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(54) Title: METHODS OF TREATING, PREVENTING OR AMELIORATING DEPRESSION OR ANXIETY WITH CAROTENOIDS

(57) Abstract: The present invention relates to the use of one or more carotenoids for treating, preventing and/or ameliorating depression and/or anxiety in a woman. In an embodiment, the woman is at a stage of pregnancy. In an embodiment, the one or more carotenoids are selected from the group consisting of lutein, zeaxanthin, β-cryptoxanthin, lycopene, α-carotene and β-carotene.

WO 2021/183059 A1

METHODS OF TREATING, PREVENTING OR AMELIORATING DEPRESSION OR ANXIETY WITH CAROTENOIDS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of Singapore application No. 10202002301W, filed on 12 March 2020, the contents of it being hereby incorporated by reference in its entirety for all purposes.

TECHNICAL FIELD

[0002] The present disclosure generally relates to methods of treating and/or preventing and/or ameliorating a mental health adversity, in particular methods of treating and/or preventing and/or ameliorating a mental health adversity selected from the group consisting of preconception, pregnancy, and postpartum related mental health adversity in a woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, and more particularly methods of treating and/or preventing and/or ameliorating a mental health adversity selected from the group consisting of preconception, pregnancy, and postpartum related mental health adversity in a woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage using carotenoids.

BACKGROUND

[0003] Anxiety and depression are both debilitating conditions affecting a large proportion of the population worldwide and emanating commonly from psychological stress. Anxiety and major depression have been shown to be linked to oxidative stress. Studies have demonstrated lower levels of antioxidants and antioxidant enzymes in depressed patients. Stress and depression have also been linked to upregulation in the inflammatory responses of the body. Before, during and post pregnancy, depression has also been shown to be associated with elevated oxidative stress and pro-inflammatory cytokines. Prevalence of mental health adversities during pregnancy in developed and developing countries are 10% and 25%, respectively. Such adversities not only influence the general well-being of the mother but also the early care environment and socio-emotional development of her offspring. As such, the optimization of maternal mental health has important economic and public health benefits.

[0004] The general protective role of dietary factors in depression owing to their anti-inflammatory and antioxidant properties has been documented. One class of antioxidants known as carotenoids, are a group of fat-soluble pigments and are found abundantly in dark leafy and yellow orange vegetables and fruits. There are over 600 carotenoids that have been identified so far in nature, and human diet contains over forty different varieties of carotenoids. However, only 6 carotenoids (α-carotene, β-carotene, β-cryptoxanthin (BCX), lycopene, lutein and zeaxanthin) have detectable concentrations in human serum (an indicator of dietary intake). Some carotenoids like β-carotene, α-carotene and BCX can be converted to vitamin A in humans thereby meeting body requirements. Epidemiological studies have indicated that dietary intake of carotenoids may be of benefit in maintaining cognitive health and reducing stress via its antioxidant, anti-inflammatory and immunomodulatory properties. However, these observations were conducted in midlife women, elderly people and younger populations, while associations with anxiety have only been shown in mice. In pregnant woman, carotenoids have been reported to be protective against preeclampsia, reduce the risk of preterm birth and giving birth to small for gestational age babies. However, the link between carotenoids and mental health adversities such as preconception, pregnancy, and postpartum related mental health adversity, for example, depression and/or anxiety, has not yet been demonstrated.

[0005] Conventional therapy for mental health adversities such as depression and/or anxiety includes pharmacological interventions, such as anti-anxiety medications, antidepressants, and so on. These pharmacological interventions have several drawbacks. First, the available evidence suggests that there is both an overuse of psychotropic medications among women with milder disorders or for a broader range of conditions than is supported by research, thus imposing a risk of addiction, as well as an underuse and inappropriate discontinuation for women with more severe disorders associated with a high relapse risk. Second, antidepressants are often associated with adverse effects. For example, use of antipsychotics may be associated with greater metabolic risks for the mother and growth impairment in infants (including the risk of being large for gestational age among babies exposed to second-generation antipsychotics). In addition, antidepressants such as selective serotonin reuptake inhibitors (SSRIs) may be associated with a small risk of prematurity, especially when used in the second and third trimesters. SSRIs have also been shown to link to an increased risk of a severe respiratory neonatal condition (persistent pulmonary hypertension of the unborn). Thus, typically, to avoid potential addiction and harm to growing fetus, pharmacological

interventions are avoided in pregnancy and instead psychological and psychosocial interventions are used. Most psychological and psychosocial intervention trials have tested cognitive behavioral therapy (CBT), and there is also evidence of clinical effectiveness for a range of other interventions, including interpersonal therapy (IPT), listening visits, and exercise. However, regarding these psychological and psychosocial intervention, the effectiveness remains uncertain. For example, a substantial minority of patients do not respond adequately to psychological and psychosocial treatment, and of those who do, a substantial proportion relapse.

[0006] Therefore, there is a need to provide a deeper insight into the link between carotenoids and mental health adversities such as preconception, pregnancy, and postpartum related mental health adversity, for example, depression and/or anxiety.

[0007] There is also a need to provide a nutritional intervention which is safe and effective to treat and/or prevent and/or ameliorate mental health adversities such as preconception, pregnancy, and postpartum related mental health adversity, which overcomes, or at least ameliorates, one or more of the disadvantages of the conventional interventions described above.

SUMMARY

[0008] In one aspect, the present disclosure refers to a method of treating and/or preventing and/or ameliorating depression and/or anxiety in a woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, comprising administering an effective amount of one or more carotenoids to the woman at a stage selected from the group consisting of preconception, pregnancy, and postpartum stage.

[0009] Advantageously, the method uses carotenoids as an effective and safe pharmaceutical and/or nutritional intervention for women with, or at risk of developing mental health adversities such as preconception, pregnancy, and postpartum related mental health adversity. It can help avoid use of conventional pharmacological interventions such as anti-anxiety medications and antidepressants, before, during or post pregnancy.

[0010] In another aspect, the present disclosure refers to an effective amount of one or more carotenoids for use in treating and/or preventing and/or ameliorating depression and/or anxiety in a woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, wherein the one or more carotenoids is to be administered to the woman

at a stage selected from the group consisting of preconception, pregnancy, and postpartum stage.

[0011] In another aspect, the present disclosure refers to use of an effective amount of one or more carotenoids in the manufacture of a medicament for treating and/or preventing and/or ameliorating depression and/or anxiety in a woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, wherein the medicament is to be administered to the woman at a stage selected from the group consisting of preconception, pregnancy, and postpartum stage.

[0012] In another aspect, the present disclosure refers to a pharmaceutical composition comprising a carotenoid and a pharmaceutically acceptable carrier, diluent and/or adjuvant.

[0013] In another aspect, the present disclosure refers to a nutritional composition comprising a carotenoid, a nutrient and an excipient.

DEFINITION OF TERMS

[0014] The following words and terms used herein shall have the meaning indicated:

[0015] The term "treating" and grammatical variations of that term, refers to administration of an agent of the disclosure (such as a carotenoid) to a subject (such as a pregnant woman as described herein) by any appropriate means as described herein. Such treatment includes any and all uses which remedy a disease state or symptoms, prevent the establishment of disease, or otherwise prevent, hinder, retard, or reverse the progression of disease or other undesirable symptoms in any way whatsoever. The disease state of symptoms may be those associated with mental health adversities such as preconception, pregnancy, and postpartum related mental health adversity, for example, depression and/or anxiety. Hence, "treatment" includes prophylactic and therapeutic treatment. Additionally, "treating" may be "*in vivo*" (performed in a living organism).

[0016] The term "preventing" a disease refers to prophylactically interfering with a pathological mechanism that results in the disease or disorder (for example, mental health adversities such as preconception, pregnancy, and postpartum related mental health adversity, for example, depression and/or anxiety). In the context of the present disclosure, such a pathological mechanism may be one associated with depression and/or anxiety, selected from the group consisting of (1) oxidative injury to neurons through hydroxyl radicals and lipid peroxidation, (2) upregulated inflammatory response, characterized by increased levels of pro-

inflammatory cytokines and other acute phase protein, and (3) hypothalamic-pituitary-adrenal axis dysregulation.

[0017] The term "ameliorating" a disease refers to causing an improvement in a condition associated with the disease or disorder (for example, mental health adversities such as preconception, pregnancy, and postpartum related mental health adversity, for example, depression and/or anxiety). In the context of the present disclosure, amelioration includes a reduction in the level of maternal depression score and/or anxiety score, and/or improvement of wellbeing of a woman suffering from or at a risk of developing mental health adversities such as preconception, pregnancy, and postpartum related mental health adversity, for example, depression and/or anxiety, and/or improvement of socio-emotional development of an offspring of a pregnant woman suffering from or at a risk of developing mental health adversities such as preconception, pregnancy, and postpartum related mental health adversity, for example, depression and/or anxiety.

[0018] The term "preconception" or "preconception stage" refers to the status or stage wherein a woman is in child bearing age, before conception. In one example, the preconception stage refers to about 6 months before conception. In another example, the preconception stage refers to about 3 months before conception. In another example, the preconception stage refers to about 2 months before conception. In another example, the preconception stage refers to about 1 month before conception. Likewise, the term "woman who is in preconception stage", or grammatical variants thereof, refers to any female human-being that is in child bearing age before conception, for example, about 6 months, about 3 months, about 2 months, or about 1 month before conception), who is desired or suitable to be administered or treated using the pharmaceutical composition, nutritional composition, and methods of the disclosure.

