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Review

Molecular modulators of celastrol as the keystones for its diverse pharmacological activities

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ABSTRACT

In the recent years, much attention has been focused on identifying bioactive compounds from medicinal plants that could be employed in therapeutics, which is attributed to their potent pharmacological actions and better toxicological profile. One such example that has come into the light with considerable interest is the pentacyclic triterpenoid, celastrol, which has been found to provide substantial therapeutic properties in a variety of diseases. In an effort to further accelerate its potential to be utilized in clinical practice in the future; along with advancing technologies in the field of drug discovery and development, different researchers have been investigating on the various mechanisms and immunological targets of celastrol that underlie its broad spectrum of pharmacological properties. In this review, we have collated the various research findings related to the molecular modulators responsible for different pharmacological activities shown by celastrol. Our review will be of interest to the herbal, biological, molecular scientist and by providing a quick snapshot about celastrol giving a new direction in the area of herbal drug discovery and development.

1. Introduction

Plant derived remedies have become novel candidates in the paradigm of drug discovery and development due to potent pharmacological effects and better toxicology profiles [1–15]. Celastrol is a bioactive constituent extracted from *Tripterygium wilfordii* (TW), a traditional Chinese medicinal herb commonly referred to as *'Thunder of God Vine'* [16,17]. Also called tripterine, it belongs to a class of natural compounds known as triterpene quinine methides and is made up of five cyclic rings, further classifying it as a pentacyclic triterpenoid [17,18] (Fig. 1). Extensive experimentation throughout the years have shown that celastrol exhibits curative properties in the treatment of cancer, obesity, inflammatory, auto-immune and neurodegenerative diseases through the modulation of a variety of molecular targets. Primarily, it affects protein function through the formation of covalent Michael adducts (Fig. 2).

1.1. Anti-cancer properties

Recent studies have shown celastrol to be a promising anti-cancer drug, and this property has been regarded as the most widely experimented property of the compound. Carcinogenesis, a complex process

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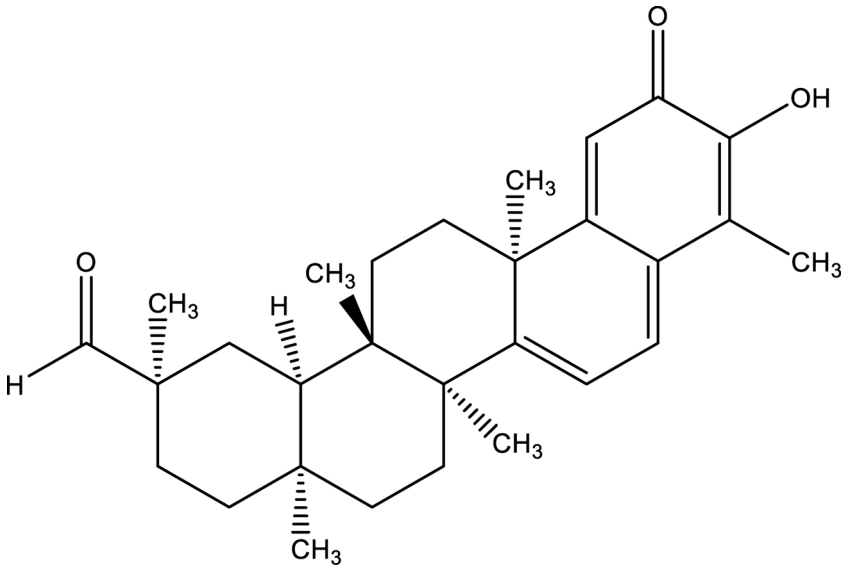

Fig. 1. Chemical structure of celastrol ($C_{29}H_{38}O_4$).

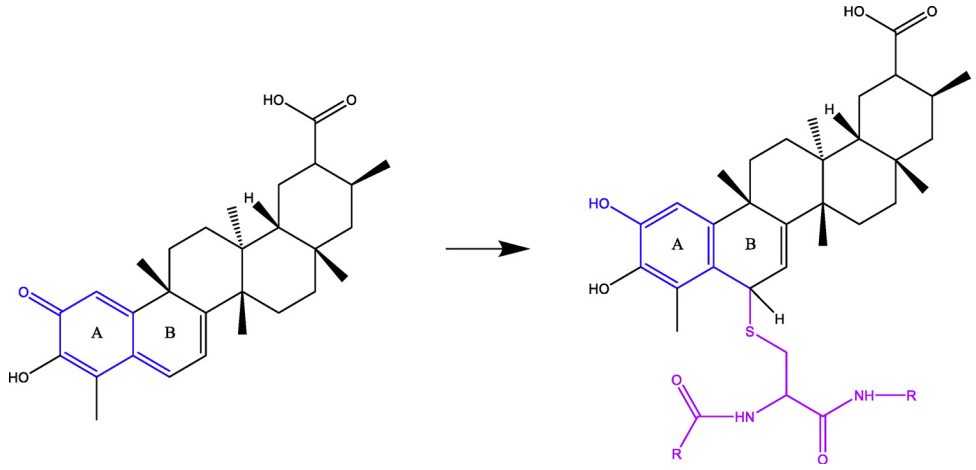

Fig. 2. Formation of Michael adducts through the binding of electrophilic sites on quinone methide rings of celastrol (blue) and nucleophilic thiol groups of cysteine residues (pink) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

