



**METHYL JASMONATE: NEW INSIGHTS INTO A POTENT PHYTOHORMONE**

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**ABSTRACT**

Current review is being prepared considering latest significant potential of plant stress hormone Methyl Jasmonate for its anticancer, anti-inflammatory and nociceptive actions. Plant stress hormones induces defense-related mechanisms in plants has been shown to be active against various cancer cells both in vitro and in vivo, without affecting normal cells. Anti-inflammatory activity of methyl Jasmonate derivatives shows significant protection against experimentally induced inflammation in animals. Study reveals that methyl Jasmonate modulated the pain mediators and shows significant Anti nociceptive actions against chemically and mechanically produced pain. Current review reveals various anticancer activities with methyl Jasmonate mode of actions in concise way.

**KEY WORDS:** Methyl Jasmonate, Plant stress hormone, Anticancer activity, anti-inflammatory agents, Anti nociceptive actions



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## INTRODUCTION

Plants and plant derivatives have always been in centre of research as a useful resource for many significant reasons. Plant active constituents have an important role as a potent candidate to cure variable degree and spectrum of diseases in human being. Currently researchers are keen interested in plant phytohormones considering a fundamental basis facts and correlation between human stress hormones and plant stress hormones. Human hormones are key players to maintain homeostasis condition and small disturbance in hormones regulation leads to disturbances in normal physiology. Phytohormones are important for plant for normal growth, flowering, bearing a fruit and importance in defense mechanism. Current review article is aimed to focus on pharmacological aspects of Jasmonate phytohormones<sup>1,2</sup>

### *i. Role of Methyl Jasmonate as a Stress Hormone in Plants*

Plant stress hormones are responsible for activating the plants cellular response to diverse stress situations, including cell death.<sup>1</sup> They are made in the cells of the plants that are faced with a massive scarcity of nutrients and other essential elements. Abscisic acid, ethylene, Jasmonic acid and salicylates are the most common PSHs that have shown positive health effects to humans<sup>2, 3</sup>. Plant stress hormones are natural bio regulators and act as a prominent intracellular mediator in plant intracellular signaling and defense in response to various wear and tear injuries or environmental stresses, such as ultraviolet radiation, osmotic shock and heat etc. Several classes of plant stress hormones have been identified among them, salicylic acid and its derivative aspirin are extensively studied as potential anti-cancer therapeutics and chemo preventive agents. The Jasmonate family consists of Cis-jasmone, Jasmonic acid, and Methyl Jasmonate (MJ), are fatty acid-derived cyclopentanones that occur abundant in the plants and regulate plant developmental processes and adaptation to environment<sup>4, 5</sup>. In barley plants exogenous treatment with JA or MeJA revealed changes in a number of photosynthetic parameters, such as a decrease in the rate of photosynthetic CO<sub>2</sub> fixation and the activity of RuBP carboxylase. There were considerable increases in the rates of dark respiration and photorespiration, in the CO<sub>2</sub> compensation point value, and in the stomatal resistance. The increased production of cell biomass and secondary metabolites from plant cell cultures through elicitation has opened up a new area of research, having important economical benefits for bio industry. Methyl jasmonate and was found to enhance accumulated cell biomass significantly<sup>6</sup>. In addition methyl Jasmonate plays significant role in developmental processes, such as seed germination, root growth, fertility, fruit ripening, and senescence In addition, Jasmonate activate plant defense mechanisms in response to insect-driven wounding, various pathogens, and environmental stresses, such as drought, low temperature, and salinity.<sup>7</sup> As a growth regulator methyl Jasmonate is a elicitor for

induction of secondary metabolite synthesis which are important for plant biochemical defenses<sup>8,9,10</sup>.

