Mini review

Jasmonates in cancer therapy

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Abstract

Several groups have reported in recent years that members of the plant stress hormones family of jasmonates, and some of their synthetic derivatives, exhibit anti-cancer activity in vitro and in vivo. Jasmonates increased the life span of EL-4 lymphoma-bearing mice, and exhibited selective cytotoxicity towards cancer cells while sparing normal blood lymphocytes, even when the latter were part of a mixed population of leukemic and normal cells drawn from the blood of chronic lymphocytic leukemia (CLL) patients. Jasmonates join a growing number of old and new cancer chemotherapeutic compounds of plant origin. Three mechanisms of action have been proposed to explain the anti-cancer activity of jasmonates. These include: (1) The bio-energetic mechanism-jasmonates induce severe ATP depletion in cancer cells via mitochondrial perturbation; (2) The re-differentiation mechanism-jasmonates induce re-differentiation in human myeloid leukemia cells via mitogen-activated protein kinase (MAPK) activity; (3) The reactive oxygen species (ROS)-mediated mechanism-jasmonates induce apoptosis in lung carcinoma cells via the generation of hydrogen peroxide, and pro-apoptotic proteins of the Bcl-2 family. Several similarities between the effects of jasmonates on plant and cancer cells have been recorded, suggesting that additional analysis of jasmonate effects in plant cells may contribute to a deeper understanding of the anti-cancer actions of these compounds. Those similarities include: induction of cell death, suppression of proliferation and cell cycle arrest, MAPK induction, ROS generation, and enhancement of heat-shock proteins (HSP) expression. Finally, jasmonates can induce death in drug-resistant cells. The drug resistance was conferred by either p53 mutation or P-glycoprotein (P-gp) over-expression. In summary, the jasmonate family of novel anti-cancer agents presents new hope for the development of cancer therapeutics, which should attract further scientific and pharmaceutical interest.

Keywords: Jasmonate; Cancer; Therapy; Drug; Plant; Stress; Mitochondria; ATP; Differentiation; ROS; MAPK; HSP; Bcl-2; p53; P-gp; Drug resistance

1. Introduction

Several groups have reported in recent years that members of the plant stress hormones family of jasmonates (Fig. 1), and some of their synthetic derivatives, exhibit anti-cancer activity in vitro and in vivo. The initial report [1] indicated that jasmonates induce suppression of cellular proliferation and death in various human and mouse cancer cell lines, including breast, prostate, melanoma, lymphoblastic leukemia and lymphoma cells. Jasmonates were also found to suppress the proliferation or kill various other cancer cells including lung and myeloid leukemia cells [2–4]. Furthermore, jasmonates increased the life span of EL-4 lymphoma-bearing mice [1], and exhibited selective cytotoxicity towards cancer cells while sparing normal blood lymphocytes, even when the latter were part of a mixed population of leukemic and normal cells drawn from the blood of chronic lymphocytic leukemia (CLL) patients [1,5].
2. The jasmonate family of plant stress hormones [6]

Plant hormones (also referred to as phytohormones) are defined as a group of naturally occurring organic substances, which influence physiological processes at low concentrations. These processes are mainly growth, differentiation and development. Plant hormones are structurally and functionally diverse. They include: auxin (the main one being indoleacetic acid), gibberellins, cytokinins (adenine derivatives), ethylene, abscisic acid, polyamines (mainly putrescine, spermidine and spermine), brassinosteroids, salicylic acid, signal peptides and, finally, jasmonates—the focus of this review.

