Journal of Medicinal Plants Research Vol. 5(10), pp. 1806-1811, 18 May, 2011
Available online at http://www.academicjournals.org/JMPR
ISSN 1996-0875 ©2011 Academic Journals

Review

Chinese traditional medicine matrine: A review of its antitumor activities

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Accepted 22 October, 2010

Matrine, a major component of the dried roots of *Sophora flavescens Ait.* (Leguminosae) has a long history of use in traditional Chinese medicine. It has been found that matrine possesses a wide range of pharmacological effects including antitumor activities on a number of cancer cell lines in recent years. However, its spectrum of practical applications is often limited due to the elusive antitumor mechanism. Thus, more and more researchers focused on the investigation of antitumor activities of matrine and active progresses have been achieved up to now. Herein, on the basis of related experimental studies, we reviewed the new progress on the antitumor mechanism of matrine and its clinical effects on cancers. Matrine could serve as an antitumor agent against many tumors by inhibiting tumor cell migration and proliferation, inducing differentiation, changing the expression of tumor relative proteins and oncogenes, interfering cell cycle, inducing cell apoptosis, inhibiting the cytokine productions and so on. The antitumor mechanism of matrine may be realized through up-regulating or down-regulating expression of the tumor relative molecules, ultimately resulting into tumor cell death mainly via cell apoptosis. Therefore, matrine has the potential to be an alternative natural product in the further clinical study.

Key words: Matrine, pharmacological effect, antitumor activity, mechanism.

INTRODUCTION

Sophora species (Leguminosae), an important source of Chinese herbal drugs, is used widely throughout China for thousands of years. As a traditional Chinese herb, the root of *Sophora flavescens Ait*. (Kushen) has long been applied in therapy of many diseases, such as viral hepatitis, cancer, cardiac diseases and skin diseases (Liu et al., 2006; Luo et al., 2007; Qin et al., 2010). Quinolizidine alkaloids have been found to be its chief active components including matrine (MT), oxymatrine (OMT), sophocarpine (SC), sophoridine (SRI) and other alkaloids (Liu et al., 2003). Basic and clinical researches have shown that these alkaloids possess variety of pharmacological effects such as anti-inflammation, immunity-regulation, antivirus and antitumor action (Azzam et al., 2007; Jiang et al., 2007; Ma et al., 2008).

Matrine, with a molecular formula of $C_{15}H_{24}N_2O$, is the major quinolizidine alkaloids. Its molecular weight is 248.36 and its chemical structure is shown in Figure 1. Matrine is important due to the potentially useful pharmacological activities. Recently, it has been proved by many researches that matrine can inhibit tumor growth, enhance the immune functions of patients and thus improve patients' life quality (Dai et al., 2005; Chen et al., 2006). In addition, it has been reported that matrine could stimulate differentiation of tumor cells (Zhang et al., 2001, 2008a), regulate expression of tumor relevant proteins (Qin et al., 2010) and induce apoptosis of tumor cells (Han et al., 2007; Luo et al., 2007; Dai et al., 2009).

However, the mechanism underlying the inhibition process by matrine remains uncertain. Our laboratory has studied the antitumor activities of matrine and focused on utilizing matrine to kill tumor cell lines for more than twenty years. Here, we reviewed the recent progress on

