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Review

Methyl jasmonate: a phytohormone with potential for the treatment of inflammatory bowel diseases

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Keywords
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Abstract

Objectives The phytohormone methyl jasmonate (MeJA) has been identified as a vital cell regulator in plants. This substance is analogous to eicosanoids and similar to that of anti-inflammatory prostaglandins. In animals and in animal cells, it displayed an efficient neuroprotective, anti-inflammatory and antioxidant action; while in tumoral strains, it demonstrates a potentially highly attractive mechanism of apoptosis induction through various cellular and molecular mechanisms. The aim of the present review was to explore two new hypotheses that explain the action of MeJA, a lipid phytohormone and its potentially anti-apoptotic mechanism for use as a therapeutic target for future treatment of Inflammatory bowel diseases (IBDs).

Key findings Methyl jasmonate is a new candidate for the treatment of IBDs, modulating the expression of the major classes of caspase-type protease families that selectively act on the extrinsic and intrinsic pathways of the apoptotic process. Its action is based on the reduction of the expression in tumour necrosis factor tissue levels and the modulating action of reactive oxygen species production, acting only on the destruction of cells that express the diseased phenotype, and preserving cells that are not transformed.

Conclusions Methyl jasmonate may represent an alternative for the transduction processes of important signals in the cellular renewal of the intestinal mucosa.

Introduction

Inflammatory bowel diseases (IBDs) comprise a number of chronic disorders that can affect the gastrointestinal tract. They include Crohn's disease (CD) and ulcerative colitis (UC), both of which represent a serious health problem in several countries. Their incidence and prevalence rates have increased globally, mainly due to lifestyle, smoking, diets that are high in fat and sugar, the use of certain drugs, stress and high socioeconomic levels. The highest incidence and prevalence of IBDs are found in populations in Northern Europe and North America; in contrast, the prevalence is lower in continental Asia, where UC is the most common form.[1–3]

In general, IBDs are characterized by recurrent chronic and inflammatory conditions in the digestive tract, with an unknown multifactorial aetiology. Clinical, experimental and genetic data suggest that dysfunction in the intestinal mucosal barrier is an exclusive characteristic of IBDs. Restoration of the epithelial barrier homoeostasis could be considered a therapeutics target to improve the health of intestinal tissue, as well as minimizing the impacts of inflammation in pathogenesis of intestinal diseases.[4,5]

The mucosa of the gastrointestinal tract consists of distinct cellular populations such as enterocytes and goblet cells, which act on the secretion of mucus, forming a layer that guarantees supplementary protection. This coating acts as a barrier for luminal antigens and, at the same time, allows the absorption of water and nutrients.[6] The regulation of the life cycle of mucosal epithelial cells varies with the period of the migration of these lineages from the site of origin in the base of the crypts to the ends of the villi to be eliminated for lumen opening.[7]

Immune system cells are also found in the lamina propria, where they act to protect against infection.[6] The mucosal T cells are a type of lymphocyte and play a central

role in cell-mediated immunity. These cells exhibit a type of phenotype characteristic of the activated effector cells, which act in the intestinal mucus via type 1 and 17 T helper cells (Th1 and Th17).[8,9]

In IBDs, the downregulation of the mucosal T cells contributes to a pathogenic state in CD and UC.[10] Apoptosis in the intestinal epithelium should occur in a highly orchestrated manner. When it takes place in excess, this process can augment monolayer permeability and reduce the function of the epithelial barrier. It can cause a type of inflammation, leading to chronification and the appearance of pathologies such as CD and UC.[10,11]

This study will discuss the specialized properties of mucosal T cells in the context of immune homoeostasis, inflammation, oxidative stress and apoptosis. The delicate balance between immune activation and tolerance at the mucosal sites of the T cells is extremely important for maintaining the integrity of the mucosa.[10,12]

The objective of the present review was to explore two new hypotheses proposed to explain the action of MeJA, a lipid phytohormone and its potentially anti-apoptotic mechanism for use as therapeutic target for the future treatment of IBDs affecting the gastrointestinal tract, contributing to the restoration of the epithelial barrier homoeostasis to improve the health of the intestinal tissue.

Pathogenesis of the principals IBDs: clinical symptoms, inflammatory mediators and colorectal cancer

The pathogenesis of IBDs is complex and intrinsically associated with a genetic predisposition. Yet, some dysfunctions related to the environment and/or the epithelial barrier can cause a persistent activation of the immune response of the intestinal mucosa.[6,13] At first, this aggressive immune response was attributed to pathogenesis, but the appearance of a primary defect in the innate intestinal immunity has been considered a new hypothesis for the pathogenic profile of IBDs.[6,14,15]

Although UC and CD are clinically similar, they are recognized as distinct diseases (Figure 1). Environmental factors may play a greater role in the pathogenesis of UC,[6,16] while genetic factors act more forcefully in the case of CD.[17] Clinically, inflammation in UC is continuously distributed in the mucosa and ulcers are restricted to the colon, whereas in CD the pathology is segmental, meaning