[0019] The term "pregnancy" refers to the pregnancy status (from conception to the time of delivery). Likewise, the term "pregnant woman" refers to any female human-being that is in the pregnancy status (from conception to the time of delivery). "Pregnancy" may be used interchangeably with "antenatal".

[0020] The term "postpartum" or "postpartum stage" refers to the status or stage after a woman has delivered an offspring. In one example, the postpartum stage refers to up to about 1 month after delivery of an offspring. In another example, the postpartum stage refers to up to about 2 months after delivery of an offspring. In another example, the postpartum stage refers to up to about 3 months after delivery of an offspring. In another example, the postpartum stage

refers to up to about 4 months after delivery of an offspring. In another example, the postpartum stage refers to up to about 5 months after delivery of an offspring. In another example, the postpartum stage refers to up to about 6 months after delivery of an offspring. In another example, the postpartum stage refers to up to about 12 months after delivery of an offspring. In another example, the postpartum stage refers to up to about 24 months after delivery of an offspring.

[0021] The term "administering" and grammatical variations of that term including "administer" and "administration", includes contacting, applying, delivering or providing an agent of the disclosure (such as one or more carotenoids) to a subject (such as a woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage as described herein), by any appropriate means, for example, topical application, oral administration, subcutaneous injection, or intradermal injection. In one example, the administration is oral administration.

[0022] The term "effective amount" includes a reference to an amount of a therapeutic or nutritional agent (for example, a carotenoid) which exhibits a detectable therapeutic or preventative (prophylactic) effect to treat, prevent, or ameliorate a desired disease or condition (for example, mental health adversities such as preconception, pregnancy, and postpartum related mental health adversity, for example, depression and/or anxiety). The effect can be detected by, for example, reduction of Edinburgh Postpartum Depression Scale (EPDS) scores, reduction of State-Trait Anxiety Inventory (STAI) state anxiety scores, and/or reduction of STAI trait anxiety scores. The specific therapeutically effective dose level for any particular subject (such as a woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage as described herein) will depend upon a variety of factors: the type and degree of the response to be achieved; activity of the specific agent or composition employed; the specific agents or composition employed; the age, body weight, general health, diet, ethnicity, and education level of the woman; the time of administration, route of administration, and rate of excretion of the agent; the duration of the treatment; drugs used in combination or coincidental with the specific agent; and like factors well known in the medical arts. Thus, it is not useful to specify an exact effective amount in advance. However, the effective amount for a given situation can be determined by routine experimentation and is within the judgement of the clinician. For example, it is well within the skill of the art to start

doses of the agents at levels lower than those required to achieve the desired therapeutic effect and to gradually increase the dosages until the desired effect is achieved.

[0023] The term “nutritional composition” refers to a product such as a food product intended to supplement the common diet, which contains one or more carotenoids, and is a concentrated source of nutrients such as vitamins and minerals, or other substances with a nutritional or physiological effect, in particular, but not limited to, amino acids, organic and inorganic salts, essential fatty acids, fiber and various plant-derived extracts, alone or in combination.

[0024] As used herein, the singular form "a," "an," and "the" include plural references unless the context clearly dictates otherwise. For example, the term "an agent" includes a plurality of agents, including mixtures thereof.

[0025] As used herein, the term "about" as used in relation to a numerical value means, for example, +50% or +30% of the numerical value, preferably +20%, more preferably +10%, more preferably still +5%, and most preferably +1%. Where necessary, the word “about” may be omitted from the definition of the disclosure.

[0026] Unless specified otherwise, the terms “comprising” and “comprise”, and grammatical variants thereof, are intended to represent “open” or “inclusive” language such that they include recited elements but also permit inclusion of additional, unrecited elements.

[0027] Throughout this disclosure, certain embodiments may be disclosed in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the disclosed ranges. Accordingly, the description of a range should be considered to have specifically disclosed all the possible sub-ranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed sub-ranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

[0028] Certain embodiments may also be described broadly and generically herein. Each of the narrower species and subgeneric groupings falling within the generic disclosure also form part of the disclosure. This includes the generic description of the embodiments with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

DETAILED DISCLOSURE OF THE EMBODIMENTS

[0029] Exemplary, non-limiting embodiments of a method of treating and/or preventing and/or ameliorating a mental health adversity selected from the group consisting of preconception, pregnancy, and postpartum related mental health adversity in a woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage will now be disclosed.

[0030] According to one aspect, the present disclosure refers to a method of treating and/or preventing and/or ameliorating a mental health adversity selected from the group consisting of preconception, pregnancy, and postpartum related mental health adversity in a woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, comprising administering an effective amount of one or more carotenoids to the woman at a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, wherein the mental health adversity is depression and/or anxiety.

[0031] In one example, the mental health adversity is depression. In another example, the mental health adversity is anxiety. In another example, the depression is selected from the group consisting of Major Depressive Disorder (MDD), Persistent Depressive Disorder (PDD), Bipolar Disorder, Postpartum Depression (PPD), Premenstrual Dysphoric Disorder (PMDD), Seasonal Affective Disorder (SAD), Situational Depression, and Atypical Depression. In another example, the anxiety is selected from the group consisting of Generalized Anxiety Disorder, Obsessive-Compulsive Disorder (OCD), Panic Disorder, post-Traumatic Stress Disorder (PTSD), Social Phobia (or Social Anxiety Disorder).

[0032] In the context of the present disclosure, it will be understood that "woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage" does not imply that symptoms of mental health adversities selected from the group consisting of preconception, pregnancy, and postpartum related mental health adversity are present. In one example, the woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage may be completely healthy, without any known diseases including any form of mental health adversity, but may be at a risk of developing mental health adversities such as depression and/or anxiety. The factors that may render a woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage at a risk of developing mental health adversities such as depression and/or anxiety are selected from the group consisting of genetic variants (for example, genetic predisposition for

depression and/or anxiety), gene environment interaction, inadequate nutrition, metabolic disorders, hormonal changes, low socioeconomic status, history of depression, increased alcohol consumption, substance abuse and dependency, smoking, lack of social support, lower education, and depressive personality. In another example, the woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage may have mental health adversities such as depression and/or anxiety, but no other known diseases.

[0033] In one example, the carotenoid is at least one or more selected from the group consisting of lutein, zeaxanthin, β-cryptoxanthin, lycopene, α-carotene, and β-carotene. In another example, the carotenoid is at least one or more selected from the group consisting of β-cryptoxanthin, lycopene, α-carotene, and β-carotene. In another example, the carotenoid is β-cryptoxanthin.

[0034] In one example, only one carotenoid is administered to the woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage. In another example, two carotenoids are administered to the woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage. In another example, three carotenoids are administered to the woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage. In another example, four carotenoids are administered to the woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage. In another example, five carotenoids are administered to the woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage. In another example, six carotenoids are administered to the woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage.

[0035] In one example, when more than one carotenoids are administered to the woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, they are each administered in the same dose, such as about 1 mg/day, about 2 mg/day, about 3 mg/day, about 4 mg/day, about 5 mg/day, about 6 mg/day, about 8 mg/day, about 10 mg/day, about 15 mg/day, about 20 mg/day, about 25 mg/day, about 30 mg/day, about 40 mg/day, about 50 mg/day, about 60 mg/day, about 70 mg/day, about 80 mg/day, about 90 mg/day, about 100 mg/day, about 150 mg/day, or about 200 mg/day. In another example, when more than one carotenoids are administered to the woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, they are each

administered in the same dose of about 3 mg/day. In another example, when more than one carotenoids are administered to the woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, they are each administered in the same dose of about 4 mg/day. In another example, when more than one carotenoids are administered to the woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, they are each administered in the same dose of about 5 mg/day. In another example, when more than one carotenoids are administered to the woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, they are each administered in the same dose of 6 mg/day. In another example, when more than one carotenoids are administered to the woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, they are administered in different doses among the following exemplary doses: about 1 mg/day, about 2 mg/day, about 3 mg/day, about 4 mg/day, about 5 mg/day, about 6 mg/day, about 8 mg/day, about 10 mg/day, about 15 mg/day, about 20 mg/day, about 25 mg/day, about 30 mg/day, about 40 mg/day, about 50 mg/day, about 60 mg/day, about 70 mg/day, about 80 mg/day, about 90 mg/day, about 100 mg/day, about 150 mg/day, or about 200 mg/day. In another example, when more than one carotenoids are administered to the woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, they are administered in different doses selected from the group consisting of 3 mg/day, 4 mg/day, 5 mg/day and 6 mg/day. In another example, when more than one carotenoids are administered to the woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, they are administered in different doses which are 3 mg/day or 6 mg/day.

[0036] In another example, when more than one carotenoids are administered to the woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, they are each administered at the same frequency, such as twice every day, once every day, once every 2 days, once every 3 days, once every 4 days, once every 5 days, once every 6 days, once every 7 days, once every 8 days, once every 9 days, once every 10 days, or once every 14 days. In another example, when more than one carotenoids are administered to the woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, they are each administered at the same frequency of once every day.In another example, when more than one carotenoids are administered to the woman who is in a stage selected from the group consisting of

preconception, pregnancy, and postpartum stage, they are administered at different frequencies, among the following exemplary frequencies: twice every day, once every day, once every 2 days, once every 3 days, once every 4 days, once every 5 days, once every 6 days, once every 7 days, once every 8 days, once every 9 days, once every 10 days, and once every 14 days. In another example, when more than one carotenoids are administered to the woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, they are administered at different frequencies, and one of the frequencies is once every day.

