Summary

In a first aspect of the present disclosure, there is provided a method for isolating an antagonist of hTAS2R14 or hTAS2R4 bitter taste receptor activity, wherein the bitter taste receptor is encoded by a polynucleotide selected from the group consisting of:

(a) polynucleotide encoding at least the mature form of the polypeptide having the amino acid sequence as shown in SEQ ID NO: 2 or 6;

(b) polynucleotide having the coding nucleotide sequence as shown in SEQ ID NO: 1 or 5 encoding at least the mature form of the polypeptide;

(c) polynucleotide encoding a fragment or derivative of a polypeptide encoded by a polynucleotide of any one of (a) to (b), wherein in said derivative one or more amino acid residues are conservatively substituted compared to said polypeptide, and said fragment or derivative has hTAS2R14 and hTAS2R4 bitter taste receptor activity, respectively;

(d) polynucleotide which is an ortholog of the polynucleotide sequences shown in SEQ ID NO: 1or 5 encoding at least the mature form of the corresponding bitter taste receptor;

(e) polynucleotide which encodes a polypeptide having hTAS2R14 or hTAS2R4 bitter taste receptor activity, and where said polypeptide is at least 80% identical to a polypeptide as shown in SEQ ID NO: 2 and 6, respectively;

comprising the steps:

(1) contacting a bitter taste receptor encoded by said polynucleotide or a host cell genetically engineered with said polynucleotide or with a vector containing said polynucleotide to express said bitter taste receptor with a potential antagonist; and

(2) determining whether the potential antagonist inhibits the bitter taste receptor activity,

wherein prior, concomitantly and/or after step (1) said bitter taste receptor or said host cell is contacted with an agonist selected from the group consisting of absinthin, artemorin, arborescin, arglabin, azathioprine, azepinon, benzoin, brucine, camphor, chlorhexidine, N,N'-diethylthiourea, herbolid A, isohumulone, noscapine, or parthenolid agonistic derivatives thereof for hTAS2R14 or selected from the group consisting of artemorin, amarogentin, azathioprine or camphor and agonistic derivatives thereof for hTAS2R4.

In a second aspect of the present disclosure, there is provided a method for the production of a modified antagonist of hTAS2R14 or hTAS2R4 comprising the steps of identifying an antagonist by the method according to the first aspect and modifying the antagonist by the addition or exchange of one or two substituents in each instance independently selected from the group consisting of halogen, in particular F, Cl, Br or I; -NO_2; -CN; -OR^c;-NR^cR^d; -$COOR^c$; -$CONR^cR^d$; -$NR2^aCOR^b$; -NR^aCOR^b; -$NR^aCONR^cR^d$;-NR^bSO_2D; -COR^c; -$SO_2NR^cR^d$; -$OOCR^a$; -CR^aR^bOH; R^aOH; and -D,