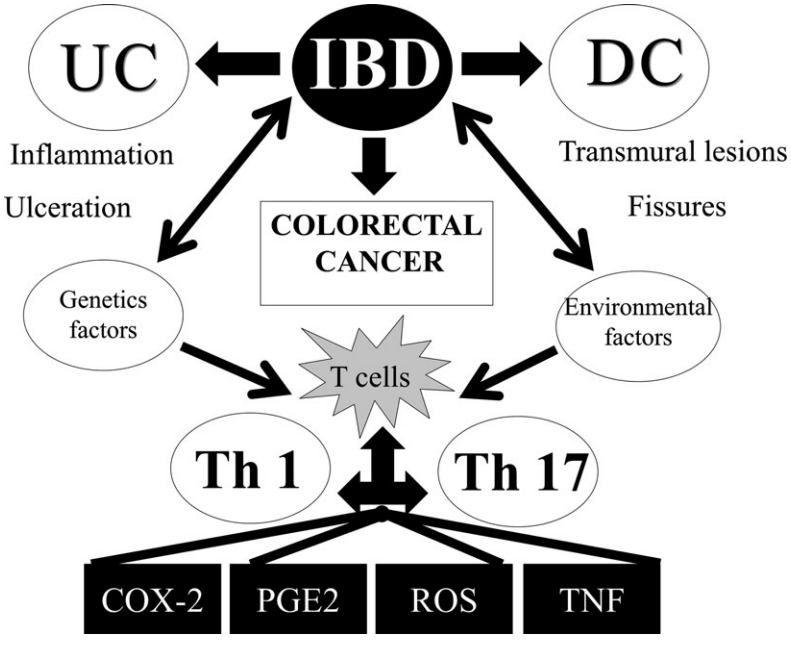

Figure 1 Inflammatory bowel diseases are intimately related to the development of colorectal cancer. An imbalance between genetic and environmental factors results in the dysfunction of the colon epithelial cells and changes in the lamina itself, resulting in the activation and differentiation of healthy T cells for the expression of different cell phenotypes. T helper lymphocyte lines are altered to yield Th1 or Th17 lineages in the tissue microenvironment. Following this inflammatory cascade involving prostanoids derived from arachidonic acids such as COX-2 and PGE2 and proinflammatory cytokines such as tumour necrosis factor are activated. Inflammatory mediators also increase oxidative stress in the microenvironment, corroborating a pathogenic condition characteristic of inflammatory bowel disease. As local inflammation increases, genetic, environmental, oxidant and inflammatory factors are activated as molecular triggers that alter homoeostasis, leading to a pathological state with remission and clinical manifestations. Inflammatory bowel diseases are manifested by two main diseases, with UC clinically characterized by ulcerative and inflammatory sites, and Crohn's disease presenting transmural lesions and fistulas distributed on the colon surface.

that it can affect any transmural region of the gastrointestinal tract.[18,19]

In UC, dysregulations of the immune response in individuals with a genetic predisposition, as well as other factors such as polymorphisms in the interleukin receptor gene and the action of other genes correlated with the inflammatory response, can modulate inflammation in the body and are recognized as the main cause of this disease.[18,19] The segmental-type lesions in CD, meanwhile, are well demarcated and have damaged areas between normal segments. Inflammation can penetrate the entire thickness of the intestinal wall, leading to the formation of deep fissures and the development of fistulas.[8]

The intestinal epithelium is highly polarized and has two discrete regions with one layer of connected cells, forming a columnar-like epithelium on the intestinal surface. The first layer is an apical surface facing the lumen and is specialized for absorption. The second, meanwhile, has a very important role in the immune defences of the bowel wall against hazardous bacteria present in the intestinal lumen. This basolateral surface is in contact with the immune compartment of the underlying lamina, forming two physical compartments that separate the outer lumen of the immune system from the internal host.[4,10]

In the epithelium, enterocytes are linked to the absorption of ions, nutrients, water, vitamins and are also related to the induction of immunological tolerance.[9] Goblet cells represent a lineage of cells scattered throughout the epithelium responsible for secretions like a protective mucus layer, being fundamental to the defence against microorganisms and aiding in the coordination of intestinal functions via hormonal secretions.[7,20]

The differentiation of Th cells into Th1, Th2 or Th17 effector type cell lines depends on the tissue microenvironment, which is generated by the dominant type of cytokines, together with other relevant mechanisms, leading to a cascade of molecular events. These include the time at which the antigen-presenting cell (APC) was activated and other factors that result in the activation of the phenotype to be developed, including antigen affinity and type, T cell receptor (TCR) signalling and the coreceptor signals.[21,22]

Previous data showed us that Th17 cells mainly work to achieve the induction of innate and adaptive host responses and contribute to the host defence against pathogens at mucosal sites.[22,23] Th1 can regulate the work of the neutrophils during the inflammatory process, promoting the re-establishing of the epithelial barrier and allowing a type of symbiotic relationship with the commensal microbiota present in this region, characterizing a dynamic profile in the control against possible invading pathogens.[22]

In patients with IBDs (CD and UC), high levels of arachidonic acid (AA) and its eicosanoid metabolites[24] were observed. Each type of eicosanoid (prostanoid, leukotriene and hydroxyheicosatetraenoic acid) preferably recognizes one or more receptors coupled to one or more signal transduction processes. Modifications in these receptors of the intestinal epithelium alter the control of the processes of proliferation, differentiation and apoptosis, contributing to the development of IBD and colorectal cancer (CRC).[25]