[0037] In one example, when more than one carotenoids are administered to the woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, they are each administered for the same period of time, such as about one week, about two weeks, about three weeks, about four weeks, about five weeks, about two months, about three months, about four months, about five months, about six months, about seven months, about eight months, about nine months, about ten months, about eleven months, about twelve months, about 13 months, about 18 months, or about 24 months. In another example, when more than one carotenoids are administered to the woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, they are each administered for the same period of time, such as any period time within the range of about 43 to 51 weeks. In another example, when more than one carotenoids are administered to the woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, they are administered for different periods of time, among the following exemplary periods of time: about one week, about two weeks, about three weeks, about four weeks, about five weeks, about two months, about three months, about four months, about five months, about six months, about seven months, about eight months, about nine months, about ten months, about eleven months, about twelve months, about 13 months, about 18 months, and about 24 months. In another example, when more than one carotenoids are administered to the woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, they are administered for different periods of time, selected among the following exemplary periods of time: in a range of about 43 to 51 weeks.

[0038] In one example, when more than one carotenoids are administered to the woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, they are each administered via the same route as disclosed herein. In another example, the same administration route is oral administration route. In another example, when

more than one carotenoids are administered to the woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, they are administered via different routes as disclosed herein. In another example, one of the different administration routes is oral administration route.

[0039] In one example, when more than one carotenoids are administered to the woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, they are administered simultaneously. In another example, when more than one carotenoids are administered to the woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, they are administered at different points of time. In one example, there are about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 8 days, about 9 days, about 10 days, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, or about 15 weeks between the administration of different carotenoids.

[0040] In one example, when more than one carotenoids are administered to the woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, they are administered in the same formulation, i.e. mixed together. In another example, when more than one carotenoids are administered to the woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, they are administered in separate formulations.

[0041] In one example, the method is a method of treating and/or preventing and/or ameliorating depression in a woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, comprising administering an effective amount of β-cryptoxanthin to the pregnant woman at a stage selected from the group consisting of preconception, pregnancy, and postpartum stage. In one example, the EDPS maternal depression score is reduced after the administration of β-cryptoxanthin.

[0042] In another example, the method is a method of treating and/or preventing and/or ameliorating anxiety in a woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, comprising administering an effective amount of β-cryptoxanthin to the pregnant woman at a stage selected from the group consisting of preconception, pregnancy, and postpartum stage. In one example, the STAI state anxiety

score is reduced after the administration of β-cryptoxanthin. In another example, the STAI trait anxiety score is reduced after the administration of β-cryptoxanthin.

[0043] In another example, the method is a method of treating and/or preventing and/or ameliorating depression in a woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, comprising administering an effective amount of carotenoids consisting of lutein, zeaxanthin, β-cryptoxanthin, lycopene, α-carotene, and β-carotene to the woman at a stage selected from the group consisting of preconception, pregnancy, and postpartum stage. In one example, the EDPS maternal depression score is reduced after the administration of an effective amount of carotenoids consisting of lutein, zeaxanthin, β-cryptoxanthin, lycopene, α-carotene, and β-carotene.

[0044] In another example, the method is a method of treating and/or preventing and/or ameliorating anxiety in a woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, comprising administering an effective amount of carotenoids consisting of lutein, zeaxanthin, β-cryptoxanthin, lycopene, α-carotene, and β-carotene to the woman at a stage selected from the group consisting of preconception, pregnancy, and postpartum stage. In one example, the STAI state anxiety score is reduced after the administration of an effective amount of carotenoids consisting of lutein, zeaxanthin, β-cryptoxanthin, lycopene, α-carotene, and β-carotene. In another example, the STAI trait anxiety score is reduced after the administration of an effective amount of carotenoids consisting of lutein, zeaxanthin, β-cryptoxanthin, lycopene, α-carotene, and β-carotene.

[0045] In another example, the method is a method of treating and/or preventing and/or ameliorating anxiety in a woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, comprising administering an effective amount of one or more carotenoids selected from the group consisting of lutein, β-carotene, and β-cryptoxanthin to the pregnant woman at a stage selected from the group consisting of preconception, pregnancy, and postpartum stage. In one example, the STAI state anxiety score is reduced after the administration of one or more carotenoids selected from the group consisting of lutein, β-carotene, and β-cryptoxanthin.

[0046] In another example, the method is a method of treating and/or preventing and/or ameliorating anxiety in a woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, comprising administering an effective amount of one or more carotenoids selected from the group consisting of lutein, β-carotene, α-

carotene, and β-cryptoxanthin to the woman at a stage selected from the group consisting of preconception, pregnancy, and postpartum stage. In one example, the STAI state anxiety score is reduced after the administration of one or more carotenoids selected from the group consisting of lutein, β-carotene, α-carotene, and β-cryptoxanthin. In one example, the STAI trait anxiety score is reduced after the administration of one or more carotenoids selected from the group consisting of lutein, β-carotene, α-carotene, and β-cryptoxanthin.

[0047] In another example, the method is a method of treating and/or preventing and/or ameliorating depression in a woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, comprising administering an effective amount of one or more carotenoids selected from the group consisting of lutein, β-carotene, and β-cryptoxanthin to the woman at a stage selected from the group consisting of preconception, pregnancy, and postpartum stage. In one example, the EDPS maternal depression score is reduced after the administration of one or more carotenoids selected from the group consisting of lutein, β-carotene, and β-cryptoxanthin.

[0048] The woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage may be of any ethnicity. The ethnicity of the woman may be selected from the group consisting of Asian, Caucasian, African, Latino or Hispanic, other ethnic group such as Arab, and mixed or multiple ethnic groups. In one example, the woman is of Asian ethnicity. In another example, the woman is Chinese. In another example, the woman is Malay. In another example, the pregnant woman is Indian.

[0049] In one example, the carotenoid is administered at a dosage such as about 1 mg/day, about 2 mg/day, about 3 mg/day, about 4 mg/day, about 5 mg/day, about 6 mg/day, about 8 mg/day, about 10 mg/day, about 15 mg/day, about 20 mg/day, about 25 mg/day, about 30 mg/day, about 40 mg/day, about 50 mg/day, about 60 mg/day, about 70 mg/day, about 80 mg/day, about 90 mg/day, about 100 mg/day, about 150 mg/day, or about 200 mg/day. In another example, the carotenoid is administered at a dosage of about 3 mg/day. In another example, the carotenoid is administered at a dosage of about 4 mg/day. In another example, the carotenoid is administered at a dosage of about 5 mg/day. In another example, the carotenoid is administered at a dosage of about 6 mg/day. It will be apparent to one of ordinary skill in the art that the optimal quantity and spacing of individual dosages will be determined by the nature and extent of the disease state being treated, the form, route and site of administration, and the nature of the particular individual being treated. Also, such optimum conditions can be

determined by conventional techniques. Agents of the present disclosure may be administered as compositions either therapeutically or preventively. In a therapeutic application, compositions are administered to a subject already suffering from a disease, in an amount sufficient to cure or at least partially arrest the disease and its complications. The composition should provide a quantity of the agent sufficient to effectively treat the subject. One skilled in the art would be able, by routine experimentation, to determine an effective, non-toxic amount of agent which would be required to treat applicable diseases. Generally, an effective dosage may be in the range of about 1 mg/day to about 200 mg/day and includes any subranges therein, as well as individual numbers within the ranges and subranges. In one example, an effective dosage is from about 1 mg/day to about 30 mg/day. In one example, an effective dosage is from about 3 mg/day to about 6 mg/day.

[0050] In one example, the carotenoid is administered at a frequency such as twice every day, once every day, every 2 days, every 3 days, every 4 days, every 5 days, every 6 days, every 7 days, every 8 days, every 9 days, every 10 days, or every 14 days. In another example, the carotenoid is administered at a frequency of once every day. It will also be apparent to one of ordinary skill in the art that the optimal course of treatment, such as, the number of doses of the composition given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

[0051] In one example, the carotenoid is administered for a period such as about one week, about two weeks, about three weeks, about four weeks, about five weeks, about two months, about three months, about four months, about five months, about six months, about seven months, about eight months, about nine months, about ten months, about eleven months, about twelve months, about 13 months, about 18 months, or about 24 months.

[0052] In one example, the one or more carotenoids is administered to a woman in a preconception stage, in child bearing age prior to conception. In another example, the one or more carotenoids is administered from about 6 months prior to conception. In another example, the one or more carotenoids is administered from about 3 months prior to conception. In another example, the one or more carotenoids is administered from about 2 months prior to conception. In another example, the one or more carotenoids is administered from about 1 month prior to conception.

[0053] In another example, the one or more carotenoids is to be administered to a pregnant woman during pregnancy. In another example, the one or more carotenoids is administered to

the pregnant woman during the first trimester of pregnancy. In another example, the one or more carotenoids is administered to the pregnant woman during the second trimester of pregnancy. In another example, the one or more carotenoids is administered to the pregnant woman during the third trimester of pregnancy. In another example, the one or more carotenoids is administered to the pregnant woman during delivery. In another example, the one or more carotenoids is administered throughout the pregnancy. In another example, the one or more carotenoids is administered during pregnancy, starting from a time such as about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, about 21 weeks, about 22 weeks, about 23 weeks, about 24 weeks, about 25 weeks, about 26 weeks, about 27 weeks, about 28 weeks, about 29 weeks, about 30 weeks, about 31 weeks, about 32 weeks, about 33 weeks, about 34 weeks, about 35 weeks, about 36 weeks, about 37 weeks, about 38 weeks, about 39 weeks or about 40 weeks after conception. In another example, the one or more carotenoids is administered during pregnancy, from about 14 weeks to about 22 weeks after conception.

