(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 April 2014 (03.04.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/048968 A1

(51) International Patent Classification:
A23G 9/42 (2006.01) *A61K 36/185* (2006.01)
A61K 36/84 (2006.01)

(21) International Application Number:
PCT/EP2013/069934

(22) International Filing Date:
25 September 2013 (25.09.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
12186620.6 28 September 2012 (28.09.2012) EP

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,

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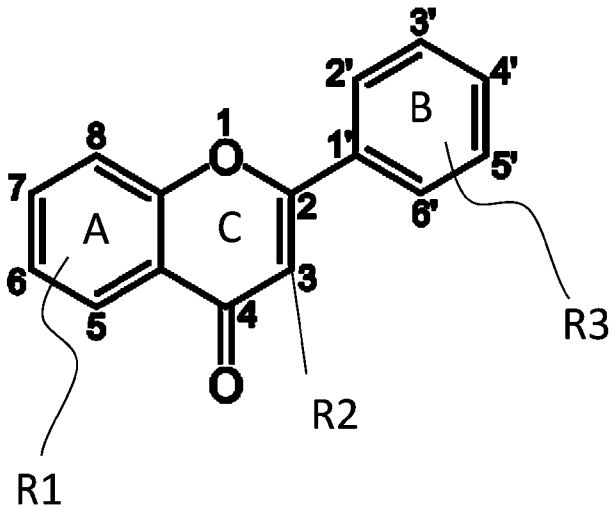
(54) Title: FROZEN CONFECTION COMPRISING VALERENIC ACID AND ONE OR MORE FLAVONES



(57) Abstract: A frozen confection comprising from 0.00005 to 0.05 wt% valerenic acid; and from 0.00005 to 0.05 wt% of one or more flavones having the structure wherein the A-ring has at least one R1 group which is a -OCH3 group attached to any of carbon atoms 5, 6, 7, or 8; R2 is -H, -OH, an alkyl, an alkene, or derivatives thereof; and R3 is -H, -OH, or -OCH3 and is attached to any of carbon atoms 2', 3', 4', 5', or 6' is provided

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MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

FROZEN CONFECTION COMPRISING VALERENIC ACID AND ONE OR MORE FLAVONES

Technical Field of Invention

The present invention relates to frozen confectionery products, in particular to frozen confectionery products that have a relaxatory effect when consumed.

Background to Invention

Gamma-aminobutyric acid (GABA) is known to be a psycho-pharmacologically active compound (Smit et al., Psychopharmacology 2004, 176, pp 412-419) and as such plays a role in the enhancement of mood. JP 2005 / 348656 discloses a food or beverage having a relaxatory effect, the product disclosed therein contains elevated levels of GABA. Frozen confections such as ice cream have been shown to have an effect on the orbitofrontal cortex, a part of the brain that is known to activate when people enjoy themselves (see for example “How ice cream tickles your brain”, The Guardian, April 29 2005). The combination of ice cream with the psycho-pharmacological effect of GABA is therefore an especially suitable means for providing a relaxing food product.

GABA acts through the potentiation of the GABA receptor. This receptor is integral to the mechanism by which GABA is capable of enhancing mood. The GABA molecule is believed to bind to the extracellular part of the GABA-alpha subunit of the GABAa receptor, thereby opening a transmembrane chloride ion-selective pore. Actives that are capable of enhancing the potentiation of this receptor are highly sought after.

Benzodiazepines are one such class of GABA receptor enhancing actives. They act upon the GABA receptor and are used for anti-anxiety treatments. In vitro assays which

measure the current of ions through the GABA receptor channel have shown that benzodiazepines are capable of enhancing the potentiation of the receptor. The benzodiazepines do not interact with the binding site of GABA itself, they interact with another site on the receptor. Therefore these chemicals are capable of enhancing the ability of GABA to activate the GABA receptor.

However, benzodiazepines are widely known as psychoactive drugs. Such pharmacological actives are not acceptable to everyday consumers, nor are they suitable ingredients for frozen confections.