### *ii. Methyl Jasmonate as a folk medicine*

*Asminum Officinale* Linn. (Synonym *J. grandiflorum* Linn) is Belonging in a Family of oleaceae. Commonly cultivated in many tropical and subtropical countries like In India, it is mainly occurs in North-Western Himalayas and Persia; cultivated in Kumaon, Uttar Pradesh, Rajasthan, and Madhya Pradesh, in gardens throughout India<sup>11</sup>. In western countries is commonly known as Spanish Jasmine. Folk name is Chameli. Flowers of *Asminum officinale* have calming and sedative, CNS depressant, astringent and mild anesthetic property. Syrup prepared from the flowers is used for coughs, hoarsenesses and other disorders of the chest. Whole plant is used as diuretic, anthelmintic, emmenagogue; used for healing chronic ulcers and skin diseases. Oil is externally used externally for relaxing. Methyl Jasmonate is concentrated in higher amount in flowers and leaf used for treating tumours.<sup>12, 13, 14, 15</sup>

## ROLE OF METHYL JASMONATE IN CANCER THERAPY

Various mechanisms have been proposed to explain the anti-cancer activity of methyl jasmonate. LOX 5 is important mediator in cancerous cell MJ inhibit generation of LOX 5 in arachidonic pathways.<sup>16</sup> Suppression of anti-apoptotic protein, arrests cell cycle and inhibition of cell growth and proliferation contributes for anticancer activity of MJ.<sup>17</sup> ATP depletion in cancer cells via mitochondrial perturbation, detachment of hexokinase from the mitochondria, induction of apoptosis in cancerous cells, decreases' expression of cancerous cell regulator etc. are some mechanism through which MJ exhibits anticancer activity.<sup>16</sup>

### *1. anti-cancer activities in prostate cancer*

vast numbers of research reveals that prostate cancer cells generates 5 LOX selective inhibition of 5 Lox generation leads to cancerous cell death. Ammad Ahmad Farooqi et al showed in their study that MJ prominently inhibits uncontrolled cell division and proliferation due to specific interaction with 5-LOX enzyme pathway<sup>17</sup>. Daniel Ezekwudo et.al. in their study proved that pro-apoptotic compounds such as methyl Jasmonate significantly causes suppression of anti-apoptotic proteins of Bcl-2 family and shows anticancer activity against radiation induces human prostate cancer cells.<sup>18</sup>

### *2. Anticancer activity against malignant skin lesions.*

Methyl jasmonate is a significant and promising novel topical treatment for precancerous and cancerous skin lesions. Study reveals that three out of the eight patients exhibited positive responses, i.e. the patient with oral lichen planus, and the patient had complete recovery (currently, for 18 months following the first treatment), while MJ treatment of the patient with lentigo maligna of the face resulted in dry tumor surface with reduction of the metaplastic area during treatment, but the cancer reappeared three months later.<sup>19</sup>

### **3. Anticancer activity against hepatocellular carcinoma**

The present study demonstrated that the combined use of methyl jasmonate and the FAP regimen might be a novel strategy for overcoming the MDR that is often observed in HCC during chemotherapy. Study were conducted a clinically simulated FAP (doxorubicin + cisplatin + 5- fluorouracil) regimen was employed in a BALB/c mouse model of multidrug resistant HCC, which was previously established and the effect of methyl jasmonate (in combination with the FAP regimen) on P-gp ATPase activity and the reversal of MDR. Methyl jasmonate is a promising MDR reversal agent that deserves further investigation<sup>20, 21</sup>.

### **4. Anticancer activity against human bladder cancer cells**

Gambogic acid (GA) and methyl jasmonate (MJ) are increasingly being recognized as novel natural anticancer compounds. Yongjun Wang et. al. investigated the antitumor effects of GA in combination with MJ on human bladder cancer cells. MJ enhanced GA-induced activation of caspase-3 and caspase-9, and down-regulated the expression. Furthermore, treatment of bladder cancer cells with a combination of GA and MJ induced synergistic inhibition of the enhancer of zeste homologue 2 (EZH2) expressions, whereas miR-101 expression was up-regulated. Conversely, knockdown of miR-101 restored this decreased expression of EZH2 and suppressed the inhibitory effect of GA and MJ on the growth of bladder cancer cells. Microarray analysis showed that genes closely associated with bladder cancer development were significantly down-regulated by GA and MJ. In a s.c. xenograft mouse model of human bladder carcinoma, the combination of GA and MJ exerted an increased antitumor effect compared with GA alone.<sup>22</sup>

