Chapter

Potential Defensive Involvement of Methyl Jasmonate in Oxidative Stress and Its Related Molecular Mechanisms

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Abstract

Jasmonic acid (JA), cytokinins (CK), gibberellins (GA), abscisic acid (ABA), ethylene (ET), and salicylic acid (SA) are potent plant stress hormones (phytohormones/PTH). Methyl jasmonate (MeJA), a volatile ester of JA, is derived from the petals of Jasminum grandiflorum (jasmine). The MeJA has been meticulously confirmed for its food, agricultural, and therapeutic uses in the treatment of a range of serious illnesses. Several scientific articles have studied and reported on the role of free radicals in the development of life-threatening clinical illnesses. The inflammatory signaling pathway is triggered by a weak or interfering endogenous antioxidant system, or the elaborated production of free radicals, which causes damage to key cellular components. The current chapter focused on and demonstrated MeJA's multifunctional role in antioxidant and anti-inflammatory signaling mechanisms such as inhibition of NF-B (nuclear factor kappa-light-chain-enhancer of activated B cells), mitogen-activated protein kinase (MAPK or MAP kinase) pathway inhibition/down-regulation of pro-inflammatory mediators (IL, TNF-), cyclo-oxygenase (COX), and (LOX). The antioxidant effect of MeJA's interaction with miRNA, transcription of nuclear factor erythroid 2-related 2 (Nfr2), activation of sirtuins (SIRTs), antioxidant and redox signaling pathway were also discussed in the chapter.

Keywords: methyl jasmonate, anti-inflammatory, oxidative stress, free radicals, plant stress hormone

1. Introduction

Oxygen is continually used by the organism for a variety of important activities [1]. reactive oxygen species (ROS) is a naturally occurring byproduct of oxygen metabolism that interacts with biological systems regularly [2, 3]. ROS has been involved in the breakdown of cell organelles such as DNA, proteins, and lipids, according to several studies. Radical scavenging molecules are important components of the antioxidative defense mechanism, protecting cells from free radical

damage [4, 5]. Endogenous antioxidant systems (enzymatic/nonenzymatic) are important for balancing and fighting ROS such as H_2O_2, ROOR (organic hydroperoxide), NO (nitric oxide), O-(superoxide), and •OH (hydroxyl radicals), among others [6, 7]. Superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), and glutathione reductase (GR) are enzymes in the human endogenous antioxidant system that play a role in the development of ROS-mediated oxidative stress [7–10]. The extensive production of free radicals manifests in serious illnesses and disorders as diabetes [11], cardiovascular [12], inflammatory [13], and neurological diseases [14]. The production of ROS is triggered by many oxidizing enzymes (xanthine oxidases, NADPH oxidase) COX [15, 16] pro-inflammatory factors. A modest rise in ROS levels disturbs and interferes with cell proliferation and normal physiological processes, but a substantial increase in ROS levels causes catastrophic damage to cellular components [17, 18]. SOD, an important endogenous antioxidant metalloenzyme that scavenges H_2O_2 produced during oxygen metabolism [19], is an important endogenous antioxidant metalloenzyme. Because of the increased and unregulated synthesis of O-depletes in SOD storage, protecting the cell from hazardous chemicals created during aerobic respiration becomes challenging [20]. Through the conversion of GSH into selenium-containing GSH (GSSH) by GR (Glutathione reductase), the thiol-containing GSH is an essential reducing agent that eliminates reactive oxygen species [20, 21]. CATase is a kind of antioxidant that is responsible for the neutralization of H_2O_2. H_2O_2 causes lipid peroxidation, which is inhibited by CAT [22]. Many compounds are produced by lipid peroxidation, but one of the most significant is MDA (malondialdehyde) [9].

