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(54) **COMPOSITION, FORMULATIONS AND METHODS OF MAKING AND USING BOTANICALS AND NATURAL COMPOUNDS FOR THE PROMOTION OF HEALTHY BRAIN AGING**

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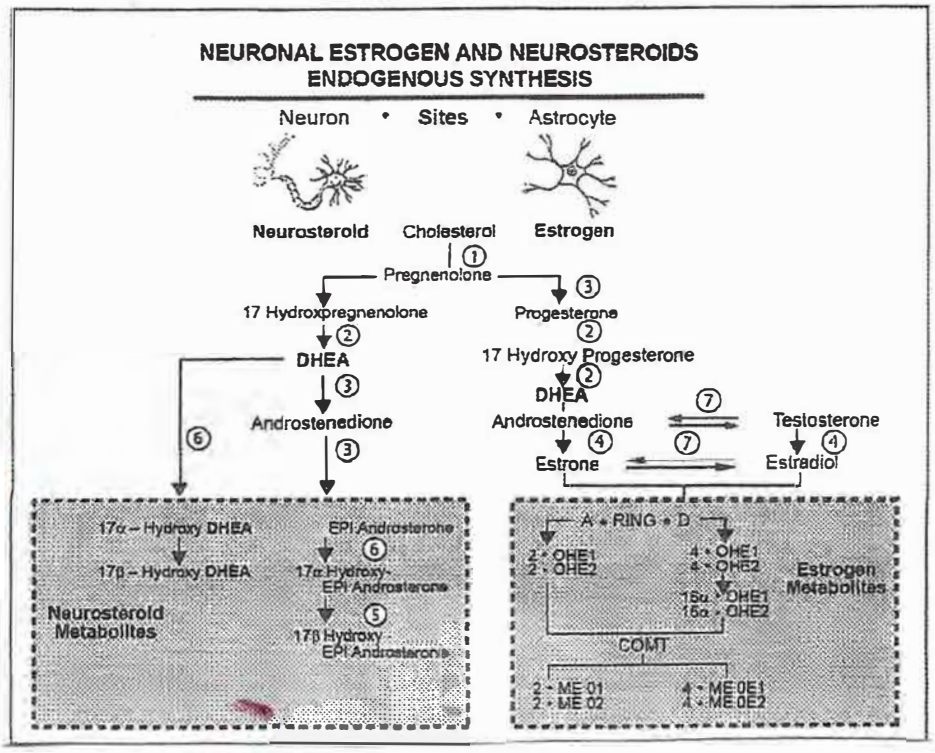
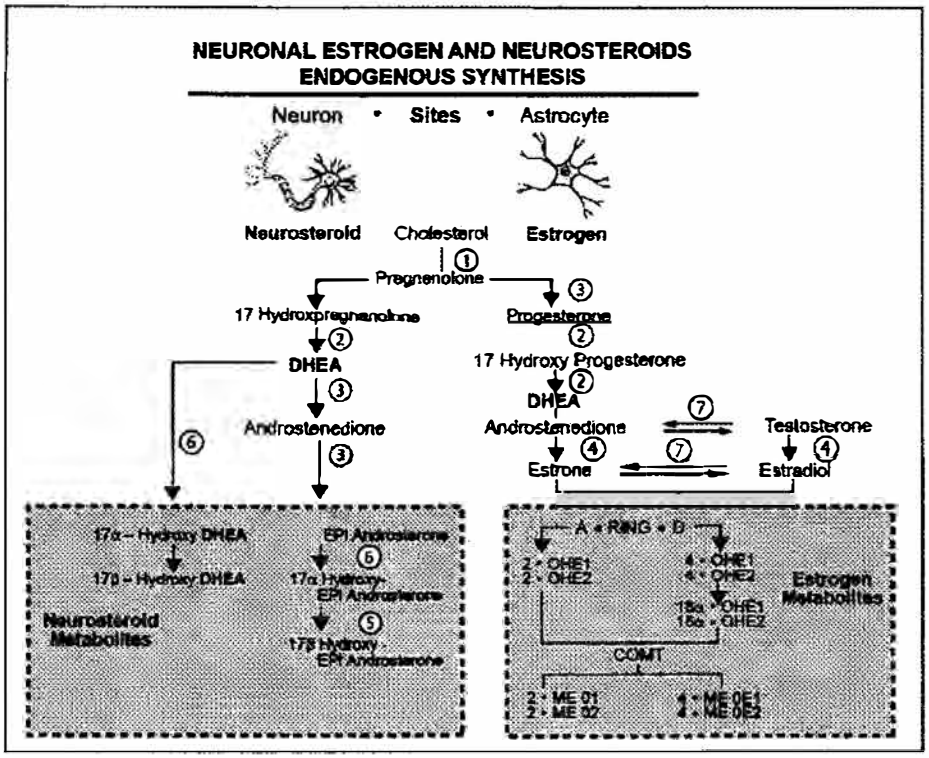
(57) **ABSTRACT**

The present disclosure provides compositions and formulations comprising botanicals and natural compounds for the promotion of healthy brain aging in adults and for prevention or inhibition of age associated neurodegenerative changes resulting in cognitive, memory and executive dysfunction including modulation of the age related predisposition to mild cognitive impairment, Alzheimer's disease, hormonal and other dementia related conditions. The present disclosure also provides methods of using the compositions and formulations in treating and preventing neurodegenerative changes resulting in cognitive, memory and executive dysfunction.





LEGEND:

1 = p450 scc (Side chain clevage enzyme)

2 = p450 c17 (Side chain clevage enzyme at carbon17)

3 = 3β .. HSD (3β Hydroxysteroid dehydrogenase)

4 = Aromatase

5 = 11β – Hydroxysteroid dehydrogenase type 1

6 = Oxysterol - 17α Hydroxylase

7 = 17β – HSD (17β – Hydroxysteroid dehydrogenase)

DHEA = Dehydroepiandrosterone

CUI et al (2013) ; TRAISH et al (2011); CHARAMPOPOULOS (2008)

Figure 1

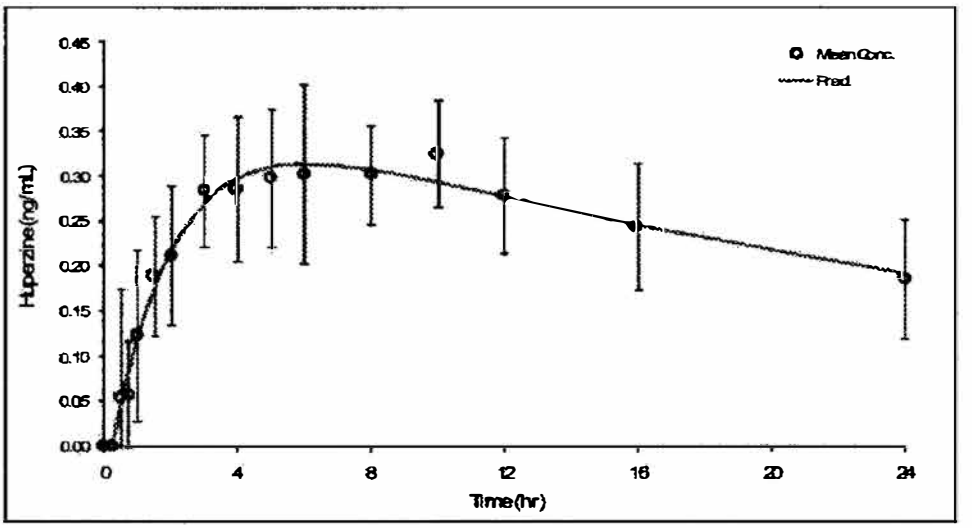

Mean Conc.
Pred
Huperzine(ng/mL)
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
0
4
8
12
16
20
24
Time(hr)

Figure 2

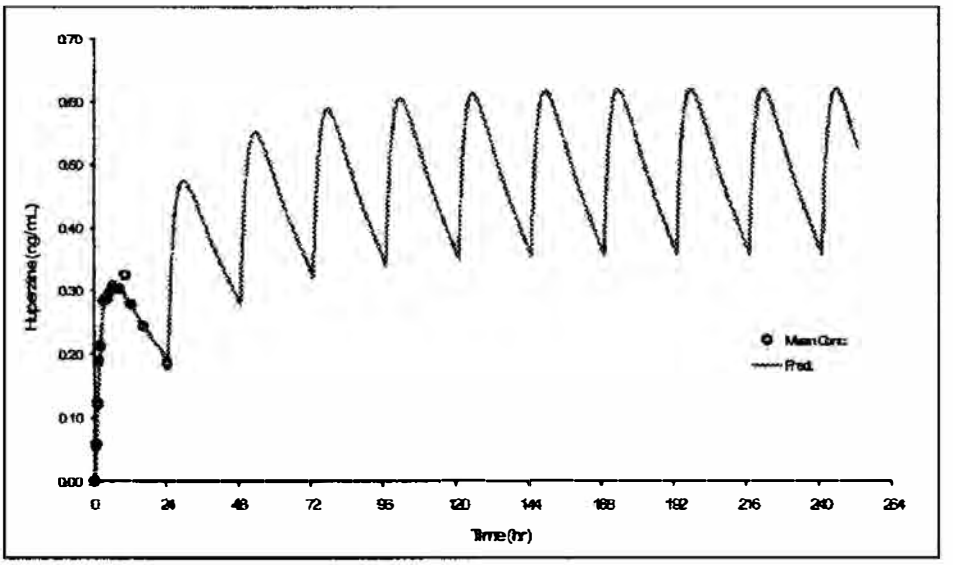
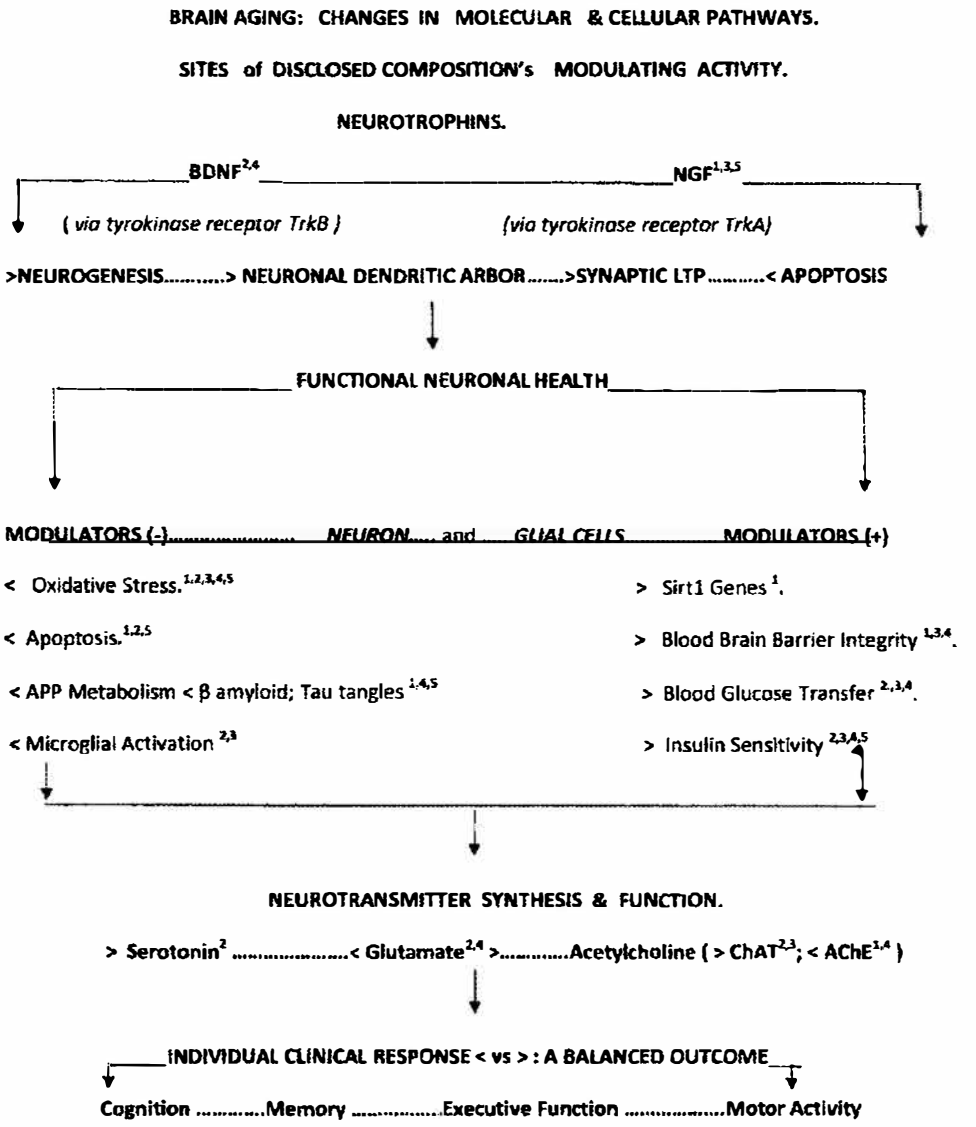

0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
Huperzine (ng/mL)
0
24
48
72
96
120
144
168
192
216
240
264
Time (hr)
Mean Conc
Pred.

Figure 3



(< = decrease ; > =increase)

Disclosed Composition : *promotes > healthy aging ; reduced risk for MCI – disease prevention.*
SITES OF ACTIVITY : *Huperzine A[1]; DHEA [2]; vitamin D[3]; caffeine[4] ; sweetener/glp-1[5]*

Figure 4

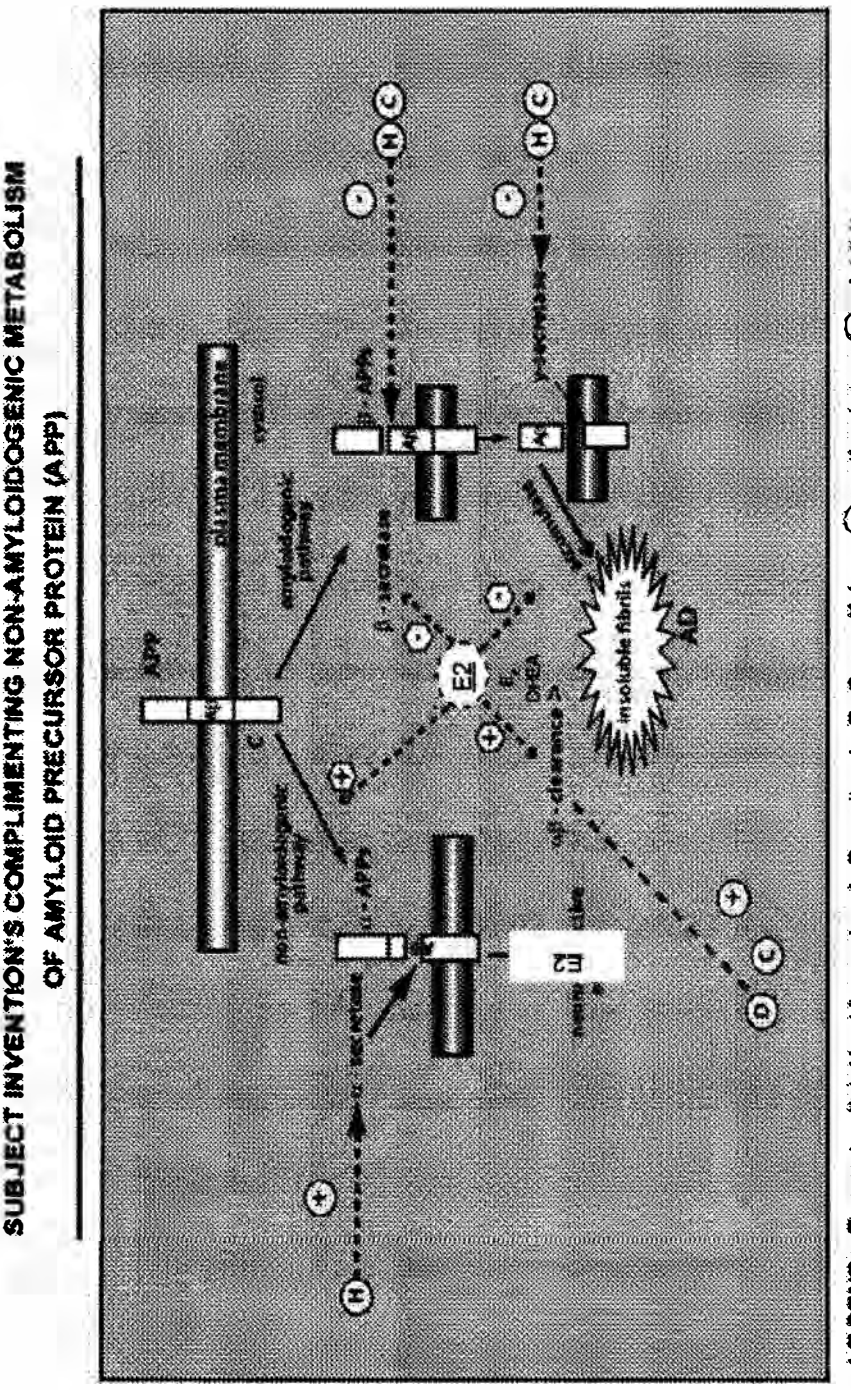

SUBJECT INVENTION'S COMPLIMENTING NON-AMYLOIDOGENIC METABOLISM
OF AMYLOID PRECURSOR PROTEIN (APP)
APP
plasma membrane
cytosol
α-APPs
β-APPs
β-secretase
γ-secretase
E2
DHEA
insoluble fibrils
AD
LEGEND: E2 = estradiol; H = Huperzine A; D = vitamin D; C = caffeine; (+) = stimulates; (-) = inhibits
> = increases the clearance of soluble Aβ; DHEA = Dehydroepiandrosterone.
Cui et al (2013)

Figure 5

BRAIN HEALTH MODULATORS : SINGLE vs DISCLOSED COMPOSITION's MULTIPLE SITE ACTIVITY.

INSULIN RESISTANCE ASSOCIATED NEURODEGENERATION.

NEURONAL GLUCOSE INSULIN IMBALANCE.

SINGLE PATHWAY MODULATORS. DISCLOSED COMPOSITION.

PATHOLOGIC EVENT.

Insulin.....< *INSULIN; >> GLUCOSE*..... > IR sensitivity,BBB glucose transport.

Secretase Inhibitors.....> β *Amyloid Metabolism*.....< β / gamma ; > α secretase.

Bapineuzumab Class..... β *Amyloid Ploques*..... .....> β Amyloid efflux.

>*Tau phosphorylation*.....inhibits tau phoshorylation

LTMX; Epothilone.....*tau bundles* ..... < tau tangle formation.

Inflamatory Microglial activity >.....< inflamatory mediators.

Curcumin; Thalidomide.....*Neurodegeneration /Apoptosis*..... < via multiple pathways.

Cell Death – Synapse Loss .....> synapse;number and LTP.

Aricept©;Excelon©;.....< *neurotransmission*..... .> ChAT < AChE;>serotonin

Reminyl©; Cognex©. normalizes synaptic Ca ++

Nemada© <glutamate excitotoxity

Clinical Cognitive Decline / Improvement

< =decrease ; > = increase

Figure 6

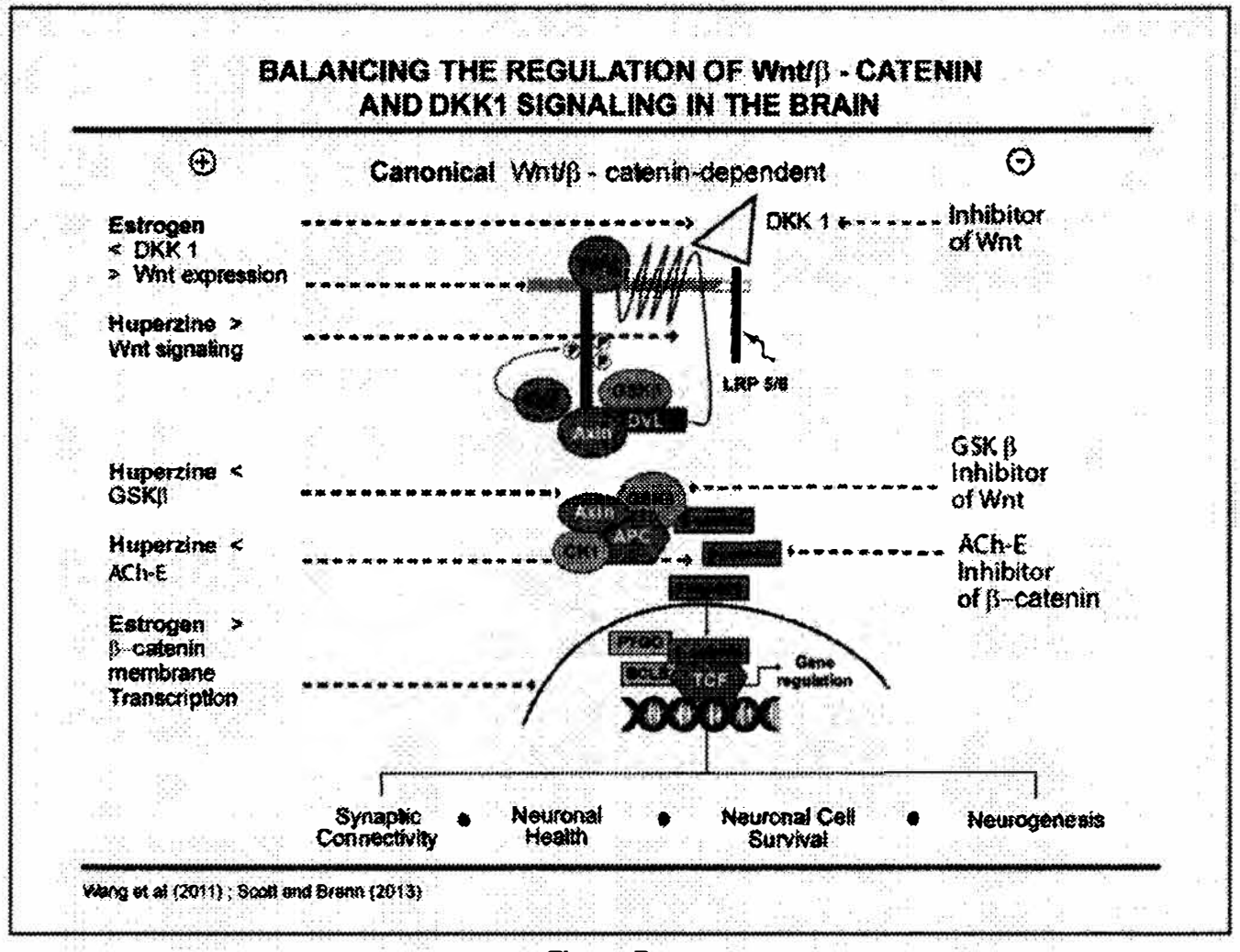
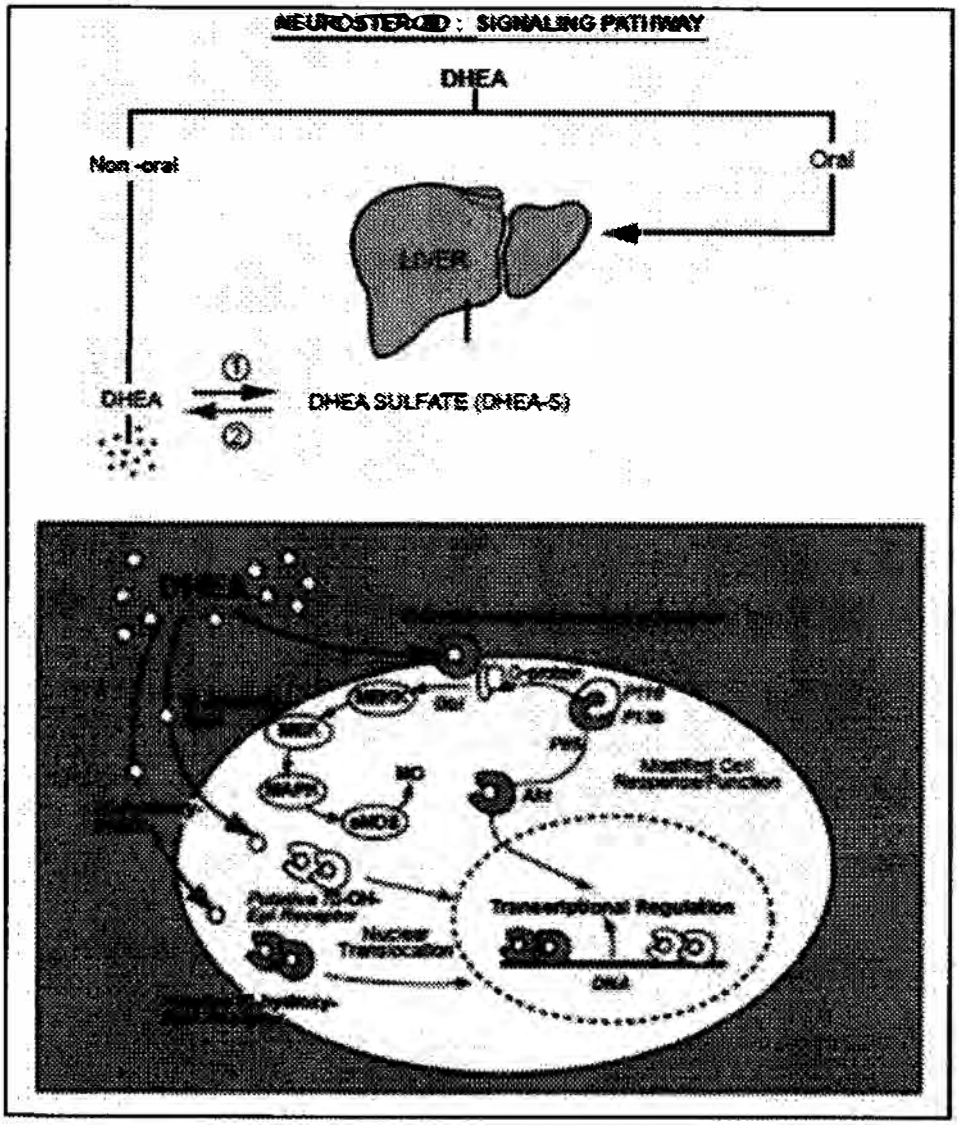

BALANCING THE REGULATION OF Wnt/β - CATENIN
AND DKK1 SIGNALING IN THE BRAIN
Canonical Wnt/β - catenin-dependent
Estrogen
< DKK 1
> Wnt expression
DKK 1
Inhibitor
of Wnt
Huperzine >
Wnt signaling
LRP 5/6
DVL
Axin
Huperzine <
GSKβ
GSK β
Inhibitor
of Wnt
Axin
APC
Huperzine <
ACh-E
ACh-E
Inhibitor
of β–catenin
Estrogen >
β–catenin
membrane
Transcription
TCF
Gene
regulation
Synaptic
Connectivity
Neuronal
Health
Neuronal Cell
Survival
Neurogenesis
Wang et al (2011) ; Scott and Brann (2013)

Figure 7



Legend: DHEA = dehydroepiandrosterone; MAPK= mitogen activated protein kinase; eNOS = endothelial nitric oxide synthase; NO = nitric oxide; EPIA = epiandrosterone; AKT = protein kinase B; MEK = mitogen extracellular kinase; MEKK = MEK kinase; P13K = phosphatidylinositol 3-kinase.

