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REVIEW

Molecular mechanism of plant stress hormone methyl jasmonate for its anti-inflammatory activity

S.M. Gunjegaonkar [a] and T.S. Shanmugarajan[b]

[a]Department of Pharmacology, JSPM's Charak College of Pharmacy and Research, Pune, Maharashtra, India; [b]School of Pharmaceutical Sciences, Department of Pharmaceutics, Vels Institute of Science, Technology and Advanced Studies, Chennai, Tamil Nadu, India

ABSTRACT

Plant stress hormones (Phytohormones/PTH) are abundantly present in numerous vascular plants. Several classes of plant stress hormones like auxins (AU) & gibberellins (GA), cytokinins (CK), abscisic acid (ABA), ethylene (ET), salicylic acid (SA), jasmonates (JA), brassinosteroids (BR) and strigolactones are synthesized within specialized plant cells. Among them, jasmonate are prominent class of stress hormones involved in survival of plants in stressful conditions. Methyl jasmonate (MeJA) is ester of jasmonic acid is extensively studied for its potential clinical benefits. MeJA is used as an effective antimicrobial agent, food preservative, antioxidant in food and agricultural sectors. The clinical benefits of MeJA have been related to their prominent interactions with inflammatory NF-κB pathways, inhibition of enzymes, gene expression for synthesis of inflammatory mediators, signaling molecules, oxidative stress and modulation of pain perception/nociceptive responses. The objective of the present review is to provide an cohesive relation of MeJA in inflammation with reference to past and recent in-vivo and in-vitro investigations in broad perspectives.

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NF-κB Pathway; methyl jasmonate; anti-inflammatory; antioxidant; inflammatory mediators

Introduction

Researchers have identified several kinds of PTH among them salicylic acid and its congener derivatives were extensively studied and implicated them as a potential therapeutic candidate. The jasmonwate family is an important class of PTH and prominent members are cis-jasmone, jasmonic acid, and MeJA (fatty acid-derived cyclopentanones). Jasmonates are abundant in the plants and regulate plant developmental processes and adaptation to the environmental conditions.[1] The PTH are important for normal growth, flowering, bearing fruit and in defense mechanism. Various cellular responses including cell death are controlled by plant stress hormones. Plants wear and tear injuries and survival in stressful conditions like osmotic shock, UV radiations the PTH are important intracellular signaling mediator and act as natural biotic regulator. Considering the important role of phytohormones in the survival of plants the researchers are keenly interested to screen the potential benefits for human beings with known principle mechanisms.[2] The hormones are important bio-molecules for the survival of plant and human beings considering fundamental basis facts and correlation between human stress hormones and plant stress hormones.[1,3] In agricultural applications, MeJA is used as an effective antimicrobial agent, food preservative, antioxidant. MeJA has proved a significant potential as an anticancer, anti-inflammatory, anti-nociceptive, anti-anxiety, and anti-malarial candidate.[4]

Role of MeJA in plants growth and defence

Jasmonic acid family is essential for the gene upregulation, synthesis, and storage of protein responsible in defence mechanism.[5,6] MeJA is vital in several stages of plant development and act as an intracellular signaling mediator in defense mechanism.[5,7] MeJA shows an vital resistance role against insect/disease and boost plant immune system.[8] The plant overall development and maturation like seed germination, root growth, flowering, fruit ripening/maturation, senescence are under direct regulation of MeJA.[9] MeJA Acts as endogenous antioxidant and compensates biotic/abiotic stress responses produced in the plant. When plants are under stressed condition due to biotic factors like injury/wound/pest/insect/pathogen attack or abiotic like ice storm/extreme drought/extreme raining enhances the release of MeJA. Such attacks are recognized and volatile organic compound (MeJA) are spread to the atmosphere through stomata. These attack messages are recognized by nearby plants through stomata as airborne refluxes and reinforce them to enhance their MeJA production against biotic/abiotic attacks.[6,8] In affected plant MeJA produces its protective effect through various pathways like enhanced production of protease inhibitors against plant predators, the effects of MeJA can range from an unpleasant digestive issue to causing cannibalistic tendencies.[7,8] When MeJA is released within a plant, it causes to produce other compounds known as protease inhibitors. These inhibitors are responsible for the painful effect towards the invaded pathogen. The underlying mechanism is sensing bad taste to pest which leads to starvation and difficulty to survive in affected plants, further extreme cases pest eats their own species. MeJA is responsible for the production of certain chemicals like phytoalexins, nicotine which acts as antimicrobial agents. In certain conditions, MeJA enhances the production of stimulating traumatic resin which acts as a vaccine against insects.[3,4,7] MeJA has effective control against plant-invaded bacteria's.[10]

