
Castanospermine	Anti-viral (hepatitis C virus)	Celgosivir, a castanospermine derivative combination with PEGylated IFNalpha2b plus ribavirin effectively treats chronic hepatitis C virus infection. In mice, single-dose celgosivir (25 mg/kg po) demonstrated a 5-fold greater uptake into the plasma at two and five minutes post-dosing than a single dose of Cast (16 mg/kg po).	Durantel (2009)

	Treatment of plasmodium infections	A unit dosage containing 25 to 500 mg of the castanospermine ester derivative can be taken one or more times per day with a pharmaceutical carrier using conventional dosage unit forms either orally or parenterally to reduce the adhesion of *P. falciparum-infected* blood cells in the treatment of malaria.	Bitonti *et al*. (1993)
	Treatment of autoimmune diseases	Reduce the development of arthritis due to the ability of the compounds to inhibit the passage of leucocytes via vascular sub-endothelial basement membranes by inhibition of function or expression of leucocyte cell surface-bound enzymes.	Willenborg *et al*. (1992)
Nor tropane alkaloid			
Calystegine	Anti-diabetic	Diabetic-induced mice (130 mg/kg streptozotocin) were orally administered with 10 mg/kg and 20 mg/kg calystegine for 20 days. As a result, both calystegine concentrations managed to reduce blood glucose levels and minimised the effects of streptozotocin damaging β-cells of islets of Langerhans, stimulating β-cells regeneration, and improving insulin secretion in the diabetic-induced mice.	Bourebaba *et al*. (2016)

Conclusions

In conclusion, polyhydroxy alkaloids represent a diverse group of nitrogen-containing compounds in heterocyclic rings. The classification of these alkaloids into distinct categories such as pyrrolidine, piperidine, pyrrolizidine, indolizidine, and not-tropane highlights their structural variations. These alkaloids exhibit various pharmacological properties, and their origin is primarily traced back to plant families like Asteraceae, Araceae, Boraginaceae, and others. The multifaceted nature of polyhydroxy alkaloids is evident in their demonstrated abilities as glucosidase inhibitors, anticancer agents, and antibacterial and antifungal compounds. The diverse pharmacological properties of polyhydroxy alkaloids are useful information for researchers to explore their hidden potential in developing new drugs for treating various diseases, fields of research and medicine.

Acknowledgements

This article is part of PhD dissertation submitted to Universiti Malaysia Terengganu. The authors thank the Ministry of Science, Technology, and Innovation Malaysia under the Strategic Research grant (vot no. 55157).

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

References

Andersson, U., Reinkensmeier, G., Butters, T. D., Dwek, R. A. & Platt, F. M. (2004). Inhibition of glycogen breakdown by imino sugars in vitro and in vivo. *Biochemical Pharmacology*, *67*(4), 697-705.

Aniszewski, T. (2007). Alkaloid chemistry. *Alkaloids-Secrets of Life, Alkaloid Chemistry,*

Biological Significance, Applications and Ecological Role (1st ed.). Elsevier Science.

Asano, N., Kato, A., Miyauchi, M., Kizu, H., Kameda, Y., Watson, A. A., Nash, R. J. & Fleet, G. W. (1998). Nitrogen-containing furanose and pyranose analogues from *Hyacinthus orientalis*. *Journal of Natural Product*, *61*(5), 625-628.

Asano, N., Kato, A., Yokoyama, Y., Miyauchi, M., Yamamoto, M., Kizu, H. & Matsui, K. (1996). Calystegin N_1, a novel nortropane alkaloid with a bridgehead amino group from *Hyoscyamus niger*: Structure determination and glycosidase inhibitory activities. *Carbohydrate Research*, *284*, 169-178.

Asano, N., Nishida, M., Kizu, H. & Matsui, K. (1997). Homonojirimycin isomers and glycosides from *Aglaonema treubii*. *Journal of Natural Product*, *60*, 98-101.

Asano, N., Yamashita, T., Yasuda, K., Ikeda, K., Kizu, H., Kameda, Y., Kato, A., Nash, R. J., Lee, H. S. & Ryu, K. S. (2001). Polyhydroxylated alkaloids isolated from mulberry trees (*Morus alba* L.) and silkworms (*Bombyx mori* L.). *Journal of Agricultural and Food Chemistry*, *49*, 4208-4213.