R^a and R^b is each independently selected from the group consisting of hydrogen; alkyl, in particular C_1-C_6 alkyl, e.g. C_1, C_2, C_3, C_4, C_5, or C_6 alkyl, preferably methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, hexyl; alkenyl, in particular C_2-C_6 alkenyl, e.g. C_2, C_3, C_4, C_5, or C_6 alkenyl, preferably ethenyl, 1-propenyl, 2-propenyl, 1-*iso*-propenyl, 2-*iso*-propenyl, 1-butenyl, 2-butenyl, 3-butenyl; alkynyl, in particular C_2-C_6 alkynyl, e.g. C_2, C_3, C_4, C_5, or C_6 alkynyl; cycloalkyl, in particular C_3-C_{14}-cycloalkyl, e.g. C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13} or C_{14}-cycloalkyl, in particular cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, spiro[3,3]heptyl, spiro[3,4]octyl, spiro[4,3]octyl, spiro[3,5]nonyl, spiro[5,3]nonyl, spiro[3,6]decyl, spiro[6,3]decyl, spiro[4,5]decyl, spiro[5,4]decyl, bicyclo[4.1.0]heptyl, bicyclo[3.2.0]heptyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[5.1.0]octyl, bicyclo[4.2.0]octyl, octahydro-pentalenyl, octahydro-indenyl, decahydro-azulenyl, adamantly, decahydro-naphthalenyl; heterocycloalkyl, e.g. C_3-C_{14}- heterocycloalkyl, e.g. C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13} or C_{14}-heterocycloalkyl, in particular piperidinyl, morpholinyl, 1,3-diazacyclohexane, 1,8 diaza-spiro-[4,5] decyl, 1,7 diaza-spiro-[4,5] decyl, 1,6 diaza-spiro-[4,5] decyl, 2,8 diaza-spiro[4,5] decyl, 2,7 diaza-spiro[4,5] decyl, 2,6 diaza-spiro[4,5] decyl, 1,8 diaza-spiro-[5,4] decyl, 1,7 diaza-spiro-[5,4] decyl, 2,8 diaza-spiro-[5,4] decyl, 2,7 diaza-spiro[5,4] decyl, 3,8 diaza-spiro[5,4] decyl, 3,7 diaza-spiro[5,4] decyl, 1-aza-7,11-dioxo-spiro[5,5] undecyl, 1,4-diazabicyclo[2.2.2]oct-2-yl, tetrahydrofuran-2-yl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydrothienyl, piperazinyl, decahydro-quinolinyl, decahydro-isoquinolinyl, decahydro-quinoxalinyl, decahydro-quinazolinyl; alkoxy, in particular C_1-C_6 alkoxy, e.g. C_1, C_2, C_3, C_4, C_5, or C_6 alkoxy, preferably methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy, *tert*-butoxy, pentoxy, or hexoxy; aryl, in particular phenyl, naphthalenyl or anthracenyl; aralkyl; preferably C_1-C_6 aralkyl, e.g. C_1, C_2, C_3, C_4, C_5, or C_6 aralkyl; heteroaryl, in particular furanyl, thienyl, oxazolyl, isoxazolyl, 1,2,5-oxadiazolyl, 1,2,3-oxadiazolyl, pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, thiazolyl, isothiazolyl, 1,2,3,-thiadiazolyl,1,2,5-thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1-benzofuranyl, 2-benzofuranyl, indolyl, isoindolyl, benzothienyl, 2-benzothienyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, indoxazinyl, 2,1-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 2,1-benzisothiazolyl, benzotriazolyl, quinolinyl, isoquinolinyl, 2,3-benzodiazinyl, quinoxalinyl, quinazolinyl, 1,2,3-benzotriazinyl, or 1,2,4-benzotriazinyl; and -NR^cR^e;