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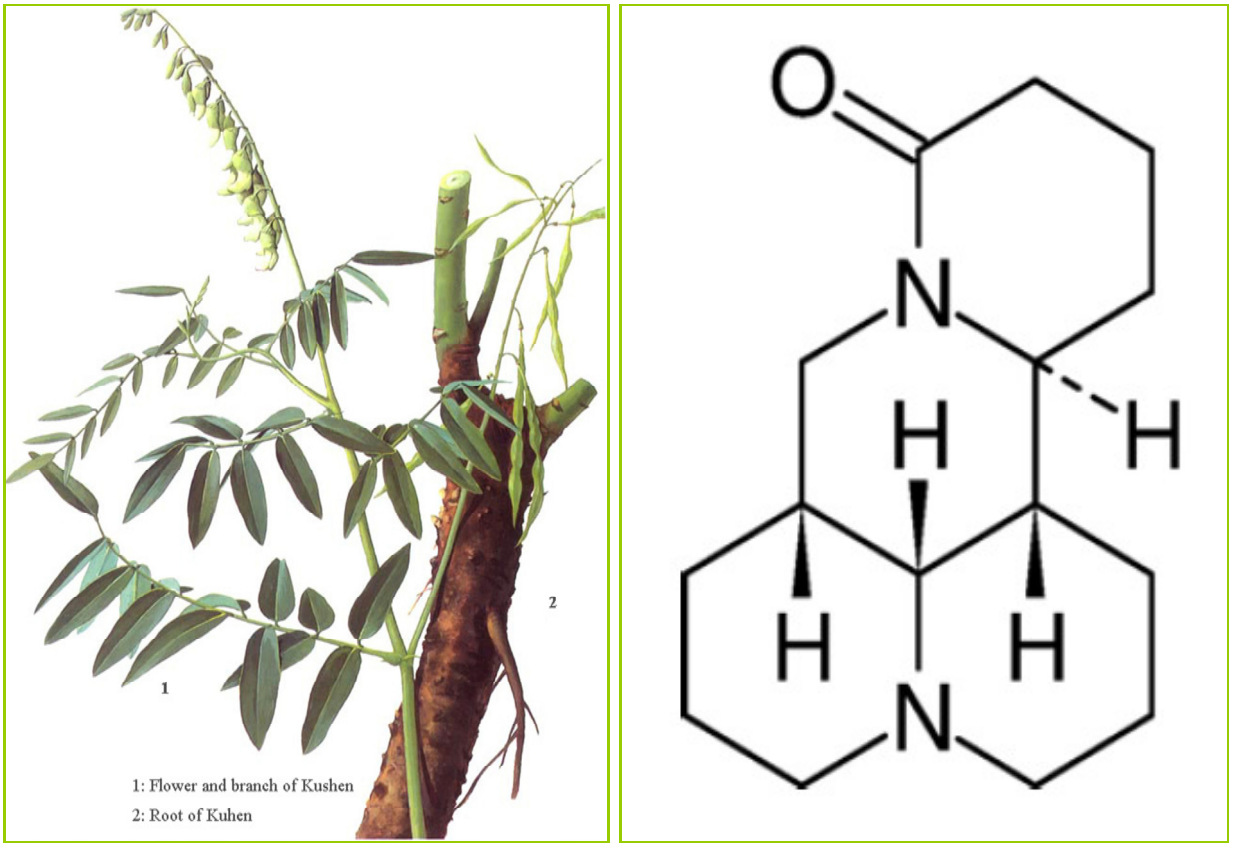

Figure 1. The flower, branch and root of Kushen (left) and its chemical structures (right). The molecular formula of matrine is $C_{15}H_{24}N_2O$ and its molecular weight is 248.36.

the antitumor mechanism of matrine and the potential future directions for research in this area.

ANTITUMOR ACTIVITIES

Inhibition of cell migration and proliferation, and induction of differentiation

Matrine has potential as an inhibiting and differentiating agent for the treatment of tumor, and the precise modes of its anti-proliferative and differentiating action have been investigated for a long time. Matrine strongly inhibited the growth of breast carcinoma cell (Bcap-37), colon adenocarcinoma cell (HT-29), Glioma cell (C6), Hela cell, hepatocellular liver carcinoma cell (HepG2), erythromyeloblastoid leukemia cell (K-562), gastric adenocarcinoma cell (MKN45), leukemic monocyte lymphoma cell (U937), melanoma cell (A375) and so forth (Deng et al., 2004; Liu et al., 2006; Jiang et al., 2007; Han et al., 2010; Qin et al., 2010). Matrine was also able to inhibit the growth of tumor cells including murine and human xenograft tumor models (Hu et al., 2005).

