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A Poly-Herbal Drug Composition and a Method for a Formulation of the Poly-Herbal Drug for the Treatment of a chronic fatigue syndrome

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Abstract

The present disclosure relates to a poly-herbal drug composition and a method for a formulation of the poly-herbal drug, for the treatment of the chronic fatigue syndrome. The method comprises: washing and drying the aerial parts of *Andrographis paniculata* and *Fumaria indica*, the roots of *Asparagus recemosus* and the fruits of *Phyllanthus emblica* L., *Terminalia chebula* Retz., *Morus alba* and *Benincasa hispida*; pulverizing a dried plant parts of each plant separately into a coarse powder and mixing each of the coarse powdered plants in a specific ratio of 1:1:1:1:1:1:1 to form a homogenous mixture; extracting an accurately weighed 1000gm of homogenous polyherbal mixture with 70% ethanol (70:30::Ethanol:Water) using a Soxhlet apparatus for 6 hours; filtering and concentrating an extract in vacuum using a rotary evaporator at 60°C and a vacuum lyophilizer; and storing a final extract at 2-4 °C in air tight containers and protected from direct sunlight.

A Poly-Herbal Drug Composition and a Method for a Formulation of the Poly-Herbal Drug for the Treatment of a chronic fatigue syndrome

FIELD OF THE INVENTION

The present disclosure relates to a poly-herbal drug composition and a method for a formulation of the poly-herbal drug, for a treatment of a chronic fatigue syndrome.

BACKGROUND OF THE INVENTION

Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is [is] a systemic disorder marked by long-term fatigue, weariness, disability, pain, neurocognitive impairments, gastrointestinal symptoms, and post-exercise malaise, as well as diminished occupational, educational, and social activities. According to the WHO's worldwide Canadian Consensus Criteria, CFS is classified as a neurological illness. There are no standardized diagnostic criteria available. Several somatic and psychiatric/psychosomatic illnesses should be explored in the differential diagnosis of chronic fatigue. There is a large overlap between major depression and somatoform disorders when somatic reasons have been ruled out. Antidepressants, exercise therapy, and psychotherapy are all effective treatment choices. There is no such thing as a gold standard treatment for CFS. Based on their clinical symptoms, therapy regimens range greatly from person to person.

Despite this heterogeneity, CFS patients are advised to use a combination of medicine, physiotherapy, and cognitive behavioural therapy. Only a small percentage of CFS patients benefit from cognitive behavioural therapy and graded exercise, and many sufferers say that activity exacerbates their fatigue symptoms. These findings led to the development of a complementary or alternate strategy for managing CFS symptoms. Herbal treatments have recently acquired appeal as an alternate technique for treating CFS.

In order to make the existing solutions more efficient there is a need to develop a poly-herbal drug composition and a method for a formulation of the poly-herbal drug, for the treatment of the chronic fatigue syndrome.

SUMMARY OF THE INVENTION

The present disclosure relates to a poly-herbal drug composition and a method for a formulation of the poly-herbal drug, for the treatment of the chronic fatigue syndrome. The poly herbal drug is effective in combating chronic mental and physical fatigue in experimental animals by increasing adaptability, vigor, and endurance by increasing allostasis and/or cellular homeostasis even in the presence of a variety of stressors (psychological, physical, and physiological). Furthermore, the poly-herbal drug's pharmacological activities can be efficiently translated to clinical efficacy in the prevention and/or treatment of chronic fatigue and related co-morbidities, such as chronic fatigue syndrome.

In an embodiment, A neuroactive poly-herbal drug composition, for a treatment of a chronic fatigue syndrome, the composition comprises: a hydro-alcoholic extract of an *Andrographis paniculata* aerial parts; a hydro-alcoholic extract of a *Fumaria indica* aerial parts; a hydro-alcoholic extract of an *Asparagus recemosus* roots; a hydro-alcoholic extract of a *Phyllanthus emblica* L. fruits; a hydro-alcoholic extract of a *Terminalia chebula* Retz. fruits; a hydro-alcoholic extract of a *Morus alba* fruits; and a hydro-alcoholic extract of a *Benincasa hispida* fruits;

