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Celastrol and its Role in Chronic Diseases

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Abstract

Celastrol, a triterpenoid derived from traditional Chinese medicinal plants, has anti-inflammatory, anti-oxidant, and anti-cancer activities. Celastrol has shown preventive/therapeutic effects in experimental models of several chronic diseases. These include chronic inflammatory and autoimmune diseases (e.g., rheumatoid arthritis, multiple sclerosis, systemic lupus erythematous, inflammatory bowel disease, and psoriasis), neurodegenerative disorders (e.g., Alzheimer's disease, Parkinson's disease, and Amyotrophic lateral sclerosis), atherosclerosis, obesity, Type 2 diabetes, and cancer. Celastrol modulates intricate cellular pathways and networks associated with disease pathology, and it interrupts or redirects the aberrant cellular and molecular events so as to limit disease progression and to facilitate recovery, where feasible. The major cell signaling pathways modulated by celastrol include the NF-kB pathway, MAPK pathway, JAK/STAT pathway, PI3K/Akt/mTOR pathway, and anti-oxidant defense mechanisms. Furthermore, celastrol modulates cell proliferation, apoptosis, proteasome activity, heat-shock protein responses, innate and adaptive immune responses, angiogenesis, and bone remodeling. Current understanding of the mechanisms of action of celastrol and information about its disease-modulating activities in experimental models have set the stage for testing celastrol in clinical studies as a therapeutic agent for several chronic human diseases.

Keywords

Celastrol; Inflammation; Autoimmune diseases; Neurodegenerative diseases; Metabolic disorders; Immune modulation; Natural products; Traditional Chinese medicine

INTRODUCTION

Celastrol is a bioactive component of several traditional Chinese medicinal plants including *Tripterygium wilfordii* (Thunder God Vine), *Celastrus orbiculatus*, *Celastrus aculeatus Celastrus reglii, Celastrus scandens,* and others that belong to the Celastraceae family [1–5]. The extracts of the root, bark and stem of some of these plants have long been used in China and other Asian countries for the treatment of a wide range of chronic inflammatory

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disorders, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and allergies [1–5]. In this article, we describe the diverse molecular and cellular pathways modulated by celastrol, with emphasis on chronic inflammatory, autoimmune, neurodegenerative, and metabolic diseases [6–12]. Celastrol also possesses anti-cancer activity [13–15,5]. A summary of the anti-cancer mechanisms employed by celastrol is also presented at the end.

PHYSICO-CHEMICAL PROPERTIES OF CELASTROL

Celastrol is a pentacyclic triterpene (Figure 1) that belongs to a small class of organic compounds called quinone methides. It has a molecular weight of 450.6 and its molecular formula is $C_{29}H_{38}O_4$. It is a pale brown to orange red crystalline powder, and its melting point is between 219–230^0 C. Celastrol has maximum UV/visible absorption spectra at 253 and 424 nm. It is sparingly soluble in water, but is soluble in nonpolar solvents such as dimethylsulfoxide (DMSO) and ethanol. Celastrol is an electrophilic compound and it can react with nucleophilic thiol groups of cysteine residues of a variety of proteins to form adducts or induce other modifications within those proteins [16,17,6,18]. Apparently, this is one of the mechanisms by which celastrol can affect biological functions of proteins. Celastrol is also known as tripterine/tripterin, but the name celastrol is commonly used.

CELASTROL CONTROLS INFLAMMATION AND OTHER PATHOLOGICAL PROCESSES IN ANIMAL MODELS OF CHRONIC DISEASES

Celastrol has been shown to be beneficial in various chronic disease conditions in studies in animal models of immune-mediated diseases, neurodegenerative diseases, and others. The preventive/therapeutic potential of celastrol in various *in vivo* and *in vitro* models of these diseases is summarized in Table 1. Also mentioned therein are the cell signaling pathways as well as cellular and molecular targets of celastrol in various disease processes. The details of these and other mechanisms of action of celastrol are described below in separate sections. In addition, celastrol has potent anti-cancer activity. The mechanisms underlying the anti-cancer activity of celastrol are summarized below in a separate section.

Inflammatory, autoimmune, and allergic diseases

For rheumatoid arthritis (RA), using the rat adjuvant arthritis (AA) model, mouse collagen-induced arthritis (CIA) model and fibroblast-like synoviocytes from RA patients (RA-FLS) culture model, celastrol has been shown to reduce the severity of clinical and histopathological features of arthritis, as well as to modulate the production of pro-inflammatory cytokines and chemokines [8,9,19], to re-set the T helper 17 (Th17)/T regulatory (Treg) balance to facilitate the suppression of arthritis [20], and to afford protection against bone damage [8,9,19] (Table 1A). Celastrol also inhibits RA-FLS invasion and protects against bone and cartilage damage [21]. For multiple sclerosis (MS), celastrol is shown to modulate Th17 responses, to shift Th1 responses towards Th2, and to increase the production of anti-inflammatory cytokines in the experimental autoimmune encephalomyelitis (EAE) model of MS [22,10]. For systemic lupus erythematosus (SLE) (also known as lupus), celastrol treatment decreases transforming growth factor (TGF)-β

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production, urine protein excretion, and serum autoantibody levels in BW F1 and BALB/c mouse models of SLE [23–25]. For ulcerative colitis, using the mouse dextran sulphate sodium (DSS)-induced colitis model, celastrol has been shown to modulate oxidative stress, inflammatory cytokines and intestinal homeostasis [11]. For asthma and other hypersensitivity reactions, celastrol inhibits histamine and eotaxin production and other mediators involved in hypersensitivity reactions [26–29]. The main mediators and pathways targeted by celastrol in above-mentioned diseases are described in Table 1A.