Based on the earlier mentioned cell lines representing different tissues, antitumor activity of matrine was significantly stronger than that observed when cells were treated with free matrine (Liu et al., 2010). Matrine significantly suppressed the growth of human lung cancer cell (A549) and hepatoma cell (SMMC-7721) *in vitro* and *ex vivo*, and the induction of apoptosis by reducing ratios of the B-cell lymphoma 2/Bcl-2-associated X protein (Bcl-2/Bax) protein levels in human lung cancer A549 and SMMC-7721 cells may be one of the important mechanisms of action of matrine against cancer cell growth (Zhang et al., 2009). On the other hand, matrine significantly suppressed the proliferation of highly-metastatic human breast cancer (MDA-MB-231) cell line, and induced the apoptosis and cell cycle arrest by reducing the ratios of Bcl-2/Bax protein and mRNA levels via epidermal growth factor (EGF)/vascular endothelial growth factor (VEGF)- vascular endothelial growth factor receptor 1 (VEGFR-1)-Akt-NF-jB signaling pathway in the cancer cells (Liu et al., 2009).

Differentiation of tumor cells is associated with a loss of proliferative capacity (Counter et al., 1995). Telomerase, a ribo-nucleoprotein enzyme, has attracted intense interest as a possible target for cancer therapeutics. It is

reported that induction of differentiation is associated with a loss of telomerase activity (Counter et al., 1995; Sharma et al., 1995). Matrine is an effective differentiation-inducing agent for K-562 cells, plays a significant role in the inhibition of the growth of K-562 cells and inducing differentiation by inhibiting telomerase activity (Zhang et al., 2001; Chui et al., 2005; Luo et al., 2007). Moreover, matrine induces differentiation depending on its concentration and exposure time. These findings establish a strong link between telomerase activity and the state of differentiation of cell lines. The more the tumor cells are differentiated, the more significant the decrease in telomerase activity (Counter et al., 1995; Qin et al., 2010; Xing et al., 2010). Thus, we attempted to speculate that the mechanism responsible for suppressing telomerase activity is activated by cell differentiation. The differentiation is associated with repression of the transcription of one or more genes coding for either the RNA or the protein subunits of telomerase, indicating that cell differentiation is the self-regulation course of the cells (Sharma et al., 1995). In addition, matrine can arrest tumor cells entering into the S-phase of the cell cycle, again supporting that treatment with matrine results in the inhibition of DNA replication and growth of tumor cells (Zhang et al., 2001).

Changing the expression of tumor relative proteins and oncogenes

Cell proliferation and cell differentiation are regulated and controlled by several elements. Among these elements, oncogenes or tumor proteins are one of the key players in the control of cell proliferation and differentiation including alpha fetal protein (AFP), N-ras oncogene, tumor suppressor gene (*p53*), proto-oncogene (*c-myc*), Transcription factor E2F-1, Apoptotic protease activating factor 1 (Apaf-1), retinoblastoma (Rb), *bcl-2* family, caspases and so on (Luo et al., 2007; Zhang et al., 2007).