The importance of the cyclooxygenase and lipoxygenase pathways and consequent eicosanoid synthesis for the physiology and pathophysiology of the intestinal epithelium is currently being established.[25] However, previous studies have shown that the production of prostanoids, specifically COX-2, is increased in the affected areas in the colonic epithelium.[26] In addition to COX-2, increased prostaglandin E2 (PGE2) contributes to the inflammatory development of T cells with altered phenotypes, favouring the production of Th1 and Th17 proinflammatory lines.[24]

Alterations in the intestinal epithelial barrier modify the control of the immune response, stopping intestinal absorption and secretion and altering epithelial homoeostasis, during which it may cause the development of IBDs and colorectal cancer (CRC).[25] In this sense, the association of COX-2 and PGE-2 with other proinflammatory mediators such as TNFα, NFκB, TGFβ contributes significantly to the development of colorectal cancer in patients with IBD.[27]

The disturbance in intestinal homoeostasis leads to the development and perpetuation of the inflammatory cascade in IBD.[28] As inflammation is related to the formation of reactive intermediates such as reactive oxygen and nitrogen species (ROS/RNS), oxidative stress has been proposed as a mechanism that underlies the pathophysiology of IBD. Much evidence suggests that IBD is associated with an imbalance between increased ROS and decreased antioxidant activity, expressing clinical pathophysiological features in both CD and UC patients.[28,29]

The Jasmonates family and methyl jasmonate

Jasmonates are important cell regulators that are involved in a number of processes in plant growth, and act in defence mechanisms in response to injuries caused by insects or other pathogens or by environmental stress.[30] They activate an intra-cellular signalling mechanism as a defence in response to damage caused by environmental injuries or aggression, such as ultraviolet radiation and osmotic shock.[31,32]

The jasmonate family comprises three classes of constituents: *Cis-jasmone* (CJ), *Jasmonic acid* (JA) and *Methyl Jasmonate* (MeJA), which are abundantly distributed in all plants and regulate various processes of growth and adaptation to the environment.[31] MeJA is a derivative of

jasmonic acid (JA), formed from an enzymatic methylation pathway, involving the action of the carboxyl methyltransferase enzyme (CMT).[30]

In 1962, a compound with the characteristics of Jasmonic Acid Methyl Ester (JAME) was isolated for the first time from the essential oil of jasmine (*Jasminum grandiflorum*) and rosemary (*Rosmarinus officianalis*).[33–35] Nine years later, JA was isolated from the culture of the *Lasiodiplodia theobromae* fungus.[36] The characterization of the first physiological effects of free JA isolated from JAME began in 1980, with studies related to senescence and the role of growth inhibitors.[37,38]

Jasmonates are oxygenated fatty acids derived from linolenic acid.[39] The biosynthesis pathway of jasmonates is analogous to the biosynthesis of eicosanoids in animal cells. In animals, these molecules are synthesized from arachidonic acid, whereas in plants, synthesis occurs via linolenic acid, which is the main source of jasmonates.[40,41] Structurally, the biosynthesis pathway of jasmonates, being analogous to eicosanoids, is similar to that of anti-inflammatory prostaglandins in animals.[30]

The phytohormone MeJA has been characterized as a vital cellular regulator involved in a number of dynamic processes, linked to the development of active responses in the defence against biotic and abiotic stresses.[31,42] It is also active in processes closely linked to oxidative stress, regulating the activity of antioxidant enzymes.[43]

Some plants contain relatively high levels of circulating MeJA: the olive tree, species of the *Jasminum* genus, the orchid *Cymbidium goeringii*, the tuberose (*Polianthes tuberosa*), Chloranthus spicatus, Ginger, *Boronia megastigma*, honeysuckle (*Lonicera japonica*), Artemisia tridentate and rosemary (*Rosmarinus officinalis*).[44]

Stress-related hormones in plants are activators of cellular responses, including cell death in some stress situations. It is known that JA induces cell death in several lineages of cancer cells, such as lymphoblastic leukaemia, in a manner that does not affect normal human lymphocytes.[45] MeJA is selectively toxic for cancer cells,[46–48] without affecting normal cells, inducing apoptosis by several mechanisms[49] and even exhibiting major antiproliferative potential.[50]

Jasmonates have proven anti-inflammatory effects, an action that is attributed to the inhibition of the release of inflammatory mediators[40] and antioxidants.[51–54] Previous studies have shown that the use of MeJA as a model of prostaglandin induces significant anti-inflammatory effects, inhibiting the production and gene expression of mediators of proinflammatory cytokines, nitric oxide (NO) and the interleukins IL-1β and IL-6, as well as tumour necrosis factor (TNF) in murine macrophages,[40,55] it also exhibits neuroprotective activity.[52]

Intestinal apoptosis

The intestinal epithelial layer is renewed every 2–3 days, establishing an important balance in the proliferation of epithelial cells in the crypts, villus cell migration in the small intestine or on the surface of the colon where enterocyte shedding will occur, regulating cell death process. The epithelium lies between the immune cells in the lamina propria and the microbiota in the gut lumen and communicates with both. In the case of occasional defects in this process, the epithelium can contribute to the beginning of the establishing of IBD, the abnormal immune responses in the intestinal mucosa could be a key event in the pathogenesis/immunopathogenesis of this disease.[56,57]