CONTACT T.S. Shanmugarajan mailshanmuga@gmail.com School of Pharmaceutical Sciences, Department of Pharmaceutics, Vels Institute of Science, Technology and Advanced Studies, Velan Nagar, P. V. Vaithiyalingam Road, Pallavaram, Chennai, Tamil Nadu 600 117, India.

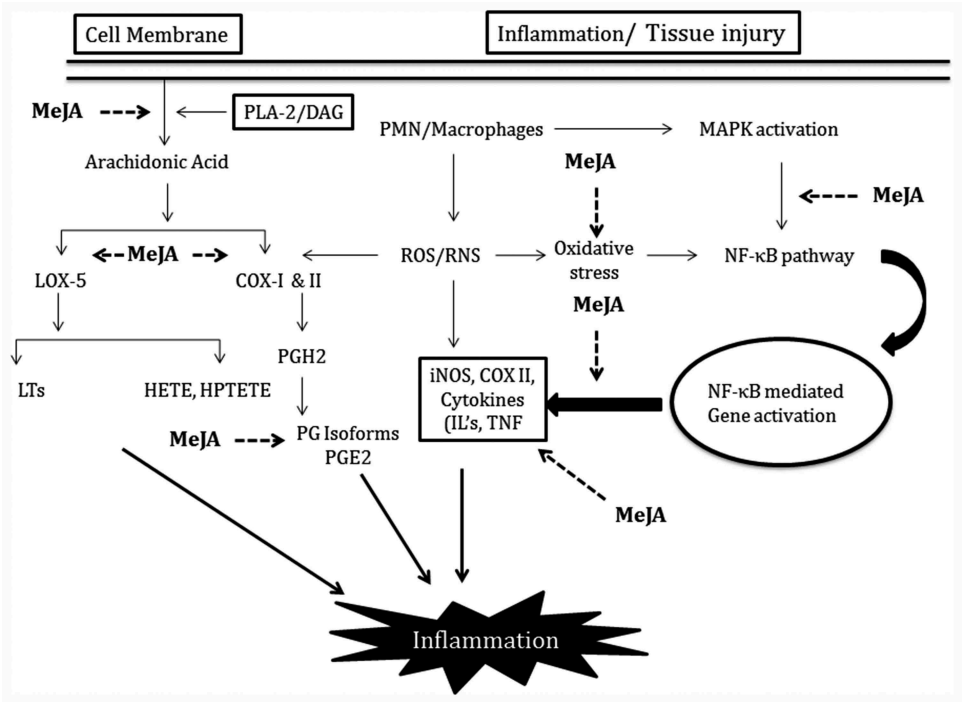

Figure 1. Molecular mechanism of MeJA for anti inflammatory activity.

On inflammation or tissue injury, the endothelial membrane permeability change and migrates immune host cell at the cyte of inflammation or injury. Phospholipids (PLA2 mediated) or diacylglycerol (DG lipase-mediated), later Lipooxygenase (LOX) and cyclooxygenase (COX) act on eicosanoate and synthesis leukotrienes and prostaglandins (PGH2) and PG isomers PGE2 produces inflammation. Mitogen-activated protein kinase (MAPK) activates NF-κB pathway which further translocated to nucleus and enhance the expression of proinflammatory genes for cytokines (IL and TNF-α), iNOS, COX-II. Reactive oxygen species (ROS)/reactive oxygen species (RNS) responsible to enhance activity of COX and increases synthesis of proinflammatory mediators.