2. Multifunctional role of MeJA in several clinical ailments

2.1 Downregulation of NF-κB, MAPK pathway, and oxidative stress

The cytokines are important mediators and signaling molecules involved in several inflammatory pathological cascades. TNF- and the IL family (IL-1, IL-6, IL-15, IL-17, IL-18) are important cytokines [23]. The vital regulator in the synthesis of cytokine induction is the NF-κB signaling pathway. NF-κB is a family of proteins associated with DNA and activates cytokine synthesis genes [24]. The inhibitory protein (IkB) binds to NF-κB and blocks the translocation it from the cytoplasm to the nucleus. The number of stimuli affects IkB function by phosphorylation and degrading it. This allows NF-B to get activated, translocated to the nucleus from the cytoplasm, and triggers genes involved in the synthesis of inflammatory mediators. Agents that activate NF-κB include cytokines, mitogens, and ROS [25]. Another important signaling pathway in inflammation is the activation of MAP kinase under the influence of ROS. ROS induces phosphorylation of the MAP kinase family, including ERK, JNK, and p38 kinases [26]. Consequently, these kinases are responsible for the activation of transcription factors similar to NF-κB and regulate pro-inflammatory genes. Through enzymatic conversion from LOX and COX, ROS also significantly contributed to the synthesis of inflammatory mediators such as PG (prostaglandins), LT (leukotrienes), 5-HETE (5-Hydroxyeicosatetraenoic acid), and others [27, 28]. Studies have shown that antioxidant treatment effectively reduces pain and inflammation via downregulation of NF-B activation and cytokine synthesis [29, 30]. Nociceptive responses are detected by nociceptors found on c and fibers that innervate higher brain centers. Several studies have advocated that the activation of nociceptors and perception is mediated by inflammatory mediators [31]. The study revealed that MeJA significantly reduces the production of ROS-mediated oxidative stress and the generation of pro-inflammatory mediators

and would be responsible for its anti-inflammatory and anti-nociceptive effects in-vivo and in-vitro [28, 32–35]. Studies have demonstrated a significant reduction in pain and inflammation in MeJA-treated experimental animals intoxicated with LPS. The proposed underlying mechanism involved is downregulating the production of pro-inflammatory cytokines (IL, TNF-), expression of COX and LOX, PG, resolving disturbed redox status, inhibiting the generation of ROS/RNS, inactivation of inflammatory cells, and downregulation of transcription in the NF-B and MAPK signaling pathways [35].

2.2 Inhibition of neuronal peroxidation and oxidative stress

The progressive loss of memory is characterized by Alzheimer's disease (AD). The common signs and symptoms include the inability to recall past events, calculate, plan and perform simple tasks, recognize people and relationships, etc. [36, 37]. The pathological lesion lies in central cholinergic pathways where the degeneration of cholinergic neuronal populations occurs [38]. Several studies have revealed that ROS and associated oxidative stress in the brain region is important in the development and progression of AD. Enhanced lipid peroxidation and diminished polyunsaturated fatty acids have been found in AD brains, which further support the role of ROS in the pathophysiology of the disease [39, 40]. Brain tissues are more susceptible to the deleterious effects of ROS because of their high rate of oxygen consumption, high iron content in many brain tissues, and generation of hydrogen peroxide in neuronal mitochondria cells [41, 42]. Postmortem studies have confirmed elevated levels of MDA, an index of lipid peroxidation in AD brains, which confirmed the role of oxidative stress in the pathogenesis of the disease [43]. Induction of AD in experimental animals can be done by the administration of chemical substances which interfere in a central cholinergic pathway. Scopolamine (SC)-induced memory dysfunction has been linked to its depletion of Ach (acetylcholine) stores, increased oxidative stress, and depletion of the endogenous antioxidant enzymes in brain tissues, which leads to neuronal damage. Tacrine, an AChE inhibitor like tacrine, was the first further donepezil and rivastigmine to be approved for the treatment of AD. It is reported that inflammation of brain cells appears to contribute to the development and progression of AD. Anti-inflammatory drugs such as NSAIDs, corticosteroids, and antioxidants may be effective strategies in Alzheimer's disease [42, 43].
In a pharmacological screening of a new molecule, lipopolysaccharide (LPS) induced neuroinflammation is a highly validated and reported model [44, 45]. The underlying mechanism involves LPS-induced synthesis of inflammatory mediators and generation of ROS followed by damage to the neurons. MeJA has been screened for its memory performance-enhancing potential against LPS-induced neurotoxicity. The studies revealed that significant memory enhancement in MeJA treated animals was observed as compared to LPS treated. The underlying mechanism has been linked to MeJA antioxidant, anti-inflammatory potential using In-vivo as well as In-Vitro screening models [46–48].

