Journal of Medicinal Plants Research Vol. 6(39), pp. 5222-5227, 10 October, 2012
Available online at http://www.academicjournals.org/JMPR
DOI: 10.5897/JMPR12.031
ISSN 1996-0875 ©2012 Academic Journals

Full Length Research Paper

Down regulation of matrix metalloproteinases by spearmint extract in Wehi-164 cells

Fatemeh Hajighasemi* and Vida Hashemi

Department of Immunology, Faculty of Medicine, Shahed University, Tehran, Iran.

Accepted 30 May, 2012

Tumor invasion and metastasis are the main causes of cancer death. Matrix metalloproteinases (MMPs) are endopeptidases which degredate the extracellular matrix proteins. MMPs have an important role in tumor progression and metastasis. Fibrosarcoma has been recognized as a highly metastatic cancer which its current therapeutic methods have not been very successful. Medicinal plants are widely used in treatment of cancers. Spearmint is a herb with well known anti-tumor activities. In the present study, the effect of hydro extract of spearmint on MMP-2/9 activities in Wehi-164 fibrosarcoma cells has been evaluated *in vitro*. Wehi-164 cells were cultured in Roswell Park Memorial Institute (RPMI) medium with 10% fetal bovine serum (FBS). Then the cells at logarithmic growth phase were incubated with different concentrations of hydro extract of spearmint (0.1 to 10 mg/ml) in the presence or absence of phorbol myristate acetate (PMA) (25 ng/ml) for 24, 48 and 72 h. The MMP-2/MMP-9 activity in conditioned medium was evaluated by gelatin zymography. Spearmint aqueous extract significantly reduced the MMP-2 and PMA-induced MMP-9 activity in fibrosarcoma Wehi-164 cells dose dependently. The aqueous extract of spearmint showed inhibitory effect on MMP-2/MMP-9 activity in Wehi-164 fibrosarcoma cells. So, the anti-tumor effects of spearmint may be in part due to its inhibitory effects on MMP-2/MMP-9 activity. Evaluation of effective component (s) in the spearmint extract with anti-MMP activity and their mechanism of action could be useful in designing novel natural MMP inhibitors.

Key words: Spearmint, matrix metalloproteinases, fibrosarcoma.

INTRODUCTION

Tumor invasion and metastasis are processes mediated by several factors including cytokines, chemokines and matrix metalloproteinases (MMPs) (Mason and Joyce, 2011; Pathak and Kumar, 2011; Calorini and Bianchini, 2010). MMPs belong to a large family of zinc and calcium-dependent endopeptidases which degredate the extracellular matrix proteins (Castro-Sanchez et al., 2011). MMPs have an important role in inflammation, tumor progression and metastasis (Gialeli et al., 2011; Watanabe, 2010; Bulbule et al., 2011). There are some reports about medicinal plants effect on MMPs (Li et al., 2011; Hwang et al., 2011a; Hseu et al., 2011; Hui et al., 2010). For example, the inhibitory effects of flavonoids on MMP-2 and MMP-9 have been revealed (Li et al., 2011). Moreover, anti-invasive, anti-angiogenesis and anti-metastatic effects of a number of herbal compounds have been attributed to their inhibitory effects on MMPs expression (Hwang et al., 2011b; Hseu et al., 2011; Hui et al., 2010). Spearmint (*Mentha spicata*) is a herb belonging to *Mentha* genus in the Labiatae family (Choudhury et al., 2006). This herb is widely used in treatment of fever, vomiting, sinusitis and common cold (Güney et al., 2006). The anti-microbial, radioprotective, anti-oxidant, anti-tumoral and anti-inflammatory effects of spearmint have been reported (Lixandru et al., 2010; Haksar et al., 2009; Pearson et al., 2010; Hussain et al., 2010; Arumugam and Ramesh, 2009). Besides, the toxic effect of *Mentha pulegium* (another specious of *Mentha* genus) on some cancer cells has been shown (Shirazi et al., 2004). Furthermore, protective effects of spearmint oil on lung tissue injury in rats with chronic obstructive

*Corresponding author. E-mail: resoome@yahoo.com. Tel: +9821 88964792. Fax: +9821 88966310.

