

Is the traditional Chinese herb, "Celastrol" effective to combat COVID-19?

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To the Editor,

Celastrol is a natural product and has been widely used in traditional Chinese medicine. It contains a pentacyclic triterpenoid isolated from the root extracts of *Tripterygium wilfordii* (Figure 1) [1].



Figure 1. Celastrol isolated from the root extracts of *Tripterygium wilfordii*.

The chemical structure of celastrol is 3-hydroxy-9 β ,13 α -dimethyl-2-oxo-24,25,26-trinoroleana-1(10),3,5,7-tetraen-29-oic acid with chemical formula C₂₉H₃₈O₄ (Figure 2) and molecular weight of 450.61 g/mol. Celastrol has a high susceptibility toward a nucleophilic attack on the carbon rings (Figure 3). By the reduction of *para*-quinone methide in celastrol, also significantly decreases its inhibitory effect on NF-kappaB activation (Figure 4). This is a key active site for the reaction mechanisms of anti-inflammatory [2].

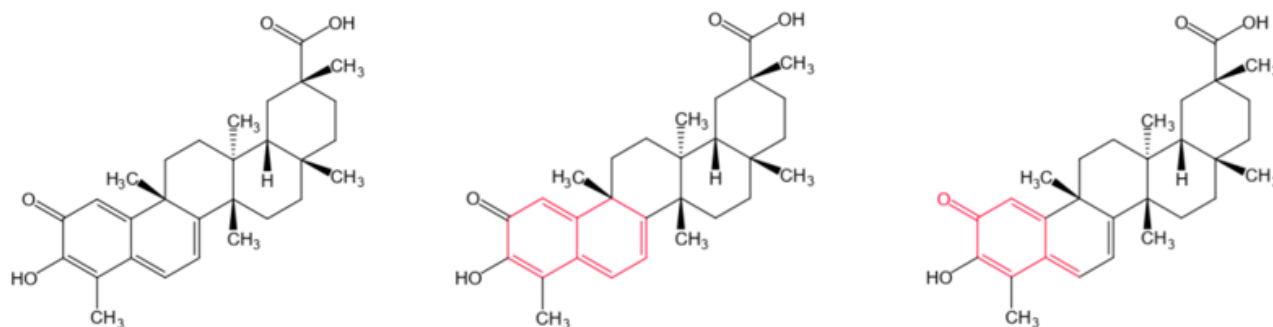


Figure 2. Chemical structure of celastrol. **Figure 3.** Sites of nucleophilic attack. **Figure 4.** *para*-quinone methide.

Celastrol has been used for the treatment of autoimmune diseases, chronic inflammation, neurodegenerative diseases, and many different types of cancers [3]. It suppresses the inflammation or oxidative stress through heat shock proteins and NF-kappaB signaling pathways [4]. Hence, celastrol has anti-inflammatory, anti-cancer, neuroprotective, and therapeutic properties.

The therapeutic potential of celastrol including (i) inhibit LPS (Lipopolysaccharide)-induced inflammatory response in macrophages, microglia, endothelial cells and decrease the proliferation of different cancer cells to prevent their malignant tissue invasion [5]; (ii) sensitize resistant melanoma cell to temozolomide treatment when used in combination therapy and potentiate radiotherapy of prostate cancer cells [6]; (iii) inhibition of I κ B kinase complex α/β [7]; (iv) inhibition of proteasomes [8]; (v) inactivation of Cdc37, p23, and co-chaperones of HSP90 [9]; (vi) activation of HSF1 and induction of HSP70 response [10].

An outbreak of pneumonia termed as “Coronavirus disease-2019 (COVID-19)” in December 2019. This caused by an enveloped positive-sense single-stranded RNA virus. It’s binding to the receptor, angiotensin-converting enzyme 2 (ACE2), and attaching the spike glycoprotein [11]. The ACE2 is then activated by the losartan and soluble in recombinant human ACE2 lead to a severe acute respiratory syndrome-2 (SARS-CoV-2) [12], infections of the respiratory tract, affect the alveoli and the air sacs to the build-up of fluid finally causing inflammatory of the lung (pneumonia).