Neurodegenerative disorders

The effects of celastrol on MS, a neurological disease of autoimmune origin, have been described above. For other neurological diseases such as Parkinson's disease, Alzheimer's disease and amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), celastrol has been shown to modulate pro-inflammatory cytokine production, to prevent the generation of reactive oxygen species (ROS), to limit oxidative damage, to protect against cell death, and to regulate heat-shock proteins (Hsps), as observed in mouse models and *in vitro* models of these diseases (Table 1B) [30–34,12,35–37]. For Gaucher disease (GD), celastrol modulates molecular chaperones and increases glucocerebrosidase activity in the GD fibroblasts model [38]. Celastrol is also known to modulate age-related macular degeneration [39].

Atherosclerotic, Metabolic, and Infectious diseases

Celastrol can inhibit platelet activation [40], prevent atherosclerotic plaque size in apo E-deficient mice [41], and decreased ratio of the plaque area and the arterial wall cross-section area in a rabbit model of carotid atherosclerosis [41], thus revealing the anti-atherosclerosis effect of this natural triterpene (Table 1C). Recently, celastrol has been reported to be a leptin sensitizer, whose effects are manifest as reduced intake of food, increased energy expenditure, and weight loss, and thereby it may potentially serve as an anti-obesity agent [42]. Celastrol is also effective in improving insulin resistance and limiting renal injury in a mouse model of Type 2 diabetes [43]. Furthermore, celastrol can modulate human immunodeficiency virus (HIV) 1- transactivator of transcription (Tat)-induced inflammatory responses in astrocytes in vitro by inhibiting the activation of JNK, MAPK, AP-1, and NF-kB as well as the expression of pro-inflammatory chemokines (e.g., CXCL10, IL-18, and monocyte chemotactic protein-1 (MCP-1)) and adhesion molecules such as intracellular adhesion molecule-1 (ICAM-1)/vascular cell adhesion molecule-1 (VCAM-1) [44]. Celastrol has also been reported to target defined functional components of pathogens such as the HIV-Tat [18] to inhibit the transcription and replication of that virus, and the enzyme enoyl-acyl carrier protein reductase of Plasmodium falciparum [45], which is a drug target for this malaria parasite. However, because of the limited scope of this article, we have not elaborated further on direct effects of celastrol on various pathogens.

CELASTROL MODULATES CELL SIGNALING PATHWAYS OF INFLAMMATION

Inflammation involves interplays among a variety of cellular, molecular and biochemical mediators that are activated/induced in response to different pro-inflammatory stimuli. These mediators comprise diverse pathways (Figure 2) that are described below. Inflammation is

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associated with multiple diseases, including chronic inflammatory diseases, autoimmune diseases, obesity, and cancer. Celastrol controls inflammation by targeting one or many of these pathways depending on the underlying disease process.

The nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) pathway is a central regulator of inflammation. A broad range of pro-inflammatory stimuli including cytokines, growth factors, and microbial products activate the I-kappa B kinase (IKK) complex consisting of IKK1, IKK2 and NF-κB essential modulator (NEMO). Activated IKK complex phosphorylates I-kappa B (IκB), which leads to ubiquitination and proteasomal degradation of IκB. The degradation of IκB in turn activates NF-κB, which then translocates to the nucleus, where it binds to DNA and regulates the expression of several target genes. NF-kB activation enhances the production of pro-inflammatory cytokines (e.g., interleukin-1 β (IL-1β), IL-6 and tumor necrosis factor α (TNFα)) and other inflammatory mediators (e.g., matrix metalloproteinases (MMPs) and inducible nitric oxide synthase (iNOS)) [46,47], without much effect on the induction of anti-inflammatory cytokines (e.g., IL-10 or IL-1 receptor antagonist (IL-1Ra)) [48]. Celastrol inhibits NF-κB activation and regulates NF-κB-regulated gene expression. It has been suggested that celastrol targets cysteine 179 in IKK [16] and blocks IKK activity as well as the degradation and phosphorylation of IκB [21,49,16]. This in turn blocks the activation of NF-κB and its nuclear translocation.