2.3 Inhibition of mitochondrial dysfunctioning, inflammatory cytokines, and oxidative stress

Stress can influence the emotional factors and neurobehavioral characteristics of human beings and manifest anxiety [49]. The association of oxidative stress and neurodegenerative disorders, including anxiety, has been reported in several studies [50]. Anxiety is a stress response such as worry, fear, overwhelm, and distress to the environment that makes it difficult to continue to work or behave normally in

day-to-day life [51]. The stress system components of the CNS are the limbic system, hypothalamus, pituitary, and endocrine hormones that play an integral part in the determination of mental health and behavioral responses [52]. These behavioral responses are regulated by the neurotransmitter/modulators and get interrupted by a variety of chemicals, xenobiotics, drugs, etc., and could change the normal neuronal function [53]. The brain tissues are rich in lipid substrates for oxidation, iron, and copper ions that catalyze free radical reactions which are abundant [54]. The sites of damage mediated by ROS are neuronal mitochondria dysfunction, which leads to psychiatric behavioral diseases like depression, anxiety, psychosis, and ataxia [55, 56]. Patients with anxiety, depression, and psychosis found enhanced levels of pro-inflammatory cytokines, specifically IL-6 and TNF-α, in their blood and brain. Pro-inflammatory cytokines degenerate neurons by activating signaling molecules such as phospholipase A2 (PLA2) and arachidonic acid (AA) [57, 58]. Activation of PLA2 and AA further increases ROS and additional inflammatory mediators like eicosanoids, which contribute to promoting inflammation and nerve degeneration [59]. AA has been found to have a direct role in apoptotic effects [63]. Anti-inflammatory, antioxidant dietary agents such as docosahexaenoic acid (DHA) have been shown in studies to prevent neuronal apoptosis and to be an important treatment option in neurodegenerative diseases [61]. NF-B expression has been found in neurodegenerative diseases, including anxiety [60]. Blocking of the NF-κB pathway remarkably reduces the levels of cytosolic and mitochondrial ROS generation and neuronal damage mediated by oxidative stress. MeJA has been studied for its antianxiety, adaptogenic, and anti-stress potential, and it has been shown to have a significant effect in animals [49, 61]. The underlying mechanism is that MeJA significantly reduces the levels of mitochondrial ROS by compensating with endogenous antioxidant enzymes like GSH, CAT, GPx, GR, SOD, and free radical scavenging activity. A significant reduction in IL and TNF-, as well as a significant inhibition of NO, which is responsible for the synthesis of pro-inflammatory mediators, has a direct effect on the inhibition of neurodegeneration. It was also reported that MeJA shows a switch-off effect on activation of the NF-B and MAPK transcription pathways, which have direct involvement in the generation of stress, anxiety, and other psychological disturbances [31, 34].

2.4 Inhibition of neuronal excitability and oxidative stress

Aggressive tendencies and behaviors in humans and animals have been demonstrated and linked to elevated inflammatory markers [62, 63]. As discussed earlier, brain tissues are more susceptible to the deleterious effects of ROS because of their high rate of oxygen consumption, high iron content in many brain tissues, and generation of hydrogen peroxide in neuronal mitochondria cells [40, 41]. ROS damages neuronal membranes, impairs the ability to deactivate receptors and ion channels, causes uncontrolled neurotransmitter release, and generally disrupts neuronal functioning [64, 65]. disturbed neuronal functioning contributes to neuronal excitotoxicity and is considered as a pathological cascade in neuronal diseases, particularly aggression. Excess excitatory neurotransmitter (glutamate) activity and weakened inhibitory (GABA) neurotransmitter signaling result in aggressive behavior changes. Over-activity of glutamate excitatory neurotransmitters progressively modulates the glutamate receptor and increases intracellular levels of Ca2+, which further disturbs the mitochondrial Ca2+ homeostasis, activates hydrolytic enzymes, and activates apoptotic signaling pathways. Several studies have established a link between increased nitric oxide synthase (NOS) activity and glutamate neurotoxicity, as well as associated behavioral aggressive tendencies [66, 67]. Evidence suggests

that MeJA treatment can control disease progression by modulating oxidative stress-mediated by ROS/RNS and controlling inflammatory mediators via direct or indirect mechanisms [61, 68]. In conclusion, the antioxidant potential of MeJA controls the modulation of glutamate/GABAergic, increased Ca2+ influx through countering NO production, oxidative stress.