involved in cancer causes genetic alteration at a cellular and molecular level, which can be further divided into three phrases; initiation, promotion, and progression. Studies on the effect of celastrol have been carried out on various cancer cell lines such as prostate, breast, lung, skin and gastric cancers. Celastrol has been shown to carry out its anticancer properties through the modulation of different molecular targets that aims to; (i) promote apoptosis/inhibit proliferation, (ii) inhibit angiogenesis and (iii) suppress cell invasion and metastasis [16,18,19]. Out of the many molecular targets involved in regulating cancer, the nuclear factor- κB (NF-κB) remains to be one of the most significant in the treatment of cancer. The activation of NF-κB inhibits apoptosis and induces pro-inflammatory cytokines, further promoting tumour growth. Therefore, inhibiting NF-κB may increase the sensitivity of tumour cells towards the apoptotic activity of TNF- α [16,19–21]. In agreement, a recent study in 2018 by Sethi et al., demonstrated that the activity of NF-κB was suppressed due to an inhibitory effect on transforming growth factor-activated kinase 1 (TAK1) and the activation of IκBα kinase [22]. Besides that, celastrol also inhibited the phosphorylation and degradation of IκBα, the nuclear translocation and phosphorylation of the p65 protein, and NF-κB-mediated reporter gene expression, all which seems to be induced by TNF-α. This promotes apoptosis and prevents proliferation, further enhancing tumour cell death in a variety of cancer cell lines [22,23]. This effect can be seen in a study by Zhao et al. on human myeloma cells, where upon celastrol administration, a cell proliferation inhibitory rate of over 80% was observed. Furthermore, increased apoptotic cell percentage could be observed [24].

Another anticancer property of celastrol can be ascribed to the inhibition of tumour angiogenesis [25]. Pang et al., showed that celastrol successfully inhibited tumour growth and angiogenesis in a human prostate tumour xenograft mouse model. Upon administration of celastrol at 2 mg/kg/day, the tumour weight was reduced by approximately 73% after 16 days, compared to the control, where an increase in tumour weight was observed [26]. Another study conducted on human glioma xenograft mice model showed that the density of micro vessel in the xenografts was reduced upon administration of 2 mg/kg of celastrol (24.5 ± 2.66 vessel/mm^2) compared to the control (37 ± 6.04 vessel/mm^2) [27]. The major mechanism attributed to these observations is the inhibition of the AKT/mTOR/P70S6K signalling pathway, and downregulation of vascular endothelial growth factor receptors (VEGFR); VEGFR-1 and VEGFR-2. The downregulation of both VEGFR-1 and VEGFR-2 seems to be a possible method to decrease cell sensitivity towards vascular endothelial growth factor (VEGF), thereby resulting in decreased vascular permeability, decreased migration and proliferation of endothelial cells [28].

Celastrol has also been reported to inhibit tumour invasion and cancer metastasis. A recent study by Yang et al., on mice implanted