[0054] In another example, the one or more carotenoids is administered to a woman postpartum, i.e. after delivery of an offspring. In one example, the one or more carotenoids is administered up to about 1 month after delivery of an offspring. In another example, the one or more carotenoids is administered up to about 2 months after delivery of an offspring. In another example, the one or more carotenoids is administered up to about 3 months after delivery of an offspring. In another example, the one or more carotenoids is administered up to about 4 months after delivery of an offspring. In another example, the one or more carotenoids is administered up to about 5 months after delivery of an offspring. In another example, the one or more carotenoids is administered up to about 6 months after delivery of an offspring. In another example, the one or more carotenoids is administered up to about 12 months after delivery of an offspring. In another example, the one or more carotenoids is administered up to about 24 months after delivery of an offspring.

[0055] In one example, the one or more carotenoids is administered from about 14 weeks after conception to about 6 months after delivery of an offspring. In another example, the one or more carotenoids is administered from about 15 weeks after conception to about 6 months after delivery of an offspring. In another example, the one or more carotenoids is administered

from about 16 weeks after conception to about 6 months after delivery of an offspring. In another example, the one or more carotenoids is administered from about 17 weeks after conception to about 6 months after delivery of an offspring. In another example, the one or more carotenoids is administered from about 18 weeks after conception to about 6 months after delivery of an offspring. In another example, the one or more carotenoids is administered from about 19 weeks after conception to about 6 months after delivery of an offspring. In another example, the one or more carotenoids is administered from about 20 weeks after conception to about 6 months after delivery of an offspring. In another example, the one or more carotenoids is administered from about 21 weeks after conception to about 6 months after delivery of an offspring. In another example, the one or more carotenoids is administered from about 22 weeks after conception to about 6 months after delivery of an offspring. In another example, the one or more carotenoids is administered from about 15 weeks after conception to about 5 months after delivery of an offspring. In another example, the one or more carotenoids is administered from about 15 weeks after conception to about 4 months after delivery of an offspring. In another example, the one or more carotenoids is administered from about 15 weeks after conception to about 3 months after delivery of an offspring. In another example, the one or more carotenoids is administered from about 15 weeks after conception to about 2 months after delivery of an offspring. In another example, the one or more carotenoids is administered from about 15 weeks after conception to about 1 month after delivery of an offspring.

[0056] In one example, the carotenoid can be administered by standard routes. In general, the carotenoid may be administered by the parenteral (e.g., intravenous, intraspinal, subcutaneous or intramuscular), oral or topical route. In one example, the administration of one or more carotenoids is by the oral route.

[0057] In one example, the carotenoid may be in a form suitable for oral ingestion (such as capsules, tablets, caplets, elixirs), in the form of an ointment, cream or lotion suitable for topical administration, in a form suitable for delivery as an eye drop, in an aerosol form suitable for administration by inhalation, such as by intranasal inhalation or oral inhalation, in a form suitable for parenteral administration, that is, subcutaneous, intramuscular or intravenous injection.

[0058] In one example, solid forms for oral administration of carotenoids may contain binders acceptable in human pharmaceutical practice, sweeteners, disintegrating agents,

diluents, flavourings, coating agents, preservatives, lubricants and/or time delay agents. Suitable binders include gum acacia, gelatine, corn starch, gum tragacanth, sodium alginate, carboxymethylcellulose or polyethylene glycol. Suitable sweeteners include sucrose, lactose, glucose, aspartame or saccharine. Suitable disintegrating agents include corn starch, methylcellulose, polyvinylpyrrolidone, guar gum, xanthan gum, bentonite, alginic acid or agar. Suitable diluents include lactose, sorbitol, mannitol, dextrose, kaolin, cellulose, calcium carbonate, calcium silicate or dicalcium phosphate. Suitable flavouring agents include peppermint oil, oil of wintergreen, cherry, orange or raspberry flavouring. Suitable coating agents include polymers or copolymers of acrylic acid and/or methacrylic acid and/or their esters, waxes, fatty alcohols, zein, shellac or gluten. Suitable preservatives include sodium benzoate, vitamin E, alpha-tocopherol, ascorbic acid, methyl paraben, propyl paraben or sodium bisulphite. Suitable lubricants include magnesium stearate, stearic acid, sodium oleate, sodium chloride or talc. Suitable time delay agents include glyceryl monostearate or glyceryl distearate.

[0059] Liquid forms for oral administration of carotenoids may contain, in addition to the above agents, a liquid carrier. Suitable liquid carriers include water, oils such as olive oil, peanut oil, sesame oil, sunflower oil, safflower oil, arachis oil, coconut oil, liquid paraffin, ethylene glycol, propylene glycol, polyethylene glycol, ethanol, propanol, isopropanol, glycerol, fatty alcohols, triglycerides or mixtures thereof.

[0060] Suspensions for oral administration of carotenoids may further comprise dispersing agents and/or suspending agents. Suitable suspending agents include sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, poly-vinyl-pyrrolidone, sodium alginate or acetyl alcohol. Suitable dispersing agents include lecithin, polyoxyethylene esters of fatty acids such as stearic acid, polyoxyethylene sorbitol mono- or di-oleate, -stearate or -laurate, polyoxyethylene sorbitan mono- or di-oleate, -stearate or -laurate and the like.

[0061] The emulsions for oral administration of carotenoids may further comprise one or more emulsifying agents. Suitable emulsifying agents include dispersing agents as exemplified above or natural gums such as guar gum, gum acacia or gum tragacanth. Some examples of suitable carriers, diluents, excipients and adjuvants for oral use include peanut oil, liquid paraffin, sodium carboxymethylcellulose, methylcellulose, sodium alginate, gum acacia, gum tragacanth, dextrose, sucrose, sorbitol, mannitol, gelatine and lecithin. In addition these oral

formulations may contain suitable flavouring and colourings agents. When used in capsule form the capsules may be coated with compounds such as glyceryl monostearate or glyceryl distearate which delay disintegration.

[0062] For administration as an injectable solution or suspension of carotenoids, non-toxic parenterally acceptable diluents or carriers can include, Ringer's solution, isotonic saline, phosphate buffered saline, ethanol and 1,2 propylene glycol.

[0063] The topical formulations of carotenoids may comprise an active ingredient (one or more carotenoids disclosed herein) together with one or more acceptable carriers, and optionally any other therapeutic ingredients. Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of where treatment is required, such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose.

[0064] Drops according to the present disclosure may comprise sterile aqueous or oily solutions or suspensions. These may be prepared by dissolving the active ingredient (one or more carotenoids disclosed herein) in an aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and optionally including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container and sterilised by, for example, autoclaving. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

[0065] Lotions according to the present disclosure include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those described above in relation to the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturiser such as glycerol, or oil such as castor oil or arachis oil.

[0066] Creams, ointments or pastes according to the present disclosure are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a

mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid such as stearic or oleic acid together with an alcohol such as propylene glycol or macrogols.

[0067] The composition may incorporate any suitable surfactant such as an anionic, cationic or non-ionic surfactant such as sorbitan esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

[0068] The compositions may also be administered in the form of liposomes. Liposomes are generally derived from phospholipids or other lipid substances, and are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolisable lipid capable of forming liposomes can be used. The compositions in liposome form may contain stabilisers, preservatives, excipients and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic.

[0069] In one example, the carotenoids are in a pharmaceutical composition comprising pharmaceutically acceptable carrier, diluent and/or adjuvant. The carriers, diluents and adjuvants must be "acceptable" in terms of being compatible with the other ingredients of the composition, and not deleterious to the recipient thereof.

[0070] Examples of pharmaceutically acceptable carriers or diluents are demineralised or distilled water; saline solution; vegetable based oils such as peanut oil, safflower oil, olive oil, cottonseed oil, maize oil, sesame oils such as peanut oil, safflower oil, olive oil, cottonseed oil, maize oil, sesame oil, arachis oil or coconut oil; silicone oils, including polysiloxanes, such as methyl polysiloxane, phenyl polysiloxane and methylphenyl polysolpoxane; volatile silicones; mineral oils such as liquid paraffin, soft paraffin or squalane; cellulose derivatives such as methyl cellulose, ethyl cellulose, carboxymethylcellulose, sodium carboxymethylcellulose or hydroxypropylmethylcellulose; lower alkanols, for example ethanol or iso-propanol; lower aralkanols; lower polyalkylene glycols or lower alkylene glycols, for example polyethylene glycol, polypropylene glycol, ethylene glycol, propylene glycol, 1,3-butylene glycol or glycerin; fatty acid esters such as isopropyl palmitate, isopropyl myristate or ethyl oleate; polyvinylpyrolidone; agar; gum tragacanth or gum acacia, and petroleum jelly. Typically, the carrier or carriers will form from 10% to 99.9% by weight of the compositions.

