Also, in these afflicted populations, the characteristic stress responses have no tendency to normalize over time and display a broad-based shift in hormonal values across the cascade that is abnormal and causes a broad range of other pathologies and comorbidities.

[0007] Severe mental diseases (including Post Traumatic Stress Disorder (PTSD), schizophrenia, bipolar disorder) are accompanied by co-morbidities including systemic pain, hyperarousal, depression, insomnia, and cognitive and behavioral abnormalities. Patients suffering from severe mental diseases in chronic stress exhibit an abnormal lipid profile that leads to increased risk of stroke and heart attack, increased risk of immune disorders, metabolic syndrome, and systemic inflammation, inflammatory bowel diseases, atherosclerosis, viral and bacterial infections.

[0008] Although chronic, untreated stress disorders have a variety of treatment options, including drugs and psychological counseling, none of the existing treatments address the characteristic and chronic imbalance in the steroidal hormone cascade. While individual elements of the cascade have been addressed by prior treatments, no known attempts have yielded a unified, yet multi-faceted approach to re-balancing the hormonal cascade, especially by reversing the global up regulation of the production of hormones at the top of the cascade and global down-regulation of hormones at the bottom of the cascade

[0009] Therefore, a need exists for new formulations and medicinal compositions and disease-specific methods of treatment that promote re-balancing of the human steroidal hormonal cascade to counteract the abnormal up-regulation of certain selected hormones and the abnormal down-regulation of other hormones. Counteracting this imbalance will reduce the adverse effects of the chronic distortion of the hormonal cascade and by restoring healthy hormonal balance, ameliorate the symptoms caused by the imbalance, including reduction of the direct symptoms of stress-related disorders, both psychological and physical, and including the related comorbidities.

SUMMARY

[0010] Aberrations in the hormonal cascade are counteracted by administering a combination of compounds that influence hormone regulation, synthesis, and metabolism and promote restoration of overall balance in the steroidal hormonal cascade. Although the range

of conditions exhibiting aberrant hormonal values are varied, and the specific alterations in aberrant hormonal values compared to normal can be different, the disclosure normalizes aberrant hormonal values, regardless of the quantitative differences in the specific abnormalities, and restores a more normal balance in the hormone cascade.

[0011] The pharmaceutical compositions of the disclosure include components that provide a synergistic effect in restoring balance to the hormone cascade. By co-administering these compositions, abnormally reduced or down regulated levels of selected steroidal hormones can be increased by metabolizing existing precursors to these compounds. Also. the abnormal decrease or down regulation of other hormones and selected precursor hormones is alleviated by administering precursors that increase biosynthesis and concentrations of compounds that are downstream in the hormonal cascade. For example, the decrease of precursor hormones (for example DHEA and pregnenalone) leads to increased biosynthesis of testosterone, the adiols, estradiol, estradiol metabolites, and cortisol.

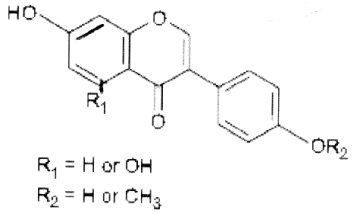
[0012] A first component is a specially selected combination of isoflavones that shift the steroidal cascade away from corticosterone and toward the "adiols," (androstenediol, aldosterone, androstenetriol, androstanediol, estradiol, 2-OH-Estradiol, and 2-Methoxy-Estradiol) and testosterone. Preferably, the combination of isoflavones is obtained from a specific natural source that yields a preferred relative and absolute concentrations between and among specific isoflavones species, specifically between and among four individual isoflavones and most specifically having minimum concentrations of two specific isoflavones that have cooperative metabolic effects to achieve the goal of restoring hormonal balance. Specifically, the natural source isoflavone preferably comprises at least formononetin and biochanin A, and preferably also further comprises genistein, and daidzein.