Fortunately, alternative actives are also capable of increasing the potentiation of the GABA receptor, for example valerenic acid. Valerenic acid is a naturally occurring chemical and is a constituent of the essential oil of the Valerian plant. Valerenic acid is believed to act on the GABA receptor in a similar way to the benzodiazepines, that is to say it acts upon the GABA-alpha subunit of the receptor but on a different site to the GABA compound. Valerenic acid also enhances the potentiation of the GABA receptor and since it is a naturally occurring substance which can be obtained the Valerian herb it is a much more suitable ingredient to use in frozen confections.

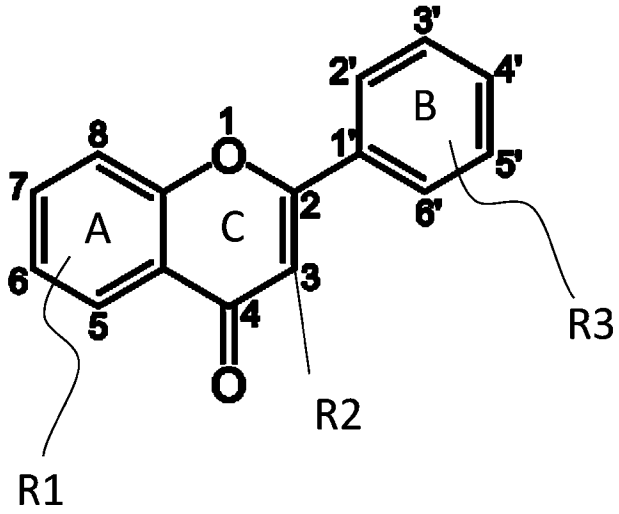
The combination of ice cream and valerenic acid is therefore an especially suitable means for providing a relaxing food product. However, there remains a need to enhance the performance of valerenic acid in such products. Moreover, there remains a need for natural components that are capable of synergistically enhancing the performance of valerenic acid.

Statement of Invention

We have now found that a specific subset of chemicals from the flavone group which comprise at least one methoxy group on the A-ring are capable of synergistically enhancing the ability of valerenic acid to increase the potentiation of the GABA receptor.

Accordingly, in a first aspect the present invention provides a frozen confection comprising

- from 0.00005 to 0.05 wt% valerenic acid; and
- from 0.00005 to 0.05 wt% of one or more flavones having the structure



wherein

- the A-ring has at least one R1 group which is a –OCH3 group attached to any of carbon atoms 5, 6, 7, or 8;
- R2 is –H, -OH, an alkyl, an alkene, or derivatives thereof; and
- R3 is –H, -OH, or –OCH3 and is attached to any of carbon atoms 2', 3', 4', 5', or 6'.

Preferably the A-ring has four R1 groups.

Preferably the A-ring has two R1 groups attached to carbon atoms 8 and 6.

Preferably the A-ring has one R1 group attached to either carbon atom 8 or 6.

Preferably the R2 group is an –OH group, more preferably an –H group.

Preferably the R3 group is an –OCH3 group, more preferably an –OH group, most preferably an –H group.

Preferably the flavone is selected from the group consisting of Wogonin, Hispidulin, and Tangeretin.

Preferably the frozen confection comprises at least 0.0001 wt% valerenic acid, more preferably at least 0.0005 wt%, more preferably still at least 0.001 wt%, yet more preferably still at least 0.005 wt%.

Preferably the frozen confection comprises at most 0.025 wt% valerenic acid, more preferably at most 0.02 wt%, more preferably still at most 0.015 wt%, yet more preferably still at most 0.01 wt%.

Preferably the frozen confection comprises at least 0.0001 wt% of the one or more flavones,

more preferably at least 0.0005 wt%, more preferably still at least 0.001 wt%, yet more preferably still at least 0.005 wt%.

Preferably the frozen confection comprises at most 0.025 wt% of the one or more flavones, more preferably at most 0.02 wt%, more preferably still at most 0.015 wt%, yet more preferably still at most 0.01 wt%.