[0071] In another example, the carotenoids are in a nutritional composition comprising one or more nutrient and excipient. In one example, the nutrient comprises one or more vitamins or vitamin like substances selected from the group consisting of Vitamin A, Vitamin B1 (Thiamin), Vitamin B2 (Riboflavin), Vitamin B3 (Niacin), Vitamin B6, Vitamin B12, Vitamin C, Vitamin D, Vitamin E, folic acid, inositol, biotin, and pantothenic acid. In another example, the nutrient comprises one or more minerals selected from the group consisting of calcium, magnesium, iron, zinc, copper, manganese, selenium, and iodine. In another example, the nutrient comprises one or more organic or inorganic salts. In another example, the nutrient comprises one or more amino acids selected from the group consisting of N-Acetyl Cysteine, and L-Arginine. In another example, the nutrient comprises one or more fatty acids selected from the group consisting of DHA (Docosahexaenoic Acid), and EPA (Eicosapentaenoic Acid). In another example, the nutrient comprises one or more fibers selected from the group consisting of lignin, cellulose, pectin, gum, psyllium, polydextrose, polyols, and maltodextrins. In another example, the nutrient comprises one or more plant-derived extracts.

[0072] In another example, the nutritional composition comprises one or more excipients such as sugar alcohols such as xylitol and other polyols, flavor, water, glyceryl stearate citrate or analogs (as an emulsifier), sucralose, pH adjusters and/or preservatives.

[0073] In another example, the nutritional composition is in the form of free or compressed liquid or powder or capsule, or in the form of liquid.

[0074] Upon administration of one or more carotenoids or a composition comprising carotenoids as described above, carotenoids influence signal transmission in cells, so that free radicals are quenched, lipid peroxidation is reduced, inflammatory response is down-regulated, characterized by decreased levels of pro-inflammatory cytokines and other acute phase protein, and the hypothalamic-pituitary-adrenal axis dysregulation is reversed. In one example, the efficacy of the one or more carotenoids for treating and/or preventing and/or ameliorating a mental health adversity selected from the group consisting of preconception, pregnancy, and postpartum related mental health adversity in a woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage is accessed by the unit change in one or more of EDPS maternal depression score, STAI state anxiety score, and STAI trait anxiety score, versus per unit change of the amount of one or more carotenoids in the blood after administration. In another example, the effect size of the one or more carotenoids in treating and/or preventing and/or ameliorating a mental health adversity selected from the

group consisting of preconception, pregnancy, and postpartum related mental health adversity in a woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage is the standardized effect size (SD/SD). Such an analysis removes the units of the variables. Hence the effects mean SD change in EDPS maternal depression score, STAI state anxiety score, and STAI trait anxiety score per SD increase in the amount of one or more carotenoids in the blood. In one example, after administration of the one or more carotenoids as disclosed herein, one or more of the following are reduced: the EDPS maternal depression score, STAI state anxiety score, and STAI trait anxiety score. In another example, after administration of the one or more carotenoids as disclosed herein, one or more of the following: the EDPS maternal depression score, STAI state anxiety score, and STAI trait anxiety score are reduced by about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% and 100% of the value before administration. In another example, after administration of the one or more carotenoids as disclosed herein, the risk of developing antenatal depression and/or anxiety in a woman is reduced by about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% and 100% compared to a woman who is not administered one or more carotenoids as disclosed herein. In another example, after administration of the one or more carotenoids as disclosed herein, the amount of pro-inflammatory cytokines in the blood in a woman is reduced by about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% and 100% compared to a woman who is not administered one or more carotenoids as disclosed herein. In another example, after administration of the one or more carotenoids as disclosed herein, the onset of antenatal depression and/or anxiety in a woman is delayed by a period such as about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 15 weeks, about 20 weeks, about 30 weeks, about 40 weeks, and about 50 weeks, compared to a woman who is not administered one or more carotenoids as disclosed herein. In another example, after administration of the one or more carotenoids as disclosed herein, the duration of manifestation of antenatal depression and/or anxiety in a woman is shortened by a period such as about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 15 weeks, about 20 weeks, about 30 weeks, about 40 weeks, or about 50 weeks, compared to a woman who is not administered one or more carotenoids as disclosed herein. As used herein, the manifestation of depression and/or anxiety may be physical symptoms and emotional symptoms. The physical symptoms may be selected from a

group consisting of decreased energy, chronic fatigue, feeling sluggish frequently, difficulty concentrating, making decisions or recalling, pain, aches, cramps, gastrointestinal problems without any clear cause, changes in appetite or weight, difficulty in sleeping, waking early, oversleeping, heart racing, and dizziness. The emotional symptoms may be selected from a group consisting of loss of interest or no longer finding pleasure in activities or hobbies, persistent feelings of sadness, anxiety, or emptiness, feeling hopeless or pessimistic, anger, irritability, or restlessness, feeling guilty or experiencing feelings of worthlessness or helplessness, thoughts of death or suicide, and suicide attempts. In one example, the manifestation of depression and/or anxiety may be detected and/or measured using clinically validated questionnaires or scales such as the questionnaire for Edinburgh Postnatal Depression Scale (EPDS), the anxiety scale of the Hospital Anxiety and Depression Scale, State Trait Anxiety Index, the Beck Anxiety Inventory, the anxiety subscale of the Hospital Anxiety and Depression Scale, Hamilton Anxiety Rating Scale, the Symptom Checklist-90, the General Health Questionnaire, and the Medical Outcomes Study Short Form 36. In another example, after administration of the one or more carotenoids as disclosed herein, the socio-emotional development of the offspring is improved, such as increased cognition scores, fine motor skills and gross motor skills compared to that of a woman who is not administered one or more carotenoids as disclosed herein. In one example, the Bayley Scales are used to measure the socio-emotional development of the offspring. The Bayley Scales means the Bayley Scales of Infant and Toddler Development, 3rd edition (BSID-III) 2006, which is a widely used comprehensive validated assessment of infant skills. It has various "scales" which assess aspects of development, including: (1) Cognitive Scale, which assesses play skills; information processing (attention to novelty, habituation, memory), and problem-solving; (2) Language Scale, which contains receptive and expressive language subtests to assess communication skills including language and gestures; and (3) Motor Scale, which assesses fine motor development and gross motor development. In one example, after administration of the one or more carotenoids as disclosed herein, the score an offspring reaches on the Bayley Scales reflects more highly developed skills as compared to the scores of an offspring whose mother who is not administered one or more carotenoids as disclosed herein.

[0075] In one example, the “treating” may be “*in vivo*” (performed in a living organism, such as a woman who is in a stage selected from the group consisting of preconception,

pregnancy, and postpartum stage) using the administration routes as disclosed herein, such as oral administration.

BRIEF DESCRIPTION OF THE DRAWINGS

[0076] The disclosure will be better understood with reference to the detailed description when considered in conjunction with the non-limiting embodiments and the accompanying drawings, in which:

[0077] **Figure 1** are boxplots of maternal plasma carotenoids at delivery in the study.

[0078] **Figure 2** is a heatmap showing the association of maternal plasma carotenoids and antenatal maternal mental health.

DETAILED DESCRIPTION OF THE DRAWINGS

EXAMPLES

[0079] Non-limiting examples of the disclosure will be further described in greater detail by reference to specific Examples, which should not be construed as in any way limiting the scope of the disclosure.

[0080] **Example 1 – Methods**

[0081] ***Study design and participants***

[0082] The pregnant women were part of the Growing Up in Singapore Towards healthy Outcomes (GUSTO) longitudinal mother-child cohort. Written informed consent was obtained from all study participants. Briefly, pregnant women aged 18 years and above and in their first trimester, who were Singapore citizens or Permanent Residents and of either Chinese, Malay or Indian ethnicities were recruited from two public hospitals in Singapore - National University Hospital (NUH) and KK Women's and Children's Hospital (KKH) for the duration between June 2009 and September 2010. Study approval was obtained from the National Healthcare Group Domain Specific Review Board and SingHealth Centralized Institutional Review Board. 700 subjects of Chinese (n = 410), Indian (n = 125) and Malay (n = 165) ethinicity were selected for this study. Maternal education, ethnicity and age were derived from survey questionnaires administered during recruitment. Maternal pre-pregnancy BMI (ppBMI) was calculated by dividing the weight in kilogram by height in squared metres, based on self-reported pre-pregnancy weight and height measured at 26-28 weeks' gestation.

[0083] ***Maternal Depression and Anxiety***

[0084] The Edinburgh Postnatal Depression Scale (EPDS) questionnaire was administered to mothers at 26 weeks of pregnancy to quantify levels of depressive symptoms. The EPDS is a 10-item self-report scale, in which each item is scored on a four-point scale (0-3), and is used to identify postpartum depression but is also validated for use in prenatal depression. The reliability of the EPDS score was 0.82 assessed using Cronbach's analysis for the cohort, with higher EPDS scores indicate a greater number of depressive symptoms. The State-Trait Anxiety Inventory (STAI) was administered to mothers at 26 weeks of pregnancy and consists of 40 items associated with anxiety, which could be of 2 types – state anxiety, which is the anxiety about an event, and trait anxiety, the anxiety level as a personal characteristic. The first 20 items were measured on a 4-point Likert scale.

[0085] ***Maternal Plasma Carotenoids***

[0086] Non-fasting maternal blood samples were collected at delivery. Ultra-High Performance Liquid Chromatography (UPLC) with Photo-Diode Array detection was used to determine plasma concentrations of six carotenoids: β-carotene, α-carotene, β-cryptoxanthin (BCX), lycopene, lutein and zeaxanthin. The precision of the method was determined using pooled and spiked plasma samples, with the relative standard deviations of inter- and intra-assays, generally <10% and <15% respectively.