Bathula, C., Tripathi, S., Srinivasan, R., Jha, K. K., Ganguli, A., Chakrabarti, G., Singh, S., Munshi, P., & Sen, S. (2016). Synthesis of novel 5-arylidenethiazolidinones with apoptotic properties via a three-component reaction using piperidine as a bifunctional reagent. *Organic and Biomolecular Chemistry*, *14*, 8053-8063.

Bitonti, A. J., McCann, P. P., & Sjoerdsma, A. (1993). Esters of castanospermine in the treatment of cerebral malaria (US Patent Number: 05214050). https://patents.google.com/patent/US5214050A/en

Bourebaba, L., Saci, S., Touguit, D., Gali, L., Terkmane, S., Oukil, N., & Bedjou, F. (2016). Evaluation of the antidiabetic effect of total calystegines extracted from *Hyoscyamus albus*. *Biomedicine and Pharmacotherapy*, *82*, (337-344).

Chen, C. Y., Zhu, G. Y., Wang, J. R., & Jiang, Z. H. (2016a). Phenanthroindolizidine alkaloids from *Tylophora atrofolliculata* with hypoxia-inducible factor-1 (HIF-1) inhibitory activity. *RSC Advances*, *6*, 79958-79967.

Chen, Y. & Wang, J. (2024). 1-Deoxynojirimycin attenuates high-glucose-induced oxidative DNA damage via activatingNRF2/OGG1 signalling. *Applied Science*, *14*, 3186. https://doi.org/10.3390/app14083186

Cook, D., Gardner, D. R., & Pfister, J. A. (2014). Swainsonine-containing plants and their relationship to endophytic fungi. *Journal of Agricultural and Food Chemistry*, *62*(30), 7326-7334.

Culvenor, C. C. J. (1968). Tumour-inhibitory activity of pyrrolizidine alkaloids. *Journal of Pharmaceutical Sciences*, *57*(7), 1112-1117.

Dorling, P. R., Huxtable, C. R., & Colegate, S. M. (1980). Inhibition of lysosomal alpha-mannosidase by swainsonine, an indolizidine alkaloid isolated from *Swainsona canescens*. *Biochemical Journal*, *191*(2), 649-651.

Dräger, B., van Almsick, A., & Mrachatz, G. (1995). Distribution of calystegines in several Solanaceae. *Planta Medica*, *61*(6), 577-579.

Dübecke, A., Beckh, G., & Lüllmann, C. (2011). Pyrrolizidine alkaloids in honey and bee pollen. *Food Additives & Contaminants. Part A*, *Chemistry*, *Analysis*, *Control*, *Exposure and Risk Assessment*, *28*(3), 348-358. https://doi.org/10.1080/19440049.2010.541594

Durantel, D. (2009). Celgosivir, an alpha-glucosidase I inhibitor for the potential treatment of HCV infection. *Current Opinion in Investigational Drugs*, *10*(8), 860-870.

Elbein, A. D., & Molyneux, R. J. (1999). Alkaloid glycosidase inhibitors. *Comprehensive Natural Products Chemistry*, *3*, 129-160. https://doi.org/10.1016/B978-0-08-091283-7.00098-9

Felpin, F. X., Girard, S., Vo-Thanh, G., Robins, R. J., Villiéras, J., & Lebreton, J. (2001). Efficient enantiomeric synthesis of pyrrolidine and piperidine alkaloids from tobacco. *The Journal of Organic Chemistry*, *66*(19), 6305-6312.

Fiaux, H., Kuntz, D. A., Hoffman, D., Janzer, R. C., Gerber-Lemaire, S., Rose, D. R., & Juillerat-Jeanneret, L. (2008). Functionalized pyrrolidine inhibitors of human type II α-mannosidases as anticancer agents: Optimising the fit to the active site. *Bioorganic and Medicinal Chemistry*, *16*, 7337-7346.

Gandhi, P. T., & Athmaram, T. N. (2016). Evaluation of novel nicotine analogues for their anti-bacterial and anti-fungal activity. *Journal of Microbiology and Experimentation*, *3*(1), 00079.

Gurusamy, R., & Natarajan, S. (2013). Current status on biochemistry and molecular biology of microbial degradation of nicotine. *The Scientific World Journal*, *2013*, Article 125385. https://doi.org/10.1155/2013/125385

Haas, M., Wirachowski, K., Thibol, L., Küpper, J. H., Schrenk, D., & Fahrer, J. (2023). Potency ranking of pyrrolizidine alkaloids in metabolically competent human liver cancer cells and primary human hepatocytes using a genotoxicity test battery. *Archives of Toxicology*, *97*, 1413-1428.