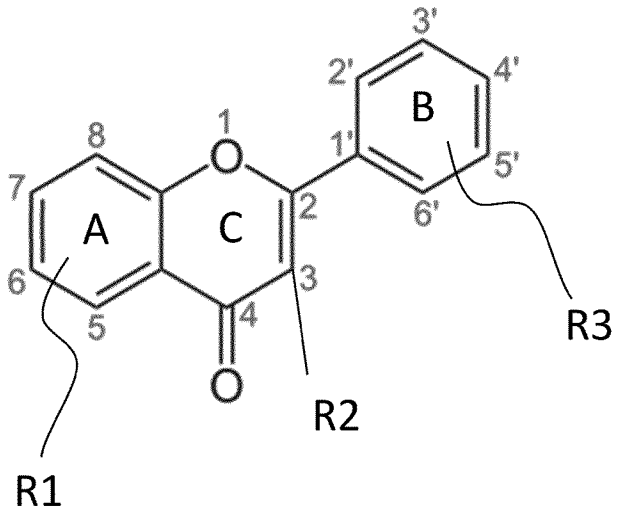
GABA can be present endogenously and therefore need not be present in the frozen confection. However, the product can also provide additional GABA. Therefore the frozen confection preferably contains at least 0.00001 wt% GABA, more preferably at least 0.0001 wt%, more preferably still at least 0.001 wt%, yet more preferably still at least 0.01 wt%.

Preferably the frozen confection comprises at most 0.5 wt% GABA, more preferably at most 0.1 wt%, more preferably still at most 0.05 wt%.

In a second aspect, the invention provides a method for enhancing the potentiation of the GABA receptor comprising the administration of the product according to the first aspect to healthy individuals.

In a third aspect, the invention provides a product for the potentiation of the GABA receptor wherein the product comprises

- A combination of valerenic acid and one or more flavones having the structure



wherein

- the A-ring has at least one R1 group which is an –OCH3 group attached to any of carbon atoms 5, 6, 7, or 8;
- R2 is –H, -OH, an alkyl, an alkene, or derivatives thereof; and
- R3 is –H, -OH, or –OCH3 and is attached to any of carbon atoms 2', 3', 4', 5', or 6'

and wherein the ratio of the valerenic acid to the flavone is from 20:80 to 80:20.

Preferably the ratio of the valerenic acid to the flavone is at least 20:80, more preferably at least 30:70, more preferably still at least 40:60, most preferably at least 45:55.

Preferably the ratio of the valerenic acid to the flavone is at most 80:20, more preferably at most 70:30, more preferably still at most 60:40, most preferably at most 55:45.

Preferably the valerenic acid and the flavone are present in approximately equal amounts.

In a fourth aspect, the invention provides a method for the enhancement of mood wherein healthy individuals consume an effective amount of the frozen confection of the first aspect.

In a fifth aspect, the invention provides a product for the enhancement of mood comprising the product of the third aspect.

Detailed Description of the Invention

Gamma aminobutyric acid (GABA, IUPAC name: 4-aminobutanoic acid) is the chief inhibitory neurotransmitter in the mammalian central nervous system. In vertebrates, GABA acts at inhibitory synapses in the brain by binding to specific transmembrane receptors in the plasma membrane of both pre- and postsynaptic neuronal processes. Binding causes the opening of ion channels to allow the flow of either negatively charged chloride ions into the cell or positively charged potassium ions out of the cell. This action results in a negative change in the transmembrane potential, usually causing hyperpolarization.

GABA has long been associated with mood. Evidence from preclinical and clinical studies has indicated that a GABA deficit may be involved in mood disorders, particularly in depression, and that increasing GABAergic neurotransmission may exert an antidepressant effect and a mood stabilizing effect. For example, a study by Abdou et al. ("Relaxation and immunity enhancement effects of gamma-aminobutyric acid (GABA) administration in humans." Biofactors. 2006, Vol. 26 Issue 3, p201-208) investigated the effect of orally administrated GABA on relaxation during stress. The effect of GABA intake by 13 subjects was investigated by measuring brain waves using electroencephalograms.