Jasmonic acid and its methyl ester, methyl jasmonate (MJ), are fatty acid-derived cyclopentanones occurring throughout the plant kingdom and playing major roles in defense against insects and disease. The widespread occurrence of jasmonates in plants and some lower eukaryotes and their capacity to regulate processes in insects, support the notion that jasmonates are of general biological importance. Structurally and biosynthetically, jasmonates belong to the family of oxygenated fatty acid derivatives, oxylipins, which are produced via the oxidative metabolism of polyunsaturated fatty acids. Jasmonate biosynthesis in plants is analogous to eicosanoid biosynthesis in animal cells. In animals, eicosanoids are synthesized from arachidonic acid (C₂₀:₄), while in plants linolenic acid (C₁₈:₃) is the major source of jasmonates. Leaf tissues exhibit a fast increase in jasmonate levels in response to various stimuli and stresses, e.g. wounding, herbivory and infection. Upon its biosynthesis, jasmonic acid can be metabolized in a number of pathways including: methylation yielding MJ, hydroxylation yielding tuberonic acid-related derivatives, conjugation of the carboxy terminus to amino acids or other adducts, reduction yielding cucurbitic acid-related derivatives, and degradation of C₁ to form jasmone. Some of these products can be further glucosylated. Most of the abovementioned metabolites occur naturally.

Jasmonates regulate plant gene expression including defense related genes. Direct defense is mediated by jasmonate-induced phytochemicals that interact directly with the plant invader (including herbivores, bacterial and fungal pathogens) to bring about its neutralization. Although a considerable body of knowledge has been accumulated regarding jasmonate-regulated gene expression and defense, relatively little is known about the signaling pathways mediating these actions of jasmonates. Interestingly, jasmonate perception in insects may allow the latter to defend themselves against jasmonate-induced toxicity, suggesting that jasmonate signaling pathways may be conserved between the plant and animal kingdoms. Notably, the primary cellular target of jasmonates in plants is yet to be identified.

3. Plant-derived compounds as anti-cancer agents

Jasmonates join a long list of plant derived compounds that exhibit anti-cancer activity, a number of which are in current clinical use. From a wider perspective, plant based compounds continue to play an essential role in the primary health care of 80% of the world’s population [7]. Out of about 250,000 species of plants, one thousand possess significant anti-cancer action. This action could be preventive and/or therapeutic. Indeed, these categories of activity may be intertwined as the ability to kill a transformed cell may be reflected both in the inhibition of the carcinogenic process as well as in the destruction of an existing neoplasm. Three major types of plant-derived chemopreventive agents include inhibitors of carcinogen formation, blockers of carcinogen interaction with its target sites, and suppressors of tumor progression [7].

In a recent review, Cragg and Newman [8] describe the various anti-cancer agents of plant origin. Currently, over 60% of the anti-cancer agents in use are derived from natural sources, i.e. plants, marine organisms and micro-organisms. Plant-derived anti-cancer agents in clinical use include vinca alkaloids, vinblastine and vincristine, isolated from Catharanthus roseus. Semi-synthetic analogs of these agents are vinorelbine and vindesine. These agents are used in
combination with other chemotherapeutics to treat leukemias, lymphomas, advanced testicular cancer, breast and lung cancer, and Kaposi’s sarcoma. Analogs of the natural epipodophyllotoxin, etoposide and teniposide, are used in the treatment of lymphoma, as well as bronchial and testicular cancers. A class of plant-derived agents of exceptional prominence are the taxanes. The natural paclitaxel (taxol) was isolated from the pacific yew bark and is used in the treatment of breast, ovarian and non-small cell lung cancer (NSCLC). Its analog docetaxel is primarily used in breast cancer and NSCLC. Campothecin, from Campotheca acuminata, induces severe bladder toxicity but its derivatives, topotecan and irinotecan, are used for the treatment of various solid tumors. In addition, homoharringtonine and elliptinium are used in leukemias and breast cancer, respectively.

A number of plant-derived agents are in clinical development [8]. Flavonoids are polyphenolic compounds that are constituents of flowering plants. They are found as integral components of the human diet. Their actions on tumor cells include inhibition of growth and kinase activity, induction of apoptosis, suppression of matrix metalloproteinases secretion and of invasiveness [9]. Flavopiridol, a synthetic flavone, is currently in 18 phase I and phase II clinical trials against leukemias, lymphomas and solid tumors [8]. Additional plant-derived agents under clinical development are the combretastatins (anti-angiogenic agents) and roscovinine, which is a synthetic derivative of a compound (olomucine) isolated from the radish Raphanus sativus [8]. Plant lectins are proteins and glycoproteins that occur in numerous foods, e.g. wheat, corn, beans, rice and potato. Several lectins exhibit anti-cancer activities [10].