[0087] ***Ethics***

[0088] ***Statistical Analysis***

[0089] Total plasma carotenoid levels were calculated by summing the levels of all six carotenoids measured in plasma at delivery. Pairwise correlation map was developed between the plasma carotenoid measures and total carotenoids at delivery, and maternal mental health measures at 26 weeks' gestation. Associations of each plasma carotenoid level and the total carotenoids and EPDS as well as STAI state and trait scores were examined using univariate linear regression models. Multiple linear regression models adjusted for ethnicity, age, education level and ppBMI were further used to test associations of depression (EPDS) and anxiety (STAI) with plasma carotenoids and total carotenoids. Matlab2019b was used for the statistical analysis.

Example 2– Results

[0090] For this study, the plasma concentration of 6 key carotenoids (lutein, zeaxanthin, β-cryptoxanthin, lycopene, α-carotene, β-carotene) and total carotenoids (consisting of lutein,

zeaxanthin, β-cryptoxanthin, lycopene, α-carotene, β-carotene) were measured in 700 women (410 Chinese, 165 Malay and 125 Indian) at delivery in GUSTO cohort. The clinical characteristics of study participants is tabulated in **Table 1**. Majority of the participants were of Chinese ethnicity (n = 410). The mean age and ppBMI of the participants was 30.86 years and 22.88 kg/m^2 respectively. **Figure 1** shows the boxplots of the levels of plasma carotenoids in μg/mL in the cohort. Amongst all the carotenoids, the median level of α-carotene was the lowest (0.051 μg/mL) and that of lutein was the highest (0.22 μg/mL). The heatmap showing the association of plasma carotenoids and antenatal maternal mental health is presented as **Figure 2**. All the six carotenoids and the total carotenoids negatively correlated with EPDS and STAI (state and trait) scores. Specifically, the correlation values with EPDS scores were: lutein --0.139, zeaxanthin --0.031, BCX --0.137, lycopene --0.047, α-carotene --0.065, β-carotene --0.128, total carotenoids --0.161, with STAI trait were: lutein --0.122, zeaxanthin --0.003, BCX --0.130, lycopene --0.046, α-carotene --0.077, β-carotene --0.123, total carotenoids --0.149 and with STAI state were: lutein --0.204, zeaxanthin --0.004, BCX --0.159, lycopene --0.046, α-carotene --0.133, β-carotene --0.171, total carotenoids --0.209. The associations of plasma carotenoids and maternal depression are shown in **Table 2(A)**. In univariate models, lutein (standardized β = -0.14, CI: -0.21, -0.07), BCX (standardized β = -0.14, CI: -0.21, -0.06), β-carotene (standardized β = -0.13, CI: -0.2, -0.05) and total carotenoids (standardized β = -0.16, CI: -0.24, -0.09) were found to be significantly associated with EPDS scores ($p<0.05$). However, in the adjusted multiple regression models, adjusted for ethnicity, age, education level and ppBMI, only BCX was found to have a significant association with EPDS, with a standardized effect size of -0.09 (CI: -0.17, -0.01). **Table 2(B)** represents the associations of plasma carotenoids and maternal anxiety scores. In the univariate analysis, four carotenoids – lutein, BCX, α-carotene and β-carotene and the total carotenoids were found to have significant inverse associations with both STAI state and trait scores. On adjusting for confounders, three carotenoids – lutein, BCX, β-carotene and the total carotenoids remained significantly associated with STAI state scores. For STAI trait, significant associations were found only for BCX and the total carotenoids in the adjusted models.

[0091] **Table 1 Clinical characteristics of participants in the study**

Category		N	Mean(STD)
Ethnicity			
Chinese		410	-
Malay		165	-
Indian		125	-
At delivery	Lutein (μg/ml)	700	0.26(0.15)
	Zeaxanthin (μg/ml)	700	0.17(0.07)
	β-cryptoxanthin (μg/ml)	700	0.25(0.18)
	Lycopene (μg/ml)	700	0.12(0.07)
	α-carotene (μg/ml)	700	0.06(0.05)
	β-carotene (μg/ml)	700	0.24(0.19)
	Total carotenoids (μg/ml)	700	1.11(0.49)
Maternal Age (years)		700	30.86(5.02)
Maternal Education Level			
Secondary and below		211	-
Post-secondary		226	-
University		258	-
Pre-pregnancy BMI (kg/m^2)		642	22.88(4.37)
26-28 weeks' gestation	EPDS	687	7.37(4.45)
	STAI State	674	34.08(9.77)
	STAI Trait	669	36.34(8.82)

[0092] **Table 2 Association between maternal plasma carotenoids and maternal mental health (β - standardized effect size)**

(A) Maternal depression (EPDS)

Variables	Univariate Analysis		Multivariate Analysis, Adjusted for ethnicity, age, education level and ppBMI	
	β (95%CI)	p-value	β (95%CI)	p-value
lutein	-0.14(-0.21--0.07)	2.50E-04	-0.02(-0.09-0.05)	5.70E-01
zeaxanthin	-0.03(-0.11-0.04)	4.18E-01	-0.07(-0.15-0.01)	6.93E-02
β-cryptoxanthin	-0.14(-0.21--0.06)	3.30E-04	-0.09(-0.17--0.01)	2.73E-02
lycopene	-0.05(-0.12-0.03)	2.20E-01	-0.02(-0.1-0.05)	5.43E-01
α-carotene	-0.06(-0.14-0.01)	8.96E-02	0.03(-0.05-0.11)	4.40E-01
β-carotene	-0.13(-0.2--0.05)	7.58E-04	-0.03(-0.1-0.05)	4.86E-01

Total carotenoids	-0.16(-0.24--0.09)	2.12E-05	-0.06(-0.14-0.01)	1.12E-01

(B) Maternal anxiety

Variables	STAI State			
	Univariate Analysis		Multivariate Analysis Adjusted for ethnicity, age, education level and ppBMI	
	β (95%CI)	p-value	β (95%CI)	p-value
lutein	-0.21(-0.28--0.13)	8.86E-08	-0.1(-0.17--0.02)	9.23E-03
zeaxanthin	0(-0.08-0.07)	9.19E-01	-0.07(-0.15-0.01)	8.59E-02
β-cryptoxanthin	-0.16(-0.24--0.09)	3.28E-05	-0.14(-0.23--0.06)	4.63E-04
lycopene	-0.05(-0.12-0.03)	2.34E-01	-0.04(-0.12-0.04)	3.31E-01
α-carotene	-0.13(-0.21--0.06)	5.32E-04	-0.05(-0.12-0.03)	2.28E-01
β-carotene	-0.17(-0.25--0.1)	8.54E-06	-0.09(-0.17--0.01)	2.13E-02
Total carotenoids	-0.21(-0.29--0.14)	4.37E-08	-0.14(-0.22--0.06)	3.42E-04
Variables	STAI Trait			
	Univariate Analysis		Multivariate Analysis Adjusted for ethnicity, age, education level and ppBMI	
	β (95%CI)	p-value	β (95%CI)	p-value
lutein	-0.12(-0.2--0.05)	1.62E-03	-0.02(-0.1-0.05)	5.62E-01
zeaxanthin	0(-0.08-0.07)	9.31E-01	-0.05(-0.13-0.03)	2.37E-01
β-cryptoxanthin	-0.13(-0.21--0.06)	7.27E-04	-0.11(-0.2--0.03)	5.73E-03
lycopene	-0.05(-0.12-0.03)	2.30E-01	-0.05(-0.13-0.03)	2.07E-01
α-carotene	-0.08(-0.15-0)	4.56E-02	0.01(-0.07-0.09)	8.03E-01
β-carotene	-0.13(-0.2--0.05)	1.43E-03	-0.05(-0.13-0.03)	2.09E-01
Total carotenoids	-0.15(-0.23--0.07)	1.12E-04	-0.08(-0.16--0.01)	3.65E-02

[0093] Interestingly, β-cryptoxanthin was the only carotenoid that was significantly associated with both depression (EPDS) and anxiety scores (STAI). Higher plasma β-cryptoxanthin levels were linked with lower depression and anxiety scores. In addition, it was noted that more carotenoid compounds were significantly associated with STAI anxiety scores.

Carotenoids had more prominent association with state anxiety (psychophysiological state) than trait anxiety (personality trait).

Example 3– Discussion

[0094] This is the first report to uncover the link between plasma carotenoid levels and maternal mental health during pregnancy. Previous studies on carotenoid levels have only been studied in young adults and the elderly with emphasis on depressive symptoms, while observations related to anxiety have been supported only in animal models. The novel insight reported herein points to the potential utility of nutritional intervention in pregnant women with antenatal depression/ anxiety, or during preconception in women at risk of developing mental health adversities. Such an approach is particularly pertinent in light of the preference to avoid pharmacological interventions such as anti-anxiety medications during pregnancy.