It was found that GABA significantly increased alpha waves and decreased beta waves (compared to water or L-theanine). The findings indicated that GABA induces relaxation and reduce anxiety. It is therefore clear that GABA plays a role in the enhancement of mood.

GABA mediates fast synaptic inhibition by interaction with the GABA type A (GABAa) receptor. GABAa receptors are assembled from individual subunits forming a pentameric structure. Nineteen isoforms of mammalian GABAa receptor subunits have been cloned and the subunit composition determines the GABA sensitivity and the pharmacological properties of the GABAa receptor. Binding sites for GABA are thought to be located at subunit interfaces. Studies suggest that the binding pocket of GABA occurs at the interfaces between alpha and beta subunits. GABAa channels are modulated by numerous structurally distinct substances including clinically important drugs such as barbiturates and various general anaesthetics and also by several compounds of plant origin.

Benzodiazepines are one such type of active that are capable of modulating the GABAa receptor and are widely used for anti-anxiety treatments. Benzodiazepines work by increasing the efficiency of GABA to decrease the excitability of neurons. This reduces the communication between neurons and, therefore, has a calming effect on many of the functions of the brain. Benzodiazepines have been shown to enhance the modulation of the receptor as demonstrated with in vitro assays which measure the current of ions through the channel. Benzodiazepines do not interact with the actual binding site of GABA itself, they interact with another site on the receptor.

It is therefore clear that actives such as benzodiazepines which are capable of modulating the GABAa receptor play an important role in providing relaxation and the enhancement of mood.

Similarly, ice cream has been shown to have an effect on the orbitofrontal cortex, a part of the brain that is known to activate when people enjoy themselves. The use of frozen confections such as ice cream is therefore another suitable means for providing a relaxing food product. The term "frozen confection" means a sweet-tasting fabricated foodstuff intended for consumption in the frozen state (i.e. under conditions wherein the temperature of the foodstuff is less than 0°C, and preferably under conditions wherein the foodstuff comprises significant amounts of ice). Frozen confections include ice cream, sorbet, sherbet, frozen yoghurt, water ice, milk ice and the like. Preferably the frozen confection is an ice cream, milk ice, frozen yoghurt, or sherbet. Frozen confection may be aerated, i.e. subjected to deliberate steps such as whipping to increase the gas content. Overrun is defined by the following equation:

$$\text{overrun (\%)} = \frac{\text{density of premix - density of frozen confection}}{\text{density of frozen confection}} \times 100 \ .$$

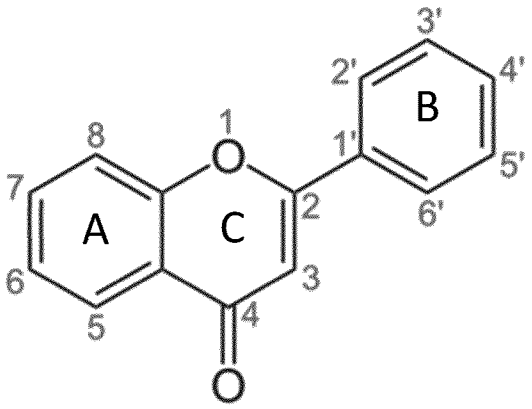
Preferably the overrun is from 30 to 200%, more preferably from 50 to 150%. Overrun is measured at atmospheric pressure.

It is therefore advantageous to combine a GABAa receptor modulator with a frozen confection to deliver mood benefits. However, it is not possible to provide consumers with frozen confections comprising pharmacological actives such as benzodiazepine. Natural alternatives are therefore preferred.