Figure 8

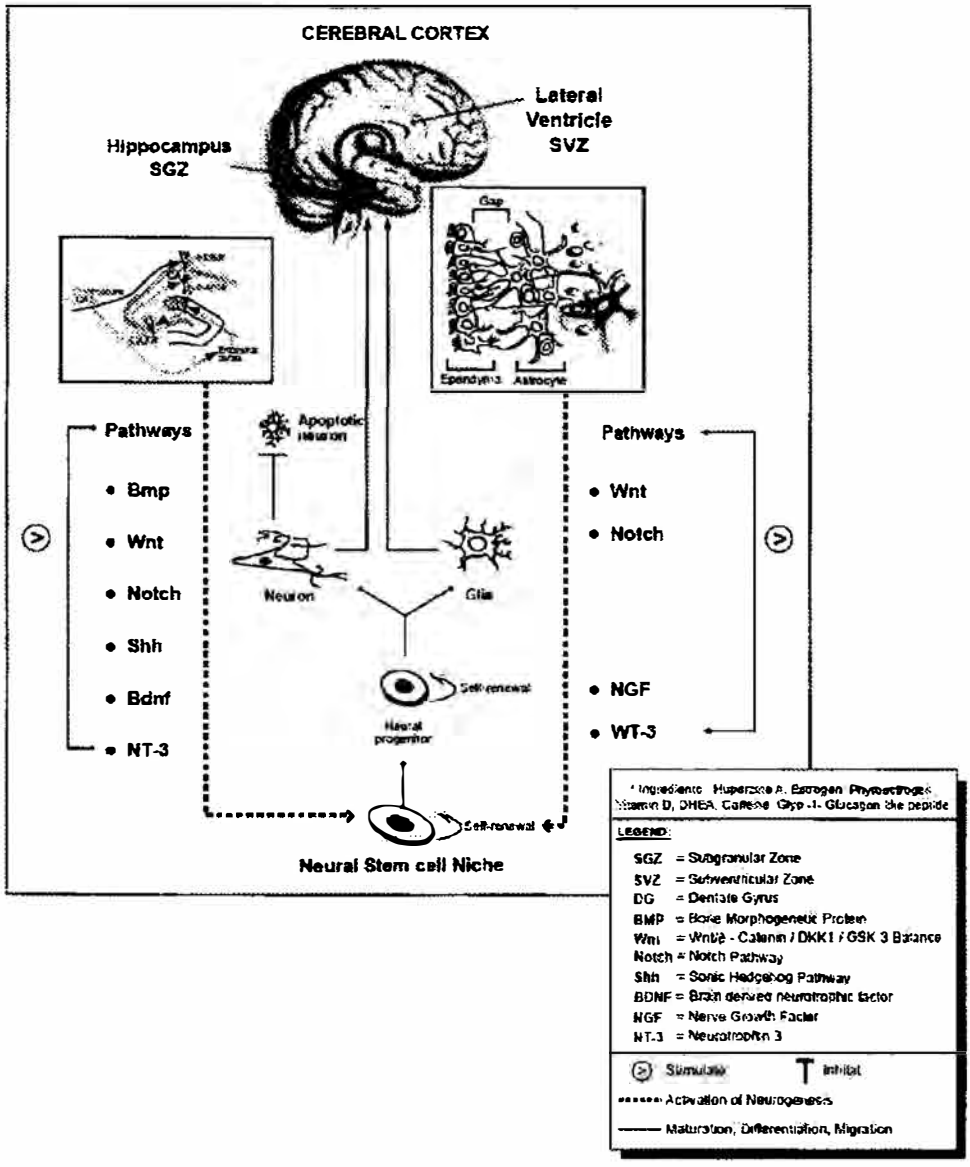

CEREBRAL CORTEX
Lateral Ventricle SVZ
Hippocampus SGZ
Gap
Ependyma
Astrocyte
Pathways
Bmp
Wnt
Notch
Shh
Bdnf
NT-3
Apoptotic neuron
Neuron
Glia
Self-renewal
Neural progenitor
Self-renewal
Neural Stem cell Niche
Pathways
Wnt
Notch
NGF
WT-3
LEGEND:
SGZ = Subgranular Zone
SVZ = Subventricular Zone
DG = Dentate Gyrus
BMP = Bone Morphogenetic Protein
Wnt = Wnt/β - Catenin / DKK1 / GSK 3 Balance
Notch = Notch Pathway
Shh = Sonic Hedgehog Pathway
BDNF = Brain derived neurotrophic factor
NGF = Nerve Growth Factor
NT-3 = Neurotrophin 3
Stimulate
Inhibit
Activation of Neurogenesis
Maturation, Differentiation, Migration

Figure 9

COMPOSITION, FORMULATIONS AND METHODS OF MAKING AND USING BOTANICALS AND NATURAL COMPOUNDS FOR THE PROMOTION OF HEALTHY BRAIN AGING

BACKGROUND

[0001] The physiologic aging of the human brain is associated with cellular, molecular and functional changes that frequently results in neurocognitive frailty: reduced cognition, memory, mood and executive function. Healthy brain aging is subject to the neurobiology of identifiable genetic factors and the influence of modifiable neuronal and glial cell modulators. The latter will determine neuronal survival; the synthesis and function of neurotrophins and their effect on neurogenesis; synaptic activity and control of its neurotransmitter long term potential; cellular dysfunction associated with inflammatory signals and oxidative stress; metabolic abnormalities linked to insulin resistance and its disruption of the vital pathways regulating brain energy requirements and neuronal survival, and the integrity of the blood brain barrier (Glorioso and Sibille 2011; Uranga et al 2010; Park and Reuer Lorenz 2009; de la Monte 2012; Zlokovic 2008).

[0002] When men and women with underlying neurodegenerative disease are excluded, normal brain aging is not characterized by neuronal death. The cognitive decline is the result of neuronal dendritic arbor shrinkage and a reduction in synaptic density and plasticity (Glorioso and Sibille 2011). The degree to which this occurs determines the continuation of normal cognition (healthy aging) versus cognitive dysfunction and resulting functional impairment (unhealthy aging). The latter also has the potential to stimulate and promote underlying neurological disease related genes into a pro-disease direction. Examples include subjects with a genetic variant of the APOE e4 mutation (Mayeux 2010) and women with insulin resistant type two diabetes (de la Monte 2012).

[0003] Although a relationship between post mortem brain levels of estrogen and aging was not observed in a recent study of women with non-neurological disease, men in the same study had a significant age associated decrease in the brain levels of the androgens, testosterone (T) and its bioactive metabolite dehydrotestosterone (DHT) (Rosario et al 2011).

[0004] Post mortem histologic confirmation of men with Alzheimer's disease (AD) was associated with significantly lower concentrations of T than normal age matched men. In cases with neuropathological changes of early AD, a significant reduction of T levels was inversely correlated with brain levels of soluble beta amyloid (Rosario et al 2011). This observation is consistent with studies demonstrating an inverse relationship between blood levels of T and beta amyloid in men with memory loss (Gillet et al 2003), a relationship that may precede the clinical diagnosis of AD by several years (Moffat et al 2004).

[0005] Androgens are positively associated with enhanced cognition (Cherrier et al 2005), neuroprotection (Pike et al 2008), a reduction in beta amyloid levels (Rosario and Pike 2008), and neurogenesis (Charalampopoulos et al 2008; Barron and Pike 2013). The age related decline in systemic levels of the sex steroids is well known, but this does not account for all of the related neurosteroidgenesis given the presence of relevant brain steroid converting enzymes (Stoffel-Wagner 2001; Charalampopoulos et al 2008; Rosario et al 2011).

[0006] Vascular dementia (VaD) is the second most prevalent cause of dementia in adults. It is a heterogeneous clinical disease induced by cerebral ischemia resulting mechanistically in two main features: cholinergic deficiency and dysfunction, and post-ischemic inflammation (Wang et al 2009).

[0007] In both animal models and in patients with VaD the vascular changes may be focal, multifocal or diffusely disseminated in various brain regions. Experimental VaD models—achieved via bilateral common carotid artery occlusion—results in loss of cholinergic neurons with decreased choline acetyltransferase (ChAT) and reduced acetylcholine (ACh) activity in the cortex and the hippocampus. This has been found in 40% of VaD patients (Court et al 2002) and confirmed post mortem in VaD patients (Gottfries et al 1994).

[0008] Inflammatory changes resulting from cerebral ischemia is associated with the up-regulation of a variety of inflammatory mediators including: interleukin-1 beta; tumor necrosis factor alpha; nitric oxide and inducible nitric oxide synthase; and cyclooxygenase with two main brain damaging consequences: recruitment and activation of microglia and astrocytes (Wang et al 2007), and disruption of the blood-brain barrier (Liu et al 2005). Inhibiting the inflammatory cascade has been shown to protect cognition. (Mehta et al 2007).

[0009] VaD is preceded by a clinical condition known as Vascular Cognitive Impairment (VCI). The latter is associated with various clinically measurable vascular risk factors that have both a significant role in the pathogenesis of VaD and can differentiate between the more prevalent AD and VaD. A recent study has shown that serum levels of homocysteine, lipoprotein (a) and DHEA-S can effectively separate AD and VaD from each other as well as from healthy controls (Ray et al 2013). Various factors are involved in promoting and maintaining brain health. Both environmental and genetic factors may play a role in healthy brain aging. As examples, neurogenesis, oxidative stress, apoptosis, and healthy blood brain barrier are involved in modulating and maintaining brain health. Different growth factors, such as neurotrophins and transforming growth factors, and neurotransmitters may be involved in neurogenesis and neuroprotection of the brain. Other factors may be involved in maintaining the molecular pathways that govern the function of the brain as a person ages.

SUMMARY

[0010] The present application provides compositions comprising Huperzine A or a derivative or analog thereof; a dehydroepiandrosterone (DHEA); and a vitamin D. DHEA includes derivatives and analogs thereof. Examples include, but are not limited to, dehydroepiandrosterone sulfate (DHEA-S), 17-α-derivatives, 17-β-derivatives, 17-spiro analogs of DHEA and the like (Gravinis A et al 2012) and combinations thereof. Examples of Vitamin D include, but are not limited, to calcitriol, doxercalciferol, paricalcitol, cholecalciferol (vitamin D3), ergocalciferol (vitamin D2), analogs and derivatives thereof, Vitamin D receptor agonists and modulators, and combinations thereof. The components of the composition can be natural or endogenous molecules, synthetic molecules, and combinations thereof. The natural or endogenous molecule can be from a mammalian source.

[0011] The composition can be a pharmaceutical composition or a nutraceutical composition. In some embodiments, the pharmaceutical composition contains one or more synthetic components. In other embodiments, the nutraceutical

composition contains one or more natural components. In other embodiments, the composition can include a combination of synthetic and natural components.

[0012] In one embodiment, the pharmaceutical composition comprises DHEA-S, vitamin D3, and Huperzine A. In another embodiment, the pharmaceutical composition comprises Huperzine A, DHEA-S, and/or vitamin D in the form of synthetic compounds. The amount of DHEA-S can be about 25 mg to about 175 mg. The amount of DHEA-S can be about 100 mg The amount of vitamin D3 can be about 600 iu, the amount of Huperzine A can be about 50 mcg to about 350 mcg.

[0013] In one embodiment, the composition comprises from about 0.01 mg to about 150 mg of Huperzine A or a analog or derivative thereof, from about 10 mg to about 500 mg of a DHEA, and from about 200 iu to about 5000 iu of vitamin D, an analog thereof, or a vitamin D receptor agonist and modulator. In another embodiment, the composition comprises about 50 mcg, about 75 mcg, about 175 mcg, about 250 mg, about 275 mcg, about 350 mg, or about 375 mcg of Huperzine A. In one embodiment, the analog or derivative can be a synthetic analog or derivative thereof.

[0014] In one aspect, the composition comprises Huperzine A, DHEA, and vitamin D. In another aspect, the composition comprises from about 40 mcg to about 400 mcg of Huperzine A, about 25 mg of DHEA, and about 1200 iu of vitamin D.

[0015] The composition can include one or more additives. Additives can be selected from the group consisting of coffee, xanthine alkaloids, chlorogenic acid, sweeteners and combinations thereof. Examples of xanthine alkoid include, but are not limited to, caffeine, theobromine, paraxanthine, and combinations thereof. The sweetener can be a low glycemic sweetener, such as sucromalt, tagatose, isomalt, sucralose, acesulfame potassium, analogs and derivatives thereof, and combinations thereof.

[0016] In one embodiment, the composition comprises from about 10 mg to about 100 mg of xanthine alkaloid and/or from about 10 g to about 100 g of a sweetener. In another embodiment, the composition comprises Huperzine A, DHEA, vitamin D, caffeine, and sucromalt. In one aspect, the composition comprises from about 40 mcg to about 400 mcg of Huperzine A; about 25 mg to 175 mg, about 50 mg to 175 mg, or about 100 mg of DHEA; about 1200 iu of vitamin D; about 75 mg of caffeine; and about 75 g of sucromalt.

[0017] The composition described herein is a pharmaceutical composition and further comprises one or more pharmaceutically acceptable carriers or excipients. In one embodiment, the composition is formulated for immediate release, extended release, or timed release. The composition can be formulated for oral administration, topical administration, transdermal administration, mucosal administration, buccal administration and combinations thereof. The composition can be formulated in the form of a tablet, a capsule, a powder, an emulsion, a suspension, a syrup, a solution, a gel, and a patch.

[0018] As described herein, the composition is useful for preventing, inhibiting, retarding, or treating neuronal degeneration in a subject. Accordingly, provided herein are methods of using the claimed composition to prevent, inhibit, retard, or treat neuronal degeneration in a subject, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof.

[0019] Described herein is also a method of preventing, inhibiting, retarding, or treating decline in cognitive function, executive function, and/or memory in a subject, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof. In one embodiment, the subject is at risk for or is being treated for type II diabetes. In another embodiment, the subject is receiving hormone therapy. The hormone is testosterone or estrogen and can be synthetic or mammalian. The subject can have hypercholesterolemia or be at risk for developing cardiovascular disease. The subject can also have osteoporosis or osteopenia.

[0020] Described herein is a method of treating an increased risk of a cognitive function, executive function, or memory disorder in a subject, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof.

[0021] Described herein is a method of modulating, treating, inhibiting, retarding, or preventing oxidative stress in the central nervous system of a subject, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof.

[0022] Described herein is a method of promoting healthy brain aging of a subject, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof.

[0023] Described herein is a method of promoting neuronal cell dendritic arborization and synaptic long term potential, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to neuronal cells.

[0024] Described herein is a method of stimulating the production of neurotrophins and neurotransmitters, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to neuronal cells. The neurotrophins are selected from the group consisting of brain derived neurotrophic factor, nerve growth factor, and combinations thereof. The neurotransmitters are selected from the group consisting of serotonin, glutamate, acetylcholine, and combinations thereof.

[0025] Described herein is a method of inhibiting apoptosis of neuronal cells, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to neuronal cells.

[0026] Described herein is a method of inducing neurogenesis of cells, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to stem cells or progenitor cells. The cells are neural stem cells or neural progenitor cells.

[0027] Described herein is a method of inhibiting apoptosis of neuronal cells, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to neuronal cells. The method comprises promoting the expression of Bcl-2 and/or inhibiting the expression of P53 or Bax.

[0028] Described herein is a method of inhibiting the formation of amyloid plaques, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to neuronal cells expressing amyloid precursor protein (APP). The method comprises stimulating cleavage of APP via the alpha secretase pathway and inhibiting beta and gamma secretase pathways.

[0029] Described herein is a method of inhibiting the formation of neurofibrillary tangles, wherein the method com-

prises administering an effective amount of the disclosed pharmaceutical composition to neuronal cells expressing tau protein. The method comprises deacetylating the tau protein.

[0030] Described herein is a method of inhibiting activation of microglial cells, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to microglial cells. The method further comprises inhibiting secretion of inflammatory cytokines.

[0031] Described herein is a method of inducing the expression of sirtuin genes, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to neuronal cells or glial cells expressing sirtuin genes. The sirtuin gene is a SIRT1 gene.

[0032] Described herein is a method of maintaining the integrity of the blood brain barrier (BBB), wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to endothelial cells of the BBB.

[0033] Described herein is a method of facilitating glucose transport across the BBB, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to endothelial cells of the BBB.

[0034] Described herein is a method of inhibiting insulin resistance in neuronal cells, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to the neuronal cells.

[0035] Described herein is a method of inducing insulin sensitivity in neuronal cells, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to the neuronal cells.

[0036] Described herein is a method of promoting an increase in efflux of beta amyloid from neuronal cells into the blood stream, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to neuronal cells.

[0037] Described herein is a method of enhancing the bioactivity of vitamin D in neuronal cells, wherein the method comprises sequenced absorption of an effective amount of the disclosed pharmaceutical composition.

[0038] The methods described herein comprise administering an effective amount the disclosed pharmaceutical composition to cells in a subject in need thereof or in need of such treatment.

[0039] Described herein is a method of preventing, modulating, or treating mild cognitive impairment and/or Alzheimer's disease, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject diagnosed with mild cognitive impairment and/or Alzheimer's disease.

[0040] Described herein is a method for alleviating the symptoms of mild cognitive impairment and/or Alzheimer's disease, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject diagnosed with mild cognitive impairment and/or Alzheimer's disease.

[0041] Described herein is a method of preventing, retarding, or substantially inhibiting mild cognitive impairment and/or Alzheimer's disease, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject at risk of developing mild cognitive impairment and/or Alzheimer's disease.

[0042] Described herein is a method of preventing, retarding, or treating dementia, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof.

[0043] Described herein is a method of promoting an increase in efflux of beta amyloid from neuronal cells into the blood stream, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to neuronal cells.

[0044] Described herein is a method of individualizing the dosage of the disclosed composition for the promotion of brain health and treatment of cognitive dysfunction and age related dementia including mild cognitive impairment and Alzheimer's Disease, wherein the method comprises administering the disclosed pharmaceutical composition to a subject in need thereof.

[0045] Described herein is a method of measuring and/or monitoring the absorption of bioactive levels of the disclosed pharmaceutical composition, wherein the method comprises administering the composition to a subject in need thereof and measuring and/or monitoring the absorption of bioactive levels of one or more components of the composition and/or measuring and/or monitoring one or more biomarkers to determine whether an optimal level has been reached. As an example, the method can involve measuring and/or monitoring the absorption of huperzine A, DHEA, DHEA-S, testosterone, 25(OH) vitamin D, or caffeine. An optimal level may be a range of concentration or level. An optimal level indicates that the subject is receiving an effective amount of the components for promoting brain health or treatment or prevention of diseases or conditions associated with mild cognitive impairment (MCI) or Alzheimer's disease (AD). An optimal level can also indicate that the subject is receiving an effective amount of components for treatment of an adjuctive disease or condition. The adjunctive disease can be selected from the group consisting of hypercholesteremia, metabolic syndrome, type II diabetes, obesity, osteopenia, osteoporosis, hypertension, post menopausal hormone replacement therapy and combinations thereof.

[0046] Described herein is a method of measuring and monitoring the bioactive brain health protective efficacy of the disclosed pharmaceutical composition, wherein the method comprises administering the pharmaceutical composition to a subject in need thereof, and measuring and/or monitoring the bioactive brain health protective efficacy. The method comprises measuring and/or monitoring the levels of one or more biomarkers of brain function such as BDNF, NGF, AChE, ChAT, Fetuin A, inflammatory markers, markers of the Wnt/beta catenin pathway, such as Dkk-1 and combinations thereof.

[0047] Described herein is a method of treating a subject in need thereof and promoting or protecting brain health of the subject, the method comprising identifying a subject diagnosed with one or more diseases selected from the group consisting of hypercholesteremia, metabolic syndrome, type II diabetes, obesity, osteopenia, osteoporosis, hypertension and post menopausal women on hormone replacement therapy and combinations thereof, and administering an effective amount of the disclosed pharmaceutical composition to the subject to treat the one or more diseases and to protect or promote the brain health of the subject.

[0048] Described herein is a method of treating an individual with one or more of hypercholesteremia, metabolic syndrome, type II diabetes, obesity, osteopenia, osteoporosis, hypertension and post menopausal hormone replacement therapy, wherein the method comprises administering indi-

vidualized dosages of the disclosed pharmaceutical composition to a subject in need thereof in addition to the specific treatment for their primary disease.

[0049] Described herein is a method of activating alpha-secretase activity, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to cells associated with the processing of APP or to a subject in need thereof.

