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" Thunder God Vine " vs Cancer (&c)
(Lei Gong Teng // Tripterygium Wilfordii Hook)

Crug Farms (UK)

Tripterygium Wilfordii Hook

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http://naturalsociety.com/chinese-plant-compound-cancer-research/
October 18th, 2012

Chinese Plant Compound Wipes out Cancer in 40 Days, Says New Research

by

Anthony Gucciardi

A little-known plant with a truly bizarre name is now making headlines as a cancer killer, with the compound of the plant vanishing tumors in mice with pancreatic cancer. Known as the 'thunder god vine' or lei gong teng, the Chinese plant is actually integrated into Chinese medicine and has been used for ages in remedying a number of conditions including rheumatoid arthritis.

According to the new research out of the University of Minnesota's Masonic Cancer Center, the thunder god plant

compound led to no signs of tumors after a 40 day period — even after discontinuing the treatment. Published in the journal Science Translational Medicine and funded by the National Institutes of Health, even the scientists working on the project were stunned by the anti-cancer properties of the compound. Known to contain something known as triptolide, which has been identified as a cancer fighter in previous research, it is thought to be the key component that may be responsible for the anti-tumor capabilities.

Study leader and vice chairman of research at the Cancer Center explained to Bloomberg how he was blown away by the effects of the simple plant:

"This drug is just unbelievably potent in killing tumor cells," he said.

And just like with numerous other powerful substances like turmeric and ginger, mainstream science is still slowly confirming what many traditional practitioners have known for their entire lives. This is, of course, due to the fact that there is simply no money for major corporations in researching the healing powers of natural herbs and compounds such as the compound found in the thunder god vine. Turmeric and ginger, for example, have been found to be amazing anti-cancer substances that are virtually free compared to expensive and dangerous cancer drugs.

Nevertheless, the Big Pharma sponsored corporate scientists have managed to ignore these spices as much as possible. In fact, they have even been caught time and time again faking thousands of studies to fraudulently demonstrate the supposed value of pharmaceutical drugs pushed by major pharma juggernauts — many of which are later forced to pay millions in fines which only slightly stack up against their billions in profits.

Profits that are threatened by the many real studies that were performed by scientists examining the rejeuvenating power of cheap ingredients like turmeric, which has been found by peer-reviewed research available on PubMed to positively influence over 590 conditions.

While it is great news that this study is bringing the beneficial effects of inexpensive and near-free plant compounds to light, the bad news is that the individuals responsible for the research are actually looking to create a pharmaceutical drug from the essential component triptolide. A drug that will seek FDA approval and ultimately be patented, nutritionally ruined, and sold for exorbitant amounts of cash. Instead, just get your hands on some thunder god vine for yourself.

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http://www.bloomberg.com/news/2012-10-17/drug-from-chinese-thunder-god-vine-slays-tumors-in-mice.html

Drug From Chinese 'Thunder God Vine' Slays Tumors in Mice

By

Drew Armstrong

A drug made from a plant known as "thunder god vine," or lei gong teng, that has been used in traditional Chinese medicine, wiped out pancreatic tumors in mice, researchers said, and may soon be tested in humans.

Mice treated with the compound showed no signs of tumors after 40 days or after discontinuing the treatment, according to researchers at the University of Minnesota's Masonic Cancer Center. The research, funded by the university and the National Institutes of Health. was published today in the journal *Science Translational Medicine.*

"This drug is just unbelievably potent in killing tumor cells," said Ashok Saluja, vice chairman of research at the center and the study's leader, said in a telephone interview. "You could see that every day you looked at those mice, the tumor was decreasing and decreasing, and then just gone."

The plant, also known as *Tripterygium wilfordii*, contains triptolide, which earlier studies have shown can cause cancer cells to die. In traditional Chinese medicine, the plant is used as a treatment for rheumatoid arthritis. While the researchers hope to start human trials in six months, Saluja said it's still a long leap from mice to people.

"Does that mean it will definitely work in humans?" he said. "We can definitely not say that."

The results pave the way for clinical trials in patients with pancreatic cancer, one of the most lethal malignancies, the researchers said in the study. About 44,000 new cases of the disease are diagnosed each year in the U.S., according to the U.S. Centers for Disease Control and Prevention in Atlanta. Only about 20 percent of patients

survive a year after diagnosis, Saluja said.

Survival Odds

Even for patients diagnosed at the earliest stages of their cancer when the odds are better, only about 14 percent survive five years or longer, according to the American Cancer Society. The current treatment is Eli Lilly & Co.'s Gemzar (LLY), which sold $452 million last year. A generic version of the drug became available in 2011, according to data compiled by Bloomberg.

"It adds six weeks -- it's nothing," Saluja said. "There's definitely a need to discover and develop more strategies for pancreatic cancer."

The researchers dubbed the drug Minnelide, a combination of Minnesota and triptolide. They developed a water soluble version that could be injected into mice, and in the future administered to patients intravenously.

Saluja and his group have formed a company, Minneamrita Therapeutics, which will attempt to take the drug into the first of three stages of human clinical trials that are generally required before U.S. regulatory approval. Saluja said the company has discussed the trials with the Food and Drug Administration.

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http://nccam.nih.gov/health/tgvine

Thunder God Vine

Common Names: thunder god vine, lei gong teng
Latin Name: Tripterygium wilfordii

Introduction

This fact sheet provides basic information about thunder god vine — common names, what the science says, potential side effects and cautions, and resources for more information.

Thunder god vine is a perennial vine native to China, Japan, and Korea. It has been used in China for health purposes for more than 400 years. In traditional Chinese medicine, it has been used for conditions involving inflammation or overactivity of the immune system. Currently, thunder god vine is used as a traditional or folk remedy for excessive menstrual periods and autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis, and lupus.

Extracts are prepared from the skinned root of thunder god vine.

What the Science Says

Laboratory findings suggest that thunder god vine may fight inflammation, suppress the immune system, and have anti-cancer effects.

Although early evidence is promising, there have been few high-quality studies of thunder god vine in people. Results from a large study funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), which compared an extract of thunder god vine root with a conventional medicine (sulfasalazine) for rheumatoid arthritis, found that participants' symptoms (e.g., joint pain and swelling, inflammation) improved more significantly with thunder god vine than with sulfasalazine.

A small study on thunder god vine applied to the skin found benefits for rheumatoid arthritis symptoms.

There is not enough scientific evidence to assess thunder god vine's use for any other health conditions.

Side Effects and Cautions

Thunder god vine can cause severe side effects and can be poisonous if it is not carefully extracted from the skinned root. Other parts of the plant—including the **leaves, flowers, and skin of the root—are highly poisonous** and can cause death.

A number of participants in the NIAMS study experienced gastrointestinal adverse effects such as **diarrhea, indigestion, and nausea, as well as upper respiratory tract infections**. (The rate of adverse effects was similar

in the thunder god vine and sulfasalazine groups.)

Thunder god vine can also cause hair loss, headache, menstrual changes, and skin rash.

There are no consistent, high-quality thunder god vine products being manufactured in the United States. Preparations of thunder god vine made outside the United States (for example, in China) can sometimes be obtained, but it is not possible to verify whether they are safe and effective.

Thunder god vine has been found to decrease bone mineral density in women who take the herb for 5 years or longer. This side effect may be of particular concern to women who have osteoporosis or are at risk for the condition.

Thunder god vine contains chemicals that might decrease male fertility by changing sperm.

Tell all your health care providers about any complementary health practices you use. Give them a full picture of what you do to manage your health. This will help ensure coordinated and safe care. For tips about talking with your health care providers about complementary and alternative medicine, see NCCAM's Time to Talk campaign.

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http://www.ncbi.nlm.nih.gov/pubmed/12124856

Benefit of an extract of Tripterygium Wilfordii Hook F in patients with rheumatoid arthritis: a double-blind, placebo-controlled study.

Tao X, Younger J, Fan FZ, Wang B, Lipsky PE.

Source

Autoimmunity Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, Bethesda, Maryland 20892, USA.

Abstract

OBJECTIVE:

To examine the safety and efficacy of an extract of Tripterygium wilfordii Hook F (TWHF) in the treatment of patients with rheumatoid arthritis (RA).

METHODS:

An ethanol/ethyl acetate extract from the roots of TWHF was prepared and used in a prospective, double-blind, placebo-controlled study in patients with longstanding RA in whom conventional therapy had failed. Patients were randomly assigned to receive either placebo or low-dose (180 mg/day) or high-dose (360 mg/day) extract for 20 weeks, followed by an open-label extension period. Clinical responses were defined as 20% improvement in disease activity according to the American College of Rheumatology criteria. Side effects were actively queried and recorded at each visit.

RESULTS:

A total of 35 patients were enrolled in the trial; 21 patients completed the 20-week study. One patient from each group withdrew because of side effects. Twelve, 10, and 10 patients in the placebo, low-dose, and high-dose groups, respectively, completed at least 4 weeks of treatment. Of these patients, 8 and 4 in the high-dose and low-dose groups, but none in the placebo group, met criteria for clinical response. Four, 4, and 7 patients in the placebo, low-dose, and high-dose groups, respectively, were enrolled in the open-label extension; of these, 2, 4, and 5 patients, respectively, met criteria for clinical response. The most common side effect was diarrhea, which caused 1 patient in the high-dose group to withdraw from the trial. No patients withdrew because of adverse events during the open-label extension.

CONCLUSION:

The ethanol/ethyl acetate extract of TWHF shows therapeutic benefit in patients with treatment-refractory RA. At therapeutic dosages, the TWHF extract was well tolerated by most patients in this study.

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http://www.sciencedirect.com/science/article/pii/S0031942207001203

Anti-inflammatory and immunosuppressive compounds from Tripterygium wilfordii

Jun Maa, et al.

Abstract

The extract of Tripterygium wilfordii Hook F. (TwHF), which showed anti-inflammatory and immunosuppressive activities in human clinical trials for rheumatoid arthritis, was subjected to the activity-guided fractionation and spectroscopic characterization of bioactives. A tetrahydrofuran lignan, tripterygiol (1), and eight known compounds, all capable of suppressing pro-inflammatory gene expression were identified. Most of the pharmacological activity of the extract can be attributed to triptolide, its most abundant and active component, with some contribution from tripdiolide.

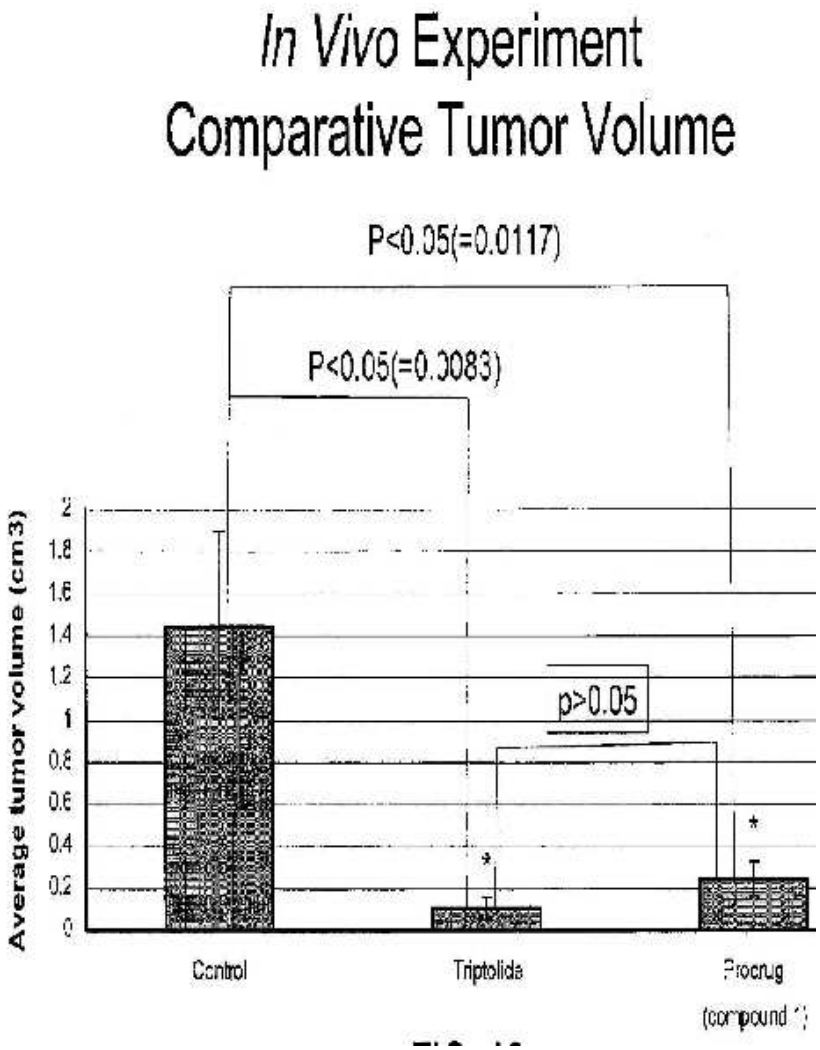
Graphical abstract

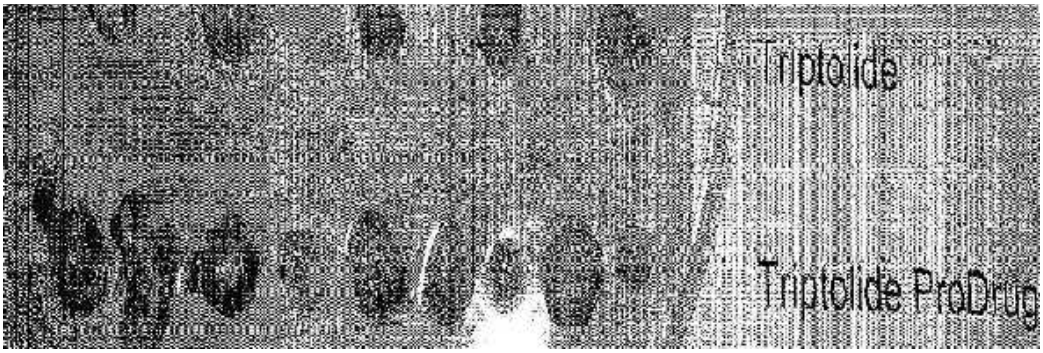
A tetrahydofuran lignan, tripterygiol (1), and eight known compounds, were isolated and structurally characterized from the ethyl acetate extract of Tripterygium wilfordii which was proven active in a clinical trial for the rheumatoid arthritis. All isolated compounds inhibited expression of pro-inflammatory genes in mouse macrophages.