Mitogen activated protein kinase (MAPK) pathway is another important signal transduction pathway besides NF-κB pathway that is critical for immune-mediated inflammatory responses [50]. MAPKs are a family of serine/threonine protein kinases [51]. Three well-defined members of this family are the extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK, and they are activated by pro-inflammatory stimuli, including cytokines [50]. ERK signal transduction pathway leads to the activation of transcription factors c-Jun, c-Fos, and activating transcription factor 2 (ATF-2), whereas JNK activation leads to the activation of c-Jun and ATF-2. Furthermore, the p38 MAPK-mediated processes involve the participation of transcription factors cAMP response element-binding protein (CREB) and ATF-2 [50,52,53]. Celastrol selectively regulates the MAPK pathway. It inhibits the phosphorylation of JNK and ERK in various models of inflammation and arthritis [27,54,8]. However, activation of JNK by celastrol has also been observed in another system [55]. For p38 MAPK, one report stated that phosphorylation of p38 MAPK is unaffected by celastrol [56], whereas another [57] indicated that celastrol can activate p38 MAPK; the latter effect has been associated with the anti-metastatic activity of celastrol against cancer.

The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway is a common signaling cascade for many cytokines [58] [59]. JAKs are known to associate with the cytoplasmic domain of cytokine receptors for interferon (IFN)-α/β, IFNγ, IL-2, IL-4, IL-6, IL-10, IL-12/23 and others [58]. In general, the binding of these cytokines to their respective receptors phosphorylates JAK, which then leads to the phosphorylation of STATs. Activated STATs dimerize and translocate to the nucleus, where they bind to promoter regions of cytokine-responsive genes and thereby activate gene transcription [58]. Different STATs are involved in the differentiation of naïve T cells into particular T cell subsets (Th1,

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Th2, Th17 and Treg). In our studies, we have shown that celastrol inhibits STAT3 activation and suppress IL-17 expression as well as Th17 differentiation in the rat AA model [20,8]. In models of cancer such as multiple myeloma and hepatocellular carcinoma, constitutive STAT3 activation plays a role in cell proliferation, survival, and metabolism, and thereby to the disease process. Celastrol is shown to inhibit STAT3-mediated cell proliferation [60,61]. It involved inhibition of activation of upstream JAK1 and JAK2. However, effects of celastrol on other JAKs and STATs remain to be determined.

Another signaling pathway affected by celastrol is phosphatidylinositol-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway, which is involved in immune-mediated diseases and cancer [62–67]. Altered activation of the PI3K/Akt/mTOR pathway is observed in many human tumors, and it regulates the proliferation, differentiation, metabolism and survival of cancer cells [68]. Furthermore, there is an association between the accumulation of hypoxia-inducible factor-1 (HIF-1) and amplified PI3K/Akt/mTOR pathway signaling [69]. HIF-1 is a transcription factor highly expressed under hypoxic conditions and regulates cell survival response to hypoxia and cancer [63,70,71]. Inhibitors of HIF-1 have been tried for cancer therapy [72]. Celastrol can inhibit both PI3 activity as well as HIF-1 [63,66]. Celastrol inhibited HIF-1 activity in various cancer cell lines by decreasing the accumulation of HIF-1 and preventing the expression of HIF-1 target genes. Furthermore, the accumulation of HIF-1 by celastrol is correlated with inhibition of the phosphorylation of mTOR, ribosomal protein S6 kinase (p70S6K), eukaryotic initiation factor 4E (eIF4E) and ERK [63]. Contrary to the above, celastrol is also reported to induce HIF-1 accumulation through the induction of ROS and Akt/p70S6K signaling, and promote transcription of HIF target genes [70]. Therefore, additional studies are needed to clearly understand the role of celastrol in the regulation of mTOR and HIF-1.

Celastrol possesses anti-oxidant activity. Oxidative stress is one of the mediators of inflammation [73]. Oxidative stress builds up with the generation of high levels of reactive free radicals, such as reactive oxygen species (ROS; e.g., chemically reactive molecules derived from O_2 mainly O_2^- (superoxide anions), H_2O_2 (hydrogen peroxide) and OH• (hydroxyl radicals)) and reactive nitrogen species (RNS; e.g., radicals derived from nitrogen and oxygen, particularly nitric oxide (NO)) in the cell [74,75]. Celastrol is shown to inhibit lipid peroxidation in rat liver mitochondria by direct radical scavenging [76] as well as neutralizing oxygen radicals [77]. Celastrol also enhanced the antioxidant defense system and offered protection against bleomycin-induced pulmonary fibrosis in rats by restoring antioxidant enzymes such as hemoxygenase-1 (HO-1), glutathione-S-transferase (GSTs) and nicotinamide adenine dinucleotide phosphate (H) (NADP(H)): quinine oxidoreductase (NQO1) via the NF-E2-related factor-2 (Nrf2) pathway [78]. Similarly, celastrol decreased obesity-induced oxidative stress by increasing antioxidant enzymes and inhibiting NADH oxidase and ROS [79]. Defense against oxidant system by celastrol has also been attributed to decreased expression of iNOS and NO production [30,34], and the blocking of reactive thiols [17]. In contrast to the above, celastrol has been reported to induce ROS accumulation and to initiate apoptosis through the down-regulation on HSP90 in tumor cells [80]. Similarly, in osteosarcoma, celastrol caused G2/M phase arrest, and induced apoptosis and autophagy via the ROS/JNK signaling pathway [81].

