Revistia
Submitted: 11/06/2015 - Accepted: 11/07/2015 - Published: 28/08/2015

The Impact of Alkaloids Structures from Natural Compounds on Public Health

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DOI: 10.26417/ejser.v5i1.p34-39

Abstract

Alkaloids are organic heterocycle substances with nitrogen, of plant origin, with basic character, arising from the secondary metabolism of plants, which give characteristic reactions and exert an effect on animal bodies, most often of a toxic nature. Alkaloids have at least one atom of heterocycle nitrogen, in which case it is often tertiary, less frequently quaternary. The heterocycles can condense among themselves or with other cycles in such a way that alkaloid molecules may become poly- or macro-cycles. Alkaloids are classified on both the criterion of chemical structure, as well as based on their origin. Thus, the known alkaloids are divided into the following categories: derivatives of pyridine, derivatives of pyrolidine, derivatives of tryptophan, derivatives of quinolone and izoquinolone, derivatives of phenetylamine, indole derivatives, derivatives of purine, terpenes, and derivatives of betaine

with quaternary nitrogen.This work presents the structures, location in natural compounds, as well as data pertaining to the extraction, identification, metering, and purification for various compounds, such as coniine, nicotine, atropine and cocaine, morphine and codeine, quinine, papaverine, strychnine, and caffeine.The effects these substances have on human health are highlighted.

Keywords: nicotine, morphine, papaverine, alkaloids, caffeine

Introduction

Although the physiological action of many active principles of plants has been known since ancient times - for example it is known that opium has been heavily utilized by the Chinese for sedation -, chemical research of alkaloids is still a preoccupation of many chemists [1].

The complex structure of alkaloids has crippled their research; knowledge regarding alkaloid structure is still imperfect, and in some cases remain a complete mystery. For this reason, it is common practice to classify the alkaloids according to basic nature, origin and toxicity, in a single class, although structural changes in the alkaloids are part of different classes of substances.

Today, the concept of alkaloids defines them as substances with complex structure, containing nitrogen, with a basic character, most often originating from plants and more rarely from animal organisms. Most alkaloids are characterized by their specific physiological action, but a large percentage of them are also powerful poisons.

Alkaloids are extensively spread in vegetation, but in uneven amounts. Plants rich in alkaloids include representatives of the *Papaveraceae* family (Poppy), *Rubiaceae* (the quinine tree), or *Solanaceae* crops (tobacco, potatoes, and so on). These plants feature more than one single type of alkaloid, most often up to 20 compounds that are typically chemically related.

Alkaloids are found in the entire plant; they are formed in tissues and then localized in the root, fruit, stem, and so on, of the plant. Alkaloids are not found solely in free state, but also in the form of salts.Acids from plants, that neutralise the alkaloids, are saturated with more complex structures, such as fumaric acid, chelidonic acid, quinic acid, and others. The concentration of alkaloids in plants is variable, and is dependent on certain factors: geographic region, climate, etc. [2] Alkaloids are organic heterocyclic substances containing alcohol, with a vegetal origin and basic character, originating as a result of plant secondary metabolism. They give characteristic reactions and their effect on animal organisms is most often toxic [3]. Consequently, the alkaloid group includes substances such as certain amines, amides, aminoalcohols, aminoacids, purines, and so on.

Research Methods

Currently, alkaloids are classified according to both chemical structure and origin [4]. In Table 1 an alkaloid classification is presented. Alkaloid compoundsare obtained through extraction, identification, and measurement, followed by purrification of extracts [5], [6].