In an embodiment, a method 100 for the neuroactive poly-herbal drug formulation, for the treatment of the chronic fatigue syndrome comprises the following steps: at step 102, washing and drying the aerial parts of *Andrographis paniculata* and *Fumaria indica*, the roots of *Asparagus recemosus* and the fruits of *Phyllanthus emblica* L., *Terminalia chebula* Retz., *Morus alba* and *Benincasa hispida*; at step 104, pulverizing a dried plant parts of each plant separately into a coarse powder and mixing each of the coarse powdered plants in a specific ratio of 1:1:1:1:1:1:1 to form a homogenous mixture; at step 106, extracting an accurately weighed 1000gm of homogenous polyherbal mixture with 70% ethanol (70:30::Ethanol:Water) using a Soxhlet apparatus for 6 hours; at step 108, filtering and concentrating an extract in vacuum using a rotary evaporator at 60°C and a vacuum lyophilizer; and at step 110, storing a final extract at 2-4 °C in airtight containers and protected from direct sunlight.

To further clarify advantages and features of the present disclosure, a more particular description of the invention will be rendered by reference to specific embodiments thereof, which is illustrated in the appended drawings. It is appreciated that these drawings depict only typical embodiments of the invention and are therefore not to be considered limiting of its scope. The invention will be described and explained with additional specificity and detail with the accompanying drawings.

BRIEF DESCRIPTION OF FIGURES

These and other features, aspects, and advantages of the present disclosure will become better understood when the following detailed description is read with reference to the accompanying drawings in which like characters represent like parts throughout the drawings, wherein:

Figure 1 illustrates a method for a formulation of the poly-herbal drug for the treatment of the chronic fatigue syndrome in accordance with an embodiment of the present disclosure.

Figure 2 illustrates **(a)** Description of ingredient plants of the polyherbal formulation (PHF) **(b)** Effect of repeated daily for 56-days treatment of PHF (100, 200 and 400 mg/kg/day, p.o.) on the learning task i.e. time spent in targeted quadrant and memory task i.e. escape latency on Morris-water-maze in chronic unpredictable stress-induced mental fatigue behaviour in rats. CUS = Chronic unpredictable stress, PHF = Polyherbal formulation. Data represent mean ± SEM, n = 6 animals in each group. $^{\#}P < 0.05$ compared to normal control, $^{*}P < 0.05$ compared to CUS- control. (One way ANOVA followed by Newman-Keuls Multiple Comparison Test); and **(c)** Effects of repeated daily for 56-days treatment of PHF (100, 200 and 400 mg/kg/day, p.o.) on the exhaustive swimming time (min.) and/or physical endurance of rats in chronic unpredictable stress-induced physical fatigue test. CUS = Chronic unpredictable stress, PHF = Polyherbal formulation. Data represent mean ± SEM, n = 6 animals in each group. $^{\#}P < 0.05$ compared to normal control, $^{*}P < 0.05$ compared to CUS- control. (One way ANOVA followed by Newman-Keuls Multiple Comparison Test) in accordance with an embodiment of the present disclosure.

Figure 3 illustrates **(a)** Effects of repeated daily for **56-days** treatment of PHF (100, 200 and 400 mg/kg/day, p.o.) on the stress markers i.e. change in body weight (A) and plasma cortecosterone level (B) in **chronic unpredictable stressed** rats. CUS = Chronic unpredictable stress, PHF = Polyherbal formulation. Data represent mean ± SEM, n = 6 animals in each group. $^{\#}P < 0.05$ compared to normal control, $*P < 0.05$ compared to CUS-control. (One way ANOVA followed by Newman-Keuls Multiple Comparison Test) **(b)** Effects of repeated daily for **56-days** treatment of PHF (100, 200 and 400 mg/kg/day, p.o.) on the inflammatory mediators i.e. (A) TNF-α and (B) IL-6 levels in brain and muscles of the **chronic unpredictable stressed** rats in accordance with an embodiment of the present disclosure.

Further, skilled artisans will appreciate that elements in the drawings are illustrated for simplicity and may not have necessarily been drawn to scale. For example, the flow charts illustrate the method in terms of the most prominent steps involved to help to improve understanding of aspects of the present disclosure. Furthermore, in terms of the construction of the device, one or more components of the device may have been represented in the drawings by conventional symbols, and the drawings may show only those specific details that are pertinent to understanding the embodiments of the present disclosure so as not to obscure the drawings with details that will be readily apparent to those of ordinary skill in the art having benefit of the description herein.