PATENTS

US2012238529
TRIPTOLIDE PRODRUGS

(Excerpts)
Inventor: GEORG INGRID GUNDA // PATIL SATISH PRAKASH





BACKGROUND OF THE INVENTION

[0001] Pancreatic cancer is a particularly aggressive and devastating disease with a five-year survival rate of less than 5%. No effective drug treatment is currently available which can effectively prolong patient survival. In 2006, over 35,000 new pancreatic cancer cases were reported with an almost equal number succumbing to the disease. Resistance to apoptosis has been investigated as a key factor in preventing response in patients to therapies to treat pancreatic and other cancers.

[0002] Triptolide is a naturally occurring compound obtained from the plant Tripterygium wilfordii. Triptolide is known to be useful in treating autoimmune diseases, transplantation rejection (immunosuppression), and possesses anticancer and anti-fertility effects as well as other biological effects (Qui and Kao, 2003, Drugs R. D. 4, 1-18). Triptolide has strong antitumor effects against xenograft tumors (for example, Yang et al. Mol. Cancer. Ther, 2003, 2, 65-72). Triptolide is an anti-apoptotic agent with multiple cellular targets that are implicated in cancer growth and metastasis. Triptolide inhibits NF-kB activation, induces bid cleavage, blocks induction of the survival gene p21 WAF1/<Cip1 >(Wang et al. Journal of Molecular Medicine, 2006, 84, 405-415) and inhibits the function of heat shock transcription factor 1 (HSF1) thereby suppressing endogenous Hsp70 gene expression (Westerheide et al. 2006, Journal of Biological Chemistry, 281, 9616-9622). Triptolide also functions as a potent tumor angiogenesis inhibitor (He et al. 2010, Int. Journal of Cancer, 126, 266-278).

[0003] Several mechanisms exist in living cells that protect against adverse conditions, including cancer cells. The synthesis of a family of proteins referred to as heat-shock proteins (HSPs) is one such protective mechanism. Major HSPs include HSP90, HSP70, HSP60, HSP40 and smaller HSPs. HSPs can be present in most intracellular compartments, with HSP70 being primarily located in cytosol.

[0004] Dysregulated expression of HSP70 is known to be associated with many diseases including cancers. HSP70 is abundantly expressed in malignant tumors of various origins (For example: Hantschel et al. 2000, Cell Stress Chaperones, 5, 438-442), which render the tumor cells resistant to therapy and poor prognosis for the patient (Fuqua et al. 1994, Breast Cancer Res, Treatment 32, 67-71). Heat shock protein 70 (Hsp70) is known to be upregulated and over-expressed in pancreatic cancer cells as compared to normal cells. Furthermore, HSP70 has a protective effect on cancer cells inhibiting apoptosis of the cells. Inhibition of HSP70 in pancreatic cancer cells has been shown to increase apoptic cell death of these cells (See for example Aghdassi et al., Cancer Research, 67(2) p. 616-625 (2007)). Triptolide has been shown to inhibit pancreatic tumor growth and metastasis in mice. It was also shown that triptolide when used in combination with ionization radiation its therapeutic effect in pancreatic cancer treatment is enhanced (Wang et al. Proc. Amer. Assoc. Cancer Res. 2006, 47, abstract #4720 and Wang et al. Clin. Cancer Res. 2007, 13, 4891-4899). It is believed that the anticancer effect associated with triptolide occurs as a result of reducing levels of the protein HSP70 expressed in significant amounts by pancreatic cancer cells as compared to normal pancreatic cells. Thus, triptolide therapies have been of interest in the medical field for their potential treatment of cancers that over-express HSP70, including pancreatic cancer. See for example, Phillips et al., Cancer Research, 67(19), p. 9407-16 (2007).

[0005] There are, however, certain disadvantages associated with administering triptolide and different solutions to address these problems have been explored. One problem associated with native triptolide is that it is insoluble in aqueous solution. Another problem associated with natural triptolide is poor bioavailability and toxic side effects. Triptolide, triptolide derivatives and certain prodrugs having improved solubility and reduced toxicity are known. For example, Dai et al. U.S. Pat. No. 6,548,537 describes triptolide prodrugs having increased solubility and reduced toxicity.

[0006] The phosphonoxymethyl moiety per se is known in the art for purposes of forming prodrug compounds of certain pharmaceutical compounds. For example, Krise et al., J. Med. Chem., 42, pp. 3094-3100 (1999) describes preparation of N-phosphonooxymethyl prodrugs of certain compounds to improve water solubility.

[0007] Nevertheless, prodrugs must possess a number of properties in order to be practically useful. For instance,

desirable prodrugs should be stable for formulation and administration. Additionally, once administered and present in the recipient's system, the prodrug must be successfully activated. Furthermore, both the prodrug and activated compound must be compatible with biological fluids, such as plasma and tissue homogenates. Ultimately, the activated compound initially delivered in prodrug form must have its desired therapeutic or pharmaceutical effect. These and other factors can be difficult to achieve simultaneously, or collectively balance, with certain types of compounds. Within the context of triptolide and triptolide prodrug compounds it has been difficult achieve improved aqueous solubility, effective bioavailability for oral dosage forms, faster in vivo release of triptolide, and relatively reduced or lower toxicity in combination with significant inhibition of cancer cell growth. For example, see Chassaing et al., Highly Water-Soluble Prodrugs of Anthelminthic Benzimidazole Carbamates: Synthesis, Pharmacodynamics and Pharmacokinetics, J. Med. Chem., 51(5), pp. 1111-1114 (2008).

[0008] Succinate prodrug forms of triptolide are known, but have been associated with certain disadvantages. See, for example, Harrousseau et al., Haematologica 2008, 93(s1), 14 Abstract 0038 and Kitzen et al. European Journal of Cancer 2009, 45, 1764-1772. Incomplete and variable conversion of the succinate prodrug of triptolide has been observed.

[0009] Thus, there exists a need in the medical and pharmaceutical fields for improved therapeutics for treating cancers including aggressive solid tumor cancers, such as pancreatic cancer. There also exists a further need for improved delivery or improved pharmacokinetic parameters or reduced toxicity of such therapeutics. There also exists a need for prodrug forms of triptolide that have improved solubility or that have faster release of the active compound triptolide or that have a more therapeutically effective release of the active compound triptolide or for prodrug forms of triptolide with improved bioavailability.

BRIEF DESCRIPTION OF THE FIGURES

[0025] FIG. 1 illustrates a chemical reaction diagram for preparing the compound 1.

DETAILED DESCRIPTION OF THE INVENTION

[0119] Triptolide is used to treat a variety of diseases such as inflammatory diseases. Triptolide has also been implicated as a therapeutic agent to treat a variety of diseases. These diseases include cancer (e.g. pancreatic cancer, bile duct carcinoma, neuroblastoma, colon cancer, breast cancer, myeloma, gastric cancer, liver cancer, glioblastoma, ovarian cancer, colorectal cancer, non-Hodgkin lymphoma, lung cancer, prostate cancer, small-cell lung cancer, large cell lung cancer, kidney cancer, esophageal cancer, stomach cancer, cervical cancer, lymphoma tumors), autoimmune diseases, transplant rejection, polycystic kidney disease, inflammatory diseases, asthma, rheumatoid arthritis, systemic lupus erythematosus and nephritis. Triptolide has also been discussed in the coating of stents (drug elution), spinal cord repair, colitis, and contraception in male and female animals. Accordingly, the invention includes but is not limited to the use of the compounds of formula I to treat diseases including cancer (e.g. pancreatic cancer, bile duct carcinoma, neuroblastoma, colon cancer, breast cancer, myeloma, gastric cancer, liver cancer, glioblastoma, ovarian cancer, colorectal cancer, non-Hodgkin lymphoma, lung cancer, prostate cancer, small-cell lung cancer, large cell lung cancer, kidney cancer, esophageal cancer, stomach cancer, cervical cancer, lymphoma tumors), autoimmune diseases, transplant rejection, polycystic kidney disease, inflammatory diseases, asthma, rheumatoid arthritis, systemic lupus erythematosus and nephritis. Compounds of formula I can also be can also be used for coating stents (drug elution), spinal cord repair, colitis, and contraception in male and female mammals.

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Application of triptolide in preparation of medicament for treating or preventing human immunodeficiency viruses (HIV)
CN102755335

Abstract

The invention discloses an application of triptolide in preparation of a medicament for treating or preventing human immunodeficiency viruses (HIV). The triptolide is diterpenoid naturally existing in roots of tripterygium wilfordii hook, and can dose-dependently inhibit replication of I type HIV (HIV-1) in cells in vitro. The half inhibitory concentrations on HIV-1 inhibition in TZM-b1 cells, JurkatT lymphocytes and human peripheral blood mononuclear cells are respectively 0.32nM, 0.45nM and 1.1nM. The triptolide has a remarkable inhibiting effect on the replication of the HIV-1 in the TZM-b1 cells, the JurkatT lymphocytes and the human peripheral blood mononuclear cells; and the triptolide is an active ingredient in Chinese medicinal tripterygium wilfordii hook, so the triptolide is wide in source. The compound has a broad prospect for developing anti-HIV-1 medicaments.

Triptolide purification method
CN1876656

Abstract

The invention discloses a method for using a diterpene lactone compound of tripterygium in the treatment of cancers. The diterpene lactone compound comprises diterpene lactone alcohol of tripterygium, diterpene lactone glycol of tripterygium, diterpene lactone ketone of tripterygium and a plurality of derivatives of the diterpene lactone alcohol of tripterygium.

Technology

The invention relates to the field of traditional Chinese medicine preparation technology, in particular to a method for purifying triptolide.

BACKGROUND

Triptolide (triptolide), that triptolide, is one of the main components of triptolide, which is immunosuppressive Tripterygium preparations the main active ingredient, but also the toxic components in the current Chinese medicine preparation for its content There are strict controls.

Since triptolide to effective dose and toxic dose is very close to the possibility of developing new drugs basic single component is negated.

However, as an effective lead drug (lead drug), nearly 20 years, domestic and foreign pharmaceutical scientists are constantly screening triptolide derivatives, and made a lot of encouraging progress.

For potential new drug development triptolide derivatives, parent structure of triptolide preparation and supply is a more realistic and urgent problem.

On the current research, the total synthesis of triptolide can not yet reached the level of practical application, that is currently a prime raw material is generally isolated from the plant extract.

Triptolide in Tripterygium wilfordii or were very low in content, generally between 10 ~ 30ppm, while by solvent extraction, purified extract of routine, the A pigment content is not high, usually in a % down.

If this and other quality of extract directly on column chromatography A hormone, the efficiency of the preparation work is definitely lower, and the cost is quite expensive and not conducive to possible future industrial production.

Therefore, how the use of economic, reasonable method or from Tripterygium wilfordii extract triptolide has been plagued by people of a problem.

SUMMARY OF THE INVENTION

The present invention is to solve the technical problem is the use of simple and economical method of purifying the extract greatly increased Tripterygium triptolide content of the preparation of high purity triptolide possible.