Table 1. Alkaloid classification according to structure of derivatives

Group	Representatives
Tropane derivatives	Atropine, cocaine, ecgonine, scopolamine
Isoquinoline derivatives	Opium alkaloids: morphine, codeine, thebaine, papaverine, narcotine, sanguinarine, narceine, hydrastiane, berberine
Quinoline derivatives	Quinine, quinidine, dihydroquinone, dihyrdoqunidine, strychnine, brucine, veratrine, cevadine
Pyridine derivatives	Piperine, coniine, trigonelline, arecaidine, guvacine, pilocarpine, cytosine, nicotine, sparteine, pelletierine
Pyrolidine derivatives	Hygrine, cuschygrine, nicotine
Terpeness	From aconite: aconitine Sterols: solanine, samandarine
Betaine derivatives (with quaternary azoth)	muscarine, choline, neurine
Phenethylamine derivatives	Mescalime, ephedrine
Indole derivatives	Tryptamie derivatives: dimethyltryptamine (DMT), NMT, psilocybin, serotonin, melatonin Ergolines: alkaloids originating from ergot: ergine, ergotamine, lyseric acid, and so on.; derivatives of lysergic acid (LSD) Beta-carbolines: harmine, yohimbine, reserpină, emetine
Purine derivatives	Xanthine derivatives: caffeine, theobromine, theophylline

Finely chopped plants are treated with alkali with the purpose of freeing alkaloids from their salts. They can be separated, either by extraction with ether or chloroform, either by distillation with water vapour. Sometimes, separation is made by passing the alkaloids through a poorly soluble salt.

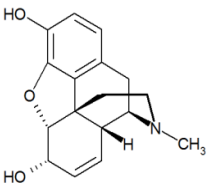
Most alkaloids are crystalline substances, hard to dissolve in water. With acids, they form soluble salts, from which they can be freed by alkali. Some generate colour reactions, which are not always characteristic. Titanium, the phosfo-wolframic acid, a solution of iodine, potassium iodide, and so on, precipitate alkaloids in their solutions.

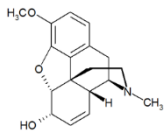
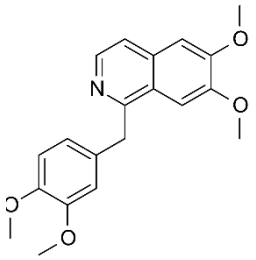
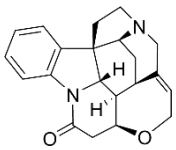
Identification is performed through precipitation with the use of general reactives (that contain metals or metalloids: mercury, bismuth, tungsten, iodine). General precipitation reactives are comprised of: complex iodines, complex anorganic acids, heavy metal salts. In reaction with these reactives, all alkaloids will produce white, yellow, or orange-brownish precipitates.

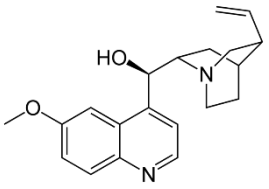
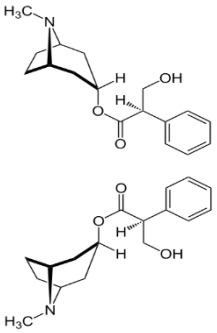
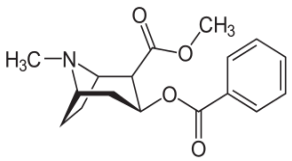
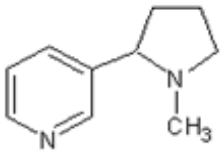
Results and Discussions

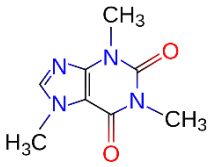
More important alkaloids are represented by: morphine, codeine, coniine, nicotine, tropane, atropine, cocaine, quinine, papaverine, strychnine, caffeine, and so on. In Table 2, some data for a series of naturally obtained alkaloids has been systematized [3], [5], [6].

Table 3. Main alkaloids and the description of their role on the human body

Alkaloid and structure	Effect on the human body
Morphine 	Morphine and Codeineare extracted from opium. Morphine leads to an insensitivity to pain due to its actions on the central nervous system. Morphine is a complete opioid agonist, whose action is localized at a central level, with affinity for the arcuate nucleus. The term is derived from Morpheus, the god of dreams Greek mythology. It is the main active agent in opium (as meconate), its concentration in opium extracts varying from 8 to 14%, with an average of 10%. It is a powerful analgesic. It is a part of the true morphinic alkaloid group, alongside codeine and tebaine. The better part of its effects (supraspinal analgesia, euphoria, significant respiratory depression, inhibition of the coughing centre, myosis, physical addiction, inhibition of digestive motility – responsible for constipation) are explained by the fact that its links with μ receptors. Morphine is used to treat acute and chronic pain. Morphine is usually administered parentally, as morphine chlorhydrate. Oral administration of morphine is not beneficial, because its bio-availability in this case is very small. Morphine sulphate has a slightly better bio-availability with oral administration. It can also be administered rectally, as suppository or enema.