[0013] The isoflavone component of the composition may also contain other constituent components that indicate that the source of selected isoflavones is naturally derived. These can include other chemical compounds identified in naturally sourced isoflavones, or plant materials that are characteristic of the isoflavone source. A particularly preferred source of the selected isoflavones is the plant commonly known as Red Clover (Trifolium pratense) and is comprised of four preferred isoflavones formononetin, biochanin A, genistein and diadzein in desirable ratios and concentrations and other trace elements,

such as plant matter consistent with the Red Clover source. These isoflavones are also anti-inflammatory and tend to couple to the same receptor sites as anti-inflammatory hormones in the cascade, thereby reducing the need for endogenous biosynthesis, and allowing a shift in hormonal synthesis away from these hormones toward the lower end of the steroidal hormone cascade. Other sources of each of the preferred isoflavones are known, and chemical synthesis of each compound disclosed herein is possible, although for economic reasons and the balance of constituent compounds, the Red Clover natural source is preferred.

[0014] A second component is pharmaceutical grade alpha-lipoic acid administered in a selected form that has high potency and physiological availability. Specifically, the preferred form of alpha lipoic acid is highly enriched in the (R +) enantiomer (RLA) and acts as a cofactor for enzyme complexes. The preferred formulation is substantially free of the (L) enantiomer¸ at a minimum, has smaller percentage of the (L) enantiomer compared to the (R) enantiomer. A particularly preferred source is an enhanced RLA having increased bioavailability, limited inactive components, and at least 85-90% of the R-enantiomer.

[0015] The third component is L-dopamine or a precursor of L-dopamine (L-3,4-dihydroxyphenylalanine) specially selected for bioactivity and is preferably derived from a natural source. Preferably, the source is naturally derived from Mucuna pruriens extract that contains L-dopa. In the presence of the other constituents of the compositions of the disclosure, L dopamine has several beneficial effects on restoration of balance to the human steroidal hormonal cascade. Catechol-O-methyltransferase (COMT) catabolizes L-dopa and degrades estradiol. Mucuna Pruriens also provides a bioavailable L-dopa precursor that is metabolized to yield measurable increases, or preservation of nominally normal, concentrations of estradiol in vivo. Estradiol is a precursor of 2-methoxy estradiol (2-ME), regulates blood pressure blood pressure and acts as a neuroprotective agent.

[0015a] In one aspect, the present disclosure refers to a composition comprising a physiologically active dose of: (1) an R(+) enantiomer of alpha lipoic acid; (2) a naturally occurring substance containing a dopamine precursor; and (3) a combination of isoflavones having the formula: 

and combinations thereof.

[0015b] In another aspect, the present disclosure refers to the composition as disclosed herein for use as a medicament.

[0016] The methods of the disclosure include treatment methods for a group of conditions characterized by persistent abnormalities in the human steroidal hormone cascade. The methods include co-administration of the compositions described herein, as well as formulation of the disclosed compositions using selected ingredients, co-factors, excipients, and precursors. The methods include targeted alterations to the human steroidal hormone cascade including down regulation, or reductions in in vivo concentrations of at least

cholesterol and corticosterone and reduction in concentrations or activity of catechol-O-methyltransferase (COMT). The methods include up regulation, or increases in in vivo concentrations of at least the adiols, including specifically 2-methoxy-estradiol, androstenediol, androstenetriol, and androstanediol, and testosterone.

[0017] The methods also include providing the compositions of the disclosure to influence the in vivo concentration of hormonal precursors to alter aberrant hormonal cascades, to return the hormonal cascade to the "normal" state, and to mitigate the deleterious effects of aberrant hormonal shifts. The methods include methods of manufacturing the three-component composition of the disclosure including combining each of the proposed agreements in their preferred, most bioavailable and active forms, including finalizing a dosage form as any orally administered dosage format, preferably including pills, suspensions, capsules, liquids, emulsions, and dispersions. The methods include administration of selected dosage ranges of the three components of the disclosure in synergistic combination, and over a time profile determined to elicit cooperative absorption and in vivo activity of each elements