The invention discloses triptolide purification method is based on extracts of Tripterygium ordinary material, solvent and dispersion by adding adsorbents, sufficiently adsorbed, filtered, concentrated and dried to obtain a purified extract of Tripterygium wilfordii extract.

The preferred purification method of the present invention is as follows:

Take 1 part of a commercially available extract of Tripterygium general, add 3 to 10 parts of the adsorbent, with the vehicle at 30 ~ 50 ?, stirring to dissolve extract is then filtered, the filter cake was washed several times with fresh solvent, the use of the total solvent extract the amount of 15 to 30 times the amount of the combined filtrate and washings were concentrated and dried to obtain a purified extract of Tripterygium wilfordii extract powder.

The present invention a commercially available extract of Tripterygium common is the use of conventional methods wilfordii extract obtained by extraction, which triptolide content of about 1%.

Said adsorbent is selected from silica gel, neutral alumina, diatomaceous earth, cellulose and other commonly used adsorption media.

Said solvent is selected from lower aliphatic hydrocarbons, lower aliphatic ketones, esters, halogenated lower alkyl or a mixture thereof.

Method of the present invention is to obtain a purified extract yield of about 50%, by HPLC assay, which triptolide content of about 2%, triptolide component transfer rate of 95% or more.

Since triptolide in traditional Chinese medicine Tripterygium wilfordii or very low content of both, so its extraction and separation process, efforts to improve the process every step of triptolide component of the actual transfer rate is especially important.

By column chromatography, triptolide there are some irresistible adsorption losses, with the absorbent material used in the different nature of triptolide component transfer rate is generally 60 to 85%, so the actual industrial production, should minimize the number of times by column chromatography in order to maximally reduce the loss of a prime ingredient to improve the preparation of the actual production yield.

The present invention addresses the above separation characteristics of triptolide to diversify Tripterygium extract adsorption treatment method, and achieved satisfactory results.

Adsorption method with regard to the dispersion characteristics of column chromatography is shown in table 1.

Table 1.

Dispersion and adsorption column chromatography separation A prime feature comparison

As can be seen from the above comparison, the present invention is a commercially available extract of Tripterygium as raw material, using conventional column chromatography adsorbent material dispersion of non-adsorption process, and the resulting purified extract volume reduced by half, and its triptolide content doubled.

Biggest advantage of this method is simple to prepare and shorter, triptolide metastasis rate and solvent usage and other small features, a more realistic approach by the extract of the invention, in a subsequent row column chromatography A prime time , the interference of impurities greatly reduced, as the ultimate easy access to high-purity triptolide foundation.

BRIEF DESCRIPTION

Figure 1 Example 1 Product HPLC chart
Figure 2 triptolide reference HPLC chart
Specific embodiments

Example 1

Take Tripterygium extract (triptolide content 1%) 2kg, 12kg silica gel, chloroform was added 15kg, under heat at 30 ? sufficiently stirred to extract fully dissolved, and then filtered, the filter cake was washed several times with chloroform, chloroform Total amount of 30kg.

Combined chloroform solution, reduced dry purified extract of Tripterygium 0.9kg, triptolide its content is 2.2% (HPLC method) in Figure 1, Figure 2 triptolide reference.

Example 2

Tripterygium wilfordii extract taken 1kg (triptolide content of 1%), neutral alumina 5kg, ethyl acetate was added 10kg, incubated at 40 ? under stirring and dissolved extract is then filtered cake was washed with the remaining 5kg washed several times with ethyl acetate, the combined ethyl acetate filtrate and washings were concentrated in vacuo and dried to yield purified extract 0.5kg, its triptolide content of 2.0%.

Example 3

Tripterygium wilfordii extract taken 1kg (triptolide content of 1%), diatomaceous earth 10kg, 15kg with acetone - cyclohexane (1:1), stirred at 35 ? sufficiently dissolved extract, then filtered, the filter cake 10kg was washed several times with the solvent, the combined filtrate and washings were concentrated in vacuo and dried to yield purified extract 0.6kg, triptolide content of which was 1.7%.

Method for planting Chinese herb triperygium wilfordii
CN1994044

The invention relates to a method for planting Tripterygium wilfordii, wherein said method comprises that: 1, collecting 1-2 year old branch, cutting into 10-15cm branches, while each section has 3-4 nodes; 2, putting low end of branch into 500-1000ppm alpha-fruitone or indolebutyric acid solution, taking out and drying to be incline inserted into the seed bed, pouring water; 3, planting seeds 60-90cm distance, and 800-1000n/km; 4, fertilizing after spring, at June and July, spraying 0.3% monobasic potassium phosphate, at October and December, spraying organic fertilizer; 5, when the seed flowers, on time taking out bulb, at May to September, when grows to 40-60cm, cutting top bulb; 6, transplanting, harvesting after 2 or 3 years.

DESCRIPTION

Technology

The present invention relates to a method of traditional Chinese medicine Tripterygium planting.

BACKGROUND

Hook, alias Gelsemium elegans, yellow vine, yellow wax vine, vegetable insecticide, etc. for Tripterygium Celastraceae species, deciduous vine-like shrub.

Currently used as medicine, there are three original plant Tripterygium: triptolide Tripterygiumwilfordii Hook.f., KMSHT T.hypogeaucum (Leve) Hutch. And the Black Man (Northeast TWH) T.regeli Sprague et Tak..

Hook the root medicine, cold, bitter, big drug has medicinal properties, Qufengchushi, swelling and pain effect, modern pharmacological study found that triptolide has anti-inflammatory, antibacterial, anti-fertility, anti-tumor, immune suppression effect, as well as lifting of the blood pool, reduce blood viscosity, improve microcirculation and reduce the role of the resistance of peripheral blood, attending rheumatoid arthritis, lupus, chronic nephritis, nephrotic syndrome and allergic skin diseases disease.

Isolated from Tripterygium has 70 kinds of chemical monomers which two terpene lactones as the main active ingredient, as well as three terpenes, alkaloids, sesquiterpenes and other chemical ingredients.

Natural state, Hook wild in the subtropical region, located in the provinces south of the Yangtze River to the southwest, such as Hunan, Hubei, Jiangxi, Anhui, Zhejiang, Fujian, Guangdong, Guangxi and Taiwan provinces.

Grown at an altitude of more than 300 ~ 500m sunny, humid, slightly fertile valleys, hills, stream thickets, woodland.

Warm and humid climate, generally grown in well-drained, pH5 ~ 6 slightly acidic sandy loam or red loam.

SUMMARY OF THE INVENTION

The purpose of the present invention is to provide a traditional Chinese medicine Tripterygium cultivation methods.

Comprising the steps of:

1) cuttage

(A) Acquisition 1 to 2 years old, robust, no pests branches, cut into 10 ~ 15cm long cuttings, each with three to four sections, the cuttings tied into bundles, or takes more than 3 years triptolide kinds of roots, clipping diameter 0.2 ~ 4cm, length 10 ~ 15cm seed roots, spare;

(2) into the bottom of the prepared cuttings 500 ~ 1000ppm of a-NAA or IBA solution immersed, remove a little dry Xiecha the prepared seedbed, or on the prepared kind of root Xiecha segment on the prepared seedbed, buried 1/2 to 2/3, inserted immediately after watering, cover film, surrounded by soil compaction;

2) colonization

(A) in the year in November to next March planting, spacing 60 ~ 90cm, with a volume of 800 to 1000 seedlings / acre, planted in well-drained pH 5 to 6 slightly acidic red loam or silt soil class ;

(2) when planted in the furrow opening 60 ~ 90cm × 60 ~ 90cm of the
planting hole, depth 40 ~ 50cm, planted one per hole, planting seedlings root system will start righting seedlings, while gently lifting the edge of the casing seedlings, casing to cover no roots, compaction;

(3) Every fertilizing before planting organic fertilizer products 100 ~ 300g, ash 200 ~ 400g, rapeseed fat 15 ~ 45g. Cast basal fertilizer, seedling roots and then to high overburden portion 5cm, compaction, irrigated;

3) fertilization

In the spring of each year after birth, a new little pumping, combined with weeding, applying fertilizer on potassium chloride-based chemical plants around the root, 15 ~ 20kg / acre, in July and August, the election evening or cloudy, spraying 0.3% phosphate potassium, 50kg / acre, in October and November, the plant four weeks at 20 ~ 30cm ring ditch, applied into organic fertilizer products, 400 ~ 600kg / acre;

4) field management

(A) in the June to August Hook flowering, election sunny, timely removal of buds, check once every 10d.

(2) in May to September, the election sunny, slightly longer in the new time to 40 ~ 60cm, pruning or removal of the terminal bud, check once every 20d.

5) cuttings after transplanting, harvesting two to three years.
The present invention NAA or IBA reagent cuttings, branches can promote triptolide rooting cuttings improve the survival rate for the production of transplant seedlings; through a suitable acid soils planted Hook, provide sufficient moisture, light conditions and fertilizers, etc., to create the right triptolide external conditions; through defloration after planting and field management practices such as topping promote triptolide medicinal parts of the underground part of the growth of transplanted 2-4 in Hook after years of medicinal use as a raw material.

Specific embodiments

Chinese medicine Tripterygium planting method comprises the following steps:

1. Cutting propagation (a) cuttings ready to collect 1 to 2 years old, robust, no pests branches, cut into 10 ~ 15cm long cuttings, each with three to four sections.

Will be tied into bundles by cuttings or root excavation three years triptolide, clipping diameter 0.2 ~ 4cm, length 10 ~ 15cm intact root segments and set aside. (

2) cutting method in late January to mid-March or late September to mid-October, will be ready cuttings (root without reagent) into the lower end 500 ~ 1000ppm of a-NAA or IBA solution immersed, remove a little dry ie the spacing of 10cm × 10cm Xiecha on prepared seedbed, buried 1/2 to 2/3.

Inserted immediately after watering, to build approximately 50cm high Shed, cover film, surrounded by soil compaction, such as the sun is strong, the need to cover shade net.

About 40 ~ 50d, after rooting, thrown off film and shade net.
Kind of root without pre-treatment, the other with cuttings.

2. Colonization (1) in the year in November to next March planting, 80cm in width planted on the plot line, spacing 60 ~ 90cm, with a volume of 800 to 1000 seedlings / acre. (2) on the open furrow at planting at 60 ~ 90cm × 60 ~ 90cm of the planting hole depth of about 40 ~ 50cm, planted a per hole, planting seedlings roots will start righting seedlings, while gently lifting the edge of the casing seedlings, casing to cover no roots, compacted.

(3) Each fertilizing before planting organic fertilizer products 100 ~ 300g, ash 200 ~ 400g, rapeseed fat 15 ~ 45g. Cast basal fertilizer, seedling roots and then to high overburden portion 5cm, compaction, irrigated.

3. Fertilizer every spring sprouted new little after mid-May on, combined with weeding, applying chemical fertilizer (potassium chloride type) in plants around the root, 15 ~ 20kg / acre.
In July and August, the election evening or cloudy, spraying 0.3% potassium dihydrogen phosphate, 50kg / acre.

In October and November, the plant four weeks at 20 ~ 30cm ring ditch, applied into organic fertilizer products, 400 ~ 600kg / acre.

4. Field management (1) in the June to August Hook flowering, election sunny, timely removal of buds, check once every 10d. (
2) In May to September, the election sunny, slightly longer in the new time to 40 ~ 60cm, cut off or removal of the terminal bud, check once every 20d.

5. Cuttings after transplanting, biennial Tripterygium wilfordii mu fresh herbs Weight 800-1000kg, three students Tripterygium wilfordii mu fresh herbs Weight 2500-3000kg.

Example 1

1. Tripterygium cultivation of traditional Chinese medicine, characterized in that it comprises the steps of:

1) cuttage

(A) collecting a year old, robust, no pests branches, cut into 10cm long cuttings, each with three sections, cuttings will be tied into bundles, or takes more than 3 years triptolide kind roots, clipping diameter 0.2cm, length 10cm seed roots, spare;

(2) into the bottom of the prepared cuttings 500ppm of a-NAA or IBA solution immersed, remove a little dry Xiecha the prepared seedbed, or on the prepared kind of root segments oblique inserted in a prepared seedbed, buried 1/2, inserted immediately after watering, cover film, surrounded by soil compaction;

2) colonization

(A) in the year in November to next March planting, spacing 60cm, with a volume of 1400 seedlings / acre, planted in well-drained slightly acidic pH 5 red loam or silt soil type;

(2) on the open furrow at planting in the planting hole 60cm × 60cm, depth 40cm, planted one per hole, planting seedlings root system will start righting seedlings, while gently lifting the edge of the casing seedlings, soil to cover no roots, compaction;

(3) fertilizing before planting organic fertilizer products per 100g, ash 200g, rapeseed fat 15g.

