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Review articles

Biological Activity of Plant Alkaloids I. Heterocyclic Alkaloids

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The different groups of heterocyclic alkaloids isolated from plants are discussed according to their chemical classification, structure and biological activity.

Key words: alkaloid, plant, heterocyclic, biological activity.

Alkaloids are nitrogen containing secondary metabolites synthesized by plants, microorganisms, higher fungi and some insects which show physiological activity on the live organisms [19]. The name "alkaloid" ("alkaline") was introduced by W. Neissner in 1899 although the first alkaloid was isolated by F. Sherturner in 1805. He obtained from opium a substance which he named "morphine" because of its narcotic activity, after the god of the sleep – Morpheus. This discovery promoted a significant interest as plant substances of alkaline properties were not known yet. As a results, for a relatively short period of time, many alkaloids, widely used even now, were isolated from medicinal plants – e.g. quinine, strichnine, codeine, atropine etc. During the last decades the chemical structure of many alkaloids was elucidated using contemporary chromatographic and spectral methods.

The huge diversity of the alkaloids requires a precise classification. There exist different approaches to classify the alkaloids:

A) After the taxonomic groups of the plants (genus and family) where they occur – for example vinca, solanum;

B) After the chemical compound they are derivatives of – pyridine, indol, quinoline;

C) After their pharmacological activity – sympathycomimetic, cholinolytic;

D) Chemical classification – according to this classification the alkaloids are divided in to: I – carbocyclic – containing nitrogen in the side chain and II – heterocyclic – containing nitrogen in the central ring. The heterocyclic alkaloids could be divided according to their central ring to pyrolidine, pyrolysidine, pyridine and piperidine.

Pyrolidine alkaloids have a pyrolidine ring as a central part of their molecule – Fig. 1. They are found in representatives of families *Solanaceae, Convolvulaceae, Boraginaceae*. The most popular of them are the alkaloids strichnine, betonicine, turicine, higrine. The folk medicine applies a drug from *Betonica officinalis – Laminaceae*. It contains the pyrolidine alkaloids betonicine, stahidrine and turicine which define its regenerative, spasmolytic, agitating the appetite and approving digestion activity [18]. The pyrolidine alkaloids are a group of chemical compounds inhibiting both α and β glucosidases. For example, the so called brousenetines isolated from the fruits of *Broussonetia kazinoki – Moraceae* family inhibit β-glucosidase, β-galactosidase and β-manosidase [15]; the alkaloid from the seeds of *Adenophora triphilla Campanulaceae* family inhibits β-manosidase [2]. Another type of inhibitory activity against eukariotic DNA polymerases is exerted by the alkaloid 1,4-dideoxy-1,4-imino-D-ribitol isolated from *Morus alba* fruits, *Moraceae* family [8].

The toxic effect of pyrolidine alkaloids is generally manifested in the liver. Cytotoxicity against liver cells is reported for the alkaloids irneine [12] and bgugaine [11] isolated from *Arisarum vulgare*. These alkaloids probably give rise to the toxic symptoms after consuming the tubers of the plant.

Pyrolysidine alkaloids are esters of specific mono- and dicarbolic acids called necine acids with aminoalkohols posessing pyrolysidine in their structure called necines – Fig. 2. The pyrolysidine alkaloids often occur in genus *Senecio – Asteraceae* family; genus *Crotalaria – Leguminosaceae* family; genera *Amsinckia, Arnebia* etc., all from *Boraginaceae* family. They possess M-quinolinolytic, spasmolytic and myorelaxant activity. The main alkaloids of this group are platyphyline and seneciphyline, both isolated from *Senecio platyphylloides*. In the practice, the platyphyline is applied as spasmolytic agent for bilious attacks, gastrointestinal problems, eye problems etc. Another representative of this group is saracine. It has more profound spasmolytic activity and is used for ulcer and spasms of urogenital tract. Recent investigation show that the pyrolysidine alkaloids possess cancerogenic activity. The pyrolysidine alkaloids themselves are not poisonous but in the liver, they are oxidized to form pyrol metabolites, which are responsible for their toxic activity. They bound to DNA and other cell components and cause a lost of function, necrosis and cell death. This affects generally the liver, lung and kidney parenchima. A very interesting alkaloid is indicine N-oxide. It is the first pyrolysidine alkaloid which has anti-tumor activity and is studied as anti-cancer drug for human application. Patients with leukemia show complete or partial remission after application of the drug [7]. The experimental data show, that the anti-tumor activity is mediated by some disturbances in mitosis and in chromosomes [10]. Some pyrolysidine alkaloids demonstrate inhibitory activity similar to the pyrolidine alkaloids – they block some glycosidases. An example is hiacintacine from *Scilla peruviana* [1/].