DETAILED DESCRIPTION

For the purpose of promoting an understanding of the principles of the invention, reference will now be made to the embodiment illustrated in the drawings and specific language will be used to describe the same. It will nevertheless be understood that no limitation of the scope of the invention is thereby intended, such alterations and further modifications in the illustrated system, and such further applications of the principles of the invention as illustrated therein being contemplated as would normally occur to one skilled in the art to which the invention relates.

It will be understood by those skilled in the art that the foregoing general description and the following detailed description are exemplary and explanatory of the invention and are not intended to be restrictive thereof.

Reference throughout this specification to “an aspect”, “another aspect” or similar language means that a particular feature, structure, or characteristic described in connection with the embodiment is included in at least one embodiment of the present disclosure. Thus, appearances of the phrase “in an embodiment”, “in another embodiment” and similar language throughout this specification may, but do not necessarily, all refer to the same embodiment.

The terms "comprises", "comprising", or any other variations thereof, are intended to cover a non-exclusive inclusion, such that a process or method that comprises a list of steps does not include only those steps but may include other steps not expressly listed or inherent to such process or method. Similarly, one or more devices or sub-systems or elements or structures or components proceeded by "comprises...a" does not, without more constraints, preclude the existence of other devices or other sub-systems or other elements or other structures or other components or additional devices or additional sub-systems or additional elements or additional structures or additional components.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. The system, methods, and examples provided herein are illustrative only and not intended to be limiting.

Embodiments of the present disclosure will be described below in detail with reference to the accompanying drawings.

Referring to **Figure 1** illustrates a method for a formulation of the poly-herbal drug for the treatment of the chronic fatigue syndrome in accordance with an embodiment of the present disclosure. The method 100 for the neuroactive poly-herbal drug formulation, for the treatment of the chronic fatigue syndrome comprises the following steps: at step 102, washing and drying the aerial parts of *Andrographis paniculata* and *Fumaria indica*, the roots of *Asparagus recemosus* and the fruits of *Phyllanthus emblica* L., *Terminalia chebula* Retz., *Morus alba* and *Benincasa hispida*; at step 104, pulverizing a dried plant parts of each plant separately into a coarse powder and mixing each of the coarse powdered plants in a specific ratio of 1:1:1:1:1:1:1 to form a homogenous mixture; at step 106, extracting an accurately

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weighed 1000 gm of homogenous polyherbal mixture with 70% ethanol (70:30::Ethanol:Water) using a Soxhlet apparatus for 6 hours; at step 108, filtering and concentrating an extract in vacuum using a rotary evaporator at 60°C and a vacuum lyophilizer; and at step 110, storing a final extract at 2-4 °C in airtight containers and protected from direct sunlight.

In an embodiment, the method, wherein, a pre-formulation characteristics of the poly-herbal drug exhibits a good flow characteristics, therefore, the poly herbal drug can be easily formulated as a tablet, a capsule and/or a powdered formulation.

In another embodiment, the method, wherein, the poly-herbal drug is helpful in combating the chronic mental and physical fatigue by improving an individual's adaptability, vigour, and endurance by boosting up allostasis and/or cellular homeostasis even in a presence of a variable (psychological, physical, and physiological) stressor by effectively quenching a lethal effects of an oxidative stress and wherein, a pharmacological activities of the poly-herbal drug can be effectively translated into clinical efficacy to prevent and/or combat the chronic fatigue and related co-morbidities i.e., chronic fatigue syndrome.

Figure 2 illustrates **(a)** Description of ingredient plants of the polyherbal formulation (PHF) **(b)** Effect of repeated daily for 56-days treatment of PHF (100, 200 and 400 mg/kg/day, p.o.) on the learning task i.e. time spent in targeted quadrant and memory task i.e. escape latency on Morris-water-maze in chronic unpredictable stress-induced mental fatigue behaviour in rats. CUS = Chronic unpredictable stress, PHF = Polyherbal formulation. Data represent mean ± SEM, n = 6 animals in each group. $^{\#}P < 0.05$ compared to normal control, $^{*}P < 0.05$ compared to CUS- control. (One way ANOVA followed by Newman-Keuls Multiple Comparison Test); and **(c)** Effects of repeated daily for 56-days treatment of PHF (100, 200 and 400 mg/kg/day, p.o.) on the exhaustive swimming time (min.) and/or physical endurance of rats in chronic unpredictable stress-induced physical fatigue test. CUS = Chronic unpredictable stress, PHF = Polyherbal formulation. Data represent mean ± SEM, n = 6 animals in each group. $^{\#}P < 0.05$ compared to normal control, $^{*}P < 0.05$ compared to CUS- control. (One way ANOVA followed by Newman-Keuls Multiple Comparison Test) in accordance with an embodiment of the present disclosure.

