Abstract

Introduction. Alkaloids are a large group of organic compounds of natural origin. One of the most popular alkaloids is magnoflorine. This compound is synthesized by plants from the Ranunculaceae, Menispermaceae and Magnoliaceae families. Magnoflorine has unique biological properties and a broad spectrum of physiotherapeutic activity. It has antibacterial, antifungal, antidiabetic, immunomodulating and anticancer properties.

Objective. The aim of the study is to present magnoflorine as a compound with anti-cancer potential.

Brief description of the state of knowledge. Magnoflorine is a compound belonging to the isoquinolone alkaloids. Metabolized by secondary metabolism it is most commonly collected in the roots, rhizomes, tubers and bark of plants. It can be isolated from all plant elements by chromatographic methods. Magnoflorine has a number of therapeutic properties, including anti-cancer. Magnoflorine has been shown to inhibit cell proliferation, migration and cause apoptosis. The possibility of using this compound in the treatment of breast and stomach cancer has been confirmed.

Results. The combination of DOX with magnoflorine reduces the expression of Bcl-2 and enhances the cleavage of caspase-9 and -3, causing apoptosis in breast cancer cells. Moreover, they block the activation of PI3K / AKT / mTOR signaling, which play an important role in regulating tumour growth. Magnoflorine inhibits the activity of caspases in liver cancer cells, resulting in inhibition of proliferation.

Conclusion. Magnoflorine is an interesting research target due to its unique anticancer properties. Detailed knowledge of the pharmacological possibilities of magnoflorine will enable its effective use in the prevention and treatment of many civilization diseases.

Key words

biosynthesis, alkaloids, antitumour activity, magnoflorine

INTRODUCTION

Alkaloids are among the most active plant metabolites. Of the several classes of these compounds which are derived from different amino acids present in their biosynthetic pathways, the isoquinolone alkaloids represent the most interesting group. Magnoflorine is one of the isoquinolone alkaloids that exhibits interesting pharmacological potential. This relationship is widespread among representatives of several botanical families. Numerous publications show the possibility of using magnoflorine in the treatment of bacterial, viral and fungal infections, as well as civilization diseases such as diabetes, obesity, and cancer.

Chemical structure of magnoflorin. One of the most popular alkaloids is magnoflorine (MGN), which is synthesized by plants from the Ranunculaceae, Menispermaceae and Magnoliaceae families [1]. MGN is a quaternary isoquinolone alkaloid, specifically an aporphyrin derivative [2, 3]. These compounds are synthesized from benzylisoquinolines in the process of subtraction of two hydrogen atoms, thus creating the 9,10-dihydrophenanthrene structure from two benzene nuclei [2]. The molecular formula of MGN is C2OH24NO4 + with the structural formula shown in Figure 1. MGN has two hydroxyl groups (-OH) at positions 1 and 11, two groups (-OCH3) at positions 2, 10 and two methyl groups (-CH3) at positions 6 which are attached to the structure of aporphyrin rings [1, 2]. In plants, magnoflorine occurs in the form of a quaternary ammonium ion. It is characterized by good solubility in water and high polarity [4, 5].

Figure 1. Structural formula of magnoflorine

Magnoflorine is synthesized by plants as a result of secondary metabolism [1]. Magnoflorine the presence of the enzyme (S)-norcoclaurine synthase (NCS), thus producing
For a long time, doxorubicin (DOX) affects proliferation, EMT and sensitizes OS cells to cisplatin [17]. It was also found that it may negatively influence the formation of metastasis, the EMT process and of a neoplasm [11]. The activation of signaling itself also causes the proliferation of OS cells and the formation of tumor growth, metastasis and chemoresistance [9, 10].