R^c and R^d is each independently selected from the group consisting of hydrogen, alkyl, in particular C_1-C_6 alkyl, e.g. C_1, C_2, C_3, C_4, C_5, or C_6 alkyl, preferably methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, hexyl; alkenyl, in particular C_2-C_6 alkenyl, e.g. C_2, C_3, C_4, C_5, or C_6 alkenyl, preferably ethenyl, 1-propenyl, 2-propenyl, 1-*iso*-propenyl, 2-*iso*-propenyl, 1-butenyl, 2-butenyl, 3-butenyl; alkynyl, e.g. C_2, C_3, C_4, C_5, or C_6 alkynyl; cycloalkyl, in particular C_3-C_{14}-cycloalkyl, e.g. C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13} or C_{14}-cycloalkyl, in particular cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, spiro[3,3]heptyl, spiro[3,4]octyl, spiro[4,3]octyl, spiro[3,5]nonyl, spiro[5,3]nonyl, spiro[3,6]decyl, spiro[6,3]decyl, spiro[4,5]decyl, spiro[5,4]decyl, bicyclo[4.1.0]heptyl, bicyclo[3.2.0]heptyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[5.1.0]octyl, bicyclo[4.2.0]octyl, octahydro-pentalenyl, octahydro-indenyl, decahydro-azulenyl, adamantly, decahydro-naphthalenyl; heterocycloalkyl, e.g. C_3-C_{14}-heterocycloalkyl, e.g. C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13} or C_{14}-heterocycloalkyl, in particular piperidinyl, morpholinyl, 1,3-diazacyclohexane, 1,8 diaza-spiro-[4,5] decyl, 1,7 diaza-spiro-[4,5] decyl, 1,6 diaza-spiro-[4,5] decyl, 2,8 diaza-spiro[4,5] decyl, 2,7 diaza-spiro[4,5] decyl, 2,6 diaza-spiro[4,5] decyl, 1,8 diaza-spiro-[5,4] decyl, 1,7 diaza-spiro-[5,4] decyl, 2,8 diaza-spiro-[5,4] decyl, 2,7 diaza-spiro[5,4] decyl, 3,8 diaza-spiro[5,4] decyl, 3,7 diaza-spiro[5,4] decyl, 1-aza-7,11-dioxo-spiro[5,5] undecyl, 1,4-diazabicyclo[2.2.2]oct-2-yl, tetrahydrofuran-2-yl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydrothienyl, piperazinyl, decahydroquinolinyl, decahydro-isoquinolinyl, decahydro-quinoxalinyl, decahydro-quinazolinyl; aryl, in particular phenyl, naphthalenyl or anthracenyl; heteroaryl, in particular furanyl, thienyl, oxazolyl, isoxazolyl, 1,2,5-oxadiazolyl, 1,2,3-oxadiazolyl, pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, thiazolyl, isothiazolyl, 1,2,3,-thiadiazolyl, 1,2,5-thiadiazolyl, pyridinyl,pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl,1-benzofuranyl, 2-benzofuranyl, indolyl, isoindolyl, benzothienyl, 2-benzothienyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, indoxazinyl, 2,1-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 2,1-benzisothiazolyl, benzotriazolyl, quinolinyl, isoquinolinyl, 2,3-benzodiazinyl, quinoxalinyl, quinazolinyl, 1,2,3-benzotriazinyl, or 1,2,4-benzotriazinyl; and aralkyl, preferably C_1-C_6 aralkyl, e.g. C_1, C_2, C_3, C_4, C_5, or C_6 aralkyl; or together form a heteroaryl, in particular, oxazolyl, isoxazolyl, 1,2,5-oxadiazolyl, 1,2,3-oxadiazolyl, pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, thiazolyl, isothiazolyl, 1,2,3,-thiadiazolyl, 1,2,5-thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, indoxazinyl, 2,1-benzisoxazolyl, 1,2-benzisothiazolyl, 2,1-benzisothiazolyl, benzotriazolyl, quinolinyl, isoquinolinyl, 2,3-benzodiazinyl, quinoxalinyl, quinazolinyl, 1,2,3-benzotriazinyl, or 1,2,4-benzotriazinyl; optionally substituted; and