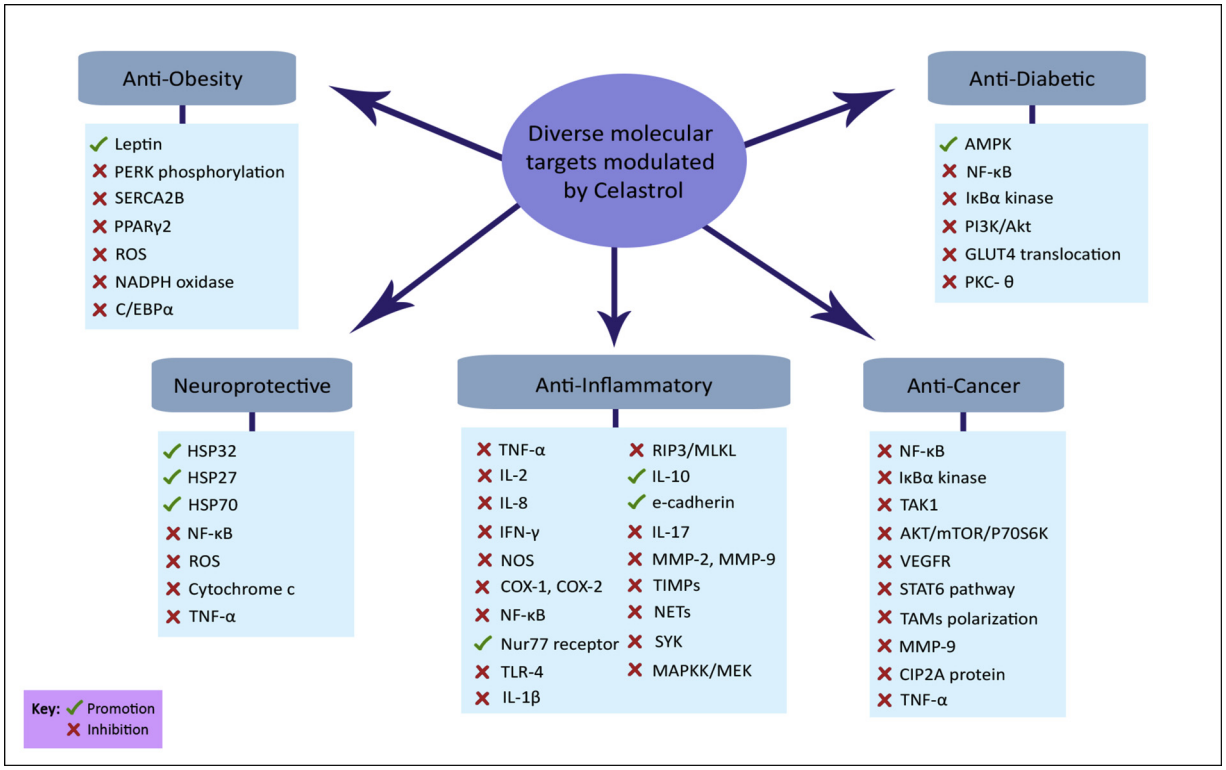

Fig. 3. Summary of the pharmacological actions of celastrol through modulation of various molecular targets.

with 4T1 (breast cancer) tumour cells showed that the number of metastasis in the celastrol treated group was significantly lesser (less than 5) compared to the control group (up to 15). This can be ascribed to the downregulation in the signal transducer and activator of transcription 6 (STAT6) signalling pathway through inhibited phosphorylation, thereby inhibiting M2-like polarization of tumour-associated macrophages (TAMs) which leads to suppressed cancer metastasis [29,30]. Moreover, studies conducted on lung adenocarcinoma cells [22] and breast cancer cells [31] demonstrated that celastrol inhibits the invasive activity from TNF, and this is correlated with the inhibition of matrix metalloproteinase-9 (MMP-9) and NF-κB pathway suppression [32]. In 2017, Wu et al., proved that celastrol inhibited migration and invasion of human chondrosarcoma cells with maximum inhibition at 5 mg/L of celastrol. This is achieved through the suppression of the cell proliferation regulating inhibitor of protein phosphatase 2 A/c-MYC (CIP2 A/c-MYC) signalling pathway, downregulating the expression of CIP2 A protein, which results not only in decreased tumour invasion, but also decreased cell proliferation and induced apoptosis [33].

1.2. Anti-inflammatory properties

Various studies have provided evidence in favour of celastrol possessing anti-inflammatory properties that may be beneficial to a variety of inflammatory diseases such as asthma, rheumatoid arthritis, inflammatory bowel disease and systemic lupus erythematosus (SLE). Celastrol exerts its anti-inflammatory effects mainly through the modulation of a variety of inflammation mediators, particularly mediators induced by lipopolysaccharides (LPS) [34]. Celastrol also suppresses the production of pro-inflammatory cytokines; TNF-α, IL-2, IL-8, IFN-γ, proinflammatory enzymes; nitric oxide synthase (NOS), cyclooxygenase (COX-1, COX-2), transcription factors; nuclear factor kappa B (NFκB), and adhesion molecules [35,36]. Besides that, celastrol has also been shown to alleviate inflammation through the promotion of mitochondrial autophagy via the nuclear receptor Nur77 [37].

Rheumatoid arthritis (RA) is an inflammatory disorder distinguished by joint inflammation, cartilage and bone damage leading to loss of function and deformities. Treatment of RA has been accompanied with notable adverse effects, posing a huge challenge in the clinical field [38,39]. This leads to an increasing interest in searching for new remedies such as celastrol. Studies carried out on rat arthritis models showed inhibition in swelling recurrence of up to an average of 55.25% when using 10 mg/kg/day of celastrol and 81.60% when using 20 mg/kg/day of celastrol. This is due to the suppressive effect of celastrol on the secretion of pro-inflammatory cytokines, IL-1β from the inhibition of caspase-1 activation, and TNF- α. This leads to decreased immune cell infiltration and proliferation into the synovial membrane, decreasing swelling and bone destruction [40,41]. The Toll-like receptor 4 (TLR4)/NFκB pathway was also inhibited by the administration of celastrol, which leads to the suppression of metalloproteinase-9 (MMP-9) expression, thereby decreasing cell infiltration from fibroblast-like synoviocytes [34]. This shows that celastrol remains an interesting candidate in treating rheumatoid arthritis.