AFP, carcinoembryonic protein, is the most established tumor marker in human hepatocellular carcinoma cell (HCC) and the gold standard by which early liver cancer is judged (Zhang et al., 1998). AFP protein does not exist in natural hepatocyte and exactly represents the malignant degree of the hepatoma. It is reported that the expression of AFP clearly decreased in HepG2 cells treated with matrine, which suggested that the malignant proliferation of HepG2 cell has been inhibited (Zhang et al., 1998; Qin et al., 2010). Both P53 and E2F-1 are known to regulate apoptosis protein-activating factor (Apaf-1), a pivotal component in apoptosome assembly (Xing et al., 2010). Matrine has been shown to stimulate differentiation of K562 cells through up-regulation of *N-ras* and *p53* mRNA and down-regulation of *c-myc* (Zhang et al., 2001). Matrine down-regulated had significant protein expression of C-myc and Bcl-2 in HepG2 cells, but the expression of Bax was up-regulated higher than untreated cells, which demonstrated that matrine inhibited cells proliferation via up-regulating or down-regulating expression of the tumor relevant proteins (Qin et al., 2010). In the same way, it has been shown that matrine inhibited proliferation of C6 cells and down-regulated expression of proto-oncogene *c-myc* (Deng et al., 2004). An apoptosis real-time PCR array was performed to explore the molecular mechanism of antitumor, and the results has demonstrated that 57 genes were at least 2-fold up-regulated, and 11 genes were at least 2-fold down-regulated in matrine-treated C6 cells when compared with untreated cells (Zhang et al., 2008a). It is concluded that matrine is an effective differentiation-inducing agent for tumor cells, plays a significant role in the inhibition of the growth of tumor cells and induces differentiation arresting cell cycle progression of tumor cells (Luo et al., 2007).

Interfering tumor cell cycle

Disturbance of the cancer cell cycle is one of the therapeutic pathways for development of new anticancer drugs (Carnero, 2002). Proliferating cell nuclear antigen (PCNA) participated in a variety of essential cellular processes including DNA replication, DNA repair and cell-cycle control by interacting with proteins involved in these processes (He et al., 2001). The PCNA protein expresses little in resting phase and more is synthesized at the end of G1 phase, reaching climax in S phase, whereas PCNA decreases obviously in G2 and M phase (Tong et al., 2005). The seasonal variation is similar to the process of cell proliferation, and its expression represents the ability of cell proliferation. The obvious decrease of PCNA protein in matrine-treated cells, may indicate that matrine could prevent HepG2 into S stage to fulfill duplication of DNA molecule and result in the failure of cell division (Leone et al., 1997; Qin et al., 2010).

Human gastric cancer cell MKN45 treated with matrine dropped remarkably as for the G0/G1 phase, and in cell apoptosis, the percentages of apoptotic MKN45 cells increased along with the dosage of matrine. This proof testified that matrine could block cell cycle progression at G0/G1 phase and induce apoptosis *in vitro* (Luo et al., 2007). It was again found that both matrine notably inhibits the growth and proliferation of human hepatoma cells SMMC-7721 and present a dose-dependence and time-dependence manner within definite reacting dose and time. Matrine blocked SMMC-7721 cells in G2/M and S phase and prevent cells entering into G0/G1 phase. It resulted in an obvious accumulation of G2/M and S phase cells and decrease of G0/G1 phase cells (Wan et al., 2009). It was also found that matrine had down-regulate expression of *bcl-2* gene and up-regulate expression of *p53* gene in SMMC-7721 cells. It demonstrated that matrine inhibit the proliferation and

induce apoptosis of human hepatoma SMMC-7721 cells, and suggest that this effect was mediated probably by a significant cell cycle blockage in G2/M and S phase, down-regulation of *bcl-2* and up-regulation of *p53* (Wan et al., 2009). At the same time, matrine had anti-proliferative effect to A549 cells and a time- and dose-dependent manner was found. The cell cycle analysis evaluated by flow cytometry analysis showed that matrine could induce G0/G1 arrest in A549 cells. The exploration of targeting regulatory molecules involving G1/S transition might be contributed to elucidate the mechanism underlying this effect of matrine in tumor cells (Tong et al., 2005; Ma et al., 2010).