D is selected from the group consisting of alkyl, in particular C_1-C_6 alkyl, e.g. C_1, C_2, C_3, C_4, C_5, or C_6 alkyl, preferably methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, hexyl; alkenyl, in particular C_1-C_6 alkenyl, e.g. C_1, C_2, C_3, C_4, C_5, or C_6 alkenyl, preferably methenyl, ethenyl, 1-propenyl, 2-propenyl, 1-*iso*-propenyl, 2-*iso*-propenyl, 1-butenyl, 2-butenyl, 3-butenyl; alkynyl, e.g. C_2, C_3, C_4, C_5, or C_6 alkynyl: cycloalkyl, in particular C_3-C_{14}-cycloalkyl, e.g. C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13} or C_{14}-cycloalkyl, in particular cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, spiro[3,3]heptyl, spiro[3,4]octyl, spiro[4,3]octyl, spiro[3,5]nonyl, spiro[5,3]nonyl, spiro[3,6]decyl, spiro[6,3]decyl, spiro[4,5]decyl, spiro[5,4]decyl, bicyclo[4.1.0]heptyl, bicyclo[3.2.0]heptyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[5.1.0]octyl, bicyclo[4.2.0]octyl, octahydro-pentalenyl, octabydro-indenyl, decahydro-azulenyl, adamantly, decahydro-naphthalenyl; alkoxy, in particular C_1-C_6 alkoxy, e.g. C_1, C_2, C_3, C_4, C_5, or C_6 alkoxy, preferably methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy, *tert*-butoxy, pentoxy, or hexoxy; alkoxyalkyl, in particular C_1-C_6-alkoxy-C_1-C_6-alkyl, e.g. methoxymethyl, ethoxymethyl, propoxymethyl, methoxyethyl, ethoxyethyl, propoxyethyl, methoxypropyl, ethoxypropyl, or propoxypropyl; heterocycloalkyl, e.g. C_3-C_{14}-heterocycloalkyl, e.g. C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13} or C_{14}-heterocycloalkyl, in particular piperidinyl, morpholinyl, 1,3-diazacyclohexane, 1,8 diaza-spiro-[4,5] decyl, 1,7 diaza-spiro-[4,5] decyl, 1,6 diaza-spiro-[4,5] decyl, 2,8 diaza-spiro[4,5] decyl, 2,7 diaza-spiro[4,5] decyl, 2,6 diaza-spiro[4,5] decyl, 1,8 diaza-spiro-[5,4] decyl, 1,7 diaza-spiro-[5,4] decyl, 2,8 diaza-spiro-[5,4]decyl, 2,7 diaza-spiro[5,4] decyl, 3,8 diaza-spiro[5,4] decyl, 3,7 diaza-spiro[5,4] decyl, 1-aza-7,11-dioxo-spiro[5,5] undecyl, 1,4-diazabicyclo[2.2.2]oct-2-yl, tetrahydrofuran-2-yl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydrothienyl, piperazinyl, decahydroquinolinyl, decahydro-isoquinolinyl, decahydro-quinoxalinyl, decahydro-quinazolinyl; an alicyclic system, which may comprise one or more heteroatoms, e.g. 1, 2, 3, or 4, preferably selected from the group consisting of O, S, or N; in particular 1,2-dihydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,4-tetrahydropyridyl, 1,2-dihydropyrazyl, 1,2,3,4-tetrahydropyrazyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl; aryl, in particular phenyl, naphthalenyl or anthracenyl; and heteroaryl, in particular furanyl, thienyl, oxazolyl, isoxazolyl, 1,2,5-oxadiazolyl, 1,2,3-oxadiazolyl, pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, thiazolyl, isothiazolyl, 1,2,3,-thiadiazolyl, 1,2,5-thiadiazolyl, pyridinyl, pyrirnidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1-benzofuranyl, 2-benzofuranyl, indolyl, isoindolyl, benzothienyl, 2-benzothienyl, 1H-1-indazolyl, benzimidazolyl, benzoxazolyl, indoxazinyl, 2,1-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 2,1-benzisothiazolyl, benzotriazolyl, quinolinyl, isoquinolinyl, 2,3-benzodiazinyl, quinoxalinyl, quinazolinyl, 1,2,3- benzotriazinyl, or 1,2,4-benzotriazinyl; optionally substituted.

In a third aspect of the present disclosure, there is provided a method for the production of food, a food precursor material or additive employed in the production of foodstuff comprising an antagonist isolated by the method of the first aspect or a modified antagonist produced by the method of the second aspect and admixing the antagonist or modified antagonist, respectively, with foodstuff, a food precursor material or additive employed in the production of foodstuff.

In a fourth aspect of the present disclosure, there is provided a method for the production of a nutraceutical or pharmaceutical composition comprising an antagonist isolated by the method of the first aspect, or a modified antagonist produced by the method of the second aspect and admixing the antagonist or modified antagonist, respectively, with an active agent and optionally with pharmaceutically acceptable carrier and/or adjuvants, in a pharmaceutically acceptable form.

8. A method for the production of a modified antagonist of hTAS2R14 or hTAS2R4 comprising the steps of identifying an antagonist by the method according to claims 1, 2 or 3 to 6 and modifying the antagonist by the addition or exchange of one or two substituents in each instance independently selected from the group consisting of halogen, in particular F, Cl, Br or I; $-NO_2$; -CN; $-OR^c$; $-NR^cR^d$; $-COOR^c$; $-CONR^cR^d$; $-NR2^aCOR^b$; $-NR^aCOR^b$; $-NR^aCONR^cR^d$; $-NR^bSO_2D$; $-COR^c$; $-SO_2NR^cR^d$; $-OOCR^a$; $-CR^aR^bOH$; R^aOH; and -D,