Apoptosis can be considered an important regulatory pathway of programmed cell death, as it is the most highly regulated process whereby cells undergo biochemical and morphological changes. This process is therefore called programmed cell death and downregulated by families of proteins called caspases, which when activated play an important role in regulating the process. The molecular mechanisms that establish the mode of action or activation of these proteins are still not fully understood, however.[10,58,59]

In the apoptosis process, biochemical and morphological changes control a cascade of events. First, a condensation of the chromatin occurs, followed by cell shrinkage. Subsequently, the nucleus and the DNA begin to fragment in an endonuclease catalysed reaction. In this regulatory step, the surface of the cell transforms, and the division of the cell in apoptosis is complete.[45,59]

For UC and CD, the apoptotic process occurs naturally and is considered normal in cells, which have some specific differences. The epithelial cells move from the crypts, migrating to the cell surface, and when they are installed, initiate apoptosis. Subsequently, two different pathways can be followed, either to the intestinal lumen or phagocytosed by the action of macrophages. In the inflammatory process, mature apoptotic T-cells signal to effector T cells during the clonal expansion process, avoiding chronic inflammation. A possible dysregulation of the apoptotic process in the immune system may affect the survival of T cells, mainly, altering innate immune and adaptive immune responses in the intestinal mucosa.[10,58,60]

Tumour necrosis factor, the TNF-related apoptosis inducing ligand (TRAIL) and the Fas ligand (FasL) act as potential precursors in the activation of necroptosis, which can be further modulated by a protease family, known as caspases, which are active in more specific processes, such as chromatin condensation. Their functions include the reduction of cell volume and nuclear fragmentation,

stimulating the formation of bubbles in the plasma membrane, promoting changes in cell morphology and decreasing nuclear content, but without extravasation to the microenvironment.[20,59,61]

The extrinsic apoptotic pathway is known as a cell death receptor activation pathway, where a ligand–receptor type interaction occurs, stimulating the formation of a destruction complex with the integrated action of cellular proteins activated by TNF, TRAIL and FasL, promoting the catalytic activation of caspase 8, considered a central protease and the main mediator of the extrinsic pathway.[20,59]

The intrinsic pathway is activated upon activation of the p53 gene, known as the 'guardian of the genome'. This gene regulates the Bcl-2 family after detecting DNA damage. The p53 gene triggers cell death via a cascade with both pre- and pro-apoptotic domains. These domains modulate the catalytic activity of caspase 9 and could be considered the central mediating proteases of the intrinsic pathway.[20]

The integrated or isolated activation of the extrinsic (caspase 8) and intrinsic (caspase 9) pathways can establish the activation of other caspase families (3, 6 and 7). The activation of these other families favours a process of cleavage in relation to other proteins and, concurrently, potentiates the possible advance of the state of cellular destruction, originating apoptotic bodies.[20]

In these IBDs, the location of the apoptotic cells has some peculiarities, such as in the spontaneous apoptotic process, which is independent of the activation of the p53 gene, and has as its main objective the homoeostatic maintenance of stem cells. It occurs only in the region of the stem cells in the small intestine, being very rarely observed in the crypts of the colon and widely distributed along the length of the crypt. In contrast, the Bcl-2 family of proteins is not widely expressed in the small intestine, being more densely expressed at the base of the colonic crypts.[62,63] The proliferative zone of the intestinal epithelial cells is located in the lower regions of the crypts. This region corresponds to the epithelial crypts, where the apoptosis process takes place.[64]

A notable apoptotic expansion in the epithelial crypt cells is visible during UC and CD. In-vitro and in-vivo assays have described this occurrence, suggesting that TNF represents an important modulator of the pathways in which it acts, inducing programmed cell death in the epithelial crypt cells. However, other studies have shown that the p53 gene is an important mediator of growth, apoptosis and cellular senescence as well as an apoptotic mediator in the colonic crypt during colitis, suggesting that signals originating from the TNF, either through tumour necrosis factor receptor 1 (TNFR1) or tumour necrosis factor receptor 2 (TNFR-2), are responsible for the stimulation of the inducible nitric oxide synthase (iNOS) enzyme mediated by the p53-dependent apoptosis of intestinal epithelial cells in the crypts.[64,65]

MeJA: a potential phytohormone for anti-TNF therapy in the treatment of IBDs

Inflammatory bowel diseases are characterized by an excessive number of apoptosis in the epithelial crypt, ulcerations, distorted crypt architecture and diarrhoea accompanied by bleeding. Another significant feature of IBDs is the large-scale expression of TNF in the mucosa. Therapy using anti-TNF antibodies contributes to patient improvement, as they reduce diarrhoea, intestinal bleeding, weight loss and act to promote healing of the mucosa, inducing a rapid re-epithelialization of the ulcerated surfaces. Previous studies have shown that other anti-TNF agents can induce apoptosis in cells of the lamina itself.[64]