2.5 Inhibition of metalloproteinases and oxidative stress

The articular cartilage is avascular and does not receive any blood supply. Hence, the essential nutrients and oxygen are supplied to the cartilage through the synovial fluid [69]. Many metabolic reactions in chondrocytes are anaerobic and adapted to survive with a minimum oxygen tension [70]. In a pathological condition, oxygen tension fluctuates, leading to the generation of ROS by the chondrocytes. The main reactive species produced by chondrocytes are O_2 radicals, NO, and their derivatives (ONOO-, H_2O_2) example, chondrocyte-derived free radical levels are important for the maintenance of ion homeostasis, but they also contribute to disease progression [71]. Enhanced levels of ROS lead to serious damage to both chondrocytes and extracellular matrix components of articular cartilage and disturb redox status [72]. The important component of the ECM like aggrecan is degraded by ONOO-and initiates the process of cartilage degradation [73]. Additionally, endogenously synthesized NO suppresses the synthesis of aggrecan. The tensile strength is primarily provided by a network of aggrecan hyaluronate collagen; free radicals disturb the collagen network and reduce the strength of the ECM. Free radicals inhibit collagen synthesis indirectly via interleukin-1 [74]. The proteoglycan synthesis is inhibited by H_2O_2 through the disturbing synthesis of triphosphate (ATP) [75]. The tissue inhibitors of metalloproteinases (TIMPs) are important inhibitors of MMP-mediated cartilage damage [76]. ONOO-and HOCl reduces the activity of TIMPs by inactivating them. The NO producing agent up regulated the synthesis of MMPs by enhancing collagenase mRNA expression [80]. Proteoglycan synthesis is down-regulated in the chondrocytes on exposure to H_2O_2 [77]. ROS participates in reducing the capacity of chondrogenic precursor cells to migrate and proliferate within the joint area. NO enhances the anti-proliferative effect of IL-1 as well as initiates chondrocyte apoptosis [78]. The fibroblast-like synoviocytes consume a large amount of oxygen as compared to chondrocytes. In oxidative stress, the accumulation of antioxidant enzymes like SOD, CAT, and GSH has been observed. These enzymes protect the chondrocytes and ECM degradation from free radicals [79]. An uncontrolled and abnormal increase in ROS levels causes apoptosis of chondrocytes. Several studies reveal that a minimum level of H_2O_2 in synoviocytes causes less damage to chondrocytes [80]. MeJA has shown a significant chondroprotective effect on LPS-induced cartilage damage. LPS induces the synthesis of pro-inflammatory mediators as well as creates severe oxidative stress. MeJA significantly reduces the inflammatory mediator's activity as well as cartilage destructive MMP. Normalization of oxidative stress is accomplished by restoring antioxidant enzyme levels [27, 32].

3. Regulation of miRNA, SIRT, and HIF1α for an antioxidant mechanism

An oxidative stress state alters the expression level of different miRNAs (microRNAs) and causes significant changes in important cellular processes like cell differentiation, lipid metabolism, apoptosis, and organ development [81]. Severe clinical conditions like inflammation, cancer, cardiovascular diseases, diabetes mellitus, rheumatoid arthritis, neurological disorders have been