The key transcription factor is nuclear factor-κB (NF-κB), which contains magnoflorine, inhibits the expression of caspase-3 cleavage and the expression of vascular endothelial growth factor (VEGF) and stimulates the angiogenesis process in hepatocellular carcinoma (HCC). CRAE in appropriate doses causes cytotoxicity on MHCC97L and HEP G2 cells. In addition, CRAE inhibits the phosphorylation level of eukaryotic phosphorylation factor 2 (eEF2), resulting in the inhibition of VEGF synthesis in MHCC97L and Hep G2 cells. In studies with mice administered CRAE, a reduction in the size of the tumours and the number of metastases have been observed. Moreover, CRAE, a reduction in the size of the tumours and the number of metastases have been observed. Moreover, CRAE, a reduction in the size of the tumours and the number of metastases have been observed. Moreover, CRAE, a reduction in the size of the tumours and the number of metastases have been observed. Moreover, CRAE, a reduction in the size of the tumours and the number of metastases have been observed. Moreover, CRAE, a reduction in the size of the tumours and the number of metastases have been observed. Moreover, CRAE, a reduction in the size of the tumours and the number of metastases have been observed. Moreover, CRAE, a reduction in the size of the tumours and the number of metastases have been observed. Moreover, CRAE, a reduction in the size of the tumours and the number of metastases have been observed. Moreover, CRAE, a reduction in the size of the tumours and the number of metastases have been observed. Moreover, CRAE, a reduction in the size of the tumours and the number of metastases have been observed. Moreover, CRAE, a reduction in the size of the tumours and the number of metastases have been observed. Moreover, CRAE, a reduction in the size of the tumours and the number of metastases have been observed. Moreover, CRAE, a reduction in the size of the tumours and the number of metastases have been observed. Moreover, CRAE, a reduction in the size of the tumours and the number of metastases have been observed. Moreover, CRAE, a reduction in the size of the tumours and the number of metastases have been observed. Moreover, CRAE, a reduction in the size of the tumours and the number of metastases have been observed. Moreover, CRAE, a reduction in the size of the tumours and the number of metastases have been observed. Moreover, CRAE, a reduction in the size of the tumours and the number of metastases have been observed.
mice treated with CRAE had a lower density of blood vessels in the tumour. Potentially, this extract can be used as an angiogenesis-reducing agent in the treatment of HCC cancer. In addition, it has been proven that magnoflorine obtained from the methanol extract of *Magnolia grandiflora* leaves inhibits the development of HeLa cervical carcinoma cells, HEPG2 hepatocellular carcinoma cell line and U251 brain tumour cell line [2]. *Ziziphus jujuba* fruit extract, which contain magnoflorine, shows a cytotoxic effect by inhibiting the proliferation of cell lines: Human breast cancer cell line MCF-7, human alveolar basal epithelial cell line A549, human liver carcinoma cell line HepG2 and human colorectal adenocarcinoma cell line HT-29 [28]. Potentially, magnoflorine can be used in the treatment of cancers with over-expression of the androgen receptor as it has been shown to be an antagonist of the androgen receptor. Over-expression of this receptor occurs in prostate cancer and in triple-negative breast cancer [1, 29].

**CONCLUSIONS**

Alkaloids have been used in traditional medicine as a part of phytotherapy. With the development of isolation methods, techniques for the identification and evaluation of the bioactivity of plant metabolites, new possibilities for the use of magnoflorine have appeared. Currently, it has been proven that magnoflorine has a number of health-promoting properties that may suggest its use in the treatment of numerous diseases, including diabetes, neurodegenerative, fungal, immune and cancer diseases. The latest research focuses on understanding the potential of magnoflorine as an anticancer substance. Due to the small number of reports on this subject, it offers great opportunities for further research.

