COMPOSITION FOR TREATING OR PREVENTING HOT FLASHES AND USE THEREOF

FIELD OF THE INVENTION

The invention relates to a composition and method for treating or preventing climacteric disorders such as hot flashes. More particularly the invention relates to use of Traditional Chinese Medicine (TCM) to treat or prevent hot flashes.

BACKGROUND TO THE INVENTION

The occurrence of hot flashes in woman can cause significant discomfort and pain. Whilst hot flashes are more commonly associated with natural menopause, they can also be caused by drug- induced menopause or surgical-induced menopause.

Natural menopause is due to the natural physiological senescence of ovaries that every woman experiences as she ages.

Drug induced menopause could refer to patients receiving treatment for a gynaecological cancer (breast, endometrial, cervix, ovarian or vaginal) or for any gynaecological disease for which estrogen and progesterone secretion must be blocked to stop the disease's progression.

Gynaecological cancers such as breast, ovary, endometrial or vaginal cancers can be estrogen-sensitive (estrogen receptors are present in the tumor cells) or non-estrogen sensitive. For the estrogen sensitive cancers, the usual therapy (also called chemotherapy) is a hormonotherapy (also known asendocrine therapy) alone or in combination with other anti cancer treatments (other chemotherapy, radiation, surgery, etc). For non-estrogen sensitive cancers, the usual therapy does not involve hormonotherapy but instead relies on typical anti-cancer treatments (chemotherapy, radiation, surgery, etc). Typically, drug-induced menopause, and thus hot flashes are induced only by the chemotherapy given for estrogen sensitive cancers, also defined as hormonotherapy.

Such hormonotherapy is also used in others gynaecological disorders such as endometriosis for which estrogen and progesterone secretion must be blocked to stop the disease' progression.

Thus, 'drugs' inducing menopause could be referred as chemotherapy, anti-cancer therapy, hormonotherapy or endocrine therapy.

Surgical induced menopause refers to menopause caused by hysterectomy (surgical removal of the uterus) performed for various gynaecological reasons. These include intolerable periods not controlled by medical means, fibroids, endometriosis, prolapse, and malignant or premalignant changes of the uterus, cervix or ovary. Hysterectomy can either be total (where both the uterus and cervix are removed), or sub-total (where the main part of the uterus is removed). Ovaries may be conserved (left behind) or removed. If one or both ovaries are conserved, they may continue producing hormones in their fluctuating manner until the normal age of menopause, or they may stop producing hormones sooner than expected, inducing a early menopause. This can even happen within 1-2 years following the hysterectomy when symptoms of oestrogen deficiency may be noticed.

The main, and only treatment to date for hot flashes is the use of hormonotherapy such as estrogens alone, estrogens combined with progesterone, or phytoestrogens. However, the use of estrogens as hormone replacement therapy (HRT) has been shown by the World Health Organisation (WHO) to increase the risk of gynaecological cancers. Whilst phytoestrogens have not yet been tested, they are also suspected of causing a similar increased risk of cancer as they are believed to bind the same estrogens-receptors.

The current lack of understanding of hot flashes is reflected both in the lack of consensus over its prevalence in woman, but also by the multitude of theories seeking to explain its aetiology. The most widely accepted theory is that hot flashes are caused by a deficiency in circulating hormones (estrogen an progesterone) as a result of declining or disturbed ovarian function. It is known that fluctuating hormones levels are at least part of the picture, because estrogen replacement therapy relieves the symptoms of hot flashes in many women.

However, this theory does not fully explain the phenomenon of hot flashes. Many menopausal and pre-menopausal women with low estrogen levels never experience hot flashes, while other women simultaneously experience hot flashes and symptoms of a relative estrogen excess. Signs of estrogen excess or estrogen dominance include weight gain, breast tenderness, heavy menstrual flow and erratic mood swings.

Hot flashes are a complex neuro-endocrine phenomenon affected by a variety of factors including our thoughts, expectations and emotions. The wide range of stimuli that trigger flushing further attests to the multi-factorial nature of hot flashes. Common triggers include: spicy food, hot drinks, alcohol, sugar, caffeine, stress, hot weather, hot tubs and saunas, tobacco and "heated" emotions.

Another explanation for hot flashes is that they are triggered by a brief but sudden downward adjustment in the body's internal temperature setting. It is known that both estrogen and progesterone play a role in temperature regulation. However, the role of these two hormones, or a multitude of others, in triggering a shift in the body's thermoregulatory centre is not known. Some research indicates that hot flashes may be triggered when declining levels of estrogen and progesterone cause a withdrawal of naturally occurring opiates (chemicals in the brain that have a significant impact on mood, pain control and hormone modulation).

Studies indicate that stabilization of either estrogen or progesterone can minimize hot flashes but data from a recent trial (refer to the National Institutes of Health finding from their Woman's Health Initiative about the benefits and risks of menopausal hormone therapy) using estrogen plus progestin (also known as progesterone) therapy in menopausal woman have shown that these treatments probably increase the risk of gynaecological cancers.

A number of medicinal plants used for centuries by indigenous cultures have gained reputations as female tonics. The tonifying effects of these herbs are most likely due to the presence of phytoestrogens, as well as the plants' abilities to nourish the endocrine glands and increase blood flow to the pelvic organs. Herbs commonly used to alleviate hot flashes include black cohosh, motherwort, chaste tree berry, blue cohosh, ginseng, dong quai, liquorice, sarsaparilla and false unicorn but the effect of these phytoestrogens on gynaecological cancers has not yet been investigated.

