Morusin A, the preparing method and the use thereof

FIELD OF THE INVENTION

[0001] The present invention relates to the field of pharmaceutical techniques. Particularly, the present invention relates to a new, purified compound Morusin A of formula (I), the preparing method thereof, and the pharmaceutical composition using the compound as an active ingredient, and its uses in treating or preventing oral diseases and in oral care products.

BACKGROUND OF THE INVENTION

[0002] The common human oral diseases include caries and periodontal disease. Caries is a chronic bacterial disease occurring in dental hard tissues, manifested as a color, shape, qualitative changes of dental hard tissues. Clinical symptoms of periodontal disease are gum bleeding, purulence, tooth mobility, absorption of alveolar bone and formation of periodontal pocket. Caries and periodontal disease are also one of the primary causes for the tooth loss of adults. It's considered now that the pathogeny of both caries and periodontal disease is endogenous infection diseases resulted from a case that the normal oral floras lose balance, namely the initial factor being plaque microorganism, and being resulted from specific pathogenic microorganisms. Bacteria is the necessary condition for the occurrence of caries, and *Streptococcus mutans*, *Actinomyces viscosus* and the like may break up the carbohydrates to yield acids, causing the teeth inorganics to demineralize and form caries cavities. *Streptococcus mutans* and *Streptococcus mutans* are also the pioneer bacteria in the formation of dental plaques, they form dental plaques together with *Actinomyces viscosus* and *Porphyromonas gingivalis*. The toxins and other detrimental substances produced by the bacteria in the dental plaques may cause the inflammatory reactions of the host, lead to the increase in vascular permeability and the spread of inflammation; destroy the gum, dental bone and alveolar bone, and cause gingivitis and periodontal diseases. Therefore, inhibiting oral pathogenic microorganisms is an important approach to prevent caries, gingivitis and periodontal diseases.

[0003] The pharmaceuticals for treating caries and periodontal disease are very limited at present. On one hand, chemical pharmaceuticals are used to eliminate or inhibit the plaque bacteria, but the long-term use of broad-spectrum antibacterial will bring drug-resistant strains and other side effects. For example, the chemical

plaque-controlling agent Chlorhexidine used both at home and abroad in recent years is a diguanido-hexane having obvious bacteriostasis, but the long-term use of gargle containing 0.12-0.20% Chlorhexidine will cause stained tooth and formation of brown tongue coat at the back of tongue, although will not form any drug-resistant strains or cause any harm to human body. On the other hand, dialectic therapeutics of Traditional Chinese Medicines are used, such as gargling Chinese medicines which are "heat-clearing" and "detoxifying" like honeysuckle, etc., as well as external-applying methods such as applying Bingpeng San (borneol and borax powder) or Asarum on the suffering part. There are many inconveniences in using these methods, and there is no conclusive evidence to prove their efficacy. However, if the gingivitis is not treated timely or properly, the inflammation symptom may spread to periodontal apex to cause the inflammation of periodontal apex tissues, and further affects the alveolar bone or the neighboring tissues. Based on the above reasons, it may be seen that it is meaningful to research and develop new medicines from natural plants for treating common oral diseases such as caries and periodontal diseases, and to develop oral pharmaceuticals or oral care products for inhibiting primary oral pathogenic microorganisms and dental plaques, gingivitis, and for countering breath odor.

[0004] Researches on natural plants inhibiting oral pathogenic microorganisms have distinct geographical characteristics. In accordance with different geographical environments and country situations all over the globe, different countries and regions found some plants of the anti-caries effects, such as *Anogeissus Wall.* and *Vernonia esculenta*, *Garcinia morella Desv.* (gamboges) of Africa and the Middle East; blood grass roots, cocoa fruit of Latin American countries; *Areca catectu L.* (betel nut) of Southeast Asia; Eucalyptus leaves of Australia. China and Japan are more concentrated on the study of Chinese herbal medicines.