Pyridine and piperidine alkaloids possess pyridine, hydropyridins heterocycles in the central part of their molecules – Fig. 3, 4. Both groups of alkaloids are divided into

Fig. 1. Pyrolidine

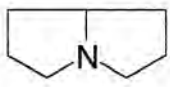

Fig. 2. Pyrolysidine

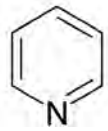

Fig. 3. Pyridine

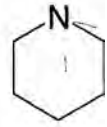

Fig. 4. Piperidine

different subgroups, depending on the side chains to the central ring.

The heterocyclic compounds pyridine and piperidine are basic compounds in many alkaloids, which depending on their chemical composition form different groups.

Piperidine group – the alkaloids of this group possess side chains, which are bound to the α-position of piperidine ring either directly or though an amide bond with some unsaturated carboxylic acid. Members of this group are piperidine, sedamine etc. The piperidine is isolated generally from the fruits of *Piper nigrum – Piperacea* family. It stimulates the stomach mucosal secretion and in this way activates the digestion. According to the scientific investigations [13] piperidine together with 12 of its derivatives possesses trypanocidal activity against epimastigotes and amastigotes of the protozoan parasite *Trypanosoma cruzi* – the cause of Chagas' disease. Some studies also showed that it can be used as suppressive agent against lung cancer [14]. Another alkaloid – piperinaline, was isolated from the fruits of *Piper longum* and shows activity against *Culex pipiens* larvae [6, 17].

Several subgroups belong to **piperidine** group. These are conine, isopeletierine, lobeline, arecoline and nicotine groups. The conine and its derivatives are the main representative of the conine group. They occur in genus *Conium*. The conine was isolated from the fruits of *Conium maculatum – Apiaceae* family. It paralyzes the motor nerves in a similar way to curare. Some data suggest that the conine together with piperidine alkaloids isolated from genera *Nicotiana* and *Lupium* possesses teratogenic and fetotoxic effects inducing skeletal deformation in domestic animals [9].

The main alkaloids from the isopeletierine group are pseudopeletierine, peletieine, isopeletierine and methylisopeletierine. They were isolated from the bark, stem and roots of the plant *Punica granatum – Punicaceae* family. The drug is used as anti-taenia remedy.

The representatives of the lobeline group have been found in plants from genus *Lobelia*. The main alkaloids of this group are lobeline, isolobinine and lelobanidine. Up to 20 alkaloids have been isolated so far. The lobeline stimulates the respiratory center. As a HCl-salt, it is applied for stimulation of breathing in cases of asphyxia after narcotic poisoning.

The arecoline group encompasses a number of derivatives of tetrahydropyridine-α-carboylic acid. The main representatives are the isolated from the seeds of the palm *Areca catechu – Aracaceae* family arecoline, arecaidine, guvacoline and guvacine. The arecoline shows pronounced cholinomimetic activity. It increases the secretion of the salivary and sudoriferous glands and activates the peristaltics.

The nicotine group contains bicyclic derivatives containing uncondensed rings - pyridine and pyrolidine (nicotine) or pyridine and piperidine (anabasine). The nicotine is isolated from the leaves of representatives of genus *Nicotiana – Solanaceae* family. Its quality varies depending on the type, climate etc. It is a typical cholinomimetic and acts on the cells of vegetative ganglia. Initially, it activates them and after that paralyses them. It exerts a similar effect on the CNS, heart, blood vessels, smooth muscles and other organs. It is very toxic and is not applicable in the medical practice.

Another important group of heterocyclic alkaloids are the **purine** alkaloids. In the free form, the purine is not found anywhere in the nature, but its derivatives are widely distributed – xantine, guanine, nucleotides etc. Coffeine, teobromine and teophyline belong to this group. They could be regarded as derivatives of xantine, which is 2,6-dioxipurine. They could be isolated from the seeds of coffee, coke and cocoa, from the leaves of *Camellia sinensis, Ilex paraguariensis* and the so called Pasta Guarana a product of *Paullinia cupana*. The purine alkaloids belong to the psycho stimulatory pharmaceuticals. Coffeine affects the central nervous system, the cerebral cortex and excites important functional centers in the brain. It stimulates the heart rate, dilatates the blood

vessels of the heart, brain, kidney and improves their blood support. It is an antagonist of alcohol and some narcotics. The teobromine and teofilline have a reduced influence on the central nervous system. They have a more pronounced diuretic activity, stimulate the heart, are vasodilatants and relax the bronchial muscles.