Codeine 	Codeine, or metylmorphine,is a natual alkaloid derived from opium. Its concentration in opium extracts varies between 0.7% and 2.5%. Industrial synthesis of codeine is performed through morphine metylation. It has less significant analgesic properties in comparison to morphine, but it is more advantageous in what regards anti-coughing and anti-diarrheic properties. It is metabolized at hepatic level into 6-glucuronide-codeine through conjugation with glucuronic acid in a percentage of 80%.
Papaverine 	Papaverine is extracted from the milky juice of raw poppy capsules (opium). Its effect is exerted directly on smooth muscles. Is an opiumalkaloidantispasmodic drug, used primarily in the treatment of visceral spasm, vasospasm (especially those involving the heart and the brain), and occasionally in the treatment of erectile dysfunction. While it is found in the opium poppy, papaverine differs in both structure and pharmacological action from the analgesic (morphine-related) opium alkaloids (opiates). Papaverine is used as an erectile dysfunction drug, alone or sometimes in combination. Papaverine, when injected in penile tissue causes direct smooth muscle relaxation and consequent filling of the corpus cavernosum with blood resulting in erection. A topical gel is also available for ED treatment.Papaverine is also present in combinations of opium alkaloid salts such as papaveretum (Omnopon, Pantopon) and others, along with morphine, codeine, and in some cases noscapine and others in a percentage similar to that in opium, or modified for a given application.
Strychnine 	Strychnine is a very toxic alkaloid, extracted from the seed of the tropical tree – *Strychnos nux vomica.* Strychnine presents itself as crystals, which are little soluble in water, colourless, odourless, and with bitter taste. The lethal dose for an adult is usually between 60 and100 mg. Symptoms of intoxication appear 60-90 from ingestion: bitter taste, anxiety, respiratory discomfort, hyperreflexia, convulsions accompanied by the forced extension of the limbs, death.
Quinine	It is extracted from the chinona tree. It is used in malaria treatment. It regulated body temperature. Quinine contains in its molecule a quinolinic heterocyclic atom. It presents itself as fine crystalline powder, odourless, with very bitter taste, little soluble in water, very soluble in alcohol. In therapy, it is used as salts: sulphate, chlorhydrate. Quinine

	has an anti-malaria action, anti-pyretic, and slight analgesic. It also desensitizes the pregnant uterus. Indications: malaria, persistent febrile states, migraine Contraindications: pregnancy, breast-feeding, cardiac insufficiency, myasthenia, atrial fibrillation, sensitivity to quinine, haemolytic anaemia, optic neuritis.
Atropine 	Atropine is a part of the group of alkaloids with a tropanic nucleus, representing a racemic mixture of hyoscyamine. Atropine is used as an antidote in muscarine intoxications due to its role as an excessive blocker of the parasympathetic system, stimulated by an excess of acetylcholine. Atropine can also be used during narcosis, in case of reduced cardiac frequency. It is no longer used as an anti-asthma agent, due to the fact that its derivatives are easier to tolerate. In ophthalmology, it is used for pupil dilation (mydriasis) in ocular examinations. Currently, it has yet to be replaced for its role in cardio-pulmonary resuscitation, such as asystole.
Cocaine 	Cocaine is a crystalline tropanic alkaloid, which is obtained from the coca tree (*Eritroxylon coca*). It is a drug with a potent stimulatory effect on the central nervoussystem and it is one of the most spreaded drugs that lead to consumer addiction.
Nicotine 	Cotinine is a metabolite of nicotine which can be used as an indicator of exposure due to the fact that it remains in the bloodstream for more than 24 hours. It is not accumulated in the body due to its rapid metabolism, with a half-life of approximately 2 hours. It is used to determine the type of receptors. It is a powerful toxic with rapid effect. Initially, the activity of ganglia is hastened. In the next phase, an inhibition of ganglia occurs, which leads to a depressive and paralysis effect. Intoxications can have different causes: accidental (when it is used for rodents) or professional for people who come into contact with nicotine solutions.