### **5. Anticancer activity against Human neuroblastoma**

Jasmonates act as key signaling compounds when plants are under oxidative stress, but little is known about their functions in mammalian cells. The cells were pretreated with individual jasmonates for 24 h and exposed to hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) for 24h. Before the resulting cytotoxicity, intracellular reactive oxygen species (ROS) levels, and mitochondrial membrane potential were measured, also measured intracellular glutathione (GSH) levels and investigated changes in the signaling cascade mediated by nuclear factor erythroid 2-related factor 2 (Nrf2) in cells treated with 12-oxo phytodienoic acid (OPDA). These results were demonstrated that among jasmonates, only OPDA suppressed oxidative stress-induced death of human neuroblastoma cells, which occurred via activation of the Nrf2 pathway.<sup>23</sup>

### **6. Anticancer activity of MJ in pretreated blackberries against human lung cancer and leukemia.**

Uncontrolled cell division is a primary key in the progression of a cancer tumor. Aberrations in mitotic regulatory pathways controlling cell proliferation are

necessary for the establishment of all tumors. Deregulation of cell proliferation together with suppressed apoptosis is the minimal common platform for all cancer evolution and progression. Study reveals that proliferation was inhibited in a dose-dependent in human lung cancer A549 cell and human promyelocytic leukemia HL-60 cell after exposure to the blackberry extracts. Pre-harvest application of MJ significantly enhanced the inhibition of proliferation A549 cells and HL-60 cells. This may be due to the presence of increased content of antioxidants and other secondary metabolites in MJ treated blackberries. These results suggested that the chemo preventive effects of fresh blackberries may be through its antioxidant properties by blocking reactive oxygen species.<sup>24</sup> Methyl jasmonate (MJ) acts in vitro and in vivo against various cancer cell lines, as well as leukemic cells from chronic lymphocytic leukemia (CLL) patients. Given the importance of multi-agent combinations in cancer chemotherapy, the purpose of this study was to identify super-additive combinations of MJ and currently-available chemotherapeutic drugs. In current study major types of malignancies, i.e., breast, lung, prostate and pancreas carcinomas as well as leukemia were studied. The chemotherapeutic drugs tested were adriamycin, taxol, BCNU and cisplatin. For instance, MJ exhibited strong cooperative effects with BCNU in MIA PaCa-2 pancreatic carcinoma cells. Furthermore, MJ enhanced significantly the anti-leukemic effect of adriamycin in vivo, in a CLL mouse model. Finally, MJ induces death of several types of carcinoma cells with the help of glycolysis inhibitor 2-deoxy-D-glucose. This can be concluded that administration of MJ with common chemotherapeutic drugs and glycolysis inhibitors bears a promise for effective anti-cancer therapy.<sup>25</sup>

### **7. Anticancer activity against oral squamous carcinoma cells**

The three jasmonic acid derivatives obtained, 3(S)-Hydroxy-2(R)-(2Z-pentenyl)-cyclopentane 1(R)-acetic acid (1), 3(R)-Hydroxy-2(R)-(2Z-pentenyl)-cyclopentane-1(R)-acetic acid (2), 3-Hydroxy-2(S)-(2Z-pentenyl)-cyclopentane-1(S)-acetic acid (3), were tested for cell-growth inhibition activity towards the human cancer epithelial cell line, the oral squamous carcinoma cells (KB). The results obtained show that jasmonic acid derivatives (1-3) are active on human cancer cells examined in different concentration ranges. The compound 3, with the same molecular structure of compounds 1 and 2, but with different stereochemistry suggest that the activity changes with change in stereochemistry. In the present study compound 3 is tested against the potential proapoptotic activity data suggest that it, as other jasmonate compounds, is able to trigger apoptotic death in cancer cells. This event may be correlated at an elevation of reactive oxygen species (ROS)<sup>26</sup>.