[0050] Described herein is a method of inhibiting beta secretase activity and/or the gamma secretase activity, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to cells associated with beta secretase activity and/or the gamma secretase activity or to a subject in need thereof.

[0051] Described herein is a method of inhibiting accumulation of beta amyloid in the brain of a subject, wherein the method comprises administering an effective amount of the disclosed composition to a subject in need thereof.

[0052] Described herein is a method of promoting efflux of soluble non-amyloidogenic amyloid precurson protein metabolites in a subject, wherein the method comprises administering an effective amount of the pharmaceutical composition to a subject in need thereof.

[0053] Described herein is a method of inhibiting phosphorylation of tau protein in a subject, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof. The subject can be a subject diagnosed with AD.

[0054] Described herein is a method of inhibiting inflammation in a subject, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof.

[0055] Described herein is a method of inhibiting cytokine levels in the brain of a subject, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof.

[0056] Described herein is a method of inhibiting oxidative stress in a subject, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof.

[0057] Described herein is a method of inhibiting neuronal apoptosis in a subject, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof.

[0058] Described herein is a method of modulating NMDA receptors in a subject, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof.

[0059] Described herein is a method of inhibiting glutamate toxicity in a subject, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof.

[0060] Described herein is a method of protecting and maintaining the blood brain barrier, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof.

[0061] Described herein is a method of neuroptorection of the brain of a subject, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof.

[0062] Described herein is a method of promoting neurogenesis in a subject, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof.

[0063] Described herein is a method of promoting expression of one or more proteins associated with neurogenesis in a subject, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof, and wherein the one or more proteins are selected from the group consisting of BDNF, NGF, BMP, Shh, Notch and combinations thereof.

[0064] Described herein is a method of activating wnt/beta catenin signaling pathway in a subject, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof.

[0065] Described herein is a method of inhibiting Dkk-1 in a subject, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof.

[0066] Described herein is a method of inhibiting GSK-3 beta antagonist in a subject, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof.

[0067] Described herein is a method of enhancing neurotransmission in a subject, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof.

[0068] Described herein is a method of stimulating acetylcholine synthesis in a subject, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof.

[0069] Described herein is a method of stimulating acetylcholine transferase activity in a subject, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof.

[0070] Described herein is a method of inhibiting cholinesterase activity in a subject, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof.

[0071] Described herein is a method of stimulating serotonin synthesis in a subject, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof.

[0072] Described herein is a method of stimulating synthesis of insulin in the brain of a subject, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof.

[0073] Described herein is a method of stimulating the wnt/beta catenin pathway in a subject, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof.

[0074] Described herein is a method of stimulating the binding of betacatenin to its receptor in a subject, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof.

[0075] Described herein is a method of stimulating the synthesis of beta catenin in a subject, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof.

[0076] Described herein is a method of stimulating synaptic transmission in a subject, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof.

[0077] Described herein is a method of inhibiting accumulation of oxygen radicals in brain of a subject, wherein the

method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof.

[0078] Described herein is a method of enhancing supply of oxygen and/or glucose to the brain of a subject, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof.

[0079] Described herein is a method of enhancing cerebral blood flow in a subject, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof.

[0080] Described herein is a method of promoting insulin sensitivity in the brain of a subject, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof.

[0081] The methods described herein can involve comparing the results of a subject at risk or diagnosed for a disease or condition with the results of a known healthy subject. Likewise, the methods of promoting, enhancing, stimulating, inhibiting, reducing, or decreasing the levels of one or more specific factors in a subject or cells can involve comparing with a control, wherein the control has a known result or is a known healthy subject, or known healthy cells.

[0082] Described herein is a method of assuring that an individual subject in need thereof has bioactive levels of the components of the disclosed pharmaceutical composition in their blood, the method comprising administering the disclosed pharmaceutical composition to the individual subject and measuring and/or monitoring the absorption of bioactive levels of the components of the disclosed pharmaceutical composition and comparing the measured and/or monitored levels of the three active components with: (1) a predetermined baseline level of each active ingredient for the individual subject; and (2) optimal bioactive levels of each active ingredient to determine if there has been a positive change in levels compared with the baseline and whether the levels fall within the optimal bioactive levels or ranges and if the results show that there has not been a positive change with respect to the baseline levels and/or the levels are not within the optimal bioactive levels or ranges, then adjusting and/or supplementing the administration of each active ingredient until a favorable change with respect to the baseline levels and/or levels or ranges within the optimal bioactive levels are achieved.

[0083] The subject can be a mammal. The mammal can be a human, a rat, a mouse, a dog, or a pig. The subject is in need of treatment or in need of the administration of the nutraceutical composition. The subject is a patient in need of treatment or in need of administration of the pharmaceutical composition. The subject can be a patient in need of maintaining hormonal balance or hormone replacement. The subject may be a male or female patient. The methods described herein can be used to treat, prevent, or monitor a male or a female subject.

[0084] As described herein lower doses are provided for promoting healthy brain aging while higher dosages are provided to the cognitively impaired, for example subjects having mild cognitive impairment or suffering from AD. The lower dosage can be formulated as a nutraceutical composition, while the higher dosage can be formulated as a pharmaceutical composition.

[0085] Described herein are methods of treating subjects at risk for developing mild cognitive impairment or AD comprising administering the disclosed composition. The methods could be combined with disease specific therapies such as for diabetes, obesity, osteopenia, osteoporosis, hypertension, cardiovascular disease and combinations thereof. Other diseases and conditions include metabolic syndrome, neuronal damage, post concussion syndrome, post traumatic stress disorder (PTSD), post traumatic brain damage, stroke, Huntington's disease, schizophrenia and combinations thereof.

[0086] Described herein is a method of treating vascular dementia, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject diagnosed with vascular dementia.

[0087] Described herein is a method of providing a balanced level of cortisol in a subject in need thereof, wherein the method comprises administering an effective amount of the disclosed pharmaceutical composition to a subject in need thereof.

[0088] Biomarkers, such as inflammatory markers or growth factors, are used to determine the absorption of the components of the disclosed composition for adjustment of the dosages as needed to aid in long term treatment of asymptomatic subjects. The increase or decrease in the presence of a particular biomarker is compared with the level of the same biomarker in a known healthy subject or a known level in a healthy subject. Examples of biomarkers include but are not limited to BDNF, NGF, acetylcholine, ChaT, AchE, Dkk1, Fetuin A, and inflammatory markers.

[0089] Described herein is a method of making the composition comprising mixing the components of the composition to form the composition.

[0090] Described herein is a kit comprising the composition, wherein the kit comprises the components in effective amounts for treatment or prevention of disease or condition or for monitoring and/or measuring the components of the composition for determining whether a subject is being effectively treated.

BRIEF DESCRIPTION OF THE DRAWINGS

[0091] FIG. 1: Neuronal Estrogen and Neurosteroids Endogenous Synthesis. The metabolic pathway for the endogenous synthesis of the estrogen and androgen sex steroids peripherally and in the brain, and their respective bioactive metabolites.

[0092] FIG. 2: Plasma huperzine A concentrations obtained after a single extended (ER) capsule etc.

[0093] FIG. 3: Predicted plasma huperzine A concentrations.

[0094] FIG. 4: Brain Aging and Pathophysiologic Changes in Molecular & Cellular pathways. An overview of the layered and multiple molecular and cellular pathways influencing brain aging, with the sites of the disclosed composition's modulating "check and balance" of individual ingredient bioactivity.

[0095] FIG. 5: Complementing Non-amyloidogenic Metabolism of APP. Complementing and "balanced" pathways stimulating the non-amyloidogenic metabolism of amyloid precursor protein by the components of the disclosed composition, with an enhanced excretion of soluble beta amyloid metabolites.

[0096] FIG. 6: Single Pathway Brain Health Modulators vs Multiple Site Activity of the Components of the Disclosed Composition: Neuronal Glucose Insulin Imbalance. Factors involved in neurodegeneration associated with brain insulin resistance, and a comparison of the single pathway modula-

tion of marketed treatments for Azlheimer's Disease compared to the multiple pathway of the disclosed composition's sites of bioactivity.

[0097] FIG. 7: Balancing the regulation of Wnt/beta catenin and Dkk1. An overview of the Wnt/beta catenin glycoprotein pathway, resulting in the binding of beta catenin to an intranuclear T-cell factor thus initiating the transcription of the brain cells target genes and function. Sites of the disclosed composition's stimulation of the Wnt signaling and its "balancing" inhibition of three Wnt inhibitors: Dkk1; GSK-3 beta; Acetylcholinesterase.

[0098] FIG. 8: Neruosteroid: Signaling Pathway

[0099] FIG. 9: Adult Neural Stem Cell Neurogenesis. Adult stem cell neurogenesis takes place throughout adult life in the subgranular zone of the hippocampal dentate gyrus, and in the subventricular zone of the lateral ventricle. These complex neural pathways are regulated by a number of integrated growth factors and neurotrophins in an environment of physiologic hypoxia. These pathways are positively modulated by the bioactivity of the disclosed composition's ingredients and additives.

DETAILED DESCRIPTION

Compositions

[0100] The present application recognizes the need to define the multiple neurologic pathways involved and to formulate combinations of natural ingredients that address and "normalize" the physiologic metabolic changes associated with brain aging per se from that of an underlying latent neurologic disease. Successful management requires viable neurons, and thus the need for early recognition (health promotion) and treatment (disease prevention) of the underlying disorder.

[0101] The present application applies the bioactivity of its combined ingredients to a number of established and interrelated molecular pathways that govern the function of the aging mammalian brain thus promoting both healthy brain aging and the prevention and/or inhibition of neurodegenerative conditions and certain neuropsychiatric disorders, with special application to cognitive, memory and mood dysfunction.

[0102] Huperzine has been reported to have selective and long-term inhibition of brain AChE with few side effects (Tang, Acta Pharmacol. Sinica 17:481 (1996)).

[0103] The present application provides compositions comprising Huperzine A or a derivative or analog thereof, a DHEA, and a vitamin D. The composition can include additives. The composition can be a pharmaceutical composition or a nutraceutical composition. The present application provides methods of administering to a subject or promoting brain health and/or preventing neurodegnerative conditions. The subject is a patient in need of treatment or in need of administration of the pharmaceutical composition such as, for example, a subject exhibiting one or more symptoms associated with brain aging, a neurodegenerative condition and/or a neuropsychotic disorder.

[0104] Described herein are methods of treating subjects in need thereof or in need of treatment, wherein the disclosed compositions are administered to the subject once daily or twice daily. In one embodiment, the disclosed compositions are administered twice daily for immediate release. In another embodiment, the disclosed compositions are administered once daily for extended release.

[0105] The components of the disclosed compositions can be provided, for example, in amounts and/or in a sequence or order to act synergistically to provide enhanced effects. The effects can be therapeutic and enhanced as compared to a composition consisting essentially of Huperazine A. The effects are enhanced about two times, about five times, about 10 times, about 20 times, or more as compared to a control composition consisting essentially of Huperazine A and DHEA.

[0106] The components of the disclosed composition can be a natural or endogenous product or a synthetic product or combinations thereof.

[0107] Provided herein are compositions comprising a combination of botanicals and natural compounds, each of which have validated and experimentally proven biologic efficacy in improving and/or modulating relevant physiologic metabolic pathways associated with the recognized alteration in memory, cognitive and executive function in aging adults. The composition and formulation disclosed herein addresses the optimization of normal "healthy" brain aging (health promotion) and also changes associated with "unhealthy" brain aging including: subjects with pre-existing risk factors for cognitive and related dysfunction and those who are predisposed to or have early evidence and/or symptoms of the pathologic features associated with mild cognitive impairment and Alzheimer's Disease (prevention).

[0108] The disclosed composition and formulation can also be provided as a nutraceutical complement for use together with marketed drug therapy for cognitive dysfunction and memory loss and as an adjunct with drugs used to treat conditions that are recognized risk factors for AD. This includes drugs for the treatment of type II diabetes, hormonal therapy for post menopausal women, lipid lowering drugs for hypercholesteremia and for obesity, drugs for treatment of the metabolic syndrome, drugs for treating osteoporosis and combinations thereof.

[0109] The composition described herein comprises a core of three ingredients: a blend of huperzine A; DHEA and vitamin D, such as vitamin D3 (1,25-(OH)2 D3). Each have similar and/or complementing efficacy on the cellular physiology, function and neurologic pathways relative to memory, cognition and executive function. The composition disclosed herein is a broad based balanced bioactive brain blend (BBBBB™) and also referred to as CogniHomme Forte.

[0110] Moreover, one or more additives can be added to the disclosed composition to form a "blend" to address specific medical conditions and/or clinical preference and/or choice of consumption. Examples of two additives are: caffeine and sucromalt (Cargill, Xtend®)—a nutritive low-glycaemic sweetener.

[0111] Exemplary combinations are formulated to take account of their individualized and combined pharmacokinetic and phamacodynamic profiles and are adjusted to meet the clinical intent of promoting brain health and/or preventing cognitive and related neurologic dysfunction. Exemplary embodiments provide combination products with additive, synergistic and/or complementary function. The latter addresses both sides of the "checks and balance" associated with many biologic functions. For example, Huperzine A prevents the breakdown of acetylcholine.

Huperzine A

[0112] The composition described herein comprises Huperzine A. The Huperzine A can be an analog and deriva-

tive thereof. The Huperzine A, including its analogs and derivatives thereof, can be a synthetic molecule. Huperzine A (HupA) is a well-described and researched natural cholinesterase inhibitor (Wang et al). HupA inhibits acetylcholinesterase (AChE) in the cerebral cortex and importantly in the hippocampus. Acetylcholine synthesis is markedly reduced in AD (Wang et al).

[0113] Huperzine A is a novel Lycopodium alkaloid that was first isolated from the Huperzia Serrata Trev and Chinese folk herb Qian Cheng Ta. It is a potent and selective brain AChE inhibitor with greater potency and fewer side effects than other currently-available AChE inhibitors. The lack of systemic side effects is attributed to HupA's negative effect on the systemic acetylcholinesterase inhibitor, butyrylcholinesterase (BuChE).

[0114] Although HupA is unable to retard neurodegeneration in patients with established AD, it does have properties that stimulate neurogenesis; provide neuroprotection; stimulate neurotransmission and most importantly regulate beta amyloid precursor protein (APP) metabolism and in so doing lessen the accumulation of both beta amyloid plaques and tau neurofibrillary tangles. The key to HupA's protective potential is its early use, so that viable and responsive neurons are still available to respond both to and with other co-administered neuroprotecting compounds.

[0115] Neurotransmitter Activity: HupA produces a more prolonged increase in ACh when compared with all other cholinesterase inhibitors. Although there is a regional variation, the maximal increase occurs in areas associated with memory and cognition: frontal and parietal cortex and the hippocampus. The time course of cortical AChE inhibition with HupA mirrors the increase in ACh at the same dose, thus confirming that the increase in extracellular ACh is primarily due to the inhibition of cortical AChE.

[0116] Brain norepinephrine (NE) and dopamine (DA) levels are also increased following systemic administration of HupA but not serotonin (5-HT). The effect is greater for DA than it is for NE. It is postulated that the effect of HupA on DA and NE is regulated by presynaptic ACh muscarinic and/or nicotinic receptors, thus contributing to the memory improvement following treatment with HupA (Wang 2006). Protection against glutamate—induced cytotoxicity: HupA protects against glutamate induced cytotoxicity. This was demonstrated in rat hippocampal neuronal cells. In a dose dependent manner, HupA acted as a non-competitive and reversible inhibitor of the NMDA receptors, via a competitive interaction with polyamine binding sites (Zhang and Hu 2001).

[0117] Neuroprotection: Plaques characteristic of AD are caused by the deposition of beta amyloid and are typical of lesions found in the brains of patients with AD. This process is initiated in part by oxygen radicals that lead to neurodegeneration. HupA protects against H2O2 by increasing antioxidant enzymes (Zhang et al 2002); HupA protects against cellular damage when exposed to oxygen—glucose deprivation (OGD) by alleviating the disturbances of oxidative and energy metabolism (Zhou et al 2001); HupA reduces oxygen free radicals in both animal experiments and clinical trials (Shang et al); HupA provides neuroprotection by modulating the intracellular Ca++ level including the transcription of calmodulin in hippocampal neurons (Lu et al 2004); decreasing apoptosis of neural cells after exposure to stressors such as H2O2; beta amyloid peptides and OGD are significantly reduced following administration of HupA and with the normalization of the anti-apoptopic Bcl-2 genes with attenuation of the pro-apoptopic Bax and P53 genes (Xiao et al 2002; Wang 2006); finally, HupA protects mitochondrial activity. In summary, the neuroprotective effect of HupA is achieved via multiple mechanisms.

[0118] Neurogenesis: The regulation of nerve growth factor (NGF) synthesis and its release is governed via cholinergic mechanisms. HupA increases the NGF regulated enhancement of neuron survival and function probably via its inhibition of AChE, as shown by the associated neurite outgrowth with the level of AChE expression (Tang et al 2005). NGF and its TrkA receptor mediate the neuroprotective actions of HupA (Wang et al 2006).

[0119] Amyloid Precursor Protein Processing: Beta amyloid is derived from a larger polypeptide amyloid precursor protein (APP). There are two pathways for the processing of APP: a non-amyloidogenic end point which is modulated via a SIRT1 directed gene encoding alpha secretase pathway. This cleaves the APP away from the toxic beta amyloid peptide and also reduces tangle formation by deacetylating tau. Metabolism via the beta and gamma pathways has the reverse effect: an increase in both extracellular beta amyloid neuronal plaque formation and intracellular tau tangles (Guerente 2011). HupA directs APP metabolism toward the non-amyloidogenic alpha secretase pathway (Peng et al 2007).

[0120] Pharmacokinetics: HupA is rapidly absorbed, is widely distributed in the body and is eliminated at a moderate rate. The elimination of HupA in elderly volunteers is slightly lower than that in the younger subjects. The definitive pK study for HupA was published in 2008 (Li et al 2008). Healthy subjects received 0.2 mg of pure huperzine A orally. Plasma levels rose rapidly after administration peaking at about hour 1.2 to 1.3. The plasma levels declined rapidly over the next 24 hours and a terminal half life of approximately 6 hours was determined. Over the major part of the day plasma levels ranged from 0.3 to about 1.0 ng/ml where 0.6 ng/ml was determined to be the optimal level. Values above this concentration produce unnecessary exposure of tissues to brief high levels of huperzine and an increased loss due to excretion. Doses of 0.15 mg twice daily have been shown to be effective for the treatment of MCI (Du et al 1996).

[0121] Based on the above data, a controlled-release formulation of HupA would be required for a once a day administration.

[0122] Clinical Studies: The efficacy and safety of HupA have been studied in a number of clinical trials, principally in China and some in the US (Wang et al 2006; Little et al 2008). Most of the studies were conducted in patients with established AD. In one of the larger trials involving some 819 patients with AD, treatment with HupA in a dose of 0.03-0.4 mg/day resulted in an improvement of their memory, cognitive skills and activities of daily living. Another double blinded randomized clinical trial evaluated patients with possible or probable AD taking 0.1-0.2 mg of HupA twice daily. Cognitive function was measured with the MMSE (Minimental State Examination Scale), the ADAS-Cog (Alzheimer's Disease Assessment Scale-Cognitive Subscale), the ADAS-non-Cog (which measures mood and behavior and activities of daily living (ADL). All showed significant improvement at week 6 and further improvement at week 12. The proportion of patients with a four point improvement on the ADA Scog was 56% in the active group and 12.5% in the placebo group (Zang et al 2002).

[0123] A longer term study extending over 48 weeks confirmed significant improvement in cognition at all time points (Wang et al 2006).

[0124] There have been fewer studies in the US (Little et al 2008). As with the trials in China, the use of HupA (in doses as high as 200 mcg b.i.d. and even 400 mcg b.i.d.) confirmed its ability to be pharmacologically effective (inhibiting AChE levels in all tested subjects by 50% or more without any significant BuChE inhibition) and clinically safe. However, the reported clinical improvement was not as robust as that noted in Chinese literature.

[0125] Summary: The mixed HupA clinical trial results may be due to differences in the populations studied and to the presence and extent of existing neurologic damage in the chosen test subjects. HupA cannot reverse the function of significantly damaged neurons, characteristic of patients with well defined clinical AD.

[0126] Given HupA's broad range of experimentally proven brain protective mechanisms, the composition described herein is designed to be used in subjects with functionally responsive neurons. This includes subjects who are asymptomatic and otherwise healthy, subjects with cognitive and memory complaints. The subjects can be at risk factors for AD and symptoms of early MCI. In each instance, formulations will include additional bioactive brain health promoting compounds and the doses of each adjusted according to the clinical indication for the use of the disclosed composition and according to individual patient's response.

DHEA

[0127] The composition described herein comprises DHEA, including natural and synthetic derivatives or analogs thereof, in addition to HupA. The DHEA includes, but is not limited to, dehydroepiandrosterone sulfate (DHEA-S), 17-α-derivatives, 17-β-derivatives, 17-spiro analogs of DHEA, and combinations thereof.

[0128] Brain Neurosteroids: DHEA Synthesis, Neuroprotection and Neurogenesis

[0129] Synthesis: Neurons and glial cells in the CNS express the enzymes needed for the local synthesis of neurosteroids (Baulieu et al 2001). The synthesis of brain neurosteroids decreases with age, stress and as a result of chronic inflammatory and neurodegenerative diseases, including AD.

[0130] Dehydotepiandrosterone (DHEA) and its sulfated derivative (DHEA-S) are the most abundant circulating steroid hormones in humans (Traish et al 2011) with a number of established physiologic functions including its local production in the brain. (Charalampopoulos et al 2008). As summarized in FIG. 1, DHEA synthesis is derived from the parent cholesterol molecule and is then regulated by a number of rate limiting reactions including P450ssc 17 (side chain cleavage at carbon 17) CYP11A1 and CYP 17 (17-alpha-hydroxylase) enzymes that convert pregnenolone to DHEA and via hepatic sulfotransferase activity to DHEA-S.

[0131] DHEA-S is more stable with a longer half life than DHEA, and can be rapidly hydrolyzed back to DHEA by sulfatases in response to metabolic demand. DHEA can also be transformed by 3 beta-hydroxysteroid dehydrogenase (3 beta-HSD) to androstenedione and via 5 alpha reducatse activity to DHT (the most potent androgen) or via aromatase and 17 beta hydroxysteroid dehydrogenase (17-beta HSD) to either testosterone or estradiol. (See FIG. 1). More recently, the metabolic derivatives of DHEA have been shown to be critical in modulating the physiological functions of DHEA, via both its receptor and non-receptor mechanisms. The CNS production of DHEA is independent of that formed systemically, and is present in a concentration 6-8 times higher than that in blood (Baulieu and Robel 1998).

[0132] Neurosteroid metabolites may also be synthesized in the CNS from systemic steroid precursors that are directly transported through the BBB (blood brain barrier) from the periphery (Kancheva et al 2011).

[0133] Additional to its action via direct DHEA receptors, the androgen and estrogen metabolites of DHEA also exert bioactivity, as do the 17 alpha and 17 beta derivatives of DHEA, which are active through their identified receptors. These derivatives have an important role in attenuating inflammatory processes (Niro et al 2010).

[0134] Apoptosis: A major physiologic function of the neurosteroids is the prevention of neuronal cell death (apoptosis), the end point of several neurodegenerative diseases including AD. DHEA protects against apoptosis in the CNS through multiple pathways: by antagonizing the NMDA (N-methyl-D-aspartic acid) receptors, DHEA modulates the glutamate neurotransmitter thereby preventing the excess influx of Ca++ into the neuron and the triggering of NMDA induced toxicity. This has been shown to be protective of hippocampal CA1/2 neurons (Kimonides et al 1998); DHEA modulates the protective GABAa (aminobutric acid) receptors and so pro-apoptotic effectors such as cytochrome C and Bax. (Waters et al 1997); both DHEA and DHEA-S bind to other anti-apoptotic membrane binding sites principally due to their metabolized products. DHEA activates the pro-survival anti-apoptotic genes, Bcl-2 and suppresses the pro-apoptotic proteins caspase-3 and Bax; by binding to the same membrane sites as glucocorticoids and testosterone, DHEA blocks the negative effect of an excess of these two steroids, a situation that may be exacerbated by the simultaneous age related lowering of brain DHEA levels and increase in CSF cortisol levels. (Charalampopoulos et al 2006; Swaab et al 1994). Finally, DHEA has anti-oxidant, anti-lipid-peroxidative and anti-inflammatory actions (Kumar et al 2008; Aly et al 2011).