The number of plant-derived anti-tumor agents in pre-clinical development is obviously quite big. Jasmonates are a family of such agents, and additional examples include bruceantin (isolated from Brueca antidysenterica), betulinic acid, indirubins and naphthaquinones (particularly β-lapachone) [8].

Another approach to the classification of plant-derived anti-cancer agents (besides the stage of their pharmaceutical development) is based on their mechanism of action. The ras G protein is a proto-oncogene activated often in human neoplasias. The incidence is especially high in bile duct, pancreas and colon carcinomas. The proliferation signaling mediated by activated ras positions it as a target for suppression of ras-expressing tumors. Two ras inhibitors, an anthraquinone called damnacanthal (from Morinda citrifolia) and III-121C (from Ervatamia microphylla), induced normal morphology in ras expressing cells, and the latter also inhibited the growth of these cells in mice [11]. Plant-derived chemicals are also capable of modulating cell cycle, thereby affecting proliferation and viability. Silymarin (a flavonoid from milk thistle) and EGCG (a polyphenol from tea) increase the expression of cyclin-dependent kinase inhibitors in human prostate carcinoma cells, resulting in G2 arrest [12]. Allyl sulfur compounds from garlic, isoflavones from soy food, and curcumin from turmeric, inhibit tumor cell proliferation by decreasing cdc2 kinase activity, thereby inducing a G2-M arrest [12]. A recent review describes plant-derived tyrosine kinase inhibitors as potential anti-cancer agents. Given the major role these enzymes play in the regulation of cell growth, differentiation and death, their aberrant activity can lead to cancer, and could theoretically be the result of over-expression, over-activation or under-utilization of the relevant signaling pathways. For instance, over-expression can result in continuous stimulation of growth factor-receptor systems. Thus, inhibition of tyrosine kinase by plant-derived compounds is clearly a valid approach towards cancer therapy [13].

Finally, and most pertinent to this review, many of the plant hormones mentioned in the former section have been evaluated as anti-cancer agents, and some have indeed been found to possess such abilities. Undoubtedly, salicylic acid and its synthetic acetylated derivative, aspirin, are the most extensively studied from among the plant hormones as potential anti-cancer therapeutics and chemopreventive agents (e.g. [1,14,15]). Another family of plant hormones that has recently attracted interest as potential anti-cancer compounds is the cytokinins and their derivatives. The impetus for studying these plant hormones is their known activity against cancer-like plant cells termed callus. Cytokinins and cytokinin ribosides induce granulocytic differentiation in human myeloid leukemia cells, and cytokinin ribosides can also induce apoptosis in these cells [16]. Analogs of olomoucine, a cytokinin analog with cyclin-dependent kinase (CDK) inhibitory activity, inhibited CDK1, CDK2 and cell proliferation in human leukemia cell lines, stronger than olomoucine [17]. Notably, some of the analogs inhibited weakly also normal myeloid growth, and most compounds inhibited the growth of peripheral blood mononuclear cells as well. There was a correlation between CDK inhibition and suppression of proliferation, and some analogs induced apoptosis as well [17]. Derivatives of the aromatic cytokinin 6-benzylaminopurine exhibited suppression of cancer cell proliferation, in correlation with their ability to inhibit CDK in
those cells [18]. Plant jasmonates are a recently explored family of stress hormones with anti-cancer activity. Their mechanisms of action are described in Section 4.

4. Jasmonate anti-cancer mechanisms of action

To date, three mechanisms have been proposed to explain the suppression of cancer cell growth by jasmonates. These mechanisms are not mutually exclusive and may, therefore, either occur concomitantly, affect different types of cancer cells, or be active in different time frames and concentration ranges.