Another area in which hot flashes are seen is following chemotherapy, anti-cancer therapy, hormonotherapy or endocrine therapy given to treat breast cancer patients. Breast cancer is the most common malignant tumour in women. The use of chemotherapy, anti-cancer therapy, hormonotherapy or endocrine therapy given targeting gynaecological organs, leads to various menopausal side-effects such as climacteric symptoms such as hot flashes due to the very low level of circulating hormones. The persistent hot flashes due to drug-induced menopause can last for 2 to 5 years and impair the quality of life in gynaecological cancer patients greatly.

Thus, the treatment/regressions of hot flashes is one of the focuses to improve the quality of life in cancer patients.

As for breast cancer patients, the treatment of hot flashes occurring in other gynaecological cancers is a difficult problem and as yet there is still no effective method of control as

Hormone Replacement Therapy which is one of the only available treatment is totally contra-indicatedbecause it could stimulate the growth and multiplication of breast cancer cells. Some selective 5-TH re-absorption inhibitors can improve hot flashes but the latest studies show that they may reduce the therapeutic effect of hormonotherapy such as tamoxifen (TAM).

There is an invaluable wealth of knowledge that has been developed thorough the use of Traditional Chinese Medicine over the last approximately 4000 years.

The use of compositions comprising a large variety of herbs are known for the treatment of hormonal imbalances including menopausal syndrome, menstrual irregularities, regulation of climacteric syndrome and the treatment of cancer.

However, these compositions generally involve the use of a large number of herbs. For example CN1321473 describes the use of an 11 component mixture for curing menopausal syndrome, CN1440776 describes the use of a 23 component mixture for regulating menstruation, US6238707 describes the use of a 26 component mixture that provides benefits on female hormonal regulation or replacement and EP1462110 describes the use of an 18 component mixture for the treatment of hormonal symptoms. In addition, these preparations all contain at least one of the following phytoestrogens

- black cohosh (*Cimicifuga racemosa*)
- dong quai (*Angelica sinensis*) or Dang Gui
- red clover (*Trifolium pratense*)
- alfalfa (*Medicago sativa*)
- licorice (*Glycyrrhiza glabra*)
- Korean ginseng (*Panax ginseng*)
- wild American ginseng (*Panax quinquefolius*)
- Kudzu root (*Puerariae lobata*).

The effects of these phytoestrogens on gynaecologicalcancers have not yet been investigated.

It should be appreciated that the use of herbal compositions can have unwanted side-effects. These side-effects are exacerbated by the use of large preparations containing a large number

of herbs which increases the likelihood that certain unwanted effects will also be passed on to the patient.

As discussed above it has recently been determined that the use of HRT provides a health risk to those woman receiving it. Such increased risks include breast cancer (Warren R et al,. "Strategies for managing breast cancer risk after the menopause." *Treatments in Endocrinology* 2004;3(5):289-307; Diamanti-Kandarakis E. "Hormone replacement therapy and risk of malignancy." *Current Opinion in Obstetrics & Gynecology* 2004;16(1):73-8; Timins J.K. "Current issues in hormone replacement therapy." *New Jersey Medicine* 2004;101(3):21-7)

Thus, there is a significant advantage in being able to administer a medicament that is able to ameliorate menopausal symptoms without the side-effects of increased cancer risks. In addition, the same advantage is seen when considering gynaecological cancers' patients for which HRT is highly contra-indicated as it causes an increased risk of cancer cells' growthand cancer relapse.

Therefore it is an object of the present invention to provide a composition that does not contain estrogens or known phytoestrogens and that can treat or prevent climacteric symptom such as hot flashes, or to at least provide the public with a useful choice.

Other objects of the invention may become apparent from the following description which is given by way of example only.

SUMMARY OF THE INVENTION

Accordingly, one aspect of the present invention provides a composition comprising Chaihu, Yujin, Mudanpi, Zicao, Baiwei, Baishao and Wuweizi or extracts thereof.

Preferably the composition is a pharmaceutical composition further comprising a pharmaceutically acceptable carrier.

Preferred extracts are water extracts.

In one embodiment a composition of the invention comprises the hormonotherapy such as tamoxifen (TAM).

In one embodiment a composition of the invention is administered simultaneously or sequentially with chemotherapies, anti-cancer drugs, hormonotherapy use for gynaecological

cancers such as taxanes, taxol, paclitaxel (taxol), doxetaxel (taxotere), cyclophosphamide (docettaxel), alkylating agents (mitotic inhibitors), doxorubicin (paditaxel, adriamycin), antibiotics, mitoxantrone (novantrone), vinorelbine (navelbine), vinca alakaloids (mitotic inhibitors), fluoro-uracile, pyrimidine analogs (antimetabolites), capecitabine (xeloda), methotrexate, folic acid analog (anti-metabolites); hormonal therapies such as tamoxifen (Nolvadex) – antiestrogens, toremifene (fareston) – antiestrogens, letrozole (Femara) – aromatase inhibitors, anastrazole (Arimidex) - aromatase inhibitors, exemestane (Aromasin) - aromatase inhibitors, goserelin (Zoladex) – LHRH inhibitors, leuprolide (Leurpon) – LHRH inhibitors, fulvestrant (Faslodex); surgery (eg, lumpectomy or mastectomy for breast cancers); radiation; monoclonal antibody therapy (trastuzumab (herceptin).

Another aspect of the invention provides a method of reducing the frequency and/or severity of climacteric symptoms such as hot flashes comprising administering to a subject in need thereof Chaihu, Yujin, Mudanpi, Zicao, Baiwei, Baishao and Wuweizi or extracts thereof.