Cast basal fertilizer, seedling roots and then to high overburden portion 5cm, compaction, irrigated;

3) fertilization

In the spring of each year after birth, a new little pumping, combined with weeding, applying fertilizer on potassium chloride-based chemical plants around the root, 15kg / acre, in July and August, the election evening or cloudy, spraying 0.3% potassium dihydrogen phosphate , 50kg / acre, in October and November, the plant four weeks of 20cm ring ditch, applied into organic fertilizer products, 400kg / acre;

4) field management

(A) in the June to August Hook flowering, election sunny, timely removal of buds, check once every 10d;

(2) in May to September, the election sunny day, when the new little longer to 40cm, pruning or removal of the terminal bud, check once every 20d;

5) cuttings after transplanting, harvesting two to three years.
Implementation of the results: the average two-year old plants per plant weight 0.557kg, converted into yield as 779kg.

Example 2

1. Tripterygium cultivation of traditional Chinese medicine, characterized in that it comprises the steps of:

1) cuttage

(A) Acquisition 2 years old, robust, no pests branches, cut into 15cm long cuttings, each with four sections, the cuttings tied into bundles, or takes more than 3 years triptolide kind roots, clipping diameter 4cm, length 15cm seed roots, spare;

(2) into the bottom of the prepared cuttings 1000ppm of a-NAA or IBA solution immersed, remove a little dry Xiecha the prepared seedbed, or on the prepared kind of root segments oblique inserted in a prepared seedbed, buried 2/3, inserted immediately after watering, cover film, surrounded by soil compaction;

2) colonization

(A) in the year in November to next March planting, spacing 90cm, with a volume of 822 seedlings / acre, planted in well-drained slightly acidic pH of 6 red loam or silt soil type;

(2) on the open furrow at planting in the planting hole 90cm × 90cm, depth 50cm, planted one per hole, planting seedlings root system will start righting seedlings, while gently lifting the edge of the casing seedlings, soil to cover no roots, compaction;

(3) fertilizing before planting organic fertilizer products per 300g, ash 400g, rapeseed fat 45g.

Cast basal fertilizer, seedling roots and then to high overburden portion 5cm, compaction, irrigated;

3) fertilization

In the spring of each year after birth, a new little pumping, combined with weeding, applying fertilizer on potassium chloride-based chemical plants around the root, 20kg / acre, in July and August, the election evening or cloudy, spraying 0.3% potassium dihydrogen phosphate , 50kg / acre, in October and November, the plant four weeks at 30cm ring ditch, applied into organic fertilizer products, 600kg / acre;

4) field management

(A) in the June to August Hook flowering, election sunny, timely removal of buds, check once every 10d;

(2) in May to September, the election sunny day, when the new little longer to 60cm, pruning or removal of the terminal bud, check once every 20d;

5) cuttings after transplanting, harvesting two to three years.
Implementation of the results: the average two-year old plants per plant weight 1.26kg, was converted into yield 1057kg.

Example 3

1) cuttage

(A) Acquisition 2 years old, robust, no pests branches, cut into 12cm long cuttings, each with four sections, the cuttings tied into bundles, or takes more than 3 years triptolide kind roots, clipping diameter 2cm, length 12cm seed roots, spare;

(2) into the bottom of the prepared cuttings 800ppm of a-NAA or IBA solution immersed, remove a little dry Xiecha the prepared seedbed, or on the prepared kind of root segments oblique inserted in a prepared seedbed, buried 1/2, inserted immediately after watering, cover film, surrounded by soil compaction;

2) colonization

(A) in the year in November to next March planting, spacing 80cm, with a volume of 1040 seedlings / acre, planted in well-drained slightly acidic pH of 6 red loam or silt soil type;

(2) on the open furrow at planting in the planting hole 80cm × 80cm, depth 450cm, planted one per hole, planting seedlings root system will start righting seedlings, while gently lifting the edge of the casing seedlings, soil to cover no roots, compaction;

(3) fertilizing before planting organic fertilizer products per 200g, ash 300g, rapeseed fat 40g.

Cast basal fertilizer, seedling roots and then to high overburden portion 5cm, compaction, irrigated;

3) fertilization

In the spring of each year after birth, a new little pumping, combined with weeding, applying fertilizer on potassium chloride-based chemical plants around the root, 18kg / acre, in July and August, the election evening or cloudy, spraying 0.3% potassium dihydrogen phosphate , 50kg / acre, in October and November, at the plant four weeks 25cm ring ditch, applied into organic fertilizer products, 500kg / acre;

4) field management

(A) in the June to August Hook flowering, election sunny, timely removal of buds, check once every 10d;

(2) in May to September, the election sunny day, when the new little longer to 50cm, pruning or removal of the terminal bud, check once every 20d;

5) cuttings after transplanting, harvesting two to three years.
Implementation of the results: the average two-year old plants per plant weight 0.824kg, converted into yield as 856kg.

1 Materials and methods

1.1 Material Selection

1.1.1 cuttage year students selected semi-woody cuttings of branches, removal of woody base and not the top

choice among strong position, cut into about 8 ~ 10cm, there are three to four buds pieces, and cut leaves go half cuttings with different concentrations of IBA, NAA speed dip method was used for processing, processing method: Cuttings were fast speed in the solution dipped about 5s (depth of about 3cm), immediately cutting.

Each treatment selection cuttings 50.

On the whole a good seedbed by spaced 1.2cm ridging, furrow between 30cm wide ditch dug, Goushen 20 ~ 25cm, 20cm × 20cm spacing will press cuttings inserted in the furrow, the cuttings into the soil deep 3 ~ 5cm .

Irrigated immediately after cutting and covering shade net, in order to maintain proper temperature and humidity.

Previous regular watering, keep moist, observe the hair root cuttings survival situation.

1.1.2 set five kinds of planting density (cm × cm); 40 × 40,50 × 50,60 × 60,80 × 80 and 100 × 100 and other five, randomized block arrangement, a total of three replicates.

Each treatment plot size of 5 × 24 = 120m2.

Each treatment on November planting seedlings, planting, the seedlings are basically the same size, in addition to density, the other management measures with the general field.

1.1.3 Fertilization

1.1.3.1 Hook N, P, K inorganic fertilizer test Test for using annual cuttings and seedlings, planting seedlings when fresh weight per clump 42.5g.

Test soil loam March 14 planting density of 50cm × 50cm.
March 15 basal application, June 17 dressing application.
Trial randomized block design as shown in Table 1, three times repeated, residential area of ??0.02 acres.
Test basal and top dressing fertilizer distribution ratio shown in
Table 2.

Table 1 TWH NPK fertilizer fertilization designed to handle the table

Table 2 Hook Test fertilizer allocation table

1.1.3.2 Hook organic manure fertilization experiment set low, medium, and high levels of fertilizer, is a random permutation block design with three replicates were set.

Residential area of ??5m × 24m = 120m2, planting 480, Qikuan to 1.2m, kind of two rows, spacing of 50cm × 50cm.

Planting time for the year in November.

Seed selection of local wild species breeding cuttings annual seedlings, basically the same size specifications.

Basal all use organic fertilizer was applied in one hole when planting, each pit into the standard as shown in Table 3.

Table 3 Fertilization Fertilization planting hole standard units: g / hole

3 times a year for dressing: 1st time in late March - late April, in the same furrow between two rows of Summer into the open, fertilization criteria in Table 4.

2 inferior August to September, select cloudy or 16:00 after the foliage top dressing, spray 0.3% potassium dihydrogen phosphate, according to low, medium and high levels, respectively, spray one, two, three times.

3 inferior to 10 months late, the same method was applied to the 1st, fertilization criteria in Table 5.

Table 4 1st top dressing fertilizer standard unit: g

Table 5 3rd top dressing fertilizer standard unit: g

1.1.5 Hook herbs growth cycle relationship with yield trials using annual Hook cuttings, planting spacing of 80cm

× 80cm, planted in November that year, planted on the plot line, with the amount of 800 to 1000 seedlings / acre.

Respectively, in the second year, third year, fourth year in November harvest roots, fresh herbs yield determination.

1.2 Results and Analysis

1.2.1 Growth Regulators speed dip method

Table 6 Growth Regulators cutting speed dip process results

Been observed, the use of growth regulators, can promote early hair roots, early bud and root vigor strong and well developed.
Do not use the hair root growth regulators and late survival rate is low, the use of growth regulators to 500ppm of IBA or NAA speed dip method is better.

Tripterygium cutting tests carried out hormone treatment were used 1000ppm, 500ppm, 100ppm Chennai acetic acid (NAA), carried out immediately after cutting and quick dip before placing 30min cuttings, cuttings clipped from the Health and semi-woody branches, cuttings spacing of 10cm × 10cm, and irrigated, covered with shade net.

The results are shown in Table 7.

Table 7 Growth Regulator cuttings result of different treatment

Through years of cuttings experimental observation, the use of 500 ~ 1000ppm of IBA or NAA, using quick dip or soak immediately after cutting, help to improve the survival rate of cuttings and promote early root; root cuttings root than stem cuttings root system, but Stem cuttings relatively low cost, easy to breed a large area. Stem cuttings used in conjunction with film and shade net, can significantly improve the survival rate.

In the cutting time, the root cuttings for 2 to 3 months is appropriate, while stem cuttings should choose nine to 10 months or for the rainy season in June.

Cuttings should use when students lignified.

1.2.2 planting density test results

Table 8 Hook density test yields results

Table 9 density test analysis of variance table

As can be seen from Table 8, as the density decreases more and more important roots of Tripterygium, process 5 to process 96% of weight 1; and the root length and longer, the process 5 58% longer than the process 1.

According to analysis of variance table, yield differences between treatments was significant.

From the root distribution, root distribution deal with high-density range is small, and low density and wide distribution.

But the handling and processing 4 5 several other differences were not significantly different, indicating that process 5 to process 4 is not particularly significant differences.

Hook for the deep roots of plants to root medicine, but also on the ground Fujimoto relatively long, so when planting triptolide, density should be smaller, not too dense.

Generally 80cm × 80cm fit, too dense, plant growth is relatively small, and poor root growth, density is too large, the root weight gain is not obvious.

Deep plowing before transplanting planting ground at 40 ~ 50cm, flat, made of 80cm wide furrows, planting a row, so that triptolide growth than the open furrow kind of two rows of 120cm better.

1.2.3 Fertilization results

1.2.3.1 N, P, K inorganic fertilizer trials

January 7 next year, each plot were randomly digging five Cong said the fresh weight, are shown in Table 10.

Table 10 TWH fertilizer production acceptance test table (5 Cong) Unit: kg

Table 11 plot yield analysis of variance table

According to test results, the five cluster production to deal with 9 being the highest, compared with the minimum production processing a high of 135%.

Yield based on 5 Cong variance analysis showed that the treatments
yield reached a very significant level, and area difference between the groups was not significant.

According to the results, the application of potassium fertilizer on yield triptolide has a great impact, and phosphate fertilizer production although triptolide have a certain impact, but the impact is not big potash.

Therefore, more should be applied in the production of potash, and phosphate may be appropriate to impose a number.

1.2.3.2 organic fertilizer test results are shown in Table 12
Table 12 TWH fertilization experiment unit of production: kg/m2
Table 13 plot yield fertilization experiment analysis of variance table
According to the test results, the cell production to the highest level, compared with the high level of 23.4%, compared with 58.3% in low-level high.

According plot yield variance analysis showed that the treatment cell production reached a significant level.

From the root morphology of view, a high level of the most developed root system, white fibrous roots is also up; horizontal roots are more developed, but the white be no more than a high level; low roots not only short, but also less fibrous roots.

Thus, the public rattan cane crop is like fertilizer, fertilizer helps triptolide more root development, because the roots for medicinal triptolide, so should be more pre tripterygium fertilization.
1.2.4 The relationship between yield and growth cycle triptolide
Hook annual cuttings after transplantation, planting fresh herbs yield of two years 800 ~ 1000kg, three students fresh herbs yield of 2000 ~ 2600kg, four students per mu yield of 2120 ~ 2750kg.

Visible, triptolide born four years compared to three students in terms of yield, yield increase is not much, considering the economic and herbs yield two factors, the production of three students to harvest herbs as raw materials.

Tripterygium wilfordii diterpene lactone compounds for curing cancer CN101273986

The invention discloses a method for using a diterpene lactone compound of tripterygium in the treatment of cancers. The diterpene lactone compound comprises diterpene lactone alcohol of tripterygium, diterpene lactone glycol of tripterygium, diterpene lactone ketone of tripterygium and a plurality of derivatives of the diterpene lactone alcohol of tripterygium.