R^a and R^b is each independently selected from the group consisting of hydrogen; alkyl, in particular C_1-C_6 alkyl, e.g. C_1, C_2, C_3, C_4, C_5, or C_6 alkyl, preferably methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, hexyl; alkenyl, in particular C_2-C_6 alkenyl, e.g. C_2, C_3, C_4, C_5, or C_6 alkenyl, preferably ethenyl, 1-propenyl, 2-propenyl, 1-*iso*-propenyl, 2-*iso*-propenyl, 1-butenyl, 2-butenyl, 3-butenyl; alkynyl, in particular C_2-C_6 alkynyl, e.g. C_2, C_3, C_4, C_5, or C_6 alkynyl; cycloalkyl, in particular C_3-C_{14}-cycloalkyl, e.g. C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13} or C_{14}-cycloalkyl, in particular cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, spiro[3,3]heptyl, spiro[3,4]octyl, spiro[4,3]octyl, spiro[3,5]nonyl, spiro[5,3]nonyl, spiro[3,6]decyl, spiro[6,3]decyl, spiro[4,5]decyl, spiro[5,4]decyl, bicyclo[4.1.0]heptyl, bicyclo[3.2.0]heptyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[5.1.0]octyl, bicyclo[4.2.0]octyl, octahydro-pentalenyl, octahydro-indenyl, decahydro-azulenyl, adamantly, decahydro-naphthalenyl; heterocycloalkyl, e.g. C_3-C_{14}- heterocycloalkyl, e.g. C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13} or C_{14}-heterocycloalkyl, in particular piperidinyl, morpholinyl, 1,3-diazacyclohexane, 1,8 diaza-spiro-[4,5] decyl, 1,7 diaza-spiro-[4,5] decyl, 1,6 diaza-spiro-[4,5] decyl, 2,8 diaza-spiro[4,5] decyl, 2,7 diaza-spiro[4,5] decyl, 2,6 diaza-spiro[4,5] decyl, 1,8 diaza-spiro-[5,4] decyl, 1,7 diaza-spiro-[5,4] decyl, 2,8 diaza-spiro-[5,4] decyl, 2,7 diaza-spiro[5,4] decyl, 3,8 diaza-spiro[5,4] decyl, 3,7 diaza-spiro[5,4] decyl, 1-aza-7,11-dioxo-spiro[5,5] undecyl, 1,4-diazabicyclo[2.2.2]oct-2-yl, tetrahydrofuran-2-yl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydrothienyl, piperazinyl, decahydro-quinolinyl, decahydro-isoquinolinyl, decahydro-quinoxalinyl, decahydro-quinazolinyl; alkoxy, in particular C_1-C_6 alkoxy, e.g. C_1, C_2, C_3, C_4, C_5, or C_6 alkoxy, preferably methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy, *tert*-butoxy, pentoxy, or hexoxy; aryl, in particular phenyl, naphthalenyl or anthracenyl; aralkyl; preferably C_1-C_6 aralkyl, e.g. C_1, C_2, C_3, C_4, C_5, or C_6 aralkyl; heteroaryl, in particular furanyl, thienyl, oxazolyl, isoxazolyl, 1,2,5-oxadiazolyl, 1,2,3-oxadiazolyl, pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, thiazolyl, isothiazolyl, 1,2,3,-thiadiazolyl,

1,2,5-thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1-benzofuranyl, 2-benzofuranyl, indolyl, isoindolyl, benzothienyl, 2-benzothienyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, indoxazinyl, 2,1-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 2,1-benzisothiazolyl, benzotriazolyl, quinolinyl, isoquinolinyl, 2,3-benzodiazinyl, quinoxalinyl, quinazolinyl, 1,2,3-benzotriazinyl, or 1,2,4-benzotriazinyl; and $-NR^cR^e$;

