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Review

Methyl jasmonate: A plant stress hormone as an anti-cancer drug

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ABSTRACT

Jasmonates act as signal transduction intermediates when plants are subjected to environmental stresses such as UV radiation, osmotic shock and heat. In the past few years several groups have reported that jasmonates exhibit anti-cancer activity *in vitro* and *in vivo* and induce growth inhibition in cancer cells, while leaving the non-transformed cells intact. Recently, jasmonates were also discovered to have cytotoxic effects towards metastatic melanoma both *in vitro* and *in vivo*.

Three mechanisms of action have been proposed to explain this anti-cancer activity. The bio-energetic mechanism – jasmonates induce severe ATP depletion in cancer cells via mitochondrial perturbation. Furthermore, methyl jasmonate (MJ) has the ability to detach hexokinase from the mitochondria. Second, jasmonates induce re-differentiation in human myeloid leukemia cells via mitogen-activated protein kinase (MAPK) activity and were found to act similar to the cytokinin isopentenyladenine (IPA). Third, jasmonates induce apoptosis in lung carcinoma cells via the generation of hydrogen peroxide, and pro-apoptotic proteins of the Bcl-2 family.

Combination of MJ with the glycolysis inhibitor 2-deoxy-D-glucose (2DG) and with four conventional chemotherapeutic drugs resulted in super-additive cytotoxic effects on several types of cancer cells. Finally, jasmonates have the ability to induce death in spite of drug-resistance conferred by either p53 mutation or P-glycoprotein (P-gp) over-expression.

In summary, the jasmonates are anti-cancer agents that exhibit selective cytotoxicity towards cancer cells, and thus present hope for the development of cancer therapeutics.

Contents

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1. Introduction

The jasmonate family which consist of *cis*-jasmone (CJ), jasmonic acid (JA), and methyl jasmonate (MJ) (Sembdner, 1993), are fatty acid-derived cyclo pentanones that occur ubiquitously in the plant kingdom (Fig. 1).

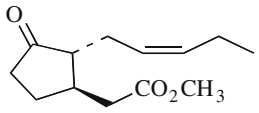
They were first isolated from the jasmine plant, and are a class of plant stress hormones similar to the salicylates.

The biosynthetic pathway of jasmonates was elucidated in the 1980's and those experiments showed that exogenous jasmonates exert effects on a wide spectrum of physiological processes. Today, jasmonates are recognized to be among the most potent and important signals for the regulation of defense-related genes in different species of the plant kingdom. It was discovered that constitutive activation of jasmonate signaling results in enhanced resistance to herbivores. In addition to anti-herbivore activity, genetic studies in *Arabidopsis* have shown that jasmonate signaling promotes direct defense responses to fungal pathogens (Davis, 2004; Samaila et al., 2004). Additionally, the jasmonate family acts as signal transduction intermediate when plants are subjected to environmental stresses such as UV radiation, osmotic shock, cytotoxic drugs and heat (Wang et al., 2007). The role of JA is the intracellular signaling response to injury, while MJ causes induction of proteinase inhibitor, which accumulates in response to wounding or to pathogenic attacks (Farmer and Ryan, 1990). The jasmonates have been reported to be involved in plant programmed cell death in a mechanism which resembles mammalian apoptosis (Wang et al., 2007). In addition to their role in plants, jasmonates were also found to have effects on cultured animal cells. These effects are anti-cancer activities which were exhibited both *in vitro* and *in vivo* (Flescher, 2007). Jasmonates and some of their synthetic derivatives, were shown to inhibit the proliferation and to induce cell death in various human and murine cancer cell lines, including breast, prostate, melanoma, lymphoblastic leukemia and lymphoma cells (Fingrut and Flescher, 2002), and exhibited selective cytotoxicity towards cancer cells even when they were a part of a mixed population of leukemic and normal cells drawn from the blood of chronic lymphocytic leukemia (CLL) patients (Fingrut and Flescher, 2002; Flescher, 2005). Furthermore, survival studies showed that jasmonates increased the life span of T-cell lymphoma-bearing mice (Fingrut and Flescher, 2002).

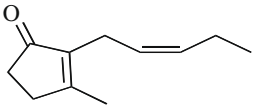
There are about one thousand species of plants that possess significant anti-cancer action. This action could be preventive and/or therapeutic. The first and most famous plant stress hormone that has been studied for many years is salicylate. Salicylic acid and its synthetic derivative – acetyl salicylic acid, i.e., aspirin, exhibit anti-cancer activity. Salicylate suppressed the proliferation of various types of cancer cells, including lymphoblastic leukemia, prostate, breast and melanoma human cancer cells (Fingrut and Flescher, 2002; Sotiriou et al., 1999), and also induced apoptosis in human myeloid leukemia cell lines (Klampfer et al., 1999), colorectal cancer cells (Elder et al., 1996; Lee et al., 2003), gastric cancer cells (Chung et al., 2003) and human glioblastoma cells (Amin et al., 2003). Aspirin, the synthetic salicylate, suppressed the proliferation of metastatic murine and human melanoma cells, human prostate cancer cell lines, and colon cancer cells (Fingrut and Flescher, 2002; Sotiriou et al., 1999).

Salicylates and jasmonates are both well known important plant signals, which share function but not structure (Fingrut and Flescher, 2002; Ryals et al., 1996). They both can cause systemic acquired resistance (SAR) to pathogens and injury in plants (Ryals et al., 1996), and share similarities in their anti-cancer activity towards mammalian cancer cells.

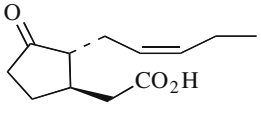
In the last 5 years we have published three reviews concerning the anti-cancer effects of MJ and its suggested mechanisms of action (Flescher, 2005, 2007; Goldin et al., 2007). This review will focus particularly on the cytotoxic effects of MJ as discovered recently, including their effect on metastatic melanoma and on the mitochondria deficient parasite – *Trichomonas vaginalis.*



Methyl jasmonate



***Cis* - jasmone**



Jasmonic acid

Fig. 1. Structures of naturally-occurring jasmonates.

2. The anti-cancer effects of MJ

We have previously reported that jasmonates can suppress the proliferation of various cancer cells and induce their death. Jasmonates were discovered for having the two desirable characteristics of anti-cancer drugs, which is to be highly selective towards cancer cells and ineffective towards normal cells, and to have the ability to act against drug resistant cells. In the case of the leukemic cell line (MOLT-4), MJ was proven to be significantly more cytotoxic towards this malignant cell line than towards normal lymphocytes (Fingrut and Flescher, 2002). The other characteristic was demonstrated using a pair of B-lymphoma clones of the same line differing in their p53 expression; wild type versus mutant p53. These clones differ drastically in their response to the cytotoxic drug Bleomycin and the radiomimetic neocarzinostatin (NCS), i.e., the mutant p53-expressing clone is by far less susceptible to these agents (Fingrut and Flescher, 2002; Flescher, 2007). In contrast, jasmonates were equally active against either clones. In the wild type cells, MJ induced mostly apoptotic death whereas in the mutant cells it induced necrotic death (Fingrut and Flescher, 2002; Flescher, 2007). This finding indicates that jasmonates can circumvent the resistance of mutant p53-expressing cells towards chemotherapy by inducing a non-apoptotic mode of cell death (Fingrut et al., 2005).