[0135] Neurotrophic Effects: DHEA exerts its neurotrophic effects by regulating a number of downstream signaling pathways: thus DHEA reacts directly with the TrkA membrane receptors of nerve growth factor (Lazaridis et al 2011; Gravanis et al 2012); increases BDNF and acetylcholine levels; potentiates the synaptic transmission and plasticity in the hippocampal dentate gyrus, and increases axonal spine density with a resultant improvement in cognition (Hajszan et al 2007; Xu et al 2012; Janowsky 2006).

Vitamin D.

[0136] The disclosed composition comprises vitamin D in addition to Huperazine A and DHEA. Examples of vitamin D includes but are not limited to calcitriol, doxercalciferol, paricalcitol, cholecalciferol (vitamin D3), ergocalciferol (vitamin D2), analogs and derivatives thereof, Vitamin D receptor agonists and modulators, and combinations thereof. Vitamin D is a neurosteroid with a defined role in brain function and in various neurological disorders including cognitive decline (Stewart et al 2010; Harms et al 2011). The vitamin D may be a natural or endogenous molecule, or a synthetic molecule.

[0137] Vitamin D receptor modulators that have disease specific actions relevant to brain health and to risk factors associated with cognitive impairment eg VS-105, a vitamin D receptor modulator with cardiovascular protective effects (Wu-Wong J R, Kawai M, Chen Y-W, Nakane M. VS-105: a

novel vitamin D receptor modulator with cardiovascular protective effects. British J Pharmacol 2011; 164: 551-560).

[0138] Similarly, there are a number of new analogs of 1 alpha, 25 (OH)2 D3 (AVD) that have been developed based on their crystal structure with various/differing functional profiles (Carlberg C, Molnar F, Mourino A. Vitamin D receptor ligands: the impact of crystal structures. Expert Opin Ther Pat 2012; 22: 417-435).

[0139] Although traditionally regarded as a "vitamin" synthesized in skin from precursor substrates (7-dehydrocholesterol) and from certain vitamin D rich foods, it is now well established that vitamin D is a member of the super family of nuclear steroid transcription regulators, with vitamin D receptors (VDR) present in most—if not all—tissues and organs.

[0140] The two way bioconversion of the biologically inert substrate—7 dehydrocholesterol—into active vitamin D3 is mediated by a two step activation involving Vitamin D3, 25-hydroxylase enzyme, and the 25-hydroxyvitamin D3-1 alpha-hydroxylase enzymes. Both of these enzyme systems are localized in the brain confirming that the brain activates the vitamin D precursor directly and is not dependent on the plasma levels of 1,25-(OH)2D3 (active vitamin D3-AVD3). This enzymatic bioconversion has been demonstrated in cells essential for cognition and memory including neurons, glial cells, and activated microglial cells. The nuclear functions of the AVD3 are mediated through the expression of the VDR in relevant anatomical areas of the brain: frontal cortex, temporal frontal lobes and hippocampus (Garcion et al 2002).

Genomics of the VDR and Vitamin D Metabolism:

[0141] VDR: The VDR is the mediator of its natural ligand—AVD3—and the latter's multiple cellular growth and differentiating effects. The gene encoding the VDR has several polymorphism that determine its tissue level activity. The longer protein (ff allele) is a less active transcriptional activator than the FF genotype. This translates into the varying efficacy of vitamin D activity in tissues such as muscle, bone and breast tissue and therefore the level of vitamin D supplementation required by individuals (depending on their genotype) for "normal" organ function (Chen et al 2005). This may have similar implications for brain function.

Balanced AVD3 Metabolism: Synthesis (Formation) and Catabolism (Breakdown).

[0142] There are two enzymes of the cytochrome -P450-hydroxylase family that are responsible for the synthesis of vitamin D (25-D3-1 alpha-hydroxylase) and its catabolism (1,25-D3-24-hydroxylase). The respective genes encoding these enzymes are CYP27B1 and CYP24. The balance between the two determines AVD3's ultimate cellular activity.

Age and Vitamin D Metabolism:

[0143] Although the ability to absorb vitamin D is not altered by aging, its metabolism from sun light exposure to skin is reduced by about 50% from age 20 to 80 years (Holick 2006). Since vitamin D deficiency is strongly correlated with cognitive impairment in the elderly (see later), age adjusted supplemental doses of vitamin D is a necessary to meet the brain's physiologic needs.

Neuroprotection.

[0144] AVD3 regulates the synthesis of nerve growth factor (NGF) (Neveu et al 1994 (a); Cornet et al 1998) and up regulates the synthesis of other neurotrophins: neurotrophin3 (NT3) (Neveu et al 1994 (b)) and glial cell line derived neurotrophic factor (GDNF) (Naveilhan et al 1996). Stimulation of these neurotrophins has been correlated with a neuroprotective effect (Wang et al 2000).

[0145] AVD3 modulates neuronal Ca++ homeostatsis by down regulating calcium channels in hippocampal neurons and hence excess excitotoxic insults; AVD3 also modulates calcium activity by

[0146] Inducing the synthesis of Ca++ binding proteins (Brewer et al 2001).

[0147] AVD3 inhibits the synthesis of inducible nitric oxide synthase (iNOS). The latter produces NO with the potential to damage both neurons and oligodendrocytes when produced at high levels (Garcion et al 1998; Dawson et al 1996).

[0148] By increasing the expression of gamma-glutamyl transpeptidase activity, AVD3 protects the glutathione cycle cross talk between neurons and astrocytes.

[0149] The astrocytes anchor neurons to their blood supply, regulate the neuronal chemical environment and recycle synaptic neurotransmitters. They also contribute to the integrity of the BBB (Dringen et al 2000).

[0150] Neurotransmission: AVD3 increases choline acetyltransferase (AChE) and hence an increase in brain acetylcholine (ACh) synthesis (Sonnenberg et al 1986).

[0151] Down-regulation of microglial activation: Activated microglia play a key role in chronic neurodegenerative disorders. When activated—by the death of neighboring neurons—the microglia promote further death and dysfunction by attacking other neurons and astrocytes. This results from the excess generation of NADPH—a potent generator of superoxide. When combined with nitric oxide, neuronal cells are sensitized to excessive levels of intracellular calcium and glutamate mediated excitotoxicity, resulting in the inability of astrocytes to sequester and metabolize the glutamate with subsequent apoptosis of neurons (McCarty 2006).

[0152] Activated microglia also produce a range of inflammatory cytokines including cyclooxygenase (COX-2), that further potentiates the neurons sensitivity to glutamate induced death. The cytokines from activated microglia stimulate the neuronal production of beta amyloid precursor protein (beta APP), and its conversion to beta Amyloid (Ge et al 2002).

[0153] The proportion of activated microglia increases as a function of age, and is one factor that explains why chronic neurodegenerative disorders are more common in the elderly (Rozovsky et al 1998).

[0154] Microglial cells express the vitamin D receptor with a resultant inhibition of iNOS synthesis and other activating agonists. AVD3 also boosts astrocyte production of glial-derived neurotrophic factor (GDNF) offering another protective mechanism. Dietary doses of AVD3 attenuate microglia activation (Wergeland y et al 2011).

[0155] ABC Efflux Transporters and The Blood Brain Barrier (BBB): ATP—binding cassette (ABC) transporters at the BBB are important contributors to the pathogenesis of CNS disorders (Hartz, Bauer 2010). P-glycoprotein, an ATP driven drug efflux transporter is a critical element of the BBB (Miller et al 2006). VDR activation up-regulates P-glycoprotein in the brain capillaries of rat and human brain microvascular

endothelia (Durk et al 2012) and may account for the experimental observation that AVD3 enhances the brain to blood efflux of beta Amyloid (1-40) through both genomic and non genomic pathways (Ito et al 2011) and also the AVD3 stimulated phagocytosis and clearance of beta Amyloid from the macrophages of patients with AD (Masoumi et al 2009).

Vitamin D and Insulin Resistance

[0156] Pancreatic beta cells express specific cytosolic/nuclear and membrane VDR's. Vitamin D deficiency—at levels below 25 nmol/L—have been linked to an increased prevalence of various metabolic disorders including type I and type II diabetes (Ross et al 2011). Conversely, a meta analysis showed a significant 55% reduction in diabetes and a 51% decrease in the metabolic syndrome (Parker et al 2010) with high serum concentrations of 25 hydroxy vitamin D.

[0157] Factors that affect insulin release and resultant insulin resistance include vitamin D associated gene polymorphism involving vitamin D production, transport and action; as a modifiable environmental factor in autoimmune disease (type I diabetes) and through its immunoregulatory function that protects pancreatic beta cells via its anti-inflammatory actions (Sung et al 2012). In addition, there is evidence that vitamin D may stimulate insulin secretion directly, provided calcium levels are adequate (Tai et al 2008). Vitamin D binds directly to the beta cell VDR, and by stimulating insulin receptor expression, enhances insulin responsiveness for glucose transport (Maestro et al 2000). Vitamin D increases bioconversion of pro-insulin which is inactive to bioactive insulin.

[0158] Clinical data regarding the benefit of vitamin D supplementation is sparse, but relevant to the multiple pathway approach to health promotion as provided herein, vitamin D has been shown to reduce free fatty acids—an important and common association with peripheral insulin resistance (Inomata et al 1986).

[0159] The optimal vitamin D concentration for reducing insulin resistance has been shown to range between 80 to 119 nmol/L (Takiishi et al 2010).

[0160] Pharmacokinetics: The pharmacokinetics of vitamin D—a fat soluble and stored hormone—is complex. In short, concentrations of serum 25(OH) after intake of vitamin D3 is biphasic: a rapid increase occurs at low vitamin D3 levels and a slower response at higher concentrations. At typical vitamin D3 dosing, there is a rapid and near quantitative conversion to 25(OH) D which then serves as both the functional status indicator of the nutrient and as its major storage form in the body. At a vitamin D3 concentration—equivalent to a daily input of 2000 IU—the 25 hydroxylase activity becomes saturated and the reaction switches from first to zero order. The constant maximal production of 25(OH)D—irrespective of the precursor concentration of vitamin D3—is probably in excess of metabolic consumption, and is the reason why serum 25(OH)D levels continue to rise as the vitamin D3 dose increases. Based on this explanation, the point at which hepatic 25(OH)D production reaches zero order, constitutes the low end of normal vitamin D status: this has been calculated to be 88 nmol/L and is consistent with the plasma serum levels required for optimal calcium absorption and normal parathyroid hormone homeostasis (Heaney et al 2008).

[0161] Epidemiology: numerous population studies have confirmed the relationship between low levels of vitamin D (hypovitaminosis D) and cognitive decline, with reduced executive function and reasoning, in the elderly. This appears to be a universal problem irrespective of the society, race and to a certain extent, the geographic location. Most of the published studies involve women 65 years and older and include subjects from the US (Llewellyn et al 2011), Italy (Llwellyn et al 2010), France (Annweiler et al 2010), England (Llwellyn 2008) including one study that compared African American women with a similar aged cohort of European Americans over age 55 years. The former had significantly lower levels of 25 (OH)D with decreased cognitive performance (Wilkens et al 2009).

[0162] Women with vitamin D (25 (OH) D) values less than 50 nmol/L were more likely to have cognitive impairment compared to cohorts with values above 75 nmol/L; plasma 25 (OH) D levels below 25 nmol/L was associated with 40 to 60% or greater risk of cognitive dysfunction.

[0163] A recent analysis of 37 studies suggested that values less than 50 nmol/L was associated with poorer cognitive function, and a greater risk of AD (Balion et al 2012).

Clinical Evidence: Randomized Clinical Trials Vs Applied Translational Medicine.

[0164] Vitamin D has an important physiologic role in promoting and maintaining brain health via validated metabolic pathways. The functional effect of vitamin D is complementary and/or additive to the other ingredients of the disclosed composition. These include: factors preventing neurodegeneration; the regulation of neurotrophins (BDNF; NGF); enhancement of acetylcholine neurotransmitter function, insulin sensitivity, BBB protection and the clearance of amyloid beta peptide.

[0165] The mechanism(s) underlying the cognitive changes associated with "normal" aging—including the pathogenesis of MCI and AD—are multiple, heterogeneous and evolve over decades of "silent" change appropriately.

[0166] It is therefore highly unlikely that a meaningful blinded randomized vitamin D alone study, will ever meet statistical power and be affordable (Annweiler and Beauchet 2011).

[0167] Instead, reliance will need to be placed on surrogate biomarkers that confirm levels of vitamin D consistent with a known brain health effect. These are described below.

Additives

[0168] The compositions and pharmaceutical compositions disclosed herein may comprise one or more additives. Examples of additives include but are not limited to coffee, xanthine alkaloids, chlorogenic acid, and sweeteners. Examples of xanthine alkaloids include but are not limited to caffeine, theobromine, and paraxanthine. Examples of sweetener includes low glycemic sweetener selected from the group consisting of sucromalt, tagatose, isomalt, sucralose, acesulfame potassium, analogs and derivatives thereof, and combinations thereof.

[0169] Caffeine: Caffeine is a xanthene alkaloid extracted from the seed of the coffee plant. It functions as a central nervous system stimulant. Caffeine is typically used to increase wakefulness, faster and clearer thought and to combat drowsiness. Caffeine is thus a naturally occurring cognitive enhancer (Simons et al 2011) and its long term use correlated with an increase in cognitive ability and memory in later life (Corley et al 2010), a reduced risk of cognitive decline and risk in midlife (Eskelinen et al 2009) and—given

the heterogeneity of results inherent in epidemiologic studies—a lowered prevalence of dementia and AD (Eskelinen and Kivipelto 2010; Santos et al 2010 (a)). This benefit of caffeine is associated with an average daily consumption of 3 to 5 cups of coffee a day and is more likely to be found in women than in men (Santos et al 2010 (b); Arab et al 2011).

[0170] Caffeine inhibits adenosine (Simons et al 2011). Adenosine is found in all tissues, and in the central nervous system, suppresses neurotransmitter activity. By antagonizing adenosine, caffeine increases the activity of acetylcholine, epinephrine, dopamine, serotonin, norepinephrine and glutamate.

[0171] Caffeine also inhibits acetylcholinesterase (Karadishem et al 1991). Through this mechanism, caffeine has—in addition to its enhancing effect on ACh cognitive mediated function—been shown to counteract the cumulative burden of anticholinergic medications commonly used by the elderly (Nebes et al 2011).

[0172] Brain Derived Neurotrophic Factor (BDNF): Long-term potentiation (LTP) modulates synaptic plasticity and is widely accepted as one of the initial events needed for memory encoding. LTP is impaired with aging and also in AD. BDNF regulates this synaptic plasticity in the adult brain (Diogenes et al. 2011).

[0173] Caffeine increases hippocampal BDNF by modulating adenosine receptors and with chronic usage stimulates the conversion of proBDNF to mature BDNF (Sallaberry et al 2013); caffeine reverses the decrease in hippocampal BDNF noted in high fat fed animals. High fat diets, obesity and resulting type 2 diabetes, are recognized risk factors for AD (Moy and McNay 2012); caffeine freely crosses the blood-brain—barrier and in so doing promotes an increase in the length, branching and density of basal dendrites in hippocampal neurons (Vila-Luna et al 2012) and via an associated increase in BDNF synthesis, prevents the stress related reduction in synaptic long-term potentiation (LTP). The latter function is key to maintenance of long term memory (Alzoubi et al 2013).

[0174] Neurodegeneration: Caffeine, by modulating the antioxidant system in the brain prevents the age associated decline in cognitive function (Abreu et al 2011); in addition, caffeine shifts the balance between neurodegeneration and neuronal survival by stimulating pro-survival cascades and inhibition of proapoptotic pathways in the cerebral cortex (Zeitlin et al 2011).

[0175] Reducing the brain beta amyloid load: A number of animal experiments have demonstrated that caffeine decreases brain amyloid and improves the cognitive impairment associated with AD. Three main mechanisms were identified:

[0176] A decrease in the synthesis of beta amyloid from APP via the suppression of the beta-secretase and gamma-secretase expression. In one study involving AD in transgenic mice, the deposition of beta amyloid was reduced by 40% in the hipocampus and 46% in the entorhinal cortex (Arendash et al 2009). This results from caffeine itself—in a dose equivalent to 5 cups of coffee—and not the metabolites of caffeine (Arendash and Cao 2010). Although treatment with other beta and gamma—secretase inhibitors also reduced APP induced damage, caffeine was the most promising therapeutic intervention in both APP and tau-induced AD models (Stoppelkamp et al 2011).

[0177] Enhanced Brain Amyloid Clearance: caffeine up regulates the low density lipoprotein receptor related protein (LRP1) and the P-glycoprotein (P-gp) at the BBB. This is associated with an enhanced efflux of beta amyloid from the brain with an increase in the brain efflux index of 80% (Qosa et al 2012).

[0178] Facilitating CSF Production and Turnover: Compromised function of the choroid plexus and defective CSF production and turnover has been associated with a diminished clearance of beta amyloid and may be one mechanism implicated in the pathogenesis of late onset AD (Wostyn et al 2011). Caffeine increases CSF production together with an increased expression of Na+-K+-ATPase and an increased cerebral blood flow. This is a result of caffeine's inhibition of the A1 adenosine receptors in the choroid plexus and its negative regulation of Na+-K+ATPase (Han et al 2009).

[0179] Increasing Insulin Sensitivity: Although the role of caffeine consumption on insulin action is still being debated, recent animal studies (Guarino et al 2012) and a large scale clinical study that included 954 multi-ethnic non-diabetic adults (Loopstra-Masters et al 2010) have confirmed that the chronic use of caffeine was associated with a decrease in age related insulin resistance via mechanisms involving beta cell function (enhanced bioconversion of proinsulin to insulin), by decreasing the production of non-esterified fatty acids (which increase peripheral insulin resistance) and by enhancing Glut 4 expression in skeletal muscle.

Relevant Clinical Outcomes:

[0180] Utilizing functional MRI (fMRI) testing, caffeine was shown to have a modulating effect on the brain regions—medial frontopolar and anterior cingulated cortex—associated with attention and executive functions (Koppelstaetter et al 2010).

[0181] Caffeine plus glucose: a double blind randomized study indicated that there is synergistic effect on sustained attention and verbal memory, when 75 mg of caffeine was combined with 75 g glucose (Adan and Serra-Grabulosa 2010).

[0182] Glucose energy drinks (Red Bull) combined with caffeine, have shown improvements in reaction times and a decrease in mental fatigue (Howard and Marczinski 2010).

Metabolism and Pharmacokinetics.

[0183] Caffeine is absorbed by the small intestine within 45 minutes of ingestion and is then distributed throughout all tissues of the body (Liguori et al 1997). Peak blood levels are reached within one hour, and subsequently eliminated via first order kinetics (Newton et al 1981; Lelo et al 1986). The half life of caffeine —the time taken to eliminate one half of the total amount of caffeine—is about 4 to 6 hours (Newton et al; Lelo et al 1986).

[0184] Caffeine is metabolized by the liver's cytochrome P450 oxidase enzyme system into three metabolic and functional dimethylxanthines: Paraxanthine (84%); Theobromine (12%) and Theophylline (4%). Paraxanthine increases lipolysis and may lead to increased glycerol and free fatty acid blood levels; theobromine dilates blood vessels and increases urine volume; theophylline relaxes the smooth muscle of the bronchi, and in much higher concentrations is used to treat asthma.

[0185] Both caffeine and its major metabolite—paraxanthine—can be quantified and their systemic levels monitored in blood, plasma or serum (Klebanoff et al 1998).

Natural Glucagon-Like Peptide-1 (GLP-1) Secretagogues

[0186] Sweeteners have been reported to enhance the release of GLP-1. GLP-1 has two main physiologic properties that are of relevance to the disclosed subject matter: stimulation of insulin secretion and enhancement of its peripheral tissue sensitivity; function as a neuroprotective peptide.

[0187] Glucagon-like peptide 1: The major source of GLP-1 is the ileal intestinal L cell that secretes GLP-1 as a gut hormone. It is the product of the proglucagon gene that is selectively cleaved into its biologically active form. GLP-1 and its receptor GLP-1R is also found in the pancreas (Hoist 2007). The GLP-1Rs have been identified throughout the CNS with binding sites present on glia and neuronal cells (Chowen et al 1999; Iwai et al 2006).

[0188] GLP-1 is an incretin and responds to nutrients in the lumen of the small intestine. The agents that stimulate its secretion—secretagogues—include nutrients such as carbohydrates, proteins and lipids. GLP-1 enhances the sensitivity of the pancreactic beta cells to glucose by increasing the expression of GLUT2. GLP-1 has a half life of only 2 minutes due to its rapid degradation by dipeptidyl peptidase IV (Thum et al 2002). It is an important anti-hyperglycemic hormone as it induces both glucose-dependent insulin secretion and the suppression of glucagon secretion. GLP-1 does not stimulate insulin when the plasma glucose levels are in a normal fasting range (Koole et al 2013).

[0189] GLP-1 and GLP-1R regulate the differentiation of pancreatic progenitor cells and stimulate beta cell mass (Harkavyi and Whitton 2010; Yabe and Seimo 2011). The GLP-1R has a well accepted role as an anti-apoptotic agent by negating or reducing the pro-apoptotic actions of peroxides including exposure to reactive oxygen species (ROS), cytokines and fatty acids (Li et al 2003). In addition, GLP-1 increases the expression of anti-apoptotic genes such as Bcl2 and Bclxl (Buteau et al 2004).

[0190] GLP-1 as a neuroprotective peptide: Evidence for the CNS effect of GLP-1 was originally based on its central control of satiety (Gunn et al 1996). As reviewed recently (Holscher 2012; Salcedo et al 2012) it has now been clearly established (in pre-clinical studies) that GLP-1 crosses the BBB and prevents neurodegeneration including preservation of memory function in AD and motor activity in PD. This is probably due to a number of processes: protection of synaptic activity and function; NGF-like induced neurogenesis (Perry et al 2002); reduced apoptosis; protection from oxidative stress; and possibly, the increased CNS effect of GLP-1 mediated insulin sensitivity. Insulin acts as a growth factor in the brain and supports neuronal repair, dendritic sprouting, synaptogenesis and negation of oxidative stress (Holscher 2012). Cell culture studies have shown that GLP-1R agonists protect neurons against beta amyloid and glutamate induced apoptotsis by modifying the processing of APP (Perry et al 2003) and by attenuating neuron atrophy following excitotoxic stimulation (Perry and Greig 2005).

[0191] Natural Stimulants of Endogenous GLP-1: The extremely short half life on GLP-1-2 minutes—was thought to preclude the clinical utility of natural GLP-1 secretagogues. A number of studies have investigated a variety of compounds that do have small intestine GLP-1 releasing activity. These include: olive leaves that secrete GLP-1 via a naturally occurring compound oleanic acid, and its activation of TGR5 receptors (Sato et al 2007); the amino acid glutamine that has been shown to stimulate GLP-1 in vitro and in vivo (Greenfield et al 2009); and chlorogenic acid, a biologically active dietary phenol found in coffee (Johnston et al 2003). This compound has an inhibitory effect on glucose absorption, has a direct action on beta cells and their response to an increase in plasma glucose and has anti-oxidant properties. Chlorogenic acid, counteracts the adverse impact of chronic free fatty acid overexposure on beta cell function in overweight insulin resistant subjects (McCarty 2005; Johnston et al 2003).