Effect of MeJA on inflammatory mediators and cascades

Inhibition of vascular endothelial permeability

Fluid accumulation and occurrence of edema arise due to excessive fluid volume accumulate within cells known as cellular edema or within the cell spaces (interstitial spaces) known as interstitial edema.[11,12] Any damage to tissue or cells initiates inflammatory responses and leads to accumulation of more blood cells/fluid and protein to the area of injury at microscopic circulatory levels.[13] The cascades occur due to change in vascular permeability (blood vessels become leaky) and causes swelling of inflamed area.[14] The mediators like histamine, bradykinin, prostaglandins (PGE2, PGI2), complement fragments (C3a, C5a) acts on the endothelial cell membrane and results in leakage of plasma.[13] The anti-inflammatory activity of MeJA was screened against LPS induced inflammation in rats. LPS (lipopolysaccharides) is comprehensively studied and validated model for induction of injury to neurons, nephrons, lungs, joints, hepatocytes, pancreas, etc.[15] The paw swelling, paw thickness, arthritis index are directly related to the accumulation of edema/swelling and indicate the severity of inflammation.[16,17] The migration of host cells like immune WBC's (white blood cells) are occurred in the edematous fluid and indicator of inflammation by determining the cell count.[18] Recently reported that MeJA decreases the edema (paw thickness, paw volume, arthritis index) and migration of WBCs that indicates its anti-inflammatory effect in experimental animals.[18–21]

Inhibition of eicosanoids

The inflammatory mediators (eicosanoids) are primarily synthesized from arachidonic acid (membrane phospholipid)[22] either from phospholipids (Phospholipase PLA2 mediated) or diacylglycerol (DG lipase-mediated), later lipoxygenase (LOX) and cyclooxygenase (COX) act on eicosanoate and synthesis of leukotrienes and prostaglandins (PGH2) and PG isomers (PGI2, PGF2, PGD2, PGE2) respectively.[23] Among the isoforms of PG's, PGE2 has a protruding role in the cascade of inflammation and produces typical sign and like swelling, redness pain, etc., due to enhanced microvascular permeability of endothelial membrane.[24] PGE2 regulates the functions of various inflammatory cells like macrophages, dendritic cells, Tand B lymphocytes through binding to eicosanoid prostaglandin (EP) receptors. The T and B lymphocytes are contributing to the enhance expression and synthesis of cytokine and are under the indirect control of PGE2.[25] The nociceptive response is a result of PGE2 effect on central and peripheral sensory neurons. Administration of bacterial endotoxin (LPS) results in the development of painful behaviors and enhances nociceptive response to cold and hot stimuli. The nociceptors sense the unwanted noxious painful stimuli which are generated in the case of tissue damage. The C fibers sensory neurons (un-myelinated small-diameter) or Aδ-fiber sensory neurons (medium-diameter thinly myelinated) bear's nociceptors. These sensory neurons are responsible to carry pain signals from peripheral tissues to the central nervous system. The C fiber and Aδ-fiber sensory neurons are present in dorsal root ganglia (DRG)

and trigeminal ganglia (TRG). The axons are extending to the periphery and viscera as well as centrally to the dorsal horn of the spinal cord. The nociceptive information is carried to higher levels of the neuraxis such as the thalamus and cortex. Several inflammatory mediators affect the pain response at multiple points along the neuraxis. The example cytokines can activate DRG neurons and rapidly convey the pain sensation through voltage-gated sodium (VGS) and transient receptor potential (TRP) channels.[25–27] Umukoro et.al 2011, Umukoro S et al. 2016, Gunjegaonkar SM et. al 2018 reported MeJA effect against modulation of pain perception and inflammation in experimental animals in a dose-dependent manner by Inhibiting PGE2. The pain associated nociceptive response was studied and reported in animal models and assessed for nociceptive behaviors like paw cold allodynia, paw thermal hyperalgesia, and tail cold hyperalgesia. The effect of MeJA against LPS induced pain showed a significant decrease in paw withdrawal latency for noxious cold and thermal stimuli induced by LPS. The significant decrease in withdrawal latency can be due to MeJA anti-inflammatory and anti-nociception activity.[27–29]