Another aspect of the invention provides a method of reducing the frequency and/or severity of symptoms caused by drug-induced (chemotherapy, anti-cancer therapy, hormonotherapy or endocrine therapy) menopause comprising administering to a subject in need thereof Chaihu, Yujin, Mudanpi, Zicao, Baiwei, Baishao and Wuweizi or extracts thereof.

Another aspect of the invention provides a method of reducing the frequency and/or severity of symptoms caused by surgical-induced (hysterectomy) menopause comprising administering to a subject in need thereof Chaihu, Yujin, Mudanpi, Zicao, Baiwei, Baishao and Wuweizi or extracts thereof.Another aspect of the invention provides a method of reducing the frequency and/or severity of climacteric symptoms such as hot flashes in natural pre-menopausal and menopausal women comprising administering to a subject in need thereof Chaihu, Yujin, Mudanpi, Zicao, Baiwei, Baishao and Wuweizi or extracts thereof .

Another aspect of the invention provides a method of reducing the frequency and/or severity of climacteric symptoms such as hot flashes in patients with a gynaecological cancer comprising administering to a subject in need thereof Chaihu, Yujin, Mudanpi, Zicao, Baiwei, Baishao and Wuweizi or extracts thereof.

In one embodiment the subjects are those for which Hormone Replacement Therapy (HRT) would increase the risk of gynaecological cancer onset or relapse.

Other aspects of the present invention provide use of Chaihu, Yujin, Mudanpi, Zicao, Baiwei, Baishao and Wuweizi or extracts thereof in the preparation of a medicament for reducing the frequency and/or severity of climacteric symptoms such as hot flashes, reducing the frequency and/or severity of symptoms before or during natural menopause reducing the frequency and/or severity of symptoms caused by drug-induced (chemotherapy, anti-cancer therapy, hormonotherapy or endocrine therapy) menopause symptoms in patients with a gynaecological cancer or in patients with gynaecological disorders that require chemotherapy, anti-cancer therapy, hormonotherapy or endocrine therapy, or reducing the frequency and/or severity of symptoms caused by surgical-induced menopause symptoms in patients with hysterectomy.

Another aspect of the invention provides method of preparing a composition of the invention comprising:

1. placing a mixture of Chaihu, Yujin, Mudanpi, Zicao, Baiwei, Baishao and Wuweizi into water,
2. heating the mixture until boiling,
3. simmering the mixture to enrich the water, and
4. collecting the enriched water.

In one embodiment the method can be repeated multiple times by adding a quantity of water to the composition that is approximately equal to the amount of enriched water that is removed.

Preferably the enriched water is administered to a subject in need thereof.

Preferably about 100 ml of enriched water is administered per day. More preferably about 100 ml of enriched water is administered at least two times per day.

In one embodiment the enriched water is freeze or spray dried. Preferably the dried enriched water is included in a suitable dosage form. Preferably the dosage form is administered at least 1, 2, 3, 4 or 5 times per day. Most preferably the dosage form is administered 2 times per day.

The following preferred embodiments may relate to any of the above aspects of the invention.

Preferably Chaihu, Yujin, Mudanpi, Zicao, Baiwei, Baishao and Wuweizi or extracts thereof are administered as a single composition.

Preferred compositions of the invention comprise 1 to 30g of each component. More preferred compositions of the invention comprise:

(a) 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 g of Chaihu or an extract thereof,

(b) 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 g of Yujin or an extract thereof,

(c) 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 g of Mudanpi or an extract thereof,

(d) 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25 g of Zicao or an extract thereof,

(e) 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 g of Baiwei or an extract thereof,

(f) 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 g of Baishao or an extract thereof, and

(g) 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 g of Wuweizi or an extract thereof,

or multiples thereof yet retaining approximate proportionality, and useful ranges may be selected between any of these forgoing values (e.g. from about 8 to about 10g).

Most preferably the composition comprises approximately 10 g of Chaihu, 10 g of Yujin, 15 g of Mudanpi, 20 g of Zicao, 15 g of Baiwei, 15 g of Baishao and 15 g of Wuweizior multiples thereof yet retaining approximate proportionality.

In one embodiment the composition comprises plant material. Said plant material may be in a dried or fresh form.

In one embodiment the composition comprises extracts, preferably water extracts, of plant material.

In one embodiment the plant material is mixed with water and soaked for 30 minutes with the water level higher than the composition level. Preferably the water level is approximately 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 cm higher than the composition level.

Alternatively, the amount of water added to the plant material can be based on the amount of plant material used. In one embodiment approximately 50, 100, 200, 300, 400, 500, 600, 700, 800, 900,1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800. 1900, 2000, 2100, 2200,

2300, 2400, 2500, 2600, 2700 or 3000 ml of water is added per 100 g of dried plant material. Preferably 300 to 3000 ml, more preferably 1000 ml of water is added per 100 g of dried herb.

Preferably the mixture is heated to boiling and simmered for approximately 10, 15, 20, 25, 30, 35, or 40 minutes. More preferably the mixture is simmered for 15 to 25 minutes, preferably 20 minutes.

The entire disclosures of all applications, patents and publications, cited above and below, if any, are hereby incorporated by reference.

The term "comprising" as used in this specification and the claims means "consisting at least in part of", that is to say when interpreting statements in this specification which include that term, the features, prefaced by that term in each statement, all need to be present but other features can also be present.

It is intended that reference to a range of numbers disclosed herein (for example, 1 to 10) also incorporates reference to all rational numbers within that range (for example, 1, 1.1, 2, 3, 3.9, 4, 5, 6, 6.5, 7, 8, 9 and 10) and also any range of rational numbers within that range (for example, 2 to 8, 1.5 to 5.5 and 3.1 to 4.7) and, therefore, all sub-ranges of all ranges expressly disclosed herein are hereby expressly disclosed. These are only examples of what is specifically intended and all possible combinations of numerical values between the lowest value and the highest value enumerated are to be considered to be expressly stated in this application in a similar manner.