[0095] In this study associations of higher maternal depression and anxiety scores were observed at 26 weeks' gestation, with lower plasma carotenoid levels at delivery. Additionally, BCX was the only carotenoid that was significantly associated with both maternal depression (EPDS) and anxiety (STAI). A probable explanation for the consistency in associations of BCX levels with different constructs of maternal mental health could be the greater bioavailability of this compound in tropical fruits and thereby, a more profound role of BCX in attenuating the adverse effects of maternal stress in populations where tropical fruit consumption is high. Studies support this hypothesis whereby it was observed that differences in fruit and not vegetable intake was responsible for differences in BCX levels. Unlike in blood and other organs, polar carotenoids, namely xanthophylls get preferentially accumulated in the brain with BCX accumulation being the highest. Two other polar xanthophylls enriched in the brain (lutein and zeaxanthin) also showed an inverse association with depression/anxiety in this study (Table 2). It was also noted that the confounders namely ethnicity, age, education level and ppBMI strongly attenuated the associations between carotenoids and EPDS as well as STAI scores. This finding indicates that environmental influences may be additional determinants of antenatal mental health. Overall, more carotenoid compounds were associated with STAI anxiety scores than with depression. Amongst the two STAI anxiety measures, more associations with carotenoid compounds were seen with state anxiety (psychophysiological state) than with trait anxiety (personality trait).

[0096] The beneficial health effects of carotenoids against some pregnancy complications has been documented. For example, the role of oxidative stress and the protection offered by

carotenoids against preeclampsia is known. In another study it was reported that women who gave birth to preterm babies had lower serum concentrations of carotenoids and that the risk for spontaneous preterm birth decreased with increased serum levels of α- and β- carotene, α- and β- cryptoxanthin and lycopene. Higher maternal plasma concentrations of carotenoids (β-carotene, lutein, zeaxanthin and α- and β- cryptoxanthin) during pregnancy has also been reported to decrease the risk of giving birth to small for gestational age babies. Mothers who gave birth with intra uterine growth restriction were reported to have lower carotenoid levels in serum and breast milk although no differences were observed in the off-springs. However, there is a dearth of studies that explore the link between plasma carotenoids and depression/anxiety during pregnancy.

[0097] Adequate nutrition during pregnancy is important for maintaining the mother's health, optimum fetal development as well the offspring health in later course of life. Maternal depression is known to associate with greater risk of anxiety/depressive disorders in offspring. Against this background, the present disclosure provides novel insights into avenues for designing potential nutritional interventions to prevent mental health adversities in the mother. Such an approach is particularly pertinent in light of the preference to avoid pharmacological interventions during pregnancy.

[0098] **Applications**

[0099] It will be apparent that various other modifications and adaptations of the disclosure will be apparent to the person skilled in the art after reading the foregoing disclosure without departing from the spirit and scope of the disclosure and it is intended that all such modifications and adaptations come within the scope of the appended claims.

CLAIMS

1. A method of treating and/or preventing and/or ameliorating depression and/or anxiety in a woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, comprising administering an effective amount of one or more carotenoids to the woman at a stage selected from the group consisting of preconception, pregnancy, and postpartum stage.

2. The method of claim 1, wherein the carotenoid is at least one or more selected from the group consisting of lutein, zeaxanthin, β-cryptoxanthin, lycopene, α-carotene, and β-carotene.

3. The method of claim 1, wherein the carotenoid is at least one or more selected from the group consisting of β-cryptoxanthin, lycopene, α-carotene, and β-carotene.

4. The method of claim 2 or 3, wherein the carotenoid is β-cryptoxanthin.

5. The method of claim 1, wherein the carotenoid consists of lutein, zeaxanthin, β-cryptoxanthin, lycopene, α-carotene, and β-carotene, and wherein the mental health adversity is anxiety.

6. The method of claim 1 or 2, wherein the carotenoid is at least one or more selected from the group consisting of lutein, β-cryptoxanthin, and β-carotene, and wherein the mental health adversity is anxiety.

7. The method of any one of the preceding claims, comprising administering the carotenoid at a dosage selected from the group consisting of about 3 mg/day, about 4 mg/day, about 5 mg/day, and about 6 mg/day.

8. The method of any one of the preceding claims, comprising administering the carotenoid at a frequency selected from the group consisting of twice every day, once every day, once every 2 days, once every 3 days, once every 4 days, once every 5 days, once every 6 days, once every 7 days, once every 8 days, once every 9 days, once every 10 days, and once every 14 days.

9. The method of claim 8, wherein the carotenoids is administered at a frequency of once every day.

10. The method of any one of the preceding claims, comprising administering the carotenoid for a period selected from the group consisting of: from about 14 weeks after conception to about 6 months after delivery of an offspring, from about 15 weeks after conception to about 6 months after delivery of an offspring, from about 16 weeks after conception to about 6 months after delivery of an offspring, from about 17 weeks after conception to about 6 months after delivery of an offspring, from about 18 weeks after conception to about 6 months after delivery of an offspring, from about 19 weeks after conception to about 6 months after delivery of an offspring, from about 20 weeks after conception to about 6 months after delivery of an offspring, from about 21 weeks after conception to about 6 months after delivery of an offspring, from about 22 weeks after conception to about 6 months after delivery of an offspring, from about 15 weeks after conception to about 5 months after delivery of an offspring, from about 15 weeks after conception to about 4 months after delivery of an offspring, from about 15 weeks after conception to about 3 months after delivery of an offspring, from about 15 weeks after conception to about 2 months after delivery of an offspring, and from about 15 weeks after conception to about 1 month after delivery of an offspring.

11. The method of any one of the preceding claims, wherein the mode of administration of the carotenoid is selected from a group consisting of oral administration, topical administration, parenteral administration, and inhalation.

12. The method of claim 11, wherein the mode of administration of the carotenoid is oral administration.

13. The method of any one of the preceding claims, wherein the carotenoid is formulated in a pharmaceutical composition comprising a pharmaceutically acceptable carrier, diluent and/or adjuvant.

14. The method of any one of claims 1-12, wherein the carotenoid is formulated in a nutritional composition comprising a nutrient and an excipient.

15. The method of any one of the preceding claims, wherein the administration reduces one or more of the scores selected from the group consisting of Edinburgh Postnatal Depression Scale (EPDS) scores, State-Trait Anxiety Inventory (STAI) anxiety scores, and/or reduces the amount of pro-inflammatory cytokines in blood of the pregnant woman.

16. The method of any one of the preceding claims, wherein the administration improves the socio-emotional development of an offspring of the woman.

17. An effective amount of one or more carotenoids for use in treating and/or preventing and/or ameliorating depression and/or anxiety in a woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, wherein the one or more carotenoids is to be administered to the woman at a stage selected from the group consisting of preconception, pregnancy, and postpartum stage.

18. Use of an effective amount of one or more carotenoids in the manufacture of a medicament for treating and/or preventing and/or ameliorating depression and/or anxiety in a woman who is in a stage selected from the group consisting of preconception, pregnancy, and postpartum stage, wherein the medicament is to be administered to the woman at a stage selected from the group consisting of preconception, pregnancy, and postpartum stage.

19. A pharmaceutical composition comprising a carotenoid and a pharmaceutically acceptable carrier, diluent and/or adjuvant.

20. A nutritional composition comprising a carotenoid, a nutrient, and an excipient.

21. The pharmaceutical composition of claim 19 or the nutritional composition of claim 20, wherein the carotenoid is at least one or more selected from the group consisting of lutein, zeaxanthin, β-cryptoxanthin, lycopene, α-carotene, and β-carotene.

22. The pharmaceutical composition of claim 19 or the nutritional composition of claim 20, wherein the carotenoid is at least one or more selected from the group consisting of β-cryptoxanthin, lycopene, α-carotene, and β-carotene.

23. The pharmaceutical composition of claim 19 or the nutritional composition of claim 20, wherein the carotenoid is β-cryptoxanthin.

24. The pharmaceutical composition of claim 19 or the nutritional composition of claim 20, wherein the carotenoid consists of lutein, zeaxanthin, β-cryptoxanthin, lycopene, α-carotene, and β-carotene.

25. The pharmaceutical composition of claim 19 or the nutritional composition of claim 20, wherein the carotenoid is at least one or more selected from the group consisting of lutein, β-cryptoxanthin, and β-carotene.