Recent studies have demonstrated that there is a strong interaction between autophagy/apoptosis, the detection of microbes and an increase in the expression of the endoplasmic reticulum in the intestinal epithelium, contributing to the pathogenesis of IBDs. In this sense, necroptosis therefore would be associated with the activation of the TNF receptors. All these mechanisms could be present in Crohn's disease and in other animal models that mimic intestinal inflammation.[64] The mechanism of action reveals that anti-TNF therapy involves the homoeostatic regulation of apoptosis in mucosal cells.[66]

In Hep3B-type cancer cell lineages treated with a synthetic derivative of MeJA, apoptosis was mediated via the signalling cascade, cell death receptors and the extrinsic pathway as well as by the action of the mitochondria associated with the activation of protein kinases. This treatment induced the expression of the Bax/Bcl-2 proteins related to the cell death receptor, as well as the downregulation of the IAP (the inhibitor of apoptosis proteins) and caspase 8 families, and also the negative regulation of the caspase 3 and 9 families.[67]

In the human breast MCF-7 and MDA-MB-435 cells, MeJA inhibited long-term proliferation and demonstrated G0/G1 and S-phase arrest with an increasing apoptotic population. The extrinsic apoptotic pathway increased the expression of TNFR1 and the activation of caspase 8 and activated caspase 3 in breast cancer cells, and also resulted in the further activation of the intrinsic apoptotic pathways.[68]

In hormone-independent human prostate PC-3 and DU 145 cancer cells, MeJA treatment resulted in the activation of Tumor Necrosis Factor Receptor 1 (TNFR1) and caspase, inhibited cell growth, induced cell cycle arrest and apoptosis.[69] In radiation-induced human prostate cancer lines (PC-3), MeJA suppressed the expression of the Bcl-2

anti-apoptotic protein family and increased caspase 3 activity.[70]

In this sense, MeJA and its analogues have the potential to inhibit TNF production in murine macrophage[40] and HCAT keratinocyte cells.[71] To date, in clinical practice, only antibody therapy has been found to be an efficient method of neutralizing the effects of TNF in patients with chronic inflammatory conditions such as IBDs.[72]

The first hypothesis is based on the possible therapeutic potential of MeJA in the modulation of IBDs, suggesting an anti-regulatory mechanism, based on the reduction of the expression of TNF tissue levels, minimizing apoptosis in the intestinal crypts with a direct effect on the apoptotic extrinsic pathway. TNF acts as a major pro-inflammatory cytokine in pathway signalling.

Thus, it is believed that MeJA can act integrally in the intrinsic pathway, as in cancerous cell lineages it altered the expression profile of the Bcl-2 proteins. Thus, MeJA could be a new candidate for pharmacological targeting in the treatment of IBDs, modulating the expression of caspase 9 (extrinsic pathway) by promoting a decrease in TNF expression and interfering with caspase 8 expression directly by maintaining the expression of the Bcl-2 proteins. Thus, a potential effect of MeJA as a blocker of the extrinsic pathway, as well as in the intestinal apoptotic intrinsic pathway, could direct the negative regulation of the gene expression of superfamilies of type 3, 6 and 7 caspases, thus, altering the tissue expression of type 8 and 9 caspase families (Figure 2).

MeJA: the possible modulating action of ROS production and maintenance of intestinal apoptosis

The mechanisms related to the apoptotic process promoted by the action of MeJA are still unknown, but it is understood that MeJA disrupts the cell cycle, even though the apoptosis is restricted and selective to cancer cells. However, the underlying mechanism of MeJA-induced apoptosis remains unclear. Its effects on the induction of p53-dependent and p53-independent apoptosis, which further modulates the production of ROS (reactive oxygen species) and results in low toxicity effects, are already established.[73]

In the treatment of cancer cell lineages causing an Ehrlich tumour (breast cancer), a type of synthetic derivative of MeJA demonstrated low anti-angiogenic and inhibitory activity for the growth of tumour cells.[74] In gastric cancer cells (SGC-7901 and MKN-45 cells lines), MeJA was able to decrease the expression of MMP-14 (matrix-14 metalloproteinases) that act in the degradation of the extracellular matrix (ECM), like a pericellular collagenase, allowing the remodeling of the ECM, aiding tumour invasion and promoting the onset of lymph node metastases. MeJA allowed cell migration and invasion inhibition and also inhibited angiogenesis.[48]

Specific enzymes produced by cancer cells and activated by certain signals, such as matrix metalloproteinases (MMPs), have been described as degrading ECM and are associated with the progression of gastric cancer.[75,76] The