Inhibition of prostaglandin-endoperoxide synthase

The expression and biosynthesis of prostaglandins from arachidonic acid are essentially depended on the activity of COX and LOX enzymes. In the need of several chronic inflammatory disease treatment researchers have developed an key approach in order to modulate the inflammatory cascade and reported great success in the treatment of inflammatory diseases.[30] Amongst several inflammatory cascade the important one considered as an eicosanoid synthetic pathway. COX causes catalytic transformation of membrane phospholipid arachidonic acid in to the first isoform of prostaglandin H2 in the initial step, furthermore PGH2 transformed in several isoforms of prostaglandins, namely, PGI2, PGF2, PGD2, PGE2.[23] The COX is bifunctional enzyme exists in two forms and expressed as COX-I and COX-II by two different encoded genes. The COX-I is abundant in mammalian cells, endothelial membrane cells, nephron, and platelets and called a housekeeping enzyme whereas COX-II is expressed and induced in pathological conditions by inflammatory stimulation.[31] The inhibitory potential of MeJA on COX has been reported in vitro and in vivo pharmacological models.[19,27,29] The COX II inducible genes are important in the expression of mRNA for the synthesis of Cyclooxygenase II enzyme. It has been reported that MeJA causes downregulation of COX-II inducible gene.[19] A recent investigation showed that the nuclear factor-B (NF-B) is involved in the regulation of COX-2 expression and synthesis.[32] The inhibition of nuclear factor-B (NF-B) pathway might be the underlying molecular mechanism for MeJA anti-inflammatory activity. Lipoxygenases causes the metabolism of arachidonic acid through the addition of oxygen at different catalytic domain prominently contributed by LOX-5. The important end metabolite produced are hydroxyeicosatetraenoic acids (HETEs), leukotrienes (LTs), and lipoxins. Leukotrienes are potent mediators of inflammation and activate several inflammatory cells like, leucocytes, macrophages and promote the synthesis of cytokines, chemokines, and endothelial membrane adhesion molecules.[33] MeJA might act through single or combination of the mechanism via inhibition of arachidonic mechanism or inhibition of COX or LOX, inhibition of PG, Cytokines (IL, TNF) or down-regulation of inflammatory mediator genes.