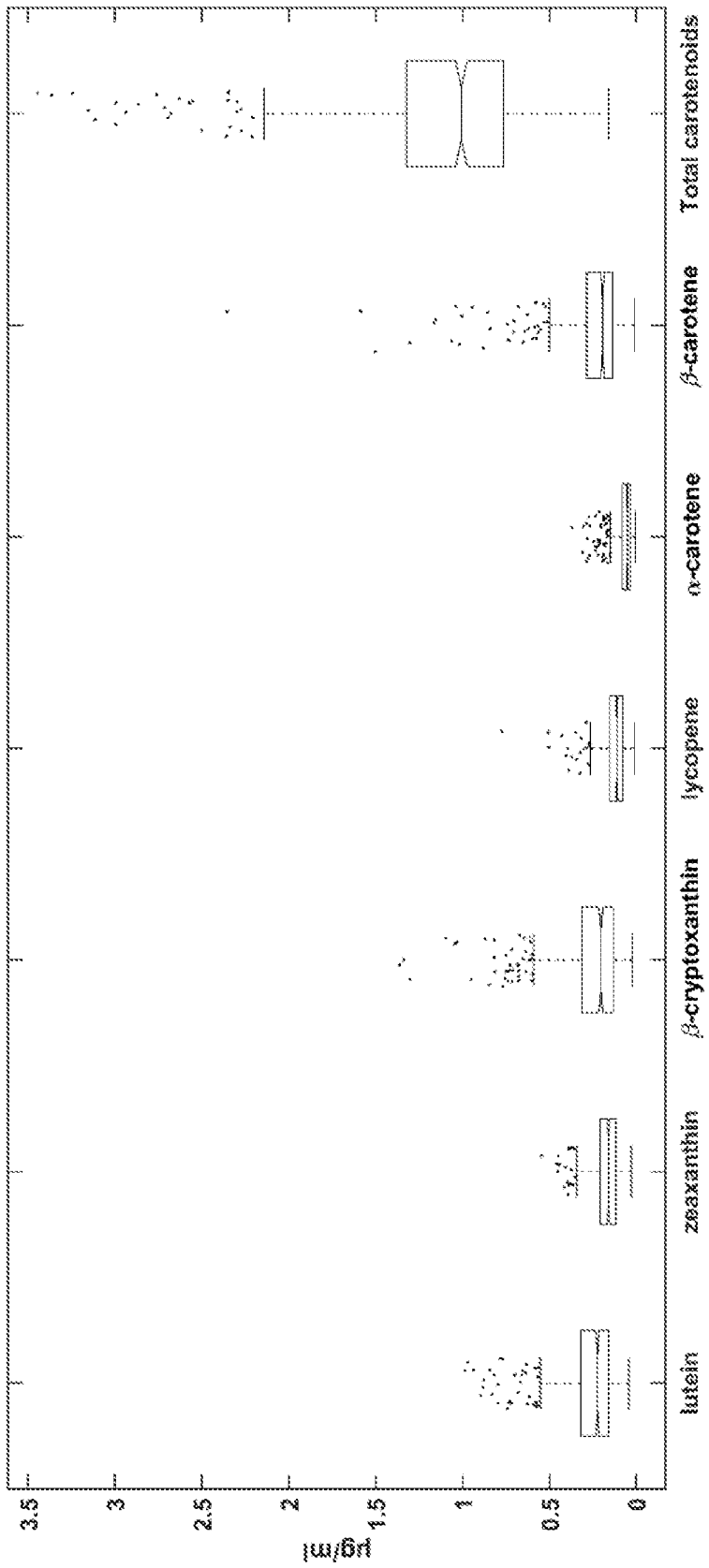
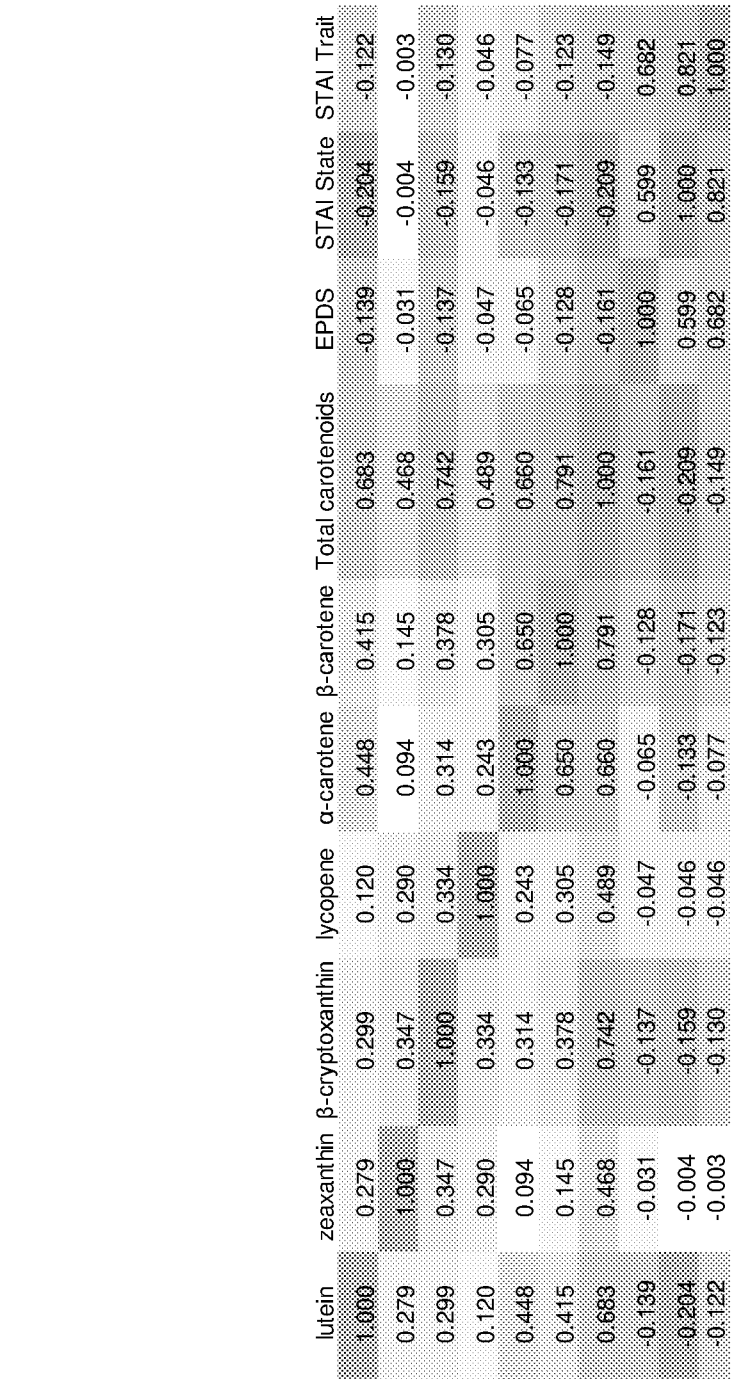

μg/ml
3.5
3
2.5
2
1.5
1
0.5
0
lutein
zeaxanthin
β-cryptoxanthin
lycopene
α-carotene
β-carotene
Total carotenoids

Figure 1



Correlation Coefficients	lutein	zeaxanthin	β-cryptoxanthin	lycopene	α-carotene	β-carotene	Total carotenoids	EPDS	STAI State	STAI Trait
lutein	1.000	0.279	0.299	0.120	0.448	0.415	0.683	-0.139	-0.204	-0.122
zeaxanthin	0.279	1.000	0.347	0.290	0.094	0.145	0.468	-0.031	-0.004	-0.003
β-cryptoxanthin	0.299	0.347	1.000	0.334	0.314	0.378	0.742	-0.137	-0.159	-0.130
lycopene	0.120	0.290	0.334	1.000	0.243	0.305	0.489	-0.047	-0.046	-0.046
α-carotene	0.448	0.094	0.314	0.243	1.000	0.650	0.660	-0.065	-0.133	-0.077
β-carotene	0.415	0.145	0.378	0.305	0.650	1.000	0.791	-0.128	-0.171	-0.123
Total carotenoids	0.683	0.468	0.742	0.489	0.660	0.791	1.000	-0.161	-0.209	-0.149
EPDS	-0.139	-0.031	-0.137	-0.047	-0.065	-0.128	-0.161	1.000	0.599	0.682
STAI State	-0.204	-0.004	-0.159	-0.046	-0.133	-0.171	-0.209	0.599	1.000	0.821
STAI Trait	-0.122	-0.003	-0.130	-0.046	-0.077	-0.123	-0.149	0.682	0.821	1.000

Figure 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SG2021/050133

A. CLASSIFICATION OF SUBJECT MATTER

See Supplemental Box

According to International Patent Classification (IPC)

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

FAMPAT, BIOSIS, EMBASE, MEDLINE: depression, anxiety, woman, carotenoid, lutein, zeaxanthin, β-cryptoxanthin, lycopene, α-carotene, β-carotene and related terms.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2012/0029088 A1 (HARA H. ET AL.) 2 February 2012 abstract; paras. [0011], [0017], [0018], [0026], [0030], [0033]-[0036]; claims 1-20	1-25
X	GAUTAM M. ET AL., Role of antioxidants in generalised anxiety disorder and depression. *Indian Journal of Psychiatry*, 31 July 2012, Vol. 54, No. 3, pages 244-247 [Retrieved on 2021-04-29] <DOI: 10.4103/0019-5545.102424> pp. 244, 246, 247	19-25
X	STRINGHAM N. T. ET AL., Supplementation with macular carotenoids reduces psychological stress, serum cortisol, and sub-optimal symptoms of physical and emotional health in young adults. *Nutritional Neuroscience*, 15 February 2017, Vol. 21, No. 4, pages 286-296 [Retrieved on 2021-04-29] <DOI: 10.1080/1028415X.2017.1286445> pp. 286, 288-291, 293, 294	19-25

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29/04/2021 *(day/month/year)*	*03/05/2021* *(day/month/year)*

Name and mailing address of the ISA/SG	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SG2021/050133

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BLACK C. N. ET AL., Oxidative stress, anti-oxidants and the cross-sectional and longitudinal association with depressive symptoms: results from the CARDIA study. *Translational Psychiatry*, 23 February 2016, Vol. 6, pages e743: 1-10 [Retrieved on 2021-04-29] <DOI: 10.1038/TP.2016.5> whole document	-

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SG2021/050133

Supplemental Box
(Classification of Subject Matter)

Int. Cl.
A61K 31/045 (2006.01)
A61K 31/01 (2006.01)
A61K 31/015 (2006.01)
A61K 31/07 (2006.01)
A61K 31/047 (2006.01)
A61P 25/22 (2006.01)
A61P 25/24 (2006.01)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/SG2021/050133

Note: This Annex lists known patent family members relating to the patent documents cited in this International Search Report. This Authority is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2012/0029088 A1	02/02/2012	JP 2012025712 A	09/02/2012