4.1. The bio-energetic mechanism

Mitochondria are widely recognized as pivotal to life and death decisions in cells. Indeed, both apoptotic and necrotic death may result from mitochondrial perturbation. However, a novel concept has emerged in recent years that may pave the road for a new class of anti-cancer drugs [19]. According to this concept, agents that can directly interfere with the normal function of mitochondria, would have the distinct advantage of by-passing pre-mitochondrial mutations. Such mutations would otherwise render the transformed cell resistant to chemotherapeutic drugs, which signal death up-stream of the mitochondria, e.g. via death receptors and DNA damage. The direct effect of jasmonates on mitochondria isolated from cancer cells was, therefore, evaluated [20]. First, jasmonates were shown to perturb mitochondria (as assayed by mitochondrial membrane depolarization and cytochrome c translocation from mitochondria to the cytosol) in intact human leukemia and hepatoma cells. Then, the effect of MJ on mitochondria isolated from cancer cells was, therefore, evaluated [20]. First, jasmonates were shown to perturb mitochondria (as assayed by mitochondrial membrane depolarization and cytochrome c release from mitochondria and mitochondrial swelling reflecting mitochondrial membrane permeability transition. While mitochondria from both types of cancer cell lines were perturbed by MJ, non-transformed 3T3 fibroblasts were not affected, demonstrating that jasmonates affect selectively transformed cells. Mitochondrial membrane permeability transition involves opening of a channel named permeability transition pore complex (PTPC) [21,22]. Cyclophilin D and adenine nucleotide translocator are components of the pore. Ligands of these proteins, that induce the closure of PTPC, prevented MJ-induced mitochondrial perturbation. These results suggest that MJ acts on cancer cells via abnormal opening of the PTPC [20]. In order to support the clinical relevance of the abovementioned findings, similar experiments were performed on ex vivo leukemic cells isolated from the blood of CLL patients. Similar to the effects on cancer cell lines, jasmonates induced perturbation of mitochondria in intact CLL leukemic cells, as well as of mitochondria isolated from these cells. On the other hand, mitochondria isolated from quiescent and mitogenically stimulated normal human peripheral blood lymphocytes were not affected by MJ, exhibiting again the selective action of jasmonates on cancer cells [20]. These results suggest that mitochondria of cancer cells have certain characteristics that render them specifically sensitive to the cytotoxic effects of jasmonates. Indeed, mitochondria from normal and cancer cells differ in composition and function: cancer cells are characterized by higher mitochondrial membrane potential, possible modulation of the expression of PTPC components, and enhanced rates of ATP generation through glycolysis rather than through oxidative phosphorylation (a phenomenon known as the Warburg effect) [21–25]. Moreover, tumors originating from colon, kidney, breast, stomach, esophagus and lung have significantly reduced expression of the β-catalytic subunit of the mitochondrial H⁺-ATP synthase [26,27]. We hypothesize that the defective ability of cancer cell mitochondria to generate ATP may turn these organelles into the Achilles heel of these cells. Rapid depletion of ATP from cancer cells may leave the cells in net negative ATP balance because glycolysis cannot yield a sufficient number of ATP molecules to overcome the jasmonate-mediated ATP depletion. In agreement with this hypothesis, MJ induced a rapid depletion of ATP in B lymphoma cells [28]. Furthermore, oligomycin (a mitochondrial ATP synthase inhibitor) did not increase ATP depletion induced by MJ, whereas inhibition of glycolysis by 2-deoxyglucose did. High glucose levels protected the B lymphoma cells from MJ-induced ATP depletion and reduced MJ-induced cytotoxicity, while high levels of the mitochondrial substrate pyruvate did not [28]. Thus, these results suggest that high rates of glycolysis can protect cells against jasmonate-induced cancer cell ATP depletion and death.

4.2. The re-differentiation mechanism

The concept of inducing re-differentiation as a strategy to ‘normalize’ undifferentiated cancer cells has attracted cancer scientists for many years. Essentially, re-differentiation is a process in which the genetic program of cancer cells is modified to bring about a more differentiated genotype and phenotype.
This modified state proliferates at a slower rate and loses its earlier neoplastic attributes. Indeed, various compounds have been suggested to act via this mechanism, retinoids being a prime example. Retinoids are a family of natural and synthetic ligands of nuclear receptors [29]. All-trans retinoic acid induces differentiation of acute promyelocytic leukemia cells (APL, [30]) and the FDA approved its use for differentiation therapy of patients with APL [29]. Papillary and follicular thyroid carcinomas are considered well-differentiated and have a good prognosis. However, 30% of the tumors de-differentiate and become highly malignant. Treatment with 13-cis retinoic acid succeeded in such tumors and this was interpreted as reflecting re-differentiation of thyroid cancer [29,31]. Moreover, the cytokinin family of plant hormones was found to induce re-differentiation in leukemic cells (Section 3). Thus, studies were undertaken to probe the possibility that jasmonates are capable of inducing cancer cell re-differentiation. The concentrations and duration of incubations were such that no cell death was induced.