[0192] Macronutrients that slow gastric emptying and stimulate insulin secretion in advance of the main nutrient load, have also been shown to stimulate endogenous GLP-1. Thus, treatment with a tagatose/isomalt mixture did result in a delayed GLP-1 secretion due in part to the slowing of gastric emptying time with distal gut production of short chain fatty acids stimulating GLP-1 (Wu et al 2012).

[0193] Artificial sweeteners synergize with glucose to enhance GLP-1 release. This is mediated via stimulation of the sweet-taste receptors on the gut mucosa (Brown et al 2009). Absent of carbohydrates, sweeteners do not stimulate GLP-1 (Ma et al 2009). Slowing and prolonging the rate of absorption elicits postprandial responses characterized by smaller rises and slower falls of blood glucose and insulin, prolonged suppression of free fatty acids and a reduced glycaemic response after a subsequent meal (Wolver et al 1995; Liljeberg et al 1999).

[0194] Sucromalt (Xtend® Cargill) is an enzymatically modified blend of sucrose and corn syrup containing fructose, leucrose and glucose oligosaccharides. In a recent randomized crossover study, sucromalt increased the plasma levels of GLP-1 (sustained over a four hour time frame) to twice that of a test meal of high-fructose corn syrup (Grysman et al 2008). This was associated with a delayed rise in FFA's. These results—together with the lack in rise of the simultaneous measurement of breath H2—confirmed that the sucromalt was absorbed more slowly, principally from the colon. This is consistent with earlier studies demonstrating that slowly digested carbohydrates travel further down the intestine before being absorbed and stimulate a late rise in GLP-1 (Krause et al 1982; Juntunen et al 2003).

[0195] In another recent randomized cross over study, subjects showed significantly improved mental and physical energy (over 4 to 5 hours) after a solution of 75 g sucromalt compared to 75 g of glucose (Dammann et al 2012).

[0196] Glucose to stimulate Glucose Intestinal Polypeptide (GIP). Glucose stimulates the secretion of GIP. In experimental models, GIP induces the proliferation of hippocampal progenitor cells (Nyberg et al 2005) and also enhances the induction of long term potential (LTP) which is the physiologic cellular mechanism controlling learning. GIP protects the synapses from the detrimental effects of beta amyloid and thus on LTP (Gault et al 2008). Over-expression of GIP increases coordination and memory recognition (Ding et al 2006)

[0197] Since GIP is rapidly degraded by the enzyme DPP IV, the added glucose will be added to the composition described herein in the form of a powder or beverage in a delayed and time released formulation.

Formulations

[0198] Described herein are compositions formulated as pharmaceutical compositions and nutraceutical compositions for use in the treatment and prevention of diseases and conditions and for promoting brain health.

[0199] The compositions described herein optionally include one or more pharmaceutically acceptable carriers, diluents, or excipients. Pharmaceutically acceptable carrier, diluent, or excipient, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Fifteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1975) discloses various carriers used in formulating pharmaceutical compositions and known techniques for the preparation thereof. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[0200] Other excipients, such as flavoring agents; sweeteners; and preservatives, such as methyl, ethyl, propyl and butyl parabens, can also be included. More complete listings of suitable excipients can be found in the Handbook of Pharmaceutical Excipients (5th Ed., Pharmaceutical Press (2005)). A person skilled in the art would know how to prepare formulations suitable for various types of administration routes. Conventional procedures and ingredients for the selection and preparation of suitable formulations are described, for example, in Remington's Pharmaceutical Sciences (2003-20th edition) and in The United States Pharmacopeia: The National Formulary (USP 24 NF19) published in 1999. The carriers, diluents and/or excipients are "acceptable" in the sense of being compatible with the other ingredients of the pharmaceutical composition and not deleterious to the recipient thereof.

[0201] The compositions described herein may be formulated into preparations in solid, semi-solid (e.g., gel), liquid or gaseous forms, such as tablets, capsules, powders, granules, ointments, solutions, suppositories, injections, inhalants and aerosols. As such, administration of the formulation may be achieved in various ways, including, but not limited to, oral, nasal, buccal (e.g. sub-lingual), rectal, topical (including both skin and mucosal surfaces, including airway surfaces), parenteral (e.g., subcutaneous, intramuscular, intradermal, intravenous and intrathecal), intraperitoneal, transdermal, intracheal, intravaginal, endocervical, intrathecal, intranasal, intravesicular, in or on the eye, in the ear canal, etc., administration. In certain embodiments, one or more pharmacological agents may be administered via a transdermal patch or film system.

[0202] In one embodiment, the compositions may be formulated for oral administration using pharmaceutically acceptable carriers well known in the art in dosages suitable for oral administration. Such carriers enable the pharmaceutical and nutraceutical formulations to be formulated in unit dosage forms as tablets, pills, powder, dragees, capsules, liquids, lozenges, gels, syrups, slurries, suspensions, etc., suitable for ingestion by the patient. Pharmaceutical and nutraceutical preparations for oral use may be obtained through combination of at least one pharmacological agent with a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable additional compounds, if desired, to obtain tablets or dragee cores.

[0203] Accordingly, the formulations suitable for oral administration can be present in discrete units, such as capsules, cachets, lozenges, tablets, and the like, each containing a predetermined amount of the active components of the composition described herein; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. Such formulations may be prepared by any suitable method of pharmacy which includes, but is not limited to, bringing into association the active pharmacological agent and a suitable carrier (which may contain one or more optional ingredients as noted above). For example, formulations for use can be prepared by uniformly and intimately admixing the active pharmacological agent(s) with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the resulting mixture. For example, a tablet may be prepared by compressing or molding a powder or granules containing the active pharmacological agent, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing, in a suitable machine, in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent, and/or surface active/dispersing agent(s). Molded tablets may be made by molding, in a suitable machine, the powdered pharmacological agent moistened with an inert liquid binder.

Composition: A Broad Based Balanced Bioactive Brain Blend.

[0204] The composition is a broad based balanced bioactive brain blend comprising Hup A, DHEA, Vitamin D, and optionally one or more additives. The composition is also referred to as CogniHomme Forte™.

[0205] Huperzine A: As an extract of the plant *Huperzia serrata* of the lycopodium alkaloid family (Lycopodiaceae) to contain from 1% to no less than 90% of pure Huperzine A, its synthetic equivalent (Wang et al 2007; Tudhope et al 2012; Koshiba et al 2009; Tun and Herzon 2012) or any derivative, analog, metabolite or combination thereof. This to include other acetylcholine esterase inhibitors: donepezil (Aricept®; Rivastigmine (Excelon®); Galantamine (Razadyne®) and Memantine (Namenda®) reference: Mayeux N. Eng. J Med 2012; 362:21942201. The dose of the hyperzine extract (and equivalence in all listed derivatives) to include 0.01 mg (10 mcg) to 150 mg (1500 mcg).

[0206] DHEA: The DHEA that are used in the disclosed composition include but are not limited to DHEA-S, 17-α-DHEA, 17-β-DHEA, combinations thereof, and the like. Also included, are natural and synthetic DHEA and analogs and derivatives thereof. Selective androgen receptor modulators (SARMS) are also included.

[0207] Vitamin D: Examples of vitamin D include but are not limited to calcitriol, doxercalciferol, paricalcitol, chole-

calciferol (vitamin D3), ergocalciferol (vitamin D2), analogs and derivatives thereof, vitamin D receptor agonists and modulators, and combinations thereof. The vitamin D component will be principally in the form of D3 cholecalciferol in a daily dose ranging between about 50 IU to about 20,000 IU and/or equivalent doses of other vitamin D3 synthetic analogs or derivates, and adjusted according to the route of administration.

[0208] Each of the above components of the composition described herein can be natural or synthetic and include natural and synthetic derivatives and analogs thereof.

Formulation: A Broad Based Balanced Bioactive Brain Blend Formulation.

[0209] The composition described herein can be formulated for administration to subjects in need thereof. The composition can be formulated for adult male or female subjects.

[0210] The manufacture and dosing of the three principal components—Huperzine A, DHEA and vitamin D—will be adjusted according to their pharmacokinetic absorptive and tissue distribution properties, so as to optimize their combined pharmacodynamic bioactivity and clinical safety.

[0211] The blends to be developed for both nutraceutical and/or pharmaceutical combinations for the treatment of all cognitive/memory dysfunction resulting from: "normal" brain aging, accelerated brain aging (benign senescent forgetfulness); mild cognitive impairment and vascular cognitive impairment; AD and vascular dementia; and associated at "increased risk" conditions: Parkinson's Disease, Huntingdon's Disease; stroke; PTSD; schizophrenia; concussion and traumatic brain injury; cardiovascular disease; diabetes; hyperlipidemia; hypertension; osteopenia/osteoporosis.

[0212] Products to be used alone as a preventive modulating nutraceutical and/or as adjunctive therapy together with disease specific drugs.

[0213] The composition described herein may be formulated as a brain health supplement, a functional nutraceutical complement, and/or as a medical nutraceutical complement. The clinical criteria determining the blend formulation, includes its use as either a supplement to support normal healthy aging; a functional nutraceutical complement for use in subjects with age related difficulties in memory, cognition and related CNS dysfunction including evidence of early mild cognitive impairment (MCI); or as a pharmaceutical complement for established MCI and evidence of early mild to moderate AD. Depending on the clinical situation and at the discretion of the supervising health care provider, all three formulations may be used adjunctive to treatments for disease specific conditions: MCI; AD; Type II diabetes: post menopausal HT; obesity; osteoporosis; osteopenia; hypertension; and other relevant cognition disabling conditions.

Immediate and Extended Release Formulations

[0214] The compositions described herein can be formulated for immediate release, timed release, or extended release. The compositions can be administered once daily or twice daily. In one embodiment, for extended release (sequenced extended release), the composition may be administered once daily. In another embodiment, for immediate release, the composition may be administered twice daily.

[0215] Huperzine A: The definitive pK study for Huperzine A was published in 2008 (Wei et al 2008). Healthy subjects received 0.2 mg of pure Huperzine A orally. Plasma levels rose rapidly after administration peaking at about hour 1.2 to 1.3. The plasma levels declined rapidly over the next 24 hours and a terminal half life of approximately 6 hours determined. Although this form of immediate release Huperzine A, at appropriately adjusted doses for a given indication, may well serve the needs as a brain health supplement in otherwise healthy men and perk and early postmenopausal women and/or as a complementary adjunct to subjects on specific disease related drugs, a controlled release formulation that would have a more prolonged therapeutic effect & provide once a day administration, is desirable.

[0216] A novel, extended release Huperzine A formulation was studied under the principal aegis of the inventor, and was designed to compare the same doses (200 mcg) of an immediate release (IR) formulation of the Huperzine A herb with a specially manufactured extended release (ER) comparator. The result: The ER formulation raised plasma levels of Huperzine A in a much more gradual manner than the IR formulation and resulted in consistent plasma levels of Huperzine A in a range found to be both beneficial and safe in human subjects. (See FIGS. **2** and **3**.)

Manufacture of the Composition.

[0217] All routes of administration for the above combinations can be used and include the following pill, capsules (hard and gel), tablet, powder, beverage, suspension, emulsion, syrup, solution, patch, gel, combinations thereof and the like.

[0218] For administrative purposes, the compositions can further include pharmaceutically acceptable, carriers, diluents, solubilizers, lubricants, binders, and the like or excipients thereof.

Formulation and Manufacture of the Composition with Additives

[0219] Caffeine: Caffeine is absorbed from the small intestine within 45 minutes of ingestion. Peak levels are reached within one hour, and subsequently eliminated via first order kinetics (Newton et al 1981; Lelo et al 1986). To optimize caffeine's complementing and additive effect on brain health promotion and function to that of the composition described herein, IR formulations of the caffeine ingredient will be added to the composition as brain health supplement; an ER formulation of caffeine that will allow for a more sustained blood level of caffeine over a 10 to 12 hour time frame, will be added to the composition in the form of a functional nutraceutical and a medical nutraceutical. The doses of caffeine will range from 25 mg to 250 mg daily.

[0220] The composition described herein can include addition of chlorogenic acid, the biologically active dietary phenol found in coffee and green coffee, in IR and ER doses equivalent to that of caffeine.

[0221] The composition comprising with caffeine can be manufactured in capsules (hard and gel); pills; tablet; powder; beverage; suspension; emulsion; syrup; solution; patch; gel, combinations thereof and the like. The compositions may include pharmaceutically acceptable carriers, diluent, solubilizers, lubricants, binders, combinations thereof and the like.

[0222] Natural Sweeteners (NS): The natural sweeteners—for the reasons noted previously—are important ingredients with important GLP-1 stimulating activity and well documented positive CNS effects, complementary to the actions of the ingredients of the composition and that of caffeine. The best NS example is that of sucromalt, a Cargill developed product (Xtend®) and a constituent of Abbot's Glucerna®.

This is for the composition in the form of a beverage, which in addition, is formulated to provide adequate and sustained amounts of glucose for brain energy.

[0223] Glucose: The addition in beverages and powder mixes of 75 G (range 25 to 200 G) of glucose for nocturnal brain energy to stimulate glucose-dependent insulinotropic polypeptide (GIP). Together with GLP-1, GIP is a physiologic incretin that is stimulated by enteroendocrine K-cells in the pancreas, adipose tissue, small intestine, bone and brain. GIP stimulates potent glucose dependent insulin and may have an important role in modulation of brain function and insulin resistance (Irwin et al 2010). GIP receptors have been identified in several areas of the brain—including the hippocampus and amygdala (Nyberg et al 2007)—as well as the GIP gene and GIP protein expression (Nyberg et al 2005).

[0224] Pharmacologic Rationale: The rationale for developing the composition, with and without additives is to provide a range of products that can promote the health of the brain as it ages and to modify metabolic abnormalities associated with the aging process per se, which would otherwise lead to the development of severe cognitive dysfunction and disease including MCI and AD. (See FIG. 4.)

[0225] The "art" of the disclosed composition alone and the composition plus additive combination products is to combine the proven pharmacologic actions of each ingredient in order to promote healthy brain aging and/or to modulate abnormal molecular pathways associated with an increased risk of cognitive dysfunction. Some examples of the pharmacological "art" include the following "balanced" pharmacodynamic brain protective combinations:

[0226] "Complementary": Enhancing acetylcholine neurotransmission. DHEA and vitamin D increase acetylcholine synthesis via increase choline acetyltransferase (ChAT) activity; Huperzine A and caffeine inhibits its breakdown by decreasing acetylcholinesterase (ACh E).

[0227] a. Enhancing neurogenesis: Huperzine A, vitamin D, and GLP-1 increase nerve growth factor via the TrkA pathway; DHEA and caffeine increase BDNF via the TrkB pathway.

[0228] b. Modulating APP metabolism: Huperzine A stimulates the alpha secretase and caffeine inhibits the beta and gamma secretase APP pathways with a resultant decrease in amyloid beta and tau protein accumulation. (See FIG. 5.)

[0229] c. Beta amyloid clearance: 17-beta estradiol (E2), vitamin D, and caffeine increase beta amyloid clearance.

[0230] "Additive": ingredients with the same biologic effect. Huperzine A and vitamin D inhibit oxidative stress and hence enhance neuronal apoptosis.

[0231] "Synergistic": First Ingredient Up-Regulates the Receptors for a Second Ingredient Thus Enhancing the Biologic Activity of the Latter.

[0232] Clinical Practice: Positive clinical outcomes of the methods provided herein are predicated on:

[0233] Timing: Subjects age and stage of cognitive disease if present. The presence of viable neurons responsive to the pharmacologic action of the various ingredients is important.

[0234] Continuence: Long term supplementation: the progression of the neuronal changes in both healthy and unhealthy aging is gradual and requires long term continuance of the indicated health supplements and/or the functional & medical nutraceutical complements. Benefit is lost when treatment is stopped.

[0235] Biomarker Measurement: Measurement of biomarkers indicative of ingredient absorption and efficacy to provide supportive evidence of healthy brain aging in otherwise asymptomatic subjects and so encourage long term continuance; in subjects with cognitive and memory dysfunction, biomarker testing for adjustment of the dosage of prescribed product depending on the clinical symptomatic response. The increase in the level of biomarkers in a subject is compared with the level of the same biomarkers in a healthy subject.

Specific Formulation Adjustments: Immediate Vs Sequenced Timed Vs Extended Release Formulations.

[0236] DHEA: Due to the relatively short half life of oral DHEA (4 to 10 hours) a formulation utilizing microcapsulation extended and time release technology designed to allow for more consistent levels of DHEA, its sulfated storage form DHEAS, and its biotransformation to testosterone, dihydrotestosterone, estrone, estradiol and metabolites of all sex steroids (Leblanc et al 2003; Arit et al 1999).

[0237] The dosage range of DHEA should be from 10 mg to 500 mg per day with the actual preferred total dose to vary from 25 to 75 mg per day: either in a twice daily immediate release or a once a day extended release formulation.

[0238] Caffeine: in once a day formulations to have early absorption and bioactivity in 6 to 10 hours, preferably 8 to 10 hours.

[0239] Vitamin D: 4 to 6 hour delayed release absorption in once a day formulations.

Molecular Biology of Brain Aging and Pharmacodynamics of the Composition

[0240] Product Formulation: Provided herein is a range of compositions and formulations that will promote the health of the brain as it ages in otherwise healthy asymptomatic subjects; to modulate the multiple metabolic pathways associated with aging resulting in reduced cognition, memory and loss of executive function; and to prevent and/or delay the progression of cellular changes associated with severe cognitive dysfunction and disease including mild cognitive impairment (MCI) and Alzheimer's Disease. The compositions will be respectively formulated as a brain supplement; a functional brain nutraceutical and a brain medical food/nutraceutical. Each of these products will be used for both single preventive management and as an adjunctive to specific drug therapy for conditions associated with an increased risk of age related cognitive decline including established MCI and AD.

[0241] Brain Health Supplement: the preferred daily dose ranges of the three ingredients will include but will not be necessarily limited to: DHEA 50 mg; Huperzine A 50 mcg; Vitamin D 800 iu.

[0242] Functional Brain Nutraceutical: this product will include three formulations to allow for a subject's individualized needs and response to a given prescribed dosage. The preferred daily dose ranges of the four ingredients will include but not be limited to the following combinations:

[0243] DHEA 25-75 mg; Vitamin D 1200 iu; Huperzine A 175 mcg; Caffeine 75 mg.

[0244] DHEA 25-75 mg; Vitamin D 1200 iu; Huperzine A 275 mcg; Caffeine 75 mg.

[0245] DHEA 25-75 mg; Vitamin D 1200 iu; Huperzine A 375 mcg; caffeine 75 mg.

[0246] Brain Pharmaceutical Composition: This product includes but is not limited to the preferred daily dose ranges

noted under "functional brain nutraceutical" and also the following: synthetic analogue of DHEA equivalent to 25 to 75 mg DHEA; synthetic huperzine in dose equivalent to Huperzine A 175, 275, and 375 mcg; vitamin D 1200 iu and caffeine 75 mg.

[0247] Product and Subject selection: successful treatment outcomes depend on matching the composition to the clinical needs of the subject and to monitor/adjust the treatment over time, depending on the clinical response. In addition to maintenance and/or symptomatic improvement in cognition, memory and executive function this requires baseline physical assessments and the measurement of biomarkers relevant to the subjects general and brain health status plus risk factors for cognitive dysfunction, including but not limited to MCI and AD.

[0248] The biomarkers that can be used in conjunction with the compositions described herein include, but are not limited to the components of the compositions, growth factors, and inflammatory markers. Examples include one or more of Hup A, DHEA (including DHEA-S), testosterone, vitamin D (including vitamin D3), caffeine, BDNF, NGF, aceyticholine, ChaT, AchE, Dkk1, fetuin A, and various inflammatory markers.

[0249] The subjects can be evaluated based on the biomarkers including the ingredients of the composition. If the amount of a particular biomarker is not at the optimal level in a subject, the amount may be adjusted by administering to the patient a formulation, which can be in the form of a tablet, containing the needed amount of the biomarker.

[0250] The present application provides formulations comprising a single ingredient of the composition, for example, 25 mcg of Hup A in a tablet form (Cogni Adjust). Other tablets include but are not limited to 500 iu vitamin D tablets, 25 mg of DHEA tablets. One or more of these tablets may be administered to a subject in need of thereof. As an example, if a subject does not have an optimal level of Hup A, a CogniAdjust tablet comprising Hup A can be administered to the subject. These tablets can be formulated for daily administration to provide subjects with optimal individualized care.

Subject Evaluation:

No Known Risk Factors

[0251] General physical examination to include: weight and body mass index (<27 kg/m2); waist/hip ratio measurement (<0.8); blood pressure (<130/75 mmHg) and the following blood tests (normative values in parenthesis).

[0252] Total cholesterol (120-200 mg/dL); HDL cholesterol (>40 mg/dL); Triglycerides (<150 mg/dL); LDL cholesterol (<130 mg/dL); free fatty acids (0.07-0.88 mmol/L); Fasting blood glucose (70-110 mg/dl); Hemoglobin A1C % (<6); C-reactive protein (<5 mgL); 25-OH Vitamin D (30-100 ng/ml); Liver Function test panel.

Known Risk Factors

[0253] Obesity and Type II Diabetes: above plus fasting insulin (4-27 uIU/ml); oral glucose tolerance test;

[0254] Hypercholesterolemia: above plus 27-hydroxycholesterol (Ghribi 2008) and Apolipoprotein panel: Apo A, Apo H and Apo J (Song et al 2012).

[0255] Osteopenia and Osteoporosis: above plus bone density measurement of the hip and lumbar spine with DEXA testing utilizing standard definitions (t score for osteopenia 1 to 2 standard deviations below young normal with no clinical radiologic fractures deformation of lumbar/thoracic vertebrae; osteoporosis: bone mineral density (BMD) t score 3 or more standard deviations below young normal with or without evidence of vertebral deformation/fracture). Also, selective use of biomarkers of excess bone turnover: urinary/serum n-telopeptide levels; excess urinary calcium excretion (ca/creatinine ratio >16).

[0256] Hypertension: above plus hypertension (blood pressure greater than 140/90) or progessive increasing blood pressure.

[0257] Inflammatory Markers: Given the significant role of inflammation in the pathogenesis of AD, the following biomarkers are included (but are not limited) to the following cytokines, chemokines, growth factors, complement and adhesion molecules: they can be selectively used as both risk factors, measures of progression of disease and response to treatment: IL-1; IL-2; IL-4; IL-8; IL-10; IL-13; TNF-alpha; osteopontin and two anti-inflammatory markers: G-CSF, Fetuin-A and combinations thereof.

[0258] Symptomatic with/without Family History of MCI & AD

[0259] Cognitive tests: Clinical dementia rating (CDR: 0 equals normal; 0.5 very mild impairment; 1 mild impairment); Mini-Mental State Examination (MMSE:0 equals severe impairment vs 30 no impairment); Wechsler Memory Scale-Revised (0 equals no recall to 25 complete recall) (Bateman et al 2012).

[0260] Blood tests: APOE genotype (Apoe4 allele); sirtuin 1 (alpha secretase; beta and gamma secretase); proteomics biomarkers assay of AD autoantibody biomarkers (Nagele et al 2011; Shi et al 2009) and other related and recognized blood, urine and CSF biomarkers of risk for MCI and AD.

[0261] Monitoring Treatment: Dosage and Efficacy.