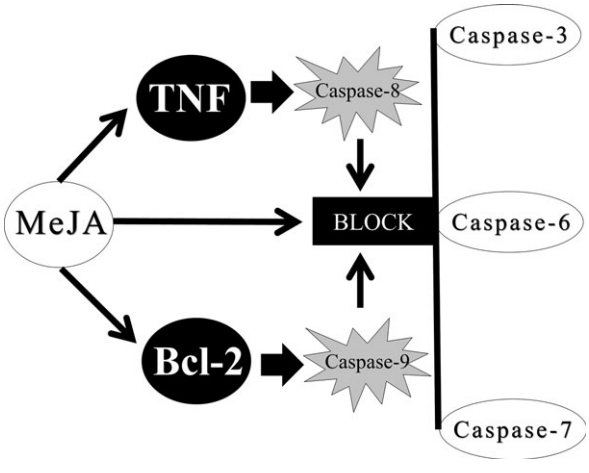

Figure 2 The hypothetical mechanism of methyl jasmonate as a therapeutic and pharmacological target in the treatment of inflammatory bowel diseases, blocking two apoptotic pathways. In the extrinsic pathway of the apoptotic process, methyl jasmonate altered the expression of tumour necrosis factor levels, blocking the expression of the caspase 8 family. In the intrinsic pathway of apoptosis, methyl jasmonate regulated Bcl-2 proteins, inhibiting the expression of the caspase 9 family. Blocking the extrinsic and intrinsic pathways would also block caspase 3, 6 and 7 families, which are dependent on the molecular signalling mediated by both pathways, thus altering the apoptotic profile of the intestinal epithelial cells, especially during migration and proliferation in the crypts.

MMP-14 is involved in the invasion of tumours and metastases, allowing cancer cells to remodel and penetrate the ECM,[48] evidencing the strong connection between MMP-14 expression and the progression of cancer.[48,77]

Methyl jasmonate is known to have great potential for reducing apoptosis. In human lung adenocarcinoma cells (lineage A549), it was involved in the production of ROS and induced an increase in the expression of pro-apoptotic members of the Bcl-2 family. Through the catalase enzyme, it was found that MeJA, despite increasing expression, did not induce changes in the members of the Bcl-2 family. In this sense, the induction of apoptosis in the A549 cell line promoted by the action of MeJA appears to be mediated by a cascade, which involves the generation of hydrogen peroxide, in addition to an increase in the expression of pro-apoptotic members of the Bcl-2 protein family and the induction of mitochondrial-mediated apoptosis via activation of the caspase 9 and 3 superfamilies.[48,78]

In prostate cancer cell lines (U145 and PC-3) and proximal tubular epithelial cells (HK-2), a cellular inhibitory effect was observed only on the growth of the cancerous lineages, while the development of the proximal tubular cells was not inhibited. The action of MeJA altered the mitochondrial morphology, leading to the release of cytochrome c, as well as transforming and activating the families of caspase 9 and caspase 3.[79]

Anticancer activity against human lung A549 cells and HL-60 leukaemia cells was evaluated using fruit extracts of blackberries treated with MeJA. The results showed enhanced inhibition of A549 cell and HL-60 cell proliferation and induced the apoptosis of HL-60 cells.[51]

In C6 glioma cell lineages, MeJA induced the expression of the heat shock protein (HSP72) via thermal shock factor I. It also induced the production of hydrogen peroxide, superoxide ions and mitochondrial ROS, showing that the different MeJA activity in cancer cell lineages can be mediated via ROS.[80] In assays using hepatocellular carcinoma cells (HepG2 lineage), apoptosis was induced by combining a MeJA analogue with TRAIL (TNF-related apoptosis inducing ligand receptors). The effect of this combination triggered the down-regulation of Bcl-X as well as the activation of a ROS-mediated caspase signalling cascade.[81]

In human myeloid leukaemia cells, the MeJA-induced gene expression profile resembles IPA (isopentenyladenine) and is very effective at inducing cell differentiation when using HL-60 myelomonocytic lineages. The gene expression profile associated with the exposure of cell lines to MeJA was verified using cDNA microarray, which revealed similarities to IPA, suggesting that both inducers share many common transduction systems for inducing the differentiation of leukaemia cells, stimulating both the morphological and functional differentiation of freshly isolated leukaemia cells from patients with haematological malignancies.[82]

In different uterine cancer strains (HeLa and CaSki), MeJA induced apoptosis by elevating the mitochondrial superoxide anion levels. Although changes in p53 and Bax expression varied, MeJA promoted the negative regulation of survivin in uterine cancer cell lineages, a protein involved in the inhibition of apoptosis.[50]

Methyl jasmonate exhibits target specificity when binding to hexokinase, the initial glycolytic pathway enzyme, disrupting its association with the anionic voltage-dependent channel (CAVD), causing an energy deficiency and promoting the release of cytochrome c from the mitochondria, triggering apoptosis in cancer cells.[44] In cells of patients with chronic myeloid leukaemia (CML), MeJA induced the release of cytochrome c and mitochondria, cell swelling and cell membrane depolarization only in Hep3B hepatoma cells, without altering mitochondria isolated from untransformed 3T3 cells.[83]

In the second hypothesis, it is believed that MeJA represents a new alternative for the treatment of IBDs, as it acts only on the destruction of cells that express the diseased phenotype and preserves cells that are not transformed. This signalling may occur via the transduction of signals, inducing morphological and functional differentiations in the cells, altering ECM composition and transforming angiogenesis.

It is also believed that MeJA may assist in the process of cell renewal of the intestinal mucosa, assisting in the cell cycle process of the transformed cells via apoptotic pathways triggered by the induction of mitochondrial ROS, negatively regulating the expression of protein families that are important for the modulation of the apoptotic process. It acts principally in the regulation of the Bcl-2 protein family, which are important in the activation of the caspase 3 and 9 families (Table 1).

Conclusion

The restoration and cell renewal of the intestinal mucosa maintains the integrity and homoeostasis of the epithelial barrier and could be considered a therapeutic target for improving the health of the intestinal tissue using synthetic substances.