DESCRIPTION OF INVENTION

[0005] The object of the present invention is to provide a new, pharmaceutically valuable compound of Morusin A of formula (I).

[0006] Another object of the present invention is to provide a method to extract the new compound of formula (I) described herein from Cortex Mori (White Mulberry Root-bark) plants.

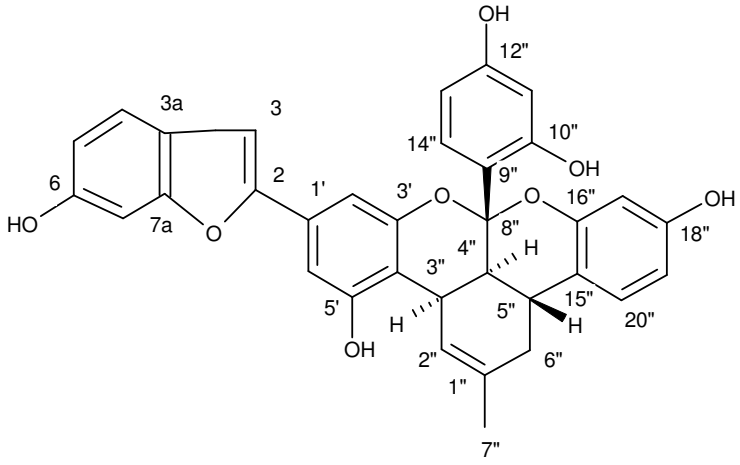
[0007] Further object of the present invention is to provide a pharmaceutical

composition using the compound of formula (I) as an effective ingredient to treat and prevent oral diseases.

[0008] Yet another object of the present invention is to provide uses of the compound of formula (I) and the composition comprising the compound of formula (I) as the effective ingredient in manufacturing pharmaceuticals for treating and preventing oral diseases and an use in the oral care products thereof.

[0009] In order to achieve the above objects, the present invention provides the following technical solution:

[0010] A compound of formula (I):



(I)

[0011] The present study provides a method for preparing the compound of formula (I), i.e., extracting Cortex Mori three times under reflux, 3h each time, and recovering to dryness to obtain an extractum; dissolving and suspending the extractum, extracting the extractum for 3 times with ethyl acetate, and recovering to dryness to obtain an ethyl acetate extractum; dissolving the resultant extractum in acetone and adsorbing the dissolved extractum on silica gel, evaporating to dryness at room temperature, and subjecting the resultant extractum to a silica gel column chromatography, eluting with petroleum ether: acetone in 8:2 (v/v); taking every 50 liters as a fraction, obtaining 27 fractions (Fr.1~Fr.27) in all; subjecting the fraction Fr.6 to a silica gel column chromatography, and eluting with chloroform: methanol in 90:10.

[0012] The present invention further provides a pharmaceutical composition for treating or preventing oral diseases, which contains an amount of the compound of

formula (I) effective for treating or preventing oral diseases, and a pharmaceutically acceptable carrier.

[0013] The present invention also provides a product for oral care, which contains an oral care effective amount of the compound of formula (I) and an oral care acceptable auxiliary.

[0014] The Morusin A compound of formula (I) in the present invention may be used in manufacturing medicaments for treating or preventing oral diseases, as well as in manufacturing oral care products.

[0015] The inventor of the present invention has found for the first time that the compound of formula (I) has certain inhibiting effect on oral pathogenic microorganisms, and has an anti-inflammatory effect. It may be applied in anti-caries and breath odor-inhibiting oral pharmaceuticals or oral care products as an effective ingredient, and may also be used in the oral pharmaceuticals or oral care products for countering gingivitis and dental plaques, removing oral sensitivity, countering tartar and whitening tooth.

[0016] The invention will be illustrated in combination with examples in the following.