[0018] The conditions subject to methods of administration of the present disclosure have a chronic stress-induced pathology characterized by a primary mental component. The methods of the disclosure include administering pharmaceutically active concentrations of the compositions described herein for treating each of Post Traumatic Stress Disorder (PTSD), fibromyalgia, high blood pressure, eclampsia, and preeclampsia, inflammatory bowel syndrome (IBS), depression, including post-partum depression, and unnatural cell growth. The methods also include reducing acute psychological stress that accompanies other physical and psychological disorders including mental disease, dementia, including particularly Lewy Body dementia, Parkinson's disease, and addiction withdrawal. The methods include administering the compositions of the disclosure together with other compounds administered for treatment of psychological stress or the underlying psychological or physical condition yielding the psychological stress. For example, treatments for high blood pressure or stress disorders frequently include other pharmaceutical compositions that are co-administered with the composition of the present disclosure. Within this context, co-administration means delivering both the compounds of the present disclosure together with another beneficial therapeutic compound such as both have simultaneous

beneficial effects within the timeframe of administration of either compound.

[0019] Additionally, because of the stress reducing effect of the compositions of the present disclosure, the compounds described herein may be administered as part of a regimen to reduce use of another composition where phasing out, reducing, or eliminating use of the other composition is desired. For reduction of the effects of addiction, for example with substances of abuse, the compounds of the present disclosure can be administered as part of a tapering regimen such that administration of the other compound or substance of abuse is reduced over time together with coadministration of the compounds described herein.

[0020] Synergism between the individual elements of the compounds of the disclosure allows relatively reduced concentrations or dosages of any individual component to be administered while still producing therapeutic effects. For example, earlier dosages of isoflavones have been reported at ranges between 700 mg two 1500 mg without significant effect across the entire range of stress -induced disorders. Compositions pursuant to the disclosure, involving isoflavones in combination with L-dopa, and L-dopa precursors, together with R+ lipoic acid significantly reduce the concentration the isoflavone compounds that must be administered for efficacy.

[0021] Any or all of the three-component composition may be formulated in a sustained release format that alters the pharmacological profile of absorption and metabolism depending on the underlying indication as described below. Timing of administration includes conforming the concentration or dosage of the administered compositions for an area-under-curve (AUC) pharmacological model or a peak C_{MAX} concentration model wherein the combination of concentrations and dosages is pharmaceutically active.

[0022] As will be described in more detail below, special selection of the source and composition of the at least three individual components of the pharmaceutical compositions of the disclosure yields important benefits in bioavailability, potency, efficacy, and tolerability. Moreover, use of the specially selected sources and compositions yields a dose that is tolerable and readily administered to a human patient as part of an ordinary lifestyle and diet plan.

[0023] As disclosed in more detail below, preferred examples of the disclosure

feature specific selected absolute and relative concentrations of and ratios between the minimal three components of the pharmaceutical combination as well as selected ratios between two of the three, and three of the three components of the disclosure. Balancing the ratios and compositions of the individual components enhances the ability of the compositions of the disclosure to restore the steroidal hormonal cascade towards a more normal balance.

[0024] Although the individual indications may vary according to the source of the stress in the underlying disease, the preferred examples have ranges of individual concentrations and ratios among the components that exhibit synergy among the individual components when administered to a patient in need thereof. Because the hormonal cascade is, as seen in the accompanying Figures, a complicated and highly dependent web of chemical reactions, minimum concentrations and an overall balance balancing between the individual compositions of the disclosure produces a more preferred systemic result.

