Importance of Alkaloids in Medicinal Chemistry

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Abstract:
Alkaloids are naturally occurring, nitrogen-containing organic compounds that serve as vital pillars in medicinal chemistry due to their potent physiological and pharmacological effects on the human body. [1, 2]
Key Importance in Medicinal Chemistry

- Pain Relief (Analgesics): Compounds like morphine and codeine derived from the opium poppy are cornerstone treatments for severe and moderate pain management. [1, 2]
- Cancer Treatment (Antitumor Agents): Vincristine and vinblastine from the Madagascar periwinkle are critical chemotherapy drugs used to inhibit cell division in cancer therapy. [1]
- Malaria Combat: Quinine from the cinchona tree and derivatives like artemisinin have a historic and ongoing role in treating drug-resistant malaria. [1, 2]
- Central Nervous System (CNS) Activity: Stimulants such as caffeine and nicotine, as well as psychotropic agents, alter neurological function and serve as models for neuropharmacology. [1, 2, 3]
- Lead Compounds for Drug Discovery: The complex heterocyclic scaffolds of natural alkaloids provide unique lead structures that medicinal chemists modify to synthesize safer, more effective synthetic and semi-synthetic drugs.

Keywords: alkaloids, medicinal, chemistry, drug, organic

INTRODUCTION

Alkaloids play an essential role in both human medicine and in an organism's natural defence. Alkaloids make up approximately 20% of the known secondary metabolites founds in plants [13]. In plants, alkaloids protect plants from predators and regulate their growth [14]. Therapeutically, alkaloids are particularly well known as anaesthetics, cardioprotective, and anti-inflammatory agents. Well-known alkaloids used in clinical settings include morphine, strychnine, quinine, ephedrine, and nicotine [15]. Recently, there is a resurgence of interest in bioactive natural products, driven both by a very proactive development in the field of traditional medicines (ethnopharmacology) as well as their potential in drug discovery [16]. As of 25 October 2020, 27,683 alkaloids were included in the Dictionary of Natural Products (DNP) with 990 hits of newly reported or reinvestigated alkaloids from nature between 2014 to 2020.[1,2,3]

The GBIF database has been used extensively in environmental research and is based on gathering species occurrence to assess the global distribution of each. GBIF occurrences are documented using preserved and living specimens, along with other ecological observations that include geographical data and the date of the record. These include collected and documented specimens, citations, and records of species including cultivated and wild occurences. In 2014, the GBIF database contained 424,254,844 occurrences of organisms in nature including 117,909,945 (27.8%) records from the kingdom Plantae. Despite nearly half a billion species having been recorded, many species demonstrated zero occurrences due to inadequate data reporting such as the non-participating countries for GBIF contributions and species inaccessibility.

Important strategic changes have been incorporated for data quality and data abundance. The GBIF database is developed using information from organizations (institutions, networks, and societies) and citizen scientists through participating projects that publish datasets through the GBIF network. Many countries remain unconnected with GBIF, which therefore aims to establish connections with these countries, thereby improving national capacity to access and mobilize biodiversity data among existing participants [17]. Compared to 76 participating countries in 2014, GBIF had over 100 participants in 2020 including countries (national government), economies, and international organizations contributing to GBIF data. It also aims to identify gaps and bias in data to achieve the highest quality data possible. One example is the updated data validator, which can flag duplicate records, inconsistences in formatting, and incomplete fields of necessary information [17].

In 2014, Amirkia and Heinrich [18] showed that historically, pharmaceutical alkaloids' market performance has been linked to the abundance of a species as defined by the GBIF dataset, which is the most comprehensive database defining the distribution of individual species currently available. However, alkaloids are underrepresented as lead compounds to discover new medicines' marketing and licensing [19]. This analysis was based on 117,909,945 records from the kingdom Plantae (27.8% of all organisms' total entries). Since 2014, GBIF has added 204,963,126 records, a 3.82-fold increase. The larger sample size for species distribution from the previous sample size in 2014 gathered by Heinrich and Amirkia (2014) [18] enables a more accurate and precise analysis of global alkaloid abundances and biodiversity. [4,5,6]

Discussion

Alkaloids are produced by a large variety of organisms including bacteria, fungi, plants, and animals.[3] They can be purified from crude extracts of these organisms by acid-base extraction, or solvent extractions followed by silica-gel column chromatography.[4] Alkaloids have a wide range of pharmacological activities including antimalarial (e.g. quinine), antiasthma (e.g. ephedrine), anticancer (e.g. homoharringtonine),[5] cholinomimetic (e.g. galantamine),[6] vasodilatory (e.g. vincamine), antiarrhythmic (e.g. quinidine), analgesic (e.g. morphine),[7] antibacterial (e.g. chelerythrine),[8] and antihyperglycemic activities (e.g. berberine).[9] Many have found use in traditional or modern medicine, or as starting points for drug discovery. Other alkaloids possess psychotropic (e.g. psilocin) and stimulant activities (e.g. cocaine, caffeine, nicotine, theobromine),[10] and have been used in entheogenic rituals or as recreational drugs. Alkaloids can be toxic (e.g. atropine, tubocurarine).[11] Although alkaloids act on a diversity of metabolic systems in humans and other animals, they almost uniformly evoke a bitter taste.[12]