Preparation method of culture composts for growing tarragon CN101624318

The present invention discloses a method which utilizes the Tripterygium wilfordii cell culturing method to produce triptolide and Tripterygium wilfordii alkaloid. The method utilizes adventitious roots formed by the annual stuck branches of Tripterygium wilfordii as raw material to conduct callus induction and subculture on explants, establish suspension cell lines and establish and screen out cell suspension systems which can suitably utilize the two-step cell culturing method to produce the triptolide and the alkaloid, and corresponding growth culture media and formulae of producing a triptolide culture medium and a Tripterygium wilfordii alkaloid culture medium thereof.; The method, which is utilized to produce the triptolide and total alkaloids from Tripterygium wilfordii, is characterized by short production cycle, high efficiency, environment-friendliness, etc. and helps to protect the

natural Tripterygium wilfordii resource.

Attenuation method of tripterygium wilfordii
CN101361779

The invention discloses a method for the attenuation of tripterygium wilfordii. The original powder of the tripterygium wilfordii is evenly mixed with wheat bran and soybean flour; fermentations obtained from the common pile fermentation of Pu-erh tea within the fourth to tenth day or hair mould or aspergillus fumigatus is taken as inoculums; the mixed material is added with boiled water to sterilize for 40min to 120min by steam and cooled to 35 DEG C, after that, the mould or the fermentations is inoculated, then purified water is added, culturing is carried out for 4 days to 10 days under the condition with temperature of 25 DEG C to 40 DEG C and relative humidity of 50 percent to 80 percent, the ethanol is recycled by ethanol-extracting, and an extract for the attenuation of tripterygium wilfordii is obtained after concentration and desiccation are carried out.; The invention utilizes the integral translation effect of microorganisms, not only realizes the goal of toxicity reduction, but also has the effect of enhancing pharmacological activity. As raw medicinal materials that are not extracted and separated are directly adopted, products of translation can be directly prepared into a proper dosage form used for clinical treatment, thereby avoiding resource waste caused by translating substances with single activity and being beneficial to the full utilization and sustainable development of tripterygium wilfordii biotic resources.

Tripterygium wilfordii Hook.f total terpenoid vesicles and preparation method
CN101797278

The invention discloses Tripterygium wilfordii Hook.f total terpenoid vesicles and a preparation method thereof and a preparation containing the Tripterygium wilfordii Hook.f total terpenoid vesicles and a preparation method thereof, and belong to the field of medicaments. The Tripterygium wilfordii Hook.f total terpenoid vesicles are prepared from Tripterygium wilfordii Hook.f total terpenoid, a non-ionic surfactant, cholesterol and an additive. The Tripterygium wilfordii Hook.f total terpenoid vesicles is preferably prepared into an external gel formulation. The external percutaneous-administration preparation of the Tripterygium wilfordii Hook.f total terpenoid has unique advantages; a novel vesicle administration system is used to increase the percutaneous absorption of the medicament, strengthen the clinical effects and avoid the side or toxic effect during oral administration or injection administration; and the external percutaneous-administration preparation has the treatment effects of preventing inflammation, relieving pain and the like and can be used for treating rheumatoid arthritis and the like.

Method for tissue culture and rapid propagation of medicinal herb tripterygium wilfordii
CN102090334

The invention provides a method for tissue culture and rapid propagation of a medicinal herb tripterygium wilfordii medicinal material. The method comprises the following steps: preparing an explant; performing primary culture; performing propagation culture; hardening-off; performing rooting culture; and transplanting tissue culture seedlings. On the theoretical basis for screening good clones and determining a scientific induction technology, through clone variation, mutagenesis, chromosome doubling, suspended cell culture, filial generation acclimation screening and other means to the optimized tripterygium wilfordii provenance, the method provided by the invention can be used for realizing cultivation of good regenerated tripterygium wilfordii plants, and constructing a tripterygium wilfordii superior variety tissue culture base.

Tripterygium wilfordii hook acclimatization and high-yielding method
CN102106231

The invention provides a tripterygium wilfordii hook acclimatization and high-yielding method. A cut section of the stem of the tripterygium wilfordii hook is adopted for culturing and breeding, and abundant materials provide a foundation for breeding and acclimatization of mass wild tripterygium wilfordii hook. The method comprises the following steps: preparing a nursery garden; raising seedlings by cutting; transplanting; and managing a base. The method is a complement for wild tripterygium wilfordii hook resources, and has great significance in developing subsequent industry of tripterygium wilfordii hook exploitation.

METHODS OF FREEZE-DRYING AND DEBARKING THE ROOTS OF A T. WILFORDII HOOK F. PLANT AND METHODS OF PROCESSING EXTRACTS WO2012154717

FIELD OF THE INVENTION

[0001] The disclosed subject matter generally relates to plants and plant products and more specifically relates to Tripterygium wilfordii Hook F. plants, plant products and methods of making and using extracts of such plants and plant products.

BACKGROUND OF THE INVENTION

[0002] Tripterygium wilfordii Hook F. (TwHF) (Celastraceae), commonly known as Thunder god vine, is a perennial shrub indigenous to China and Southeast Asia. TwHF contains a number of chemical compounds that are toxic. Parts of the TwHF plant, such as the leaves, the stem, flowers, and the skin and/or bark of the roots are poisonous and may cause death if ingested. TwHF has been used in traditional Chinese medicine to treat diseases and disorders, but the uses are limited by the significant toxicity risk. Administration of TwHF has also been shown to inhibit interleukin-2-mediated immunosuppression.

Administration of a TwHF extract or its components, {e.g., triptolide and tripdiolide, compounds obtained from TwHF), has been shown to inhibit interleukin-2 (IL-2).

Purification of such compounds is costly and time-consuming, but necessary in view of the toxins. Use of less purified materials from the plant presents the risk that the benefits of therapy will be outweighed by the risks of deleterious consequences resulting from administration of toxic substances.

[0003] The inflammatory response is associated with invasion of a body by a foreign object or injury. On occasion, inflammatory responses, both acute and chronic, develop under circumstances where the body is not under true threat, and the inflammatory response itself becomes a condition or disorder requiring treatment. Analogously and closely aligned, the immune response wards off invasion by foreign objects, but that response also occurs under inappropriate circumstances, such as when there is no foreign object. A variety of disorders are characterized by inappropriate immune responses, exemplified by the various auto-immune disorders known to man. A continuing effort is being made to provide more effective and safer treatments for disorders involving inappropriate immune responses and/or inappropriate inflammatory responses.

[0004] For the foregoing reasons, a need continues to exist in the art for compositions comprising the beneficial biologically active compounds of TwHF with an acceptably reduced presence of TwHF toxins, that are useful in preventing, mitigating, treating or ameliorating a symptom of an inappropriate inflammatory response and/or an inappropriate immune response.

SUMMARY OF THE INVENTION

[0005] Described herein are methods for obtaining and processing extracts of the Tripterygium wilfordii Hook F. (TwHF) plant that provide beneficial biologically active compounds with an acceptably reduced level of toxic substances that improves the safety profile. The methods yield natural products that provide the benefits of TwHF without undue risk of harming recipients that characterizes use of the native plant...

DETAILED DESCRIPTION OF THE INVENTION

[0066] The present application is based on the discovery that freeze-drying the roots of a TwHF plant facilitates comprehensive removal of the bark from the root core, which allows for the preparation of extracts that substantially lack the toxic compounds (e.g., celastrol) present in the bark.

[0067] The present application is also based on the discovery that non-polar organic solvents and formulation excipients are capable of transforming conventional extracts of a TwHF plant into a freely flowable solid. Conventional extracts of a TwHF plant produced by methods known in the art (e.g., solids isolated from alcoholic extractions of a TwHF plant without any further processing steps) are waxy, amorphous solids (i.e., a native extract) with poor flow characteristics that require extraordinary means to manipulate and produce a useable drug product. The freely flowable solids produced by the processing methods described herein contain useful levels of extract compounds (e.g., triptolide and tripdiolide), and these extract compounds can be formulated into a drug

product for the treatment of various disorders, including anti-inflammatory disorders such as rheumatoid arthritis.

II. Methods of Freeze-Drying Roots of the TwHF plant.

[0076] As demonstrated in the Examples provided herein, freeze-drying the roots or root portions of a TwHF plant prior to removing the bark allows for easy, quantitative removal of the bark compared to conventional methods. Freeze-drying is a dehydration process in which water is removed from the root of a TwHF plant without exposing the plant material to protracted periods of exposure to the potentially deleterious effects of liquid water and/or excessive heat. The freeze-drying process can be performed with any method known in the art as well as in any freeze-drying apparatus known in the art.

[0077] One aspect of the disclosure provides a method of producing freeze-dried root portions from the roots of a TwHF plant, wherein the method comprises placing a plurality of frozen root portions in a container within a freeze-drying chamber, wherein the roots are sufficiently close in proximity to each other within the container to facilitate heat transfer; lowering the pressure within the chamber; and heating the container by an amount sufficient to sublimate the water in the root portions, thereby producing freeze-dried root portions of a TwHF plant.

[0078] The first step of the freeze-drying process is the freezing of the root portions. The roots of the TwHF plant can grow to a length of up to 12 meters, which is too large to fit into most commercial freeze-drying chambers. Thus, in some embodiments, it is desirable to process or mill the roots of the TwHF plant prior to beginning the freeze-drying process in order to produce root portions of a more manageable size. The TwHF roots are processed to a desired length or range of lengths before or after freezing, but prior to freeze-drying. For example, in some embodiments, the roots of the TwHF plant are processed to produce root portions of a length of about 24 inches or less. In some embodiments, the roots of the TwHF plant are processed to produce root portions of a length of about 12 inches, about 11 inches, about 10 inches, about 9 inches, about 8 inches, about 7 inches, about 5 inches, about 4 inches, about 3 inches, about 2 inches, about 1 inch, about [1/2] inch, or less. In some embodiments, the roots of the TwHF plant are processed to produce root portions of a length of about 6 inches.

[0079] In some embodiments, a root of the TwHF plant has a diameter of about [1/2] inch or less. In some embodiments, a root has a diameter of about 1/3 inch, [1/4] inch, 1/8 inch, 1/16 inch or less. In other embodiments, a root of the TwHF plant has a diameter of about 1 inch or more. In one embodiment, the roots of the TwHF plant are processed to produce root portions of a length of about 6 inches and a diameter of about [1/2] inch. Typically, TwHF roots are not processed to alter the average diameter thereof, but the disclosure contemplates such processing using any conventional milling technique where reduced diameters and increased surface are desired (or at least not undesired) to more efficiently freeze-dry the preparation. Given that the roots or root portions are subject to extraction, various lengths and diameters of roots and root portions are acceptable, including ground, macerated or pulverized roots and root portions.

[0082] Root portions are obtained from a TwHF plant of any age. In some embodiments, the root portions are obtained from a TwHF plant that is grown for less than about 30 months. In related embodiments, the root portions are obtained from a TwHF plant that is cultivated for about 29 months, 28 months, 27 months, 26 months, 25 months, 24 months, 23 months, 22 months, 21 months, 20 months, 19 months, 18 months, 17 months, 16 months, 15 months, 14 months 13 months, 12 months, 11 months, 10 months, 9 months, 8 months, 6 months or less. In other embodiments, the root portions are obtained from a TwHF plant that is grown for at least 30 months or longer. In such embodiments, the root portions are obtained from a TwHF plant that is cultivated for about 31 months, 32 months, 33 months, 34, months, 35 months, 36 months, 37 months, 38 months, 39 months, 40 months, 41 months, 42 months, 43 months, 44 months, 45 months, 46 months, 47 months, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years or more...

[0083] A variety of approaches are suitable for freezing the TwHF roots or root portions from which extracts are to be prepared. In some embodiments, the freezing process is performed by placing the root portions in a container and placing the container in a dedicated freezing apparatus (i.e., a freezing apparatus that is separate from the freeze-drying chamber) overnight prior to beginning the freeze-drying process. The root portions are placed sufficiently close to each other within the container to facilitate heat transfer during the freeze-drying process. Preferably a root portion is in contact with at least one other root portion and/or with the container to facilitate heat transfer by conduction. The container may be composed of any material or materials, preferably conductive material(s). The container is of any shape or footprint compatible with the freeze-drying chamber. The container is any depth compatible with the internal dimensions of the freeze-drying chamber; in some embodiments, the container has a depth of no more than 2 inches, such as a depth in the range of 0.125-2.0 inches, or a nominal height. In some embodiments, the root portion is cooled below its eutectic point to ensure the absence of liquid-phase material, regardless of the pressure.

