



E-ISSN: 2788-9254
P-ISSN: 2788-9246
IJPSDA 2021; 1(2): 01-03
Received: 04-05-2021
Accepted: 08-06-2021

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 ability of 10 μ M 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 μ M [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.

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

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 diffusion technique against a Gram-positive-bacterium *S. aureus*, two Gram-negative bacteria *E. coli* and *P. aeruginosa*, and *Candida albicans* [8]. Pancracine displayed activity against *S. aureus* and *P. aeruginosa* 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 cerevisiae* (ATCC 2601), *Pseudomonas aeruginosa* (ATCC 27853), *Staphylococcus aureus* (ATCC 6538), *Staphylococcus epidermidis* (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 pharmacotoxicological 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, antidepressant 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.

References

1. De Andrade JP *et al.* The Brazilian Amaryllidaceae as a source of acetyl cholinesterase inhibitory alkaloids. *Phytochem Rev*, <https://doi.org/10.1007/s11101-015-9411-7>, 2015.
2. Oliveira P *et al.* Anti-inflammatory and immunomodulatory properties of montanine, an alkaloid isolated from *Rhodophiala bifida* 2014, 98-98.
3. Rhee IK, Van De Meent M, Ingkaninan K, Verpoorte R. Screening for acetylcholinesterase inhibitors from Amaryllidaceae using silica gel thin-layer chromatography in combination with bioactivity staining. *J Chromatogr A* 2001;915:217-223.
4. Da Silva AFS. Anxiolytic, antidepressant and anticonvulsant-like effects of the alkaloid montanine isolated from *Hippeastrum vittatum*. *Pharmacol. Biochem. Behav* 2006;85:148-154.

5. Silva AFS, De Andrade JP, Machado KRB, Rocha AB, Apel MA, Sobral MEG *et al.* Screening for cytotoxic activity of extracts and isolated alkaloids from bulbs of *Hippeastrum vittatum*. *Phytomedicine* 2008;15:882-885.
6. Breiterová K, Koutová D, Maríková J, Havelek R, Kuneš J, Majorošová M *et al.* Amaryllidaceae alkaloids of different structural types from *Narcissus L. cv. Professor Einstein* and their cytotoxic activity. *Plants* 2020;9:137.
7. Evidente A, Andolfi A, Abou-Donia AH, Touema SM, Hammouda HM, Shawky E *et al.* Amabilisine, a lycorine-type alkaloid from *Amaryllis belladonna L.* growing in Egypt. *Phytochemistry* 2004;65:2113-2118.
8. Mathew S, Faheem M, Al-Malki AL, Kumosani TA, Qadri I. *In silico* inhibition of GABARAP activity using antiepileptic medicinal derived compounds. *Bioinformation* 2015;11:189-195.
9. Labraña J, Machocho AK, Kricsfalusy V, Brun R, Codina C, Viladomat F *et al.* Alkaloids from *Narcissus angustifolius* subsp. *transcarpathicus*. *Phytochemistry* 2002;60:847-852.
10. Farinon M, Clarimundo VS, Pedrazza GP, Gulko PS, Zuanazzi JA, Xavier RM *et al.* Disease modifying anti-rheumatic activity of the alkaloid montanine on experimental arthritis and fibroblast-like synoviocytes. *Eur. J Pharmacol* 2017;799:180-187.
11. De Oliveira PG, Pedrazza GPR, Farinon M, Machado XR, Zuanazzi JAS, Spies F. Process for Extracting the Alkaloid Fraction of *Rhodophiala bifida* (Herb.) Traub and Uses Thereof. US Patent 2020/0000798.
12. Da Silva AFS, De Andrade JP, Bevilaqua LRM, De Souza MM, Izquierdo I, Henriques AT *et al.* Anxiolytic-, antidepressant- and anticonvulsant-like effects of the alkaloid montanine isolated from *Hippeastrum vittatum*. *Pharmacol. Biochem. Behav* 2006;85:148-154.
13. Tatiana Castilhos S, Raquel Giordani B, Amélia Henriques T, Fábio Menezes S, José Ângelo Zuanazzi S. *In vitro* evaluation of the antioxidant, anti-inflammatory and antimicrobial activities of the montanine alkaloid. *Brazilian Journal of Pharmacognosy* 2007;17(2):209-214.
14. Ana Flávia Schürmann Da Silva, Jean Paulo De Andrade, Lia RM Bevilaqua, Márcia Maria De Souza, Ivan Izquierdo, Amélia Teresinha Henriques *et al.* Anxiolytic, antidepressant and anticonvulsant-like effects of the alkaloid montanine isolated from *Hippeastrum vittatum*. *Pharmacol Biochem Behav* 2006;85(1):148-54.