EXAMPLE 1 Preparation of the compound of formula (I) and Structure identification of the compound

[0017] 50kg Cortex Mori (White Mulberry Root-bark) is extracted with 500kg 90% ethanol for 3 times under reflux, 3h each time, and recovered to dryness to obtain 10.5kg extractum. The extractum is dissolved and suspended with 8kg hot water and 4kg 90% ethanol, and extracted with 50kg ethyl acetate for three times, recovered to dryness to obtain 4kg ethyl acetate extractum. The resultant extractum is dissolved with acetone and adsorbed on 6kg silica gel, evaporated to dryness at room temperature, and subjected to a silica gel column chromatography (30 meshes, 30kg), eluted with petroleum ether: acetone (v/v, 8:2). Every 50 liters is taken as a fraction, obtaining 27 fractions (Fr.1~Fr.27) in all. The fraction Fr.6 is subjected to a silica gel column chromatography, and eluted with chloroform: methanol (90:10) to obtain the compound of formula (I).

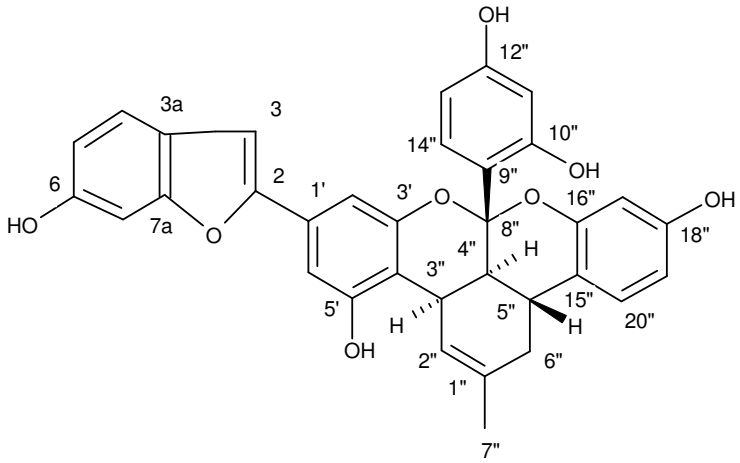
[0018] The compound of formula (I) prepared by this method may have a quite high

concentration. In certain examples, the concentration of the compound of formula (I) prepared by this method is higher than 98%. In certain other examples, the concentration of the compound of formula (I) prepared by this method is from 50% to 99.9%. In some other examples, the concentration of the compound of formula (I) prepared by this method is from 75% to 99.9%.

[0019] In the examples above, Cortex Mori (White Mulberry Root-bark) is used to extract the compound of formula (I). It may be understood by those of ordinary skills in the art that other plants may also be applicable, such as those of the same genus or the same family with Cortex Mori (White Mulberry Root-bark).

[0020] The structure formula of the compound of formula (I) is determined by mass spectrometry (MS) and nuclear magnetic resonance spectrometry (^{1}H NMR and ^{13}C NMR). Auto SPEC type 3000 mass spectrometer is used for mass spectrometry analysis. Bruker DRX-500 superconductive NMR spectrometer is used to determine the nuclear magnetic resonance spectrometry (^{1}H NMR and ^{13}C NMR) of the compound, with TMS as an internal standard. The silica gel for column chromatography and thin layer column chromatography is product of Qingdao Meigao Group Co. Ltd.

[0021] Chemical structure of the compound Morusin A is identified as formula (I):



(I)

Properties: brown powder (methanol), melting point: 103-105˚C

Molecular Formula: $C_{34}H_{26}O_9$

Molecular Weight: 578

FAB-MS (-) m/z(%):561(M+, 100).^{1}H-NMR(CD_3OD, 400 MHz) δ : 7.95(1H, d, J=8.8Hz, H-4), 7.45(1H, s, H-14"), 7.26 (1H, d, J=8.4Hz, H-13"), 7.22(1H, d, J = 2.4 Hz, H-7), 7.21(1H, s, H-20"), 7.05(2H, d, J=2.0Hz, H-2', 6'), 7.02(1H, s, H-3),

6.97(1H, d, J = 8.0Hz, H-19''), 6.70(1H, dd, J=9.8, 2.0Hz, H-5), 6.13(1H, d, J=4.0Hz, H-2''), 4.15(1H, dd, J=12.4, 4.8Hz, H-3''), 3.92(1H, s, H-4''), 3.29(1H, m, H-5''), 2.63(1H, dd, J=17.2, 4.8Hz, H-6''), 2.12(1H, dd, J=16.0, 12.0Hz, H-6''), 1.74(3H, s, H-7'').