**REFERENCES**

1. Xu T, Kuang T, Du H, et al. Magnoflorine: A review of its pharmacology, pharmacokinetics and toxicity. Pharmocol Res. 2020 Feb; 152: 104632. doi: 10.1016/j.phrs.2020.104632. Epub 2020 Jan 3. PMID: 31911246.  
2. Okon E, Kukula-Koch W, Jarab A, et al. Advances in Chemistry and Bioactivity of Magnoflorine and Magnoflorine-Containing Extracts. Int J Mol Sci. 2020 Feb 16; 21(4): 1330. doi: 10.3390/ijms21041330. PMID: 32079131; PMCID: PMC7072879.  
3. Okon E, Luszczki J, Kukula-Koch W, et al. Synergistic or Additive Pharmacological Interactions between Magnoflorine and Caspatin in Human Cancer Cells of Different Histological Origin. Int J Mol Sci. 2020 Apr 29; 21(8): 2848. doi: 10.3390/ijms21082848. PMID: 32335867; PMCID: PMC7215826.  
4. Morris JS, Facchini PJ. Isolation and Characterization of Reticuline N-Methyltransferase: Involved in Biosynthesis of the Aporphine Magnoflorine in Opium Poppy. J Biol Chem. 2016 Nov 4; 291(45): 23416–23427. doi: 10.1074/jbc.M116.750893. Epub 2016 Sep 15. PMID: 27634038; PMCID: PMC5095398.  
5. Kukula-Koch W, Kruk-Slomka M, Stepniki K, et al. The Evaluation of Pro-Cognitive and Antiinmastic Properties of Berberine and Magnoflorine Isolated from Barberry Species by Centrifugal Partition Chromatography (CPC), in Relation to QSAR Modelling. Int J Mol Sci. 2017 Nov 24; 18(12): 2511. doi: 10.3390/ijms18122511. PMID: 29186770; PMCID: PMC5751114.  
6. Kim J, Ha Quang Bao T, Shin YK, et al. Antifungal activity of magnoflorine against Candida strains. World J Microbiol Biotechnol. 2018 Oct 31; 34(11): 167. doi: 10.1007/s11274-018-2549-x. PMID: 30382403.  
7. Chen J, Liu G, Wu Y, et al. CircMYO10 promotes osteosarcoma progression by regulating miR-370-3p/RUVBL1 axis to enhance the transcriptional activity of β-catenin/LEF1 complex via effects on chromatin remodeling. Mol Cancer. 2019 Oct 29; 18(1): 150. doi: 10.1186/s12933-019-1076-1. Erratum in: Mol Cancer. 2020 Apr 14; 19(1): 75. PMID: 31650676; PMCID: PMC6819556.  
8. Mirabelli L, Troisi RI, Savage SA. International osteosarcoma incidence patterns in children and adolescents, middle ages and elderly persons. Int J Cancer. 2009 Jul 1; 125(1): 329–34. doi: 10.1002/ijc.24320. PMID: 19308040; PMCID: PMC3048853.  
9. Effert T, Oesch F. Repurposing of plant alkaloids for cancer therapy: Pharmacology and toxicology. Semin Cancer Biol. 2019 Dec 26: S1044-55X9(19)30408-0. doi: 10.1016/j.semcancer.2019.12.010. Epub ahead of print. PMID: 31883912.  
10. Lu Y, Li F, Xu T, et al. Tetrandrine prevents multidrug resistance in the osteosarcoma cell line, U-2OS, by preventing Pgp overexpression through the inhibition of NF-κB signaling. Int J Mol Med. 2017 Apr; 39(4): 993–1000. doi: 10.3892/ijmm.2017.2895. Epub 2017 Feb 17. PMID: 28260091.  
11. Zhang C, Chen B, Jiang K, et al. Activation of TNF-α/NF-κB axis enhances CRL4BDCAF11 E3 ligase activity and regulates cell cycle progression in human osteosarcoma cells. Mol Oncol. 2018 Apr; 12(4): 476–494. doi: 10.1002/1878-0261.12176. Epub 2018 Feb 20. PMID: 29377600; PMC5891038.  
12. Li R, Shi Y, Zhao S, et al. NF-κB signaling and integrin-β1 inhibition attenuates osteosarcoma metastasis via increased cell apoptosis. Int J Biol Macromol. 2019 Feb 15; 123: 1035–1043. doi: 10.1016/j.ijbiomac.2018.11.003. PMID: 30399378.  
13. Ling J, Sun Y, Pan J, et al. Feedback modulation of endothelial cells promotes epithelial-mesenchymal transition and metastasis of osteosarcoma cells by Vennillebrand Factor release. J Cell Biochem. 2018 Sep; 129(9): 15971–15979. doi: 10.1002/jcb.28875. Epub 2019 May 17. PMID: 31099074.  
14. Lu J, Song G, Tang Q, et al. XR11 hypomethylation promotes osteosarcoma metastasis via induction of CXCL14/NF-κB signaling. J Clin Invest. 2015 May; 125(5): 1839–56. doi: 10.1172/JCI78437. Epub 2015 Mar 30. PMID: 25822025; PMCID: PMC4463998.  
15. Zhao P, Wang S, Jiang J, et al. TIPPE2 sensitizes osteosarcoma cells to cis-platin by down-regulating MDRI via the TAK1- NF-κB and – AP-1 pathways. Mol Immunol. 2018 Sep 10; 141: 471–478. doi: 10.1016/j.molimm.2018.08.010. Epub 2018 Aug 14. PMID: 30114619.  
16. Guo S, Jiang K, Wu H, et al. Magnoflorine Ameliorates Lipopoly saccharide-Induced Acute Lung Injury via Suppressing NF-κB and MAPK Activation. Front Pharmacol. 2018 Aug 30; 9: 892. doi: 10.3389/ fphar.2018.00892. PMID: 30214410; PMCID: PMC6125661.  
17. Wang Y, Shang G, Wang W, et al. Magnoflorine inhibits the malignant phenotypes and increases cisplatin sensitivity of osteosarcoma cells via regulating miR-410-3p/IRX1/NF-κB pathway. Life Sci. 2020 Jun 15; 256: 117967. doi: 10.1016/j.lfs.2020.117967. Epub ahead of print. PMID: 32553931.  
18. Sáez-Freire MDM, Blanco-Gómez A, Castillo-Lluva S, et al. The biological link aged to oxidative stress modifies breast cancer aggressiveness. Free Radic Biol Med. 2018 Jul; 117: 246–258. doi: 10.1016/j.freeradbiomed.2018.04.015. Epub 2018 Apr 26. PMID: 29793523; PMCID: PMC6006726.  
19. Peiris D, Spector AF, Lomax-Browne H, et al. Cellular glycosylation affects Herceptin binding and sensitivity of breast cancer cells to doxorubicin and growth factors. Sci Rep. 2017 Feb 22; 7: 43006. doi: 10.1038/srep43006. PMID: 28223691; PMCID: PMC5320443.  
20. Lee SI, Jeong YI, Park HK, et al. Elavase-sensitive doxorubicin release from dendrimer nanoparticles for anticancer drug delivery. Int J Nanomedicine. 2015 Aug 25; 10: 5489–503. doi: 10.2147/ijnm.2015.012798.  
21. Veit S, Xiaojun X, Peilong C. Magnoflorine improves sensitivity to doxorubicin (DOX) of breast cancer cells via inducing apoptosis and
autophagy through AKT/mTOR and p38 signaling pathways. Biomed Pharmacother. 2020 Jan; 121: 109139. doi: 10.1016/j.biopha.2019.109139. Epub 2019 Nov 7. PMID: 31707337.