In the case of inflammatory bowel diseases, Pinna et al., discovered that celastrol successfully decreases the levels of pro-inflammatory cytokines, namely TNF- α, IL-1β, IL-6 and IL-8 in biopsies of the inflamed intestinal mucosa of patients with Crohn's disease. This occurs through the inhibition of the translocation of NFκB receptor induced by LPS into the nucleus, thereby inhibiting cytokine transcription [42]. Furthermore, studies carried out on dextran sulphate sodium (DSS) induced mice to determine the activity of celastrol on ulcerative colitis (UC) have shown alleviation in colon injury, reduced severity and prevents impairment of intestinal homeostasis. This is carried out through (i) decreased production of TNF- α and IL-1β, (ii) increase in IL-10 levels, (iii) countering oxidative stress in the colon and (iv) upregulation of e-cadherin expression. Moreover, celastrol also inhibits the necroptosis process in colonic epithelial cells through suppression of the RIP3/MLKL pathway [43,44].

Besides that, asthma, which is a condition affecting the conducting airways, is characterized by excessive bronchiole contraction, resulting in reversible airflow obstruction. Currently, the cornerstone for the

Table 1
Summary of studies and trials that report the various pharmacological properties of celastrol.

Property	Findings	Type of study	Reference(s)
Anti-cancer	Promotes apoptosis and prevents cell proliferation, thus enhancing tumour cell death.	*In-vitro* on human cell lines	[22]
	Cell proliferation inhibitory rate of over 80% was observed. In addition, increased apoptotic cell percentage was observed.	*In-vitro* on human myeloma cells	[24]
	Tumour weight reduced by approximately 73% after administration of celastrol at 2 mg/kg/day for 16 days.	*In-vitro* on human prostate tumour xenograft mouse model	[26]
	The density of micro vessels in xenografts was reduced upon administration of 2 mg/kg celastrol.	*In-vitro* on human glioma xenograft mice model	[27]
	The number of metastasis in celastrol treated group was significantly lesser as compared to the control group.	*In-vivo* on mice implanted with 4T1 tumour cells	[29]
	Migration and invasion of human chondrosarcoma cells inhibited with a maximal inhibitory concentration of 5 mg/L.	*In-vitro* on human chondrosarcoma cell lines SW1353	[33]
Anti-inflammatory	Average inhibition in swelling recurrence up to 55.25% using 10 mg/kg/day celastrol, and up to 81.60% using 20 mg/kg/day celastrol. In addition, decreased immune cell filtration and proliferation into the synovial membrane, leading to decreased swelling and bone destruction.	*In-vivo* on adjuvant-induced arthritis rats	[40]
	Decreased levels of proinflammatory cytokines, such as TNF-alpha, IL-1β, IL-6 and IL-8	*In-vitro* on biopsies of inflamed intestinal mucosa in Crohn's disease	[42]
	Alleviation in colon injury, as well as reduced severity and prevention of intestinal homeostasis impairment.	*In-vivo* on dextran sulphate sodium-induced mice	[43]
	Both serum and lung expression of IL-17 A significantly decreased upon administration of celastrol. In addition, alleviation of airway hyper-responsiveness was observed and there was overall reduction in inflammation and thickness of airway walls.	*In-vivo* on obese asthmatic mice	[47]
	Decreased levels of circulating immunoglobulin, anti-ss DNA, anti-ds DNA and IgG antibodies upon administration of celastrol at 12 mg/kg/day. Moreover, decreased production of IL-10 and NO was observed.	*In-vivo* on BALB/c mice	[52]
	Decreased serum antibodies which alleviates clinical symptoms of systemic lupus erythematosus, thus improving survival rate.	*In-vivo* on NZBxW mice models	[53]
Anti-obesity	Reduction in body weight of leptin-resistant mice up to 45% through a decrease in the consumption of food.	*In-vivo* on leptin-resistant mice	[59]
	Celastrol prevented accumulation of lipid and decreases expression of adipocyte-specific markers.	*In-vitro* signalling studies in 3T3-L1 adipocytes	[61]
	Decrease in levels of low-density lipoprotein and triglyceride was observed in obese mice.	*In-vivo* on Male Sprague-Dawley rats fed with high fat emulsion	[62]
Neuroprotective	Increased removal of cytotoxic haem and reduced formation of haem-amyloid beta complexes were observed, that are responsible for symptoms of Alzheimer's disease.	*In-vitro* on cerebral cortical cultures of 19 days embryonic rats	[65,66]
	Prevention of Aβ molecule accumulation and increased clearance seen.	*In-vivo* on APP/PS1 mice	[67]
	Increased Aβ clearance, decreased oligomerization of Aβ, restoration of tau homeostasis and inhibition of neurons apoptosis observed.	*In-vitro* on Cos-1, Hela and 293 cells line	[68]
	Reduced aggregation and accumulation of α-synuclein protein that is responsible for the pathogenesis of Parkinson's disease. Moreover, decreased liberation of reactive oxygen species, cytochrome C and apoptosis promotion factors observed, thus showing prevention of further cell death.	*In-vitro* on human neuroblastoma SH-SY5Y cells	[69]
Anti-diabetic	• Lower mean fasting plasma glucose level in celastrol-treated mice after 8 weeks. • Approximate drop of 42% in HbA1C levels and drop of 30% in basal glucose at the time of 60 minutes of celastrol treatment. • Decrease in epididymal fat mass and saturated fatty acid levels, leading to decreased inflammation and oxidative stress. • Lower creatinine levels in celastrol-treated mice.	*In-vivo* on mice	[75]
	• Celastrol significantly improved uptake of glucose up to 86% upon insulin stimulation. • Rise in protein phosphorylation of insulin signalling cascades. • Elevation in levels of phosphorylated 5' AMP-activated protein kinase and decreased activity of protein kinase C theta.	*In-vitro* on human skeletal muscle cells	[82]