Celastrol is a potential anti-inflammatory Chinese medicine herb for COVID-19. The possible pharmacological mechanism of celastrol is significantly inhibited lipopolysaccharide-induced the expression of protein and mRNA expression levels encoding the pro-inflammatory cytokines, IL-6, IL-8, and MCP-1 which exhibited a substantial decrease in phosphorylation of the NF- κ B pathway regulators, IKK α/β and I κ B α subsequently inactivated P65. The LPS-induced inflammation by suppressing the NF- κ B signaling pathway [13]. Celastrol inhibits the action of single-stranded RNA virus (SARS-CoV-2), it does not bind to receptors and attaches to the spike glycoprotein for the prevention of respiratory tract inflammation.

Over the past, celastrol has been studied the inhibition activity of SARS-CoV 3CL^{pro}. As the SARS-CoV 3CL^{pro} is a major protease (Mpro) that mediates the proteolytic processing of replicase polypeptides into functional proteins such as S (spiked protein), polymerase, M (membrane protein), N (nucleocapsid protein), and E (small envelope protein), also plays an important role in viral replication. It has been reported celastrol suppressed more than 70% at 30 μ g/mL of SARS-CoV 3CL^{pro}. Celastrol acts as an inhibitor for SARS-CoV 3CL^{pro} because the structure of quinone-methide triterpenes has an anti-inflammatory effect. Thus, celastrol possible to inhibit the SARS-CoV-2 in COVID-19 since this is the same situation [14].

Based on the theory of traditional Chinese medicine, COVID-19 has been defined as dampness toxin pestilence (濕毒瘟). This is a kind of *pestilent Qi* (瘟氣) which has high contagious and powerful toxic

features on severe infectious diseases [15]. This dampness toxin entry interior turns into heat, and repressing the motion of *Qi* (氣) causing the blockage, damage, and infection from the respiratory tract to the lung. Therefore, the applications of celastrol to treat COVID-19 must be clearing heat, removing dampness, and resolving phlegm in the respiratory system [16].

According to the Guangxi Zhuang Autonomous Region, Traditional Chinese Medicine Bureau in China issued a new coronavirus pneumonia treatment plan (trial third version), the traditional Chinese medicine prescription of celastrol has been used to treat the cold dampness lung syndrome (寒濕鬱肺證) for the mild to moderate patients with infection of COVID-19. It's focusing on the expel pathogenic cold and dampness (驅寒化濕) and regulate the motion of *Qi* (氣).

The recommended prescription including 15g Guizhi (*Cinnamomi Ramulus*, 桂枝), 6g Mahuang (*Ephedrae Herba*, 生麻黃), 15g Huoxiang (*Agastache rugose*, 藿香), 15g Cangzhu (*Atractylodis Rhizoma*, 蒼朮), 20g Shichangpu (*Acori Tatarinowii Rhizoma*, 石菖蒲), 15g Shanzha (*Crataegus pinnatifida*, 焦山楂), 15g Baikouren (*Amomun kravanh Pirreex Gagmep*, 白蔻仁), 12g Xingren (*Ansu Apricot Seed*, 杏仁), 12g Zi Yuan (*Aster tataricus*, 紫苑), 12g Chenpi (*Citri Reticulatae Pericarpium*, 陳皮), 15g Fa ban xia (*Ternate Pinellia*, 法半夏), 15g Fuling (*Poria*, 茯苓), 15g Gualou (*Trichosanthis Fructus*, 瓜蒌殼), 15g Tinglizi (*Descurainia Semen*, 葶苈子), 12g Lianqiao (*Forsythiae Fructus*, 連), 15g Huangqin (*Scutellariae Radix*, 黃芩), 5g Zhi Gan Cao (*Glycyrrhizae Radix et Rhizoma*, 炙甘草), 30g Shengjiang (*Zingiberis Rhizoma Recens*, 生姜). The following three Chinese medicine herbs must according to the actual situation be decocted first for 2 hours including 15g Baizhi (*Angelicae Dahuricae Radix*, 白芷), 15g Houpo (*Magnoliae Officinalis Cortex*, 厚朴), 12g Lei Gong Teng (*Tripterygium wilfordii* Hook. f, 雷公藤) [17].

To conclude the above information, it has been shown that the Chinese herb, "celastrol" is effective to combat COVID-19 because of its anti-inflammatory property. However, more work must be done such as a meta-analysis and systematic review for celastrol efficiency and safety, compare to the other anti-inflammatory traditional Chinese herbs such as artemisinin or curcumin before widely used.

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