This invention may also be the broadly to consist in the parts, elements and features referred to or indicated in the specification of the application, individually or collectively, and any or all combinations of any two or more of the parts, elements or features, and where specific integers are mentioned herein which have known equivalents in the art to which this invention relates, such known equivalents are deemed to be incorporated herein as if individually set forth.

Other aspects of the invention may become apparent from the following description which is given by way of example only and with reference to the accompanying drawings.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compositions and methods which are useful to treat or prevent climacteric symptoms such as hot flashes, whether they arise spontaneously following natural

menopause or they are cause by drug-induced (chemotherapy, anti-cancer therapy, hormonotherapy or endocrine therapy) menopause or surgical-induced menopause.

Natural menopause is due to the natural physiological senescence of ovaries that every woman experiences as she ages.

Rug induced menopause could refer to patients receiving treatment for a gynaecological cancer (breast, endometrial, ovarian, cervix or vaginal) or for any gynaecological disease for which estrogen and progesterone secretion must be blocked to stop the disease's progression.

Surgical induced menopause refers to menopause caused by hysterectomy (surgical removal of the uterus) performed for various gynaecological reasons.

Particularly the compositions and methods are useful to reduce the frequency and/or severity of hot flashes. Preferably the frequency and/or severity of hot flashes is reduced. Preferably hot flashes cease.

The compositions and methods of the invention therefore are useful to treat or prevent climacteric symptoms such as hot flashes resulting from natural menopause, drug-induced (chemotherapy, anti-cancer therapy, hormonotherapy or endocrine therapy) menopause or surgical-induced menopause.

The method of the invention generally comprises preparing a decoction from herbs and then administering to a patient or subject in need thereof.

As used herein the term "hot flashes" refers to the intense heat sensation, flushing, profuse sweating, palpitations, and/or sense of anxiety experienced by subjects undergoing natural menopause, drug-induced (chemotherapy, anti-cancer therapy, hormonotherapy or endocrine therapy) menopause or surgical-induced metnopause. Hot flashes can also occur independent of any such therapy or condition. Hot flashes impact on a subject's quality of life, including their ability to sleep.

Chaihu, Yujin, Mudanpi, Zicao, Baiwei, Baishao and Wuweizi are all herbs commonly used in Traditional Chinese Medicine.

Chaihu is commonly known as hares ear root or Chinese thorowax root. Its Latin name is Radix Bupleuri and the botanical species are known as Bupleurum chinense DC (Northern

Chinese Thorowax Root) and Bupleurum scorzonerifolium Willd. (Southern Chinese Thorowax Root).

Yujin is commonly known as turmeric root tuber. Its Latin name is Radix Curcumae and its botanical names are Curcuma wenyujin, Curcuma longa or Curcuma phaeocaulis Val. .

Mudanpi is commonly known as tree peony bark and is the dried root bark of Paeonia suffruticosa andr.. Its Latin name is Cortex Moutan.

Zicao is commonly known as Arnebia root or gromwell root. Its Latin name is Radix Arnebiae and its botanical names are Arnebia euchroma (Royle) Johnst., Lithospermum erythrorhizon Sieb. Et Zucc., or Arnebia guttata Bunge.

Baiwei is commonly known as blackened swallowwort root. Its Latin is Radix Cynanchi Atrati and botanical names are Cynanchum atratum Bge. or Cyanchum versicolor Bge.

Baishao is commonly known as white peony root, and is known by the Latin and botanical names of Radix Paeoniae Alba and Paeonia lactiflora Pall. respectively.

Wuweizi is commonly known as Chinese Magnoliavine fruit and is known by the Latin and botanical names of Frutus Schisandrae Chinensis and Schisandra chinensis (Turcz.) Barll. (northern Wuweizi) or Schisandra sphenanthera Rehd. (southern Wuweizi) respectively.

Each of Chaihu, Yujin, Mudanpi, Zicao, Baiwei, Baishao and Wuweizi are commercially available and referred to in common Traditional Chinese Medicine texts.

As used herein the term "treat" includes the prevention, amelioration or reduction in severity or frequency of any one or more of the symptoms associated with hot flashes. The term "treat" and its derivatives should be interpreted in their broadest possible context. The term should not be taken to imply that a subject is treated until total recovery.

As used herein the term "and/or" means "and" or "or" or both.

As used herein the term "extract" includes an efficacious concentrate of a herb. It will be appreciated that either the herb itself or an extract thereof may be useful according to the present invention. The extract may be obtained by known art methods including but not limited to infusion, decoction, macero-expression, percolation, expression, distillation and supercritical extraction. Said processes may use mixtures such as solvents to aid in the extraction of the soluble components of the herb. The mixtures used to aid extraction include

those solutions known in the art to be useful in such extraction processes. Preferably said solvents are selected from an alcohol, organic solvent, halogenated solvent or water or a mix thereof. Useful solvents for supercritical extraction include compressed carbon dioxide. Reference to an herb herein is also intended to include an extract derived from that herb. A skilled worker with regard to that skill and the teaching of the present specification will readily be able to prepare an extract of a herb useful herein.

It should be understood that combinations of extracts or combinations of fresh or dried herbs and extracts may be used in a composition of the invention.

In one embodiment the use of a maceration procedure comprises soaking the herb or herbs in a solution such as alcohol or water or a mix thereof prior to filtering.

