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Khaled Rashed
Department of Pharmacognosy, National Research Centre, 33 El Bohouth, Dokki, Giza, Egypt

Correspondence
Khaled Rashed
Department of Pharmacognosy, National Research Centre, 33 El Bohouth, Dokki, Giza, Egypt

Biological evidences of montanine type alkaloids: A short review

Khaled Rashed

Abstract
Amaryllidaceae alkaloids (AA), have attracted considerable attention due to their interesting pharmacological activities. One of them, galantamine, is already used in the therapy of Alzheimer's disease as a long acting, selective, reversible inhibitor of acetyl cholinesterase. One group of AA is the montanine-type, such as montanine, pancracine and others, which share a 5, 11-methanomorphanthridine core. Compared with other structural-types of AA, montanine-type alkaloids are predominantly present in plants in low concentrations, but some of them display promising biological properties, especially *in vitro* cytotoxic activity against some cancer cell lines.

Keywords: montanine, chemical compounds, plants, bioactivities

Introduction
Amaryllidaceae is a family of monocotyledonous plants that are widely distributed over the tropical and warm regions of the world, especially in the southern African region. Species of some genera are also found in the Mediterranean area and temperate regions of Asia. Plants that belong to the Amaryllidaceae family produce alkaloids that have been extensively studied because of their pharmaceutical properties [1]. The genus Rhodophiala (Amaryllidaceae) is endemic in South America and contains more than 30 bulbous species showing ornamental potential. Amaryllidaceae alkaloids such as galanthamine present anticholinesterase activities used for the treatment of Alzheimer's disease; lycorine presents cytotoxicity and antitumor properties. Recently, it was shown that montanine has anxiolytic, antidepressive and anticonvulsive activities as well as immunomodulatory properties. Moreover, montanine has acetylcholinesterase inhibition, anti-reumatic, antimicrobial and antiproliferative effects [2, 3, 4]. These important pharmaceutical properties justify an increasing of interest towards this class of compounds. The present review gives the previous research that has been published on the Amaryllidaceae alkaloids of montanine-type.

Biological potentials
Anticancer Potential
The first evidence for montanine-type as an interesting group of plant-derived compounds that display growth inhibition and cytotoxicity to cancer cells *in vitro* was reported for montanine isolated from bulbs of Hippeastrum vittatum in 2008 [5]. Since then, there have been other studies dealing with a group of montanine-type and their effect on proliferation and viability of cancer cells. Another important montanine-type AA, pancracine, isolated from Professor Einstein, displayed significant cytotoxic effects. The first screening test for cytotoxicity revealed the abilityof 10 µM pancracine treatment to reduce the viability of 9 cancer cell lines, including Jurkat, MOLT-4, A549, MCF-7, A2780, HT-29, PANC-1, HeLa and SAOS-2. Except for PANC-1, the IC50 values for all the remaining cell lines were determined; values ranged from 2.20 to 5.15 µM [6]. From the papers published so far, it appears that montanine, the main representative of montanine-type, is the most effective in reducing the growth of cancer cell lines within this group of structurally related compounds. On the other hand, the relevance of this conclusion is uncertain, since only four of these compounds have been tested for cytotoxicity so far. It is evident from the results described that further efforts should be made to reveal the mechanism of the cytotoxic effect of these substances and a detailed mode of action can lead to better subsequent *in vivo* testing. Since many different types of solid and leukemic cancer cell lines have been used to study cytotoxicity, it can be concluded that montanine type are promising agents in the field of therapy of human cancer diseases.

Antibacterial activity

Montanine and pancracine were screened for their antibacterial activity in two different studies [7]. Montanine was the more active of the two alkaloids against pathogenic Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus and S. epidermis, giving values of 5, 20, 5 and 15 µg, respectively, as minimum quantities required for activity [7]. The antibacterial and antifungal activity of pancracine has been studied using an agar diusion technique against a Gram-positive-bacterium S. aureus, two Gram-negative bacteria E. coli and P. aeroginosea, and Candida albicans [8]. Pancracine displayed activity against S. aureus and P. aeroginosea and moderate activity against C. albicans, with a MIC of 188 µg/mL.