[0262] Early brain aging is asymptomatic with multiple molecular pathways regulating neuronal health and function. The metabolic heterogeneity of individual subjects adds an additional variable that will determine whether clinically effective concentrations of the composition's constituents are absorbed. Only measurement of relevant biomarkers can confirm that adequate dosing has been achieved and in addition, allow for the adjustment of the composition disclosed herein over time if needed. The goal is for the tested components and biomarkers to reach the optimal bioactive level after administration of the composition. The optimal level indicates that the subject is being effectively treated for the disease or condition or that the composition is effective in promoting and maintaining the health of the brain of the subject. Tests include, but are not limited, to the following:

[0263] Measurements of Tested Components: Assays are performed to measure the levels of various components in the subject. Plasma assays of Huperzine A (to be within the range of 0.3 to 1.5 ng/ml); total DHEA-S (to be within the range of 5 to 253 mcg/dl); DHEA (61 to 1636 ng/dl); testosterone (to be within the range of 300 to 720 mcg/dl); testosterone free (to be within a range of 47 to 244 pg/ml); sex hormone binding globulin (to be within the range of 11 to 80 nmol/l); hemoglobin (to be within a range of 14 to 18 g/dl); about 38.5 to 50% hematocrit (volume of red blood cells in blood); 25-OH vitamin D (to be within the range of 30 to 110 ng/ml); caffeine (to be within the range 2 to 10 mg/L). The suggested test time intervals: three months after treatment; 6 months later and then annually.

[0264] Brain Health & Function Biomarkers: The following assays for measuring biomarkers were performed, before treatment commences, at 3 months, 9 months and then annually. The measured neurotrophic factors serve as surrogate biomarkers of neurogenesis, the balance between acetylcholine synthesis and catabolism and the metabolism of Amyloid Precursor Protein (APP) and the Wnt/beta catenin pathway.

[0265] Brain Derived Neurotrophic Factor (BDNF) Eliza Immunoassay: (to be within the range of 0.066 to 16 ng/ml); Nerve Growth Factor Immunoassay (NGF): (to be within the range of 3.9 to 250 pg/ml); Acetylcholinesterase activity (to be within the range of 10 to 600 U/L); Acetylcholine (Quantitative Colormetric assay: to be within the range of 10 to 200 micoM; fluormetric assay: to be within the range of 0.4 to 10 microM acetylcholine); assays measuring the expression of alpha secretase and beta/gamma secretase enzyme activity; titers of AD autoantibodies using proteonomic; plasma Dkk 1 and related assay technology before and after treatment.

Microencapsulation: A Technique for Controlled Drug Delivery.

[0266] The compositions described herein can be in a microencapsulated formulation and administered once per day for sequenced extended release. Microencapsulation is a process by which small droplets or particles of liquid or solid material are coated with a continuous film of polymeric material. The principle reasons for microencapsulation are to provide for a sustained or prolonged rate of drug release and to alter the site of absorption. This can be accurately controlled over a period of hours or even days and designed for pre-programmed drug release profiles in order to meet the therapeutic needs of the patient. Microencapsulation technology is particularly suited to orally controlled release drug formulation systems (Singh et al 2010; Bansode et al 2010), especially when multiple doses are required.

[0267] Given the varying pharmacokinetic profiles of the constituents of the disclosed composition (see individual pharmacokinetics in the text), specifically designed immediate and extended release combinations will be formulated to optimize local tissue bioactivity and function

[0268] Examples include an ER form of Huperzine A and twice daily or ER DHEA to allow for their 24 hour tissue availability; slow release of caffeine over 8 to 10 hours and slightly delayed vitamin D absorption to allow for optimal up-regulation and expression of the VDR to enhance the latter's in situ activity.

Comparison of Immediate Release (IR) with an Extended Release (ER) Formulation of Huperzine A.

[0269] This pK study was performed at Cetero Laboratories (St. Louis, Mo.) under the aegis of CogniFern LLC and Osmopharm Capsules USA. IR and matching ER formulated capsules containing 200 mcg of the Huperzine A herb were prepared by Osmopharm USA to meet specified clinical requirements.

Huperzine A: Duration and Dose.

[0270] The definitive pK study for Huperzine A was published in 2008 (Li et al). Healthy subjects received 0.2 mg of pure Huperzine A orally. Plasma levels rose rapidly after administration peaking at about hour 1.2 to 1.3. The plasma levels declined rapidly over the next 24 hours and a terminal half life of approximately 6 hours was determined. Based on this data, an extended release product would be required for once daily administration, in order to meet optimal brain tissue concentrations.

[0271] Over the major part of the day plasma levels ranged from 0.3 to about 1.0 ng/ml where 0.6 ng/ml was determined to be the optimal level (Li et al 2008). Values above this level produce unnecessary exposure of the tissues to brief high levels of Huperzine A and increased loss due to excretion. Doses of 0.15 mg pure Huperzine A twice daily was shown to effective for the treatment of mild cognitive impairment, a potential pre-condition to AD (Li et al 2008).

Pharmacokinetics: Molecular Pathway Counter Balancing Thus Formulation.

[0272] (a) Huperzine A has short half life: thus formulation in twice daily dosage or as extended release.

[0273] (b) DHEA---has a short half life thus formulation in twice daily dosage or as extended release.

[0274] (c) Ingredients have complementing pharmacologic actions: eg Huperzine A & vitamin D increases the blood level of NGF and DHEA and caffeine increases the blood level of BDNF.

[0275] (d) Natural product extracts vs synthetic active component: huperzine A and vitamin D, derivatives and analogs thereof and Vitamin D receptor modulators. In some embodiments, the natural product or extracts are used to make nutraceuticals and synthetic active components are used in pharmaceutical compositions.

[0276] As an example, the method of using the disclosed compositions is as follows.

[0277] (a) Gender specific: as an example, a female versus a male subject.

[0278] (b) Timing and thus dosage of nutraceutical and pharmaceutical compositions: lower dosage is administered during early "critical window" for healthy brain aging vs higher dosage is administered for cognitively impaired and with MCI/AD. The disclosure compositions are formulated for nutraceutical and pharmaceutical use. In one embodiment, the "critical window" is within 10 years of menopause of a female subject.

[0279] (c) Primary therapy or adjunctive use with disease specific therapies in subjects at greater risk of MCI/AD.

[0280] (d) Risk factors: type II diabetes; metabolic syndrome; obesity; osteopenia/osteoporosis; hypertension; and cardiovascular disease;

[0281] (e) Other conditions associated with neuronal damage: post concussion; PTSD; stroke; Huntingdon's disease; schizophrenia.

[0282] (f) Biomarkers are used to determine and measure risk factors, absorption of ingredients and biomarkers of brain efficacy. The level of biomarkers can be used to adjust dosages if needed and to aid with long term compliance in asymptomatic women.

Results:

[0283] Five volunteer subjects were tested in a blinded cross over study with both the IR and ER formulated capsules, all containing 200 mcg of the Huperzine A herb. As expected, the plasma levels following the immediate release formulation rose rapidly after administration, peaking at about 1.4 hours. This was followed by a rapid decline over the next 24 hours. These data are similar to the results obtained by Wei et al, using the pure huperzine alkaloid. The ER formulation was

absorbed more slowly and a smoother peak was obtained by 5.4 hours. The levels then declined slowly for the next 20 hours giving a blood half life that was significantly greater than was observed after the IR form.

[0284] Using a standard model {Phoenix™ WinNonlin 6.0 (Pharsight Corp, St. Louis, Mo.)} for simulating "steady state" plasma levels following multiple doses and using data obtained in the single dose study described above, it was demonstrated that within 5 days a steady state level was reached with an estimated Cmax of 0.62 ng/ml and a Cmin of 0.36 ng/ml. These values were identical to those observed in the Chinese studies where positive effects on mild cognitive loss had been observed.

Conclusions:

[0285] In comparison with the IR formulation, the ER formulation Huperzine A was absorbed over a longer period of time with a resulting increase in the plasma half life. The initial gradual rise in plasma levels were then maintained at a steady level over an extended period.

[0286] Unlike the IR formulation, absorption from the ER formulation did not cause a spike in the plasma levels of Huperzine A. Less material is therefore lost due to early excretion following the administration of the ER formulation.

[0287] The ER formulation generated more consistent absorption of Huperzine A between subjects than the absorption observed following the IR formulation.

[0288] Steady-state simulations using an accepted computer model predict that by the fifth dose a steady state will be reached with plasma levels fluctuating over a narrow range of blood levels consistent with beneficial effects on memory dysfunction.

Methods of Use

[0289] The compositions described herein can be formulated for use in the promotion or maintaining a healthy brain. Various pathways and factors are involved in maintaining a healthy brain or for the prevention or treatment of diseases or conditions associated with the brain health.

[0290] The compositions can be formulated for administering to subjects in need of treatment or in need thereof such as to increase level of neurotrophins, improve neuronal health, and promote neurogenesis.

[0291] The compositions described herein includes its use as either a supplement to support normal healthy aging; a functional nutraceutical complement for use in subjects with age related difficulties in memory, cognition and related CNS dysfunction including evidence of early mild cognitive impairment (MCI); or as a medical nutraceutical complement for established MCI and evidence of early mild to moderate AD. Depending on the clinical situation and at the discretion of the supervising health care provider, all three formulations may be used adjunctive to treatments for disease specific conditions: MCI; AD; Type II diabetes: post menopausal HT; obesity, osteopenia and/or osteoporosis; cardiovascular disease; and hypertension; and other relevant cognition disabling conditions. The composition can be used alone or as adjunctive therapy with other drugs.

[0292] The compositions can be formulated in the form of blends of a nutraceutical and/or pharmaceutical combination for the treatment of all cognitive/memory dysfunction resulting from and/or associated with Parkinson's Disease, Huntingdon's Disease; Stroke; Post Traumatic Concussion; Post Traumatic Stress Disorder, Schizophrenia. The composition can be used alone or as adjunctive therapy with disease specific drugs.

[0293] Glucocorticoids, DHEA and Cognitive Dysfunction

[0294] Increased levels of cortisol have been shown in many observational studies to have a negative impact on cognition including stress induced memory impairment (Lupien et al 1997).

[0295] The mechanism for the negative effect of glucocorticoids on cognition may be due to its disruption of synaptic plasticity and atrophy of the dendritic processes (Kimonides et al. 1999), blocking the anti-apoptotic Bcl-2 proteins (Charalampopoulos et al. 2006), and selectively the expression of the 11 beta-hydroxysteroid dehydrogenase enzymes that are responsible for the local concentration and activity of glucocorticoids in cells and tissues (Webb et al 2006).

[0296] Whereas short term mild increases in cortisol may have a beneficial effect on attention and memory, (Groeneweg et al 2011) higher cortisol levels or chronic long term exposure are related to impaired executive function, memory and cognitive flexibility (Campeau et al 2011).

[0297] DHEA and DHEA-S counterbalance these cortisol effects, with higher DHEA/cortisol ratios decreasing the negative effects of cortisol in the hippocampus (Apostolova et al. 2005; Dong et al. 2011); thus allowing for better cognitive performance under stress (Russo et al. 2012).

[0298] With the gradual age-related decrease in brain DHEA levels but not cortisol, glucocorticoid neurotoxicity may occur at relatively lower plasma cortisol levels due to the decrease in the DHEA/cortisol ratio and the diminution of DHEA associated hippocampal glucocorticoid inhibition (Ceresini et al. 2000).

[0299] Since DHEA-S has a greater half life, the ratio of DHEA-S/cortisol may be a better marker of glucocorticoid over activity than the DHEA/cortisol ratio or just DHEAS alone. (Valenti et al. 2009).

[0300] The DHEA ingredient in the compositions described herein is designed to compensate for the age related decrease in DHEA/DHEA-S and so reduce the relative hippocampal glucocorticoid.

[0301] The "methods of use" of the composition described herein (with and without additives) includes the optional monitoring of its use with the measurement of either plasma cortisol and/or 24 hour urinary cortisol.

Neurotrophins and Neuronal Health

[0302] Linking the clinically observed age related changes in cognition, memory and executive/motor function that occur in "healthy" aging with that associated with "unhealthy" aging (benign senescent forgetfulness) and as a pre-condition to and risk for mild cognitive impairment and its later progression to Alzheimer's Disease.

[0303] Linking these observations with validated molecular brain research—in animal experiments and observational & noninvasive human studies—that establishes and defines the multiple interconnected pathways responsible for the clinically noted changes in cognition, memory and executive/motor function associated with "healthy" and "unhealthy" aging.

[0304] Linking the known molecular function(s) of botanicals and other natural compounds and their physiologic/pharmacologic effect on the established neurocognitive pathways associated with the altered cognition, memory and executive function, in both "healthy" and "unhealthy" aging Linking

the multiple biologically altered molecular pathways associated with "healthy" and "unhealthy" aging, and combinations of botanicals and other natural compounds, that have complementary, additive and or synergistic effects on brain function and health (see FIG. 4).

[0305] Linking the pharmacokinetics of the botanical and natural compounds into blends—with or without additional additives—in order to optimize their combined brain cellular function.

[0306] Linking the utility of adding clinically proven bioactive combination botanical products with complimenting molecular activity, to that of disease specific conditions associated with an increased risk of cognitive and other brain dysfunction and their treatment: Mild cognitive impairment and early stages of Alzheimer's Disease; post menopausal hormonal therapy; type II diabetes; obesity; osteoporosis; osteopenia; hypertension; chronic use of anticholinergic preparations, anti-depressant SSRI treatment (Deltheil et al 2008).

[0307] Brain-Derived Neurotrophic Factor (BDNF): Brain derived neurotrophic factor is a neurotrophin that regulates a variety of neural functions including selection of neural progenitor cells; increases the number and growth of hippocampal neuronal dendritic spines and their development into mature spines; enhances the production and survival of new neurons from stem cells in the hippocampus; matures and integrates new neurons into existing neuronal circuits.

[0308] Most importantly, BDNF increases synaptic number and enhances their plasticity and resistance to injury and disease. Together with its tyrokinase membrane receptor, full length TrkB, BDNF stimulates long term synaptic potentiation (LTP) an essential information storage function. Insulin-like growth factor interfaces with BDNF to enhance exercise induced synaptic plasticity (Ding et al)

[0309] BDNF also increases presynaptic glutamate release and induces neuronal proteins encoded for mitochondrial biogenesis, anti-oxidant and DNA repair enzymes (Rothman et al 2012; Gomez-Pinilla et al 2008; Yoshi and Constantine-Paton 2010).

[0310] Nerve Growth Factor. Nerve Growth factor is the first described member of the neurotrophin family. The mature form of NGF is derived from a precursor form (ProNGF) and in its activated form has both pro-apoptopic and neurotrophic properties. NGF binds to high affinity tyrosine kinase receptor TrkA.

[0311] Although NGF circulates throughout the body, its most important function with respect to the methods and compositions provided herein is its synthesis in the cerebral cortex and hippocampus and its promotion of the survival and outgrowth of CNS cholinergic neurons especially in the basal forebrain complex. As such, it is regarded as a potential protective factor for neurodegenerative disorders associated with these neurons (Aloe et al 2012).

[0312] Cholinergic pathways are associated with the regulation of NGF synthesis. Some acetylcholine esterase inhibitors (AChE) stimulate NGF like activity by potentiating the neuritogenic effect of NGF, and by increasing mRNA in primary astrocytes promote NGF-induced neuronal survival and function. NGF also protects responsive neurons from oxidative injury (Wang et al 2006).

Neurotransmitters

[0313] Changes in neurotransmitters have an important role in modulating normal brain aging. The three main neurotransmitters relevant to the methods and compositions disclosed herein include serotonin, glutamate and most importantly acetylcholine. The composition described herein can be used to increase the levels of neurotransmitters, to inhibit the activity or level of cholinesterase, to increase the level of or activity of acetyl choline transferase, and to promote normal brain aging. Neurotransmitters include, but are not limited to, serotonin, glutamate, acetycholine and combinations thereof.

[0314] Serotonin: The levels of serotonin, which is principally associated with executive function, are age related and in addition, influence brain function by the signaling pathways with other age related molecules such as BDNF and IGF-1(Glorioso and Sibille 2011).

[0315] Glutamate: Glutamate is the main excitatory neurotransmitter in the central nervous system, with important roles in both neurotransmission and functional plasticity. Thus, glutamate facilitates the release of BDNF, is essential for LTP synaptic plasticity, neurogenesis and other activities associated with neuronal survival including changes in dendritic architecture (Glorioso and Sibille). Conversely even though the glutamate receptors decrease with age, excessive glutamate signaling in the aging brain may lead to neuronal death through excitotoxicity (Uranga et al). This is the result of an excessive Ca++ influx, with elevated intracellular concentrations of Ca++ and resulting cellular necrosis and apoptosis. Blockade of the glutamate receptors reduces the Ca++ influx and neuronal death due to glutamate exposure (Wang et al). Neuronal death by overstimulation of glutamate receptors is thought to be the final common pathway for a number of neurodegenerative diseases, including AD.

[0316] Acetylcholine (ACh): ACh is the neurotransmitter used by cholinergic neurons at the neurotransmitter junction and plays a key role in the brain's memory related circuit. ACh is synthesized from choline and acetyl coenzyme A by the enzyme choline acetyltransferase (ChAT). This requires the transport of choline into cells from the extracellular space and the activity of ChAT. The levels of acetylcholine and cholinergic activity decline in the aging brain (Uranga et al) and especially in patients with cognitive dysfunction, including Alzheimer's Disease (AD). The synthesis, and therefore the levels of Ach, is balanced by acetylcholinesterase inhibitors (AChE). Reduction in AChE activity is the basis for most currently available AD treatment and is associated with a variable increase in ACh. Although positive correlations have been noted between ACh levels and AChE activity in the frontal cortex and whole brain, the efficacy of AChE inhibitor treatment is ultimately dependent on the presence of sufficient cholinergic neurons capable of synthesizing acetylcholine. AChE treatment does not retard the loss of cholinergic neurons, and at best only provides temporary symptomatic improvement in cognition.

Oxidative Stress, Cellular Damage, and Cellular Death

[0317] The compositions described herein can be used to reduce cellular damage and cell death. Excess oxidative stress results in cellular damage with subsequent tissue and organ dysfunction. Oxidative stress induces an increase in inflammatory signaling within the aging brain resulting in dysregulation of neurotransmitter function. This is due to the accumulation of nuclear and mitochondrial DNA damage and via an ROS-mediated mechanism leads to accelerated brain aging and neurodegeneration. Studies have shown that oxygen radicals also initiate the build up of amyloid and

enhanced neurodegeneration. The severity of age related memory loss has been correlated with brain and plasma levels of antioxidants.

[0318] Cellular death (apoptosis) is a physiologic consequence of normal aging but is also a feature of various acute and chronic neurodegenerative diseases. Typical apoptotic changes occur when neuronal cells are exposed to stressors such as H2O2, beta amyloid peptides and oxygen—glucose deprivation. The likelihood of neuronal apoptosis is in large measure regulated by the Bcl-2 family of proteins. High levels of Bcl-2 expression inhibit apoptosis. Conversely, an increase expression of P53 and Bax is associated with the initiation of apoptosis (Wang et al).

[0319] The sirtuin family of longevity genes has been identified as key brain aging modulators. Their effects have been noted in both neuronal and glial cells and are associated with a reduction in the accumulation of misfolded proteins, the response to stress and the prevention of inflammatory pathways in glial cells that lead to mitochondrial dysfunction and cell death. SIRT1 has been shown to be a key player in neurogenesis by activating the gene for BDNF and potentiating its transcription factor, as well as that of other CREB target genes in the brain. SIRT1 regulates glucose homeostasis, controls insulin sensitivity in skeletal muscle and energy expenditure in the brain (Dong 2012).

[0320] SIRT1 activates the alpha secretase pathway that directs the processing of the amyloid precursor protein away from the production of beta amyloid peptide, thereby reducing the risk of AD. Over expression of brain SIRT1 in mice has been shown to reduce the load of the beta amyloid protein aggregates characteristic of the extracellular amyloid plaques in AD. In separate studies, SIRT1 was shown to destabilized the tau protein and reduce intracellular tau tangles (Guarente 2011). A loss of SIRT1 is closely associated with the accumulation of beta amyloid and tau in the cerebral cortex of patients with AD (Julien et al 2009).

Inflammation and Brain Health

[0321] The compositions described herein can be used to reduce inflammation and promote brain health. Inflammation has a significant role in the pathogenesis of brain health including both MCI (Roberts et al 2009; Sun et al 2013) and AD (Leung et al 2013; Kim et al). A number of cytokines and chemokines have been identified as contributing to activation of the microglia leading to the formation of beta amyloid/microglial complexes that in the early stages of AD precedes subsequent tau related neurofibrillary pathology and neuronal death (Eikelenboom et al 1996; Griffin 2006; Ray et al 2007).

[0322] Elevation of a number of different plasma cytokines have been positively correlated with severity of disease and progression of disease as assessed by memory tests, and even neuroimaging studies (Leng et al 2013). Plasma cytokines communicate with the brain, and circulating levels of peripheral cytokines have been shown to reflect brain cytokine levels (Banks et al 2002). One route involves diffusion of cytokines from the blood to the brain through an impaired blood brain barrier (BBB), with active transport across the BBB (Banks et al 2002). Another involves cytokine activation of the endothelium signaling to macrophages in the brain (Perry 2004). Apart from inflicting cellular damage, certain cytokines may stimulate the GSK-3 beta and p38-MAPK kinase pathways and via the up-regulation of Dkk1 antagonist, decrease Wnt/beta catenin signaling. Disruption of the Wnt/beta ctenin pathway has been implicated in neurodevelopment and many neurologic diseases such as AD and schizophrenia. Over expression of GSK-3beta impairs neurogenesis (He and Shen 2009) and increases tau hyperphosphorylation in the hippocampus (Lucas et al 2001). Blocking interleukin-1 signaling, improves cognition, attenuates tau pathology and restores the Wnt/beta catenin function in an animal model (Kitazawa et al 2011).

[0323] There are two protective proteins: G-CSF (granulocyte colony stimulating factor) which suppresses the production or activity of pro-inflammatory cytokines (Sanchez-Ramos et al 2009) with reduced plasma levels found in patients with AD (Laske et al 2009). Fetuin A, an abundant plasma protein that is synthesized in the liver and in the context of cerebral ischemia has been shown to be anti-inflammatory. A recent study correlated plasma levels of fetuin-A and the pro-inflammatory cytokine TNF-alpha in subjects with early AD and age matched controls. The patients with AD had significantly lower levels of fetuin A and higher concentrations of TNF-alpha (Smith et al 2011).

[0324] In addition, higher plasma levels of plasma fetuin-A have been associated with better performance on tests of global cognitive and executive function, with a lower likelihood of decline in theses cognitive parameters in older adults (mean age 75) when followed for 4 years (Laughlin et al 2013).

[0325] Examples of pro-activating inflammatory markers include but are not limited to cytokines, chemokines, growth factors, complement and adhesion molecules: they can be selectively used as both risk factors, measures of progression of disease and response to treatment: IL-1; IL-2; IL-4; IL-8; IL-10; IL-13; TNF-alpha; osteopontin and two anti-inflammatory markers: G-CSF and Fetuin-A.

Blood-Brain Barrier (BBB) and Brain Health

[0326] The compositions described herein can be used to promote and maintain the blood-brain barrier (BBB). The BBB consists of a specialized endothelium of brain capillaries that protects the central nervous system by separating it from the systemic circulation. It serves as both a physical and metabolic barrier that protects the microenvironment of the brain and hence its functional activities. Disruption of the BBB leads to compromised synaptic and neuronal function. The integrity of the BBB is due to tight junctions between adjacent endothelial cells that consist of three highly specialized transmembrane proteins that exert their protective effect via the blockage of cell surface adenosine receptors, inhibition of cAMP phosphodiesterase activity and by modulationg the release of calcium from intracellular stores (Chen et al).

[0327] Altered BBB function is key to the processes leading to mild cognitive impairment (MCI) and AD, due in part to the accumulation of beta amyloid in the brain. This results from allowing an increased beta amyloid influx into the brain and an inadequate beta amyloid efflux from the brain. In addition, beta amyloid is synthesized in and around the BBB and in the brain microvasculature. The presence of beta amyloid adversely effects brain endothelial cell function. BBB dysfunction is one of the earliest pathologic events leading to AD.