treatment of asthma is inhaled corticosteroids (ICS). However, the increasing incidence of steroid-resistant asthma limits the use of ICS, warranting the discovery of new compounds as an alternative treatment [45,46]. Many studies have reported the effect of celastrol on steroid resistant asthma. In an experiment carried out on obese asthmatic mice, Zheng et al., demonstrated that celastrol produces an effect on IL-17, which inhibits the production and differentiation of CD4 + T cells (Th17). It is proposed that Th17 cells play a major role in mediating SRA. It was shown that both the serum level and lung expression of IL-17 A were significantly lower upon administration of celastrol. This inhibition leads to an alleviation in airway hyper-responsiveness (AHR), as the decreased amount in Th17 cells is correlated with a reduction in neutrophilic inflammatory response in the lungs. Generally, this leads to a reduction in inflammation and the thickness of wall in obese asthmatic mice [47,48]. Furthermore, celastrol has also been shown to regulate the imbalance between matric metalloproteinases (MMPs); MMP-2 and MMP-9, and tissue inhibitors of metalloproteinases (TIMPs); TIMP-1 and TIMP-2. This results in reduced cellular infiltration and accumulation, reduced airway modelling, and alleviation in asthma symptoms [49,50]. The balance between MMPs and TIMPs occur as celastrol inhibits the activity of the NK-xB receptor, and the phosphorylation of mitogen-activated protein kinases (MAPK) found in broncho-alveolar lavage cells and lung tissues. This decreases the production of inflammatory cytokines responsible for asthmatic symptoms such as TNF-α and IL-13 [49].

On the other hand, SLE is a complex autoimmune disorder characterized by elevated levels of autoantibodies in the body, affecting different organ systems [51]. In 2005, a study conducted out by Li et al., in BALB/c mice exhibited decreased levels of circulating immunoglobulin; anti-ss DNA, anti-ds DNA, and IgG antibodies upon administration of celastrol at 12 mg/kg/day. This result was better in comparison to the standard treatment of prednisolone at 5 mg/kg/day. Furthermore, the production of IL-10 and NO were also decreased [52]. In the agreement, studies using NZBxW mice model also showed a

Table 2
Summary of clinical trials performed using *Tripterygium wilfordii* and its reported adverse effects.