Han, Y., & Lau, Y. (2014). Nicotine: An anti-inflammation molecule. *Inflammation and Cell Signaling*, *1*(2), 1-8. https://doi.org/10.14800/ics.155

Hino, M., Nakayama, O., Tsurumi, Y., Adachi, K., Shibata, T., Terano, H., Kohsaka, M., Aoki, H., & Imanaka, H. (1985). Studies of an immunomodulator, swainsonine. I. Enhancement of immune response by swainsonine in vitro. *The Journal of Antibiotics*, *38*(7), 926-935.

Hoang, L. S., Tran, N. H., Lee, J. S., To, D. C., Nguyen, V. T., Kim, J. A., Lee, J. H., Woo, M. H., & Min, B. S. (2015). Anti-inflammatory activity of pyrrolizidine alkaloids from the leaves of *Madhuca pasquieri* (Dubard). *Chemical and Pharmaceutical Bulletin*, *63*(6), 481-484. https://doi.org/10.1248/cpb.c14-00855

Jayawickreme, K., ́Swistak, D., Ozimek, E., Reszczy ́nska, E. Rysiak, A., Makuch-Kocka, A., & Hanaka, A. (2023). Pyrrolizidine alkaloids: Pros and cons for pharmaceutical and medical applications. *International Journal of Molecular Science*, *24*, Article 16972. https://doi.org/10.3390/ijms242316972

Johnson, A. E., Molyneux, R. J., & Merrill, G. B. (1985). Chemistry of toxic range plants. Variation in pyrrolizidine alkaloid content of Senecio, Amsinckia, and Crotalaria species. *Journal of Agricultural and Food Chemistry*, *33*(1), 50-55. https://pubs.acs.org/doi/abs/10.1021/jf00061a015

Kalra, R., Singh, S. P., Pena-Philippides, J. C., Langley, R. J., Razani-Boroujerdi, S., & Sopori, M. L. (2004). Immunosuppressive and anti-inflammatory effects of nicotine administered by patch in an animal model. *Clinical and Diagnostic Laboratory Immunology*, *11*(3), 563-568.

Kang, M. S., & Elbein, A. D. (1983). Mechanism of inhibition of Jack Bean-mannosidase by swainsonine. *Plant Physiology*, *71*(3), 551-554.

Katavic, P. L., Venables, D. A., Forster, P. I., Guymer, G., & Carroll, A. R. (2006). Grandisines C-G, indolizidine alkaloids from the Australian rainforest tree *Elaeocarpus grandis*. *Journal of Natural Product*, *69*, 1295-1299.

Kato, A., Asano, N., Kizu, H., Matsui, K., Suzuki, S., & Arisawa, M. (1997). Calystegine

alkaloids from *Duboisia leichhardtii*. *Phytochemistry*, *45*(2), 425-429.

Kowalczyk, E., & Kwiatek, K. (2018). Pyrrolizidine alkaloids in honey: Determination with liquid chromatography-mass spectrometry method. *Journal of Veterinary Research*, *62*(2), 173-181.

Li, Y. G., Ji, D. F., Zhong, S., Lv, Z. Q. & Lin, T. B. (2013). Cooperative anti-diabetic effects of deoxynojirimycin-polysaccharide by inhibiting glucose absorption and modulating glucose metabolism in streptozotocin-induced diabetic mice. *PLOS ONE*, *8*(6), Article e65892.

Luescher, M. U., & Bode, J. W. (2016). SnAP-ex reagents for the synthesis of exocyclic 3-amino- and 3-alkoxy pyrrolidines and piperidines from aldehydes. *Organic Letters*, *18*(11), 2652-2655.

Major, M., Peterson, R., & Kosinski, S. (2011). *Imino and amino sugar purification* (Patent No. US 7,973,157 B2). Google Patent. Cranbury, NJ, USA: Amicus Therapeutics Inc. https://patentimages.storage.googleapis.com/2c/60/ca/beb5e4d6b30904/US7973157.pdf

Michael, J. P. (2007). Indolizidines and quinolizidines: Natural products and beyond. *Beilstein Journal of Organic Chemistry*, *3*, Article 27.