[0328] Associated risk factors for disruption of the BBB include atherosclerosis, stroke, diabetes and proinflammatory and other neurotoxic factors such as reactive oxygen species (ROS). The result: a leaky BBB that allows peripheral inflammatory cells to infiltrate into the brain parenchyma

with subsequent activation of astrocytes and microglia both of which have been implicated in the pathogenesis of AD (Chen et al).

Regulation of Brain Glucose and Insulin Resistance

[0329] The compositions described herein can be used to regulate the supply of glucose and facilitate the transport of glucose across the BBB. Glucose is the essential nutrient for brain glucose metabolism and the energy needs of neurons. To meet ongoing mental demands and since the brain only maintains a 2 minute supply of glucose, two essential physiologic processes are needed: facilitation of glucose transport across the BBB; utilization of this glucose, and hence brain tissue insulin sensitivity. (See FIG. 6.)

[0330] Regulation of Glucose in the Brain: Three coupling steps are involved to initiate neuron activation and their need for glucose: release of glutamate from astrocytes signaling glucose metabolism and via this neurobarrier process stimulating the second stage; allowing for movement of glucose from plasma into the brain via the endothelial BBB cells glucose carrier protein GLUT1; with a final coupling step involving the relaxation of smooth muscles of the relevant arterioles, an increase in the blood vessel diameter and blood flow. This neurovascular and neurobarrier coupling is mediated through the metabolic activities of the neurons and astrocytes. The need for neuronal glucose is thus predicated by: brain activation, glucose transport, glucose support and the ability of the brain to utilize this energy source (Dormire 2009).

[0331] Brain glucose uptake and its metabolism is compromised in AD. This has been linked to a deficiency in the glucose transporters GLUT 1 and GLUT 3, and correlated with hyperphosphorylation of tau and to the density of neurofibrillary tangles (a hall mark of AD) in human brains (Liu et al 2008).

Brain Insulin Resistance and Type Three Diabetes

[0332] The compositions described herein can be used to prevent or inhibit insulin resistance in the central nervous system (CNS). Insulin is present in the adult CNS and is primarily derived from pancreatic beta cells. This insulin crosses the BBB via a carrier-mediated active process that is limited by the tight junctions between endothelial cells in the BBB. Chronic hyperinsulinemia down regulates insulin receptors (IR) at the BBB, thus impairing insulin transport into the brain. There is some animal data to suggest that insulin may be synthesized in the CNS following the detection of preproinsulin mRNA in the neurons (but not glial cells) of the hippocampus and prefrontal cortex.

[0333] Insulin is essential for normal CNS function. Once in the brain, insulin binds to IR that are widely distributed throughout the CNS, especially in the cerebral cortex and hippocampus. Both insulin and IGF-1 signaling pathways are involved in the regulation of brain metabolism, neuronal growth and differentiation and neuromodulation. Brain insulin increases neurite outgrowth, regenerates small myelinated fibers and by stimulating neuronal protein synthesis enhances synaptic activity and plasticity with resulting memory formation and storage. This effect is mediated via the expression of NMDA receptors, an increase in neuronal Ca++ influx and by reinforcing synaptic communication between neurons enhanced long-term potentiation (LTP).

[0334] Insulin and IGF-1 are also neuroprotective: brain neuronal apoptosis induced by oxidative stress is attenuated by insulin; IR/IGF-1 signaling mediates the gene transcription of anti-apoptotic factors such as increased Bcl-2 expression (Duarte et al 2012).

[0335] Insulin resistance: A number of studies have suggested that AD may represent the outcome of a metabolic disorder characterized by a deficit in brain glucose utilization. This is based on the demonstrated progressive decline in cerebral glucose utilization in subjects with AD. The abnormalities in insulin and insulin like growth factor (IGF) signaling and expression of insulin regulated genes results in insulin resistance and contributes the following AD like neurodegenerative changes: an increase in the activity of kinases that hyperphosphorylate tau; the expression and accumulation of beta Amyloid Precursor Protein (beta APP) and its metabolism to its end product beta Amyloid; oxidative and endoplasmic reticulum stress; generation of ROS and reactive nitrogen species that damage RNA and DNA; mitochondrial dysfunction; activation of pro-inflammatory and pro-apoptopic (death) cascades (de la Monte 2012).

[0336] Although the "physiologic" insulin resistance associated with aging is the dominant risk factor for MCI and AD, insulin resistance associated with the following conditions also contribute to the neurodegenerative changes characteristic of AD: obesity; type two diabetes; and metabolic syndrome. Treatment with hypoglycemic or insulin sensitizing drugs may contribute to reducing the prevalence and/or severity of AD pathology and its clinical outcome (Luchsinger JA 2010).

[0337] At a functional level, insulin and IGF resistance down regulates the genes for the cholinergic activity that mediate neuronal plasticity and its concomitant effect on memory and cognition (de la Monte 2012).

[0338] Insulin resistance is associated with an increase risk of AD and is indeed the underlying pathology for what is now termed type 3 diabetes. This condition is coupled with the generation of inflammatory cytokines and resultant damage to the pro-apoptotic neuronal cascades (dela Monte 2012). Type 3 diabetes is also linked to obesity, type two diabetes and the metabolic syndrome (Luchsinger 2010). DHEA treatment of experimentally produced obesity, reduces total and visceral fat accumulation and improves the associated muscle insulin resistance (Hansen et al 1997). The one year use of DHEA (50 mg per day) in elderly men and women (mean age 70 years) resulted in a significant improvement in insulin resistance and a normalization of their response to an oral glucose test. Visceral fat, measured by MRI, was reduced by about 10% in men and women (Weiss et al 2011).

[0339] Key findings of clinical relevance in this study (Weiss et al. 2011) was that DHEA improved glucose tolerance/insulin resistance only in those subjects who had impaired glucose tolerance, and that DHEA treated (vs placebo controls) had significant decrease in the circulating cytokines: TNF alpha and IL-6. Chronic inflammation in adipose tissue is a factor mediating insulin resistance (Feve and Bastard 2009).

[0340] Other mechanisms of DHEA's reversal of insulin resistance include activation of the PPAR alpha receptors for which DHEA is a ligand (Peters et al 1996); a reduction in triglyceride levels and via a metabolite of DHEA, that stimulates Akt/PkB phosphorylation in muscle with improvement in insulin resistance (Lu et al 2010).

Wnt/Beta-Catenin Signaling and Regulation of its Dkk1 Antagonist

Wnt/Beta Catenin Signaling

[0341] The compositions described herein may be used to regulate the Wnt/Beta catenin pathway which is associated with the health of the brain and the development of AD. The compositions described herein can inhibit the activity of GSK-3 beta and increase the level of beta catenin, which inhibits the formation of amyloid plaques.

[0342] Wnt signaling is a transduction pathway governed by a variety of Wnt glycoproteins, which in addition to having a role in the development of the forebrain and the hippocampus (see later), are associated via alterations in its level and/or mutations with several pathologies including mood disorders, schizophrenia and Alzheimer's Disease (Inestrosa et al 2012; Maguschak and Ressler 2012; Kim et al 2013). (See FIG. 7.)

[0343] Although the Wnt proteins are traditionally classified as either canonical (eg Wnt-1 and Wnt 3a) or non-canonical (Wnt-4; Wnt-5 and Wnt-11), their activity at the cellular level depends in large measure to the presence of the frizzle (Fz) receptor on the receiving cell, and in the canonical pathway, a low density lipoprotein co-receptor (LRP 5/6). There are 19 Wnt ligands, 10 Frizzled receptors and 3 LRP co-receptors. There are over 120 target genes (Inestrosa et al 2012).

[0344] The classical canonical signaling pathway involves the binding of the extra-cellular Wnt ligand to the Fz receptor protein forming a cell surface complex with the related low density lipoprotein co-receptor (LRP5/6). This complex activates the phosphorylation of the cytoplasmic protein Dishevelled (Dvl), which in turn inactivates Glycogen---synthase-kinase-3beta (GSK-3 beta), thus preventing the degradation of beta catenin, which is then able to enter the nucleus of the receiving cell. Beta-catenin binds to a T-cell factor thus initiating the transcription of Wnt target genes. This results in a number of CNS functions including: development of the cerebral cortex and hippocampus; cell differentiation and adult neurogenesis (see later); cell proliferation, migration and differentiation; synaptic differentiation and glutamatergic functioning; inactivation of the inhibitor GSK-3beta; intracellular calcium dependent regulation thus strengthening the synaptic efficacy in developing neurons (Inestrosa et al 2012).

[0345] In short, the expression in the mature CNS of the Wnt ligand and its associated protein signaling pathways is central to its neuroprotection, pre and post synaptic plasticity including an increase in its LTP (Chen et al 2006); axon guidance and dendritic morphogenesis (Zhou et al 2006); the up regulation of synaptic NMDA receptors (Cerpa et al 2011) and an increased efficacy of GABAergic synapses (Cuitino et al 2010). More recently, non-canonical Wnt/Ca signaling in the hippocampus has been shown to trigger nitric oxide production (NO) which in turn enhances NMDA trafficking and fine tuning of synaptic activity (Munoz et al 2012; Varela-Nallar et al 2011).

Beta Amyloid and Wnt Signaling Pathways

[0346] Wnt signaling protects against beta amyloid induced neuronal damage, and the activation of its pathway has been suggested as a therapeutic approach to the prevention of Alzheimer's Disease (Inestrosa et al 2012). There is a strong association between impaired Wnt signaling, beta amyloid induced neuronal damage and an increase in tau protein phosphorylation---all hallmarks of AD.

[0347] A number of the aforementioned components of the Wnt pathway are involved. For example, elevated levels of the Wnt inhibitory GSK-3 beta has been found in brains with established AD neurofibrillary changes and increased tau hyperphosphorylation with a concomitant decrease in the protective beta catenin (Pei et al 1999). Inhibition of GSK-3beta (with Lithium) protects rat neurons from beta amyloid damage (Inestrosa et al 2012) and up regulation of beta catenin prevents tau protein induced neuronal apoptosis (Li et al 2007). In short, exposure of hippocampal neurons (in rats) to beta amyloid results in the following three main Wnt related consequences: destabilization of the protective endogenous levels of beta-catenin; an increase in the inhibitory GSK-3beta activity; a decrease in Wnt target gene transcription.

Wnt signaling, acetylcholinesterase (AChE), Alzheimer's Disease and Huperzine A

[0348] Acetylcholinesterase is found in the neuritic plaques in the brain of AD sufferers (Guela and Mesulam 1995; Guillozet et al 1997) and enhances beta amyloid aggregation and plaque formation. The AChE-beta amyloid complexes may result in greater neuronal loss than just the beta-amyloid (Alvarez et al 1998; Reyes et al 2004). In addition, AChE-beta amyloid complexes have been shown to reduce the levels of cytoplasmic beta-catenin in cultured hippocampal neurons (Alvarez et al 2004) which is reversed by up regulation of the Wnt signaling by co-treatment with cascade activators (lithium) or antagonists (Alvarez et al 1999).

[0349] Huperzine A---in addition to its other neuroprotective effects (see before)---inhibits the activity of GSK-3 beta and increases the level of beta catenin, in both mouse brain and in cultured human neuroblastoma cells (Wang et al 2011). A recent study has shown that cross talk between the Wnt signaling system and PKC inhibits the activity of GSK-3 beta and modulates the Wnt-catenin signaling thus regulating the phosphorylation of tau protein (and inhibiting neurofibrillary tangle formation) plus the processing of APP (Amyloid Precursor Protein) via the non-amyloidogenic pathway. The result: decreased amyloid plaque formation and neuronal apoptosis (Alvarez et al 2004; DeFerrari et al 2003; Wang et al 2011). These actions are complimentary to studies demonstrating Huperzine A's processing of APP via the non-amyloidogenic alpha-secretase pathway (Zhang et al 2004; Peng et al 2007; Wang et al 2011) and more recently, Huperzine A's inhibition of the amyloidogenic beta secretase pathway via its mediator, BACE1 (Wang et al 2011).

Dickkopf-1 (Dkk-1) a Physiologic Wnt/Beta-Catenin Antagonist

[0350] Memory impairment is associated with an age related decline in neurogenesis, with Dkk-1 a notable promoting factor via its inhibition of the canonical Wnt signaling pathway (Mac Donald et al 2009; Scott and Brann 2013). Long term estrogen deprivation leads to an elevation of Dkk-1 and dysregulation of Wnt/beta catenin signaling in the hippocampal neurons (Scott et al 2012). Conversely, loss of Dkk-1 in old age, restores hippocampal neurogenesis (Seib et al 2013).

[0351] Many studies have linked elevated levels of Dkk-1 to neurodegenerative diseases such as Alzheimer's Disease, Parkinson's disease, stroke and temporal lobe epilepsy (Scott and Brann 2013).

[0352] The cellular mechanism leading to Dkk-1 related neuronal dysfunction and death may result from an excess release of the excitatory neurotransmitter glutamate, with subsequent dose dependent (Cappuccio et al 2003) NMDA receptor activation and intracellular calcium overload (Zipfel et al 2000); the loss of protective Bcl-2, the induction of harmful Bax with hyperphosphorylation of microtubular tau protein (Scali et al 2006) following cerebral ischemic insults (Cappucio et al 2005; Scali et al 2006). The latter observation is complimented by the observation that patients with both ischemic stroke and confirmed coronary atherosclerotic plaques have elevated plasma levels of Dkk-1 compared with matched controls (Seifert-Heald et al 2011; Kim et al 2011). Dkk1 may therefore serve as a biomarker for these two diseases, and their association with an increased risk of cognitive dysfunction.

[0353] The accumulation of beta amyloid in cultured neuronal cells induces an over expression of Dkk-1 with subsequent hyperphosphorylation of tau protein and neuronal death (Caricasole et al 2004); higher levels of Dkk-1 expression is also found in post mortem human AD brain specimens (Caricasole et al 2004). Dkk-1 is up-regulated in the mouse model of fronto-temporal dementia and as in humans, was co-localized with neurons containing tau neurofibrillary tangles (Rosi et al 2010).

[0354] By blocking Wnt signaling, Dkk-1 prevents astrocyte associated neuroprotection (L'Episcopo et al 2011) and most importantly a decrease in the size of both the presynaptic and post synaptic terminals in mature neurons—without affecting cell viability—a feature typical of early memory loss due to "physiologic" brain aging related change (Purro et al 2012).

Adult Stem Cell Neurogenesis.

[0355] The compositions described herein can be used to promote adult stem cell neurogenesis. As an example, the compositions described herein can be used to increase the level of bone morphogenetic proteins in the brain, which is associated with the activation of neural stem cells. The compositions described herein can be used to activate the Wnt/beta-catenin signaling pathway and inhibit the Dkk1 and GSK3 beta activity.

[0356] It has been clearly established that neurogenesis continues throughout life in the mammalian brain, including that of humans (Faigle and Song 2013; Encinas et al 2013; Eriksson et al 1998; Roy et al 2000; Wang et al 2011). This complex process takes place in just two regions of the mammalian brain: the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the hippocampal dentate gyrus (DG). This complex and dynamic process is governed by a number of integrated factors that create a local "check and balance" microenvironment in the so-called "stem cell niche". It is in this part of the brain where neural precursors—via cell to cell interaction—react to secreted factors and neurotransmitters resulting in differentiated glial cells and neurons, and some into hippocampal astrocytes (Song et al 2002). (See FIG. 8.)

[0357] A number of soluble extracellular factors have been identified that regulate stem cell signaling pathways: bone morphogenetic protein (Choe et al 2013-review); Wnt/beta catenin pathway (see before); Notch (Louvi et al 2006; Yoon and Gaiano 2005); sonic hedgehog (Traiffort et al 1998; Lai et al 2003); neurotrophins and neurotransmitters (see before).

[0358] Neurogenesis: MRI studies have documented the reduction in volume of the aging frontal and temporal lobes of the cerebral hemispheres, a "physiologic" atrophy of cortical neurons (neuropenia) that is also characteristic of many neurodegenerative diseases including AD, Parkinson's Disease, Huntington's Disease, post traumatic brain injuries and stroke. (Forma et al. 2004).

[0359] Wnt/beta-catenin pathway. The Wnt glycoprotein is highly expressed in the DG hilar cells and in cultured hippocampal astrocytes. Through its signaling pathway, Wnt mediates neuroblast proliferation and the neuronal differentiation of adult hippocampal progenitor cells (Lie et al 2005). The latter occurs via NeuroD1 transcriptional activation (Kuwabara et al 2009). The Wnt pathway, by stabilizing beta catenin and its cytoplasmic inclusion, activates other downstream transcription factors that prevent premature cell cycle exit and so promote neuronal differentiation (Mao et al 2009).

[0360] Over expression of Wnt subtypes have been shown to promote proliferation and neuronal differentiation of adult SVZ neuronal progenitor cells (Adachi et al 2007).

[0361] Application: Huperzine A activates Wnt/beta-catenin signaling (Wang et al 2001).

[0362] Notch pathway. The Notch pathway participates in many cellular processes in the developing nervous system including cell proliferation, differentiation and apoptosis (Louvi et al 2006; Yoon et al 2005). Notch is expressed in both the SVZ and the SGZ and regulates the NSC by controlling cell cycle exit, as well as maintenance and differentiation of adult neural stem cells (Breunig et al 2007; Imayoshi et al 2010). Notch has an important role in the dendritic arborization of immature neurons in the adult brain (Breunig et al 2007).

[0363] Sonic Hedgehog pathway (Shh). Sonic Hedgehog is a soluble extracellular signaling protein that is important for neurogenesis in the adult mammalian brain. In addition to increasing hippocampal progenitor cell proliferation in the DG, Shh promotes the self-renewal and proliferation of adult neural stem cells and regulates their cellular migration (Angot et al 2008; Ihrie et al 2011

[0364] Neurotrophic factors. Of the four identified neurotrophic factors—brain derived neurotrophic factor (BDNF); nerve growth factor (NGF), neurotrophin 3 (NT-3) and neurotrophin 4/5 (NT-4/5)—it is mainly BDNF that has been linked to the activation of the various downstream effectors involved in neurogenesis. This occurs via the binding of BDNF to its tyrosine kinase receptor, TrkB. Studies have documented that functional TrkB signaling is required to stimulate the proliferation of neural stem cells in the hippocampus (Li et al 2008) and that the survival, dendritic arborization and functional integration of newborn neurons in the adult DG is dependent on TrkB receptor activity (Bergami et al 2008). The role of BDNF in the SVZ is less clear.

[0365] NGF does not have an effect on the proliferation of progenitor cells in the DG, but has been associated with the enhanced survival of neurons in the adult hippocampus (Frielingsdorf et al 2007). NT-3 has been shown to mediate spatial learning and memory in the adult brain (Shimazu et al 2006; Frielingsdorf et al 2007).

[0366] Given their mode of action, the neurosteroids have the potential to stimulate the self-renewal, proliferation and differentiation of neural stem and progenitor cells via the expression of the specific genes involved in neural stem cell fate (see FIG. 8) in addition to the function of extra-cellular

signaling molecules: Wnt/beta catenin; Notch; Sonic Hedgehog- and various growth factors—TGF alpha; EGF and FGF (Hagg 2005). (See FIG. 9).

[0367] All estrogens and most androgens in post menopausal women are made locally in peripheral target tissues according to the physiological mechanism of intracrinology. These locally synthesized sex steroids exert their action and are inactivated intracellularly without significant contribution from steroids in the systemic circulation, except in older men (age 65 to 75), where approximately 40% is contributed by the adrenal gland (Labrie 2010; Luu-The et al 2010).

[0368] DHEA is the exclusive and tissue specific source of these sex steroids, and with its age associated decrease, is related to a number of medical problems such as osteoporosis, muscle wasting, type II diabetes, memory loss, cognitive dysfunction, and possibly Alzheimer's disease (Labrie 2010).

[0369] As noted in FIG. 1, all neurosteroids and brain estrogens (and their metabolites) are synthesized via DHEA and result in both local androgenic and estrogenic activity. Thus, in addition to neurosteroid specific actions (Hagg 2005), estrogen mediated growth factors such as bone morphogenic proteins (bmp) are up-regulated (Otani et al 2009) and control a number of CNS cell processes including cell survival, proliferation, and differentiation (Harvey et al 2005, Liu et al 2005) plus Wnt signaling responsiveness (Chloe et al 2013; Faigle et al 2013).

[0370] As previously stated, the Wnt/beta catenin pathway is highly expressed in DG hilar cells and in cultured hippocampal astrocytes. Through this signaling pathway, Wnt mediates neuroblast proliferation and the neuronal differentiation of adult hippocampal progenitor cells (Lie et al 2005).

[0371] Similar cellular processes in the developing nervous system are modulated via the Notch pathway (Louvi et al 2006; Yoon et al 2005; Breunig et al 2007; Imayosi et al 2010) and sonic hedgehog pathway (Angot et al 2008; Ihrie et al 2011) by the subject invention's ingredients. (See FIG. 9.)

[0372] Vitamin D and Neurogenesis.

[0373] The human brain has established pathways for both the synthesis and degradation of vitamin D3 (Garcion et al; Eyles et al 2005). Clinical studies have confirmed a linkage with low vitamin D and cognitive impairment (Morris 1993) and with vitamin D treatment, slowing down the cognitive impairment and deterioration of patients with AD (Buell and Dawson-Hughes 2008). These clinical observations are supported by the demonstration of reduced mRNA levels of the vitamin D receptor (VDR) in the hippocampal CA1 and CA2 regions in post mortem AD brains (Sutherland et al 1992) and the increased frequency of VDR polymorphisms in AD brains compared with age-matched normal controls (Gezen-Ak 2007).

[0374] Stem cells and neural progenitor cells in the hippocampal dentate gyrus (DG) retain the ability to proliferate and develop into neurons in adults (Christie and Cameron 2006). Vitamin D3 deficiency promotes the death of newly generated neurons and their neurite growth (Brown et al 2003) before they reach maturation (Zhu et al 2012). This occurs as a result of a decline in the level of hippocampal NGF which is needed for the late stage of normal neurogenesis. The decrease in NGF is associated with a reduction of the neuronal 1 alpha (OH)ase (CYP27B1) gene (Zhu et al 2012) and, experimentally, is corrected by treatment with NGF. Vitamin D3 regulates important cell functions such the multiple Ca++-dependent signaling processes.

[0375] Vitamin D regulates the synthesis of NGF and other neurotrophins: NT3 and Glial derived neurotrophic factor. Two of the proposed additives also function as neuropeptides: GLP-1 and NGF induced neurogenesis and caffeine increases hippocampal BDNF.

Oxygen and the Regulation of Neurogenesis in Health and Disease

[0376] The compositions described herein can be used to up regulate CNS acetylcholine synthesis. The compositions described herein can also be used to regulate blood flow and angiogenesis. The two major substrates for brain energy and cellular function are glucose and oxygen.

[0377] The brain consumes about 20% of the total body requirements at a relatively low oxygen tension: 27+− 6 mmHg in the cerebral cortex and 20+− 3 mmHg in the hippocampus (Ivanovic 2009). This so-called "physiologic hypoxia" is central to neurogenesis and to the local brain demands of brain metabolic activity.

[0378] Within the stem cell "neurogenic niche" (in the DG and SVZ) is the "vascular niche", comprised of blood vessels adjacent to and within the neuroblast complexes, and which serves as an essential component of the "oxygen niche" (Shen et al 2008). Dividing stem cells are closely apposed to the vascular endothelial cells.

[0379] Proliferation of neural stem cell (NSC) is promoted and apoptosis is reduced when in an environment of low 02 tension. This includes the differentiation of precursor cells into neurons with specific neurotransmitter function. Reduced oxygen levels also promote cell survival and proliferation of CNS stem cells (Morrison et al 2000). Hypoxia promotes the proliferation of NSC via the hypoxia-inducible transcription factor 1 alpha (HIF-1) (Zhao et al 2008; Panchision 2009). The following molecular mechanisms modify the behavior and function of NSC's in lower oxygen levels: Notch pathway (Diez et al 2007); Bone morphogenetic protein pathway (Pistollato et al 2007) and the Wnt/beta-catenin pathway (Jolly et al 2009).