25. Porta C, Paglino C, Mosca A. Targeting PI3K/Akt/mTOR Signaling in Cancer. Front Oncol. 2014 Apr 14; 4: 64. doi: 10.3389/fonc.2014.00064. PMID: 24782981; PMCID: PMC3995050.

26. Fock KM. Review article: the epidemiology and prevention of gastric cancer. Aliment Pharmacol Ther. 2014 Aug; 40(3): 250–60. doi: 10.1111/apt.12814. Epub 2014 Jun 10. PMID: 24912650.

27. Sun XL, Zhang XW, Zhai HJ, et al. Magnoflorine inhibits human gastric cancer progression by inducing autophagy, apoptosis and cell cycle arrest by JNK activation regulated by ROS. Biomed Pharmacother. 2020 May; 125: 109118. doi: 10.1016/j.biopha.2019.109118. Epub 2020 Feb 25. PMID: 32106366.

28. Bai L, Zhang H, Liu Q, et al. Chemical characterization of the main bioactive constituents from fruits of Ziziphus jujuba. Food Funct. 2016 Jun 15; 7(6): 2870–7. doi: 10.1039/c6fo00613b. Epub 2016 May 27. PMID: 27232543.

29. Lutz SZ, Hennenlotter J, Scharpf MO, et al. Androgen receptor overexpression in prostate cancer in type 2 diabetes. Mol Metab. 2018 Feb; 8: 158–166. doi: 10.1016/j.molmet.2017.11.013. Epub 2017 Dec 5. PMID: 29249638; PMCID: PMC5985051.