### **8. Anticancer activity against endometrial cancer cells.**

The present study evaluated the cytotoxic activity of methyl jasmonate (MJ) in endometrial cancer cells and examined the hypothesis that the apoptotic and anti-proliferative actions of MJ in these cell lines can be enhanced by co-targeting the insulin-like growth factor-1 receptor (IGF1R) signaling pathway. MJ had a potent pro-apoptotic effect and exhibited significant toxicity in all cell lines tested. MJ in combination with NVP-AEW541, a selective IGF1R tyrosine kinase inhibitor, had significantly increased cytotoxicity. MJ decreased IGF1R phosphorylation; however, it enhanced AKT phosphorylation and abolished the anti-apoptotic effect of IGF1. These findings suggest that combined IGF1R inhibitor and MJ administration may constitute an attractive modality for treating endometrial cancer.<sup>27</sup>

### **9. Anticancer activity against in cervical cancer cells**

In the present study the effectiveness of methyl jasmonate (MJ) against cervical cancer cell lines was investigated. It has been shown that MJ is cytotoxic to a range of cervical cancer lines; Cytotoxicity of MJ was dose and time dependent, and associated mainly with the induction of cell death and to a less extent with inhibition of cell growth. Cell death induced by MJ displayed features characteristic to both apoptosis and necrosis, and was associated with different changes in the levels of p53, p21, bcl-2 and bax in the various cervical cancer lines. In conclusion, MJ a novel anticancer agent, acts via multiple pathways to induce death of cervical cancer cells, thus making it a promising candidate for the treatment of cervical cancer.<sup>28</sup>

### **10. Anticancer activity against colon carcinoma cells.**

Massive cell damage could be observed as an increased incidence of loosely rounded up cells in the MJ and TRAIL combined treatment compared to non-treated cells, or to cells treated by MJ or TRAIL alone. It is shown that pre incubation with MJ, at concentrations inducing low cytotoxicity, followed by TRAIL administration, resulted in a significant enhanced TRAIL-induced apoptosis in CRC cell lines, thereby illustrating an efficient combination of two highly selective anti-cancer agents. Thus it is assumed that MJ has other characteristics in addition to its direct mitochondrial-cytotoxic effect. MJ-induced increased DAPI-stained nuclear fragments, increased TRAIL-induced cytochrome c release to the cytoplasm and increased TRAIL-induced caspase cleavage.<sup>29</sup>

### **11. Anticancer action against gastric cancer cells**

Human gastric cancer cell lines SGC-7901 and MKN-45 were treated with different concentrations of MJ. Cell viability, proliferation, migration, invasion and angiogenesis capabilities of cancer cells were measured. Sub-cytotoxic MJ attenuated the migration, invasion and angiogenesis, but not the cell viability or proliferation, of gastric cancer cells in a time- and dose-dependent manner, with down-regulation of matrix metalloproteinase 14 (MMP-14) and its downstream gene vascular

endothelial growth factor. Sub-cytotoxic MJ attenuates the MMP-14 expression via decreasing the Sp1 expression and binding on MMP-14 promoter, thus inhibiting the migration, invasion and angiogenesis of gastric cancer cells.<sup>30</sup>

## **METHYL JASMONATE ACTIONS OTHER THAN ANTICANCER ACTIVITY**

### **1. Anti nociceptive effects of methyl jasmonate in experimental animals**

Present investigation evaluated the anti nociceptive activity of MJ in animal models of pain. The anti nociceptive activity of MJ was screened using the acetic acid induced writhing, tail immersion; formalin-induced paw licking and Randall–Selitto paw pressure tests in rodents. MJ exhibits inhibitory activity against acetic acid-induced abdominal constrictions in mice. It further produced a significant suppression of the inflammatory pain associated with formalin test in mice. In the Randall–Selitto paw pressure test MJ significantly prolonged the paw withdrawal latency in the inflamed hind paw but did not alter the pain response in the non-inflamed hind paw of rats.<sup>31</sup>

