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ORIGINAL ARTICLE

Great Burdock Extract on Rabbit Corpus Cavernosum

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Great burdock (*Arctium lappa*) is an edible vegetable that is also used as herbal medicines in many countries. Traditionally, burdock is used to slow aging, cure male impotence and in beauty care. However, the relevant mechanisms and scientific proof of its actions have not yet been elucidated. The expansion of the corpora cavernosum smooth muscle cells of the penis is the main regulating factor of erection, and the nitric oxide-soluble guanylyl cyclase-cyclic guanine monophosphate (NO-sGC-cGMP) pathway plays an important role in maintaining expansion of the corpora cavernosum. The current study aims are to investigate the effects of burdock extract on a rabbit's corpora cavernosum. The effects of burdock on the protein expression in the cavernosum tissues and smooth muscle cells were investigated, and the changes in cGMP level were determined via enzyme-linked immunosorbent assay kit analysis. Our results showed that burdock extract increased the expression of neuronal nitric oxide synthase, cGMP-dependent kinase, sGC_{α1} and sGC_{β1} in the smooth muscle cells and tissues of the corpora cavernosum, while the expression of phosphodiesterase-5 was inhibited. Additionally, cGMP levels become elevated in the smooth muscles after treatment with burdock extract. In summary, our data suggest that burdock can facilitate in the relaxation of the corpora cavernosum; however, the benefits of burdock in treating erectile dysfunction remain to be resolved.

Key Words: Burdock extract; corpus cavernosum; male impotence; NO-sGC-cGMP pathway

Introduction

Arctium lappa, Linn is a herbaceous plant classified in the Asteraceae family, and its common English

name is great burdock. Burdock roots are similar in shape to those of Ginseng. The abundant nutrients of *Arctium lappa* Linn include inulin,¹ polyphenols, chlorogenic acid, proteins, carbohydrates, vitamins,

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amino acids, minerals, and unsaturated fatty acids. Inulin is a polysaccharide that stimulates hormonal secretion, improves strength, muscular and skeletal development and reduces male impotence. Aside from being a food, *Arctium lappa* Linn may also be used as medicine. The aglycone in burdock is an active ingredient that inhibits urinary protein excretion, and can improve serum biochemical indicators.^{2,3} It is demonstrated to have anti-nephritis activity, and can be used to treat acute nephritis, nephrotic syndrome, and prevent senile dementia.^{4,5} Moreover, the ingredients of burdock have been shown to reduce acid-induced chronic gastric ulcers, reduce oxidative stress and cell injury in liver cells,^{2,3} and exhibit anti-tumor activity.⁶ Pharmaceutical companies have also developed *Arctium lappa* Linn as a health supplement for the market.

Erectile dysfunction (ED), known as male impotence, is a sexual dysfunction in which men are unable to achieve full erections or can sustain only brief erections for sexual performance.^{7,8} While erectile dysfunction can occur at any age, it is more common in the elderly. The penis contains two chambers, called the corpora cavernosum, which run the length of the upper side of the penis. Filling the corpora cavernosum is a spongy tissue consisting of smooth muscles, fibrous tissues, spaces, veins, and arteries. An erection occurs as a hydraulic effect due to blood entering and being retained in sponge-like bodies within the penis. The pathogenesis of psychogenic ED is still unclear. However, it was suggested that organic and psychogenic factors may cause an abnormal function in the NO-cGMP pathway and affect the smooth muscle relaxation, thereby resulting in ED.⁹

It is known that nitric oxide (NO) facilitates in the functions of the smooth muscles of the corpora cavernosum.¹⁰ Nitric oxide induces the functions of GTP and leads to the release of large amounts of cyclic guanine monophosphate (cGMP), which in turn activates the cGMP-dependent kinase (PKG) inside the muscle cells.¹¹ The kinase then phosphorylates ion channels and decreases the calcium concentration inside the cells, leading to relaxation of the corpus cavernosum.¹² As a result, the blood flow and perfusion in the cavernous artery increases, the corpus cavernosum and cavernous sinus expand, and the cavernous vein is obstructed. Erection is then achieved when the blood inflow is greater than outflow.^{10,13}

The relaxation of smooth muscles of the corpora cavernosum is the main regulating factor of erection, and NO-soluble guanylyl cyclase (sGC)-cGMP regulating pathway plays an important role in maintaining the relaxation of the smooth muscles of the corpora cavernosum. The goals of the current study are to investigate the effects of burdock extract on the corpora cavernosum of rabbits by

detecting the expression of the NO-sGC-cGMP pathway related proteins and the changes of cGMP level in the smooth muscle cells of the corpora cavernosum treated with burdock extract.

Materials and Methods

Culture of smooth muscle cells of corpora cavernosum

Male white rabbits were provided from National Laboratory Animal Breeding and Research Center (Taipei, Taiwan) and housed under conditions of constant temperature and controlled illumination. All animals used for this study were approved by the Animal Care and Use Committee at the Kaohsiung Medical University. The excised rabbit corpora cavernosum tissues were cultured in Dulbecco's modified Eagle's medium (Invitrogen Corp., Carlsbad, CA, USA) containing 20% fetal bovine serum, 2 mM L-glutamine, penicillin (100 U/mL), streptomycin (0.1 mg/mL), and amphotericin B (0.25 µg/mL). After the cell concentration had reached 90% confluency, cells were washed in phosphate buffered saline and treated with 0.05% trypsin/0.02% EDTA at 37°C. After cells detached from the plate, 4 mL medium containing serum was added to the culture to halt the actions of the trypsin. Cell suspensions were placed in sterile centrifuge tubes and washed with a medium once in a centrifuge. A fraction of cell pellets was used in subsequent cultures. The morphology of the smooth muscle cells were confirmed under optical microscope.

Drug toxicity test

Burdock extracts were provided by the manufacturer (Dong Yuan Biotech Pharmaceutical Co., Ltd, Taiwan) and was extracted by water at 95°C. The extracted solution was filtered and then freeze dried. MTT [3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay was used to assess drug toxicity. Smooth muscle cells were cultured in 24-well plates at a concentration of 10⁵ cells per well. After culturing for 24 hours, cells were treated with indicated concentrations (0.2, 0.4, 0.6, 0.8, 1 mg/mL) of burdock extract for 24 hours. The medium was removed and 0.5 mg/mL of MTT reagent was added to the wells and incubated for 4 hours. The medium was again removed and 300 µL of acidified isopropanol was added to dissolve the purple crystallized formazan on the bottom of the wells. The supernatants (100 µL) were transferred to a 96-well plate and the absorbance at 540 nm (OD₅₄₀) and 630 nm (OD₆₃₀) was measured using a spectrophotometer. Cytotoxicity of burdock

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