Michalik, A., Hollinshead, J., Jones, L., Fleet, G. W. J., Yu, C. Y., Hu, X. G., van Well, R., Horne, G., Wilson, F. X., Kato, A., Jenkinson, S. F., & Nash, R. J. (2010). Steviamine, a new indolizidine alkaloid from *Stevia rebaudiana*. *Phytochemistry Letter*, *3*, 136-138.

Mohla, S., Humphries, M. J., White, S. L., Matsumoto, K., Newton, S. A., Sampson, C. C., Bowen, D., & Olden, K. (1989). Swainsonine: A new antineoplastic immunomodulator. *Journal of the National Medical Association*, *81*(10), 1049-1056.

Molyneux, R. J., Gardner, D. R., James, L. F., & Colegate, S. M. (2002). Polyhydroxy alkaloids: Chromatographic analysis. *Journal of Chromatography A*, *967*, 57-74.

Molyneux, R. J., Pan, Y. T., Goldmann, A., Tepfer, D. A., & Elbein, A. D. (1993b). Calystegins, a novel class of alkaloid glycosidase inhibitors. *Archives of Biochemistry and Biophysics*, *304*(1), 81-88.

Molyneux, R. J., Pan, Y. T., Tropea, J. E., Benson, M., Kaushal, G. P., & Elbein, A. D. (1991). 6,7-diepicastano-spermine, a tetrahydroxy-indolizidine alkaloid inhibitor of amylo-glucosidase. *Biochemistry*, *30*(41), 9981-9987.

Molyneux, R. J., Pan, Y. T., Tropea, J. E., Elbein, A.D., Lawyer, C. H., Hughes, D. J. & Fleet, G. W. (1993a). 2-hydroxymethyl-3,4-dihydroxy-6-methyl-pyrrolidine (6-deoxy-DMDP), an alkaloid beta-mannosidase inhibitor from seeds of *Angylocalyx pynaetii*. *Journal of Natural Product*, *56*(8), 1356-1364.

Molyneux, R. J., Tropea, J. E. & Elbein, A. D. (1990). 7-deoxy-6-epi-castanospermine, a trihydroxyindolizidine alkaloid glycosidase inhibitor from *Castanospermum australe*. *Journal of Natural Product*, *53*(3), 609-614.

Moreira, R., Pereira, D. M., Valentão, P. & Andrade, P. B. (2018). Pyrrolizidine alkaloids: Chemistry, pharmacology, toxicology, and food safety. *International Journal of Molecular Sciences*, *19*(6), 1668.

Nash, R. J., Fellows, L. E., Dring, J. V., Fleet, G.W.J., Girdhar, A., Ramsden, N. G., Peach, J. M., Hegarty, M. P., & Scofield, A. M. (1990). Two alexine (3-hydroxymethyl-1,2,7-trihydroxypyrrolizidines) from *Castanospermum australe*. *Phytochemistry*, *29*, 111-114.

Niger, T., Ohtani, K., & Ahamed, B. F. (2018). Inhibitory effects of Japanese plant leaf extracts on α-glucosidase activity. *Journal of Molecular Studies and Medicine Research*, *3*(2), 161-168.

Oredipe, O.A., Furbert-Harris, P.M., Laniyan, I., Green, W.R., Griffin, W.M. & Sridhar, R. (2003). Coadministration of swainsonine and doxorubicin attenuates doxorubicin-induced lethality in mice. *Cellular and Molecular Biology (Noisy-le-Grand, France)*, *49*(7), 1037-1048.

Pant, N., Jain, D. C., Bhakuni, R. S., & Sharma, R. P. (2000). Polyhydroxy alkaloids from plants: NMR shielding behaviour. *Indian Journal of Chemistry*, *39B*, 483-496.

Pastuzak, I., Molyneux, R. J., James, L. F. & Elbein, A. D. (1990). Lentiginosine is a dihydroxy-indolizidine alkaloid that inhibits amyloglucosidase. *Biochemistry*, *29*(7), 1886-1891.

Reshmi, S. K., Sathya, E., & Suganya, Devi P. (2010). Isolation of piperidine from *Piper nigrum* and its antiproliferative activity. *Journal of Medicinal Plants Research*, *4*(15), 1535-1546.

Schimming, T., Jenett-Siems, K., Mann, P., Tofern-Reblin, B., Milson, J., Johnson, R.W., Deroin, T., Austin, D. F., & Eich, E. (2005). Calystegines as chemotaxonomic markers in the Convolvulaceae. *Phytochemistry*, *66*(4), 469-480.