As well as synthetic drugs, phytormones or other natural products such as MeJA and its derivatives have displayed potential for the reduction of inflammation and oxidative damage impact in the pathogenesis of intestinal diseases, including most of those with IBD profiles.

Due to its anti-apoptotic potential, the lipid phytohormone MeJA represents a new therapeutic target for the treatment of inflammatory bowel diseases. It acts effectively on the regulation of the gene expression of the extrinsic and intrinsic pathways of the superfamily of caspase-type proteases, eliminating only cells expressing a diseased phenotype, and preserving untransformed and healthy cells.

Table 1 In-vitro or ex-vivo studies on the antitumoral activity of methyl jasmonate or synthetic derivative

MeJA or synthetic derivative (dose/concentration)	Activity measured	Assay (*in vitro* or *in vivo*)	Experimental results	Conclusion	Reference
0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 mM of MeJA	Antitumor activity	EL-4 (mouse T lymphoma cell line). *in vivo*; LNCaP cell (androgen-responsive human prostate adenocarcinoma), MCF7 cell line (Human breast carcinoma), Molt-4 is a human T lymphoblastic leukaemia cell line, SK-28 (human melanoma cells) *in vitro*	MeJA induced apoptotic death and elevation of caspase 3 activity. Mice bearing EL-4 lymphoma, survived for longer periods of time after the treatment than untreated mice	MeJA induced death in each of the cell lines.	[45]
0.25; 0.5; 1.0; 1.5; 2.0 and 2.5 mM of MeJA	Antitumor activity	Two clones of murine B-lymphoma cells (wild-type (wt) p53 and Mutated type p53) *in vitro*	Each MeJA was equally cytotoxic and induced a rapid depletion of ATP by compromising oxidative phosphorylation in the mitochondria in both clones, mostly leading to apoptotic death in the wt p53-expressing cells	MeJA can circumvent the resistance of mutant p53-expressing cells towards chemotherapy by inducing non-apoptotic cell death	[46]
0.5; 0.75, 1.5 and 3,0 mM of MeJA	Antitumor activity	Human bladder cancer cell lines T24 and BIU-87 *in vitro*	In a xenograft mouse model of human bladder carcinoma, the combination of GA and MJ exerted increased antitumour activity compared with gamboic acid (GA) alone	MeJA enhanced GA-induced activation of caspase 3 and caspase 9, and downregulated the expression of XIAP	[47]
0.05; 0.01 and 0.2 mM of MeJA	Antitumor activity	Human gastric cancer/SGC-7901 and MKN-45 cells lines) *in vitro*	MeJA attenuates the migration, invasion and angiogenesis of gastric cancer cells in a time- and dose-dependent manner, with downregulation of matrix metalloproteinase 14 (MMP-14)	MeJA was able to decrease the expression of MMP-14, allowing the remodeling of the ECM, aiding tumour invasion and promoting the onset of lymph node metastases, and also inhibited angiogenesis	[48]
1 and 2 mM of MeJA	Antitumor activity	CaSki, SiHa, HeLa, C33A cervical carcinoma cell lines *in vitro*	MeJA induced apoptosis by elevating the mitochondrial superoxide anion levels in different uterine cancer strains (HeLa and CaSki)	MeJA promoted the negative regulation of survivin protein involved in the inhibition of apoptosis in uterine cancer cell lineages	[50]
Fruit extracts of blackberries treated with MeJa (0.01 and 0.1 mM)	Antitumor activity	Human lung A549 cells and HL-60 leukaemia cells *in vitro*	The MeJA treatment significantly enhanced the content of flavonoids, antioxidant capacities and the inhibition of cancerous lines	The results showed enhanced inhibition of A549 cell and HL-60 cell proliferation and induced the apoptosis of HL-60 cells	[51]
50 μM of J-7 ([methyl 5-chloro-4,5-didehydrojasmonate] (7))	Antitumor activity	Human hepatoma Hep3B cells *in vitro*	J-7 induced the expression of the Bax/Bcl-2 proteins related to the cell death receptor, as well as down-regulation of the IAP (inhibitor of apoptosis proteins) and caspase 8 families, and also the negative regulation of the caspase 3 and 9 families	The apoptosis was mediated via the signalling cascade, cell death receptors, the extrinsic pathway and also by the action of the mitochondria associated with the activation of protein kinases	[67]

Table 1 (*Continued*)