Antiparasitic activity

The *in vitro* antiparasitic activity of nangustine and pancracine isolated from N. angustifolius subsp. transcarpathicus against the protozoans Trypanosoma brucei rhodesiense, T. cruzi, *Leishmania donovani* and *P. falciparum* was reported in 2002 [9]. Pancracine showed a higher activity than nangustine against all four protozoan parasites tested. While nangustine has been classified as inactive, pancracine showed weak activity against T. brucei rhodesiense and T. cruzi, but no activity against L. donovani. The IC50 values of 0.75 and 0.70 µg/mL, respectively, for two strains of Plasmodium falciparum, represented the weak antimalarial activity of pancracine. No cytotoxic activity was demonstrated for either alkaloid against L-6 cells (rat skeletal myoblasts) within this study [9].

Antiarthritic activity

Montanine has also been studied for its antiarthritic activity in antigen-induced and collagen-induced arthritis models [10]. The alkaloid significantly attenuated the development of experimental arthritis in both acute and chronic models [10], dose-dependently, with the lower dose being more effective in arthritis severity and paw nociception. This finding hypothesized that increased availability of montanine leads to an acute activation that culminates in mechanisms of desensitization of the receptor, reducing the activation of receptor cell signaling and, consequently, decreasing the biological effect seen at lower doses [10]. The obtained results indicated that montanine has a potential as a drug for autoimmune diseases, such as arthritis.

Anti-rheumatic effect

Montanine type alkaloid is then evaluated by *in vivo* and *in vitro* tests as very promising in the treatment of anti-inflammatory diseases such as rheumatoid arthritis, ulcerative colitis, sepsis, acute pulmonary disease, inflammatory infections; in particular, inflammatory and fibrosing diseases related to the lungs and kidneys, osteoporosis. These drug candidate bioactivities were determined through biologically significant effect on the nociception, migration and proliferation of fibroblasts and lymphocytes and without changing or depressing the immune system [11].

It has been found that montanine reduces locomotor activity and has sedative, anxiolytic, anticonvulsant and antidepressant effects in mice. Da Silva *et al.* suggested that montanine may act on the benzodiazepine site of the GABA receptor in mouse brain, and thus the anxiolytic, hypnotic effects of montanine could be caused by its combined action on several neurotransmitter receptor systems, including GABA receptors [12]. Both montanine and coccinine exhibited lower SERT affinity than estimated and did not explain the higher activity observed in the extracts.

Antioxidant, anti-inflammatory potentials

The antioxidant activity and inhibitory action on the growth of cell cultures of Saccharomyces cerevisae (ATCC 2601), Pseudomonas aeruginosa (ATCC 27853), Staphylococcus aureus (ATCC 6538), Staphylococcus epidermides (ATCC 12228) and Escherichia coli (ATCC 25922) were observed to the montanine alkaloid, isolated from the bulbs of Rhodophiala bifida (Herb.) Traub (Amaryllidaceae). The anti-inflammatory activity, which was evaluated through the sample antichemotaxis ability determination, was not significant in the used dose [13].

Anxiolytic-, antidepressant- and anticonvulsant effects

We report on the behavioral and pharmaco-toxicological characterization of montanine, an isoquinoline alkaloid isolated from Hippeastrum vittatum, an ornamental plant found throughout the world. In mice, montanine showed a LD (50) of 64.7 mg/kg and 67.6 mg/kg for male and female, respectively. When given i.p., montanine dose-dependently decreased sodium pentobarbital-induced sleep, protected against pentylenetetrazole-provoked convulsions, increased the number of entries and the time spent in the open arms of an elevated plus maze and augmented the time spent struggling during a forced swimming test. When given immediately after inhibitory avoidance training, montanine did not affect avoidance memory retention in rats. Our results suggest that montanine, as other alkaloids isolated from Amaryllidaceae species, has psychopharmacological activities including anxiolytic, antidepressive and anticonvulsive effects [14].

Conclusion

This review summarizes the biological investigations of montanine-type alkaloid. These alkaloids bear a characteristic 5, 11-methanomorphanthridine structural core. In the light of the presented overview of scientific data, the montanine-type can be recognized as an interesting source for the development of new drugs for the treatment of various diseases and so this review showed the importance of Montanine type alkaloid as a medicinal compound.

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