^{13}C-NMR(CD_3OD, 100MHz) δ :156.7(s, C-2), 102.0(d, C-3), 121.0(d, C-4), 122.5(s, C-3a), 104.7(d, C-5), 155.0(s, C-6), 99.4(d, C-7), 151.0(s, C-7a), 133.3(s, C-1'), 105.2(d, C-2'), 156.7(s, C-3'), 117.6(s, C-4'), 161.0(s, C-5'), 104.3(d, C-6'), 134.8(s, C-1''), 124.5(d, C-2''), 36.5(d, C-3''), 27.8(d, C-4''), 35.8(d, C-5''), 35.9(t, C-6''), 23.8(q, C-7''), 102.7(s, C-8''), 114.2(s, C-9''), 161.0(s, C-10''), 161.0(d, C-11''), 104.3 (s, C-12''), 107.2(d, C-13''), 130.8(d, C-14''), 117.1(s, C-15''), 154.0(s, C-16''), 104.6(d, C-17''), 158.9(s, C-18''), 110.4(d, C-19''), 128.0(d, C-20'').

[0022] In accordance with the compound structure formula disclosed in the present invention, those skilled in the art may synthesize said compound easily by chemical methods without creative work, to substitute the extract or purified substance used in the present invention. Therefore, those skilled in the art should understand that, in addition to extraction or purification from Cortex Mori (White Mulberry Root-bark) as listed in the examples of the present invention, the present invention may also be achieved through chemical synthesis methods. Other obvious modifications of the compound disclosed in the present invention will also be included within the protection scope of the present invention.

EXAMPLE 2 The inhibition experiment of the compound of formula (I) on primary oral pathogenic microorganisms

[0023] **A. The Cultivation of the bacteria species:**

Table 1: Related oral pathogenic microorganisms

Strains	**ATCC number**	**Gram properties**	**Culture medium**
Streptococcus mutans **(S. m)**	25175	G(+)	TSB
Porphyromonas gingivalis **(P. g)**	33277	G(-)	FTM / RCM (3:1)
Actinomyces viscus **(A. v)**	27044	G(+)	TSB

[0024] A single colony is picked from the Trypticase Digested Soybean peptone agar blood plate (TSA5B) of ordinarily stored bacteria species to corresponding broth culture medium, cultivated in microaerobic environment (P.g needs anaerobic cultivation) with 95% air, 5% CO_2 at 37.0 ˚C ± 1.0 ˚C, wherein S.m is cultivated for 18-24 h, and the remaining two species are cultivated for 40-48 h. Then corresponding broth cultivate medium is used to adjust the turbidity of the bacteria suspension to 0.5#McFarland standard, equivalent to 1.0×10^8 CFU/mL.

B. Experiment method: Broth dilution method (Broth dilution)

[0025] After they are performed a series of 2-fold dilutions, the anti-bacteria pharmaceuticals are quantitatively inoculated with tested bacteria, and are observed after incubated at 37 ˚C for 18-24 h, wherein the lowest pharmaceutical concentration that inhibits the growth visible to the naked eye of the tested bacteria is the minimum inhibitive concentration (MIC) of the tested pharmaceuticals to the tested bacteria. The operating steps are:

a. Preparation of the stock solution of antibacterial pharmaceutical: Preparing 1% stock solution of various antibacterial pharmaceuticals with 100% pure ethanol as solvent. The prepared stock solution is filtered to eliminate bacteria, and is distributed into small portions to be used.

b. Range of measured concentration: the present experiment chooses 250 ppm as the ceiling measured concentration of the anti-bacteria pharmaceutical.

c. Measuring method: micro-dilution method.