Induction of tumor cell apoptosis

Recently, it has been reported that matrine exhibits antitumor effects by inhibiting proliferation and inducing apoptosis of cancer cells from cervical cancer, leukemia, gastric cancer, hepatocellular carcinoma, breast cancer and lung cancer (Chui et al., 2005; Hu et al., 2005; Liu et al., 2006; Jiang et al., 2007; Luo et al., 2007). The anticancer activity of matrine may rely on its effects on apoptosis-genes or proteins (Zhang et al., 2008a). However, the molecular mechanism of cell apoptosis induced by matrine remains elusive. Many researchers are all long focused on the precise molecular mechanisms involved in matrine-induced cell death via apoptosis. Apoptosis, the best-described form of programmed cell death, involves the activation of catabolic enzymes in signaling cascades, which leads to the rapid demolition of cellular structures and organelles (Danial et al., 2004; Green, 2005).

Classical apoptosis is characterized morphologically by cell shrinkage, chromatin condensation, nucleosomal DNA degradation and finally fragmentation of the cell into apoptotic bodies (Gozuacik et al., 2007). Matrine could inhibit cell proliferation and induce apoptosis in a dose-dependent manner (Liu et al., 2006; Zhang et al., 2008a; Han et al., 2010). The apoptosis in matrine-treated human gastric cancer MKN45 cells were observed in matrine-treated cells, whereas, caspase-3, -7 were activated and the pro-apoptotic molecules Bok, Bak, Bax, Puma and Bim were also up-regulated, which indicated that matrine induced gastric cancer MKN45 cells apoptosis via increasing pro-apoptotic molecules of Bcl-2 family (Luo et al., 2007). Besides, the changes in expression and localization of several apoptosis-related proteins in K562 cells exposed to matrine, revealed that E2F-1 protein is up-regulated in response to matrine (Zhang et al., 2001). Expression of Rb, an inhibitor of E2F-1 activity, was rapidly decreased and expression of Apaf-1, a target protein in E2F-1-induced apoptosis, was increased. These changes were accompanied by cytochrome *c* efflux and activation of caspase-9 and -3, indicating that apoptosis occurred primarily through the mitochondrial pathway (Jiang et al., 2007). Furthermore, matrine inhibited human gastric cancer cells (SGC-7901) proliferation in a dose-dependent and time-dependent manner. Florescence intensity levels of factor associated suicide (Fas) and Fas ligand (FasL) were found to be equally up-regulated after matrine treatment, which were both correlated with apoptosis rate. The activity of caspase-3 enzyme increased in matrine groups, positively correlated with apoptosis rate. It is proved that apoptosis induction of SGC-7901 cells appears to proceed by up-regulating Fas/FasL expression and activating caspase-3 enzyme (Wan et al., 2009).

Human myeloma (MM) cells had a reduction of the ratio Bcl-2/Bax protein after treatment with matrine (Han et al., 2010). Bcl-2 inhibits apoptosis, which displays on the outer membranes of mitochondria in healthy cells (Debatin et al., 2002). Matrine might have caused Bax to migrate from cytosol to the surface of the mitochondria, where it inhibited the protective effect of Bcl-2 and inserted itself into the outer mitochondrial membrane, punching holes in it and causing mitochondrial membrane potential (△φm) loss and cytochrome *c* leak-out. Cytosolic cytochrome *c* can bind to Apaf-1, a cytosolic protein containing a caspase-recruitment domain, and caspase-9 to form a complex, which activates procaspase-3 (Brown et al., 2008). Subsequently, the activated caspase-3 effect on a target cell leads to final destruction of the cell. Caspase-3 is the primary activator of apoptotic DNA fragmentation (Karamitopoulou et al., 2007). Matrine-induced apoptosis occurred concomitantly with activation of caspase-3 in myeloma cells, which demonstrated that the activation of caspase-3 might lead to apoptosis. It is concluded that matrine-induced apoptosis in myeloma cells was partially dependent on the mitochondria-mediated pathway: decrease of Bcl-2Bax ratioloss of △φmrelease of cytochrome *c* activation of caspase-3apoptosis (Han et al., 2010).