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CELASTROL HAS ANTI-ANGIOGENIC ACTIVITY AND PROTECTS AGAINST ENDOTHELIAL BARRIER DYSFUNCTION

Angiogenesis, the formation of new blood vessels, is a hallmark of cancer [82–84]. However, autoimmune diseases such as RA are also characterized by angiogenesis in the target organ, the inflamed joints [85,86]. Accordingly, anti-angiogenic therapy has been considered for both these categories of disorders [87,86]. As discussed above, celastrol treatment inhibits the progression of autoimmune arthritis in experimental models of AA and CIA [20,9,8,88]. Similarly, celastrol suppresses tumor growth, for example, in mouse models and *in vitro* models of human prostate cancer [89,90]. Interestingly, celastrol has been shown to inhibit angiogenesis, both in vitro and in vivo [91,83], and to inhibit vascular endothelial growth factor (VEGF)-induced Akt/mTOR/p70S6K signaling [83]. Furthermore, celastrol can inhibit hypoxia-mediated angiogenesis, which involves inhibition of HIF-1α and its downstream genes such as VEGF [92]. Celastrol's ability to inhibit Hsp90 was also implicated in reduced HIF-1α in this process. In another study, celastrol was shown to inhibit vasculogenesis by decreasing VEGF secretion, adhesion of endothelial cells to the extracellular matrix (ECM) and their subsequent migration, and tubule formation [93]. Inhibition of Akt/endothelial nitric oxide synthase (eNOS) signaling was implicated in this process. Celastrol has also been reported to inhibit lipopolysaccharide (LPS)-induced angiogenesis, which involved suppression of Toll like receptor- 4 (TLR-4)-mediated NF-kB activation [94], and to inhibit angiogenesis via suppression of VEGFR-1 and VEGFR-2 expression [95].

In RA, vascular endothelial cell physiology is relevant not only for angiogenesis but also for immune cell interaction and migration through blood vessels, as well as for maintaining a healthy endothelial barrier. In this regard, celastrol has been shown to inhibit the expression of cytokine-induced adhesion molecules such as ICAM-1 and VCAM-1 [96], and to prevent endothelial barrier dysfunction by inhibiting endogenous peroxynitrite formation in endothelial cells exposed to pro-inflammatory stimuli [97]. The latter effect involved inhibition of JAK-2-dependent iNOS and NADPH oxidase type 1 (Nox-1) induction.

CELASTROL-INDUCED MODULATION OF HEAT-SHOCK RESPONSE AND ITS POTENTIAL THERAPEUTIC APPLICATIONS IN CHRONIC DISEASES

Heat-shock proteins (Hsps), also known as Stress proteins, can be induced by heat and other types of stimuli that cause cellular stress [98,99]. These are highly conserved proteins evolutionarily. Hsps can be categorized into different families based on their molecular mass (kD), for example, Hsp110, Hsp90, Hsp70, Hsp60, Hsp40, and small Hsps. One of the major functions of Hsps is to protect cells from damage under different types of stressful conditions [98,99]. Acting as chaperones, Hsps bind to cellular proteins, ensure proper folding of cellular proteins, attempt to repair defective proteins, and protect them against denaturation and other types of damage. Hsps are also involved in signal transduction and apoptosis. Thus, heat-shock response is cytoprotective under situations that otherwise would promote apoptosis of cells. Stress-inducible heat-shock transcription factor-1 (HSF1) plays

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an important regulatory role in response to environmental stress and pathophysiological conditions.

Dysregulation of cellular stress pathways and protein folding can lead to intracellular accumulation of protein aggregates, which is turn can induce tissue pathology [100,101]. Many pathophysiological conditions including neurodegenerative disorders (e.g., Alzheimer's disease, Parkinson's disease), cardiovascular diseases, cancer, diabetes, and aging are associated with accumulation of misfolded and/or aggregated proteins within certain tissues, attributable in part to defective cellular stress response pathways [32,17,102,100,101]. In addition, inflammation and oxidant damage also contribute to the pathogenic processes in these disorders. Accordingly, pharmacological agents that possess anti-inflammatory and anti-oxidant activities, and can reset these defective pathways are increasingly being sought [32,17,102].

Celastrol has been shown to have a cytoprotective effect in response to stress-induced cell death. Celastrol can induce the expression of various Hsps, for example, Hsp70, Hsp40, and Hsp27, by activation of HSF1 and these Hsps might contribute to its cytoprotective effect [103]. Celastrol's anti-oxidant attributes can also contribute to its cytoprotective effects. As described under cell signaling, the anti-oxidant response involves transcription factors Nrf-2 and Atf4, and celastrol has been shown to activate both these transcription factors [17]. In one study, celastrol's cytoprotective effect was shown to be mediated via induction of Hsp32 (also known as heme oxygenase-1; HO-1) [104]. This induction of Hsp32 was mediated via Nrf-2 instead of HSF-1, and Hsp32 in turn inhibited pro-apoptotic JNK. Besides the induction of Hsps mentioned above, inhibition of Hsp90 has been shown to have a therapeutic effect in certain neurodegenerative diseases; the latter effect is attributable to selective proteasomal degradation of Hsp90 client proteins [100]. Importantly, celastrol is an inhibitor of Hsp90 [105,106], and it can modulate several nuclear transcription factors that are Hsp90 clients, including the aryl hydrocarbon receptor (AhR) [105],[106]. The involvement of celastrol-induced inhibition of Hsp90 and its anti-cancer effect is discussed below.