Disease	Dosage of *Tripterygium wilfordii*	Outcomes	Reported adverse effects of *Tripterygium wilfordii*	Reference
Rheumatoid arthritis	360 mg/day (high dose); 180 mg/day (low dose)	80% of patients with high-dose and 40% of patients with low-dose achieved ACR20 response	Diarrhea, nausea	[88]
	60 mg three times daily	68% of patients achieved ACR20 response as compared to 36% in patients treated with sulfasalazine	Diarrhea, nausea, abdominal pain, dyspepsia, upper respiratory tract infection	[89]
	20 mg three times daily	55.1% of patients achieved ACR50 response as compared to 46.4% in patients treated with methotrexate; 76.8% in patients achieved ACR50 response in combination therapy	Diarrhea, nausea, vomiting, abdominal discomfort, loss of appetite, ALT elevation, leukocytopenia, skin and mucous events, irregular menstruation	[92]
Diabetic nephropathy	120 mg/day for 3 months followed by 60 mg/day for 3 months	Significant reduction of urine protein levels as compared to valsartan	Hyperkalemia, decrease in white blood cell count, vomiting, liver impairment	[91]
Crohn's disease	2.0 mg/kg/day; 1.5 mg/kg/day	2.0 mg/kg/day well tolerated and prolonged remission as compared to mesalazine	Leucopenia, hepatic dysfunction, renal dysfunction, gastrointestinal discomfort	[93]
	60 mg daily	Crohn's Disease Activity Index (CDAI) showed rapid decline during first eight week and lowest at week 10; endoscopic improvement observed in week 12	Diarrhea, headache, nausea	[94]
Psoriasis	20 mg three times daily	No significant difference in treatment efficacy with acitretin, but has lesser adverse effects as compared with acitretin	Menstrual disorders, dry mouth, gastrointestinal discomfort, swelling of lower limbs	[95]
Renal transplantation	1 mg/kg/day for 7 to 14 days before transplantation and continued for 5 years (regular dosage); 2 mg/kg/day for 7 to 14 days before transplantation and within 3 months after transplantation, followed by 1 mg/kg/day for 5 years (double dosage)	Effective in prevention of renal allograft rejection and increased long-term renal allograft survival	Leukopenia, nausea, vomiting, hypertension, hyperlipidemia, diabetes, elevated liver enzymes, opportunistic infections	[96]

decrease in serum autoantibodies, in addition alleviating clinical symptoms and improving survival rate [53]. The reduction in autoantibody production in SLE can be correlated to celastrol's ability to inhibit the formation of neutrophil extracellular traps (NETs) which causes endothelial damage leading to inflammation. This inhibition is mainly associated with the ability of celastrol to inhibit phosphorylation of spleen tyrosine kinase (SYK) and mitogen-activated protein kinase-kinase (MAPKK/MEK), thereby preventing neutrophil oxidative burst and subsequent formation of NETs [54,55].

Together, these findings have demonstrated that celastrol possesses the capability to treat arthritis, inflammatory bowel diseases, asthma, and SLE through the modulation of different molecular targets, and this may pave a pathway for further exploration towards the treatment of other inflammatory diseases.

1.3. Anti-obesity properties

Obesity is the world's foremost cause of mortality, as it is accompanied by other health risks such as cardiovascular disease, cancer, poor mental health, and diabetes mellitus. Obesity is defined as the accumulation of excess fat, leading to a body mass index of more than 30 kg/m^2. Obesity remains a huge disease burden as there are limited remedies available, which encourages a search for new anti-obesity drugs [56,57]. In regard to this, celastrol has been demonstrated to show effects that control obesity in several mice models. Leptin, a hormone produced by adipose tissue, is a hallmark of obesity as it is responsible for suppressing food intake and regulating energy expenditure [58]. However, the development of leptin resistance has become a huge problem in the treatment of obesity, leading to a decrease in weight loss. Celastrol possesses the ability to reverse leptin resistance in cells, thereby increasing leptin sensitivity [59].

A study by Liu *et al.*, in 2015 showed that celastrol reduced the body weight of leptin-resistant mice up to 45% through a decrease in the consumption of food. However, it showed no change in the lean mass of normal mice. Additionally, an increase in leptin levels in lean-mice has shown an increase in the effect of celastrol on the reduction of food consumption and body weight. This shows that the action of celastrol is dependent on the concentration of leptin, further strengthening the hypothesis of celastrol being a leptin sensitizer [54]. The increase in leptin sensitivity is due to the alleviation in hypothalamic endoplasmic reticulum stress through a decrease in PERK phosphorylation and SERCA2B protein levels by celastrol [59,60].

Besides that, a team led by Choi et al., have managed to demonstrate that celastrol prevents the accumulation of lipid and decreases the expression adipocyte-specific markers via an inhibitory effect on the differentiation of adipocytes. This decrease is associated with a reduction in GPDH activity and inhibition of $PPAR\gamma^2$- and C/EBPα-induced transcriptional activity in 3T3-L1 adipocytes [61]. Another study showed that celastrol exerts its anti-obesity actions through (i) inhibiting the generation of reactive oxygen species (ROS), (ii) increasing the activity of antioxidant enzymes, and (iii) inhibiting the activity of the enzyme NADPH oxidase. The combination of these actions is associated with a decrease in the levels of low-density lipoprotein (LDL) and triglyceride in obese mice [62]. However, the exact mechanism of celastrol on obesity has yet to be elucidated and further studies are required to determine its potential for clinical application in the treatment of obesity.