Various human malignant cell lines were exposed to MJ and suppression of proliferation was determined. Leukemic cells were more sensitive than solid tumor cells, and among the leukemic cells, the human myeloid leukemia HL-60 cells were the most sensitive [2]. Several markers of differentiation were induced by MJ in HL-60 cells. These included: NBT reduction, a typical marker of myelomonocytic differentiation (which was also induced by MJ in other myelomonocytic leukemia cells, e.g. U937 and THP-1); Morphologic differentiation into granulocytes with some properties of monocytes such as monocyte granules; expression of both monocyte-specific surface antigen CD14 and granulocyte-specific antigen CD15; Finally, MJ induced α-naphthyl acetate esterase activity, a marker of monocytic differentiation [2]. Known inducers of granulocytic and monocyte differentiation, all-trans retinoic acid and 1α,25-dihydroxyvitamin D3, respectively, synergized with MJ in the induction of HL-60 differentiation [2]. Furthermore, the authors evaluated the role of several signaling pathways in the MJ-induced re-differentiation of HL-60 cells. Based upon direct measurements of cAMP cellular levels and the use of a cAMP analog, it does not appear that cAMP mediates MJ-induced differentiation. Similarly, phosphoinositide 3-kinase, PKC, PKA and G-protein do not appear to play a role in the induction of differentiation by MJ in leukemia cells. On the other hand, MJ induces mitogen activated protein kinase (MAPK) activity in HL-60 cells, and PD98059 (a MAPK inhibitor) suppressed differentiation (NBT reduction) induced by MJ. Thus, MAPK signaling is probably instrumental in the re-differentiation induced by MJ [2]. In a recent publication, MJ (and cytokinins) were reported to induce the transcription factor CCAAT/enhancer-binding protein (C/EBP)δ in HL-60 cells, which might contribute to MJ’s ability to induce granulocytic differentiation in human myeloid leukemia cells [32]. Finally, the mRNA for the calcium-binding protein S100P is immediately up-regulated upon induction of re-differentiation by cytokinin in HL-60 cells and plays an important role in this process [33]. MJ also induces S100P up-regulation, in correlation with its growth-inhibitory activity [33]. These studies suggest that cytokinins and jasmonates, two groups of plant hormones, may share similar mechanisms through which they induce human leukemia cells re-differentiation.

4.3. The reactive oxygen species (ROS)-mediated mechanism

The cytotoxic nature of various oxygen-containing molecules, e.g. superoxide ion, hydrogen peroxide, hydroxyl radical and singlet oxygen, has been the subject of numerous studies. It is, therefore, no wonder that the potential involvement of ROS in MJ-induced apoptosis was evaluated. Analysis of MJ-induced death in A549 human lung adenocarcinoma cells revealed that MJ-induced apoptosis (determined by DNA condensation/fragmentation and caspase 3 activation) can be suppressed by certain anti-oxidants, including N-acetyl cysteine and catalase (specific for hydrogen peroxide), but not by inhibitors of hydroxyl radicals and superoxide ions [3]. MJ induced an increase in the pro-apoptotic members of the Bcl-2 family, Bax and Bcl-Xs, while leaving the levels of anti-apoptotic proteins, Bcl-2 and Bcl-XL, unchanged [3]. Catalase prevented the MJ-induced modification in the levels of Bcl-2 family members. Thus, induction of apoptosis in A549 cells by MJ appears to be mediated by a cascade involving hydrogen peroxide generation, and an increase in the expression of pro-apoptotic members of the Bcl-2 family of proteins [3]. In a recent article, MJ was shown to induce heat shock protein 72 (HSP72) in C6 glioma cells via heat shock factor I [34]. Cellular hydrogen peroxide and superoxide ions, as well as mitochondrial ROS, increased upon treatment of these cells with MJ. The MJ-induced expression of HSP72 and heat shock factor I were prevented by specific inhibition of hydrogen peroxide and hydroxyl radicals [34]. It thus appears that different activities of MJ in
cancer cells may be mediated via distinct ROS, possibly dependent upon the type of cell under study.