[0026] Firstly, 100 μL broth medium is added to each hole of the 96-well plate, and 100 μL sterile anti-bacteria pharmaceutical solution which is diluted 10-folds (1000mg/l) is added to each hole of the first column, then each hole of the first column is blowed repeatedly for 7-8 times using multi-channel micropipet, and 100μL sample is transferred to the second column after sufficiently mixing the pharmaceutical with TSB. After similarly being blowed for 7-8 times, 100μL sample is transferred to the third column, and analogously to the last column. Thus the concentration of the pharmaceutical is 2-fold gradiently diluted, from 500 mg/L of the first column to 0.24mg/L of the last column (the 12th column).

[0027] The bacteria to be tested and standard bacteria are prepared as above. The bacteria solution is diluted with broth medium to a bacteria content of about 10^6 CFU/mL. Then 100μL for each hole is inoculated. Thus the final diluted concentration of the anti-bacteria pharmaceutical in each line are 250, 125,

62.5…0.12 mg/L, and the final inoculation quantity is about 5×10^7 CFU/mL or 5×10^6 bacteria each hole. The 96-well plate is placed on a microshaker and is shaken for 1 min to mix the solution in each hole. The microwell plate is covered and is sealed with adhesive paper to reduce the evaporation during the incubation process and is placed in a humid box, cultivated in microaerobic environment with 95% air, 5% CO_2 (or in anaerobic environment with 90% N_2, 5% H_2, 5% CO_2) at 37.0 ˚C ± 1.0 ˚C for 18-24h . The 96-well plate is placed under an enzyme-labeling instrument, and by comparing the growing characteristics of the tested bacteria with the standard bacteria, the lowest anti-bacteria pharmaceutical concentration contained in the hole without bacteria is taken as MIC.

C. Experiment results (see Table 2)

Table 2: the effect of compound of formula (I) on oral pathogenic microorganisms

	A.v ATCC 27044	**S.m ATCC 25175**	**P.g ATCC 33277**
Negative control (DMSO)	-	-	-
Positive control (Triclosan)	3.9	3.9	7.8
Compound of formula (I)	3.9	3.9	15.6

EXAMPLE 3: Anti-inflammatory experiment of the compound of formula (I)

[0028] A. Experiment by using KB cell (the epidermic cancer cell in human oral cavity):

During the experiment, the KB cell inoculated in the cultivating plate is treated with or without (control) the compound of formula (I). After the treatment, the supernatant of the cultivating liquid is collected and stored in -80°C refrigerator. The PGE_2 in the supernatant is detected by Enzyme-linked immunsorbent assay, and Luminex multifunctional liquid-phase chip analysis system is used for the detection of GM-CSF, TNF-α, IL-1β and IL-6 (the results are shown in Table 3).

B. Detection of PGE_2 by Enzyme-linked immunsorbent assay:

[0029] The assay is performed as standard Enzyme-linked immunsorbent assay.

[0030] Result (the smaller the value, the better the anti-inflammatory activity): The 50% inhibitory concentration of the compound of formula (I) to the growth of oral KB cell is 0.02ppm, equivalent to the positive control Triclosan. The result shows that the compound of formula (I) has significant anti-inflammatory activity.

C. Luminex multifunctional liquid-phase chip analysis of GM-CSF, TNF-α, IL-1 and IL-6:

[0031] The 96-well plate is enclosed with disclosing liquid for 30 min. The fluorescent microspheres are added into the 96-well plate after dilution. The standard sample and the sample to be measured are added, and are stayed overnight at 4˚C. In the next day, the supernatant is discarded and 50 μl GM-CSF, TNF-α, IL-1β and IL-6 antibodies are added to each hole. After being rinsed for 4 times, the 96-well plate is placed in a shaking table under ambient temperature to shade from light for 1h; rinsed for 4 times, and added PE labeled with streptavidin and shaded from light for 15min at room temperature, and then, rinsed for 4 times. The microspheres is suspended in the rinsing buffer, and the 96-well plate is placed immediately on Luminex (Luminex Corporation, Austin, Tx.) to analyze.