Inhibition of proinflammatory cytokines

The inflammatory cytokines plays central role in the activation of many cells including immune cells and confirmed that inhibition of cytokines has a greater contribution to the anti-inflammatory effect. Their causative contribution is studied to a greater extent from human and animal experimentations. Cytokines promote catabolic destruction process and disturb the homeostasis of many tissues. The main cytokines involved in pathogenesis and signaling pathways are IL-1β, IL-6, IL-15, IL-17, IL-18, and TNF. Interleukin-1 Beta (IL-1β) is a family of 11 cytokines and IL-1β is an important cytokine involved in pathogenesis and catabolic effect on articular cartilage.[34] It is initially shaped as a cytosolic precursor protein (pro-IL-1β) consisting of 269 amino acid residues. The synthesis of IL-1β is governed by chondrocytes, host immune cells, and synovial cells and have an important role in pain, inflammation and autoimmune conditions. Uncontrolled and enhanced synthesis of IL-1β was found in several diseased states like RA, OA, Inflammatory bowel syndrome, neuropathic pain, etc.[35] The IL-1β stimulates the autocrine synthesis of several interleukin cytokines as well as TNF.[36] In addition, IL-1β is responsible for the expression and synthesis of iNOS (NO), phospholipase A2 (PLA2), COX-2, PGE2.[37] Recently the MeJA potential was screened In Vivo and In vitro for inhibition of IL-1β activity.[19,27,29] The result reported that MeJA has significantly inhibited the activity of IL-1β. Interleukin-6 (IL-6) contains184 amino acids and plays a significant role in the activation of host immune cells. Under the influence of IL-1β and TNFα, the synthesis of IL-6 is carried out by osteoblasts, chondrocytes, macrophages, etc. The IL-6 binds to membrane receptor mIL-6R and the soluble SIL-6R and follows activation of cells. The intracellular signaling involves phosphorylation of tyrosine residues mediated by JAK kinase and phosphorylation of MAPK, and activation of the PI3 K/AKT pathway.[38] IL-6 activates PMN and produces local inflammatory responses acting on the endothelial membrane.[39] Dang HT et al. in his study reported that MeJA inhibits IL-6 synthesis and responsible for anti-inflammatory activity.[19] Interleukin-2 (IL-2) is a member of the γ-chain cytokine family and involved in generating pain hypersensitivity. IL-2R receptors are expressed by DRG neurons and activated by IL-2. Several studies reported that the administration of IL-2 enhances mechanical sensitivity and pain sensation in OA patients.[26] Gunjegaonkar SM et al. 2018 studied the anti-arthritic in vitro activity of MeJA against LPS induced inflammation in chondrocyte cell line CHN 001 and reported that MeJA has significant potential in inhibition of IL-2 synthesis.[27] Tumor Necrosis Factor Alpha (TNFα) is homotrimeric transmembrane protein secreted by the cells in the joint. The cytokine bind and activates two receptors, namely, TNF-R1 and TNF-R2. The intracellular signaling involved in the course of TNF-α is NF-κB, JNK kinase, extracellular regulated kinase (ERK) pathway. TNF prominently acts on endothelial cells and promotes several inflammatory cascades like leukocyte adhesion, enhanced membrane

permeability, and edema. Several studies advocated that blocking of TNF actions is useful in the treatment of RA, OA, Psoriasis and other inflammatory diseases. TNFα induces the production of iNOS, COX-2, and PGE2 synthase and shows a synergize effect with IL-1β.[40,41] Umukoro S et al. 2016, Dang HT et al. 2012, Gunjegaonkar SM et al. 2018 reported that the anti-inflammatory activity of MeJA is contributed by inhibition of TNFα in vivo and in vitro.[19,27,29]

Downregulation of pro-inflammatory gene expression

Several studies advocated that the down-regulation of inflammatory mediators gene have an effective contribution in the treatment of inflammatory conditions. Among several signaling pathways the nuclear factor NF-κB pathway is considered a classical proinflammatory signaling pathway. NF-κB in involved in the expression of proinflammatory genes for cytokines (IL and TNF), chemokines (chemoattractant protein MCP-1 or CCL2), adhesion molecules and also regulates leukocyte recruitment or cell existence.[42,43] NF-κB pathway is also responsible for the regulation of COX-II gene expression and enhancing the synthesis of same.[44] The down-regulation of NF-κB is responsible for MeJA anti-inflammatory activity.[19,29] Inducible nitric oxide synthase (iNOS) enzyme activity is regulated by iNOS genes induced by cytokines. The iNOS is responsible for the synthesis of nitric oxide (NO) which act as a regulatory and pro-inflammatory mediator in inflammatory cascades. Several investigations reported that inhibition expression of iNOS has important consideration in the anti-inflammatory effect.[45] Amyloid proteins are primarily involved in the development of neurodegenerative diseases. It was reported that PGE2 has a role in enhancing the gene amyloid expression and synthesis of amyloid protein plague in the brain. Prostaglandins E2 produced in brain injury or inflammation stimulate the amyloid-mediated neurodegeneration.[46] MeJA causes downregulation of amyloid which was due to inhibition of PGE2 and leads to decrease in associate inflammatory responses.[27,29]