pulmonary disease (COPD) have been accredited to its anti-inflammatory effects on pulmonary interstitial inflammation and inflammatory cell infiltration (Zhao et al., 2008). Also, the beneficial effects of peppermint oil (another genus of mint specious) on regression of inflammatory pulmonary tuberculosis have been reported (Shkurupiĭ et al., 2006). Moreover, the anti-inflammatory effect of L-mentol (an organic compound obtained from peppermint or other mint oils) on lipopolysaccharide (LPS)-stimulated monocytes through suppression of interleukin-1 (IL-1) beta, polyethylene glycol (PEG) and LT-B4 has been reported (Juergens et al., 1998). In addition, the anti-inflammatory effect of *Mentha piperita* against acute and chronic inflammation has been detected (Atta and Alkofahi, 1998). Furthermore, spearmint oil diminished the expression of MMP-9 in lung tissues of rat *in vivo* (Liu et al., 2011a). The existing therapeutic methods for fibrosarcoma have not been very successful (Vello et al., 2011; Grivas et al., 2010; Okuno et al., 2011). To the best of our knowledge, no well-documented study about spearmint aqueous extract effect on MMPs in fibrosarcoma cells has been declared. In the present study, the effect of aqueous extract of spearmint on MMPs activities in Wehi-164 fibrosarcoma cells has been evaluated *in vitro*.

MATERIALS AND METHODS

Reagents

RPMI-1640 medium, penicillin, streptomycin, trypan blue (TB) and phorbol myristate acetate (PMA) were from sigma (USA). Fetal calf serum (FCS) was from Gibco (USA). 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) was obtained from Merck (Germany). *M. spicata* leaves were purchased from Pakan Bazr company from Esfahan province of Iran (the specious was identified and authenticated by Dr. Shams). Microtiter plates, flasks and tubes were from Nunc (Falcon, USA).

Extract preparation

150 g of *M. spicata* dried leaves were boiled in 3 L distilled water for 2 h. Then solution was filtered and dried. The extract was dissolved in Roswell Park Memorial Institute (RPMI-1640) medium and filtered by 0.2 µm filter and stored at -20°C until use in experiments. The extract was diluted in culture medium to prepare the required concentrations before use.

Cell line

Mouse fibrosarcoma cells [Wehi-164 (NCBI C200)] was obtained from NCBI (National Cell Bank of Iran, Pasteur Inst. of Iran, Tehran). The cells were maintained in RPMI-1640 medium supplemented with 10% FCS at 37°C in 5% CO_2.

Cell culture and treatment

The Wehi-164 cells were cultured in RPMI-1640 medium supplemented with 10% FCS, penicillin (100 IU/ml) and streptomycin (100 µg/ml) at 37°C in 5% CO_2. The cells were seeded at a density of 4×10^5 cells/ml and then incubated with different concentrations of *M. spicata* (0.1 to 10 mg/ml) in the presence or absence of PMA (25 ng/ml) for 24, 48 and 72 h. The supernatants of cell cultures were collected, centrifuged and stored at -20°C for next experiments. All experiments were done in triplicate.

Determination of MMP-2/MMP-9 activity by gelatin zymography

MMP-2/ MMP-9 activity in cell-conditioned media was evaluated by gelatin zymography technique according to the modified Kleiner and Stetler-Stevenson method (Kleiner and Stetler-Stevenson, 1994). Briefly, cell culture supernatants were subjected to sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) on 10% polyacrylamide gel copolymerized with 2 mg/ml gelatin in the presence of 0.1% SDS under non-reducing conditions at a constant voltage of 80 V for 3 h. After electrophoresis, gels were washed in 2.5% Triton X-100 for 1 h to remove SDS and then incubated in a buffer containing 0.1 M Tris-Hcl, PH 7.4 and 10 mM $CaCl_2$ overnight at 37°C. Afterwards, the gels were stained with 0.5% Coomassie brilliant blue and then destained. Proteolytic activities of enzymes were detected as clear bands of gelatin lysis against a blue background. The relative intensity of lysed bands to control were measured by using UVI Pro gel documentation system and expressed as relative gelatinolytic activity.

Statistical analysis

Effect of the *M. spicata* extract on MMPs activities in Wehi-164 cells was performed in three independent experiments and the results were expressed as mean ± SEM. Statistical comparisons between groups were made by analysis of variance (ANOVA). $P < 0.05$ was considered significant. Test of multiple comparison of Tukey was applied (5%) for statistically significant differences. The software SPSS 11.5 and Excel 2003 were used for statistical analysis and graph making, respectively.