In an implementation, the aerial parts of *Andrographis paniculata* and *Fumaria indica*, roots of the *Asparagus recemosus* as well as fruits of *Phyllanthus emblica* L.,

Terminalia chebula Retz., *Morus alba* and *Benincasa hispida* was washed separately, dried in oven at 45 °C and powdered (sieve #65). Further, the formulation has been made by blending all seven crud powdered drugs i.e., *Andrographis paniculata*, *Fumaria indica*, *Asparagus recemosus*, *Phyllanthus emblica, Terminalia chebula, Morus alba* and *Benincasa hispida*, in a ration 1:1:1:1:1:1:1 (Figure 2a). Homogenous mixture of the polyherbal blend was further subjected to the hydroalcoholic extraction wherein, weighed 1000 gm of homogenous polyherbal mixture and extracted with 70% ethanol (70: 30::Ethanol:Water) using Soxhlet apparatus for 6 h. The extract was then filtered and concentrated in vacuum using rotary evaporator at 60°C and a vacuum lyophilizer. Prepared pwdered extract is our final polyherbal formulation (PHF) and was stored at 2-4°C in airtight containers and protected from direct sunlight.

Stress induces dramatic changes in the brain structure and function, as well as severely influences mood and cognitive functions as well as reinforced long-term depression and fatigue. Accumulated evidence demonstrated that chronic unpredictable stress (CUS) negatively affects neural plasticity and neurogenesis which produce stress, impairment in memory and learning processes (Fig. 2b) and physical endurance (Fig. 2c).

Thus, the disclosed polyherbal formulation is helpful in combating the chronic mental and physical fatigue induced in the experimental animals by improving the individual's adaptability, vigor and endurance via boosting up allostasis and/or cellular homeostasis even in presence of variable (psychological, physical and physiological) stressor by effectively quenching the lethal effects of oxidative stress. Furthermore, the pharmacological activities of the PHF can be effectively translated to clinical efficacy to prevent and/or combat the chronic fatigue and related co-morbidities i.e. chronic fatigue syndrome.

Figure 3 illustrates **(a)** Effects of repeated daily for **56-days** treatment of PHF (100, 200 and 400 mg/kg/day, p.o.) on the stress markers i.e. change in body weight (A) and plasma cortecosterone level (B) in **chronic unpredictable stressed** rats. CUS = Chronic unpredictable stress, PHF = Polyherbal formulation. Data represent mean ± SEM, n = 6 animals in each group. $^{\#}P < 0.05$ compared to normal control, $*P < 0.05$ compared to CUS-control. (One way ANOVA followed by Newman-Keuls Multiple Comparison Test) **(b)** Effects of repeated daily for **56-days** treatment of PHF (100, 200 and 400 mg/kg/day, p.o.) on the inflammatory mediators i.e. (A) TNF-α and (B) IL-6 levels in brain and muscles of the

chronic unpredictable stressed rats in accordance with an embodiment of the present disclosure.

In an implementation, the deleterious effect of CUS mediated by the modulation of the stress hormone i.e., change in body weight and plasma corticosterone level (Fig. 3a), wherein, change in body weight and the plasma corticosterone level were considered as primary feature of stress marker and plasma corticosterone levels were estimated using an Enzyme Immunoassay (EIA) kit.

TNF-α levels were estimated in the rat's brain and skeletal muslces using rat-specific TNF-α sandwich ELISA. Further, IL-6 was measured in tissue samples using a rat-specific IL-6 ELISA kit. Because the CUS-induced chronic fatigue syndrome has several causes, the traditional technique of modifying only one target may not be adequate. Treatment with the poly-herbal drug, which comprises seven medicinal plants, was found to reduce CUS-induced chronic fatigue syndrome, HPA-axis hyperactivity, and oxidative and inflammatory brain damage, implying that the poly-herbal drug acted on a broad range of targets involved in the pathologic cascade. As a result, the poly-herbal medication can help with chronic fatigue syndrome brought on by persistent unpredictable stress.