Inhibition of oxidative stress

The ROS are usually eliminated by the host antioxidant enzymes and protect the severe damage to the organ system. The disturb homeostasis between ROS synthesis and antioxidant enzymes results in oxidative stress.[47] The important ROS are hydrogen peroxide, organic hydroperoxides, nitric oxide, superoxide and hydroxyl radicals, etc. Numerous studies advocated that the ROS are the causative factor in the development of inflammations like arthritis, neuritis and cartilage damage.[48] Studies reveals that oxidation of nucleic acid causes cardiovascular, joint, neurological, lung, eye, kidney, liver, pancreatic diseases, etc. To manifest the oxidative stress the human antioxidant system synthesis anti-oxidant enzymes like superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione reductase together with a number of low molecular-weight antioxidants such as ascorbate, α-tocopherol, and glutathione, cysteine, thioredoxin, vitamins, etc.[47,48] In experimental animals administration of LPS causes disturbed host antioxidant system and is inadequate to protect the body from ROS and further if it forms highly reactive radicals.[47] The normal intracellular metabolic reaction in mitochondria and peroxisomes generates oxidants by using several cytosolic enzymes. The external stimuli like pro-inflammatory factors also trigger the synthesis of ROS. The endogenous antioxidant system involves enzymatic control over the generation of ROS by reduced glutathione (GSH), catalase (CAT), superoxide dismutase (SOD) to maintain physiological homeostasis. A low or moderate increase in ROS levels interferes and disturbs the normal physiological process and cellular proliferation however a significant increase in ROS levels leads to serious damage to cellular components. The cell death occurs due to random damage to proteins, DNA and lipid components, etc., due to reactive species. The increase in oxidative stress initiates cellular signaling pathways may have either protective or damaging potential.[49] Inflammatory responses are able to produce ROS in greater amount importantly from host immune cells like macrophages and infiltrating neutrophils.[50] The SOD is present in many cells like neurons, cartilage, liver, etc., and reduced levels of SOD are correlated with inflammatory diseases like OA. The enhanced production of superoxides depletes the stores of SOD and as well as uncontrolled metabolism of superoxide leads to the generation of molecular oxygen and peroxide. Several studies revealed that there is an association between a decrease in extra cellar SOD and arthritis.[51,52] Correlated Anti-inflammatory effect of MeJA is due to restoration of SOD levels,[20] Enhanced memory performance effect of MeJA due to restoration of SOD in brain tissues,[53,54] antipsychotic activity of MeJA and advocate significant increase in levels of SOD in blood,[55] Anti-arthritic and antioxidant activity of MeJA has significant SOD restoration activity and attenuates LPS induced oxidative stress and arthritis.[21] Glutathione is most studied antioxidants and plays central role in detoxification of electrophilic xenobiotics, regulates redox status, signal transduction, mobilization and utilization of amino acid, in host immune response, the proliferation of cells, etc.[56,57] Catalases are responsible to neutralize the hydrogen peroxide. The CAT (heam containing) oxidizes the one H_2O_2 into oxyferryl species whereas the second H_2O_2 is used as a reductant to produce water and oxygen. The catalase inhibits the lipid peroxidation is caused by H_2O_2. Peroxidation of lipids is particularly more important in damaging the cellular component because the formation of lipid peroxidation products leads to a facile propagation of free radical reactions. The initiation of lipid peroxidation of the membrane occurs due to the utilization of H^+ of the polyunsaturated fatty acid (PUFA) moiety of membrane phospholipids. The formed alkyl radicals cause rearrangement and forms conjugated dienes and start cascades of autocatalytic lipid peroxidation.[58] The inflammatory cascades produce reactive oxygen species and their derivatives are involved in several degenerative reactions in a biological system. Several finding showed that MeJA has significantly reduced the oxidative burden, a free radical abundance which is responsible for inflammatory cascades by the restoration of endogenous anti-oxidant enzymes, i.e., catalase, glutathione, superoxide dismutase, etc., the depletion of endogenous antioxidant enzymes creates imbalance and causes ROS mediated cellular damage.[20,21,27,29,53–55,59–62]