D. Result: The compound of formula (I) has a very strong anti-inflammatory ability. The detailed results are shown in Table 3.

Table 3: the anti-inflammatory effect of the compound of formula (I) (the larger the value, the stronger the anti-inflammatory ability)

Extract/compound	GM-CSF	IL-1β（interleukin）	IL-6（interleukin）	TNF-α（Tumor Necrosis Factor）
Compound of formula (I)	11%	23%	53%	93%
Triclosan (Positive control)	5%	7%	31%	81%

[0032] It may be verified by the above experiment results that: compound of formula (I) according to the present invention has excellent inhibitory effect on oral pathogenic microorganisms (*Actinomyces viscosus, Actinobacillus actinomycetemcomitans, Streptococcus mutans*, *Porphyromonas gingivalis*), has significant anti-inflammatory activity to oral KB cells, and also has significant

inhibitory effect on inflammatory factors.

EXAMPLE 4: use of the compound shown in formula (I)

[0033] When used as pharmaceuticals, the compound of formula (I) according to the present invention may be used directly, or may be applied in the oral pharmaceuticals or oral care products such as toothpaste, mouthwash, paste, instant tablet or thin film, chewing gum and the like as the effective ingredient. It may be used in an effective amount together with other ingredients such as humectant, abrasive, surfactant, pharmaceutically acceptable carrier and/or additive to prepare oral pharmaceuticals or oral hygiene products. The resultant oral medicaments or oral hygiene products include but not limited to toothpaste, mouthwash, chewing gum and oral pastes, etc.

[0034] The term "effective amount" indicated herein refers to an amount sufficient to produce a positive effect. Such an effective amount will vary in particular embodiments. In addition, there may be multiple effective dosage or effective dosage range. In some examples, the compound of formula (I) may be mixed with other ingredients in an added amount of 0.0005-99% (mass percentage). In some other embodiments, the content of compound of formula (I) is 0.001-10% (mass percentage). In some preferred examples, the content of compound of formula (I) is 0.025-5% (mass percentage). In some other examples, the content of compound of formula (I) is 0.05-0.5% (mass percentage). In other examples, the content of compound of formula (I) is 0.5-90% (mass percentage).

[0035] Preferably, in tablets, the content of compound of formula (I) is 4% (mass percentage); in nasal sprays, the content of compound of formula (I) is 4% (mass percentage); in dropping pills, the content of compound of formula (I) is 10% (mass percentage); in toothpastes, the content of compound of formula (I) is 0.5% (mass percentage); in mouthwash, the content of the compound of formula (I) is 0.5% (mass percentage); and in oral pastes, the content of compound of formula (I) is 0.01% (mass percentage).

[0036] Other effective amount may also be applicable in the present invention.

[0037] The composition of formulation according to the present invention may also contain cationic surfactants and/or non-ionic surfactants. Cationic surfactants include, but not limited to, cetyltrimethylammonium chloride, di(isobutyl-phenoxy-ethoxy-ethyl)-di(xylene-benzyl) ammonium bromide. Non-ionic surfactants include Poloxamer, polyethoxy ether, and ethoxy fatty acid

and the like. Poloxamer is a block copolymer of polyoxyethylene and polyoxypropylene, having industrial applications, such as that produced by BASF under the trade name “Pluronic”. Polyethoxy ether includes polyoxyethylene sorbitol fatty acid ester (a typical monoester of polyethoxy alcohol), which is produced by ICL company with the trade name Tween. Other non-ionic surfactants include polyoxyethylene alkylphenol, polyoxyethylene alcohols, fatty acids, polyoxyethylene esters, polyoxyethylene alkyl amine glyceride, polyglyceride, tetritol ester, pentitol ester, hexitol ester, dehydrated tritol ester and polyoxyalkylamine polyalkyl ester. Typically, the mass content of surfactant in the formulation is 0.001%-3.0%. Divalent metal ions, such as zinc, copper, selenium, calcium or magnesium, may be included in the formulation. They will be in the form of soluble inorganic salts such as zinc chloride or the form of organic/inorganic compounds. The amount of divalent metal ions added into the mixture will be 0.001% - 3.0%. The formulation may contain oligosaccharides, which will be in the water-soluble state, and may convert into soluble salt, if added, in an amount of at least 0.01%