The drawings and the forgoing description give examples of embodiments. Those skilled in the art will appreciate that one or more of the described elements may well be combined into a single functional element. Alternatively, certain elements may be split into multiple functional elements. Elements from one embodiment may be added to another embodiment. For example, orders of processes described herein may be changed and are not limited to the manner described herein. Moreover, the actions of any flow diagram need not be implemented in the order shown; nor do all of the acts necessarily need to be performed. Also, those acts that are not dependent on other acts may be performed in parallel with the other acts. The scope of embodiments is by no means limited by these specific examples. Numerous variations, whether explicitly given in the specification or not, such as differences in structure, dimension, and use of material, are possible. The scope of embodiments is at least as broad as given by the following claims.

Benefits, other advantages, and solutions to problems have been described above with regard to specific embodiments. However, the benefits, advantages, solutions to problems,

and any component(s) that may cause any benefit, advantage, or solution to occur or become more pronounced are not to be construed as a critical, required, or essential feature or component of any or all the claims.

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WE CLAIM:

1. A neuroactive poly-herbal drug composition, for a treatment of a chronic fatigue syndrome, the composition comprises:

a hydro-alcoholic extract of an *Andrographis paniculata* aerial parts;
a hydro-alcoholic extract of a *Fumaria indica* aerial parts;
a hydro-alcoholic extract of an *Asparagus recemosus* roots;
a hydro-alcoholic extract of a *Phyllanthus emblica* L. fruits;
a hydro-alcoholic extract of a *Terminalia chebula* Retz. fruits;
a hydro-alcoholic extract of a *Morus alba* fruits; and
a hydro-alcoholic extract of a *Benincasa hispida* fruits;

2. The composition as claimed in claim 1, wherein, the aerial parts of *Andrographis paniculata* and *Fumaria indica*, the roots of *Asparagus recemosus* and the fruits of *Phyllanthus emblica* L., *Terminalia chebula* Retz., *Morus alba* and *Benincasa hispida* are dried and pulverized into a powder wherein, a powder of each of the plants are mixed in a ratio of 1:1:1:1:1:1:1 and wherein, a hydro-alcoholic extract of a plant powder mixture is extracted;

3. The composition as claimed in claim 1, wherein, an oral administration of the poly-herbal drug at a limited dose (2000 mg/kg body weight) level showed no mortality, significant body weight variation and sign of toxicity in a rodent model organisms after 14 days dosing.

4. The composition as claimed in claim 1, wherein, a LD_{50} value of the poly-herbal drug was found to be more than 2000 mg/kg in a female rodent model organisms.

5. The composition as claimed in claim 1, wherein, any abnormal signs nor symptoms attributable to the sub-chronic administration for 90-days with graded dose (40, 200 and 1000mg/kg/day, *p.o.*) of poly-herbal drug in males and female rodent organisms.

6. A method for the neuroactive poly-herbal drug formulation, for the treatment of the chronic fatigue syndrome, the method comprises:

washing and drying the aerial parts of *Andrographis paniculata* and *Fumaria indica*, the roots of *Asparagus recemosus* and the fruits of *Phyllanthus emblica* L., *Terminalia chebula* Retz., *Morus alba* and *Benincasa hispida*;

pulverizing a dried plant parts of each plant separately into a coarse powder and mixing each of the coarse powdered plants in a specific ratio of 1:1:1:1:1:1:1 to form a homogenous mixture;

extracting an accurately weighed 1000gm of homogenous polyherbal mixture with 70% ethanol (70:30::Ethanol:Water) using a Soxhlet apparatus for 6 hours;

filtering and concentrating an extract in vacuum using a rotary evaporator at 60°C and a vacuum lyophilizer; and

storing a final extract at 2-4 °C in airtight containers and protected from direct sunlight.

7. The method as claimed in claim 6, wherein, a pre-formulation characteristics of the poly-herbal drug exhibits a good flow characteristics.

8. The method as claimed in claim 7, wherein, the poly herbal drug can be easily formulated as a tablet, a capsule and/or a powdered formulation.

9. The method as claimed in claim 6, wherein, the poly-herbal drug is helpful in combating the chronic mental and physical fatigue by improving an individual's adaptability, vigour, and endurance by boosting up allostasis and/or cellular homeostasis even in a presence of a variable (psychological, physical, and physiological) stressor by effectively quenching a lethal effects of an oxidative stress.

10. The method as claimed in claim 6, wherein, a pharmacological activities of the poly-herbal drug can be effectively translated into clinical efficacy to prevent and/or combat the chronic fatigue and related co-morbidities i.e., chronic fatigue syndrome.