In an alternate embodiment a counter-current process may be used for extraction. In this process a herb or herbs enter into a column of a large percolator comprised of several smaller columns. Material to be extracted is pumped through the different columns at a given temperature and flow speed where it continuously mixes with solvent. The extract-rich solvent then passes into another column, while fresh solvent once again comes into contact with herbal material as it is passed into a new chamber. The extract rich solvent can then be concentrated by known art methods such as distillation, evaporation or percolation.

In one embodiment the extraction process may use a supercritical process of extraction. Preferably a gas is pressurised and heated to its supercritical temperature such that it remains a gas. Preferably said gas is CO_2 although it should be appreciated that any suitable gas could be used.

The composition of the invention is useful in methods of reducing the frequency and/or severity of climacteric symptoms such as hot flashes following natural menopause.

The composition of the invention is useful in methods of reducing the frequency an/or severity of climacteric symptoms such as hot flashes caused by drug-induced (chemotherapy, anti-cancer therapy, hormonotherapy or endocrine therapy) menopause when such drug are given to treat gynaecological (breast, ovarian, endometrial) cancer patients or to improve patients with gynaecological disorders such as endometriosis.

The composition of the invention is useful in methods of reducing the frequency and/or severity of climacteric symptoms such as hot flashes caused by surgery (hysterectomy).

The present invention therefore also provides for use of Chaihu, Yujin, Mudanpi, Zicao, Baiwei , Baishao and Wuweizi or extracts thereof in the preparation of a medicament for reducing the frequency and/or severity of hot flashes, reducing the frequency and/or severity of climacteric symptoms such as hot flashes, reducing the frequency and/or severity of symptoms before or during natural menopause, reducing the frequency and/or severity of symptoms caused by drug-induced (chemotherapy, anti-cancer therapy, hormonotherapy or endocrine therapy) menopause symptoms in patients with gynaecological cancer or in patients with gynaecological disorders that require such treatment, reducing the frequency and/or severity of symptoms caused by surgical-induced menopause in patients who underwent hysterectomy.

Preferred compositions of the invention comprise 1 to 30g of each component. More preferred compositions of the invention comprise:

(a) 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 g of Chaihu or an extract thereof,

(b) 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 g of Yujin or an extract thereof,

(c) 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 g of Mudanpi or an extract thereof,

(d) 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25 g of Zicao or an extract thereof,

(e) 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 g of Baiwei or an extract thereof,

(f) 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 g of Baishao or an extract thereof, and

(g) 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 g of Wuweizi or an extract thereof,

or multiples thereof yet retaining approximate proportionality, and useful ranges may be selected between any of these forgoing values (e.g. from about 8 to about 10g), or multiples thereof yet retaining approximate proportionality, and useful ranges may be selected between any of these forgoing values (e.g. from about 10 to about 15g).

Most preferably the composition comprises approximately 10 g of Chaihu, 10 g of Yujin, 15 g of Mudanpi, 20 g of Zicao, 15 g of Baiwei, Baishao and 15 g of Wuweizior multiples thereof yet retaining approximate proportionality.

It should be appreciated that larger amounts of the herbs could be prepared. However, the relative amounts of each herb to one another should still remain proportionally approximately the same.

In one embodiment the composition comprises plant material. Said plant material may be in a dried or fresh form.

In one embodiment the composition comprises extracts, preferably water extracts, of plant material.

A preferred method of preparing a composition of the invention comprises mixing appropriate amounts of the herbs together and decocting the herbal composition in water.

Preferably the amount of water that is used is approximately 1, 2, 3, 4, 5 ,6 7, 8, 9, or 10 cm above the herbal composition. Most preferably the water level is 5 cm above the herbal composition.

Alternatively, the amount of water added to the plant material can be based on the amount of plant material used. In one embodiment approximately 50, 100, 200, 300, 400, 500, 600, 700, 800, 900 or 1000 ml of water is added per 100 g of dried plant material. Preferably 500 ml of water is added per 100 g of dried herb.

Once the water and herbal composition have been combined in a container the herbal composition is allowed to soak in said water for approximately 10, 15, 20, 25, 30, 35, or 40 minutes. More preferably the herbal composition is allowed to soak for 30 minutes. Following this the mixture is then heated and, once heated to a boil, is simmered for approximately 10, 15, 20, 25, 30, 35, or 40 minutes. More preferably the mixture is heated for 20 to 30 minutes. Preferably said container is non-aluminium.

Following this, an aliquot of the enriched water is removed. Preferably the quantity of enriched water removed is 70, 80, 90, 100, 110, 120 or 130 ml. More preferably the quantity of enriched water removed is 100 ml.

Another aspect of the invention provides method of preparing a composition of the invention comprising:

1. placing Chaihu, Yujin, Mudanpi, Zicao, Baiwei , Baishao and Wuweizi into water,

2. heating the mixture, and

3. collecting the enriched water.

Preferably the herbs are placed in 2, 3, 4, 5, 6, 7, 8, 9, or 10 cm of water. More preferably the herbs are placed in 5 cm of water. Alternatively, the amount of water added to the plant material can be based on the amount of plant material used. In one embodiment approximately 50, 100, 200, 300, 400, 500, 600, 700, 800, 900 or 1000 ml of water is added per 30 g of dried herb. Preferably 500 ml of water is added per 100 g of dried herb.

Preferably the herbs are soaked in the water for 10, 20, 30 or 40 minutes before heating.

Preferably the mixture is heated for 10 to 40 minutes. Preferably the mixture is heated until boiling.

Preferably the mixture is simmered for 10 to 40 minutes.