1.4. Neuroprotective properties

Studies have identified celastrol as a potential agent in slowing down neurodegenerative diseases namely Alzheimer's disease (AD) and Parkinson's disease (PD) in animal models. Neurodegenerative diseases are characterized by misfolding and continuous polymerisation of proteins leading to accumulation of protein aggregates. This process is controlled and reversed by a group of intracellular proteins known as

heat shock proteins (HSP), with the class of HSP70 playing the most significant role in influencing protein refolding, reactivation and preventing the formation of aggregates [63,64]. Celastrol has been shown to induce and modulate the activity of these HSPs in the cerebral cortex, thereby exerting a neuroprotective effect [65,66].

Two studies conducted by Chow *et al.*, during the years 2013-14 have demonstrated that celastrol induces the expression of a variety of HSP classes, such as HSP27 and HSP32 in glial cells and HSP70 in neurons in rat models. The increased expression of HSP32 results in the increase in the removal of cytotoxic haem which is elevated in AD through conversion into beneficial antioxidant by-products, reducing the formation of haem-amyloid beta complexes responsible for AD symptoms [66]. As for HSP27, its increased expression allows it to normalize synaptic excitability in AD through preventing the accumulation of Aβ molecules and increasing its clearance [67]. On the other hand, the induction of HSP70 confers the greatest protective effects, contributing not only to its neuroprotective properties but also towards anti-inflammatory properties. The protein works by (i) promotion of apoptosis through TNF, and (ii) suppressing inflammatory responses through NFκB receptor. In the AD, the combination of these mechanisms results in increased Aβ clearance, decreased oligomerization of Aβ, restoration of tau homeostasis, and inhibiting the apoptosis of neurons [68].

Moreover, the neuroprotective properties of celastrol also stems from its ability to induce autophagy, which plays a crucial role in both AD and PD [69]. Autophagy, in short, refers to the degradation of protein aggregates and is largely responsible for removing toxic or damaged proteins. In PD, this mechanism is deregulated, causing the toxic protein aggregates to accumulate and collect in the brain. Moreover, mitochondrial clearance is further impaired, leading to an accumulation of damaged mitochondria [70]. Deng *et.al* conducted a study to test the effects of celastrol using human neuroblastoma SH-SY5Y cells to demonstrate autophagy induction. Through this, it is shown that celastrol protected the cells from death through enhanced autophagy activation. The activation of autophagy reduced the aggregation and accumulation of the α-synuclein protein which is believed to be accountable for the pathogenesis of PD. In addition, it also leads to “mitophagy”, which is the elimination of damaged and dysfunctional mitochondria. This decreases the liberation of reactive oxygen species (ROS), cytochrome C and apoptosis promotion factors, preventing further cell death [71,72].

1.5. Anti-diabetic properties

Lately, the prevalence of diabetes mellitus has substantially increased, resulting in major health challenges and increasing disease burden. Type 2 diabetes mellitus, where decreased utilization of insulin by tissues due to desensitisation occurs is known as insulin resistance which leads to a condition known as hyperglycaemia [73,74]. This has shifted the focus of drug development and discovery to synthetic drugs formulated from medicinal plants, such as celastrol. Studies of celastrol on Type 2 diabetes models have been extensively studied throughout the years, and the compound has demonstrated several anti-diabetic properties, particularly on insulin-resistant models. Kim et al., treated insulin resistant diabetic mice with celastrol for a duration of 2 months and discovered that the compound significantly decreased fasting plasma glucose and haemoglobin A1c levels (HbA1C). This was seen by a lower mean fasting plasma glucose in celastrol treated diabetic mice in comparison to non-treated diabetic mice, with values of 16.2 mmol and 32.1 mmol respectively after 8 weeks of treatment. Moreover, an approximate drop of 42% in HbA1C levels and a drop in basal glucose by 30% at time of 60 min could be observed [75]. This effect can be attributed to the inhibition of NFκB activation, as insulin resistance has been shown to be associated with this protein complex. This inhibition is a direct result of celastrol’s ability to inhibit the degradation and phosphorylation of the IκBα kinase through modification of a cysteine residue of the kinase [76,77]. Concurrently, a decrease in epididymal fat mass and saturated fatty acid levels were observed, and this led to an overall decrease in inflammation and oxidative stress, causing a reduction in diabetic nephropathy. This was further shown by lower creatinine levels in the celastrol treated diabetic mice (29 μmol) - in contrast to both the non-treated diabetic mice (45 μmol) and non-treated normal mice (35 μmol) [75]. Similarly, the effect was due to the inhibition of NFκB by celastrol, leading to improved renal lipid metabolism, hence exerting a reno-protective effect [78,79].