[0084] The use of any commercial freezing apparatus (e.g., freezer) that is capable of reducing the temperature of the root portions to a temperature ranging from -10[deg.]C to -70[deg.]C is specifically contemplated. In some

embodiments, the temperature of the root portions is reduced to a temperature ranging from -20[deg.]C to about -70[deg.]C. In some embodiments, the temperature of the root portions is reduced to a temperature of about -20[deg.]C, -25[deg.]C, -30[deg.]C, -35[deg.]C, -40[deg.]C, -45[deg.]C, -50[deg.]C, -55[deg.]C, -60[deg.]C, -65[deg.]C or about -70[deg.]C. In some embodiments, the temperature of the root portions is reduced to a temperature of about -20[deg.]C. Once the roots have been frozen at the desired temperature, the container comprising the frozen root portions is placed in a freeze-drying chamber, the temperature of which is maintained at a temperature of about -20[deg.]C or lower...

[0086] Once the freeze-drying chamber has reached the desired temperature and the root portions have been placed in the freeze-drying chamber, the pressure in the chamber is lowered in order for water within the root portions to sublimate. In some embodiments, heat is applied to the root portions to facilitate removal of water from the root portions. During this process, at least 50% of the water in the root portions is sublimated. In some embodiments, at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more of the water in the root portions is sublimated. In some embodiments, heat is applied to the root portions indirectly by incrementally increasing the temperature of the freeze-drying chamber from about 10[deg.]C to about 70[deg.]C. In some embodiments, the temperature of the chamber is first increased to about 10[deg.]C and the temperature is stabilized at about 10[deg.]C overnight. The temperature of the chamber is then increased to about 35[deg.]C for about 8 hours and then increased to about 50[deg.]C for about 8 hours. At the end of the freeze- drying process, the final residual water content in the freeze-dried root portions is, in some embodiments, about 20% or lower. In some embodiments, the freeze-dried root portions contain no more than 15% water. In other embodiments, the freeze-dried root portions contain no more than 10% water. In other embodiments, the freeze-dried root portions contain no more than 5% water or less. In other embodiments, the freeze-dried root portions contain no more than 2% water or less.

[0087] The pressure of the freeze-drying chamber is controlled through the application of a vacuum. The vacuum is employed to facilitate sublimation. In some embodiments, the pressure within the freeze-drying chamber ranges from about 3 to about 10 millibar. In some embodiments, the pressure within the freeze-drying chamber is no more than 0.01 atm.

[0088] A cold condenser chamber and/or a condenser plate is/are used, in some embodiments, to provide a surface upon which water vapor may be contained and/or collected. By utilizing a condenser, water vapor is prevented from reaching the vacuum pump, which could degrade the performance of the pump. The condenser is maintained at a temperature known in the art as useful in de-humidification. In some embodiments, the temperature of the condenser is maintained at -50[deg.]C or lower. In some embodiments, the temperature of the condenser is maintained at -30[deg.]C or lower.

[0089] The resulting freeze-dried root portion of the TwHF plant comprises a root core and bark, wherein the attachment of the bark to the root core is altered, thereby reducing the strength of attachment of the bark to the root core relative to a fresh TwHF root portion of comparable dimensions. Without wishing to be bound to any particular theory, it is contemplated that a thoroughly dried root portion of a TwHF plant prepared, for example, according to a freeze-drying method described herein, allows for more quantitative removal of bark from the root core. Extracts obtained from such freeze-dried debarked root cores are expected to contain considerably lower levels of toxic compounds (e.g., celastrol) compared to extracts obtained from root cores in which the bark has been removed by conventional methods without first being freeze-dried or obtained from root cores that are freeze-dried, but wherein the freeze-drying process did not result in substantial sublimation of the water within the root portions.

[0090] III. Methods of Debarking the Roots of the TwHF Plant

[0096] Compounds present in the bark of a TwHF plant can be used as markers to determine whether a measurable amount of bark is present on the freeze-dried debarked root portions. Celastrol is a triterpenoid antioxidant compound present in the bark a TwHF plant. Thus, in some embodiments, a method of identifying residual bark in a preparation of freeze- dried debarked root portions of a TwHF plant comprises determining the amount of a bark marker {e.g., celastrol) in the preparation of freeze-dried debarked root portions, wherein lower amounts of the marker in the preparation of freeze-dried debarked root portions identifies the preparation as containing lower amounts of residual bark. The amount of celastrol in the freeze-dried root portions can be determined by methods known in the art, such as NMR or HPLC. [0097] In some embodiments, the freeze-dried debarked root portions comprise less than 10% celastrol compared to the amount of celastrol present in bark of comparably dimensioned fresh root portions of a TwHF plant. In some embodiments, the freeze-dried debarked root portions comprise less than 5%, 4%, 3%, 2%, 1%, or less celastrol compared to the amount of celastrol present in bark of comparably dimensioned fresh roots of a TwHF plant.

IV. Methods of producing an extract of a TwHF plant

[0098] Methods of producing an extract from the roots of a TwHF plant are known in the art. Conventional extraction methods comprise grinding, milling or pulverizing plant material (e.g., debarked roots of a TwHF plant); extracting the plant material in a solution containing a sufficient amount of extractant fluid (e.g., an alcohol); and collecting the fluid to obtain an extract mixture (e.g., an alcoholic extract). The extract mixture may be further processed by removing solid matter from the extract mixture. Solid matter is removed from the extract by any method known in the art including, but not limited to, filtration and centrifugation. In some embodiments, the roots or root portions of the TwHF plant are debarked using the freeze-drying and debarking methods described herein. In other embodiments, the roots or root portions of the TwHF plant are fresh roots or portions that have been debarked using methods known in the art.

[0099] Grinding, milling or pulverizing debarked roots of a TwHF plant can be performed by any conventional milling process to increase the surface area of the root cores exposed to an extractant fluid.

[00100] In some embodiments, the extractant fluid for use in the extraction method is a solvent. Suitable extractant fluids include, but are not limited to, water, alcohols, aqueous solutions, halocarbons, esters and supercritical fluids. Suitable alcohols include primary alcohols such as ethanol, N-propanol, N-butanol, N-pentanol, N-hexanol, N-octanol, N- nonanol and N-decanol as well as secondary alcohols such as isopropanol, isobutanol, and the secondary alcohol derivatives of, e.g., any of butane through decane. For those lower molecular weight compounds that are gases at room temperature and about one Atm, pressurized extractions in which the compounds are in a liquid state are contemplated. In one embodiment, the extractant fluid is ethanol. A benefit of incorporating an ethanolic fluid during the extraction process is that an ethanolic fluid is compatible with an ingestible product, and therefore is suitable for use in preparing an extract for incorporation into a pill, capsule, tablet, and other ingestible forms known in the art.

[00101] In one aspect, the extracting step comprises combining debarked roots, milled if desired, with an excess of extractant fluid such as 2- to 20-volumes of extractant fluid per unit volume of milled roots, and the combined materials are stirred for a time sufficient to extract the compounds of interest from the milled roots. In some embodiments, the mixture comprising the extractant fluid and the milled roots is stirred for about 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours or longer.

Optionally, the mixture is stirred at reflux. The extraction process is conducted at a temperature of between room temperature and the boiling point of the extractant fluid.

[00102] In some embodiments, the mixture is filtered and the filtrate is concentrated until the concentrated filtrate is a fraction of the volume of the initial filtrate. In some embodiments, the concentrated filtrate is less than 1, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, 0.1 or fewer volumes relative to the initial filtrate. In some embodiments, the roots, milled if desired, are subjected to a series of extractions with the extractant fluid. In such embodiments, the roots are again combined with an excess of extractant fluid and the extraction process is repeated. The filtrates obtained from the various extractions are then combined and concentrated as described below.

[00103] Concentration of the filtrate(s) is accomplished by methods known in the art, such as through the use of a vacuum to remove a volatile fluid, e.g. , solvent. The concentration of the filtrate occurs at any temperature. In some embodiments, the temperature does not exceed 50[deg.]C. Concentrating the filtrate at a temperature of about 20[deg.]C, 25[deg.]C, 30[deg.]C, 35[deg.]C, 40[deg.]C, 45[deg.]C, 55[deg.]C, 60[deg.]C, 65[deg.]C, or 70[deg.]C is also contemplated.

[00104] In some embodiments, solvent exchange is included in the extraction (U.S. Patent Nos. 5,294,443; 5,500,340; 5,580,562; 5,846,742; 5,916,564, the disclosures of which are incorporated herein by reference in their entireties). In such embodiments, the extracting step comprises combining the concentrated filtrate with an excess (v/v) of a polar organic solvent (e.g., ethyl acetate) relative to original root mass to produce an extract mixture, which also may be concentrated as described above. The polar organic solvent (e.g. , ethyl acetate) is different from the alcohol solvent used to prepare the extract in the extracting step. This process is repeated until the solvent exchange reduces the extractant fluid (e.g., alcohol) concentration in the extract mixture to 15% or less by weight. In some embodiments, the process is repeated until the extractant fluid concentration in the extract mixture is 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1% or less by weight. The concentration of the extractant fluid can be determined by methods known in the art (e.g., NMR).

[00105] In some embodiments, the extract mixture is filtered to remove insoluble components, and the filtered extract solution is processed further by one of the methods described herein.

V. Methods of processing an alcoholic extract of a TwHF plant into a freely flowable solid

[00106] In another aspect, described herein is a method of processing an alcoholic extract of a TwHF plant into a freely flowable solid. In some embodiments, the method comprises obtaining an alcoholic extract of a TwHF plant,

combining the alcoholic extract with a non- polar organic solvent to produce an extract/non-polar organic solvent mixture; filtering the extract/non-polar organic solvent mixture to isolate a solid precipitate and drying the solid precipitate, thereby processing the alcoholic extract into the form of a freely flowable solid. In some embodiments, the alcoholic extract is subjected to solvent exchange prior to the combining step, wherein the solvent exchange comprises exchanging the alcohol in the alcoholic extract for a polar organic solvent such as ethyl acetate. In such embodiments, the extract/ethyl acetate mixture is combined with the non-polar organic solvent in the combining step.

[00107] Suitable non-polar organic solvents include any of the C4-C10 straight- or branched-chain alkanes and cycloalkanes. In some embodiments, the non-polar organic solvent is a straight-chain alkane such as pentane, hexane, heptane, octane, nonane or decane. In some embodiments, the non-polar organic solvent is heptane. In other embodiments, the non-polar organic solvent is a branched-chain alkane, such as isopentane, isohexane, isoheptane, isooctane, isononane or isodecane. In some embodiments, the non-polar organic solvent is isooctane.

[00108] The combining step comprises contacting, mixing or putting together the alcoholic extract (or extract/ethyl acetate mixture) with an excess volume, such as 2- to 20-volumes, of a non-polar organic solvent relative to the original root mass to produce an admixture. In some embodiments, the combining step occurs under vacuum. In some embodiments, the combining step is repeated until the level of non-polar organic solvent in the admixture is undetectable. The admixture is filtered to collect solid precipitate material and subjected to one or more washes with the non-polar organic solvent. Filtering the admixture can be performed by conventional methods known in the art and can be repeated, if desired.

[00109] In an alternative aspect, the method comprises obtaining an alcoholic extract of a TwHF plant, combining the alcoholic extract with an excipient under vacuum to produce an extract/excipient mixture; and drying the concentrated mixture, thereby producing the extract in the form of a freely flowable solid. In some embodiments, the alcoholic extract is subjected to solvent exchange prior to the combining step, wherein the solvent exchange comprises exchanging the alcohol in the alcoholic extract for a polar organic solvent such as ethyl acetate. In such embodiments, the extract/ethyl acetate mixture is combined with the excipient in the combining step.

[00110] The combining step comprises contacting, mixing and/or putting together the alcoholic extract (or extract/ethyl acetate mixture) with an appropriate amount of excipient (compared to the total solid content in the extract), such as 0.5- to 20-fold (w/w), and optionally stirring for a time sufficient to mix the excipient and the extract. Use of an excipient in an amount of about 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 11-, 12-, 13-, 14-, 15-, 16-, 17-, 18-, 19-fold excess (w/w) relative to the solid content of the extract is also contemplated. Suitable excipients for use in the methods described herein include microcrystalline cellulose (MCC), maltodextrin, Aerosil(R) (fumed silica), corn starch, and Neusilin (magnesium aluminometasilicate). In some embodiments, the excipient is MCC. In some embodiments, the combining step comprises concentrating the extract/excipient mixture under full vacuum at a temperature not to exceed 50[deg.]C (e.g., about 20[deg.]C, 30[deg.]C, 35[deg.]C, 36[deg.]C, 37[deg.]C, 38[deg.], 39[deg.]C, 40[deg.]C, 41[deg.]C, 42[deg.]C, 43[deg.]C, 44[deg.]C, 45[deg.]C, 46[deg.]C, 47[deg.]C, 48[deg.]C or about 49[deg.]C) until a dry solids content of approximately 80% is achieved in the concentrated excipient mixture.

