Review Article

Traditional Chinese medicine, "Celastrol" and its nanotechnology for cancers: a narrative review

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Abstract: Nanotechnology is widely used in traditional Chinese medicine. The nanonization technology provides a platform for the development of molecular medicine such as detection and treatment of illnesses, body part replacement, regenerative medicine, nanoscale surgery, and targeted delivery of drugs. Nano Chinese medicine delivery system plays a significant role in the drug formulations, targeting area, and controlled its drug release. These can be utilized as delivery agents by encapsulating drugs, attaching therapeutic drugs, and delivering the drug to target tissues. Some of the bioactive natural compounds in traditional Chinese medicine such as celastrol have been incorporated with nanoparticles for curing diseases through enhancing bioavailability, targeting, and controlling its release, resulting in better therapeutic effects regarding the use of nanomaterials in drug delivery. There are several nanosystems for celastrol that have been reported also discussed the mechanism, and the toxicity of several types of celastrol nanoparticles. Its nano-system helps to increase solubility and stability, avoid toxicity, enhance pharmacological activity, improve tissue distribution, sustain delivery, and protect from physical or chemical degradation. Folic acid is the most common cancer targeting agent. This is water-soluble and delivers celastrol selectively to cancer cells only. Thus, nanotechnology of traditional Chinese medicine is attracting scientists' attention.

Keywords: Traditional Chinese medicine; celastrol; nanotechnology

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Introduction

Nanotechnology was a "technology on the nanoscale" identified in the late 1960s at ETH Zurich (1). It employs single atoms and molecules form functional structures to improve the chemical (2), physical, biological properties, processes, and phenomena of the materials (3). This includes the design, characterization, manufacture, shape, and size-controlled application of matters in the nanoscale (4). The size of nanoparticle system is ranged from a few nanometers (micelles) to several hundreds of nanometers

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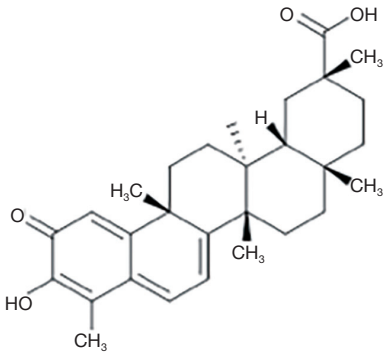

Figure 1 Chemical structure of celastrol.

(liposome) and the size of nanoscale protein material is often between 3 to 10 nanometers (nm) (5). Its nano-drug delivery system could interact with biomolecules locate inside or on the cell surface. The nanoparticle of the encapsulated drug would be delivered and penetrated into the cell. It could also be modified with fragments of antibodies or ligands, which targeting antigens or receptors on the cell surface for improving the specificity of drug delivery (6). The nano-drug delivery systems include organic nanoparticles such as nanoscale liposomes and micelles and inorganic nanoparticles such as gold or magnetic nanoparticles (7). Nanoparticles can penetrate the tissue system, facilitate cellular uptake of the drug, ensure action at the targeted location, and be affixed to the surface (8). This strategy applies to traditional Chinese medicine such as celastrol. In this mini-narrative review, we discuss the background of traditional Chinese medicine, "Celastrol" and its mechanisms of the nano-system for cancers as well as the toxicity and cancer targeting agent. We present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/lcm-20-48).

Methods

This mini-review summarized the articles on celastrol in nanotechnology for treating cancers through some library search engines such as SCI/SCIE, PubMed, and Scopus for at least 30–40 journals.

Background of celastrol

Celastrol is a pentacyclic triterpenoid, belongs to the family of quinone methides. Its formula $C_{29}H_{38}O_4$ (*Figure 1*) with a molecular weight of 450.619 $gmol^{-1}$, isolated from the root extracts of *Tripterygium wilfordii* and used to treat chronic inflammatory and autoimmune diseases (9). Celastrol induces apoptosis in various cancer cell lines via inhibition of inhibitor of kappa B kinase (IKK) (10), proteasome (11), topoisomerase activity (12), vascular endothelial growth factor (VEGF) receptor expression (13), and induction of heat shock proteins (14).