In conclusion, these proposed mechanisms suggest that induction of apoptosis on the one hand, and re-differentiation on the other, are two possible outcomes of interactions between jasmonates and cancer cells (Fig. 2). As to whether the mechanisms described above are significant for the anti-cancer effects of jasmonates, the fact that re-differentiation is associated with suppression of proliferation points towards this mechanism as instrumental in the anti-cancer action of jasmonates. The two mechanisms leading to cell death have been demonstrated as relevant to the anti-cancer action since inhibitors of the bio-energetic collapse and of ROS have suppressed the anti-cancer effects of jasmonates [3,20,28].

5. Similarities between jasmonate actions in plants and animal cells

While the anti-cancer effects of jasmonates may differ totally from their actions in plants in terms of mechanism, it is tempting to assess the possibility that the mediation of jasmonate action in plant and animal cells may share certain similarities. Beyond the value of such an endeavor at the level of fundamental biology, identification of such similarities could open potential avenues towards the synthesis of jasmonate-based new chemical entities with superior chemotherapeutic efficacy.

The first report on jasmonate-induced anti-cancer activities [1] exhibited their capacity to cause both cell death and suppression of cell proliferation. Accordingly, jasmonic acid-induced signaling mediates programmed cell death in Arabidopsis protoplasts [35]. Inhibition of cell proliferation and perturbation of cancer cell cycle (including cell cycle arrest at different phases) have been observed by several groups [1–4]. In analogy, elicitation of *Taxus cuspidate* suspension cultures with MJ decreased significantly cell cycle progression, resulting in more than 70% of the cells being arrested at the *G0/G1* phase of the cell cycle [36]. Also, jasmonic acid induced *G2* arrest in tobacco cells and prevented the accumulation of *B*-type CDK and the expression of cyclin *B1*; 1, which are both essential for the initiation of mitosis. These results suggest that jasmonic acid affects an early *G2* checkpoint [37].

Activation of various MAPK in cancer cells by jasmonates has been reported. The first study focused on stress-regulated MAPK (c-Jun N-terminal kinase (JNK) and p38), given the role jasmonates play in plant stress [38]. MJ induced activation of both stress-regulated MAPK in Molt-4 leukemia cells but these signaling events did not appear to mediate the cytotoxic effects of MJ [38]. In accordance, MJ induced the activation of these MAPK in A549 lung carcinoma as well, and again, these activities did not mediate the apoptotic effect of MJ [3]. Whereas activation of the MAPK of the ERK1/2 group by MJ mediates its re-differentiation action [2], it did not affect its apoptotic action [3]. Before discussing the MAPK activities associated with MJ effects on plant cells, it should be clarified that we will focus on MJ-induced MAPK activities and not on MAPK acting upstream of jasmonate biosynthesis. Several MAPK and their upstream kinases, involved in stress response and disease resistance, have been described in rice cells upon jasmonate treatment. These include OsMSRMK2 [39], OsBIMK1 [40], OsMSRMK3 [41], and the MAPK kinase kinase OsEDR1 [42]. Thus, jasmonate plant stress hormones are capable of inducing analogous stress signaling pathways in evolutionarily remote...
cells, suggesting that stress-regulated MAPK signaling has been conserved over extremely long evolutionary distances. This reflects probably the fundamental role that stress responses play in the ability of organisms to survive environmental challenges.

The role of ROS in jasmonate anti-cancer activity has been discussed (Section 4.3). Several studies reported the role of ROS in jasmonate effects on plants. It should be noted that ROS can induce stress that results in jasmonate biosynthesis in plants, but this aspect is beyond the scope of this review. MJ induced hydrogen peroxide production in plant cells in a manner dependent on NAD(P)H oxidase [43], suggesting the involvement of superoxide ions and their dismutation. Furthermore, jasmonic acid promoted singlet oxygen-dependent cell death in Arabidopsis thaliana [44].