In one embodiment the method can be repeated multiple times by adding a quantity of water to the composition that is approximately equal to the amount of enriched water that is removed.

Preferably the amount of enriched water that is removed at the end of each cycle is 70, 80, 90, 100, 110, 120 or 130 ml. More preferably the amount of enriched water that is removed at the end of each cycle is 100 ml.

Once removed the enriched water can be administered to a patient in need thereof. Preferably about 100 ml of enriched water is administered per day. More preferably about administered 100 ml of the enriched water is administered at least two times per day.

In one embodiment the enriched water is further processed to produce a suitably dosage form, such as a granule or tablet containing the enriched water in liquid or dried from. Preferably the granule or tablet is administered to the patent or subject at least 1, 2, 3, 4 or 5 times per day. Most preferably the granule or tablet is administered to the patient or subject 2 times per day.

In one embodiment the enriched water is concentrated and dried. Preferred concentration and drying steps include filtration, distillation, evaporation (including heat and or pressure evaporation), freeze drying and spray drying.

The present invention therefore also provides a dietary, nutraceutical or oral pharmaceutical composition consisting of Chaihu, Yujin, Mudanpi, Zicao, Baiwei , Baishao and Wuweizi or extracts thereof.

A composition of the invention may be formulated for administration in any chosen dosage form. Thus, for oral administration a dietary (a food, food additive or food supplement for example), nutraceutical or pharmaceutical composition useful herein may be formulated by a skilled worker according to known formulation techniques.

For example, foods, food additives or food supplements comprising a composition described herein for use according to the invention include any edible consumer product which is able to carry plant extracts. Examples of suitable edible consumer products include confectionary products, reconstituted fruit products, snack bars, muesli bars, spreads, dips, diary products including yoghurts and cheeses, drinks including dairy and non-dairy based drinks, milk powders, sports supplements including dairy and non-dairy based sports supplements, food additives such as protein sprinkles and dietary supplement products including daily supplement tablets. Suitable nutraceutical compositions useful herein may be provided in similar forms.

A suitable pharmaceutical composition may be formulated with appropriate pharmaceutically acceptable excipients, diluents or carriers selected with regard to the intended dosage form and standard pharmaceutical formulation practice. A dosage form useful herein can be administered orally as a powder, liquid, tablet or capsule. Suitable dosage forms may contain additional agents as required, including emulsifying, antioxidant, flavouring or colouring agents. Dosage forms useful herein may be adapted for immediate, delayed, modified, sustained, pulsed or controlled release of the active components. A preferred composition described herein for use herein comprises Chaihu, Yujin, Mudanpi, Zicao, Baiwei or extracts thereof and one or both of Baishao and Wuweizi or extracts thereof. Preferably the composition comprises Chaihu, Yujin, Mudanpi, Zicao, Baiwei, Baishao and Wuweizi or extracts thereof.

A composition as described herein may also be administered by parenteral routes including but not limited to subcutaneous, intravenous, intraperitoneal, intramuscular and intratumoural administration. Preferably the composition is administered via oral administration. Those skilled in the art will be able to prepare suitable formulations for parenteral administration without undue experimentation. The composition may be used alone or in combination with

one or more other therapeutic agents. When used in combination with another therapeutic agent the administration of the two agents may be separate, simultaneous or sequential. Simultaneous administration includes the administration of a single dosage form that comprises both agents and the administration of the two agents in separate dosage forms at substantially the same time. Sequential administration includes the administration of the two agents according to different schedules, preferably so that there is an overlap in the periods during which the two agents are provided. Suitable agents with which the compositions of the invention can be co-administered include chemotherapeutic and immunotherapeutic agents, and other suitable agents known in the art. Such agents are preferably administered parenterally, preferably by intravenous, subcutaneous, intramuscular, intraperitoneal, intramedullar, epidural, intradermal, transdermal (topical), transmucosal, intra-articular, and intrapleural, as well as oral, inhalation, and rectal administration. Additionally, it is contemplated that a composition in accordance with the invention may be formulated with additional active ingredients which may be of benefit to a subject in particular instances. For example, therapeutic agents that target the same or different facets of the disease process may be used. As will be appreciated, the dose of the composition administered, the period of administration, and the general administration regime may differ between subjects depending on such variables as the severity of symptoms of a subject, the type of disorder to be treated, the mode of administration chosen, and the age, sex and/or general health of a subject. It should be appreciated that administration may include a single daily dose or administration of a number of discrete divided doses as may be appropriate. It should be understood that a person of ordinary skill in the art will be able without undue experimentation, having regard to that skill and this disclosure, to determine an effective dosage regime (including daily dose and timing of administration) for a given condition.

In one embodiment a composition of the invention is administered simultaneously or sequentially with chemotherapy, anti-cancer therapy, immunotherapeutic agents, hormonotherapy or endocrine therapy given for gynaecological cancers such as taxanes, taxol, paclitaxel (taxol), doxetaxel (taxotere), cyclophosphamide (docettaxel), alkylating agents (mitotic inhibitors), doxorubicin (paditaxel, adriamycin), antibiotics, mitoxantrone (novantrone), vinorelbine (navelbine), vinca alakaloids (mitotic inhibitors), fluoro-uracile, pyrimidine analogs (antimetabolites), capecitabine (xeloda), methotrexate, folic acid analog (anti-metabolites); hormonal therapies such as tamoxifen (Nolvadex) – antiestrogens, toremifene (fareston) – antiestrogens, letrozole (Femara) – aromatase inhibitors, anastrazole (Arimidex) - aromatase inhibitors, exemestane (Aromasin) - aromatase inhibitors, goserelin

(Zoladex) – LHRH inhibitors, leuprolide (Leurpon) – LHRH inhibitors, fulvestrant (Faslodex); surgery (eg, lumpectomy or mastectomy for breast cancers); radiation; monoclonal antibody therapy (trastuzumab (herceptin).

