

METHODS FOR IMPROVING SLEEP QUALITY AND/OR SUBSEQUENT BEHAVIOURAL OUTCOMES USING A FLAVONOID OR PHENOLIC ACID

The present invention generally relates to the use of a composition to improve sleep quality and/or subsequent behavioural outcomes, in particular whole day sustained cognitive performance. More particularly, the present disclosure relates to administration of a composition comprising a flavonoid and/ or phenolic acid compound, at a predetermined time before consumption of a meal, concurrently with consumption of a meal or at a predetermined time before sleep.

10 BACKGROUND

Sleep is a crucial biological function and is considered an important driver of health and well-being across the lifespan. Good sleep quality has been associated with benefits for brain functions, mood and mental performance, cardio-metabolic health, as well as immunity, (Alvarez et al., 2004) whilst poor sleep quality can lead to negative consequences for health and well-being (Hublin et al., 2007).

Typical sleep architecture is comprised of two components: non-rapid eye movement (NREM; Slow Wave Sleep - SWS) and rapid eye movement (REM) sleep. Overall, sleep quality is thought to be driven by the total duration of SWS, whereas both SWS and REM have been found to jointly contribute to next-day benefits, such as improved cognition. SWS and REM are associated with distinct physiological states, including different requirements in nocturnal energy metabolism, substrate oxidation and blood glucose management.

Sleep quality is strongly associated with cognitive functioning, mood, and feelings of vitality and energy the next day. From a scientific perspective, sleep has been consistently linked with cognitive and mood benefits in humans (for reviews, see Palmer & Alfano, 2017; Rasch & Born, 2013; Walker, 2009). Among the different sleep stages, it has been suggested that SWS duration is more closely linked to declarative memory, whereas REM sleep underlies the ability to synthesize abstract information such as detecting patterns in newly acquired information (non-declarative; Rasch & Born, 2013; Walker, 2009). More recent views on the role of each sleep stage have suggested that SWS and REM might

have complementary roles in the consolidation of newly acquired information (for different theories, see Rasch & Born, 2013).

Moreover, sleep requirements change across the lifespan and quality of sleep declines as we age (Madrid-Valero JJ et al. (2017). *Gac sanit*, 31, 18-22.). Poor sleep across adulthood has been associated with ramifications on subjective health, quality of life (Magee CA et al.(2011). *Sleep med.*, 12(4), 346-350) and advancement of cognitive decline and dementia (Hudon C et al (2020). *Neuropsychol Rev*, 30, 558-579).

The majority of evidence on the role of sleep for next-day performance comes from sleep deprivation studies, with evidence suggesting that both sleep disruption and sleep deprivation can negatively impact aspects of cognition, including declarative memory, memory encoding and recall, and cognitive flexibility in using existing information to combine them in novel ways (Walker, 2009). Among the cognitive domains strongly influenced by sleep, levels of daytime vigilance and subjective alertness are highly correlated with sleep duration (Jewett et al., 1999). In fact, vigilance tasks have been consistently used as highly sensitive measures of sleep loss (Basner & Dinges, 2011). Furthermore, sleep difficulties can have significant negative effects on emotion regulation through a range of mechanisms, including reduced ability to downregulate amygdala activation to negative information. Specifically, studies have found that sleep deprivation can cause an increase of almost 60% in amygdala activity when participants are presented with negative images (review, Palmer & Alfano, 2017).

Overall, while the knowledge on direct effect of nutrients on the brain and their mode of action to promote sleep is developed, there are still some needs to identify dietary intervention for improving next-day benefits, and the mechanisms through which it might affect subjective and objective cognitive performance and mood.

SUMMARY

Accordingly, it is an object of the present invention to provide a method of improving sleep quality and/or subsequent behavioural outcomes. It also provides a method of treating, preventing, and/or reducing at least one of risk, incidence or severity of at least one condition for which improved sleep quality is beneficial. The method comprises orally

administering to an individual in need, a composition comprising an effective amount of at least one compound selected from the group consisting of a flavonoid, a phenolic acid or combination thereof.

5 In some embodiments, the subsequent behavioural outcome is subsequent behavioural outcome includes one or more of (a) less frequent and/or less severe sleepiness, stress, tension/anxiety, fatigue/inertia or depression/dejection, anger/hostility, subjective frustration and/or (b) more and/or better sleep initiation, relaxation, calmness, alertness, vigor/activity, friendliness, cognition, memory, working memory, attention, vigilance, processing speed, fat utilization, weight management, immunity, subjective perceptions of mental, physical,
10 temporal demands, subjective performance perception or next-day mood.

In another embodiment, the subsequent behavioural outcome is whole day sustained cognitive performance.

In some embodiments, the flavonoid is one of rutin, quercetin, isoquercetin, luteolin or combination thereof.

15 In some embodiments, the phenolic acid is one of caffeic acid, vanillic acid, chlorogenic acid, syringic acid or combination thereof.

In some embodiments, the composition is administered to the individual at a predetermined time before consumption of a meal and/or concurrently with consumption of a meal.

20 In another embodiment, the composition is administered to the individual in the evening, preferably at a predetermined time before sleep.

Additional features and advantages are described in, and will be apparent from, the following Detailed Description and the Figures.

BRIEF DESCRIPTION OF DRAWINGS

25 **FIG 1 (A, B, C, D)** shows the effect of the active treatment compared to placebo on actigraphy measure of sleep onset latency (A), self-reported sleep onset latency(B), next-day self-reported effects on sleepiness/alertness(C). Values represent least mean square ($\pm$ SE). p-value represent significant difference between the control and treatment group.

FIG. 2 (A, B) shows the effect of active treatment compare to placebo on Mood assessments. A. Profile Of the Mood States – Vigor/activity domain; B. Brief Mood Introspection Scale (BMIS) – Negative-relaxed dimension respectively. Values represent least mean square ($\pm$ SE). p-value represent significant difference between the control and treatment group.

DETAILED DESCRIPTION

Definitions

Some definitions are provided hereafter. Nevertheless, definitions may be located in the “Embodiments” section below, and the above header “Definitions” does not mean that such disclosures in the “Embodiments” section are not definitions.

All percentages are by weight of the total weight of the composition unless expressed otherwise. Similarly, all ratios are by weight unless expressed otherwise. As used herein, “about,” “approximately” and “substantially” are understood to refer to numbers in a range of numerals, for example the range of -10% to +10% of the referenced number, preferably -5% to +5% of the referenced number, more preferably -1% to +1% of the referenced number, most preferably -0.1% to +0.1% of the referenced number.

Furthermore, all numerical ranges herein should be understood to include all integers, whole or fractions, within the range. Moreover, these numerical ranges should be construed as providing support for a claim directed to any number or subset of numbers in that range. For example, a disclosure of from 1 to 10 should be construed as supporting a range of from 1 to 8, from 3 to 7, from 1 to 9, from 3.6 to 4.6, from 3.5 to 9.9, and so forth. Ranges defined using “between” include the referenced endpoints.

As used herein and in the appended claims, the singular form of a word includes the plural, unless the context clearly dictates otherwise. Thus, the references “a,” “an” and “the” are generally inclusive of the plurals of the respective terms. For example, reference to “an ingredient” or “a method” includes a plurality of such “ingredients” or “methods.” The term “and/or” used in the context of “X and/or Y” should be interpreted as “X,” or “Y,” or “X and Y.” Similarly, “at least one of X or Y” should be interpreted as “X,” or “Y,” or “both X and Y.”

Similarly, the words “comprise,” “comprises,” and “comprising” are to be interpreted inclusively rather than exclusively. Likewise, the terms “include,” “including” and “or” should all be construed to be inclusive, unless such a construction is clearly prohibited from the context. However, the embodiments provided by the present disclosure may lack any
5 element that is not specifically disclosed herein. Thus, a disclosure of an embodiment defined using the term “comprising” is also a disclosure of embodiments “consisting essentially of” and “consisting of” the disclosed components. “Consisting essentially of” means that the embodiment or component thereof comprises more than 50 wt.% of the individually identified components, preferably at least 75 wt.% of the individually identified
10 components, more preferably at least 85 wt.% of the individually identified components, most preferably at least 95 wt.% of the individually identified components, for example at least 99 wt.% of the individually identified components.

Where used herein, the term “example,” particularly when followed by a listing of terms, is merely exemplary and illustrative, and should not be deemed to be exclusive or
15 comprehensive. Any embodiment disclosed herein can be combined with any other embodiment disclosed herein unless explicitly indicated otherwise.

“Animal” includes, but is not limited to, mammals, which includes but is not limited to rodents, aquatic mammals, domestic animals such as dogs and cats, farm animals such as sheep, pigs, cows and horses, and humans. Where “animal,” “mammal” or a plural thereof
20 is used, these terms also apply to any animal that is capable of the effect exhibited or intended to be exhibited by the context of the passage, e.g., an animal benefitting from reduced postprandial glucose. While the term “individual” or “subject” is often used herein to refer to a human, the present disclosure is not so limited. Accordingly, the term “individual” or “subject” refers to any animal, mammal or human that can benefit from the
25 methods and compositions disclosed herein.

The relative terms “improve,” “promote,” “enhance” and the like refer to the effects of the method disclosed herein on sleep quality, particularly the administration of a composition comprising a mulberry extract, at a predetermined time before consumption of an evening meal and/or concurrently with consumption of an evening meal, relative to consumption of
30 an identically formulated meal but without the mulberry extract provided by the composition. In some embodiments, sleep quality can be quantified by one or both of (a) a

total duration of slow wave sleep (SWS) and/or (b) a total duration of rapid eye movement (REM). For example, an improved sleep quality can be established by one or both of a longer total duration of SWS and/or a total duration of REM. In some embodiments, improvement in sleep quality is improvement of one or more of i) sleep efficiency (e.g. measured by actigraphy data); ii) change in sleep latency (e.g. actigraphy data); iii) change in wake after sleep onset (e.g. by actigraphy); iv) change in total sleep duration (mins, actigraphy); v) time in bed; vi) minutes spent in bed after waking up. In other embodiments, sleep quality may be assessed by self reporting (e.g. Karolinska Sleepiness Scale (KSS) or Epworth Sleepiness Scale (ESS)).

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As used herein, the terms "treat" and "treatment" mean to administer a composition as disclosed herein to a subject having a condition in order to lessen, reduce or improve at least one symptom associated with the condition and/or to slow down, reduce or block the progression of the condition. The terms "treatment" and "treat" include both prophylactic or preventive treatment (that prevent and/or slow the development of a targeted pathologic condition or disorder) and curative, therapeutic or disease-modifying treatment, including therapeutic measures that cure, slow down, lessen symptoms of, and/or halt progression of a diagnosed pathologic condition or disorder; and treatment of patients at risk of contracting a disease or suspected to have contracted a disease, as well as patients who are ill or have been diagnosed as suffering from a disease or medical condition. The terms "treatment" and "treat" do not necessarily imply that a subject is treated until total recovery. The terms "treatment" and "treat" also refer to the maintenance and/or promotion of health in an individual not suffering from a disease but who may be susceptible to the development of an unhealthy condition. The terms "treatment" and "treat" are also intended to include the potentiation or otherwise enhancement of one or more primary prophylactic or therapeutic measures. As non-limiting examples, a treatment can be performed by a patient, a caregiver, a doctor, a nurse, or another healthcare professional. The terms "prevent" and "prevention" mean to administer a composition as disclosed herein to a subject is not showing any symptoms of the condition to reduce or prevent development of at least one symptom associated with the condition. Furthermore, "prevention" includes reduction of risk, incidence and/or severity of a condition or disorder.

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As used herein, an “effective amount” is an amount that treats or prevents a deficiency, treats or prevents a disease or medical condition in an individual, or, more generally, reduces symptoms, manages progression of the disease, or provides a nutritional, physiological, or medical benefit to the individual. As used herein, “administering” includes another person providing a referenced composition to an individual so that the individual can consume the composition and also includes merely the act of the individual themselves consuming a referenced composition.

The terms “food,” “food product” and “food composition” mean a composition that is intended for ingestion by an individual, such as a human, and that provides at least one nutrient to the individual. “Food” and its related terms include any food, feed, snack, food supplement, treat, meal substitute, or meal replacement, whether intended for a human or an animal. The food supplement can be an oral nutritional supplement (ONS), it can be in a form of a solid powder, a powdered stick, a capsule, or a solution. Animal food includes food or feed intended for any domesticated or wild species. In preferred embodiments, a food for an animal represents a pelleted, extruded, or dry food, for example, extruded pet foods such as foods for dogs and cats.

Within the context of the present disclosure, the term “beverage,” “beverage product” and “beverage composition” mean a potable liquid product or composition for ingestion by an individual such as a human and provides water and may also include one or more nutrients and other ingredients safe for human consumption to the individual.

Embodiments

An aspect of the present disclosure is a method of improving sleep quality and/or subsequent behavioural outcomes. In another aspect, the present disclosure provides a method of treating, preventing, and/or reducing at least one of risk, incidence or severity of at least one condition for which improved sleep quality is beneficial. The method comprises orally administering a composition comprising an effective amount of at least one compound selected from the group consisting of a flavonoid, phenolic acid or combination thereof.

In an embodiment, the composition is administered to the individual at a predetermined time before consumption of a meal and/or concurrently with consumption of a meal.

Alternatively, the composition is administered to the individual in the evening, preferably at a predetermined time before sleep.

Preferably the meal is an evening meal, for example a balanced evening meal.

5 If the composition is administered outside of a meal, it can be delivered in the form of a capsule, liquid, etc..

Subsequent behavioural outcomes enhanced by improved sleep quality include one or more of (a) less frequent and/or less severe sleepiness, stress, tension/anxiety, fatigue/inertia or depression/dejection, anger/hostility, subjective frustration and/or (b) more and/or better sleep initiation, relaxation, calmness, alertness, vigor/activity, friendliness, 10 cognition, memory, working memory, attention, vigilance, processing speed, fat utilization, weight management, immunity, subjective perceptions of mental, physical, temporal demands, subjective performance perception or next-day mood.

In a preferred embodiment, the subsequent behavioural outcome is whole day sustained cognitive performance.

15 The individual may be a mammal such as a human, canine, feline, equine, caprine, bovine, ovine, porcine, cervine or a primate. Preferably the individual is a human.

In some embodiments, the composition is administered to a human adult with sleep complaints.

20 In some embodiments, the flavonoid is one of rutin, quercetin, isoquercetin, luteolin or combination thereof. The flavonoid may be from any suitable source and may be isolated and/or chemically synthesized. In a preferred embodiment, rutin, quercetin, isoquercetin and/or luteolin are obtained from plant sources.

25 Rutin may be obtained from onions, buckwheat, lime tree flowers, elder flowers, hawthorn, rue, St. John's Wort, Ginkgo, apples, and other fruits and vegetables. Quercetin is the aglycone form of a number of other flavonoid glycosides, such as rutin and quercitrin, found in citrus fruit, buckwheat and onions, green tea, apples, berries, Ginkgo biloba, St. John's wort, American elder and others. Isoquercetin, is the 3-O-glucoside of quercetin. Isoquercitrin can be isolated from various plant species including *Mangifera indica* (mango)

and *Rheum nobile* (the Noble rhubarb). It is also present in the leaves of *Annona squamosa*, *Camellia sinensis* (tea). Luteolin may be found in fruits and vegetables, such as celery, chrysanthemum flowers, sweet bell peppers, carrots, onion leaves, broccoli, and parsley.

- 5 In an embodiment, the flavonoid is from mulberry extract. It can be of any *Morus* origin, including, but not limited to, White Mulberry (*Morus alba* L.), Black Mulberry (*Morus nigra* L.), American Mulberry (*Morus celtidifolia* Kunth), Red Mulberry (*Morus rubra* L.), hybrid forms between *Morus alba* and *Morus rubra*, Korean Mulberry (*Morus australis*), Himalayan Mulberry (*Morus laevigata*), and combinations thereof.
- 10 The mulberry extract applicable to the present invention can be derived from different parts of mulberry tree, including barks (trunk, twig or root), roots, buds, twigs, young shoots, leaves, fruits or a combination thereof. The mulberry extract can be in the form of e.g. dried powders such as dried powders milled from different parts of the tree. The starting plant material of mulberry extracts can be fresh, frozen or dried mulberry materials. The extract
- 15 may be used as a liquid or dried concentrated solid. Typically, such an extract includes from at least about 1% w/v 1-DNJ. In a preferred embodiment, the mulberry extract is a mulberry leaf extract.

Vegetable and plant extracts according to the present invention can be prepared by procedures well known in the art.

- 20 The compositions of the present invention may typically comprise from about 1% to about 50%, including from about 2% to about 30%, such as from about 5% to about 20%, and also including from about 10% to about 15% of such extract by weight of the composition.

- The composition may comprise an amount of flavonoid effective to promote better sleep quality to the individual. It may range from 0.01 mg to about 1 g, preferably from 0.1 mg to
- 25 1 g, even more preferably from 1 mg to about 1 g of each component per serving of the composition.

In some embodiments, the phenolic acid is one of caffeic acid, vanillic acid, chlorogenic acid, syringic acid or combination thereof.

Caffeic acid may be found in the bark of *Eucalyptus globulus* the barley grain *Hordeum vulgare* and the herb *Dipsacus asperoides*, freshwater fern *Salvinia molesta* and in the mushroom. Vanillic acid It is found in some forms of vanilla and many other plant extracts, such as the root of *Angelica sinensis*. Chlorogenic acid (CGA) is produced by certain plant species and is a major component of coffee. Syringic acid is a naturally occurring phenolic compound and dimethoxybenzene that is commonly found as a plant metabolite. Syringic acid can be found in several plants including *Ardisia elliptica* and *Schumannianthus dichotomus*.

Preferably the total amount of the phenolic acid in the composition effective to promote better sleep quality to the individual.

In an embodiment, the composition further comprises an ingredient that lowers glycemic response in the individual. In some embodiments, the ingredient that lowers glycemic response is one or more of tryptophan (e.g., as a free amino acid and/or in a protein such as whey protein), a glucosidase inhibitor such as 1-deoxynojirimycin (DNJ) (e.g., isolated or in a mulberry leaf or fruit extract) or phloridzin (e.g., isolated or in an apple extract), arginine-proline (AP) dipeptide (e.g., isolated or in a milk protein hydrolysate), a fiber, a resistant starch, a beta-glucan, A-cyclodextrin, glucosidase (e.g., isolated and/or as part of a composition such as mulberry leaf extract), or an amylase inhibitor (e.g., isolated and/or in a composition such as white kidney bean or wheat albumin).

In some embodiments, the composition is administered once a day (e.g., with the evening meal, preferably not at other meals and/or not at other times of the day) for a total duration of at least 3 days, preferably for at least one week, more preferably for at least two weeks.

In some embodiments, the composition is administered at a predetermined time before sleep. It may be administered immediately before bedtime up to 3 hours before, preferably up to 2 hours before, 1 hour before, 30 minutes before bedtime.

In some embodiments, the composition is a cereal snack, a beverage (e.g., RTD beverage) containing cereal, a soup, a porridge, a broth, or flan and is administered to a human adult. In some embodiments, the composition is administered to a human toddler.

The composition according to the invention may be added to, or mixed into, the meal, or may be consumed in accompaniment to the meal. In a preferred embodiment the

composition comprising ME according to the invention is in the form of a powder or granulate intended to be added to, or mixed into, the meal, preferably sprinkled onto the meal.

As used herein, "meal" refers to one or more food products consumed at substantially the same time as each other; preferably such that one or more proteins, one or more carbohydrates, one or more fats and at least one micronutrient are provided by consuming the meal; more preferably such that one or more proteins, one or more carbohydrates, one or more fats, one or more vitamins and one or more minerals are provided by consuming the meal. Preferably the meal comprises a plurality of food products. As used herein, "balanced meal" refers to meal which provides all of protein, carbohydrate, fat, vitamins and minerals, in quantities and proportions suitable to maintain health or growth of an individual. The quantities and proportions of protein, carbohydrate, fat, vitamins and minerals suitable to maintain health or growth may be determined in line with the current food and nutrition regulations, and any specific requirements of the individual, for example based on age, physical activity, and/or gender.

For example, the Food and Nutrition Board of the Institutes of Medicine (IOM) current energy, macronutrient, and fluid recommendations, recommend an acceptable macronutrient distribution range for carbohydrate (45%-65% of energy), protein (10%-35% of energy), and fat (20%-35% of energy) for active individuals. In an embodiment, the balanced meal provides 45–65% of total calories from carbohydrate, 20–35% of total calories from fat and of total calories 10–35% from protein. In an embodiment, the meal provides 200 kcal to 1,000 kcal to the individual, preferably 250 kcal to 900 kcal, more preferably 300 kcal to 850 kcal, and most preferably 350 kcal to 800 kcal.

In some embodiments, "evening meal" means a meal consumed about 1.0 hours to about 6.0 hours before the onset of sleep, preferably a meal about 2.0 hours to about 5.0 hours before the onset of sleep, more preferably a meal about 2.5 hours to about 4.5 hours before the onset of sleep, most preferably about 3.0 hours to about 4.0 hours before the onset of sleep.

In some embodiments, "evening meal" means a meal consumed at about 4:30pm to about 11:30pm in the geographic region where the individual is located, preferably a meal consumed at about 5:00pm to about 11:00pm in the geographic region where the individual

is located, more preferably a meal consumed at about 5:30pm to about 10:30pm in the geographic region where the individual is located, most preferably a meal consumed at about 6:00pm to about 10:00pm in the geographic region where the individual is located.

5 Preferably the food or supplement according to the present invention, is orally administered to the individual in a form selected from the group consisting of a dairy beverage and a non-dairy beverage, and the unit dosage form is a predetermined amount of the beverage.

In some embodiments, the composition can be a ready to drink (RTD) beverage in a container, and the unit dosage form is a predetermined amount of the RTD beverage sealed in the container, which is opened for the oral administration.

10 In other embodiments, the method comprises forming the composition by reconstituting a unit dosage form of a powder, in water or milk to thereby form the composition subsequently orally administered to the individual (e.g., within about ten minutes after reconstitution, within about five minutes after reconstitution, or within about one minute after reconstitution). The unit dosage form of the powder can be sealed in a sachet or
15 other package, which can be opened for the reconstitution and subsequent oral administration.

In some embodiments, the unit dosage form of the composition can further comprise one or more of melatonin, for example as pistachio powder (e.g., about 0.1 to about 0.3 mg melatonin), Vitamins B3 and B6 (e.g., from about 15% NRV to about 2 mg), magnesium
20 (e.g., about 40 mg magnesium), and/or zinc (e.g., from about 15% NRV to about 15 mg). In some embodiments, the composition can further comprise one or more of gamma aminobutyric acid (GABA), alpha-casozepine, or theanine.

The unit dosage form of the composition can additionally contain excipients, emulsifiers, stabilizers and mixtures thereof. The composition may include any nutritional or non-
25 nutritional ingredient that adds bulk, and in most instances will be substantially inert, and does not significantly negate the blood glucose benefits of the composition. The filler material most typically includes a fiber and/or carbohydrate having a low glycemic index.

Carbohydrate sources suitable for inclusion in the compositions disclosed herein include those having a low glycemic index, such as fructose and low DE maltodextrins, because
30 such ingredients do not introduce a high glycemic load into the composition. Other suitable

components of the composition include any dietary fiber suitable for human or animal use, including soluble and insoluble fiber, especially soluble fibres. Beneficial effects of soluble fibres on glucose response have been widely reported. Non-limiting examples of suitable soluble fibres include FOS, GOS, inulin, resistant maltodextrins, partially hydrolysed guar gum, polydextrose and combinations thereof.

A non-limiting example of a commercially available fiber for the composition include Sunfiber® (Taiyo International, Inc.), which is a water-soluble dietary fiber produced by the enzymatic hydrolysis of Guar beans; Fibersol 2™ (Archer Daniels Midland Company), which is a digestion resistant maltodextrin; and polydextrose.

10 In an embodiment, the composition may also comprise tryptophan. In a preferred embodiment, the composition comprises protein that comprises at least a portion of the tryptophan in the composition, preferably whey protein such as whey protein isolate; a mixture of whey protein and casein; or soy protein. In some embodiments, the supplement is administered in a unit dosage form comprising about 120 mg to about 5 g of the
15 tryptophan.

In an embodiment, the composition can comprise tryptophan, an extract as a source of flavonoid and/or phenolic acid and a soluble fibre. In a preferred embodiment, the composition comprises a soluble fibre selected from polydextrose, a resistant maltodextrin (such as the soluble corn fiber Fibersol-2) and combinations thereof.

20 The composition may also comprise other filler, stabilizers, anti-caking agents, anti-oxidants or combinations thereof.

The composition may further comprise one or more additional components such as minerals; vitamins; salts; or functional additives including, for example, palatants, colorants, emulsifiers, antimicrobial or other preservatives. Non-limiting examples of suitable
25 minerals for the compositions disclosed herein include calcium, phosphorous, potassium, sodium, iron, chloride, boron, copper, zinc, magnesium, manganese, iodine, selenium, chromium, molybdenum, fluoride and any combination thereof. Non-limiting examples of suitable vitamins for the compositions disclosed herein include water-soluble vitamins (such as thiamin (vitamin B1), riboflavin (vitamin B2), niacin (vitamin B3), pantothenic acid
30 (vitamin B5), pyridoxine (vitamin B6), biotin (vitamin B7), myo-inositol (vitamin B8) folic acid

(vitamin B9), cobalamin (vitamin B12), and vitamin C) and fat-soluble vitamins (such as vitamin A, vitamin D, vitamin E, and vitamin K) including salts, esters or derivatives thereof.

All references herein to treatment include curative, palliative and prophylactic treatment. Treatment may also include arresting progression in the severity of a disease. Both human and veterinary treatments are within the scope of the present disclosure. Preferably the composition is administered in a serving or unit dosage form that comprises a therapeutically effective or prophylactically effective amount of the ingredient that lowers glycemic response.

Non-limiting examples:

EXAMPLE 1

The following non-limiting example presents experimental data developing and supporting the concepts of embodiments provided by the present disclosure.

The aim of the current study was to evaluate the effectiveness of an active formulation of mulberry leaf extract, tryptophan and vitamins and minerals (MIT) containing 0.75g Mulberry Leaf Extract (with 1% 1-deoxyjirinomycin) and 120mg tryptophane to promote better sleep and next day mood and cognitive performance in healthy adult poor sleepers.

Methods

The clinical trial design was a double-blind, controlled, randomized, 2-arm, sequential groups cross-over (ClinicalTrials.gov Identifier: NCT05372900). Adult (aged 25-50) poor sleepers Pittsburgh Sleep Quality Index SQI>5 and <85% sleep efficiency over 14-days of screening) received standardized meals and concurrent intake of the active formulation MIT or placebo consumed approximately 4 hours before bedtime. Intervention phases lasted 14-days, with a 28 to 42- day washout period. Primary outcomes were; Sleep Efficiency (SE) and Sleep Onset Latency (SOL) measured by actigraphy. Secondary outcomes included self-reported mood, sleep quality (measured 1-hour post waking) and objective daily average cognitive performance measures.

Results

Linear mixed model analysis was conducted with intention to treat, adjusting for baseline and treatment order for sleep, mood, and cognitive outcomes.. There was no significant effect of treatment on SE ($p=0.23$). However, there was a significant improvement in actigraphy SOL ($p=0.026$) and self reported SOL ($p=0.048$) (see figure 1.A&B) following comparing active treatment compared with control. Subjective self-report measures (Karolinska Sleepiness Scale) also showed that participants felt less sleepy ($p=0.042$) (see figure 1C) in the next morning.

Vigor-activity subscale (1-hour post-wake) score assessed through the Profile Of Mood States questionnaire was significantly increased under the active treatment condition (6.63 ± 0.43) compared to the control (5.82 ± 0.40) ($p=0.038$) (Figure 2A). In the post wake state, there was also a significant difference with the treatment condition (11.65 ± 0.31) in the Negative/relaxed dimension of the Brief Mood Introspection Scale in comparison to the control condition (12.05 ± 0.31) ($p=0.003$).