Shuang, E., Yamamoto, K., Sakamoto, Y., Mizowaki, Y., Iwagaki, Y., Kimura, T., Nakagawa, K., Miyazawa, T., & Tsuduki, T. (2017). Intake of mulberry 1-deoxynojirimycin prevents colorectal cancer in mice. *Journal of Clinical Biochemistry and Nutrition*, *61*(1), 47-52.

Singh, B., Sahu, P. M., & Singh, S. (2002). Antimicrobial activity of pyrrolizidine alkaloids from *Heliotropium subulatum*. *Fitoterapia*, *73*, 153-155.

Tian, S., Tang, M., & Zhao, B. (2016). Current anti-diabetes mechanisms and clinical trials using *Morus alba* L. *Journal of Traditional Chinese Medical Sciences*, *3*(1), 3-8.

Trapero, A., & Llebaria, A. (2012). A prospect for pyrrolidine iminosugars as antidiabetic α-glucosidase inhibitors. *Journal of Medicinal Chemistry*, *55*, 10345-10346.

Tulsiani, D.R. & Touster, O. (1983). Swainsonine, a potent mannosidase inhibitor, elevates rat liver and brain lysosomal alpha-D-mannosidase, decreases Golgi alpha-D-mannosidase II, and increases the plasma levels of several acid hydrolases. *Archives of Biochemistry and Biophysics*, *224*(2), 594-600.

Verduyckt, J., Hoof, M. V., de Schouwer, F., Wolberg, M., Kurttepeli, M., Eloy, P., Gaigneaux, E. M., Bals, S., Kirschhock, C. E. A., & de Vos, D. E. (2016). PdPb-catalysed decarboxylation of proline to pyrrolidine: Highly selective formation of a bio-based amine in water. *ACS Catalysis*, *6*(11), 7303-7310.

Wang, M., Feng, Y., Li, T., Zhao, C., Barcenas, A. R., Serrano, B. R., Qu, L., Shen, M., & Zhao, W. The effects of 1-deoxynojirimycin from mulberry on oxidative stress and inflammation in laying hens and the direct effects on intestine epithelium cells in vitro. *Animals*, *13*, 2830.https://doi.org/10.3390/ani13182830

Watson, A. A., Fleet, G. W. J., Asano, N., Molyneux, R. J., & Nash, R. J. (2001). Polyhydroxylated alkaloids – natural occurrence and therapeutic applications. *Phytochemistry*, *56*, 265-295.

Wei, X., Ruan W., & Vrieling K. (2021). Current knowledge and perspectives of pyrrolizidine alkaloids in pharmacological applications: A mini-review. *Molecules*, *26*(7), 1970. https://doi.org/10.3390/molecules26071970

Willenborg, D.O., Parish, C. R., & Cowden, W. B. (1992). Inhibition of adjuvant arthritis in the rat by phosphosugars and the alpha-glucosidase inhibitor castanospermine. *Immunology and Cell Biology*, *70*(Pt.6), 369-377.

Yang, Y. (2015). Building polyfunctional piperidines: A stereoselective strategy of a

three-component Mannich reaction inspired by biosynthesis and applications in the synthesis of natural alkaloids (+) -241D; (-) -241D; isosolenopsin A and (-) – epimyrtine. *RSC Advances*, *5*, 18894-18908.

You, N., Liu, W., Wang, T., Ji, R., Wang, X., Gong, Z., Dou, K., & Tao, K. (2012). Swainsonine inhibits growth and potentiates the cytotoxic effect of paclitaxel in hepatocellular carcinoma in vitro and in vivo. *Oncology Reports*, *28*(6), 2091-2100.

Yu, H., Tang, H., Li, Y., & Xu, P. (2015). Molybdenum-containing nicotine hydroxylase genes in a nicotine degradation pathway that is a variant of the pyridine and pyrrolidine pathways. *Applied and Environmental Microbiology*, *81*(24), 8330-8338.

Zhang, W., Lin, H. Zou, M., Yuan, Q., Huang, Z, Pan X., & Zhang W. (2022). Nicotine in inflammatory diseases: Anti-inflammatory and pro-inflammatory effects. *Frontiers in Immunology*, *13*, Article 826889. https://doi.org/10.3389/fimmu.2022.82688