[0038] The present invention may include various commonly used oral pharmaceuticals or oral hygiene products, such as mouthwash, oral spray, toothpaste, gels, oral mucosa plasters, oral pellicle, instant tablet and film, chewing gum and the like products for mammals, especially human and animals, to inhibit plaque and prevent dental caries and periodontal diseases.

[0039] Other additives may be used due to different approaches: mouthwash may contain acidic substances; mouthwash may also contain desensitizing substance such as potassium nitrate; toothpaste may contain abrasives such as sodium carbonate, calcium phosphate, alumina and silica; solubilizer such as PEG, glycerol, ethanol; other taste masking agents such as xylitol; thickener such as carrageenan; and surfactant such as SLS, etc. may all be used.

[0040] Waxes such as beeswax may be used in toothpaste or oral mucosa plaster; thickener and pellicle-forming agents such as carrageenan, CMC, HPMC, xanthan gum and the like may also be added.

[0041] For essences, it may use essences such as mint, spearmint, eucalyptus leaf oil, menthol, carvone, wintergreen, cloves, cinnamon, lemon, grapefruit, orange and some essences decomposed and digested from yeast and protein.

[0042] In tablets and pellicles, inert excipients may be used for the formation of the products. Adjuvants such as colorant, taste masking agent and the like are mainly included to improve the taste and appearance.

[0043] The composition of the formulation related with the use of the present invention in tablets may contain filler, adhesive, lubricant, disintegrant. Fillers include, but not limited to, starch, lactose, microcrystalline cellulose and the like. Adhesives include, but not limited to, starch slurry, cellulose derivatives, polyvidone, gelatin and the like. Lubricants include, but not limited to, magnesium stearate, micropowder silica gel, talcum powder, polyethylene glycols and the like. Disintegrants include, but not limited to, sodium carboxymethyl starch, low substituted hydroxylpropyl cellulose, cross-linked polyvidone, cross-linked sodium carboxymethyl cellulose and the like. All these ingredients are pharmaceutically acceptable adjuvants recorded in the Chinese Pharmacopoeia and the Pharmacopoeia of many countries such as United Kingdom and United States.

[0044] Matrix such as polyethylene glycol and the like may be used in the pastes of the present invention. Polyethylene glycol in solid may be combined with its liquid form to adjust the consistency. Ingredients such as magnesium stearate may also be added to adjust the consistency.

EXAMPLE 5: Specific Uses

[0045] Following experiments and examples will make those skilled in the art understand the present invention more comprehensive, but they will not limit the present invention in any way.

Compound of formula (I) toothpaste formulation 1：

Components	**Content (mass percentage, %)**
Compound of formula (I)	0.0005 – 20
Abrasive	10-30
Humectant	50-69
Water, Flavor, Flavoring	proper amount

Compound of formula (I) toothpaste formulation 2：

Components	**Content (mass percentage, %)**
Compound of formula (I)	5
Silica	30

Glycerol	5
Sorbitol	50
Water, Flavor, Flavoring	proper amount

Compound of formula (I) toothpaste formulation 3：

Components	**Content (mass percentage, %)**
Compound of formula (I)	0.001
Silica	10
Sorbitol	69
Water, Flavor, Flavoring	proper amount

Compound of formula (I) toothpaste formulation 4：

Components	**Content (mass percentage, %)**
Compound of formula (I)	10
Abrasive	25
Humectant	65