R^c and R^d is each independently selected from the group consisting of hydrogen, alkyl, in particular C_1-C_6 alkyl, e.g. C_1, C_2, C_3, C_4, C_5, or C_6 alkyl, preferably methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, hexyl; alkenyl, in particular C_2-C_6 alkenyl, e.g. C_2, C_3, C_4, C_5, or C_6 alkenyl, preferably ethenyl, 1-propenyl, 2-propenyl, 1-*iso*-propenyl, 2-*iso*-propenyl, 1-butenyl, 2-butenyl, 3-butenyl; alkynyl, e.g. C_2, C_3, C_4, C_5, or C_6 alkynyl; cycloalkyl, in particular C_3-C_{14}-cycloalkyl, e.g. C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13} or C_{14}-cycloalkyl, in particular cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, spiro[3,3]heptyl, spiro[3,4]octyl, spiro[4,3]octyl, spiro[3,5]nonyl, spiro[5,3]nonyl, spiro[3,6]decyl, spiro[6,3]decyl, spiro[4,5]decyl, spiro[5,4]decyl, bicyclo[4.1.0]heptyl, bicyclo[3.2.0]heptyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[5.1.0]octyl, bicyclo[4.2.0]octyl, octahydro-pentalenyl, octahydro-indenyl, decahydro-azulenyl, adamantly, decahydro-naphthalenyl; heterocycloalkyl, e.g. C_3-C_{14}-heterocycloalkyl, e.g. C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13} or C_{14}-heterocycloalkyl, in particular piperidinyl, morpholinyl, 1,3-diazacyclohexane, 1,8 diaza-spiro-[4,5] decyl, 1,7 diaza-spiro-[4,5] decyl, 1,6 diaza-spiro-[4,5] decyl, 2,8 diaza-spiro[4,5] decyl, 2,7 diaza-spiro[4,5] decyl, 2,6 diaza-spiro[4,5] decyl, 1,8 diaza-spiro-[5,4] decyl, 1,7 diaza-spiro-[5,4] decyl, 2,8 diaza-spiro-[5,4] decyl, 2,7 diaza-spiro[5,4] decyl, 3,8 diaza-spiro[5,4] decyl, 3,7 diaza-spiro[5,4] decyl, 1-aza-7,11-dioxo-spiro[5,5] undecyl, 1,4-diazabicyclo[2.2.2]oct-2-yl, tetrahydrofuran-2-yl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydrothienyl, piperazinyl, decahydroquinolinyl, decahydro-isoquinolinyl, decahydro-quinoxalinyl, decahydro-quinazolinyl; aryl, in particular phenyl, naphthalenyl or anthracenyl; heteroaryl, in particular furanyl, thienyl, oxazolyl, isoxazolyl, 1,2,5-oxadiazolyl, 1,2,3-oxadiazolyl, pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, thiazolyl, isothiazolyl, 1,2,3,-thiadiazolyl, 1,2,5-thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1-benzofuranyl, 2-benzofuranyl, indolyl, isoindolyl, benzothienyl, 2-benzothienyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, indoxazinyl, 2,1-

benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 2,1-benzisothiazolyl, benzotriazolyl, quinolinyl, isoquinolinyl, 2,3-benzodiazinyl, quinoxalinyl, quinazolinyl, 1,2,3-benzotriazinyl, or 1,2,4-benzotriazinyl; and aralkyl, preferably C_1-C_6 aralkyl, e.g. C_1, C_2, C_3, C_4, C_5, or C_6 aralkyl; or together form a heteroaryl, in particular, oxazolyl, isoxazolyl, 1,2,5-oxadiazolyl, 1,2,3-oxadiazolyl, pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, thiazolyl, isothiazolyl, 1,2,3,-thiadiazolyl, 1,2,5-thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, indoxazinyl, 2,1-benzisoxazolyl, 1,2-benzisothiazolyl, 2,1-benzisothiazolyl, benzotriazolyl, quinolinyl, isoquinolinyl, 2,3-benzodiazinyl, quinoxalinyl, quinazolinyl, 1,2,3-benzotriazinyl, or 1,2,4-benzotriazinyl; optionally substituted; and