ANTI-CANCER ACTIVITY OF CELASTROL

Celastrol is known to have anti-cancer and anti-metastatic activities [107,82,83,15,108]. In addition, celastrol is shown to enhance the therapeutic efficacy of other anti-cancer drugs when used with them, and to potentiate the beneficial effects of radiotherapy [109,110]. The major processes involved in these activities and affected by celastrol include, the inhibition of cellular proliferation, induction of apoptosis, prevention of malignant tissue invasion, and blockade of angiogenesis [82,7,111,15]. Celastrol can inhibit cell proliferation and induce apoptosis via multiple actions. These include, potentiation of TNF-induced apoptosis via suppression of the NF-kB pathway [4]; downregulation of cytokines such as IL-6, which is an inducer of cell proliferation [112]; activation of caspases [113–115]; inhibition of the expression of anti-apoptotic proteins such as cellular inhibitor of apoptosis protein 1 and 2 (cIAP1 and cIAP2), cellular FLICE-inhibitory protein (FLIP), and B-cell lymphoma 2 (Bcl-2) [4,114]; induction of cell cycle arrest [81,116]; and downregulation of cell survival proteins coupled with upregulation of death receptors [117]. Furthermore, celastrol inhibits

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adhesion, migration and invasion of tumor cells via reduced expression of specific integrins, as well as reduced MMP activity [118–120]. In addition, as described above, celastrol can suppress angiogenesis [63,83].

Two additional mechanisms contribute to the anti-cancer effects of celastrol, namely inhibition of Hsp90 and proteasome inhibition. In regard to Hsp90, celastrol directly binds to the C-terminal domain of Hsp90 inducing oligomerization, and it interferes with specific biological functions through modulation of Hsp90-associated nuclear transcription factors [121,106]. In addition, celastrol has been shown to inhibit Hsp90 in thiol-related reactions[116], and to downregulate Hsp90 client proteins via inhibition of enzymes of mitochondrial complexes and accumulation of ROS [80]. Furthermore, celastrol-induced inhibition of Hsp90 contributes to HIF-1α inhibition and cell cycle arrest [92]. As far as the proteasome is concerned, celastrol has been shown to inhibit proteasome function by targeting its chymotrypsin-like activity. This in turn results in accumulation of ubiquitinated proteins and some of the known proteasomal substrates such as cell cycle-regulating proteins and others (IkBa, Bax and p27, etc.) leading to inhibition of cell proliferation coupled with induction of apoptosis [122,123]. Accordingly, proteasomal inhibition has also been exploited in cancer therapy [124,123]. Inhibition of NF-kB activation may contribute to the beneficial effect of proteasomal inhibition therapy. In addition, NF-kB inhibitors combined with standard chemotherapy drugs might be of benefit in the chronic inflammatory stage of tumor progression [125]. However, this aspect of cancer therapy needs further evaluation.

Another beneficial effect of celastrol in cancer relates to its ability to remodel bone by relatively reducing osteoclastic activity, while maintaining or increasing osteoblastic activity. Metastasis of cancer to the bone may cause osteolysis, which involves increased bone resorption. In regard to bone remodeling, the receptor activator of nuclear factor-κB ligand (RANKL) promotes the proliferation and differentiation of osteoclasts, whereas osteoprotegerin (OPG) secreted by the osteoblasts is a soluble decoy receptor for RANKL, and it serves as a natural inhibitor of osteoclast activation. In a study on an osteolytic bone metastasis model, celastrol suppressed trabecular bone loss, reduced the number and size of osteolytic bone lesions, osteoclast number, and bone resorption [126]. In another study on human osteosarcoma cells, celastrol caused G2/M phase cell cycle arrest, and induced apoptosis and autophagy [81]. These observations in cancer studies are supported by the results of our study in rat AA model [9]. Celastrol protected against bone and cartilage damage by regulating pro-inflammatory cytokines, inhibiting RANKL, increasing RANKL/OPG ratio, inhibiting the secretion of matrix-degrading enzymes such as MMPs, and reducing the number of osteoclasts without much effect on osteoblasts [9].

USE OF CELASTROL-CONTAINING NATURAL PRODUCTS FOR THE TREATMENT OF CHRONIC INFLAMMATORY AND AUTOIMMUNE DISEASES IN HUMANS.

