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REVIEW ARTICLE

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Magnoflorine – a compound with anti-tumour activity

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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, magnoflorin

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 structure 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].

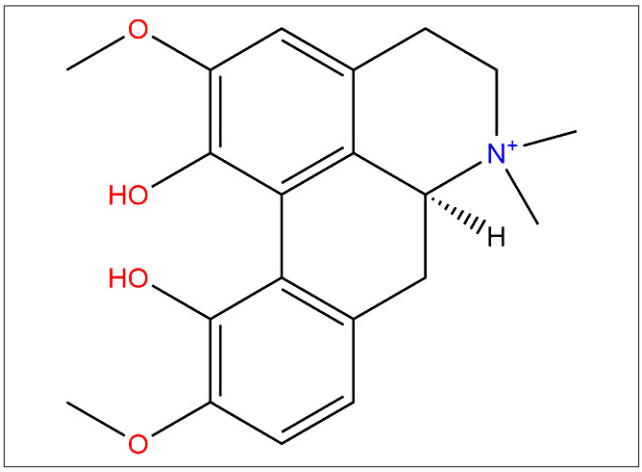

Figure 1. Structural formula of magnoflorine

Magnoflorine is synthesized by plants as a result of secondary metabolism [1]. Magnoflorine the presence of the enzyme (S)-norcoclaurine synthase (NCS), thus producing

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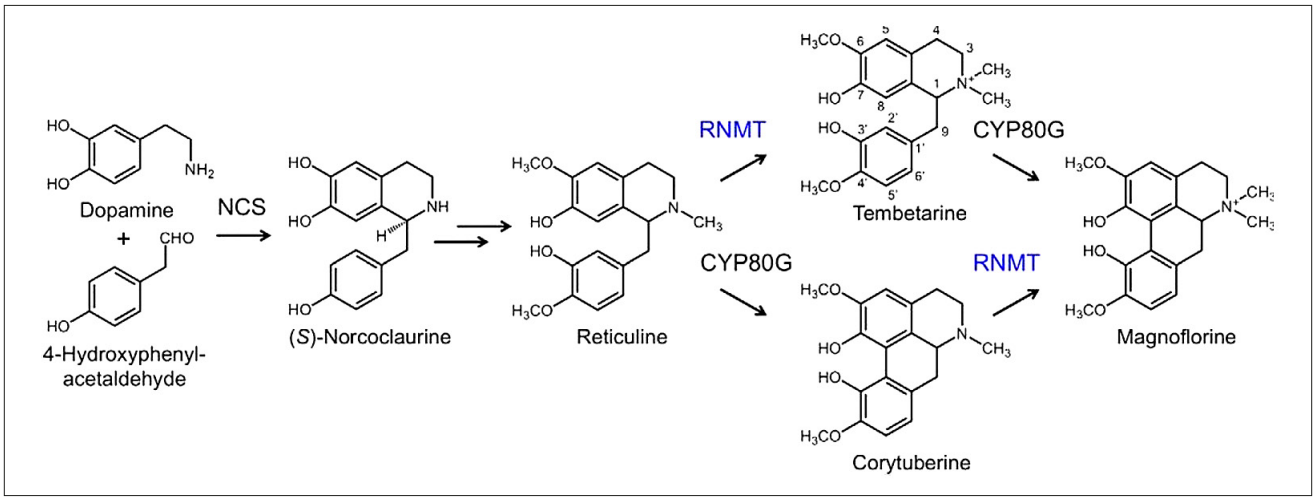

Figure 2. Magnoflorine biosynthesis [4]

(S)-norcoclaurine. This is followed by O-methylation, N-methylation and hydroxylation of the aromatic (S) -reticulin ring. The conjugation of carbon with the phenol of S-reticulin by cytochrome P-450 forms the aporphyrin skeleton in coribirin which is N-methylated to magnoflorine. Alternatively, magnoflorine may be produced by the N-methylation of reticulin to form tembetarine, which may be a substrate for the synthesis of magnoflorine. Magnoflorine biosynthesis always requires the presence of the enzyme N-methyltransferase (NMT). Fig. 2 [4].

Magnoflorine was isolated from the rhizomes, roots, stems and bark of plants from the Rutaceae, Menispermaceae, Ranunculaceae, Magnoliaceae, and Berberidaceae families [1]. MGN can be isolated by the LC-MS liquid chromatography method using silica gel (RP-18). Magnoflorine, as a compound containing nitrogen in its structure, is easily detectable in the positive ionization mode by mass spectrometry [2]. Magnoflorine has unique biological properties. It has been shown to have antifungal, anticancer, antiviral, anti-inflammatory and antioxidant properties [2, 6].

Antitumour activity. Magnoflorine exhibits a broad spectrum of pharmacological properties, including anti-inflammatory, anti-diabetic, immunomodulating, antioxidant, antifungal, anti-diabetic, antihypertensive and anti-cancer properties. [1]. In The current study focuses on the latest reports confirming the possibility of using magnoflorin in the treatment of cancer.

Osteosarcoma (OS) is a bone tumour originating from malignant mesenchymal cells and is most common in children and adolescents [7, 8]. Alkaloids have been shown to be beneficial in anti-cancer therapy because they inhibit tumour growth, metastasis and chemoresistance [9, 10]. The key transcription factor is nuclear factor-κB (NF-κB), activated in human OS cells. Inhibition of the activation of this factor causes the proliferation of OS cells and the formation of a neoplasm [11]. The activation of signaling itself also influences the formation of metastasis, the EMT process and induces resistance to cisplatin [12–15]. It has been shown that magnoflorine in acute lung injury by lipopolisachadydy (LPS) inhibits the NF-kB [16]. It was also found that it may negatively affect proliferation, EMT and sensitize OS cells to cisplatin [17].

Breast cancer is the most common cancer among women worldwide. [18, 19]. For a long time, doxorubicin (DOX) has been a chemotherapeutic agent used in the treatment of this cancer [20, 21]. Unfortunately, its effectiveness is limited by side-effects such as carotoxicity. The combination of magnoflorine and DOX has been shown to reduce cell viability and migration. Additionally, magnoflorine increases the expression of caspase-3 cleavage and the expression of LC3-II, which enhances the apoptosis and autophagy induced by DOX [22]. Over-expression of proteins, such as Bcl-2 and reduction of pro-apoptotic proteins necessary to induce caspase-3 activation, increases the resistance of cancer cells to apoptosis [23]. 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. In addition, they block the activation of PI3K / AKT / mTOR signaling, which play an important role in regulating tumour growth [24, 25].

Gastric cancer (GC) is another common cancer worldwide, causing 723,000 deaths annually [26]. Alkaloids are potential therapeutic substances. Cell proliferation is regulated by signaling molecules and checkpoints (CDKs), which are additionally regulated by cyclins. Cyclin-A and cyclin-B1 are involved in the progression of the cell cycle to the S and G2 phases. Magnoflorine has been shown to exert anti-tumour activity in GC cells by regulating autophagic cell death, apoptosis, and S / G2 cell cycle arrest. Additionally, magnoflorine inhibits AKT and activates JNK signaling pathways dependent on ROS accumulation, which are associated with autophagy, apoptosis and cell cycle arrest in various types of cancer cells [27]. This compound inhibits the growth of liver cancer cells. It suppresses the expression of hTERT mRNA and increases the expression of caspase 3, i.e. the protein responsible for cell apoptosis [1].

The aqueous extract of Coptidis rhizoma (CRAE), which contains magnoflorine, inhibits 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 synthesis and secretion of VEGF. This extract increases 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,

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 hale 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.

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