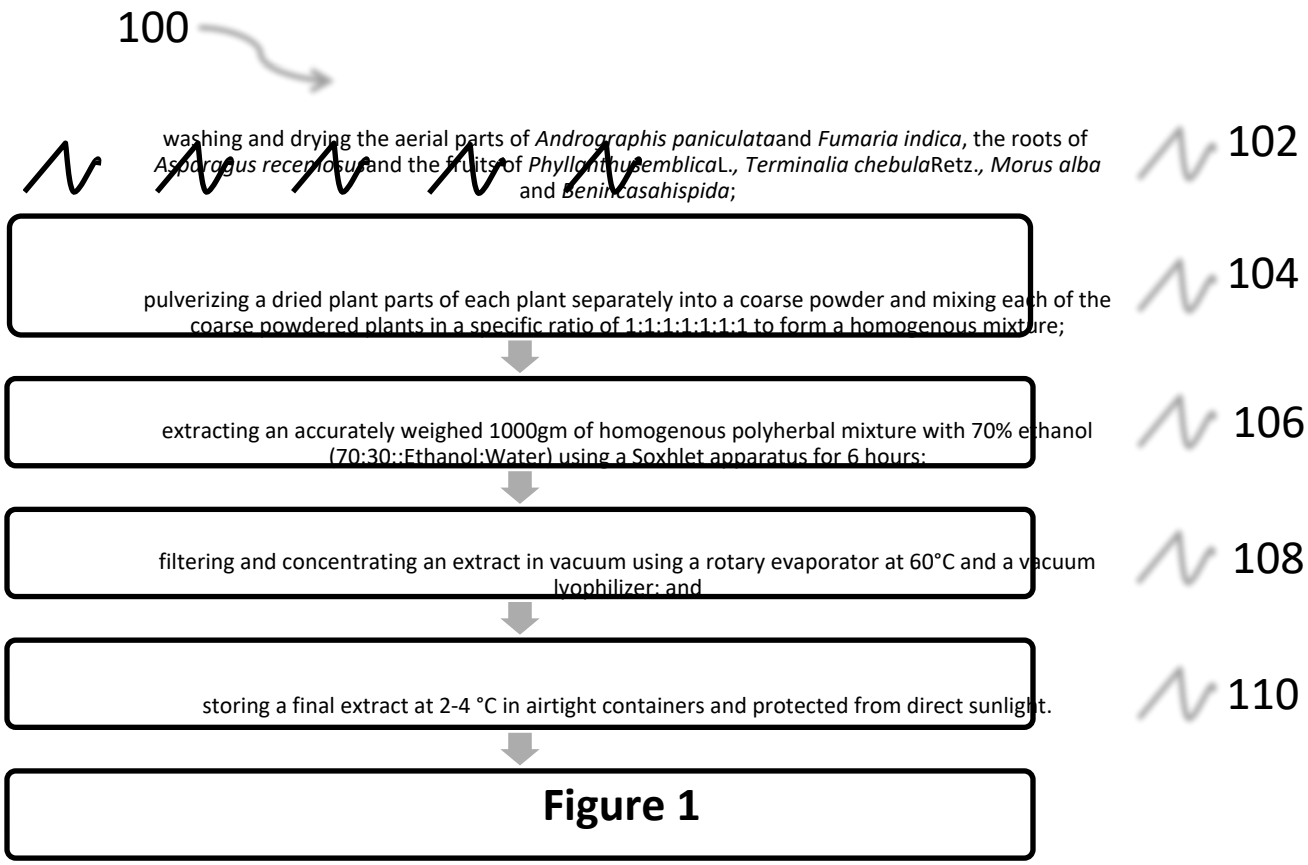
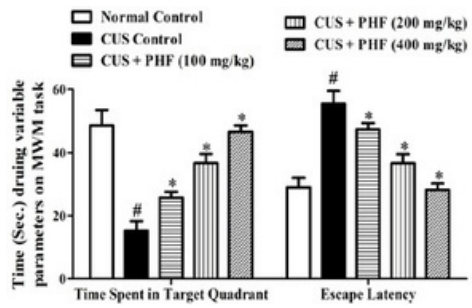