Inhibition of peroxidase/serine proteases/elastase

The heme-containing enzyme present in granules of neutrophils known as myeloperoxidase (MPO). MPO catalases and produces ROS in presence of hydrogen peroxide, and halides like bromide, chlorides. The formed reactive species are like hypochlorous have prominent biological effects and affects DNA, proteins, and lipids. The microbial killing through neutrophils is mediated by the MPO/HOCl system. However, MPO generated reactive intermediates can cause tissue damage at sites of inflammation. Targeting the MPO is a new dimension in the treatment of various inflammatory conditions as a local mediator in the tissue damage.[63] Myeloperoxidase assay demonstrates as an index of polymorphonuclear cell infiltration in the synovial tissue joints.[64] LPS induced inflammation in animals showed a significant increase in the activity of MPO and indicates an increase in polymorphonuclear infiltration in the joint tissue. Treatment with MeJA significantly decreases activity of MPO in joint tissues and confirms minimum infiltration of neutrophils as an index of the anti-arthritic activity. A class of proteases enzymes is largely involved in the destruction of cartilage and associated arthritis. The proteases consist of 15 member family and mainly reside in the endosomal/lysosomal compartment and involved in non-specific proteolysis. Several studies revealed that the cathepsin protease family is involved in cartilage degradation and destroys the important components of the ECM of cartilage.[65] They mainly affect articular collagen and have collagenolytic effects.[51] It was confirmed by various researchers that the cysteine cathepsin expression and activity is significantly increased in arthritic patient synovial fluid and synovial membrane.[52,66] LPS treated animals showed a significant increase in levels of cathepsin D. Treatment with MeJA showed a significant decrease in the levels of cathepsin D in articular tissue and shows promising cartilage protective effect. Proteases are important in normal and pathophysiological inflammatory process. Two important proteases are synthesized by many cells are matrix metalloproteinases (MMPs 23), the disintegrin-metalloproteinases (ADAMs 21). The MMP predominantly involved in arthritic pain and inflammatory cascades. Chondrocytes and synovium produce the collagenolytic MMPs (MMP 1, MMP 2, MMP 8, MMP 13, and MMP 14). The main underlying mechanism for arthritis involves degradation of the ECM of cartilage and coordinated by both MMPs and ADAM TSs. The typical essential components of articular cartilage namely proteoglycan, aggrecan, and type II collagen are degraded by proteases. The aggrecan molecule is cleaved at Glu 373/Ala 374 (the 'aggrecanase' site) was identified as the major site of aggrecan degradation in human joint disease. The unclear mechanism is involved in proteolysis at specific sites in the core protein of type II collagen. The exact contribution of MMPs is still not fully elaborated but the activity depends on expression, location, availability for substrated and characteristics of inflammatory disease. Investigation reported broadly that MMP regulates the inflammatory cascades by regulating expression and biosynthesis of inflammatory cytokines, chemokine, and barrier function.[61] Recent study advocated that human chondrocytes The significant reduction was observed in MMP levels in stimulated and MeJA-treated chondrocytes. The MeJA confirms its potential role in cartilage protection against experimentally induced cartilage damage induced by LPS.[27]

In summary, MeJA interacts with NF-κB signaling pathways involved in crucial inflammatory cascades and regulate facets of human innate and adaptive immune responses. NF-κB greatly contribute in expression of various pro-inflammatory mediators including cytokines, chemokines, ROS, RNS, regulates activation of innate immune and T cells and involved in inflammatory diseases like multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, lupus erythematosus, atherosclerosis, diabetes mellitus (type-I), asthma and chronic obstructive pulmonary disease, etc. Inhibition or down regulation of NF-κB signaling pathway, iNOs, and COX-II gene expression will hinder the inflammatory disease progression and pathogenesis. The correlation of stress and inflammation is crucial and involved in the pathogenesis of number of diseases such as cardiovascular, metabolic, psychotic and neurodegenerative disorders, cancer, etc. The potential of natural drug substances has been well studied in several inflammatory diseases however the phytohormones like MeJA may be a prominent alternative candidate to current inflammatory pharmacotherapy and in new drug discovery.

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ORCID

S.M. Gunjegaonkar http://orcid.org/0000-0001-7822-2859

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