Valerenic acid ((2E)-3-[(4S,7R,7aR)-3,7-dimethyl-2,4,5,6,7,7a-hexahydro-1H-inden-4-yl]-2-methylacrylic acid) is one such natural alternative. Valerenic acid is the major constituent of valerian, one of the most commonly used herbal medicines for the treatment of anxiety and insomnia. Valerian has anxiolytic, tranquilizing, and sleep inducing effects that have been demonstrated in both animal studies and clinical trials. Valerenic acid is believed to induce these effects by enhancing the potentiation of the GABAa receptor and is believed to act on this receptor in a similar way to benzodiazepines. Since valerenic acid is a naturally occurring substance it is more acceptable to consumers than actives such as benzodiazepines and is therefore a suitable ingredient to use in frozen confections.

Nevertheless it would still be preferred to enhance the effect that valerenic acid has on the potentiation of the GABAa receptor and hence enhance the effect that GABA has on mood. Moreover, it is sought to provide natural components that are capable of synergistically enhancing the performance of valerenic acid.

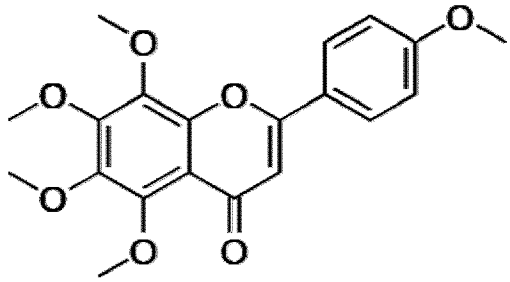
It has now been found that a specific type of falvones are capable of synergistically enhancing the effect provided by valerenic acid. Flavones are a sub-class of flavonoids and are based on the backbone of 2-phenylchromen-4-one (2-phenyl-1-benzopyran-4-one) shown below:



In particular the flavones that have been found to enhance the effect of valerenic acid have at least one methoxy group (–OCH3) on the A-ring. More particularly, the invention utilises flavones having at least one–OCH3 group attached to any of carbon atoms 5, 6, 7, or 8 of the A-ring; an –H, -OH, an alkyl, an alkene, or derivatives thereof at position 2 of the C-Ring; and an –H, -OH, or –OCH3 attached to any of carbon atoms 2', 3', 4', 5', or 6' of the B-Ring.

In a preferred embodiment, the A-ring has a methoxy group attached to each of carbon atoms 5, 6, 7, & 8. In a particularly preferred embodiment the flavone has a methoxy group attached to either or both of carbon atoms 6 and 8 of the A-ring.

Such preferred flavones are exemplified by Tangeretin (5,6,7,8,4'-pentamethoxy-flavone):



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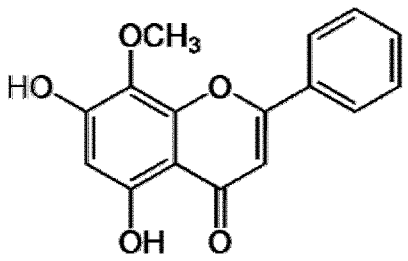
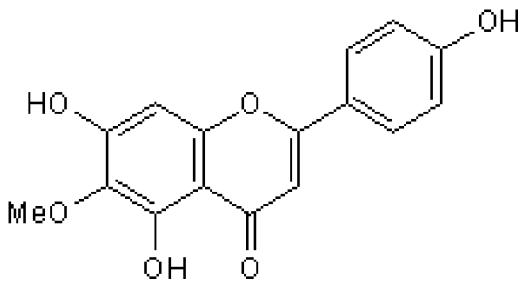
Such preferred flavones are also exemplified by Wogonin (5,7-dihydroxy-8-methoxy-flavone):



Such preferred flavones are futher exemplified by and Hispidulin (5,7,4'-trihydroxy-6-methoxy-flavone):



As set out above, the combination of the natural GABAa receptor modulator valerenic acid with frozen confections (which have been shown to have an effect on the orbitofrontal cortex) is particularly attractive. Accordingly, the invention provides a frozen confection containing at least 0.00005 wt% valerenic acid. Preferably the frozen confection contains at least 0.0001 wt% valerenic acid, more preferably at least 0.0005 wt%, more preferably still at least 0.001 wt%, yet more preferably still at least 0.005 wt%. The frozen confection contains at most 0.05wt%, valerenic acid. Preferably the frozen confection contains at most 0.025 wt% valerenic acid, more preferably at most 0.02 wt%, more preferably still at most 0.015 wt%, yet more preferably still at most 0.01 wt%.