RESULTS

Effect of spearmint extract on MMP-2 activity in Wehi-164 cells

Wehi-164 cells cultured alone (with no inducer), showed clear bands related to MMP-2 activity. Effect of different concentrations of spearmint aqueous extract on MMP-2 activity in Wehi-164 fibrosarcoma cells at three time intervals are shown in Figures 1A and B. Spearmint aqueous extract significantly decreased MMP-2 activity in Wehi-164 fibrosarcoma cells dose- dependently compared to untreated control cells as shown in Figures 1A and B. The decrease of MMP-2 activity was shown at ≥ 0.5 mg/ml concentration of the extract after 24 h incubation time and there was no significant difference in MMP-2 activity between different time intervals (Figure 1B) ($P < 0.05$).

Effect of spearmint extract on MMP-9 activity in Wehi-164 cells

MMP-9 activity in un-stimulated Wehi-164 cells used in

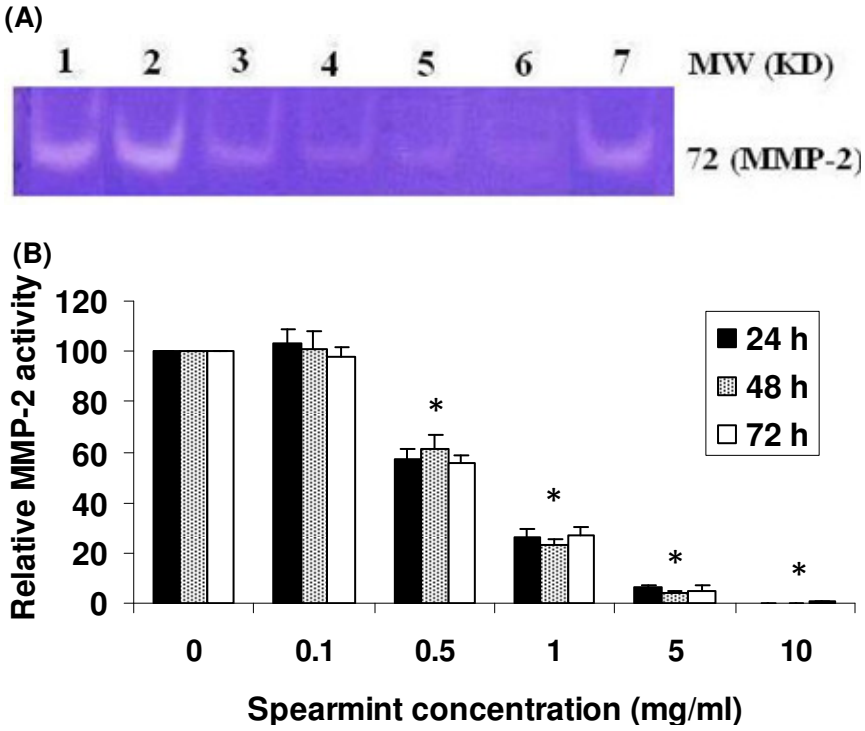

Figure 1. The Wehi-164 cells (4×10^5 cells/ml), were treated with different concentrations of spearmint hydro extract (0.1 to 10 mg/ml) for 24, 48 and 72 h. At the end of treatment, MMP-2 activity in conditioned medium was measured by gelatin zymography. (A), Zymogram of MMP-2 activity in Wehi-164 cells treated with spearmint hydro extract. Lane 1 represents untreated Wehi-164 cells. Lanes 2 to 6 represent spearmint hydro extract at 0.1, 0.5, 1, 5 and 10 mg/ml concentrations, respectively. Lane 7 represents control. (B)MMP-2 activity in Wehi-164 cells was measured by scanning the zymograms and densitometric analysis of MMP-2 bands. Data are mean ± SEM of three independent experiments. *$P < 0.05$ was considered significant.

this study was not detectable after 24 and 48 h incubation time. Nonetheless, faint bands related to MMP-9 activity were detected in un-stimulated Wehi-164 cells after 72 h incubation time (data not shown). PMA induced MMP-9 activity in Wehi-164 cells after 24 h incubation time compared with untreated control cells. Effect of different concentrations of spearmint aqueous extract on MMP-9 activity in Wehi-164 fibrosarcoma cells at three time intervals are shown in Figures 2A and B. Spearmint aqueous extract significantly decreased MMP-9 activity in Wehi-164 fibrosarcoma cells dose-dependently compared with untreated control cells as shown in Figures 2A and B. The decrease of MMP-9 activity was shown at ≥ 0.5 mg/ml concentration of the extract after 24 h incubation time and there was no significant difference in MMP-9 activity between different time intervals (Figure 1B) ($P < 0.05$).