Accumulating evidence indicated that celastrol owns therapeutic potentials and diverse biological activities, including anti-inflammatory and anticancer properties. Celastrol inhibits swelling recurrence up to 55.25% when 10 mg/kg/day is used. It decreases immune cell filtration and proliferation into the synovial membrane, leading to decrease swelling, bone destruction as well as prevent inflammation. Prostate tumor weight is reduced by approximately 73% after administration of celastrol at 2 mg/kg/day for 16 days (15). However, its poor water solubility (13.25±0.83 mg/mL at 37 ℃) (16), low bioavailability (17.06%) in the oral administration (17,18), and poor tumor selection represent major pitfalls for its clinical applications.

Mechanisms

In general, celastrol inhibits cell proliferation and induces cell apoptosis in tumors (19). It acts as a natural inhibitor of proteasome for regulating the activity of NF-κB. The pro-apoptotic protein Bax degrade the misfolding intracellular proteins because NF-κB transcription contributed to the cell migration, cell apoptosis as well as cell cycle progression and this is also one of the important factors for oncogenesis (20,21). By the deactivation of NF-κB activity, it would be influenced the level of proteasome leading to cell deaths or cancers. Thus, celastrol is an inhibitor for NF-κB transcription. Besides, celastrol blocks the JAK/STAT signaling pathway by reducing the levels of cytokines or growth hormones that trigger JAK/STAT protein activation. It inhibits STAT3 phosphorylation and STAT3-mediates IL-17 expression, and T-helper 17 (Th17) differentiation and proliferation in multiple myeloma cells (22).

Nano-system

The efficacy of a nano-system in drug delivery depends on the size, shape, and other inherent biophysical or chemical characteristics. Polymeric nanomaterials act as carriers that exhibit high biocompatibility and biodegradability

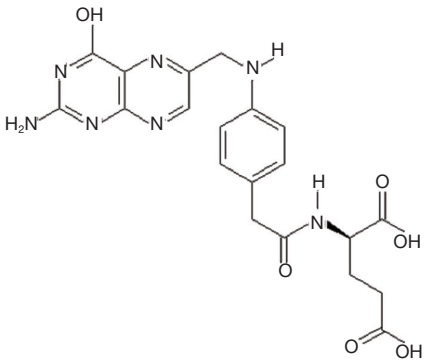

Figure 2 Chemical structure of folic acid.

properties, various synthetic polymers such as polyvinyl alcohol, poly-L-lactic acid, polyethylene glycol, and poly(lactic-*co*-glycolic acid), and natural polymers (e.g., chitosan) that are useful in targeted drug delivery (23).

Growing studies showed that nanoparticle encapsulation improved the solubility of active components because the surface area increases and consequently its dissolution rate to have better bioavailability such as triptolide-loaded nanoparticles changed the solubility of triptolide, controlled its release, realized the target delivery of triptolide, and avoided the toxicity at non-target sites (24). Triptolide was another active component from *Tripterygium wilfordii*. Its cytotoxicity similar to the celastrol. However, celastrol is better in term of tolerance and efficacy in cancer since it was more soluble in water when combined the usage of nanotechnology (25). The as-prepared berberine-loaded chitosan nanoparticles were prepared and investigated the characteristics of *in vitro* release. Its encapsulation ratio of berberine-loaded chitosan nanoparticles and the total drug release degree are 65.4%±0.7% and 56.8%±1.7% respectively (26).