The performance of the product containing valerenic acid will be enhanced by the addition of the specific type of flavones set out above. This is demonstrated in the examples which follow wherein the effects of the flavones are assessed using in vitro assays. In these assays, micro-molar amounts of the flavones were used to determine their ability to enhance the effect of valerenic acid. In order to determine what levels of the flavones must be consumed in a frozen confection in order to deliver the necessary levels of the flavones in the blood plasma, an ADME-toxocolgy analysis was carried out. Accordingly, it was ascertained that the frozen confection should contain at least 0.00005 wt% of the flavones, preferably at least 0.0001 wt%, more preferably at least 0.0005 wt%, more preferably still at least 0.001 wt%, yet more preferably still at least 0.005 wt%. The frozen confection contains at most 0.05 wt% of these flavones, preferably at most 0.025 wt%, more preferably at most 0.02 wt%, more preferably still at most 0.015 wt%, yet more preferably still at most 0.01 wt%.

In order for the product of the invention to deliver a GABA-related enhancement of mood it is clear that GABA should be present in order to interact with the GABAa receptor in combination with the flaovones and the valerenic acid. GABA can be present endogenously in the body of the consumer and therefore need not be present in the product of the invention. However, the product may also provide additional GABA in order to facilitate the GABA-related mood effects. Therefore the frozen confection preferably contains at least 0.00001 wt% GABA, more preferably at least 0.0001 wt%, more preferably still at least 0.001 wt%, yet more preferably still at least 0.01 wt%.

Although frozen confections are a particularly suitable product form for this invention, it is not necessarily the only one. Therefore this present invention also provides a product

which comprises valerenic acid in combination with the specific type of flavones set out above in a ratio of from 20:80 to 80:20. This product is capable of potentiating the GABAa receptor and may be incorporated into other product types such as foods and beverages.

The invention will now be further explained in the following examples.

EXAMPLES

Cellular assays were carried out using the GABAA (GABAA-CHO, automated patch-clamp, agonist) functional assay as described in Sieghart, W. (1995) Pharmacological Reviews, 47(2): 181-234.

The control agonist response was defined as the response of the GABAa receptor to an EC20 concentration of muscimol, Muscimol was used as the mimetic of GABA. The "% of control against agonist response" was calculated by comparing the response of the GABAa receptor to the test compounds against the response to muscimol (i.e. the response of the GABAa receptor to this GABA mimetic was used as the "baseline" of 0%). If the "% of control against agonist response" is greater than the baseline of 0% (i.e. greater than the induction caused by muscimol alone) it indicates that the test compound exhibits potentiation of the GABAa receptor. If the "% of control against agonist response" is less than 0% it indicates an antagonist effect. All assays were performed in triplicate, the mean values are given below.

Assays were carried out to asses the enhanced response provided by valerenic acid. In these assays the effect of valerenic acid alone and in combination with a range of flavones was assessed. Synergistic effects were defined as follows:

The response provided by valerenic acid alone is denoted 'A'.

The response provided by the flavone alone is denoted 'B'.

The response provided by the combination of the valerenic acid and the flavone is denoted 'C'.

If the response provided by the combination of the valerenic acid and the flavone is greater than the sum of the response provided by valerenic acid alone plus the response provided by the flavone alone then the effect is deemed to be synergistic. IE, if C>(A+B) then the effect is synergistic.