[0025] The compositions of the disclosure are tailored for oral administration in a dosage form that is well tolerated, and it does not result in gastrointestinal distress or interfere with other medications used to treat stress disorders or their co-morbidities.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] Figures 1A-1D: Figures 1A-1D are a hormonal cascade showing the progression of up regulation and down regulation across normal to stress-induced conditions. Figure 1 A is a representation of the basic hormonal cascade with the anti-anxiety hormones shown in the "top" of the cascade and the immune and cardioprotective hormones shown in the "bottom" of the cascade. Figure 1B shows both up and down regulation in well-trained marathon runners. Figure 1C shows both up and down regulation in elite soldiers undergoing extreme physical stress and starvation in survival training. Figure 1D shows up and down regulation in severe mental disease.

[0027] Figure 2 shows the impact of the compositions and methods of the invention on the same human steroidal hormone cascade showing specifically selected up and down regulation of various components of the cascade to ameliorate a chronic stress condition

CLAIMS

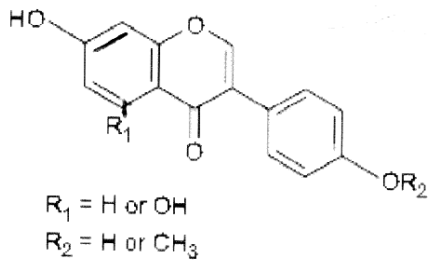
WHAT IS CLAIMED IS:

1. A composition comprising a physiologically active dose of:

(1) an R(+) enantiomer of alpha lipoic acid;

(2) a naturally occurring substance containing a dopamine precursor; and

(3) a combination of isoflavones having the formula:



and combinations thereof.

2. The composition of claim 1, wherein the isoflavone combination is further comprised of an isoflavone compound having R1 = H and R2 = CH_3 and R1 = OH and R2 = CH_3 and combinations thereof.

3. The composition of claim 1, wherein the isoflavone combination is further comprised of an isoflavone having R1 = H and R2 = H and R1= H and R2 = OH and combinations thereof.

4. The composition of claim 1, wherein the isoflavone combination is further comprised of naturally occurring, non—isoflavone constituents of red clover.

5. The composition of claim 1, wherein the naturally occurring substance is further comprised of non—dopamine constituents naturally occurring in Mucuna Pruriens.

6. The composition of claim 1, wherein the dopamine precursor is present in a plant species selected from the group consisting of the genus listed in Table 1 and combinations thereof.

7. The composition of claim 1, wherein each of the alpha lipoic acid, the naturally occurring dopamine precursor, and the isoflavone combination are combined in a single dosage form with a concentration of the naturally occurring dopamine precursor of at least 2 mg active ingredient.

8. The composition of claim 1, wherein each of the alpha lipoic acid, the naturally occurring dopamine precursor, and the isoflavone combination are combined in a single dosage form having a content of the naturally occurring dopamine precursor of between approximately 2 mg and 6 mg active ingredient 5mg and 30mg.

9. The composition of claim 1, wherein each of the alpha lipoic acid and the naturally occurring dopamine precursor are combined in a single dosage form having a content of the isoflavone combination of between 100-500 mg.

10. The composition of claim 1, wherein each of the alpha lipoic acid, the naturally occurring dopamine precursor, and the isoflavone combination are combined in a single dosage form with a total isoflavone content comprised of combination of biochanin A and formononetin of at least 240 milligrams.

11. The composition of claim 1, wherein each of the alpha lipoic acid, the naturally occurring dopamine precursor, and the isoflavone combination are combined in a single dosage form having a total isoflavone content of at least 300 milligrams.

12. The composition of claim 1, wherein composition is further comprised of natural plant tissue from Red Clover.

13. The composition of claim 1, wherein the dopamine precursor is substantially comprised of an L-form of dopamine and is substantially free of a D-form of dopamine.

14. The composition of claim 1, further comprising a peripheral nervous system decarboxylase inhibitor.

15. The composition of claim 1, further comprising composition B6.

16. The composition of claim 1, wherein the dose of the alpha lipoic acid is at least 85 % enriched for the (R) (+) enantiomer.

17. The composition of 16 wherein the alpha lipoic acid is a sodium salt thereof.

18. The composition of any of claims 1 -17 for use as a medicament.