correlated with altered miRNA expression [82]. Upregulation or downregulation of mRNA addresses pathophysiological modulation in retardation or development of diseases. Anticancer activity of MeJA against bladder, colorectal cancer cells has been shown via the downregulation of EZH2 (enhancer of zeste homolog 2) expression by induction of microRNA-101 [83–85]. MeJA antioxidant activity has been demonstrated via two pathways: first, inhibition or down-regulation of pro-inflammatory factors such as IL, TNF-mediated mitochondrial ROS production, and second, restoration of endogenous antioxidant enzymes [86, 87]. The latter mechanism involves an effect on the regulation of microRNA. Cellular redox status is regulated by redox-sensible transcription Nfr2 through the upregulation of antioxidant defense genes for SOD, CAT, GSH enzymes [88–90]. The activity of Nfr2 is regulated by miRNAs via downregulating the same [91, 92]. In conclusion, MeJA improves the antioxidant status and regulates oxidative stress by downregulating specific miR-155 and upregulating miR-101, which leads to the upregulation of Nfr2 activity. The indirect effect of MeJA on sirtuins (SIRTs) as an antioxidant and redox signaling pathway has been established through upregulation of Nfr2 activity by induction of miR-101. Researchers have extensively studied and reported that SIRTs are key signaling molecules that regulate the redox status of the cell and modulate cellular responses in a variety of pathological conditions over the last two decades [93]. SIRTs protect the cell from the deleterious effect of ROS and enhance the expression of genes responsible for the production of endogenous antioxidant enzymes. SIRTs are important for the fine balance between oxidant and antioxidant systems, regulating cellular biochemical reactions as well as maintaining an oxidative state. SIRTs, in association with antioxidant response elements (ARE), is involved in the regulation of gene expression when a cell is exposed to oxidative stress responses. ARE senses the altered cellular redox status and elicits transcriptional responses through activation of Nfr2. Nfr2 regulates the expression and production of several antioxidant enzymes and detoxification genes [94, 95]. Several studies have reported that MeJA significantly restores the levels of antioxidant enzymes and reduces oxidative stress and mediated damage [27, 50, 51, 96, 97]. The underlying mechanism may be Nfr2 mediated increased gene transcription for antioxidant enzymes through the upregulation of miRNA-101. MeJA down-regulates the expression of miRNA-155, leading to the stabilization of HIF-1 (hypoxia-inducible factor 1 alpha) [88]. The fall in oxygen tension in the cell below that needed for normal physiological demand causes a cellular hypoxic adaptive response. The hypoxic condition is crucial and important to target for a therapeutic approach, particularly in cardiovascular disease and cancer [98]. The key regulators of oxygen tension in cells are HIFs. HIF-1 regulates acute hypoxia, whereas HIF-2 and HIF-3 regulate chronic hypoxia. Recently, investigation suggests that miRNAs play an important role in the regulation of HIF [99]. Chronic hypoxic conditions lead to cellular apoptosis, which contributes to severe stroke or myocardial infarction. Alternatively, an intentional cellular hypoxia approach is practiced in the treatment of various types of cancer. Hypoxia induces oxidative stress via the overgeneration of reactive oxygen species (ROS). Targeting HIF through downregulation of miRNA-155 is a new dimension in the induction of cancer cell apoptosis [100]. MeJA anticancer activity has been largely correlated with the downregulation of miRNA-155, which inhibits expression of HIF, which insults cancerous cells and induces apoptosis. In summary, MeJA indicates unique and imperative aspects concerning the assimilated biological roles against oxidative stress, viz. reducing infiltration of inflammatory cells and their activation, inhibition of proinflammatory mediators (IL, TNF-), LOX and COX,