[00112] Extracts of TwHF contain more than 200 compounds, including diterpenoids, triterpenoids, sesquiterpenoids, [beta]-sitosterol, dulcitol and glycosides. Exemplary compounds include, but are not limited to, triptolide, tripdiolide, polpunonic acid (wilfortrine) and the methyl ester thereof, triptophenolide, triptophenolide methyl ether, triptonoterpenol, wilformine, wilforine, wilforgine, and wilforzine. In some embodiments, it is desirable to determine the amount of one or more of these compounds in the freely flowable solid. The determination of compounds in a sample can be determined by methods known in the art such as NMR or HPLC...

[00116] The native extract of a TwHF plant is a waxy, amorphous solid that requires extraordinary means to produce a useable drug product. Described herein are improved methods of processing the native extract of a TwHF plant into a freely flowable solid (e.g., a flowable powder).

[00117] In one aspect, the method comprises combining the native extract with a non- polar organic solvent to produce a mixture thereof; filtering the mixture to collect a solid precipitate and drying the solid precipitate, thereby producing the native extract in the form of a freely flowable solid. Suitable non-polar organic solvents include any of the C4-C10 straight- or branched-chain alkanes and cycloalkanes. In some embodiments, the non-polar organic solvent is a straight-chain alkane such as pentane, hexane, heptane, octane, nonane or decane. In some embodiments, the non-polar organic solvent is heptane. In other embodiments, the non-polar organic solvent is a branched-chain alkane, such as isopentane, isohexane, isoheptane, isooctane, isononane or isodecane. In some embodiments, the non- polar organic solvent is isooctane.

[00118] In some embodiments, the non-polar organic solvent/extract mixture is filtered to collect solid precipitate material. Filtering the non-polar organic solvent/extract mixture can be performed by conventional methods known

in the art. Once collected, the solids are subjected to one or more washes with a non-polar organic solvent.

[00119] In another aspect, the method comprises mixing a native extract of a TwHF plant with a polar organic solvent (e.g., an alcohol) to produce an extract/polar organic solvent mixture; combining the extract/polar organic solvent mixture with an excipient under vacuum at a temperature of no more than 50[deg.]C to produce a concentrated mixture; and drying the concentrated mixture at a temperature suitable to remove remaining polar solvent from the mixture, thereby producing the native extract in the form of a freely flowable solid. Suitable polar organic solvents for use in this processing method include, but are not limited to, ethanol, ethyl acetate, isopropanol, n-butanol, n-propanol and methanol. In some embodiments, the polar organic solvent is ethanol.
[00120] In some embodiments, the adding step comprises incorporating an excess amount of an excipient (w/v), such as 0.5- to 20-fold, into the polar solvent/extract mixture and optionally stirring for a time sufficient to mix the excipient into the polar solvent/extract mixture to produce an excipient mixture. Mixing an excipient amount of about 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 11-, 12-, 13-, 14-, 15-, 16-, 17-, 18-, 19-fold excess (w/v) over the polar solvent/extract mixture is also contemplated. Suitable excipients for use in the methods described herein include microcrystalline cellulose (MCC), maltodextrin, Aerosil(R) (fumed silica), corn starch, and Neusilin (magnesium aluminometasilicate). In some embodiments, the excipient is MCC.

[00121] In embodiments where an excipient is added to the organic solvent/extract mixture, no filtration step is performed.

[00122] The washed solids, or excipient mixture, are then dried for a time sufficient to remove the organic solvent from the solids, or excipient mixture, respectively. In some embodiments, the drying step is performed for a time period of about 8-24 hours. Drying the washed solids, or excipient mixture, for about 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 24 hours or more is specifically contemplated. Drying the washed solids, or excipient mixture, for less than 8 hours is also contemplated. The washed solids, or excipient mixture, can be dried in the air or in any drying apparatus known in the art including, but not limited to, a tray dryer, a vacuum oven or an oven. In some embodiments, the washed solids, or excipient mixture, are dried in a drying apparatus at a temperature of about 20[deg.]C, 25[deg.]C, 30[deg.]C, 35[deg.]C, 40[deg.], 45[deg.]C or about 50[deg.]C.

VII. Pharmaceutical compositions and routes of administration of a TwHF extract

[00128] The amount and administration regimen of the processed TwHF extract is based on various factors relevant to the purpose of administration, for example human or animal age, sex, body weight, hormone levels, or nutritional need of the human or animal. In some embodiments, the TwHF extract is administered daily to an animal in an amount from about 0.001 mg/kg body weight to about 10 g/kg body weight. In some embodiments, the processed TwHF extract is administered to an animal in an amount of about 0.005 mg/kg body weight per day, or about 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, or about 10 mg/kg body weight per day...

[00130] Treatment with a processed TwHF extract is continued for at least about 1 week. Duration of treatment lasting about 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year, 5 years or up to lifetime treatment is also contemplated...

Example 1. Preparation of a freeze-dried debarked root of a TwHF plant.

[00133] The improved TwHF extracts according to the disclosure are more amenable to manipulation as a result of improved flow properties and exhibit improved safety profiles as a result of reduced toxin contamination from T. wilfordii bark components. The reduction in toxin content is achieved by preparing T. wilfordii roots and root portions in a manner that facilitates quantitative or near-quantitative bark removal in an efficient manner. More particularly, the TwHF roots and/or root portions are freeze-dried in preparation for debarking.

[00134] A total of 308g of fresh TwHF root material (91g medium roots (3-10mm in length), 15g small (1.00-3.00 mm in length), 29g root hairs (1.00 or less in length), 30g stumps and 143g large roots (10.00 mm or larger in length)) were placed in Pyrex trays and frozen overnight at -20[deg.]C. The freeze-drying (Labconco) chamber was adjusted to -50[deg.]C and allowed to equalize overnight. The root material was then placed in the freeze-drying chamber and the vacuum was set to a pressure of 3-10 millibar. The chamber temperature was raised to 10[deg.]C for four hours, then raised to 25[deg.]C for an additional four hours, and then finally raised to 35[deg.]C for overnight. The resulting freeze-dried root material was removed from the freeze-drying chamber.

[00135] Freeze-drying the root material caused cracking of the bark from the root core, which was observed upon visual inspection of the freeze-dried root material. To remove the bark, the freeze-dried root material was pressed or rolled with mild pressure on a flat surface or in a compression device (e.g., a pasta roller) to remove the bark from the root core. The process of removing the bark created a fine beige to pink dust/powder, which was

attributed to the bark. Seventeen grams of dried debarked root material were obtained.

[00136] The mild pressure did not pulverize the TwHF roots and/or root portions, and these materials were readily separable from any residual dust or powder, ensuring minimal bark toxins would be found in any subsequent root extract. It will be apparent to one of skill in the art that many other mechanical and electromechanical operations will prove suitable for removing the bark from the freeze-dried roots and/or root portions, and all such operations known in the art are contemplated by the disclosure.

[00137] The foregoing Example demonstrates that any known method of freezing TwHF root portions known in the art is suitable for use in the methods described herein. Additionally, the freeze-drying process may involve any apparatus capable of controlling the pressure of the atmosphere immediately surrounding the TwHF root portions. As with most freeze-drying methodologies, moreover, the length of time that the initially frozen TwHF root portions are exposed to the freeze-drying process may vary, provided that sufficient time is allowed to reduce the water content of the root portions to acceptable levels, e.g., less than 2%.

Example 2. Preparation of a freely flowable solid from a native extract of a TwHF plant using a non-polar organic fluid as a co-processing agent.

[00138] TwHF root portions debarked according to the disclosure provide a desirable substrate for extract preparation because the efficient and thorough debarking minimizes, or eliminates, bark toxins that can contaminate TwHF extracts. In addition to addressing the issue of toxins by providing improved debarking procedures, the disclosure provides processes for improving the flow characteristics of extracts prepared from the debarked TwHF root portions. This Example describes a method of producing a freely flowable solid from an extract of a TwHF plant using a non-polar organic fluid (e.g., hexane) as a coprocessing agent.

[00139] Briefly, 10 g of the native extract obtained from debarked roots from Chinese TwHF plants (i.e., TwHF plant grown in China) were combined with 100 mL hexane (Fisher Reagent Grade) in a 250 mL beaker. A stainless steel spatula was used to break up the extract into pieces. The hexane/extract mixture was then sonicated for 30 minutes at room temperature. The hexane/extract mixture was then placed in a Buchner funnel, filtered and washed with 100 mL hexane to produce a filtrate (which was yellow/orange in color) comprising the hexane wash flow-through and a retentate (which was brown/red in color) comprising the solids in the hexane/extract mixture. The hexane/extract mixture was filtered until the retentate was dry. The retentate was then subjected to repeated washings with 100 mL hexane until a colorless filtrate was observed. The retentate was dried overnight in a vacuum oven (100 millibar, 40[deg.]C) to remove any residual hexane from the retentate. The dried retentate was in the form a freely flowable solid with a yield of 6.7g.

[00140] To assess the scalability of the method to commercial quantities, the process was also applied to a larger quantity of the native extract. Fifty grams of an ethanol extract obtained from debarked roots of Chinese TwHF plants were combined with 250 mL hexane in a 500 mL beaker. Simple extracts of TwHF, such as the ethanol extract, are viscous, almost tar-like, amorphous masses that are difficult to manipulate. A stainless steel spatula was used to break up the extract into pieces. The hexane/extract mixture was then stirred for 30 minutes at room temperature. The hexane/extract mixture was then placed in a Buchner funnel, filtered and washed with 100 mL hexane to produce a filtrate (which was
yellow/orange in color) comprising the hexane wash flow-through and a retentate (which was brown/red in color) comprising the solids in the hexane/extract mixture. The hexane/extract mixture was filtered until the retentate was dry. The retentate was then subjected to repeated washings with 100 mL hexane until a colorless filtrate was observed. The retentate was dried overnight in a vacuum oven (CascadeTek; 100 millibar) at room temperature to remove any residual hexane from the retentate. The dried retentate was in the form of a freely flowable solid with a yield of 35.5 g. The results established that the method would scale to commercially useful quantities.

[00141] These results showed that a TwHF extract processed by exposure to a non-polar organic fluid such as hexane, would result in a TwHF extract that was a freely flowable solid amenable to manipulations to formulate the extract in forms suitable for nutritional supplementation or therapeutic treatment, including but not limited to such forms as capsules, tablets, gels, creams, and the like. It is expected that any C4-C10 straight-chain or branched-chain alkane or alkene will be suitable in processing TwHF extracts to yield freely flowable extract solids.

Example 3. Preparation of a freely flowable solid from a native extract of a TwHF plant using another non-polar organic fluid as a co-processing agent.

[00142] Consistent with the expectation, stated in Example 2, that any C4-C10 straight- or branched-chain alkane or alkene would be useful in producing a freely flowable solid form of TwHF extract, this Example describes a method of producing a freely flowable solid from an extract of a TwHF plant using a non-polar organic fluid (e.g., heptane) as a co-processing agent.

[00143] Ten grams of a native extract from the root of a Chinese TwHF plant was combined with 100 mL heptane (Fisher Reagent Grade) in a 250 mL beaker. A stainless steel spatula was used to break up the extract into pieces. The heptane/extract mixture was then stirred for about 20-30 minutes at room temperature until the extract had dissolved. The heptane/extract mixture was then placed in a Buchner funnel, filtered and washed with 100 mL heptane to produce a filtrate (which was yellow/light orange in color) comprising the heptane wash flow-through and a retentate comprising the solids in the heptane/extract mixture. The heptane/extract mixture was filtered until the retentate was dry. The retentate was then subjected to repeated washings with lOOmL heptane until a colorless filtrate was observed. The retentate was dried overnight in a vacuum oven (100 millibar; 50[deg.]C) to remove any residual heptane from the retentate. The dried retentate was in the form of a freely flowable solid with a yield of 6.4g.

[00144] The experiment was then scaled up and repeated. The native extract (50 g) obtained from debarked roots of Chinese TwHF plants were combined with 300 mL heptane in a 500 mL beaker. A stainless steel spatula was used to break-up the extract into pieces. The heptane/extract mixture was then stirred for about 20-30 minutes at room temperature until the extract had dissolved. The heptane extract mixture was then placed in a Biichner funnel, filtered and washed with 100 mL heptane to produce a filtrate comprising the heptane wash flow-through (which was yellow/light orange in color) and a retentate comprising the solids in the heptane/extract mixture. The heptane/extract mixture was filtered until the retentate was dry. The retentate was then subjected to repeated washings with 100 mL heptane until a colorless filtrate was observed. The retentate was dried overnight in a vacuum oven (CascadeTek; 100 millibar; 50[deg.]C) to remove any residual heptane from the retentate. The dried retentate was in the form of a freely flowable solid with a yield of 30.0 g, establishing that the method would be suitable for commercially useful quantities.

[00145] The freely flowable character of TwHF extracts processed with either hexane (Example 2) or heptane (the present Example) establish that contacting a TwHF extract with a non-polar organic fluid, such as a C4-C10 straight- or branched-chain alkane will produce a freely flowable solid form of the extract, amenable to formulation into nutritional supplements or therapeutics.