Moreover, the mechanism of antitumor effect was elucidated that matrine were able to induce tumor cell apoptosis by acting on the other pathways or targets. The nuclear factor-kappa B (NF-κB) signaling pathway and the gene transcription that it activates, such as the *bcl-2* gene family, have now emerged as the critical regulators of cell survival signal and cell apoptosis (Hu et al., 2005). It was demonstrated that matrine inhibited NF-κB activation in human renal epithelial cell line 293. The *in vivo* data of down-regulation of *bcl-2* in tumors treated with marine was in agreement with the *in vitro* observation (Han et al., 2007). It was also found that the reduction of phosphorylated IκBα (nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha) in matrine-treated cells stimulated by tumor necrosis factor α (TNF-α) resulted in the inhibition of NF-κB activation (Zhou et al., 2003). In addition to the NF-κB pathways, marine was able to up-regulate caspase 8 and caspase 3 *in vivo*, leading to tumor cell apoptosis (Han et al., 2007).

Inhibition of the cytokin productions

The past few years have seen a rapid advance in our understanding of the immune-pathological basis of cancer. The presence of tumor results in a persistent host inflammatory response, characterized by the production of pro-inflammatory cytokines. In the acute setting, such as infection, this response is beneficial to the host, as it up-regulates the immune system and aids recovery. However, in cancer patients, the continuing presence of tumor results in a chronic inflammatory state that leads to the development of cancer cachexia (Zhang et al., 2008b).

Cytokines play an important role in the pathogenesis of cancer. It is now clear that pro-inflammatory cytokines such as TNF-α, interleukin-1 (IL-1), IL-6 and VEGF, which are secreted from both cancer cells and host tissues, are involved in the induction of cancer (Lelbach et al., 2007). Previous studies have found that matrine markedly inhibited the production of pro-inflammatory cytokines (TNF-α, IL-1 or IL-6) in cancer cachexia (Hu et al., 1996; Lin et al., 1997). The mechanisms underlying the anti-cachectic effect of matrine have showed that tumor-bearing caused a marked increase in serum levels of both TNF-α and IL-6. Administration of matrine significantly reduced the concentrations of TNF-α and IL-6 in serum of tumor-bearing mice. Consistent with this effect, matrine suppressed the mRNA expressions of TNF-α and IL-6 in murine macrophage cell line (RAW264.7) (Zhang et al., 2008b). The serum levels of TNF-α and IL-6 in colon 26-bearing mice were significantly higher than in healthy control mice (Zhou et al., 2003).

Matrine inhibited cyclooxygenase-2 (COX-2)-catalyzed prostaglandin E2 (PGE2) and inducible nitric oxide synthase (iNOS)-catalyzed NO production by lipopolysaccharide (LPS)-treated RAW 264.7 cells, and these effects primarily occurred via COX-2 inhibition and iNOS down-regulation, respectively. These researches indicate that matrine may have the potential for treatment of chronic inflammatory disorders and cancer (Jin et al., 2010). As for another important cytokine, VEGF is a positive regulator of angiogenesis and its expression is up-regulated in many carcinomas. A report shows that suppression of VEGF expression in human lung cancer cell lines including A549 cells leads to the inhibition of growth in the lung cancer *in vitro* and *in vivo* (Liu et al., 2009). Matrine reduces the rate of A549 cell migration more than 30 to 48%, which suggested that the reduction of VEGF secretion in A549 cells by matrine may be one of important mechanisms of action of matrine against the migration and growth of A549 cells (Zhang et al., 2009).

CONCLUSION

In conclusion, matrine could inhibit tumor cell proliferation by down-regulating or up-regulating the expression tumor relative genes and proteins, and induce tumor cell death mainly via cell apoptosis. Matrine has the potential to be an alternative natural product in the further clinical study.

ACKNOWLEDGEMENT

This work was financially supported by the Research Foundation of Master, HeiLongJiang BaYi Agricultural University (S2005-38).

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