Celastrol is present in several plants belonging to the celastraceae family. Some of these plants have been used in traditional Chinese medicine (TCM) for several decades/centuries as medicinal herbs for the treatment of a wide range of chronic inflammatory disorders. For

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example, the extracts of the root, bark and stem of *Tripterygium wilfordii* (Thunder God Vine), *Celastrus orbiculatus*, *Celastrus aculeatus* and some other members of the Celastraceae family have been used for the treatment of RA, SLE, and other disorders [5,1,3,2,127]. However, a large part of this information is based on folklores as well as documented descriptions of the use of these herbal products in old archived literature. Limited available information is derived from studies on small numbers of patients and/or scientifically-controlled randomized clinical studies on the use of *T. wilfordii* in chronic inflammatory and autoimmune diseases such as RA, juvenile RA, ankylosing spondylitis, and SLE [5,128–132]. Of these, the most reliable clinical studies have been performed using *T. wilfordii* in patients with RA. The efficacy of *T. wilfordii* extract against RA was compared with that of two of the mainstream anti-arthritic drugs, namely sulphasalazine and methotrexate. Interestingly, *T. wilfordii* extract reduced the severity of RA as assessed by well-established criteria, and the efficacy of *T. wilfordii* was comparable to, or better than, that of sulphasalazine/ methotrexate [128,133–136]. Furthermore, the combination of *T. wilfordii* and methotrexate was better than methotrexate alone. However, the toxicity profile of this natural product needs further assessment before *T. wilfordii* is approved for therapeutic purposes.

CONCLUDING REMARKS

Celastrol, a natural triterpene, has anti-inflammatory, anti-oxidant, and anti-cancer activities. Besides targeting multiple cell signaling pathways, celastrol modulates several other pathophysiological processes involved in chronic inflammatory diseases, autoimmune diseases, and cancer. Most of this information on celastrol is based on *in vitro* model systems in the laboratory and preclinical studies in animal models of human diseases. These studies have also offered mechanistic insights into the use of celastrol-containing herbal extracts from celastraceae family of plants for the treatment of some of these disorders in the traditional systems of medicine. Taken together, this knowledge has encouraged the clinical testing of *T. wilfordii* and related herbal preparations. In particular, the testing of *T. wilfordii* in RA patients has shown promising results. It is hoped that in the near future, T. *wilfordii* and similar other natural products might be approved for use in mainstream therapy as adjuncts for, or in place of, conventional allopathic drugs for RA and some other chronic diseases. This would be a significant contribution to the therapeutic arsenal against several chronic debilitating human diseases.

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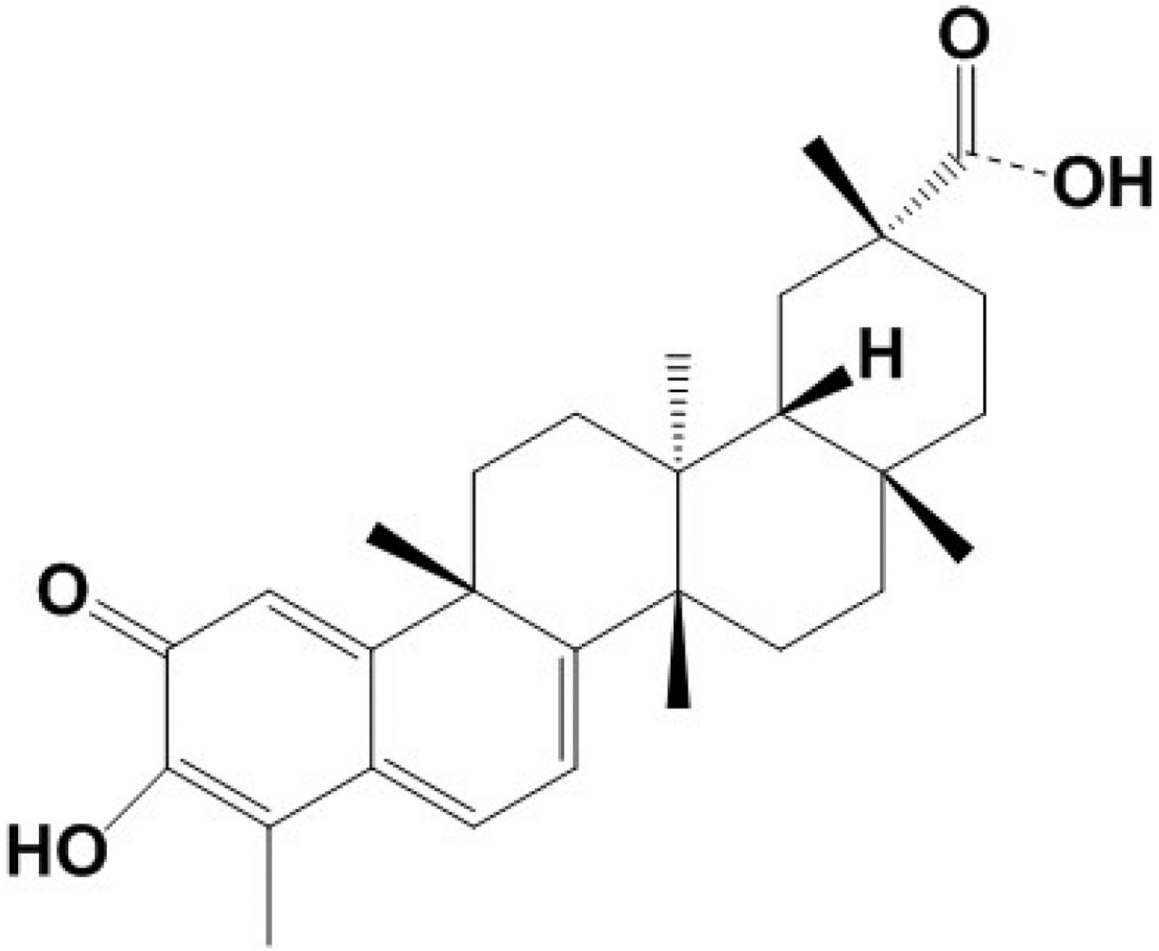

Figure 1. Molecular structure of celastrol.