DISCUSSION

Cancer is one of the major health problems in the world (Seffrin, 2011). Some of the present chemotherapeutic agents have not been promising and their side effects limit their uses. Medicinal plants are widely used for the treatment of various diseases (Lu et al., 2011; Kuete and Efferth, 2011; Engel et al., 2011). Natural compounds seem to be good choices for cancer therapy (Yamazaki and Tokiwa, 2010; Hamsa and Kuttan, 2010; Shia et al., 2011; Yang et al., 2007). Fibrosarcoma is one of the cancers which its current therapeutic strategies have not been very successful (Vello et al., 2011; Grivas et al., 2010; Okuno et al., 2011). By the way, fibrosarcoma cells produce high rates of MMPs (Park et al., 2011a). MMPs play an important role in tumor progression and metastasis (Watanabe, 2010; Bulbule et al., 2011). According to the results of present study, the aqueous extract of spearmint had inhibitory effect on MMP-2/MMP-9 activity in Wehi-164 fibrosarcoma cells. This inhibitory effect on MMP-2/MMP-9 activity was seen at ≥ 0.5 mg/ml concentration of the extract after 24 h incubation time onwards and there was no significant difference in MMP-2 activity between different time intervals. Consistent to our results, the decrease of MMP-

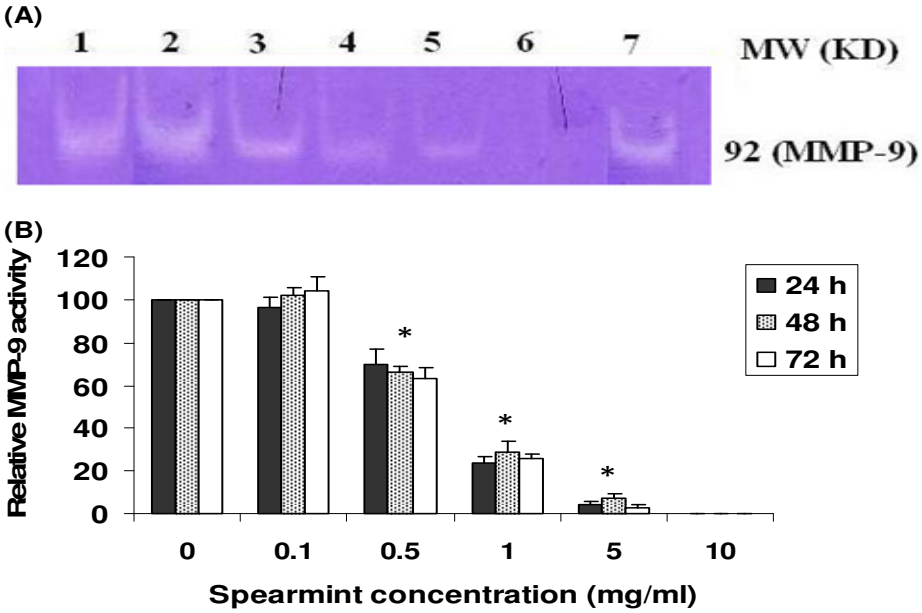

Figure 2. The Wehi-164 cells (4 ×10 ^{5} cells/ml), were stimulated with PMA (25 ng/ml) and then treated with different concentrations of spearmint hydro extract (0.1 to 10 mg/ml) for 24, 48 and 72 h. At the end of treatment, MMP-9 activity in conditioned medium was measured by gelatin zymography. (A), Zymogram of MMP-9 activity in Wehi-164 cells treated with spearmint hydro extract. Lane 1 represents PMA-stimulated Wehi-164 cells. Lanes 2 to 6 represent PMA-stimulated Wehi-164 cells with spearmint hydro extract at 0.1, 0.5, 1, 5 and 10 mg/ml concentrations respectively. Lane 7 represents control. (B), MMP-9 activity in Wehi-164 cells was measured by scanning the zymograms and densitometric analysis of MMP-9 bands. Data are mean ± SEM of three independent experiments.
*P < 0.05 was considered significant.