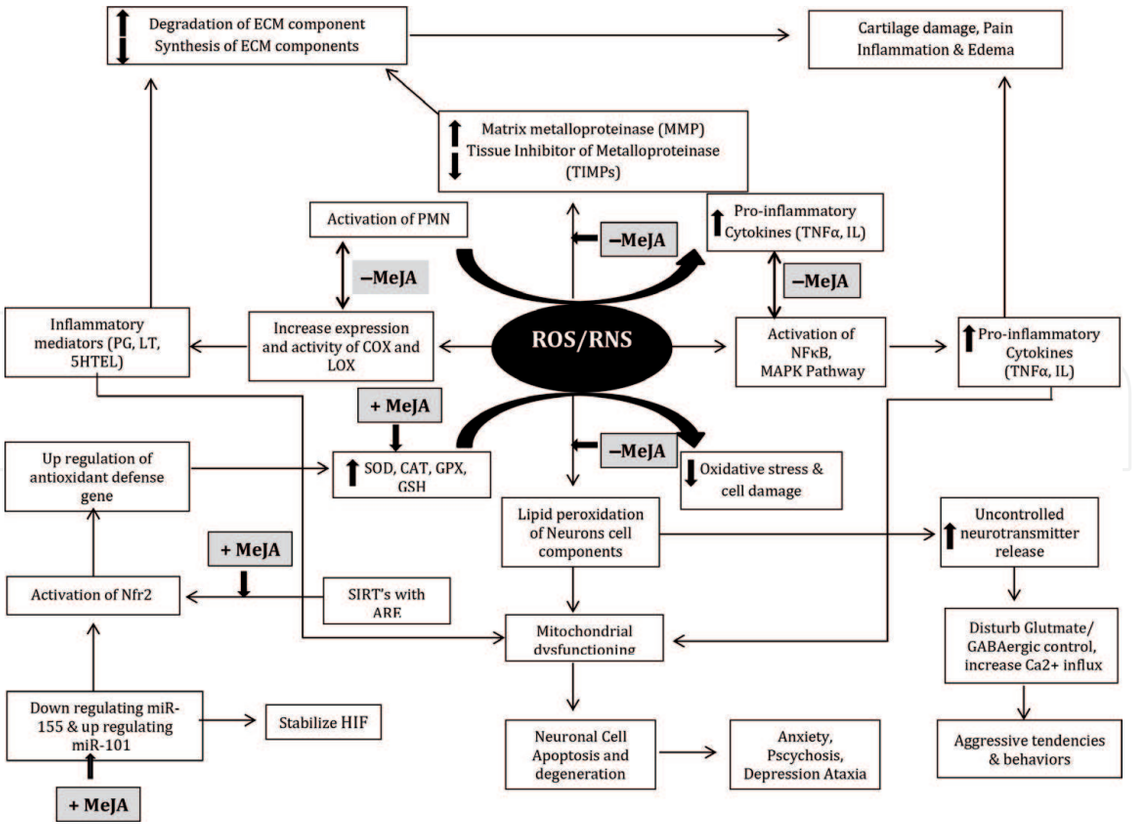

Figure 1.
MeJA multifunctional role in oxidative stress and molecular interactions in antioxidant defense mechanism.

downregulation of NF-B and MAPK transcription pathways, downregulation of miRNA-155, and upregulation of miRNA-101 and Nfr2 pathway (**Figure 1**).

Reactive oxygen species (ROS)/reactive oxygen species (RNS) initiates signaling inflammatory pathways NF-κB (nuclear factor-kB)/MAPK (Mitogen-activated protein kinase) and induces synthesis of cytokines (IL and TNF-α), (MAPK) responsible to enhance activity of COX and increases the synthesis of pro-inflammatory mediators. Activity of COX (cyclooxygenase)/LOX (Lipoxygenase) is enhanced by ROS/RNS and induces synthesis of inflammatory mediators like (PGs, LTs, 5HTEL). The formed inflammatory mediators contribute to destructive effects on the different cells. Lipid peroxidation caused by ROS/RNS leads to damage to neuronal cells component and disturbs mitochondria functioning and induces neuronal cell degeneration and death and develops anxiety, psychosis, depression etc. The disturbed neuronal cell functioning cause's uncontrolled release of neurotransmitter and causes imbalance between inhibitory (GABAergic) and excitatory (Glutmate) neuronal mechanism leads to aggressive tendencies & behaviors. On induction of inflammation PMN (polymorphonuclear neutrophil) activates and are important source for generation of ROS/RNS which further participate in inflammatory cascades. ROS/RNS increases activity of destructive MMP (matrix metalloproteinase) whereas protective tissue TIMPs (Inhibitor of metalloproteinase) is diminished. MMP selectively degrades the component of cartilage ECM (Extra cellular matrix) and causes cartilage damage, pain inflammation due to wear and tear of joints. MeJAregulates miR-155, miR-101 as well as sirtuins (SIRTs) antioxidant and redox signaling pathway leads to the upregulation of the Nfr2 (nuclear factor erythroid 2-related 2) activity. Up regulation of the Nfr2 increases gene transcription for antioxidant enzymes and reduces cellular oxidative stress.