Caffeine 	Caffeine is a purine alkaloid, which can be found in coffee, tea, cola nuts, mate, guarana, and cocoa. It is one of the oldest natural stimulants used by mankind. According to the IUPAC, caffeine is represented by 1,3,7–Trimethyl– 2, 6–purinidione or, for short, 1, 3, 7-Trimethylxanthine. Caffeine is a part of the purine group, as are theophylline and theobromine. Xanthine derivatives, classified as vegetal alkaloids (of which caffeine is a representative) are considered as being soft bases, due to the fact that azoth atoms can accept protons. Despite this, xanthine derivatives are not alkaline, when in solution state. Caffeine acts as: stimulant of the CNS, increase of pulse and arterial blood pressure, bronchial dilator, stimulant of intestinal peristalsis. The effect of caffeine depends on a series of factors such as: age, tobacco smoking habits, the body's excretion rates and so on. Caffeine excretion can be more rapid for people who consumer more coffee compared to those who drink occasionally.

The impact of natural compounds with alkaloid structure is described by pharmacologic and toxic action on the human body. It is generally considered that, due to the fact that alkaloids help defend plants against aggression, theyare toxic for the vast majority of animals, with the exception of rabbits who can consume Atropa belladonna leaves without suffering from intoxication, due to the presence of an enzyme called tropanon esterase. Others consider alkaloids as being storage compounds of organic azoth and hypothesize that they have a role in the biosynthetic transformation of certain substances [5]. Because alkaloids have a very diverse structure, their functions are also complex:

- CNS: stimulant alkaloids (caffeine, strychnine), depressing alkaloids (morphine)
- VNS: sympathomimetic alkaloids (cocaine, ephedrine) sympatholytic alkaloids (yohimbine), anticholinergic alkaloids (atropine), ganglioplegic alkaloids (nicotine, sparteine)
- Adrenergic, dopaminergic, or serotinergic receptors (alkaloids derived from Secale cornutum)
- Malignant cells can manifest cytostatic activity: vinblastine, vincristine.
- Parasites: quinine.

Alkaloids are very toxic substances, at relatively low doses. They can exert their effect on various systems, [5]. For example: vincristine has central neurotoxic effects, vinblastine (an antimitotic alkaloid) has a powerful leucopoenia effect and leads to gastrointestinal and neurological distress, aconitine is toxic for bulbar centres, quinine and morphine lead to respiratory depression, cocaine and morphine lead to pharmacologic addiction.

Conclusion

- The toxicity of these species has been demonstrated according to the nature of the content, and is represented by symptoms such as: nausea, vomiting, convulsions, cardiac arrhythmias, hallucinations, and so on. Some plant toxin may lead to death even in small quantities.
- Other plants are apparently not at all harmful, even in large doses. Administration of these species preparations does not lead to the manifestation of any toxic syndromes. Even though there are no plant species harmful to humans, due to the cytotoxicity manifested by alkaloids, which accumulate in the body, delayed effect ailments can be triggered or promoted.
- Some plants or plant components containing such principles are still used in internal phytotherapeutic treatments, although their toxicity has already been demonstrated.
- All compounds with an alkaloid structure described in this paper initially had beneficial effects on the human body, which has lead to their use in medical practice. Alongside these effects, they also present a high level of toxicity, which has been proven in time.
- The toxicity and very diverse effects on the central and vegetative nervous systems have outlined the importance of limiting consumption and their application as therapeutic agents in medical practice.

Acknowledgement

This paper is supported by the Sectoral Operational Programme Human Resources Development (SOP HRD), financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/187/1.5/S/156040/

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