100
washing and drying the aerial parts of *Andrographis paniculata*and *Fumaria indica*, the roots of *Asparagus racemosus*and the fruits of *Phyllanthusemblica*L., *Terminalia chebula*Retz., *Morus alba* and *Benincasahispida*;
102
pulverizing a dried plant parts of each plant separately into a coarse powder and mixing each of the coarse powdered plants in a specific ratio of 1:1:1:1:1:1:1 to form a homogenous mixture;
104
extracting an accurately weighed 1000gm of homogenous polyherbal mixture with 70% ethanol (70:30::Ethanol:Water) using a Soxhlet apparatus for 6 hours;
106
filtering and concentrating an extract in vacuum using a rotary evaporator at 60°C and a vacuum lyophilizer; and
108
storing a final extract at 2-4 °C in airtight containers and protected from direct sunlight.
110

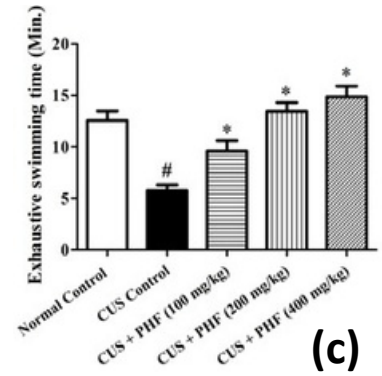
Figure 1

S. No.	Name of plant	Family	Vernacular name	Part used
1	*Andrographis paniculata* (Burm. F.) Wall. Ex Nees.	Acanthaceae	King of Bitter, Kalmegh	Aerial
2	*Fumaria indica* Linn.	Fumariaceae	Pitpapra	Aerial
3	*Asparagus recemosus* Willd.	Asparagaceae	Satavari	roots
4	*Phyllanthus emblica* L.	Phyllanthaceae	Indian gooseberry, Amalaki	Fruits
5	*Terminalia chebula* Retz.	Combretaceae	Haritaki	Fruits
6	*Morus alba* L.	Moraceae	White mulberry	Fruits
7	*Benincasa hispida* (Thunb.) Cogn.	Cucurbitaceae	Kushmanda, Wax Gourd	Fruits

(a)

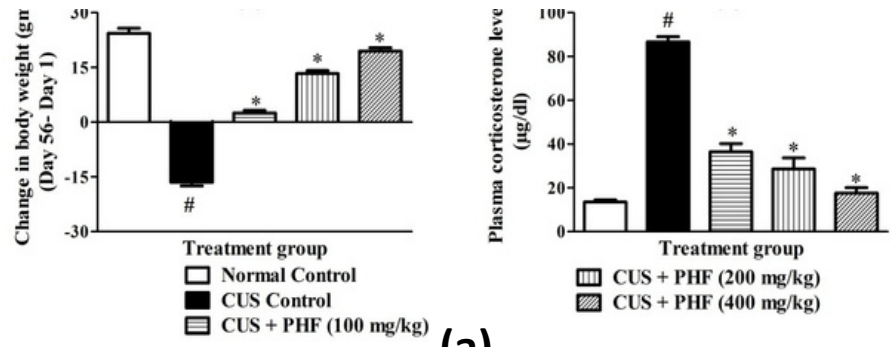


(b)

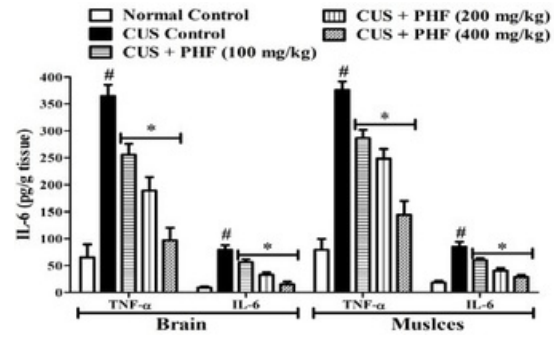


(c)

Figure 2


Change in body weight (gm
(Day 56- Day 1)
30
15
0
-15
-30
#
*
*
*
Treatment group
Normal Control
CUS Control
CUS + PHF (100 mg/kg)
Plasma corticosterone leve
(µg/dl)
100
80
60
40
20
0
#
*
*
*
Treatment group
CUS + PHF (200 mg/kg)
CUS + PHF (400 mg/kg)

(a)


Normal Control
CUS Control
CUS + PHF (100 mg/kg)
CUS + PHF (200 mg/kg)
CUS + PHF (400 mg/kg)
IL-6 (pg/g tissue)
400
350
300
250
200
150
100
50
0
#
*
#
*
#
*
#
*
TNF-α
IL-6
TNF-α
IL-6
Brain
Muslces

(b)

Figure 3