In a first experiment, valerenic acid in combination with wogonin and hispidulin was tested at 5.0uM concentrations. The results are shown in Table 1

Compound(s) tested	**% of control against agonist response**
Valerenic acid	21.5
Wogonin	25
Valerenic acid + Wogonin	88
Hispidulin	7
Valerenic acid + Hispidulin	71

Table 1 – results of experiment: valerenic acid in combination with wogonin and hispidulin

Table 1 shows that valerenic acid in combination with wogonin gave a higher (i.e. synergistic) response than the sum of valerenic acid and wogonin alone (88 > (21.5+25)). It also shows that valerenic acid in combination with hispidulin gave a higher response than the sum of valerenic acid and hispidulin alone (71 > (21.5+7)).

In a second experiment, valerenic acid in combination with tangeretin was tested at 5.0uM concentrations. The results are shown in Table 2.

Compound(s) tested	**% of control against agonist response**
Valerenic acid	43
Tangeretin	56
Valerenic acid + Tangeretin	123

Table 2 – results of experiment: valerenic acid in combination with tangeretin

Table 2 shows that valerenic acid in combination with tangeretin gave a higher response (i.e. synergistic) than the sum of valerenic acid and tangeretin alone (123 > (43+56)).

In a third experiment, valerenic acid in combination with apigenin, chrysin, naringenin, and pinocembrin was tested at 5.0uM concentrations. The results are shown in Table 3. It is notable that:

- Naringenin and pinocembrin are both flavanones – they have no double bond between carbons 2 and 3 of the C-ring; and

- Although apigenin and chrysin are both flavones, they have no methoxy groups on the A-ring.

Compound(s) tested	**% of control against agonist response**
Valerenic acid	38
Apigenin	-28
Valerenic acid + apigenin	-1
Chrysin	-13
Valerenic acid + chrysin	23
Naringenin	-8
Valerenic acid + naringenin	28
Pinocembrin	4
Valerenic acid + pinocembrin	-1

Table 3 – results of experiment: valerenic acid in combination with apigenin, chrysin, naringenin, and pinocembrin

It can clearly be seen that no synergistic effects were achieved through the combination of valeranic acid with the compounds shown in table 3. In fact all of these compounds actually reduced the effect of valerenic acid.

From the foregoing data it has been demonstrated that only a very specific subset of the flavone family are capable of synergistically enhancing the modulation of the GABAa receptor by valerenic acid.

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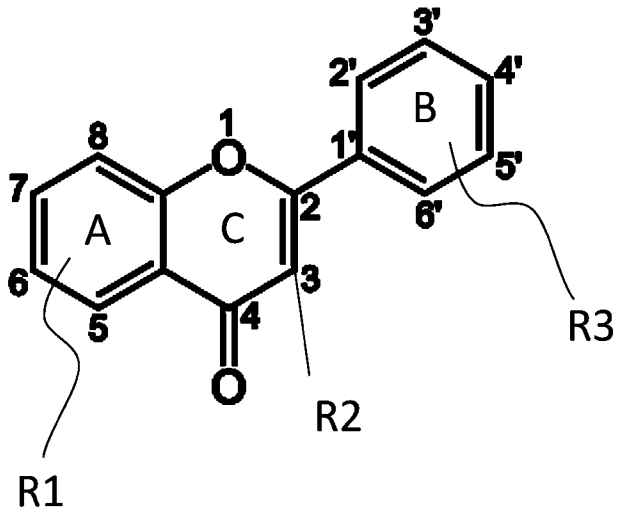
Claims

1. A frozen confection comprising

   - from 0.00005 to 0.05 wt% valerenic acid; and
   - from 0.00005 to 0.05 wt% of one or more flavones having the structure



   wherein

   - the A-ring has at least one R1 group which is a –OCH3 group attached to any of carbon atoms 5, 6, 7, or 8;
   - R2 is –H, -OH, an alkyl, an alkene, or derivatives thereof; and
   - R3 is –H, -OH, or –OCH3 and is attached to any of carbon atoms 2', 3', 4', 5', or 6'.

2. A frozen confection according to claim 1 wherein the A-ring has four R1 groups.

3. A frozen confection according to claim 1 wherein the A-ring has two R1 groups attached to carbon atoms 8 and 6.

4. A frozen confection according to claim 1 wherein the A-ring has one R1 group attached to either carbon atom 8 or 6.

5. A frozen confection according to any of claims 1 to 4 wherein the R2 group is an –OH group, more preferably an –H group.

