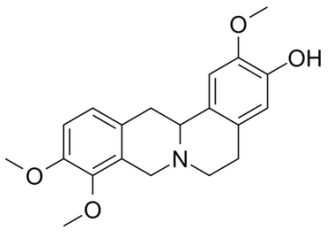
APPLICATION OF CORYPALMINE IN PREPARATION OF OSTEOARTHRITIS TREATMENT DRUG

Field of the Invention

The present invention relates to the field of pharmaceutical technology, specifically the application of corypalmine in preparation of osteoarthritis treatment drug.

Background to the Invention

Osteoarthritis (OA) refers to a chronic inflammatory disease characterized by synovitis and progressive cartilage degeneration. According to data from the World Health Organization, by 2020, OA had risen to become the fourth leading cause of disability. Its main symptoms include joint pain, stiffness, limited mobility, and joint deformities. In severe cases, it can cause disability and seriously affect the patient's physical and mental health and quality of life. Non steroidal anti-inflammatory drugs are commonly used in clinical practice to treat osteoarthritis. Although they can alleviate joint inflammation and pain, they cannot effectively prevent disease progression and may lead to inevitable side effects. Research has shown that regulating macrophage polarization can alleviate synovial inflammation and improve joint cartilage damage, which is a new direction for the treatment of osteoarthritis. Monomer compounds of traditional Chinese medicine are active extracted ingredients with various medicinal properties, such as antioxidant, anti apoptotic, antibacterial and anti-inflammatory effects. Their single composition and minimal side effects make them valuable resources for new drug development. corypalmine is an alkaloid derived from Chinese medicinal herbs such as corydalis yanhusuo. The molecular formula of corypalmine is $C_{20}H_{23}NO_4$:



The patent with application number 20201005359.9 discloses a dopamine receptor antagonist and its use, wherein the dopamine receptor antagonist is D-corypalmine and their pharmaceutically acceptable salts or precursor compounds. The dopamine receptor antagonist can antagonize calcium ion influx caused by dopamine receptor activation. Animal experiments have shown that D-corypalmine have good analgesic effects as dopamine receptor antagonists in acute pain, inflammatory pain, and bone cancer pain, but their role in osteoarthritis is not clear. Corypalmine can effectively inhibit the secretion of inflammatory factors, inhibit M1 macrophage polarization, promote M2 macrophage polarization, inhibit synovial inflammation, promote cartilage repair, and effectively treat osteoarthritis.

Statement of Invention

The purpose of this section is to outline some aspects of the embodiments of the present invention and briefly introduce some preferred embodiments. Simplification or omission may be made in this section, as well as in the abstract and title of the present application, to avoid blurring the purpose of this section, abstract, and title, and such simplification or omission cannot be used to limit the scope of the present invention.

Therefore, the purpose of the present invention is to provide the application of corypalmine in preparation of osteoarthritis treatment drug. By using corypalmine, the secretion of inflammatory factors can be effectively inhibited, M1 macrophage polarization can be suppressed, M2 macrophage polarization can be promoted, synovial inflammation can be

suppressed, cartilage repair can be promoted, and osteoarthritis can be effectively treated.

To solve the above technical problems, according to one aspect of the present invention, the present invention provides the following technical solution:

Application of corypalmine in preparation of osteoarthritis treatment drug.

As a preferred solution for the application of corypalmine in preparation of osteoarthritis treatment drug according to the present invention, wherein: the osteoarthritis is synovitis and cartilage degeneration.

As a preferred solution for the application of corypalmine in preparation of osteoarthritis treatment drug according to the present invention, wherein: the synovitis is caused by polarization imbalance of macrophages.

As a preferred solution for the application of corypalmine in preparation of osteoarthritis treatment drug according to the present invention, wherein: the corypalmine is used to inhibit the secretion of pro-inflammatory factors Il-1β and Il-6.

As a preferred solution for the application of corypalmine in preparation of osteoarthritis treatment drug according to the present invention, wherein: the corypalmine is used to promote the expression of inflammatory regulatory proteins Arg1 and Igf1.

As a preferred solution for the application of corypalmine in preparation of osteoarthritis treatment drug according to the present invention, wherein: the corypalmine is used to inhibit chondrocyte apoptosis.

As a preferred solution for the application of corypalmine in preparation of osteoarthritis treatment drug according to the present invention, wherein: the corypalmine is used to inhibit the expression of matrix metalloproteinase Mmp13.

As a preferred solution for the application of corypalmine in preparation of osteoarthritis

treatment drug according to the present invention, wherein: the corypalmine is used to promote the expression of extracellular matrix Col2a1 and Acan in chondrocytes.

As a preferred solution for the application of corypalmine in preparation of osteoarthritis treatment drug according to the present invention, wherein: the medicine includes tablet, capsule, injection, sustained-release microsphere and gel, and the medicine takes the corypalmine as the active ingredient, supplemented by pharmaceutically acceptable auxiliary materials or carriers.

As a preferred solution for the application of corypalmine in preparation of osteoarthritis treatment drug according to the present invention, wherein: the auxiliary materials include any one or more of microcrystalline cellulose, magnesium stearate, hydroxypropyl methylcellulose, and lactose.