Type 2 diabetes has been implicated with mitochondrial dysfunction and inflammation, hence, celastrol has been shown to modulate these processes [80]. Mitochondrial dysfunction leads to a decrease in mitochondrial oxidation of substances such as lipid, which reduces the occurrence of oxidative phosphorylation, hence affecting insulin sensitivity [81]. In 2015, intensive studies have demonstrated the ability of celastrol to modulate the signalling pathways of insulin in an *in vitro* model of insulin resistant human skeletal muscle cells. Results of the study have shown that celastrol significantly improved the uptake of glucose by up to 86% upon insulin stimulation [82]. This enhancement was related to the regulation of PI3K/Akt pathways, where its stimulation affects mitochondrial functions through the promotion of GLUT4 translocation. This stimulation is achieved through the NFκB receptor, where celastrol has been known to inhibit [83]. (1,2) A rise in the protein phosphorylation of insulin signalling cascades such as NFκB could also be observed, resulting in lower IκBα kinase activity. In addition, the ameliorative properties of celastrol caused an elevation in the levels of phosphorylated 5′AMP-activated protein kinase (AMPK), while concurrently, the activity of protein kinase C theta (PKC- θ) was decreased [82]. AMPK is an enzyme that has been reported to be a key regulator in lipid and glucose metabolism. Activation of this enzyme causes an antagonistic effect on pro-inflammatory cytokines, which modulates the process of mitochondrial dysfunction [81,84]. As for PKC- θ, downregulation of this protein results in a decrease in total and cytosolic diacylglycerol (DAG), which has a positive effect on insulin sensitivity due to the ability of DAG to regulate insulin signalling [85,86]. These findings have shown the ability of celastrol as a potent anti-diabetic agent primarily in the cases of insulin resistance (Fig. 3 and Table 1).

2. Prospects for clinical use

In paving the way for celastrol to be utilised therapeutically, several clinical trials had been conducted for a variety of diseases using TW plant extract. A randomised clinical trial involving 35 rheumatoid arthritis patients was conducted in 2002, whereby 80% of the patients who were given high-dose TW extract (360 mg/day) and 40% of patients who were given low-dose TW extract (180 mg/day) had shown American College of Rheumatology 20% (ACR20) response criteria, signifying improvement in both inflammation and physical function, in contrast to those taking placebo. Nevertheless, diarrhoea and nausea were identified as the most common adverse effects following TW therapy [20,87]. Another randomised trial on RA conducted by Goldbach-Mansky in 2009 had also demonstrated that 68% of patients treated using TW extract (60 mg three times daily) achieved ACR20 response after six months, as compared to 36% in patients treated using sulfasalazine. However, several adverse effects were reported in patients on TW, such as diarrhoea, nausea, abdominal pain, dyspepsia, as well as upper respiratory tract infection [20,88].

On the other hand, TW had also been employed in the clinical trials for cancer. A Phase I trial for the treatment of solid tumour was performed by Kitzen et al. in 2009, using water-soluble derivative of triptolide (F60008), which is a TW diterpernoid. F60008 was given intravenously in 35 cycles to patients with advanced solid tumours. The most common adverse effects observed in the study include mild anaemia, diarrhea, nausea and vomiting, constipation, and fatigue [20,89].

Besides, TW extract was also studied in diabetic nephropathy. In a randomized clinical trial performed in 2013 by Yongchun et al., 65 patients were randomized into 2 treatment groups; (i) 120 mg per day of TW extract for 3 months, followed by 60 mg per day for another 3 months, (ii) 160 mg per day of valsartan for 6 months. Though it was found that TW extract contributed to significant reduction of urine protein levels, there were several reported adverse effects, such as hyperkalaemia, decrease in white blood cell count, vomiting, as well as liver impairment [20,90].

In short, though TW plant extracts provide substantial therapeutic benefits, inappropriate usage of the herb may lead to severe consequences, in which diarrhoea, nausea, and infertility are the most commonly observed side-effects [20,59,91–95]. Therefore, the application of TW extract for the treatment of diseases may be limited due to its toxicological profile. (Table 2) However, as clinical experiences suggest that TW extract possesses great therapeutic potential, and celastrol being the most abundant bioactive compound present in TW, these pharmacological properties may circumvent its toxicological drawbacks, which supports the growing interest on celastrol as the future of drug development. Hence, further trials may be conducted to provide a clear insight on the safety profile of celastrol, as well as to determine its optimum dosage of this compound.

3. Conclusions

Based on the evidences from studies performed by different researchers over the years, celastrol has indubitably a diversity of pharmacological actions that are modulated by various molecular targets and signalling pathways. In spite of that, further studies on the pharmacokinetic properties of celastrol have to be done in order to establish a clear safety profile of celastrol, followed by well-designed clinical trials to evaluate the efficacy of celastrol for the therapeutic use in humans, which paves a new path in the field of drug discovery and development.

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