MeJA or synthetic derivative (dose/concentration)	Activity measured	Assay (*in vitro* or *in vivo*)	Experimental results	Conclusion	Reference
0.5 and 3 mM of MeJA	Antitumor activity	Human breast MCF-7 and MDA-MB-435 cells *in vitro*	MeJA inhibited long-term proliferation, exhibited G0/G1 and S-phase arrest with increased apoptotic population. In the extrinsic apoptotic pathway it increased expression of TNFR1 and activation of caspase 8 and activated caspase 3 in breast cancer cells	Activation of the extrinsic and intrinsic apoptotic pathways	[68]
2 mM of MeJA	Antitumor activity	Hormone-independent human prostate PC-3 and DU 145 cancer cells *in vitro*	MeJA treatment resulted in Tumour Necrosis Factor Receptor 1 (TNFR1) activation and caspase 3 activation	MeJA promoted inhibited cell growth, induced cell cycle arrest and apoptosis	[69]
0.5; 1.0 and 2.0 mM of MeJA	Antitumor activity	Human prostate adenocarcinoma cell line (PC-3) *in vitro*	MeJA suppressed the expression of the Bcl-2 anti-apoptotic protein family and increased caspase 3 activity	Modulation of Bcl-2 and caspase 3	[70]
0.4; 0.8 and 1.6 mM of MeJA	Antitumor activity	Human NSCLC (non-small cell lung cancer): A549/CTRL,A549/CFLAR, H157/CTRL, H157/CFLAR and U87-MG-EGFP-MAP1LC3B (*in vitro)*	MeJA induced apoptosis via the DDIT3-TNFRSF10B-CASP pathway and induced pro-apoptotic autophagy in NSCLC cells. MeJA induced pro-apoptotic autophagy in NSCLC cells by triggering the ROS pathway	MJ inhibited cell proliferation and induced apoptosis via TNFRSF10B upregulation human NSCLC	[73]
MeJA	Antitumor activity	Human lung adenocarcinoma cells/ lineage A549 *in vitro*	MeJA promoted the induction of apoptosis in the A549 cell line involving the generation of hydrogen peroxide, in addition to increasing the expression of pro-apoptotic members of the Bcl-2 protein family and the induction of mitochondrial-mediated apoptosis via activation of the caspase 9 and 3 superfamilies	In lineage A549, MeJA was involved in the production of ROS and induced an increase in the expression of pro-apoptotic members of the Bcl-2 family	[78]
2,5; 5 and 10 mg/kg of MJ (methyl dihydrojasmonate)	Antitumor activity	Ehrlich tumour cells (*in vivo* by weekly subcultures in mice)	Antiangiogenic effects	In-vivo antitumor activity, MJ revealed that the effect of the MeJA was comparable to DOX (doxorubicin) positive control effect by inhibiting tumour growth and killing tumour cells	[74]
1 mol/l of MeJA	Antitumor activity	Human prostate carcinoma cells DU145, PC-3 and human proximal tubular epithelial cells HK-2 *in vivo*	MeJA treatment promoted a cellular inhibitory effect which was observed only on the growth of the cancerous lineages, while the development of the proximal tubular cells was not inhibited	The treatment altered the mitochondrial morphology, leading to the release of cytochrome c, as well as transforming and activating the families of caspase 9 and caspase 3	[79]

Table 1 (*Continued*)

MeJA or synthetic derivative (dose/concentration)	Activity measured	Assay (*in vitro* or *in vivo*)	Experimental results	Conclusion	Reference
MeJA	Antitumor activity	Human C6 glioma cells *in vitro*	MeJA induced the production of hydrogen peroxide, superoxide ions and mitochondrial ROS and also, the expression of the heat shock protein (HSP72) via thermal shock factor I	The results showed that the different MeJA activity in cancer cell lineages can be mediated via ROS	[80]
0, 10, 25 and 50 μM of J7 (methyl 5-chloro-4,5-didehydrojasmonate (7))	Antitumor activity	Human hepatocarcinoma cells (HepG2) *in vitro*	Apoptosis was induced by combining a MeJA analogue with TRAIL (TNF-related apoptosis inducing ligand receptors). The effect of this combination triggered the down-regulation of Bcl-X as well as the activation of a ROS-mediated caspase signalling cascade	The effect of this combination triggered the down-regulation of Bcl-X as well as the activation of a ROS-mediated caspase signalling cascade	[81]
0.15 and 0.4 mM of MeJA	Antitumor activity	Human myeloid leukaemia (HL-60 cell line) *in vitro*	MeJA induced gene expression profile resembled IPA (isopentenyladenine) and was very effective at inducing cell differentiation when using HL-60 myelomonocytic lineages	The gene expression revealed similarities between MeJA and IPA, suggesting that both inducers share many common transduction systems for inducing the differentiation of leukaemia cells, stimulating both the morphological and functional differentiation of leukaemia cells	[82]
10, 20, 30 and 40 μM of two enantiomers of DDHJ (Methyl 4,5-didehydrojasmonate)	Antitumor activity	Human myeloid leukaemia (HL-60 cell line) *in vitro*	DDHJ was around 30 times more potent than MJ and the natural form of the stereoisomer was more efficient than the unnatural isomer	Jasmonate derivatives may be promising therapeutic agents for differentiation therapy of leukaemia	[82]
1, 2 mmol/l of MeJA	Antitumor activity	Human Hep 3B hepatoma cells and 3T3 is a human fibroblast immortal	MeJA induced the release of cytochrome c and mitochondria, cell swelling and cell membrane depolarization only in Hep3B hepatoma cells, without altering mitochondria isolated from untransformed 3T3 cells	Jasmonates act directly on mitochondria derived from cancer cells	[83]

It can also modulate signal transduction processes during the cell renewal of the intestinal mucosa and assist in the cell cycle process of transformed cells in UC and DC.

Declarations

Conflicts of interest

The Authors declare that they have no competing interests related to this work.

Ethical approval

The study had no ethical approval requirements.

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