As a preferred solution for the application of corypalmine in preparation of osteoarthritis treatment drug according to the present invention, wherein: the carrier comprises any one or more of hyaluronic acid, polylactic acid hydroxyacetic acid copolymer, physiological saline, cholesterol, and hydroxymethylcellulose.

Compared with existing technologies, the present invention has the following beneficial effects:

1. Dual regulation of macrophage polarization:

Significantly inhibited LPS induced activation of M1 macrophages (with a 30% decrease in Cd86 expression);

Promote polarization of M2 macrophages (Mrc1 expression increased by 50%, Cd200r4 expression increased by 100%);

Reduce the secretion of pro-inflammatory factors (Il-1β, Il-6) by 30-70% and increase the

expression of inflammatory regulatory proteins (Arg1, Igf1) by 30-100%;

2. Efficient cartilage protection effect:

Inhibition of chondrocyte apoptosis (reduced Tunel staining)

Significantly enhance the expression of key components Col2a1 and Acan in cartilage matrix;

Reduce cartilage OARSI score by 45% in mouse OA model;

Brief Description of the Drawings

In order to more clearly illustrate the technical solution of the embodiments of the present invention, the present invention will be described in detail below in conjunction with the accompanying drawings and detailed embodiments. It is obvious that the accompanying drawings described below are only some embodiments of the present invention. For those skilled in the art, other drawings can be obtained based on these drawings without creative labor. Among them:

FIG. 1 shows the effect of corypalmine on the cellular activity of macrophages;

FIG. 2 shows M2 polarization of macrophages promoted by corypalmine;

FIG. 3 shows the inhibition of M1 polarization in macrophages by corypalmine and the reduction of inflammatory cytokine secretion;

FIG. 4 shows the alleviation of synovitis in mice with osteoarthritis by corypalmine;

FIG. 5 shows the inhibition of articular cartilage degeneration by corypalmine.

Detailed Description

In order to make the above objectives, features, and advantages of the present invention more obvious and understandable, the specific embodiments of the present invention will be described in detail below in conjunction with the accompanying drawings.

The following description elaborates on many specific details to facilitate a full understanding of the present invention, but the present invention can also be implemented in other ways different from those described herein. Those skilled in the art can make similar generalizations without violating the connotation of the present invention. Therefore, the present invention is not limited by the specific embodiments disclosed below.

In order to clarify the purpose, technical solution, and advantages of the present invention, the embodiments of the present invention will be further described in detail with reference to the accompanying drawings.

The present invention provides the application of corypalmine in preparation of osteoarthritis treatment drug. By using corypalmine, the secretion of inflammatory factors can be effectively inhibited, M1 macrophage polarization can be suppressed, M2 macrophage polarization can be promoted, synovial inflammation can be suppressed, cartilage repair can be promoted, and osteoarthritis can be effectively treated. Please refer to Figures 1-5:

The osteoarthritis is synovitis and cartilage degeneration.

The synovitis is caused by polarization imbalance of macrophages.

The corypalmine is used to inhibit the secretion of pro-inflammatory factors Il-1β and Il-6.

The corypalmine is used to promote the expression of inflammatory regulatory proteins Arg1 and Igf1.

The corypalmine is used to inhibit the expression of matrix metalloproteinase Mmp13.

The corypalmine is used to promote the expression of extracellular matrix Col2a1 and Acan in chondrocytes.

The medicine includes tablet, capsule, injection, sustained-release microsphere and gel, and the medicine takes the corypalmine as the active ingredient, supplemented by pharmaceutically acceptable auxiliary materials or carriers.

The auxiliary materials include any one or more of microcrystalline cellulose, magnesium stearate, hydroxypropyl methylcellulose, and lactose.

The carrier comprises any one or more of hyaluronic acid, polylactic acid hydroxyacetic acid copolymer, physiological saline, cholesterol, and hydroxymethylcellulose.

1. In vitro experimental data:

1) Inhibition of inflammatory cytokine secretion:

Experimental model - LPS induced macrophage inflammation model;

Result: Il-1β secretion decreased by 30% (vs. LPS group), and Il-6 secretion decreased by 70%;

Experimental model - IL4 induced macrophage M2 polarization model;

Result: Argl expression increased by 30% (vs. IL4 group), and Igf1 secretion increased by 100%;

2) Regulating macrophage polarization:

M1 macrophages (pro-inflammatory):

The expression of Cd86 (M1 surface marker) decreased by 30%;

M2 macrophages (anti-inflammatory type):

The expression of Mrc1 (M2 surface marker) increased by 50%, and the M2 marker Cd200r4 increased by 100%;

2. In vivo experimental data:

Mouse OA model (induced by meniscus instability surgery):

Dosage regimen: Corypalmine (intra-articular injection of 50 μ M, 100 μ M, 250 μ M, once a week for 8 weeks);

Result: Synovitis was significantly reduced and cartilage damage was significantly repaired (vs. model group);

Although the present invention has been described with reference to embodiments in the preceding text, various improvements can be made and components can be replaced with equivalents without departing from the scope of the present invention. Especially, as long as there is no structural conflict, the various features disclosed in the embodiments of the present invention can be combined with each other in any way. The lack of exhaustive description of these combinations in this specification is only for the sake of omitting space and saving resources. Therefore, the present invention is not limited to the specific embodiments disclosed herein, but includes all technical solutions falling within the scope of the claims.