In one embodiment a composition of the invention comprises tamoxifen (TAM).

Various aspects of the invention will now be illustrated in non-limiting ways by reference to the following examples.

EXPERIMENTAL

EXAMPLE 1

The following herbs in a dried form were weighed out and placed in a container: 10 g of Chaihu, 10 g of Yujin, 15 g of Mudanpi, 20 g of Zicao, 15 g of Baiwei, 15 g of Baishao, 15 g of Wuweizi.

Approximately 500 ml of water was added per 100 g of dried herbs. The herbs were then left in the water for approximately 30 minutes. Following this a decoction of the herbs was prepared by simmering the mixture of water and herbs for approximately 20 to 30 minutes.

An aliquot (approximately 100 ml) of the enriched water was removed from the container and collected. Further 100 ml aliquots were prepared by filling the container with an amount of cold water equal to the amount of enriched water that was removed.

The 100 ml aliquots of enriched water were then stored for use.

EXAMPLE 2

Thirty female breast cancer patients who were using TAM were administered 100ml of a composition of the invention twice per day. Each patient had been diagnosed pathologically. The average age of the patients was 48 (38-64). Of all these patients, 21 (70%) patients were both ER+/PR+ (estrogen receptor and progesterone receptor positive); 5 patients (16%) were ER+/PR- (estrogen receptor positive and progesterone receptor negative) and 4 patients (13%) were ER-/PR+. The average time from starting use of TAM to occurrence of hot flashes symptoms was 2.4 months (1-5 months). According to the method of Kupperman HS et al. ("Comparative clinical evaluation of estrogenic preparation by the menopausal and amenorrheal indices." *Journal of Clinical Endocrinology* 1953;13:688-703) the symptoms were divided into mild grade (5 times /day) and serious grade (>5 times /day). Symptom

improvement was observed after three weeks of taking the TCM and the results are shown in **Table 1** . The grade of serious symptom in 16 (53%) patients became mild. The grade of the mild symptom in 14 (46%) patients almost disappeared.

Table 1 – Patient Data

Patient	Age	ER/PR	Symptoms Before (flashes/day)	Symptoms After (flashes/day)
1	41	–/+	>5	<5
2	38	+/+	>5	<5
3	41	+/+	>5	<5
4	47	+/+	5	0
5	61	+/+	5	0
6	64	+/+	5	0
7	58	+/+	>5	<5
8	64	+/+	5	0
9	52	+/+	>5	<5
10	62	+/+	5	0
11	64	+/–	5	0
12	57	+/–	5	0
13	60	+/+	5	0
14	52	+/+	>5	<5
15	48	–/+	>5	<5
16	47	–/+	5	0
17	64	+/–	5	0
18	62	+/+	5	0
19	56	+/+	>5	<5
20	47	+/–	>5	<5
21	51	+/–	>5	<5
22	63	+/+	5	0
23	45	+/+	>5	<5
24	43	+/+	>5	<5
25	54	+/+	>5	<5
26	44	+/+	>5	<5
27	58	+/+	5	0
28	40	–/+	>5	<5
29	52	+/+	>5	<5
30	41	+/+	5	0

EXAMPLE 3

49 breast cancer patients suffering hot flash symptoms (caused by tamoxifen) 3 times per day or more were given a composition of the invention or a placebo in a double blind randomized trial. Patients were orally administered 100 ml of a composition of the invention, 3 times per day for 3 weeks. Patients recorded the number of hot flashes per day for 1 week before

treatment began. This record was used as the baseline to appraise the improvements in occurrence and severity of hot flashes and in improvement in sleep. The method Kupperman referred to above was used to record the severity of hot flashes: 5 times / day = mild; > 5 times / day = severe. 45 patients (91%) submitted their records: 22 patients in the treatment group and 23 patients in the placebo group. The distribution of the two groups was similar in terms of age, body condition & severity of hot flashes.

Prior to treatment, the number of patients who recorded experiencing mild hot flashes was:

Treatment Group: 31% (7/22)

Placebo Group: 26% (6/23)

Prior to treatment, the number of patients who recorded experiencing severe hot flashes was:

Treatment Group: 68% (15/22)

Placebo Group: 73% (17/23)

Following treatment, the patients in the treatment group reported:

No change in severity of hot flashes: 50%

Improvement (reduction) in severity of hot flashes: 27%

Hot flashes disappeared: 23%

Following treatment, the patients in the placebo group reported:

No change: 70%

Improvement: 30%

Disappeared: 0%

Comparison of the treatment and placebo groups shows an improvement in quality of sleep:

TCM Group: 73% ($P<0.05$)

Placebo Group: 35% ($P<0.05$)

No patients reported any side effects. Heart, liver, kidney and blood tests were all normal.

Conclusion: oral administration of a composition of the invention improves the symptoms of hot flashes caused by tamoxifen and improves the quality of sleep for breast cancer patients.

INDUSTRIAL APPLICATION

The compositions and methods of the invention may be used to treat or prevent climacteric symptoms such as hot flashes.

WHAT WE CLAIM IS:

1. A composition comprising Chaihu or an extract thereof, Yujin or an extract thereof, Mudanpi or an extract thereof, Zicao or an extract thereof, Baiwei or an extract thereof, Baishao or an extract thereof and Wuweizi or an extract thereof.