Example 4. Alternative method of producing a freely flowable solid from an ethanol extract of the roots of a TwHF plant using heptane as co-processing agent.

[00146] This Example describes an alternative method of producing a freely flowable solid from an ethanol extract of a TwHF plant. Freeze-dried debarked roots of a TwHF plant were milled and then combined with 8 volumes of ethanol relative to the volume of the roots and stirred at reflux (78[deg.]C) for 6 hours. The ethanol extract was then filtered to produce a first filtrate and moved to a holding tank. The debarked and milled roots were then combined with an additional 8 volumes of ethanol in a second ethanol extraction and stirred at reflux (78[deg.]C) for 6 hours. The second ethanol extract was filtered to produce a second filtrate. The first and second filtrates were combined and then concentrated under vacuum at room temperature to produce a concentrated filtrate mixture. The resulting concentrated filtrate mixture was approximately 0.9 volumes relative to the original root mass.

[00147] The concentrated filtrate mixture was then combined with 1.2 volumes ethyl acetate, relative to original root volume, and concentrated under vacuum with the ethanol removed by distillation. This process was repeated until the solvent exchange reduced the ethanol concentration to less than 15% by weight, as determined by NMR, resulting in an ethyl acetate mixture. The ethyl acetate mixture was combined with 3.3 volumes of heptane relative to the original root volume, to produce a heptane mixture, and the mixture concentrated under vacuum, with the ethyl acetate removed by distillation. This process was repeated until the solvent exchange reduced the ethyl acetate concentration to undetectable levels, as determined by NMR. The heptane mixture was then filtered and the solids were collected. The solids were washed with heptane until the flow-through was colorless. The washed solids were then dried in a tray dryer at about 40[deg.]C for about 8-12 hours.

[00148] The dried material was a freely flowable solid. This Example confirms that processing an extract of the TwHF plant with a straight-chain C4-C10 alkane, i.e., heptane, results in a freely flowable solid that is suitable for therapeutic or nutritional formulations. Moreover, the Example establishes that there are alternative methods for exposing a TwHF extract to a non-polar organic fluid to produce the extract in the form of a freely flowable solid.

Example 5. Large-scale preparation of a freely flowable solid from an ethanol extract from the roots of a TwHF plant using heptane as co-processing agent.

[00149] The process described in Example 4 was repeated multiple times with debarked root portions from Chinese TwHF plants in amounts of approximately 100 kg (n=3), 250.4 kg (n=2), 250.2 kg (n=3) 211.2kg (n=l) and 286.6 kg (n=l) to produce a freely flowable solid. The starting root material and resulting freely flowable solid material were analyzed by HPLC to fractionate components of the extract and to determine the concentration of triptolide and tripdiolide in the various samples tested. The results of the experiment are set forth in Table 1...

[00153] Tables 1-3 reveal that the freely flowable solid contains concentrated triptolide and tripdiolide compared to the fresh root samples tested. The concentrated levels of triptolide and tripdiolide present in the freely flowable solid produced by processing a native extract of TwHF with heptane allows for the administration of lower dosages of the freely flowable solid to subjects in need of treatment with triptolide and/or tripdiolide in comparison to an extract of TwHF processed by conventional methods.

[00154] In addition, the data in this Example demonstrate that the celastrol content is low in extracts obtained from root portions that were freeze-dried prior to bark removal. Thus, the freeze-drying of TwHF root portions prior to bark removal allows for the preparation of extracts containing not only concentrated levels of bioactives (e.g., triptolide and tripdiolode) but also having a reduction in toxicity (e.g., celastrol content) in comparison to the toxicity of an extract of TwHF processed from root portions that were not freeze-dried prior to being debarked using conventional methods...

[00157] Results showed that microcrystalline cellulose (MCC) performed better than any other tested excipient in that it produced a TwHF extract in the form of a non-cakey, flowable solid. Although other excipients are expected to prove suitable for use in preparing freely flowable solid forms of TwHF extracts, further work described herein addressed freely flowable solids produced using MCC. Based on the flowability of extracts processed with MCC, the processing of extracts with MCC was scaled up in a manner analogous to the commercial scale experiments described in Examples 3 and 4 and the triptolide and tripdiolide concentrations in the resulting freely flowable solid were analyzed. The results are set forth in Table 5...

Example 7. An alternative method of producing a freely flowable solid from an ethanol extract of a TwHF plant using microcrystalline cellulose as a co-processing agent.

[00159] Described in this Example is an alternative method of producing a TwHF extract in a freely flowable solid form by exposing an ethanol extract of a TwHF plant part to an excipient such as MCC. Freeze-dried debarked root portions of a TwHF plant were milled and then combined with 8 volumes of ethanol (approximately 4 L) relative to the mass of the root portions (approximately 500 g) and stirred at reflux (78[deg.]C) for 6 hours. The ethanol extract was then filtered to produce a first filtrate and moved to a holding tank. The debarked and milled root portions were then combined with an additional 8 volumes of ethanol in a second ethanol extraction and stirred at reflux (78[deg.]C) for 6 hours. The second ethanol extract was filtered to produce a second filtrate. The first and second filtrates were combined and then concentrated under vacuum to produce a concentrated filtrate. The resulting concentrated filtrate was approximately 0.9 volumes relative to the original root volume.

[00160] The concentrated filtrate was then combined with 1.2 volumes ethyl acetate, relative to original root mass, and concentrated under vacuum at 50[deg.]C with the ethanol removed by distillation. This process was repeated until solvent exchange reduced the ethanol concentration to 15% or less by weight as determined by NMR, resulting in an ethyl acetate mixture. The ethyl acetate mixture was then combined with an appropriate amount of an excipient (compared to the total solid content in the ethyl acetate mixture) and mixed thoroughly. The ethyl acetate/excipient mixture was then concentrated under full vacuum at a temperature not to exceed 55[deg.]C until a dry solids content of approximately 80% was achieved in the ethyl acetate/excipient mixture. The concentrated mixture was then dried in a vacuum dryer under full vacuum at a temperature not to exceed 55[deg.]C to remove ethyl acetate from the concentrated mixture. After the drying process was completed, the dried solid was in the form of a freely flowable solid.

Application of triptolide in preparation of medicament for treating or preventing human immunodeficiency viruses (HIV)
CN102755335

Abstract -- The invention discloses an application of triptolide in preparation of a medicament for treating or preventing human immunodeficiency viruses (HIV). The triptolide is diterpenoid naturally existing in roots of tripterygium wilfordii hook, and can dose-dependently inhibit replication of I type HIV (HIV-1) in cells in vitro. The half inhibitory concentrations on HIV-1 inhibition in TZM-b1 cells, JurkatT lymphocytes and human peripheral blood mononuclear cells are respectively 0.32nM, 0.45nM and 1.1nM. The triptolide has a remarkable inhibiting effect on the replication of the HIV-1 in the TZM-b1 cells, the JurkatT lymphocytes and the human peripheral blood mononuclear cells; and the triptolide is an active ingredient in Chinese medicinal tripterygium wilfordii hook, so the triptolide is wide in source. The compound has a broad prospect for developing anti-HIV-1 medicaments.

Other Pertinent Patents via the European Patent Office Advanced Search

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CN102807974

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Novel anti-leukemic diterpenoid triepoxides
US4005108

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JPS572699

Method for producing tripdiolide, triptolide and celastrol
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Medicine containing tripdiolide for preventing and treating graft acute rejection
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Tripterygium wilfordii regenerated plant and its preparation process
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Novel botanical extract of Tripterygium Wilfordii Hook F.
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CN1543804

Preparation method of thunder godvine extract
CN1656899

Suspended cultured thunder godvine cell prepared insecticide and method thereof
CN1675999

Chinese traditional medicine Tripterygium wilfordii and improving technique for attenuation and synergy of its extract
CN1634493

METHODS FOR ISOLATION OF TRIPTOLIDE COMPOUNDS FROM TRIPTERYGIUM WILFORDII
WO2005077008

Method for extracting catechin and epicatechin from Tripterygium wilfordii plant

CN1884276

Method for inducing, breeding and transplanting triperygium wilfordii cluster buds
CN1732756

Enteric coated/sustained release formulation of triperygium wilfordii and preparation process thereof
CN1969928

Method for separating and preparing triptolide diol from tripterygium wilfordii
CN1800188

Compound miro-emulsified pesticide of triperygium wilfordii alkaloid
CN1826904

Compound pesticide of triperygium wilfordii alkaloid
CN1826905

Processing method for reducing the poison of triptolide and the corresponding preparation
CN101062083

Tripterygium glycosides and their preparation triptolide content determining method
CN1851452

Tripterygium glycosides and their preparation wilforlide A content determining method
CN1851453

Farm chemical composition, preparing method and use
CN101069508

A botanical pesticide
CN1883277

Method for separating preparing tripterygium wilfordii monomer from tripterygium wilfordii by countercurrent flow chromatography
CN1911932

Medicine for treating osteoporosis and its preparation method
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Slow-release preparation containing polyheteroside of tripterygium wilfordii
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Dry coating sustained-release tablet for treating arthritis and preparation process thereof
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Foot nourishing and protecting mist made of pure traditional Chinese medicinal and preparation method thereof
CN101011546

Chinese medicinal formulation for treating rheumatic and rheumatoid disease
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Nano-emulsion drug of triperygium wilfordii polycoride and preparation method thereof
CN1961866

Biological pesticide for pollution-free vegetables and its manufacturing method
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Chinese traditional medicine compound took orally for treating ankylosing spondylitis
CN101040927

Chinese traditional medicine compound took orally for treating ankylosing spondylitis
CN101040908

Fuming and steaming medicine for treating arthropathy
CN101040916

Decoction for treating arthritis
CN101062198

Environment friendly pesticides for paddy field and preparation thereof
CN101317583

Environment friendly pesticides for accelerating plants growth and preparation thereof
CN101317584

Broad spectrum environment friendly pesticide and preparation thereof
CN101317585

Environment friendly pesticide for vegetables and preparation thereof
CN101317586

Optimizing method for attenuation processing of Tripterygium wilfordii and related formulation
CN101322735

Biology plant pesticides and preparation technique thereof
CN101361492

Four kinds of tripterygium wilfordii derivative and preparing method of pharmaceutics thereof
CN101235041

Method for inducing adventitious root by thunder god vine suspending cell
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Tripterygium wilfordii compound pesticides for high effectively preventing and curing tea geometrid
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Method for extracting triptolide from Tripterygium wilfordii
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Method for establishing Tripterygium wilfordii fingerprint chromatography and standard fingerprint chromatography thereof
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Method for cultivating and managing tripterygium wilfordii
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Tripterygium wilfordii hook extract cataplasm and preparation method thereof
CN102008536

Method for inducing production of tripterygium wilfordii hairy root by agrobacterium rhizogenes
CN102321664

METHODS OF PROCESSING EXTRACTS OF A T. WILFORDII HOOK F. PLANT
WO2012118942

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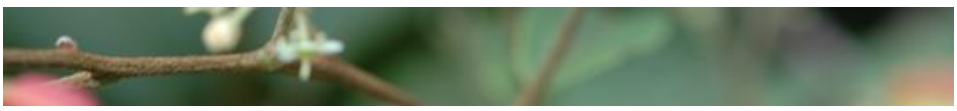
http://eol.org/pages/2888865/overview

Tripterygium wilfordii J. D. Hooker



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http://davesgarden.com

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http://www.pfaf.org/user/Plant.aspx?LatinName=Tripterygium+wilfordii

Tripterygium wilfordii - Hook.f.

Common Name
Family Celastraceae
Synonyms T. forrestii. T. hypoglaucum.
Known Hazards All parts of the plant are highly toxic[147, 218].
Habitats Field and ditch edges and on the banks of streams[147].
Range E. Asia - S. China to Burma.
Edibility Rating
Medicinal Rating
Care
Half Hardy Moist Soil Semi-shade Full sun

Summary

Physical Characteristics

Tripterygium wilfordii is a deciduous Climber growing to 12 m (39ft 4in). It is hardy to zone 9. It is in flower in September. The flowers are hermaphrodite (have both male and female organs)

Suitable for: light (sandy), medium (loamy) and heavy (clay) soils. Suitable pH: acid, neutral and basic (alkaline) soils and can grow in very alkaline soils.

It can grow in semi-shade (light woodland) or no shade. It prefers moist soil.

Other Names:

Huang-T'eng Ken, Lei Gong Teng, Lei-Kung T'eng, Taso-Ho-Hua, Threewingnut, Tonnerre de la Vigne de Dieu, Tripterigium Wilfordii, Tripterygium wilfordii, Vigne du Tonnerre Divin, Yellow Vine.