Celastrol is a pentacyclic triterpenoid with a molecular weight 450.6 and molecular formula $C_{29}H_{38}O_4$. It belongs to a small class of organic compounds known as quinone methides. Celastrol has an acidic group at one end and a phenolic quinone at the other end.

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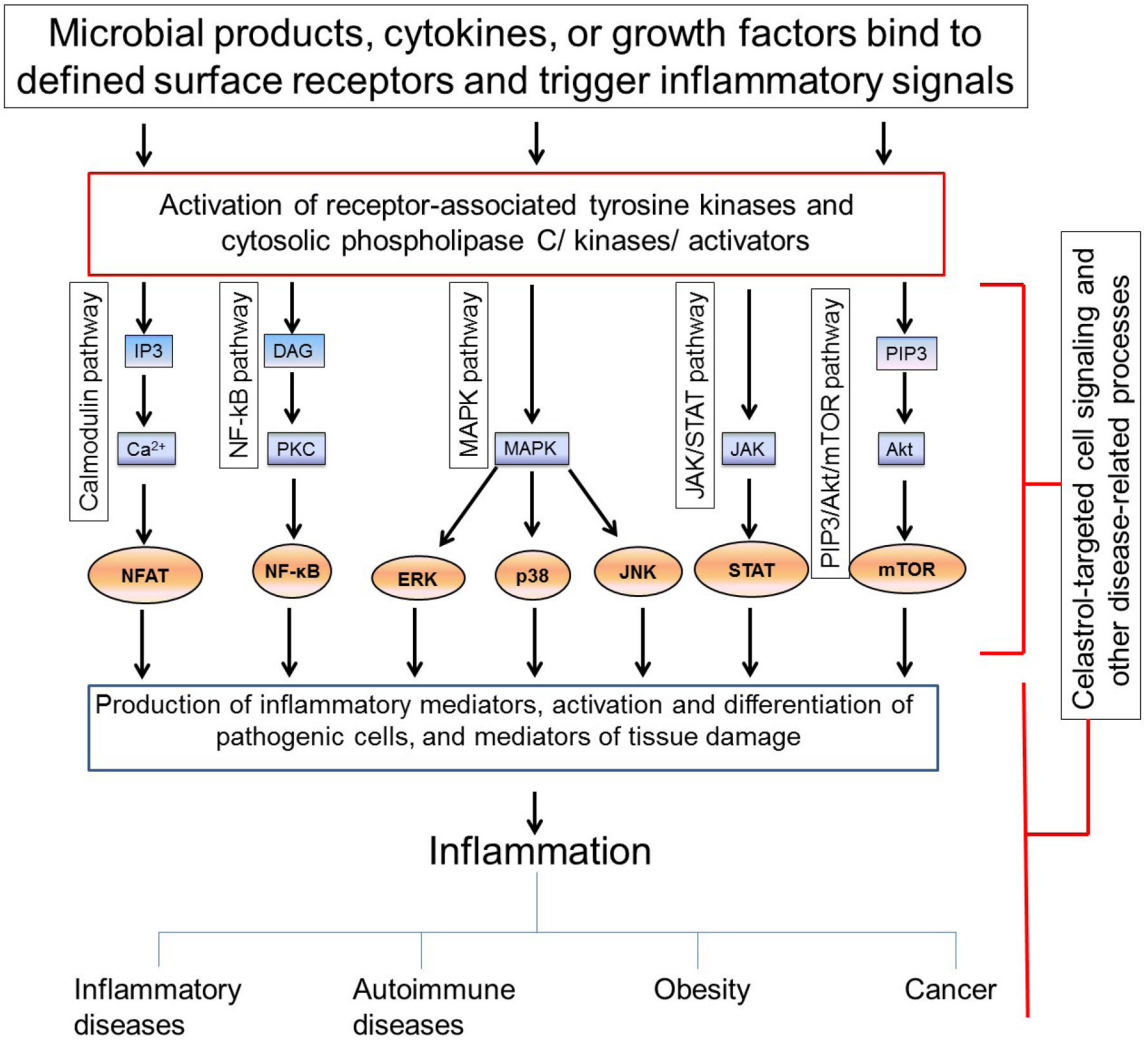

Figure 2. Cell signaling pathways and other disease-related processes modulated by celastrol for the control of chronic diseases.

A schematic representation of the cell signaling pathways that are regulated by celastrol. These pathways are activated in response to diverse stimuli. Celastrol is known to target one or more of these pathways leading to the suppression of inflammation associated with various chronic diseases including inflammatory diseases, autoimmune diseases, obesity, and cancer. Besides cell signaling, celastrol modulates other disease-related processes such as angiogenesis, heat-shock protein responses, proteasome activity, etc. to limit disease progression and to facilitate recovery, where feasible.