6. A frozen confection according to any of claims 1 to 5 wherein R3 group is an –OCH3 group, more preferably an –OH group, most preferably an –H group.

7. A frozen confection according to any of claims 1 to 6 wherein the flavone is selected from the group consisting of Wogonin, Hispidulin, and Tangeretin.

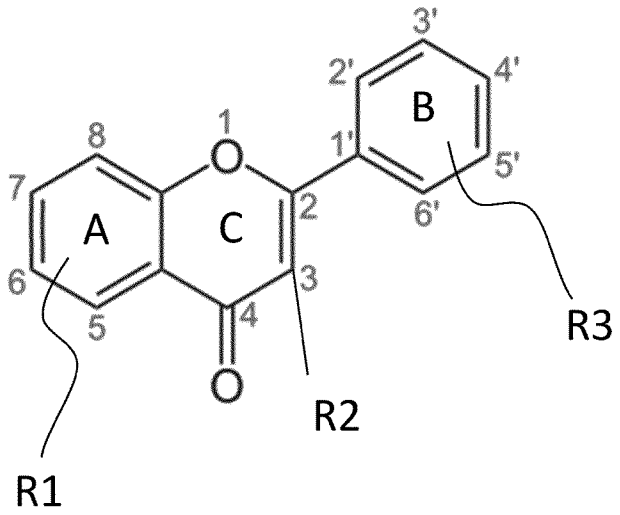
8. A frozen confection according to any of claims 1 to 7 wherein the frozen confection comprises at least 0.0001 wt% valerenic acid.

9. A frozen confection according to any of claims 1 to 7 wherein the frozen confection comprises at least 0.0001 wt% of the one or more flavones

10. A frozen confection according to any of claims 1 to 9 wherein the frozen confection comprises at least 0.00001 wt% GABA.

11. A product for the potentiation of the GABA receptor wherein the product comprises

- a combination of valerenic acid and one or more flavones having the structure



wherein

- the A-ring has at least one R1 group which is an –OCH3 group attached to any of carbon atoms 5, 6, 7, or 8;
- R2 is –H, -OH, an alkyl, an alkene, or derivatives thereof; and
- R3 is –H, -OH, or –OCH3 and is attached to any of carbon atoms 2', 3', 4', 5', or 6'

and wherein the ratio of the valerenic acid to the flavone is from 20:80 to 80:20.

12. A product according to claim 11 wherein the ratio of the valerenic acid to the flavone is at least 30:70.

13. A product according to claims 11 or 12 wherein the ratio of the valerenic acid to the flavone is at most 70:30

14. A product according to any of claims 11 or 13 wherein the valerenic acid and the flavone are present in approximately equal amounts.

15. A product for the enhancement of mood comprising the product of claim 11.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/069934

A. CLASSIFICATION OF SUBJECT MATTER
INV. A23G9/42 A61K36/84 A61K36/185
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A23G A23L A61K

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)

EPO-Internal, WPI Data, COMPENDEX, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Graham A.R. Johnston ET AL: "Modulation of Ionotropic GABA Receptors by Natural Products of Plant Origin" In: "GABA", 1 January 2006 (2006-01-01), Elsevier, XP055055265, ISSN: 1054-3589 ISBN: 978-0-12-032957-1 vol. 54, pages 285-316, DOI: 10.1016/S1054-3589(06)54012-8, Page 293, section C. Page 299, lines 4-13 ----- -/--	1-15

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 October 2013	11/11/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Götz, Michael

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/069934

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	WO 2005/115377 A1 (KGK SYNERGIZE INC [CA]; GUTHRIE NAJLA [CA]) 8 December 2005 (2005-12-08) page 10, paragraph 0042 claims 1,5, 12 -----	1-15

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Information on patent family members

International application No
PCT/EP2013/069934

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