D is selected from the group consisting of alkyl, in particular C_1-C_6 alkyl, e.g. C_1, C_2, C_3, C_4, C_5, or C_6 alkyl, preferably methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, hexyl; alkenyl, in particular C_1-C_6 alkenyl, e.g. C_1, C_2, C_3, C_4, C_5, or C_6 alkenyl, preferably methenyl, ethenyl, 1-propenyl, 2-propenyl, 1-*iso*-propenyl, 2-*iso*-propenyl, 1-butenyl, 2-butenyl, 3-butenyl; alkynyl, e.g. C_2, C_3, C_4, C_5, or C_6 alkynyl: cycloalkyl, in particular C_3-C_{14}-cycloalkyl, e.g. C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13} or C_{14}-cycloalkyl, in particular cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, spiro[3,3]heptyl, spiro[3,4]octyl, spiro[4,3]octyl, spiro[3,5]nonyl, spiro[5,3]nonyl, spiro[3,6]decyl, spiro[6,3]decyl, spiro[4,5]decyl, spiro[5,4]decyl, bicyclo[4.1.0]heptyl, bicyclo[3.2.0]heptyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[5.1.0]octyl, bicyclo[4.2.0]octyl, octahydro-pentalenyl, octabydro-indenyl, decahydro-azulenyl, adamantly, decahydro-naphthalenyl; alkoxy, in particular C_1-C_6 alkoxy, e.g. C_1, C_2, C_3, C_4, C_5, or C_6 alkoxy, preferably methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy, *tert*-butoxy, pentoxy, or hexoxy; alkoxyalkyl, in particular C_1-C_6-alkoxy-C_1-C_6-alkyl, e.g. methoxymethyl, ethoxymethyl, propoxymethyl, methoxyethyl, ethoxyethyl, propoxyethyl, methoxypropyl, ethoxypropyl, or propoxypropyl; heterocycloalkyl, e.g. C_3-C_{14}-heterocycloalkyl, e.g. C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13} or C_{14}-heterocycloalkyl, in particular piperidinyl, morpholinyl, 1,3-diazacyclohexane, 1,8 diaza-spiro-[4,5] decyl, 1,7 diaza-spiro-[4,5] decyl, 1,6 diaza-spiro-[4,5] decyl, 2,8 diaza-spiro[4,5] decyl, 2,7 diaza-spiro[4,5] decyl, 2,6 diaza-spiro[4,5] decyl, 1,8 diaza-spiro-[5,4] decyl, 1,7 diaza-spiro-[5,4] decyl, 2,8 diaza-spiro-[5,4]

decyl, 2,7 diaza-spiro[5,4] decyl, 3,8 diaza-spiro[5,4] decyl, 3,7 diaza-spiro[5,4] decyl, 1-aza-7,11-dioxo-spiro[5,5] undecyl, 1,4-diazabicyclo[2.2.2]oct-2-yl, tetrahydrofuran-2-yl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydrothienyl, piperazinyl, decahydroquinolinyl, decahydro-isoquinolinyl, decahydro-quinoxalinyl, decahydro-quinazolinyl; an alicyclic system, which may comprise one or more heteroatoms, e.g. 1, 2, 3, or 4, preferably selected from the group consisting of O, S, or N; in particular 1,2-dihydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,4-tetrahydropyridyl, 1,2-dihydropyrazyl, 1,2,3,4-tetrahydropyrazyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl; aryl, in particular phenyl, naphthalenyl or anthracenyl; and heteroaryl, in particular furanyl, thienyl, oxazolyl, isoxazolyl, 1,2,5-oxadiazolyl, 1,2,3-oxadiazolyl, pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, thiazolyl, isothiazolyl, 1,2,3,-thiadiazolyl, 1,2,5-thiadiazolyl, pyridinyl, pyrirnidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1-benzofuranyl, 2-benzofuranyl, indolyl, isoindolyl, benzothienyl, 2-benzothienyl, 1H-1-indazolyl, benzimidazolyl, benzoxazolyl, indoxazinyl, 2,1-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 2,1-benzisothiazolyl, benzotriazolyl, quinolinyl, isoquinolinyl, 2,3-benzodiazinyl, quinoxalinyl, quinazolinyl, 1,2,3-benzotriazinyl, or 1,2,4-benzotriazinyl; optionally substituted.

9. The method according to claim 8, wherein a modified antagonist is selected that reduces the activity of hTAS2R14 or hTAS2R4 stimulated by absinthin, artemorin, arglabin, azathioprine, azepinon, benzoin, brucine, camphor, chlorhexidine, N,N'-diethylthiourea, herbolid A, isohumulone, noscapine, or, parthenolid for hTAS2R14 or by artemorin, amarogentin, azathioprine or campor for hTAS2R4 at least as good as the identified antagonist at the same molar concentration.

10. A method for the production of food, a food precursor material or additive employed in the production of foodstuff comprising an antagonist isolated by the method of claims 1 to 7 or a modified antagonist produced by the method of claims 8 to 9 and admixing the antagonist or modified antagonist, respectively, with foodstuff, a food precursor material or additive employed in the production of foodstuff.

11. A method for the production of a nutraceutical or pharmaceutical composition comprising an antagonist isolated by the method of claims 1, 2, 3 to 6, or 7, or a modified antagonist produced by the method of claims 8 to 9 and admixing the antagonist or modified antagonist, respectively, with an active agent and optionally with pharmaceutically acceptable carrier and/or adjuvants, in a pharmaceutically acceptable form.