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Table 1.

Celastrol-induced prevention/treatment of chronic diseases of diverse etiology

Type of disease	Experimental model(s)	Targets/mechanisms of celastrol action	References
A. Inflammatory and Autoimmune Diseases			
Rheumatoid Arthritis (RA)	Rat AA, Rat/Mouse CIA, Human RA-FLS	Modulates pro-inflammatory cytokines, chemokines, and T helper 17 (Th17)/T regulatory cell balance. Inhibits RA-FLS invasion and apoptosis. Decreases production of antibodies to the disease-related antigens and anti-cyclic citrullinated peptides (aCCP) antibodies. Also inhibits osteoclast differentiation, and reduces cartilage and bone damage.	[8, 9, 19–21, 88, 118, 137–140]
Multiple sclerosis (MS)	Rat/mouse experimental autoimmune encephalomyelitis (EAE)	Modulates Th17 responses, shifts Th1 response towards Th2, decreases TNFα but increases IL-10. Inhibits NF-κBexpression, nitrites levels, and expression of Toll-like receptor (TLR)2.	[10, 22]
Systemic lupus erythematosus (SLE) (or Lupus)	BW F1 mice, BALB/c mice (chromatin injection)	Decreases transforming growth factor (TGF)-β, renal collagen type IV, urine protein excretion, and serum autoantibodies.	[23–25]
Ulcerative colitis	DSS-induced colitis in mice	Modulates oxidative stress, inflammatory cytokines, and intestinal homeostasis.	[11]
Psoriasis	HACaT keratinocytes	Inhibits NF-κB expression and induces apoptosis through caspase-3 activation	[141]
Hypersensitivity (e.g., Asthma and skin inflammation)	Ovalbumin/allergen-induced airway inflammation, phorbol myristate acetate-induced skin inflammation, and skin hypersensitivity to dinitrochlorobenzene in mice	Downregulates the expression of stem cell factor (SCF) in fibroblasts, and inhibits the production of histamine and eotaxin in mast cells. Inhibits antibody responses and immunoglobulin Fc epsilon receptor I signaling. Regulates the balance between isoforms of MMPs (MMP-2/9) and TIMPs (TIMP-1/2).	[26–29]
B. Neurodegenerative Diseases			
Parkinson's disease (PD)	MPTP mouse model, SH-SY5Y cells	Modulates pro-inflammatory cytokines, prevents the generation of ROS, lipid peroxidation, and mitochondrial membrane potential. Protects against cellular injury and apoptotic cells death.	[12, 31, 34]
Alzheimer's disease	Transgenic mouse model	Inhibits pro-inflammatory cytokines and expression of MHC-II molecules. Induces neuroprotective heat-shock proteins (Hsps). Lowers oxidative stress and regulates BACE-1 expression level via an NF-κB-dependent mechanism.	[30, 32, 33, 36, 37]
Amyotrophic lateral sclerosis (ALS)	G93A SOD1 transgenic mouse model	Blocks neuronal cell death, reduces TNF-α, iNOS, CD40, and GFAP immunoreactivity.	[35]
Gaucher disease (GD)	GD fibroblasts	Modulates molecular chaperones and increases glucocerebrosidase activity.	[38]
Age-related macular degeneration (AMD)	Human retinal pigment epithelial cells (ARPE-19 cells)	Reduces IL-6 and inhibits NF-κB.	[39]
C. Atherosclerotic and Metabolic Diseases			
Atherosclerosis	Apo-E-deficient mice, Rabbit carotid atherosclerosis model, and human platelets	Inhibits lectin-like oxidized low density lipoprotein receptor-1 (LOX-1) and generation of ROS. Reduces serum level of low density lipoproteins and VEGF expression. Inhibits platelet aggregation by reducing the expression of P-selectin and glycoprotein IIb/IIIa on platelets.	[40, 41, 142]
Obesity	Hyperleptinemic diet-induced obese mice	Reduces food intake, increases energy expenditure, leading to weight loss by increasing leptin sensitivity.	[42]

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Type of disease	Experimental model(s)	Targets/mechanisms of celastrol action	References
Type 2 diabetes	The db/db mouse	Acting on the liver, adipose tissue, and kidney, it Inhibits NF-kB, reduces insulin resistance, improves abnormal lipid metabolism and oxidative stress, reduces pro-inflammatory cytokines, and limits renal injury.	[43]

AA, Adjuvant-induced arthritis; CIA, Collagen-induced arthritis; DSS, Dextran sulfate sodium; FLS, Fibroblasts-like synoviocytes; Hsp, Heat-shock proteins; MMPs, Matrix metalloproteases; TIMPs, Tissue inhibitor of matrix metalloproteases; MPTP, 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridin;, ROS, Reactive oxygen species; MHC-II, Major histocompatibility complex class II; BACE1, Beta-site APP-cleaving enzyme 1; iNOS, Inducible nitric oxide synthase; GFAP, Glial fibrillary acidic protein; p-JNK, Phospho c-Jun N-terminal kinase; NF-κB, Nuclear factor-kappa B; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor.