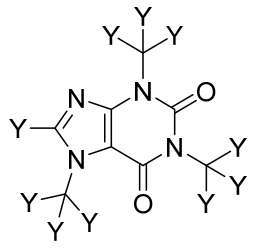
($t_{1/2}$), and rapid clearance, mainly by hepatic cytochrome P450 (CYP450) demethylation to afford paraxanthine, theobromine, and theophylline. In other words, ingestion of caffeine results in a large "spike" in caffeine plasma concentration (*i.e.*, large C_{max}) shortly after caffeine ingestion (*i.e.*, short T_{max}) followed by a "crash" in caffeine plasma concentration due to rapid metabolism and clearance. It is believed that the magnitude of this "spike" and the rapidity of this "crash" are at least partially responsible for the aforementioned adverse effects. Therefore, one approach to mitigate these adverse effects is to develop compounds and compositions that harness the positive attributes of caffeine without the negative effects, that is, with pharmacokinetic profiles exhibiting lower C_{max} values, longer half-life, and/or longer T_{max} values than caffeine.

SUMMARY

[0004] The present disclosure relates to compositions (*e.g.*, pharmaceutical compositions, nutraceutical compositions, foods, beverages, cosmetic compositions, diet supplements) comprising deuterated caffeine. In certain examples, the composition is suitable for oral administration. In certain examples, the composition is suitable for intravenous (IV) administration. In certain examples, the composition is suitable for topical administration. In certain examples, the composition is suitable for delivery to the lungs. In certain examples, the composition is administered using an electronic cigarette or other vaping device, a nebulizer, a pressurized metered dose inhaler (pMDI), or a dry powder inhaler (DPI). In certain examples, the composition is a solid dose composition (*e.g.*, tablet, capsule, granule, powder, sachet, or chewable), solution, gel, suspension, emulsion, shampoo, conditioner, cream, foam, gel, lotion, ointment, transdermal patch, tincture, or paste. Also provided herein are kits containing the compositions and instructions for use. Further provided herein are use of the compositions described herein for treating a disease, preventing a disease, treating a condition, and/or preventing a condition.

[0004a] In one aspect of the present disclosure, there is provided a beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition comprising a compound of Formula (**I**):

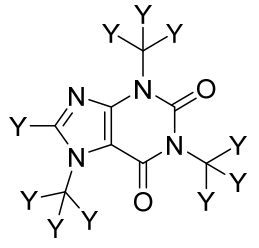

(**I**),

or a pharmaceutically acceptable salt thereof;

wherein each Y is independently hydrogen or deuterium; and

at least one Y is deuterium.

[0004b] In another aspect of the present disclosure, there is provided a use of a pharmaceutical composition or nutraceutical composition disclosed herein; or a compound of Formula (**I**):


(**I**),

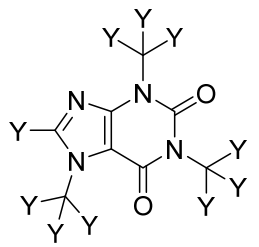
or a pharmaceutically or nutraceutically acceptable salt thereof;

wherein each Y is independently hydrogen or deuterium; and

at least one Y is deuterium;

in the manufacture of a medicament for increasing energy levels, treating obesity, causing weight loss, increasing metabolic rate, reducing appetite, increasing energy expenditure, increasing urine output, increasing sodium excretion, reducing edema, treating a pain disorder, treating apnea, treating hypotension, treating an encephalopathy, treating aneurological or psychiatric disorder, or treating an inflammatory disorder in a subject.

[0004c] In a further aspect of the present disclosure, there is provided a pharmaceutical composition or nutraceutical composition disclosed herein; or a compound of Formula (**I**):


(**I**),

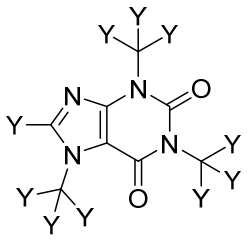
or a pharmaceutically or nutraceutically acceptable salt thereof;

wherein each Y is independently hydrogen or deuterium; and

at least one Y is deuterium;

for use in therapy.

[0005] The compositions described herein comprise deuterated caffeine (*i.e.*, wherein at least one of the hydrogen atoms of caffeine is replaced with deuterium). In certain examples, the composition comprises a compound of Formula (**I**):



(**I**),

or a pharmaceutically or nutraceutically acceptable salt, hydrate, or solvate thereof;

wherein each Y is independently hydrogen or deuterium; and

at least one Y is deuterium.

[0006] Compounds of Formula (**I**) may comprise stable isotopes of carbon, nitrogen, and oxygen in amounts greater than their natural abundance. For example, one or more carbon atoms may be enriched with ^{13}C in an amount greater than about 1.1% (e.g., 1.2-1.5%, 1.5-2%, 2-10%, or more than 10%). One or more nitrogen atoms may be enriched with ^{15}N in an amount greater than about 0.4% (e.g., 0.5-1%, 1-2%, 2-10%, or greater than 10%). Likewise, one or more oxygen atoms may be enriched with ^{16}O in an amount greater than about 0.24% (e.g., 0.25-0.5%, 0.5-1%, 1-2%, 2-10%, or greater than 10%).

[0007] In certain examples, the composition comprises about 1 mg to about 10,000 mg of a compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt, hydrate, or solvate thereof. In certain examples, the percentage of the amount of the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt, hydrate solvate, or prodrug thereof, relative to the total amount of caffeine present in the composition ranges from about 5% to about 99%. In certain examples, the percentage of the amount of the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt, hydrate solvate, or prodrug thereof, relative to the total amount of caffeine present in the composition ranges from about 5% to about 100%. In another example, the composition is an oral composition. In another example, the composition is a solid dose composition (*e.g.*, tablet, capsule, granule, powder, sachet, or chewable). In another example, the composition is suitable for intravenous (IV) administration. In another example, the composition is a topical composition. In another example, the composition is a shampoo, conditioner, cream, foam, gel, lotion, ointment, transdermal patch, tincture, or paste. In another example, the composition is suitable for inhalation. In another example, the composition is administered using an electronic cigarette or other vaping device, a nebulizer, a pressurized metered dose inhaler (pMDI), or a dry powder inhaler (DPI). In another example, the composition is suitable for buccal admistration.

[0008] The disclosure further provides a food product comprising deuterated caffeine (*e.g.*, a compound of Formula (**I**)).

[0009] The disclosure further provides a beverage (*e.g.*, energy drink, vitamin water) comprising deuterated caffeine (*e.g.*, a compound of Formula (**I**)).

[00010] The disclosure further provides kits comprising one or more compositions described herein and instructions for using the composition(s).

[00011] The disclosure further provides methods of delivering the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt, hydrate solvate, composition, or prodrug thereof, to a subject in need thereof comprising administering to the subject in need thereof the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt, hydrate solvate, composition, or prodrug thereof.

[00012] The disclosure further provides methods of treating a disease in a subject in need thereof comprising administering to the subject in need thereof the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt, hydrate, solvate, composition, or prodrug thereof. In certain examples, the method comprises administering a compound of Formula (**I**), wherein each Y is deuterium.

[00013] The disclosure further provides methods of preventing a disease in a subject in need thereof comprising administering to the subject in need thereof the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt, hydrate, solvate, composition, or prodrug thereof. In certain examples, the method comprises administering a compound of Formula (**I**), wherein each Y is deuterium

[00014] The disclosure further provides methods of treating a condition in a subject in need thereof comprising administering to the subject in need thereof the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt, hydrate, solvate, composition, or prodrug thereof. In certain examples, the method comprises administering a compound of Formula (**I**) wherein each Y is deuterium

[00015] The disclosure further provides methods of preventing a condition in a subject in need thereof comprising administering to the subject in need thereof the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt, hydrate, solvate, composition, or prodrug thereof. In certain examples, the method comprises administering a compound of Formula (**I**) wherein each Y is deuterium

[00016] In certain examples, the subject is a human. In certain examples, the subject is an animal.

[00017] In another example, the side effects experienced after administration of a compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt, hydrate, solvate, composition, or prodrug thereof, are reduced relative to the administration of caffeine at an equivalent dose. In another example, the side effect is anxiety, insomnia, gastrointestinal issues (*e.g.*, loose stools, diarrhea, stomach ulcers, gastroesophageal reflux, etc.), rhabdomyolysis, addiction, hypertension, rapid heart rate, atrial fibrillation, fatigue, irritability, nervousness, restlessness, nausea, or muscle tremors.

[00018] In another example, the administration of a compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt, hydrate, solvate, composition, or prodrug thereof, results in an increased duration of action, reduction in frequency of administration, increase in patient compliance and/or ease of use relative to the administration of caffeine at an equivalent dose.

[00019] In another example, the administration of a compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt, hydrate, solvate, composition, or prodrug thereof, results in a similar relative magnitude of exposure in plasma and the central nervous system as compared to the administration of non-isotopically enriched caffeine at an equivalent dose.

[00020] The details of one or more examples of the present disclosure are set forth herein. Other features, objects, and advantages of the present disclosure will be apparent from the Detailed Description, Examples, and Claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[00021] The present invention is further described below with reference to the following non-limiting examples and with reference to the following figures, in which:

[00022] *Figure 1*. depicts the mean (+SD) concentrations of caffeine and D9-caffeine (Compound **14**) in plasma and brain over 14 hours following an oral (gavage) dose of caffeine or D9-caffeine (Compound **14**) to fasted male Sprague Dawley rats at a dose of 2 mg/kg.

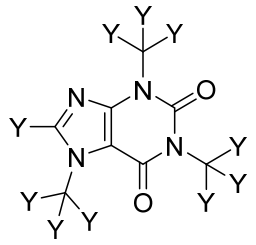
[00023] *Figure 2*. depicts the class and subclass analysis of Compound 14. Reported doses are in mg/kg.

[00024] *Figure 3.* depicts the class and subclass legend.

CLAIMS

What is claimed is:

1. A beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition comprising a compound of Formula (**I**):



(**I**),

or a pharmaceutically acceptable salt thereof;

wherein each Y is independently hydrogen or deuterium; and

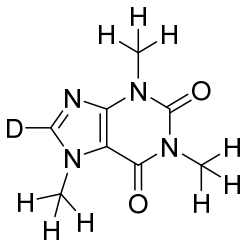
at least one Y is deuterium.

2. A beverage according to claim 1.

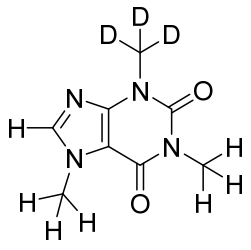
3. A food product according to claim 1.

4. The beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition of any one of claims 1-3, wherein at least three instances of Y are deuterium.

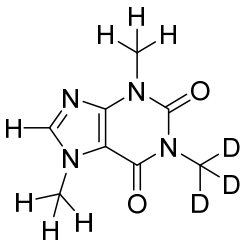
5. The beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition of any one of claims 1-4, wherein the compound is selected from the group consisting of:



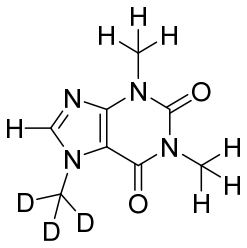
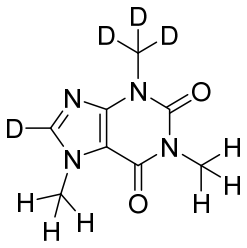
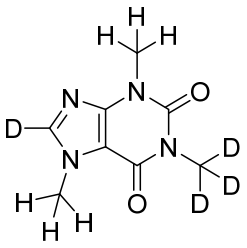
(**1**);

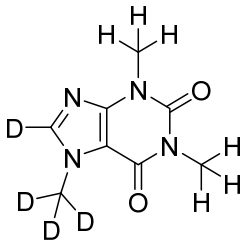
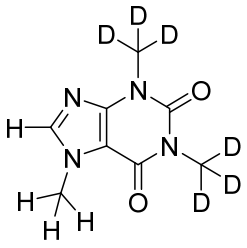
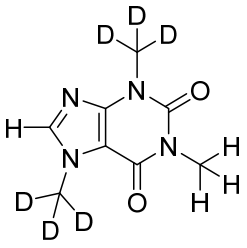


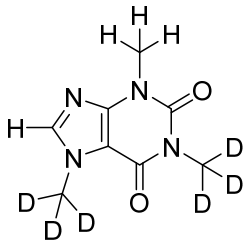
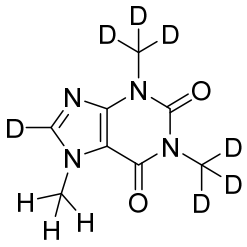
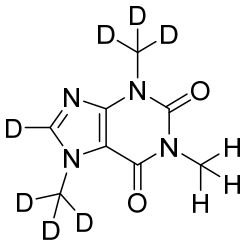
(**2**);

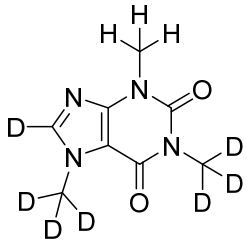
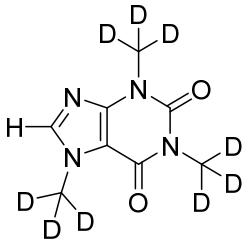
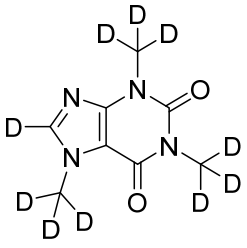


(**3**);

 (**4**);  (**5**);  (**6**);

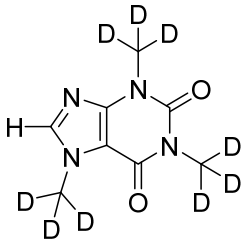
 (**7**);  (**8**);  (**9**);

 (**10**);  (**11**);  (**12**);

 (**13**);  (**14**);  (**15**);

or a pharmaceutically or nutraceutically acceptable salt thereof.

6. The beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition of any one of claims 1-4, wherein the compound is

 (**14**), or a pharmaceutically or nutraceutically acceptable salt thereof.

7. The beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition of any one of claims 1-6, further comprising a pharmaceutically or nutraceutically acceptable carrier.

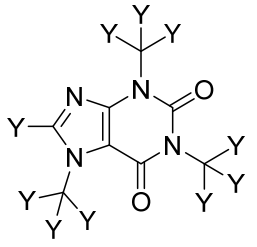
8. The beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition of any one of claims 1-7 further comprising an additional agent.

9. The beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition of any one of claims 1-8, comprising about 1 mg to about 200 mg of the compound of Formula (**I**), or a salt thereof.

10. The beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition of any one of claims 1-8, comprising about 1 mg/ml to about 25 mg/ml of the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt thereof.

11. The beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition of any one of claims 1-10, wherein the percentage of the amount of the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt thereof, relative to the amount of caffeine ranges from about 10% to about 99%.

12. Use of a pharmaceutical composition or nutraceutical composition of any one of claims 1-11; or a compound of Formula (**I**):



(**I**),

or a pharmaceutically or nutraceutically acceptable salt thereof;

wherein each Y is independently hydrogen or deuterium; and

at least one Y is deuterium;

in the manufacture of a medicament for increasing energy levels, treating obesity, causing weight loss, increasing metabolic rate, reducing appetite, increasing energy expenditure,

increasing urine output, increasing sodium excretion, reducing edema, treating a pain disorder, treating apnea, treating hypotension, treating an encephalopathy, treating aneurological or psychiatric disorder, or treating an inflammatory disorder in a subject.

13. The use of claim 12, wherein side effects are reduced relative to the administration of caffeine at an equivalent dose.

14. The use of claim 13, wherein the side effect is anxiety, insomnia, gastrointestinal issues, rhabdomyolysis, addiction, hypertension, rapid heart rate, atrial fibrillation, fatigue, irritability, nervousness, restlessness, nausea, or muscle tremors.

15. The beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition of any one of claims 1-11, wherein the beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition is to be administered, and wherein the maximum plasma concentration (C_{max}) of the compound of Formula (I) after administration is lower than that of non-isotopically enriched caffeine at an equivalent dose.

16. The beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition of any one of claims 1-11, wherein the beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition is to be administered, and wherein the time of maximum plasma concentration (T_{max}) of the compound of Formula (**I**) after administration is longer than that of non-isotopically enriched caffeine at an equivalent dose.

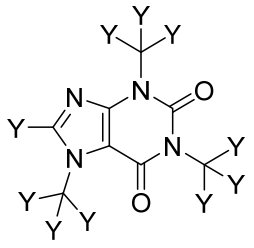
17. The beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition of any one of claims 1-11, wherein the beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition is to be administered, and wherein the plasma half-life ($t_{1/2}$) of the compound of Formula (**I**) after administration is longer than that of non-isotopically enriched caffeine at an equivalent dose.

18. The beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition of any one of claims 1-11, wherein the beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition is to be

administered, and wherein the maximum concentration (C_{max}) of the compound of Formula (**I**) in the central nervous system (CNS) of the subject after administration is lower than that of non-isotopically enriched caffeine at an equivalent dose.

19. The beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition of any one of claims 1-11, wherein the beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition is to be administered, and wherein the time of maximum concentration (T_{max}) of the compound of Formula (**I**) in the central nervous system (CNS) of the subject after administration is longer than that of non-isotopically enriched caffeine at an equivalent dose.

20. A pharmaceutical composition or nutraceutical composition of any one of claims 1-11; or a compound of Formula (**I**):



(**I**),

or a pharmaceutically or nutraceutically acceptable salt thereof;

wherein each Y is independently hydrogen or deuterium; and

at least one Y is deuterium;

for use in therapy.