4. Conclusion

PTH jasmonic acid and its derivatives like MeJA are important in the survival of plants in biotic and abiotic stressful conditions as well as have proved their effectiveness in the treatment of several clinical ailments. An important consideration has been pointed out to oxidative stress-mediated by ROS in the development of several pathological conditions like cardiovascular, metabolic, psychosis, and neurodegenerative disorders, cancer, etc. MeJA is not only effective in plants to relieve oxidative stress, but also effectively relieves the same in human beings. ROS activates several pathways like the NF-B and MAPK signaling pathway, increases the activity of inflammatory (PG, LT, 5HTEL) and pro-inflammatory mediators (IL, TNF-), triggers classes of degradative enzymes, disturbs cellular redox status and depletes antioxidant enzymes, induces lipid peroxidation of important cell components, and disturbs cellular normal physiology and construction. Targeting ROS/RNS by antioxidant molecules or disabling signaling pathways activated by ROS are important concerns for treatment options in severe diseases and disorders. MeJA has shown a prominent role in controlling and neutralizing signaling pathways like NF-κB and MAPK also effectively reduces the activity of inflammatory mediators, oxidative stress, and protects the cell and its components from ROS. On the other hand, methyl jasmonate has a positive interaction with miRNA-101 which activates Nfr2mediated upregulation of antioxidant defense genes for SOD, CAT, and GSH enzymes as well as indirectly boosts SIRT antioxidant and redox signaling pathways. Considering the potent role of MeJA and significant interference in oxidative stress and facilitated disease causative pathways, it could be an influential candidate in the treatment of numerous pathological conditions. Several molecules have been screened from natural and synthetic sources for their potential antioxidant benefits. Among them, MeJA has a multifaceted role against oxidative stress-mediated cellular damage. In conclusion, phytohormones like MeJA may be a protruding candidate for new drug discovery and a highly promising molecule for the pharmacotherapy of severe diseases or disorders.

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Conflict of interest

The authors declare no conflict of interest.

Acronyms and abbreviations

JA	Jasmonic Acid
CK	Cytokinins
GA	Gibberellins
ABA	Abscisic Acid
ET	Ethylene
SA	Salicylic Acid

PTH	Phytohormones
MeJA	Methyl Jasmonate
NF-B	Nuclear Factor Kappa-Light-chain-enhancer of Activated B cells
MAPK	Mitogen-Activated Protein Kinase
IL	INTERLEUKIN
TNF-α	Tumor Necrosis Factor alpha
COX	Cyclo-Oxygenase
LOX	LIPO-OXYGENASE
miRNA	microrna
Nfr2	Nuclear Factor Erythroid
SIRTs	Sirtuins
ROS	Reactive Oxygen Species
RNS	Reactive Nitrogen Species
H_2O_2	Hydrogen Peroxide
ROOR	Organic Hydroperoxide
NO	Nitric Oxide
O-	Superoxide
•OH	Hydroxyl Radicals
SOD	Superoxide Dismutase
CAT	Catalase
GSH	Glutathione
GR	Glutathione Reductase
MDA	Malondialdehyde
IkB	Inhibitory Protein B
PG	Prostaglandins
LT	Leukotrienes
5-HETE	5-Hydroxyeicosatetraenoic Acid
AD	Alzheimer's Disease
Ach	Acetylcholine
AChE	Acetylcholine Esterase
NSAIDs	Non-Steroidal Anti-inflammatory drugs
LPS	Lipopolysaccharides
PLA2	Phospholipase A2
AA	Arachidonic Acid
DHA	Docosahexaenoic Acid
GABA	Gamma-Aminobutyric Acid
NOS	Nitric Oxide Synthase
ECM	Extracellular Matrix
TIMPs	Tissue Inhibitors of Metalloproteinases
MMP	Matrix Metalloproteinases
HOCl	Hypochlorous Acid
EZH2	Enhancer of Zeste Homolog 2
ARE	Antioxidant Response Elements
HIFs	Hypoxia Induced Factors

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