### **2. Methyl Jasmonate analogue as potential anti-inflammatory agents**

In current study a series of methyl jasmonate analogues (2–20) were synthesized and evaluated for their inhibitory effects on the production of pro-inflammatory mediators (NO, IL-6, and TNF- $\alpha$ ) in lipopolysaccharide (LPS)-activated RAW264.7 murine macrophage cells. The introduction of an enone functionality to the structure of a plant hormone (1) rendered the product (2) a significant anti-inflammatory activity. Analogues further derived from 2 (7, 9, 13, and 15) exhibited even more enhanced activity, and these compounds were much more potent than natural anti-inflammatory prostaglandins (PGA1, PGA2, and 15-deoxy-D12,14-PGJ2). Among them, compounds 9 and 15 showed the highest potency, while compounds 7 and 13 would be more desirable with respect to safety. This is the first study demonstrating the anti-inflammatory potential of jasmonate derivatives, and the present results suggest MJ analogues (7, 9, 13, and 15) may serve as potential anti-inflammatory Leads.<sup>32</sup>

## **RESULTS AND CONCLUSION**

Anticancer activity of MJ is mainly exhibited through inhibition of LOX 5 which is generated in arachidonic pathways and important mediator in cancerous cells.<sup>16</sup> Suppression of anti-apoptotic proteins of the Bcl-2 family exposed to radiation and increase in cytotoxicity PC-3 cells arrests cell cycle, inhibiting cell growth and proliferation, causes cell death through the intrinsic/extrinsic proapoptotic, p53-independent apoptotic, and non-apoptotic (necrosis) pathways<sup>17, 24, 27</sup>. Methyl Jasmonate is prominent multi drug resistant reversal agent and deserves significant value in cancer patients.<sup>20</sup> Some investigator demonstrated anticancer activity against human bladder cell line and proposed that the anticancer activity is due to activation and induction of

caspase 3 and caspase 9 and decreases expression of cancer cell regulators.<sup>22</sup> Methyl Jasmonate shows significant antioxidant activity against hydrogen peroxide generated free radicals in cytotoxic cells as well as change in glutathione signaling as natural free radicals scavenger.<sup>23</sup> Cooperative properties MJ with other chemotherapeutic agents clearly indicates that MJ in dose dependent manner helps to glycolysis inhibitor 2-deoxy-D glucose in inducing death of several types of carcinoma cells.<sup>25</sup> The complete lack of toxicity to normal cells and the rapidity by which MJ causes damage to cancer cells turn MJ into a promising anticancer agent

that can be used alone or in combination with other agents. Finally the anti-inflammatory activity of MJ is associated with inhibitory effect on production of pro-inflammatory mediators like NO, IL and TNF and also exhibits potent anti-inflammatory potential similar to PGA1, PGA2.<sup>32</sup> In conclusion remark it can be stated that the new era would be benefited by MJ to the medical field with significant activities other than anticancer. Further studies are required to screen the various potentials of MJ scientifically.

## ABBREVIATIONS

CO <sub>2</sub> : Carbon dioxide	miR: Mitochondrial Ribosome
JA: Jasmonic Acid	H <sub>2</sub> O <sub>2</sub> : Hydrogen peroxide
MJ: Methyl Jasmonate	ROS: Reactive oxygen species
PSH: Plant Stress Hormone	GSH: Glutathione Hormone
CNS: Central Nervous System	hr: Hours
ATP: Adenosine Tri Phosphate	LOX: Lipo oxygenase
MAPK: Mitogen Activated Protein Kinase	i.e.: That is
IPA: Isopentenyl Adenine	GA: Gambogic Acid:
Bcl2: Beta Cell Lymphoma	Pa Ca: Pancreatic Carcinoma
CLL: Chronic Lymphocytic Leukemia	Ic: Inhibitory Concentration
MDR: Multi Drug Resistance	HPV: Human papilo virus
ATPase: Adenosine Tri Phosphatase	PGA: Prostaglandins A
EZH-2: Enhancer of zeste homologue-2	PC: Prostate Cancer
HCC: Hepatocellular carcinoma	HC: Human Cancer Cells
Nrf2: Nuclear Factor erythroid 2 related factor 2	OPDA: 12-oxo phytodienoic acid
BCNU: Bis-chlorethylnitrosourea (Carmustine)	

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