An additional mechanism through which MJ may generate oxidative stress in plant cells was suggested by a study showing that MJ suppressed the expression of the antioxidant enzyme cytosolic ascorbate peroxidase [45]. Exposure to MJ induced HSP72 in glioma cells, but not HSP73 and HSP90. The expression of HSP72 was mediated via heat shock factor 1. Both phenomena as well as HSP70 promoter-driven CAT activity were inhibited by anti-oxidants including N-acetyl cysteine, catalase and sodium formate [34]. As for induction of HSP expression in plants, MJ induced the expression of low molecular weight HSP’s in seeds of Douglas fir [46]. Also, MJ induced the synthesis of low molecular weight HSP’s in Nicotiana attenuata leaves, as well as the abundance of HSP70 [47]. It thus appears that MJ induces HSP in both plants and cancer cells.

As can be seen in Fig. 3 and Table 1, jasmonates can induce similar metabolic, signaling and stress-associated modifications (that could lead to decreased growth and viability) in plant cells as well as in cancerous animal cells. This analysis suggests that as information regarding the actions of jasmonates in plant cells accumulates, it could provide insights for the rational design of novel anti-cancer agents.

6. Jasmonate activity against drug resistant cells

The influence of drug resistance on the success rates of cancer chemotherapy needs no elaboration. Accordingly, jasmonates have been tested as to their ability to kill drug-resistant cancer cells, the resistance being induced by two mechanisms: p53 mutation and multidrug resistance mediated by the P-glycoprotein (P-gp)

![Diagram A](image1)

![Diagram B](image2)

Fig. 3. Comparison between the effects of jasmonates on plant and on cancer cells. A. Effects common to both types of cells. B. Effects unique to cancer cells. Please note that effects on cancer cells that are not conceivable for plant cells, e.g. induction of markers of immune cells, are not included.

| Table 1 | Cellular effects common to jasmonate-treated plant and cancer cells |
|------------------|------------------|------------------|
| **Cellular parameter** | **Plant cells** | **Cancer cells** |
| Cell death | [35] | [1,3,4,20,28,38] |
| Suppression of proliferation and cell cycle arrest | [36,37] | [1–4] |
| MAPK induction | [39–42] | [2,3,38] |
| ROS generation | [43–45] | [3,34] |
| HSP expression | [46,47] | [34] |

The table indicates the relevant references.
Jasmonates comprise a new family of anti-cancer agents, natural and semi-synthetic, with proven efficacy against a number of neoplastic growths. These compounds exhibit selective cytotoxicity towards transformed cells. Jasmonates are plant stress hormones and are part of a growing number of old and new cancer chemotherapeutic compounds of plant origin. Three mechanisms of action have been proposed by different research groups to explain the anti-cancer activity of jasmonates. These include: (1) The bio-energetic mechanism-jasmonates induce severe ATP depletion in cancer cells via mitochondrial perturbation; (2). The re-differentiation mechanism-jasmonates induce re-differentiation in human myeloid leukemia cells via MAPK activity; (3) The ROS-mediated mechanism-jasmonates induce apoptosis in lung carcinoma cells via the generation of hydrogen peroxide, and pro-apoptotic proteins of the Bcl-2 family. Several similarities between the effects of jasmonates on plant and cancer cells have been recorded, suggesting that additional analysis of jasmonate effects in plant cells may contribute to deeper understanding of the anti-cancer actions of these compounds. Those similarities include: induction of cell death, suppression of proliferation and cell cycle arrest, MAPK induction, ROS generation, and enhancement of HSP expression. Finally, jasmonates are equally cytotoxic towards drug-sensitive and drug-resistant cells. The drug resistance was conferred by either p53 mutation or P-gp over-expression. In summary, the jasmonate family of novel anti-cancer agents presents new hope for the development of cancer therapeutics, which should attract further scientific and pharmaceutical interest.

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References