The **diterpene** alkaloids are selectively accumulated in representatives of genera *Aconitum, Delphinium* and *Consolida* all of *Ranunculaceae* family. Most of them are very poisonous neurotoxins and have scarce practical application. A natural compound named taxol was isolated from *Taxus brevifolia.* It was found to be useful in the treatment of various cancers [3]. The natural taxol, however, is in very limited quantities. Using analytical methods, from the needle and stems of *Taxus* species a related compound was isolated – 10-diacetylbaccatin III which could be converted to taxol through a semi-synthetic route [16]. Taxol mechanism of antitumor activity is unique, because it promotes microtubule assembly and stabilizes the microtubules, thus preventing mitosis. The Taxol activity includes reversible and specific bindings to the B subunit of tubulin and formation of microtubule polymers, which leads to growth arrest in the G2/M phase of cell cycle [4]. All this makes taxol unique in comparison to vincristine and vinblastine which cause microtubule disassembly. The microtubule system is also essential for the release of different cytokines and the modulation of cytokine release may play an additional role in the taxol antitumor activity.

The **steroid** alkaloids combine the features of alkaloids and steroid saponins – Fig. 5. In contrast to saponins, they contain nitrogen and have alkaline properties. Similarly to saponins they possess sugar moieties in their structure. Depending on their chemical structure they are divided into two groups – nitrogen containing analogues of sapogenins and nitrogen containing steroids with E and F condensed rings. They can also be grouped according to the plants they are isolated from – Solanum alkaloids and Veratrum alkaloids.

The Solanum alkoloids are nerve and muscle poisons and provoke paralysis. Some of them show anesthetic and anti-inflammatory activity. The chemical structure of Veratrum alkaloids is of nitrogen containing steroids with E and F condensed rings. They contain hydroxy groups, which are free in aminoalkohols (alkylamines), esterified in ester alkaloids or glycosylated in glycoalkaloids. Alkylamines are veratramine and yervine, glycoalkaloids are veratrosine and pseudoyervine, ester alkaloids are cevadine, gerverine etc. The ester alkaloids have hypotensive activity. They follow interesting pattern - the more hydroxy groups esterified the more pronounced hypotensive activity [5]. The Veratrum alkaloids are also applied as anti-taenia remedies.

The central part in the chemical structure of **quinolisidine** alkaloids is the quinolisidine, which is composed of two rings with a common nitrogen atom. To this group belong the alkaloids lupanine, citisine, sparteine, anagerine etc. They are isolated from plants of *Fabaceae* family – genera *Lupinus, Genista, Laburnum, Termopsis* and genera *Caulophyllum* and *Leontice* from *Berberidaceae* family. The cytosine is applied as respiratory analeptic. As Tabex it is used to quit smoking. The sparteine activates the muscles of the heart, guts and urinary tract.

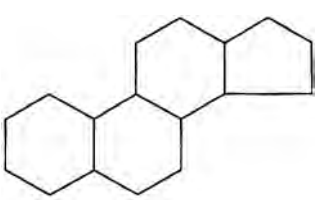

Fig. 5. Steran

The alkaloids as well as other plant derived chemical structures should be identified and biologically tested to enrich the possible sources with application in medicine.