The boundary between alkaloids and other nitrogen-containing natural compounds is not clear-cut.[13] Most alkaloids are basic, although some have neutral[14] and even weakly acidic properties.[15] In addition to carbon, hydrogen and nitrogen, alkaloids may also contain oxygen or sulfur. Compounds like amino acid peptides, proteins, nucleotides, nucleic acid, amines, and antibiotics are usually not called alkaloids.[14] Natural compounds containing nitrogen in the exocyclic position (mescaline, serotonin, dopamine, etc.) are usually classified as amines rather than as alkaloids.[16] Some authors, however, consider alkaloids a special case of amines.[7,8,9]

Results

Preparations of plants and fungi containing alkaloids and their extracts, and later pure alkaloids, have long been used as psychoactive substances. Cocaine, caffeine, and cathinone are stimulants of the central nervous system.[200][201] Mescaline and many indole alkaloids (such as psilocybin, dimethyltryptamine and ibogaine) have hallucinogenic effect.[202] Morphine and codeine are strong narcotic pain killers.

There are alkaloids that do not have strong psychoactive effect themselves, but are precursors for semi-synthetic psychoactive drugs. For example, ephedrine and pseudoephedrine are used to produce methcathinone and methamphetamine. Thebaine is used in the synthesis of many painkillers such as oxycodone.

Alkaloids are a group of naturally occurring chemical compounds mostly containing basic nitrogen atoms. They are primarily found in plants and have significant pharmaceutical importance due to their diverse biological activities. The pharmaceutical importance of alkaloids can be summarized as follows:

1. Analgesic Properties: Some alkaloids act as pain relievers. For example, morphine from the opium poppy is a powerful analgesic used to relieve severe pain.
2. Antimalarial Activity: Alkaloids like quinine, obtained from the cinchona tree, are used to treat malaria effectively.
3. Stimulant Actions: Alkaloids such as caffeine and nicotine stimulate the central nervous system, increasing alertness and reducing fatigue.
4. Anticancer Effects: Certain alkaloids, such as vincristine and vinblastine from the periwinkle plant, are used in chemotherapy to treat cancers.
5. Antimicrobial Properties: Some alkaloids exhibit antibacterial, antifungal, and antiviral activities, making them useful in fighting infections.
6. Muscle Relaxants and Antispasmodics: Alkaloids like atropine are used to relax muscles and reduce spasms.
7. Cardiovascular Effects: Alkaloids such as ajmaline and reserpine affect the cardiovascular system and are used in treating arrhythmias and hypertension.
8. Respiratory Treatments: Ephedrine, an alkaloid from Ephedra species, is used as a bronchodilator in asthma treatment. [10,11,12]

Traditional medicine: Alkaloid-containing plants have been utilized in traditional medicine by various cultures for centuries. The knowledge of alkaloids and their medicinal properties has been passed down through generations. Alkaloids, a diverse group of naturally occurring nitrogenous compounds, exhibit a wide range of pharmacological activities, making them valuable in the pharmaceutical and medical industries. To harness their therapeutic potential, efficient extraction methods are crucial. This article explores the advancements in alkaloid extraction, focusing on the application of modern chromatographic techniques to enhance efficiency and yield.

Methods of alkaloid extraction

Traditionally, alkaloids were extracted using conventional methods like Soxhlet extraction or maceration. However, these methods often involve prolonged extraction times and the use of large volumes of solvents. Modern chromatographic techniques, such as High-Performance Liquid Chromatography (HPLC) and Gas Chromatography (GC), have emerged as superior alternatives.

HPLC, known for its high resolution and sensitivity, enables the separation and quantification of alkaloids with remarkable precision. The use of a chromatographic column with a specific stationary phase allows for selective isolation, resulting in purer alkaloid extracts. Additionally, the speed of HPLC reduces extraction time, making the process more efficient.

Gas chromatography, on the other hand, is particularly effective for volatile alkaloids. By vaporizing the sample and separating its components based on their affinity for the stationary phase, GC achieves rapid and

precise extraction. This technique is especially valuable for alkaloids found in plants with volatile secondary metabolites.[13,14,15]

Advantages of modern chromatographic techniques

The adoption of modern chromatographic techniques offers several advantages in alkaloid extraction. First and foremost, these methods provide enhanced selectivity, allowing researchers to target specific alkaloids of interest. This selectivity is crucial when working with complex plant extracts containing numerous compounds.

Furthermore, modern chromatography reduces the need for large quantities of solvents. This not only aligns with the principles of green chemistry but also addresses environmental concerns associated with traditional extraction methods. The reduced solvent usage contributes to cost-effectiveness and minimizes the ecological impact of alkaloid extraction processes.

Moreover, the speed of chromatographic techniques significantly accelerates the extraction process. Traditional methods often involve extended extraction times, leading to the degradation of sensitive alkaloids. In contrast, HPLC and GC can achieve rapid separation, minimizing the risk of degradation and ensuring the preservation of alkaloid integrity.[16,17,18,19]

Conclusion

The efficient extraction of alkaloids using modern chromatographic techniques has profound implications for pharmaceutical research. Researchers can obtain high-purity alkaloid extracts, facilitating the isolation of individual compounds for in-depth pharmacological studies. The precise quantification enabled by these techniques is essential for establishing dosage guidelines in drug development.

Additionally, the use of chromatography in alkaloid extraction contributes to the discovery of novel bioactive compounds. The ability to analyze complex mixtures with high sensitivity allows researchers to identify previously unknown alkaloids, expanding the pharmacological repertoire of natural products.[20]

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