[0380] In addition, cholinergic pathways regulate cerebral vascular resistance, relaxation and regional blood flow (Sato et al 2004). This is also mediated via muscarinic Ach receptors that trigger the release of the actual relaxing factor: NO. Acetylcholine induced relaxation occurs in cerebral but not peripheral blood vessels (Yamada et al 2001).

[0381] Androgens and Beta Amyloid: Production and Clearance.

[0382] Amyloid production: Testosterone promotes the non-amyloidogenic APP processing through the ERK1/2 signaling pathway thus increasing the APP alpha metabolic pathway and decreasing the accumulation of amyloid beta (Gouras et al 2000). This action is complementary to that of huperzine A and caffeine. Androgens provide further protection by also down regulating BACE (beta secretase) expression and thus the harmful amyloidogenic metabolism of APP (McAllister et al 2010).

[0383] Amyloid clearance: Androgens are endogenous modulators of the amyloid beta, and strongly up regulate the neuronal expression of neprilysin (Yao et al 2008) a powerful amyloid degrading enzyme. The neprilysin gene has at least two androgen response elements (Shen et al. 2000). Androgens thus act through a classic genomic AR-dependent mechanism. This activity allows for the clearance of the more soluble non-amyloidogenic APP through the BBB, a process

that is facilitated by an increase in CSF production and turnover, a function enhanced by the caffeine additive.

[0384] Androgens and AD: Clinical Studies.

[0385] The aging rat male brain is less responsive to androgens and may be due in part to low levels of AR binding and thus poor responsiveness to testosterone treatment (Chambers et al 1991). Treatment is more effective in middle aged rats both in terms of regulating AR activity and in behavior (Wu et al. 2010).

[0386] There are few studies evaluating androgen based therapy for the prevention of dementia in men. Some studies have shown improvement in spatial memory in men with MCI and AD (Cherrier et al. 2001; Lu et al. 2005). Hypogonadal males treated with testosterone did exhibit marked improvements in cognition. (Tan and Pu 2003).

[0387] SARM's: Brain Specific Androgen Therapy.

[0388] To separate the potential risk of an adverse effect of systemic testosterone based therapy (e.g. undesired effect on the prostate) a number of androgen like ligands tailored to tissue specific organs—selective androgen receptor modulators (SARMS)—are being developed (Barron and Pike 2013). This includes SARMS with specific CNS activity. Recently, a synthetic analog DHEA neurosteroid has been developed that binds directly to the NGF receptors and avoids systemic estrogenic and androgenic properties (Gravanis et al. 2012).

[0389] Vascular Dementia (VaD): A Multimodal Cause of Cognitive Impairment.

[0390] Huperzine A: The therapeutic efficacy of huperzine A in VaD has been extensively evaluated in both the animal model and in human trials. This includes benefits in learning deficits and reduced neuronal brain damage in rats following long term treatment with huperzine A subsequent to induced chronic cerebral hypoperfusion (Wang et al 2000) and similarly, long term huperzine A treatment in a gerbil transient global ischemia model. This study showed Huperzine A partially restored ChaT hippocampal activity and reduced memory impairment, and hippocampal neuronal degeneration (Zhou et al 2001).

[0391] A recent randomized, double blinded placebo controlled study concluded that huperzine A in a twice daily dose of 100 mcg for 12 weeks significantly improved cognitive function in patients with mild to moderate VaD (Xu et al 2012). This result was confirmed by a recent meta-analysis of huperzine A treatment of AD and VaD (Shu-huai Xing et al 2014). Huperzine A has multiple neuroprotective effects through several molecular sites as noted previously.

[0392] DHEA: DHEA and DHEA-S are produced in the brain and as neurohormones that stimulate neuronal differentiation, neuronal function and promote synaptic density. (Leranth et al 2003; see before).

[0393] DHEA increases the expression of BDNF as well as CNS acetylcholine. In a recent rat model study of VaD, treatment with DHEA significantly increased the working and reference memories of the surgically treated vs the untreated control rats (Sakr et al 2014). BDNF is a key protein that regulates the maintenance and growth of neurons and is necessary for cell proliferation, cell differentiation, neuronal protection and the regulation of synaptic function. This includes the long term potentiation (LTP) of neurons, learning, memory and mood (Yamada et al (2002).

[0394] The rat VaD model also produces a significant decrease in the central concentration of acetylcholine in the hippocampus. This is reversed by treatment with DHEA due both by a decrease in acetylcholine esterase activity and an increase in the release of acetylcholine from the hippocampus (Rhodes 1996).

[0395] DHEA has vascular benefits in patients with impaired glucose metabolism and diabetes, significant risk factors for VaD. This includes inhibition and dysfunction of endothelial cells (Huerta-Garcia et al (2011); platelet aggregation (Monoz et al 2012; Bertoni et al 2012); and improvement in insulin resistance (Weiss et al 2011). The improvement in insulin sensitivity was associated with reduced plasma triglycerides and the inflammatory cytokines: interleukin-6 and tumor necrosis factor alpha.

[0396] Vitamin D: A recent 30 year follow up study of over 10,186 citizens from the general Danish population, confirmed a significant relationship between reduced plasma vitamin D (25-hydroxyvitamin D) and both AD and VaD (Afzal et al 2014).

[0397] Cerebrovascular lesions lower the threshold of AD related changes associated with cognitive decline and dementia (Esiri et al 1999).

[0398] Multiple systemic reviews and meta-analyses have correlated cardiovascular risk factors (hypertension, hypercholesteremia, diabetes) with low levels of vitamin D and an increased risk of CNS events such as stroke. Vitamin D is protective to the cardiovascular system via a number of pathways including modulating blood pressure, endothelial response to injury and blood coagulation, and insulin sensitivity.

[0399] Insulin is essential for normal CNS function, with insulin resistance being a major contributor to the hyperphosphorylation of tau protein, the accumulation of amyloid precursor protein and its metabolism to beta amyloid and thus AD. Vitamin D stimulates insulin receptor expression, enhances insulin response to glucose and increases the bioconversion of inactive pro-insulin to bioactive insulin (Tai et al 2008; Maestro et al 2000).

[0400] Studies have noted that vitamin D supplementation might have a protective effect on cognition (Annweiler et al 2013; Barnard and Colon-Emeric 2010).

EXAMPLES

[0401] The examples illustrate exemplary methods provided herein. These examples are not intended, nor are they to be construed, as limiting the scope of the disclosure. It will be clear that the methods can be practiced otherwise than as particularly described herein. Numerous modifications and variations are possible in view of the teachings herein and, therefore, are within the scope of the disclosure.

Examples 1-3

Bioavailability of Huperzine A, DHEA and Vitamin D3 of CogniHomme Forte™ in Male Volunteers: Translational Pharmacokinetic and Pharmacodynamic Studies

[0402] Goal: To apply experimental proof of concept principles by combining selected botanical and natural compounds and/or their synthetic derivatives, and to demonstrate their systemic bioavailability (pharmacokinetics) and bioactivity as brain health modulators (pharmcodynamics) in adult patients with and without symptoms of cognitive, memory and/or mood impairment, and as promoters of healthy brain aging.

[0403] Rationale: CogniHomme Forte™ is a broad based balanced bioactive brain blend that comprises DHEA, Huperzine A vitamin D, and one or more additives. The following study allows assessment of the combined effects of DHEA, Huperzine A, and vitamin D with a caffeine and/or other additives on varying aspects of cognition, executive function and memory. The advantage of the CogniHomme Forte™ is based on the combination's additive and/or synergistic bioactivity of each ingredient's independent effect on relevant aspects of the multiple molecular signaling pathways involved in brain health and function, including but not limited to the non-amyloidogenic metabolism of amyloid precursor protein (APP).

[0404] Assessments are based on the evaluation of differing dosage regimens to meet the clinical needs of patients with asymptomatic physiologic brain aging, those with accelerated and symptomatic change (benign senescent forgetfulness), and patients at risk of developing mild cognitive impairment (MCI).

[0405] The studies include the measurement of each ingredient's pharmacokinetic profile based on the CogniHomme Forte™'s proprietary sequenced and time released formulation, and the standardized assay of biomarkers associated with neurotrophic function, neurotransmission and brain health protective activity. Clinical response is based on standardized neuropsychologic tests sensitive to the effects of the ingredients in the blend.

[0406] Pharmacokinetic Study: To measure the absorption, bioavailability and bioactivity of three strengths of the CogniHomme Forte™ with a caffeine additive.

[0407] Aim: To determine the blood levels of each of the CogniHomme Forte™ proprietary formulated ingredients with specific assays (Huperzine A; DHEA; 25 (OH) vitamin D3) plus caffeine over a 48 hour time interval, and to assay alterations in the biomarkers of two neurotrophic proteins: brain derived neurotrophic factor (BDNF) and Nerve Growth Factor (NGF); two biomarkers of acetylcholine metabolism: Choline acetyltransferase (ChAT) and Acetylcholinesterase (AChE); biomarker of Wnt/beta catenin: Dkk1; fetuin A, and inflammatory markers.

Example 1

Formulation with Immediate Release (IR) Natural Ingredients

[0408] Study Design: Randomized single dose three way open label crossover under fasted conditions of three prototype formulations of CogniHomme Forte™ designated A, B and C is administered to male subjects.

[0409] Test Products:

[0410] A DHEA 25 mg, Vitamin D3 600 i.u., Huperzine A 100 mcg, Caffeine 75 mg (AM dose)

[0411] DHEA 25 mg, Vitamin D3 600 i.u., Huperzine A 75 mcg (PM dose)

[0412] B DHEA 25 mg, Vitamin D3 600 i.u., Huperzine A 100 mcg, Caffeine 75 mg (AM dose)

[0413] DHEA 25 mg, Vitamin D3 600 i.u., Huperzine A 150 mcg (PM dose)

[0414] C DHEA 25 mg, Vitamin D3 600 i.u., Huperzine A 100 mcg, Caffeine 75 mg (AM dose)

[0415] DHEA 25 mg, Vitamin D3 600 i.u., Huperzine A 225 mcg (PM dose)

[0416] Study Subjects:

[0417] Ten healthy adult male subjects aged 40-65

[0418] Currently not using a Vitamin D supplement (at least 1 month washout).

[0419] Currently not using DHEA Supplement (at least three months washout).

[0420] Dosing Regimen:

[0421] Single capsule of test product is ingested with 8 fl oz of room temperature water, after an overnight fast of at least 10 hours and by 8:00 AM, followed at 8:00 PM with the PM dose test product also ingested with 8 fl oz of room temperature water.

[0422] Washout: At least 7 days

[0423] Confinement:

[0424] At least 10 hours prior to dosing to 24 hr after each dosing period.

[0425] pK sampling:

[0426] 17 blood samples per subject for each dosing period for biochemical analysis

[0427] 120 min prior to dosing then at 0.25, 0.5, 0.75, 1.0, 1.25, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours post dose.

[0428] Bioanalytical Sample Analysis:

[0429] Huperzine A

[0430] DHEA, DHEA-S, and testosterone

[0431] 25 hydroxy vitamin D3

[0432] Caffeine

[0433] Acetylcholinesterase

[0434] BDNF

[0435] Dkk1

[0436] Inflammatory cytokine profile

[0437] Pharmacokinetic and Statistical Data Analysis:

[0438] Pharmacokinetic analyses are performed using standard non-compartmental methods.

[0439] Statistical analyses are performed using SAS® and 90% confidence interval and ratios for relative mean ln-transformed AUC0-t, AUC0-∞, and Cmax of each test formulation are calculated.

Example 2

Formulation with Extended/Timed Release (ER) Natural Ingredients

[0440] Study design: Subject selection, preparation, sampling, and analyses are performed in the same as described in Example 1.

[0441] Test Products: Once daily dosing.

[0442] A. DHEA 50 mg, Vitamin D 1200 i.u., Huperzine A extract 175 mcg; caffeine 75 mg.

[0443] B. DHEA 50 mg, Vitamin D 1200 i.u., Huperzine A extract 250 mcg; caffeine 75 mg.

[0444] C. DHEA 50 mg, Vitamin D 1200 i.u., Huperzine A extract 325 mcg; caffeine 75 mg.

Example 3

Formulation with Extended/Time Release Synthetic Huperzine A

[0445] Study design: Subject selection, preparation, sampling, and analyses are performed in the same manner as described in Example 1.

[0446] Test products: Dosing (once daily) and the amounts of DHEA and Vitamin D are the same as in Example 2 with an equivalent amount of synthetic Huperzine A (as natural Huperzine A).

[0447] A. DHEA 50 mg, Vitamin D 1200 i.u., synthetic Huperzine A equal to huperzine A extract 175 mcg; caffeine 75 mg.

[0448] B. DHEA 50 mg, Vitamin D 1200 i.u., synthetic Huperzine A equal to huperzine A extract 250 mcg; caffeine 75 mg.

[0449] C. DHEA 50 mg, Vitamin D 1200 i.u., synthetic Huperzine A equal to huperzineA extract 325 mcg; caffeine 75 mg.

[0450] All publications, patents and patent applications cited in this specification are incorporated herein by reference in their entireties as if each individual publication, patent or patent application were specifically and individually indicated to be incorporated by reference. While the foregoing has been described in terms of various embodiments, the skilled artisan will appreciate that various modifications, substitutions, omissions, and changes may be made without departing from the spirit thereof.

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1.-106. (canceled)

107. A composition comprising Huperzine A or a derivative or analog thereof; a dehydroepiandrosterone (DHEA) or a derivative or analog thereof; and a vitamin D.

108. The composition of claim **107**, wherein the DHEA is selected from the group consisting of a 17-α derivative, a 17-β derivative, 17-spiro analog of DHEA, testosterone, androstenedione, androstenediol and a sulfated derivative (DHEA-S).

109. The composition of claim **107**, wherein the vitamin D is selected from the group consisting of calcitriol, doxercalciferol, paricalcitol, cholecalciferol (vitamin D3), ergocalciferol (vitamin D2), analogs and derivatives thereof, vitamin D receptor agonists and modulators, and combinations thereof.

110. The composition of claim **107**, further comprising one or more additives selected from the group consisting of coffee, xanthine alkaloids, chlorogenic acid, sweeteners, and combinations thereof; and wherein the xanthine alkaloid is selected from the group consisting of caffeine, theobromine, paraxanthine, and combinations thereof, and the sweetener is selected from the group consisting of sucromalt, tagatose, isomalt, sucralose, acesulfame potassium, analogs and derivatives thereof, and combinations thereof.

111. The composition of claim **107**, wherein the composition comprises from about 0.01 mg to about 150 mg of Huperzine A or a analog or derivative thereof.

112. The composition of claim **107**, wherein the composition comprises from about 0.01 mg to about 1000 mg of a DHEA.

113. The composition of claim **107**, wherein the composition comprises from about 200 iu to about 5000 iu of vitamin D, an analog thereof, or a vitamin D receptor agonist and modulator.

114. The composition of claim **110**, wherein the composition comprises from about 10 mg to about 100 mg of the xanthine alkaloid.

115. The composition of claim **110**, wherein the composition comprises from about 10 g to about 100 g of the sweetener.

116. The composition of claim **107**, wherein the composition comprises Huperzine A or an analog or derivative thereof, DHEA, and vitamin D.

117. The composition of claim **116**, wherein the composition comprises from about 40 mcg to about 400 mcg of Huperzine A or an analog or derivative thereof, about 50 to 175 mg of DHEA, and about 1200 iu of vitamin D.

118. The composition of claim **110**, wherein the composition comprises from about 40 mcg to about 400 mcg of Huperzine A or an analog or derivative thereof, about 50 to 175 mg of DHEA, about 1200 iu of vitamin D, about 75 mg of caffeine, and about 75 g of sucromalt.

119. The composition of claim **107**, wherein the composition is formulated for immediate release, extended release, or timed sequential release.

120. The composition of claim **107**, wherein the composition is formulated in the form of a tablet, a capsule, a powder, an emulsion, a suspension, a syrup, a solution, a gel, and a patch.

121. The composition of claim **107**, wherein the composition is a nutraceutical composition.

122. The composition of claim **107**, wherein the composition is a pharmaceutical composition comprising vitamin D, Huperzine A, and a DHEA.

123. The composition of claim **107**, wherein Huperzine A, and vitamin D are synthetic compounds and DHEA or a derivative or analog thereof.

124. A pharmaceutical composition comprising the composition of claim **107** and a pharmaceutically acceptable carrier.

125. A method of promoting healthy brain aging of a subject, wherein the method comprises administering an effective amount of the pharmaceutical composition of claim **124** to the subject in need thereof.

126. A method of promoting neuronal cell dendritic arborization, synaptic transmission and synaptic long term potential, wherein the method comprises administering an effective amount of the pharmaceutical composition of claim **124** to neuronal cells.

127. A method of promoting, stimulating or inducing neurogenisis of cells, wherein neurogenisis comprises production of neurotrophins and/or neurotransmitters, the method comprising administering an effective amount of the pharmaceutical composition of claim **124** to a subject in need thereof; and

wherein the neurotrophins are selected from the group consisting of brain derived neurotrophic factor, nerve growth factor, bone morphogenic proteins, Sonic hedgehog, Notch and combinations thereof, and the neurotransmitters are selected from the group consisting of serotonin, glutamate, acetylcholine, and combinations thereof.

128. The method of claim **126**, wherein the cells are neural stem cells or neural progenitor cells.

129. A method of stimulating and/or activating the wnt/beta catenin pathway by a combination of stimulating the synthesis of beta catenin and the binding of beta catenin to its receptor, and/or by inhibiting natural antagonists of the wnt/beta catenin pathway, wherein the method comprises administering an effective amount of the pharmaceutical composition of claim **124** to a subject in need thereof

130. The method of stimulating and/or activating the wnt/beta catenin pathway according to claim **128**, wherein the natural antagonist is selected from Dkk-1 and GSK-3 beta.

131. A method of inhibiting apoptosis of neuronal cells, wherein the method comprises administering an effective amount of the pharmaceutical composition of claim **124** to a subject in need thereof to promote the expression of Bcl-2 and/or inhibit the expression of P53 or Bax.

132. A method of providing neuroprotection of the brain, the method comprising administering an effective amount of the pharmaceutical composition of claim **124** to a subject in need thereof.

133. The method of claim **132**, wherein the method inhibits the formation and/or accumulation of beta amyloid in neuronal cells expressing amyloid precursor protein (APP) by stimulating the cleavage of APP via the alpha secretase pathway and/or inhibiting the beta and gamma secretase pathways.

134. A method of inhibiting the formation of neurofibrillary tangles and deacetyalating of tau protein, wherein the method comprises administering an effective amount of the pharmaceutical composition of claim **124** to a subject in need thereof.

135. A method of inducing the expression of sirtuin genes, wherein the sirtuin genes comprise a SIRT1 gene, and wherein the method comprises administering an effective amount of the pharmaceutical composition of claim **124** to a subject in need thereof.

136. A method of promoting an increase in efflux of beta amyloid from neuronal cells into the blood stream, wherein the method comprises administering an effective amount of the pharmaceutical composition of claim **124** to a subject in need thereof.

137. A method of maintaining the integrity of the blood brain barrier (BBB), and/or facilitating glucose transport across the BBB, wherein the method comprises administering an effective amount of the pharmaceutical composition of claim **124** to a subject in need thereof.

138. A method of enhancing brain insulin metabolism by stimulating synthesis of insulin and/or promoting insulin sensitivity in the brain of a subject and/or by inhibiting insulin resistance in neuronal cells, wherein the method comprises administering an effective amount of the pharmaceutical composition of claim **124** to the subject in need thereof.

139. A method of inhibiting inflammation in a subject, wherein the method comprises administering an effective amount of the composition of claim **124** to a subject in need thereof such that the secretion of inflammatory cytokines is inhibited and/or cytokine levels in the brain are reduced.

140. A method of modulating, treating, inhibiting, retarding, or preventing oxidative stress in the central nervous system of a subject, wherein the method comprises administering an effective amount of the pharmaceutical composition of claim **124** to a subject in need thereof.

141. A method of enhancing cerebral blood flow in a subject, and/or supply of oxygen and/or glucose to the brain of a subject, wherein the method comprises administering an effective amount of the pharmaceutical composition of claim **124** to the subject in need thereof.

142. A method of stimulating acetylcholine synthesis by stimulating acetylcholine transferase activity and/or inhibiting cholinesterase activity in a subject, wherein the method comprises administering an effective amount of the pharmaceutical composition of claim **124** to the subject in need thereof.

143. A method of inhibiting glutamate toxicity in a subject, wherein the method comprises administering an effective amount of the pharmaceutical composition of claim **124** to a subject in need thereof.

144. A method of modulating N-methyl-D-aspartate (NMDA) receptors in a subject, wherein the method comprises administering an effective amount of the pharmaceutical composition of claim **124** to the subject in need thereof.

145. A method of preventing, inhibiting, retarding, or treating neuronal degeneration and/or a decline in cognitive function in a subject at increased risk of impaired cognitive function, executive function or memory disorder, wherein the method comprises administering an effective amount of the pharmaceutical composition of claim **124** to the subject in need thereof.

146. A method of alleviating the symptoms of a subject diagnosed with mild cognitive impairment and/or Alzheimer's disease, wherein the method comprises administering an effective amount of the pharmaceutical composition of claim **124** to the subject in need thereof.

147. A method of preventing, retarding or inhibiting mild cognitive impairment and/or Alzheimer's disease in a subject at risk of developing or diagnosed with mild cognitive impairment and/or Alzheimer's diseases, wherein the method comprises administering an effective amount of the pharmaceutical composition of claim **124** to the subject in need thereof.

148. A method of preventing, retarding or treating vascular dementia, wherein the method comprises administering an effective amount of the pharmaceutical composition of claim **124** to a subject in need thereof.

149. A method of treating individuals with hypercholesteremia, metabolic syndrome, type II diabetes, obesity, osteopenia, osteoporosis, and hypertension, wherein the method comprises administering an effective amount of the pharmaceutical composition of claim **124** to a subject in need thereof as adjunctive therapy with other drugs, wherein the other drugs are for treating a primary disease in the subject.

150. A method of individualizing the dosage of the pharmaceutical composition of claim **124** to promote brain health and treatment of cognitive dysfunction and age related dementia in a subject, wherein the method comprises administering an individual effective amount of the composition of the pharmaceutical composition of claim **124** to the subject in need thereof.

151. A method of measuring and monitoring absorption of bioactive levels of the components of pharmaceutical composition of claim **124**, wherein the method comprises;

(a) administering an effective amount of the pharmaceutical composition of claim **124** to a subject in need thereof;

(b) measuring and/or monitoring the absorption of bioactive levels of one or more components and/or biomarkers; and

(c) determining whether an optimal level or range of each component has been reached for maintaining a healthy brain or for the treatment of the symptoms of mild cognitive impairment, dementia, or Alzheimer's disease.

152. A method of measuring and monitoring bioactive brain health protective efficacy of the pharmaceutical composition of claim **124**, wherein the method comprises:

(a) assaying brain specific biomarkers;
(b) measuring and/or monitoring oxidative stress; and
(c) assessing clinical tests of cognitive function.

153. The method of claim **152**, wherein the brain specific biomarker is selected from the group consisting of brain derived neurotrophic factors, nerve growth factor, acetylcholine esterase, acetylcholine transferase, Dkk-1, GSK-3 beta, fetuin and inflammatory cytokines.

154. A method of treating stress related cognitive impairment in a subject, the method comprising administering an effective amount of the pharmaceutical composition of claim **124** to the subject in need thereof to restore and/or maintain a balanced DHEA/cortisol ratio and/or DHEA-S/cortisol ratio, wherein DHEA and/or DHEA-S is present as the major component.

155. A method of treating a subject following post concussion syndrome, post traumatic stress disorder, or post traumatic brain damage, wherein the method comprises administering an effective amount of the pharmaceutical composition of claim **124** to the subject in need thereof.

156. The composition of claim **123**, wherein the DHEA is dehydroepiandrosterone sulfate.

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