2. A composition of claim 1 comprising:

(a) 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 g of Chaihu or an extract thereof,

(b) 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 g of Yujin or an extract thereof,

(c) 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 g of Mudanpi or an extract thereof,

(d) 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25 g of Zicao or an extract thereof,

(e) 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 g of Baiwei or an extract thereof,

(f) 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 g of Baishao or an extract thereof, and

(g) 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 g of Wuweizi or an extract thereof,

or multiples thereof yet retaining approximate proportionality.

3. A composition of claim 1 or 2 wherein said composition comprises approximately 10 g of Chaihu, 10 g of Yujin, 15 g of Mudanpi, 20 g of Zicao, 15 g of Baiwei, 15 g of Baishao and 15 g of Wuweizior multiples thereof yet retaining approximate proportionality.

4. A composition of any one of claims 1 to 3 wherein the plant material is in a dried form.

5. A composition of any one of claims 1 to 3 wherein said plant material is in a fresh form.

6. A composition of any one of claims 1 to 5 wherein said composition further comprises tamoxifen.

7. A composition of claim 1 to 6 wherein said composition further comprises a pharmaceutically acceptable carrier.

8. A composition of any one of claims 1 to 7 wherein said extract is a water extract.

9. Use of a Chaihu or an extract thereof, Yujin or an extract thereof, Mudanpi or an extract thereof, Zicao or an extract thereof, Baiwei or an extract thereof, Baishao or an extract thereof and Wuweizi or an extract thereof in the preparation of a medicament for reducing the frequency or severity of climacteric symptoms such as hot flashes.

10. Use according to claim 9 wherein said patient is a natural pre-menopausal or menopausal woman.

11. Use according to claim 9 wherein said patient is suffering symptoms caused by drug-induced (chemotherapy, anti-cancer therapy, hormonotherapy or endocrine therapy) menopause or surgical-induced menopause.

12. Use according to claim 9 wherein said patient is a patient With a gynaecological (breast, ovarian, endometrial, cervix, vaginal) cancer, a patient with gynaecological disorders such as endometriosis that require such treatment, or a patient with hysterectomy.

13. Use according to claim 9 wherein said patient is one for which Hormone Replacement Therapy would increase the risk of gynaecological cancer onset or relapse.

14. Use according to any one of claims 9 to 13 wherein said medicament is administered simultaneously or sequentially with hormonotherapy such as tamoxifen.

15. Use according to any one of claims 9 to 13 wherein said medicament further comprises hormonotherapy such as tamoxifen.

16. Use according to any one of claim 9 to 15 wherein said medicament further comprises a pharmaceutically acceptable carrier.

17. Use according to any one of claims 9 to 16 wherein said extracts are water extracts.

18. A use of any one of claim 9 to 17 wherein said composition is administered as a single composition.

19. A method of preparing a composition comprising the steps of:

(a) placing a mixture of Chaihu, Yujin, Mudanpi, Zicao, Baiwei, Baishao and Wuweizi into water,

(b) heating the mixture until boiling,

(c) simmering the mixture to enrich the water and

(d) collecting the enriched water.

20. A method of claim 19 wherein steps (b) to (c) are repeated multiple times by adding a quantity of water to the composition that is approximately equal to the amount of enriched water that is removed.

21. A method of claim 19 or 20 wherein the composition comprises:

(a) 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 g of Chaihu or an extract thereof,

(b) 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 g of Yujin or an extract thereof,

(c) 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 g of Mudanpi or an extract thereof,

(d) 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25 g of Zicao or an extract thereof,

(e) 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 g of Baiwei or an extract thereof,

(f) 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 g of Baishao or an extract thereof, and

(g) 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 g of Wuweizi or an extract thereof,

or multiples thereof yet retaining approximate proportionality.

22. A method of claim 21 wherein said composition comprises approximately 10 g of Chaihu, 10 g of Yujin, 15 g of Mudanpi, 20 g of Zicao, 15 g of Baiwei, 15 g of Baishao and 15 g of Wuweizior multiples thereof yet retaining approximate proportionality.

23. A method of any one of claims 19 to 22 wherein said plant material is in a dried form.

24. A method of claim 23 wherein approximately 50, 100, 200, 300, 400, 500, 600, 700, 800, 900 or 1000 ml of water is added per 100 g of plant material prior to heating for the first time.

25. A method of any one of claims 19 to 22 wherein said plant material is in a fresh form.

26. A method of claim 25 wherein approximately 50, 100, 200, 300, 400, 500, 600, 700, 800, 900 or 1000 ml of water is added per 100 g of plant material prior to heating for the first time.

27. A method of any one of claims 19 to 26 wherein said plant material is soaked for 10, 15, 20, 25, 30, 35, or 40 minutes prior to boiling.

28. A method of any one of claims 19 to 27 wherein said plant material is simmered for 10, 15, 20, 25, 30, 35, or 40 minutes.

29. A method of any one of claims 19 to 28 wherein said plant material is soaked for 10, 15, 20, 25, 30, 35, or 40 minutes prior to simmering.

30. A method of any one of claims 19 or 20 wherein said enriched water is administered to a subject in need thereof.

31. A method of claim 30 wherein about 100 ml of enriched water is administered per day.

32. A method of claim 30 wherein about 100 ml of enriched water is administered at least two times per day.

33. A method of any one of claims claim 30 to 32 wherein said enriched water is freeze or spray dried prior to administration to a patient in need thereof.

34. A method of claim 33 wherein said dried enriched water is included in a suitable dosage form prior to administration to a patient in need thereof.

35. A method of claim 34 wherein said dosage form is administered at least 1, 2, 3, 4 or 5 times per day.