The active treatment resulted in participants objectively falling to sleep faster, feeling less sleepy and more relaxed, and more energetic(vigor) the following morning.Also, the findings demonstrate that sleep onset, quality and mood outcomes can be ameliorated via supplemental nutritional intervention and may represent a simple and convenient strategy to support the betterment of sleep and its related health outcomes in adult populations. A number of observational studies have shown a link between sleep duration and cognitive performance, including working memory and arithmetic tasks [1, 2]. Additionally, other studies have demonstrated a connection between sleep quality and cognitive performance in tasks involving sustained attention, memory (emotional memory, working memory, memory recall, visuospatial memory), and verbal fluency [2-5]. Furthermore, sleep quality has been found to be associated with academic performance as well [6, 7].

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It should be understood that various changes and modifications to the presently preferred embodiments described herein will be apparent to those skilled in the art. Such changes and modifications can be made without departing from the spirit and scope of the present subject matter and without diminishing its intended advantages. It is therefore intended that such changes and modifications be covered by the appended claims.

CLAIMS

1. A method of improving sleep quality and/or subsequent behavioural outcomes, the method comprising orally administering to an individual, a composition comprising an effective amount of at least one compound selected from the group consisting of a flavonoid, a phenolic acid or combination thereof.

2. A method of treating, preventing, and/or reducing at least one of risk, incidence or severity of at least one condition for which improved sleep quality is beneficial, the method comprising orally administering to an individual, a composition comprising at least one compound selected from the group consisting of a flavonoid, a phenolic acid or combination thereof.

3. The method according to any of claim 1 or 2, wherein the flavonoid is one of rutin, quercetin, isoquercetin, luteolin or combination thereof.

4. The method according to any of claim 1 to 3, wherein the phenolic acid is one of caffeic acid, vanillic acid, chlorogenic acid, syringic acid or combination thereof.

5. The method of any of Claims 1-4, wherein subsequent behavioural outcome includes one or more of (a) less frequent and/or less severe sleepiness, stress, tension/anxiety, fatigue/inertia or depression/dejection, anger/hostility, subjective frustration and/or (b) more and/or better sleep initiation, relaxation, calmness, alertness, vigor/activity, friendliness, cognition, memory, working memory, attention, vigilance, processing speed, fat utilization, weight management, immunity, subjective perceptions of mental, physical, temporal demands, subjective performance perception or next-day mood.

6. The method of any of Claims 1-5, wherein the subsequent behavioural outcome is whole day sustained cognitive performance.

7. The method of any of Claims 1-5, wherein the total amount of the at least one flavonoid and/ phenolic acid compound in the composition is effective to promote better sleep quality to an individual.

8. The method of any of Claims 1-6, wherein the at least one flavonoid and/ or phenolic acid is in the form of a vegetable or plant extract.

9. The method of any of Claims 1-8, wherein the composition further comprises one or more of melatonin, Vitamin B3, Vitamin B6, magnesium, zinc, gamma aminobutyric acid (GABA), alpha-casozepine, or theanine.

5 10. The method of any of claims 1-7, wherein the composition further comprises an ingredient that lowers glycemic response, wherein the ingredient that lowers glycemic response is one or more of tryptophan, a glucosidase inhibitor, polymeric piperidine, 1-deoxynojirimycin (DNJ), arginine-proline (AP) dipeptide, a fiber, a resistant starch, a beta-glucan, A-cyclodextrin, glucosidase or an amylase inhibitor.

10 11. The method of any of Claims 11, wherein the composition comprises protein having at least a portion of tryptophan, preferably whey protein such as whey protein isolate; a mixture of whey protein and casein; or soy protein.

12. The method of any of Claims 1-10, wherein the composition is a liquid beverage, preferably a ready to drink beverage or a beverage formed by reconstitution of a powder in a diluent.

15 13. The method of any of Claims 1-11, wherein the individual is a mammal, preferably a companion animal or a human.

14. The method of any of Claims 1-12, wherein the composition is administered to the individual at a predetermined time before consumption of a meal and/or concurrently with consumption of a meal.

20 15. The method of any of claims 1-14, wherein the composition is administered to the individual in the evening, preferably at a predetermined time before sleep.