There are several nanosystems for celastrol that have been reported including: (I) The celastrol nanoparticle is modified to amphipathic molecules for enhancing the passive targeting effect on tumor through absorption and metabolism. Polyethylene glycol (PEG) has been introduced to make the celastrol dissolve in water easily (27). (II) Celastrol-loaded poly(ethylene glycol)-block-poly(ε-caprolactone) nanopolymeric micelles were also developed to improve the hydrophilicity of celastrol and PEGylated polyaminoacid-capped celastrol-loaded mesoporous silica nanoparticles (CMSN-PEG) to control the *in vitro* drug release behavior which exhibited high cytotoxicity in different cancer cells (28). (III) Axitinib (AXT) and celastrol (CST) combination nanoparticles (ACML) with CST loaded in the mesoporous silica nanoparticles (MSN) and AXT in PEGylated lipidic bilayers showed effective inhibition on angiogenesis and mitochondrial function. It's efficiently internalized in SCC-7, BT-474, and SH-SY5Y cells (29-31).

These celastrol nanoparticles increased water solubility and cellular uptake (32-34). Most of the studies focused on intra-peritoneal injection and oral administration (35-38). It mainly focused on the solubility, cellular uptake, and *in vitro* drug release behavior of celastrol nanoparticles.

Toxicity

The toxicity of several types of celastrol nanoparticles are based on physicochemical properties such as interaction within the cells and the size of nanoparticles are related to the cytotoxicity. Smaller nanoparticles have a large surface area and penetrate the cells easily lead to cellular damage (39). Particle surface charges are another factor affecting the cellular uptake of nanoparticles. It's correlated to cytotoxicity because of the interaction between the cell organelles and their biomolecules (40). The stronger the electrostatic attraction, the more likely is the nanoparticles are to be internalized and would be damaged the other molecules through surface charges (41). Different shapes of the nanoparticles are also influenced by their toxicity as they generate different levels of reactive oxygen species (ROS) at the active sites in the cells for specific functions (42).

Cancer targeting agent

Basically, folic acid (*Figure 2*) or folate (pteroylglutamate) is water-soluble and often used as a targeting agent that can deliver celastrol selectively to cancer cells with overexpression of folate receptor on the surface (43,44). Folate receptor undergoes endocytosis within tumors. When the nano-carrier is passively targeted to tumors, it remains within the tumor or it diffuses out of the tumor and back into the bloodstream due to the high interstitial pressure within solid tumors and random diffusion. Folate modification makes the nano-carriers achieve a greater affinity in the tumor. The nano-conjugate is internalized by the folate-receptor via an endocytic pathway and is transported to an endosome or lysosome by intracellular vesicle transport.

Caveolae is small (approx. within 50 nm in diameter) flask-shaped pits in the membrane that resembles the shape

of a cave. It constitutes up to the plasma membrane and uptake extracellular molecules via the specifically mediated folate-receptor by potocytosis that uses caveolae vesicles to bring molecules of various sizes into the cell and released into the cytosol (45). This specific binding of folic acid to folate receptor on cancer cells. For instant, folic acid-modified Doxorubicin nanoparticles (Dox-PLD-FA) showed a specific target to cancer cells, which overexpress the folate receptor (FR) (46).

Conclusions

Nanotechnology serves as an efficient tool to make celastrol into nanoscale and modify its physical properties. Incorporation of celastrol in the nano-system helps to increase solubility and stability, avoid toxicity, enhance pharmacological activity, improve tissue distribution, sustain delivery, and protect from physical or chemical degradation.

Some nano-systems for celastrol were developed such as polyethylene glycol (PEG) celastrol, celastrol-loaded poly(ethylene glycol)-block-poly(ε-caprolactone) nano-polymeric micelles, and the combination of axitinib (AXT) with celastrol nanoparticles in the mesoporous silica. Recently, folic acid-modified Doxorubicin nanoparticles (Dox-PLD-FA) are designed and showed a specific target to cancer cells compared with the other nano-systems. Hopefully, nano-systems of celastrol would be further developed in the future to improve its therapeutic efficacy.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/lcm-20-48). The authors have no conflicts of interest to declare. This manuscript is part of the Mr. Siukan Law, 2019 PhD in Chinese medicine thesis (CUHK).

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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