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Could Celastrol Nanosystem be Suitable for the Treatment of COVID-19?

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Abstract: The COVID-19 pandemic occurred over two years and has not yet been finished. There are some possible Chinese medicines formulations used to prevent and treat COVID-19. Single pure herbal such as curcumin is the most common to combat SARS-CoV-2 with antioxidant, anti-inflammatory, antibacterial, antiviral, antitumor, and hepatoprotective properties. This short communication describes another single pure herbal, "Celastrol", research progress and its nanosystem for the treatment of COVID-19.

Keywords: celastrol; nanosystem; treatment; COVID-19.

1. Introduction

The COVID-19 pandemic has occurred for over two years. This infection is caused by the SARS-CoV-2 virus. It binds to an angiotensin-converting enzyme 2 (ACE2) receptor of spike glycoprotein. The transmembrane protease serine 2 (TMPRSS2) and a disintegrin metallopeptidase domain 17 (ADAM17) interact, leading to a high level of angiotensin-converting enzyme 2 (ACE2) expression that increases the lung vascular permeability causing pulmonary edema, then pneumonia in the lung [1-6].

Some possible Chinese medicines formulations are used to prevent and treat SARS-CoV-2 such as *qingfei paidu* decoction (QPD), *gancao ganjiang* decoction, *sheganmahuang* decoction, *qingfei touxie fuzheng* recipe, etc. [7-11]. These are the compound prescriptions that may have fewer and less severe side effects than single pure herbals [12]. This is seldom to use a single pure herbal for curing human disease; it is only dietary supplements. However, researchers continually investigate single pure herbs' active ingredients and fractions.

The most common single pure herbal is "curcumin" to fight against COVID-19, which possesses antioxidant, anti-inflammatory, antibacterial, antiviral, antitumor, and hepatoprotective properties [13]. This inhibits SARS-CoV-2 entry into the host cell because H-bonds for its keto and enol forms strongly bind with viral spike protein on the angiotensin-converting enzyme 2 (ACE2) receptor [14]. There is one clinical study for oral administration of 1000 mg curcumin supplement (turmeric extract contains 95% curcuminoids), and 10 mg black pepper extract could reduce the symptoms of anosmia and ageusia caused by COVID-19 infection [15]. Therefore, curcumin has been used as a single-drug therapy in clinical

application. Still, it exhibits poor bioavailability with low solubility or undetectable concentrations in blood and extra-intestinal tissues (poor absorption) of the human body [16]. Besides curcumin, celastrol is used as a single pure herbal to combat COVID-19. It contains a pentacyclic triterpenoid isolated from the root extracts of *Tripterygium wilfordii* (TW) [17].

2. Research Progress

Evidence has shown that celastrol has antiviral and anti-inflammatory biological activities (Table 1) [18-20]. This is a usual natural herbal and has been used widely in traditional Chinese medicine to treat chronic diseases. Oral administration of TW tablets (120 mg daily) for 12 weeks to reduce the symptom of inflammation [21]. This is a therapeutic agent in the clinical study, but celastrol has some limitations, which are the same as curcumin. It has low solubility and results in poor bioavailability. How can we minimize these problems?

Nanotechnology is a good choice of Chinese medicine for enhancing pharmacological effects and improving the administration route, which changes the bioavailability, reduces the adverse effects, achieves sustained release, and achieves targeted delivery [22]. Like curcumin, it has been developed into nanoemulsions, liposomes, nano-gels, micelles, and nanoparticles [23].

Table 1. Application of celastrol in COVID-19.

	Yapasert R et al. (2021) [18]	**Habtemariam S et al. (2020) [19]**	**Caruso F et al. (2020) [20]**
Topic	Coronavirus Infection Associated Cell Death Signaling and Potential Therapeutic Targets	Should we try the natural anti-inflammatory product celastrol for COVID-19	*Tripterygium wilfordii*, Inhibits Main Protease $3CL^{pro}$ of COVID-19
Function	Antiviral & Anti-inflammatory	Anti-inflammatory	Antiviral & Anti-inflammatory
Mechanism	Celastrol is a proteasome inhibitor to modify NF-κB signaling and provides a responsible method for treating SARS-CoV-2 infected patients which inhibits the viral life cycle, including viral entry, replication, assembly, and release of COVID-19 virions	Celastrol is a viral inhibitor for the host cells to replicate and release, which suppresses the NF-κB signaling to reduce the levels of inflammatory cytokines such as interleukin-8 (IL-8), tumor necrosis factor-α (TNF-α), and monocyte chemoattractant protein-1	The antioxidant property of celastrol, when scavenging the superoxide radical, with its inhibitory profile on the main protease COVID-19 active site, $3CL^{pro}$, which covalent binding with Cys145 through the H-bond
Result & significant	SARS-CoV-2-infected cell death through the regulation of cell death, i.e., apoptosis, necroptosis, pyroptosis, autophagy, and PANoptosis	SARS-CoV-2 infection and its inflammatory response are reduced by celastrol through the NF-κB pathway for alleviating chronic obstructive pulmonary disease in the lung	The anti-SARS-CoV-2 biological activity is stimulated by celastrol, which is also a protease inhibition for curing some lung diseases disorder

3. Discussion

In past studies, there are several celastrol nanosystems have been developed which enhance its bioavailability, increase water solubility, control the rate of release, and target delivery (Table 2) [24-27]. We proposed that celastrol nanosystems could be a powerful tool for COVID-19 infection, which increases its effectiveness of antiviral properties and target the human immune response. As the SARS-CoV-2 virus causes the COVID-19 infection, the celastrol nanosystem might inhibit virus-cell interaction, membrane fusion, cell internalization,

transcription, translation, and even suppress the SARS-CoV-2 replication, causing SARS-CoV-2 damage or degradation [28].

Table 2. Nano-systems of celastrol.

	Harris JM et al. (2005) [25]	**Veronese FM et al. (2005) [26]**	**Bareiss B et al. (2010) [27]**
Topic	Effect of pegylation on pharmaceuticals	PEGylation, a successful approach to drug delivery	Controlled release of acyclovir through bioengineered corneal implants with silica nanoparticle carriers
Nanosystem	Polyethylene glycol (PEG) incorporated with celastrol	Celastrol-loaded poly(ethylene glycol)-block-poly(ε-caprolactone) nanopolymeric micelles	Axitinib (AXT) and celastrol (CST) combination nanoparticles (ACML)
Result & significant	Increase the water solubility of celastrol, enhance the passive targeting effect on tumors through absorption and metabolism	Improve the hydrophilicity of celastrol and PEGylated polyaminoacid-capped celastrol-loaded mesoporous silica nanoparticles (CMSN-PEG) to enhance the targeted delivery of celastrol	Increase the water solubility of celastrol, cellular uptake, and inhibit angiogenesis as well as the mitochondrial function in SCC-7, BT-474, and SH-SY5Y cells

4. Conclusion

The above information demonstrates that the celastrol nanosystem is possible to treat COVID-19. However, much more work needs to be done, including the safety assessment of the celastrol nanosystem in clinical trials. Although celastrol has been considered a lead Chinese medicine for several human illnesses, its toxicity, dosage, and absorption into the human body remain to be investigated.

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Conflicts of Interest

The authors declare no conflict of interest.

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