References

1. Asano, N., K. Ikeda, M. Kasahara, Y. Arai, H. Kizu. Glycosidase-inhibiting pyrrolidines and pyrrolizidines with a long side chain in Scilla peruviana. – J. Nat. Prod., **67,** 2004, No 5, 846-50.
2. Asano, N., M. Nishida, M. Miyauchi, K. Ikeda, M. Yamamoto, H. Kizu, Y. Kameda, A. A. Watson, R. G. Nash, G. W. Fleet. Polyhydroxylated pyrrolidine and piperidine alkaloids from Adenophora triphylla var. japonica (Campanulaceae). – Phytochemistry, **53,** 2000, No 3, 379-82.
3. Foa, R., L. Norton, A. D. Seidman. Taxol (paclitaxel): a novel anti-microtubule agent with remarkable anti-neoplastic activity. – Int. J. Clin. Lab. Res., **24,** 1994, No 1, 6-14.
4. Gatzemeier, U., M. Heckmayr, R. Neuhauss, I. Schluter, J. V. Pawel, H. Wagner, A. Dreps. Phase II study with paclitaxel for the treatment of advanced inoperable non-small cell lung cancer. – Lung Cancer., Suppl 2:S,1995, 101-6.
5. Kimura, I., A. Islam, R. Honda, H. Nojima, Y. Tezuka, W. Zhao. Blood-pressure lowering, positive chronotropy and inotropy by the veratrum alkaloids germidine and germerine but negative chronotropy by veratridine in mice. – J. Asian Nat. Prod. Res., **2,** 2000, No 2, 133-44.
6. Lee , S.E. Mosquito larvicidal activity of pipernonaline, a piperidine alkaloid derived from long pepper, Piper longum. – J. Am. Mosq. Control Assoc., **16,** 2000, No 3, 245-7.
7. Letendre, L., W. A. Smithson, G. S. Gilchrist, J. R. Burgert, C. H. Hoagland, M. M. Ames, G. Powis, J. S. Kovach. Activity of indicine N-oxide in refractory acute leukemia. – Cancer, **47,**1981, No 3, 437-41.
8. Mizushina, Y., X. Xu, N. Asano, N. Kasai, A. Kato, M. Takemura, H. Asahara, S. Linn, F. Sugawara, H. Yoshida, K. Sakaguchi. The inhibitory action of pyrrolidine alkaloid, 1,4-dideoxy-1,4-imino-D-ribitol, on eukaryotic DNA polymerases. – Biochem. Biophys. Res. Commun., **304,** 2003, No 1, 78-85.
9. Panter, K. E, L. F. James, D. R. Gardner. Lupines, poison-hemlock and Nicotiana spp.: toxicity and teratogenicity in livestock. – J. Nat. Toxins., **8,** 1999, No 1, 117-34.
10. Poster, D. S., S. Bruno, J. Penta, J. S. Macdonald. Indicine-N-oxide: a new antitumor agent. – Cancer Treat. Rep.,**65,**1981, No 1-2, 53-6.
11. Rakba, N, A. Melhaoui, P. Loyer, J. Guy Delcros, I. Morel, G. Lescoat. Bgugaine, a pyrrolidine alkaloid from Arisarum vulgare, is a strong hepatotoxin in rat and human liver cell cultures.– Toxicol. Lett., **104,** 1999, No 3, 239-48.
12. Rakba, N., A. Melhaoui, M. Rissel, I. Morel, P. Loyer, G. Lescoat. Irniine, a pyrrolidine alkaloid, isolated from Arisarum vulgare can induce apoptosis and/or necrosis in rat hepatocyte cultures.– Toxicon., **38,** 2000, No 10, 1389-402.
13. Ribeiro, T. S., L. Freire-de-Lima, J. O. Previato, L. Mendonca-Previato, N. Heise, M. E. de Lima. Toxic effects of natural piperine and its derivatives on epimastigotes and amastigotes of Trypanosoma cruzi. – Bioorg. Med. Chem. Lett., **14,** 2004, No 13, 3555-8.
14. Selvendiran, K., S. M. Banu, D. Sakthisekaran. Protective effect of piperine on benzo(α)pyrene-induced lung carcinogenesis in Swiss albino mice. – Clin. Chim. Acta., **350,** 2004, No 1-2, 73-8.
15. Shibano, M., D. Tsukamoto, R. Fujimoto, Y. Masui, H. Sugimoto, G. Kusano. Studies on the constituents of Broussonetia species. VII. Four new pyrrolidine alkaloids, broussonetines M, O, P, and Q, as inhibitors of glycosidase, from Broussonetia kazinoki SIEB. – Chem. Pharm. Bull. (Tokyo), **48,** 2000, No 9, 1281 -5.
16. Witherup, K. M, S. A. Look, M. W. Stasko, T. J. Ghiorzi, G. M. Muschik, G. M. Cragg. Taxus spp. needles contain amounts of taxol comparable to the bark of Taxus brevifolia: analysis and isolation. – J. Nat. Prod., **53,** 1990, No 5, 1249-55.
17. Yang, Y. C., S. G. Lee, H. K. Lee, M. K. Kim, S. H. Lee, H. S. Lee. A piperidine amide extracted from Piper longum L. fruit shows activity against Aedes aegypti mosquito larvae. – J. Agric. Food Chem., **50,** 2002, No 13, 3765-7.
18. Асенов, И., С. Николов. Фармакогнозия. София, Медицина и физкултура, 1988.
19. Петров, Г. Органична химия. София, Университетско издателство „Св. Кл. Охридски", 1996. 659 с.