9 expression in lung tissues of rat by spearmint oil has been demonstrated *in vivo* (Liu et al., 2011b).

The inhibitory effects of several medicinal plant or their derivatives on MMP-2/MMP-9 expression/activity in various tumor cell lines such as human acute monocytic leukemia cell line (THP-1) cells has been reported (Ou et al., 2009; Park et al., 2011b).

We have previously shown the cytotoxic effect of spearmint aqueous extract on WEHI-164 cells at ≥ 2.5 mg/ml concentration of the extract (Hajighasemi et al., 2011).

In the present study, the inhibitory effect of spearmint extract on MMP-2/MMP-9 activity was shown at ≥ 0.5 mg/ml concentration of the extract. Thus, it seems that the inhibitory effect of the spearmint extract on MMP-2/MMP-9 activity at its non-toxic concentrations (0.5 and 1 mg/ml concentration) is not due to its cytotoxicity and may be due to other mechanism(s).

The anti-inflammatory effects of spearmint oil on lung tissue injury in rats with COPD (Zhao et al., 2008) and protective effect of a biological extract of spearmint on LPS-induced cartilage explants inflammation (Pearson et al., 2010) has been reported. Moreover, anti-tumor, antioxidant, anti-inflammatory and immunosuppressive effects of rosmarinic acid (a polyphenoli carboxylic acid exist in spearmint has been shown (Furtado et al., 2008; Agata et al., 2010; Da Silva et al., 2008; Yun et al., 2003). MMPs have important role in inflammation, tumor invasion and metastasis (Gialeli et al., 2011; Watanabe, 2010; Bulbule et al., 2011). Spearmint oil diminished the expression of MMP-9 in lung tissues of rat *in vivo* (Liu et al., 2011a). Therefore, anti-tumor and anti-inflammatory effects of spearmint may be in part due (as a result of) to its inhibitory effects on MMP-2/MMP-9 activity. Anti-cancer and anti-inflammatory effects of other mint specious including peppermint (Shkurupiĭ et al., 2006; Atta and Alkofahi, 1998) and *Mentha pulegium* (Shirazi et al., 2004) has been revealed. Moreover, anti-inflammatory effects of L-mentol (an organic compound obtained from peppermint or other mint oils) on LPS-stimulated monocytes through suppression of IL-1 beta, PEG and LT-B4 has been detected (Juergens et al., 1998). Fibrosarcoma has been recognized as a highly metastatic cancer (Dong et al., 2011). Anti-metastatic effect of a MMP inhibitor in fibrosarcoma cells has been reported (Lee and Kim, 2011). Also, therapeutic potential of an anti-cancer agent in fibrosarcoma metastasis has been suggested to be mediated through down-regulation

of MMP-9 expression (Hwang et al., 2011a, b). Furthermore, the anti-invasive effect of some MMP-suppressors in fibrosarcoma cells has been shown (Yang et al., 2001; Ngeow et al., 2011; Yamazaki and Tokiwa, 2010).

Therefore, modulations of MMPs production/activity may be useful for fibrosarcoma treatment. Also, targeting of these enzymes may have clinical value for management of fibrosarcoma and its pathogenesis. Recently, development of anti-MMPs agents for tumor therapy has been concerned by many investigators (Lee and Kim, 2011; Ngeow et al., 2011). In this regard, medicinal plants have been in special attention (Yamazaki and Tokiwa, 2010; Hamsa et al., 2010). The beneficial effect of some herbal drugs with ant-MMP activities has been reported (Yang et al., 2007; Shia et al., 2011). Spearmint preparations with anti-MMPs activities could have potential implications in design of novel therapeutic strategies for fibrosarcoma.

To best of our knowledge, this is the first report on inhibitory effect of hydro extract from spearmint on MMPs activities in fibrosarcoma. Spearmint could have potential implication in treatment of cancers as well as inflammatory- associated diseases and may be a good candidate for developing of natural-derived therapeutics in related disorders.

Further studies are required to determine the molecular mechanisms of spearmint anti-MMPs activities as well as isolation and characterization of its effective components with inhibitory effect on MMP activity. Also, *in vivo* studies are required to validate the *in vitro* experiments and arrangement the intellectual therapeutic approaches.

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