Compound of formula (I) toothpaste formulation 5：

Components	**Content (mass percentage, %)**
Compound of formula (I)	0.0005
Silica	10
Sorbitol	70
Water, Flavor, Flavoring	proper amount

Compound of formula (I) toothpaste formulation 6：

Components	**Content (mass percentage, %)**
Compound of formula (I)	20
Abrasive	25
Humectant	55

Compound of formula (I) toothpaste formulation 7：

Components	**Content (mass percentage, %)**
Compound of formula (I)	0.025
Silica	20
Glycerol	5
Sorbitol	60
Sodium fluoride	0.221

Sodium saccharin	0.3
Water	7.954
Polyethylene glycol	3
Sodium dodecyl sulfate	2
Essence	1.5

Compound of formula (I) toothpaste formulation 8：

Components	**Content (mass percentage, %)**
Compound of formula (I)	0.3
Silica	20
Glycerol	5
Sorbitol	60
Sodium fluoride	0.221
Sodium saccharin	0.3
Water	7.679
Polyethylene glycol	3
Sodium dodecyl sulfate	2
Essence	1.5

Compound of formula (I) toothpaste formulation 9：

Components	**Content (mass percentage, %)**
Compound of formula (I)	0.5
Silica	20
Glycerol	5
Sorbitol	60
Sodium fluoride	0.221
Sodium saccharin	0.3
Water	7.479
Polyethylene glycol	3
Sodium dodecyl sulfate	2
Essence	1.5

Compound of formula (I) mouthwash formulation 1:

Components	**Content (mass percentage, %)**
Compound of formula (I)	0.0005 – 20
Water	70-94
other additives	proper amount

Compound of formula (I) mouthwash formulation 2:

Components	**Content (mass percentage, %)**
Compound of formula (I)	5
Water	80
Pluronics	3.00
other additives	proper amount

Compound of formula (I) mouthwash formulation 3:

Components	**Content (mass percentage, %)**
Compound of formula (I)	0.001
Water	94
Alcohol	5.00
other additives	proper amount

Compound of formula (I) mouthwash formulation 4:

Components	**Content (mass percentage, %)**
Compound of formula (I)	0.5
Water	90
Pluronics	3.00
Alcohol	3.00
other additives	proper amount

Compound of formula (I) mouthwash formulation 5:

Components	**Content (mass percentage, %)**
Compound of formula (I)	0.025
Water	85
Pluronics	5.00
Alcohol	3.00
other additives	proper amount

Compound of formula (I) mouthwash formulation 6:

Components	**Content (mass percentage, %)**
Compound of formula (I)	0.05
Water	91.7
Pluronics	3.00
Alcohol	5.00

Essence	0.25

Compound of formula (I) mouthwash formulation 7:

Components	**Content (mass percentage, %)**
Compound of formula (I)	0.0005
Water	94
Alcohol	5.00
other additives	proper amount

Compound of formula (I) mouthwash formulation 8:

Components	**Content (mass percentage, %)**
Compound of formula (I)	20
Water	70
Pluronics	3.00
Alcohol	3.00
other additives	proper amount

Compound of formula (I) paste formulation 1:

Components	**Content (mass percentage, %)**
Compound of formula (I)	10
Polyethylene glycol	90

Compound of formula (I) paste formulation 2:

Components	**Content (mass percentage, %)**
Compound of formula (I)	0.001
Polyethylene glycol	80
other additives	proper amount

Compound of formula (I) paste formulation 3:

Components	**Content (mass percentage, %)**
Compound of formula (I)	0.01
Polyethylene glycol	90
other additives	proper amount

Compound of formula (I) paste formulation 4:

Components	**Content (mass percentage, %)**
Compound of formula (I)	5

Polyethylene glycol	95

Compound of formula (I) paste formulation 5:

Components	**Content (mass percentage, %)**
Compound of formula (I)	0.025
Polyethylene glycol	99.975

Compound of formula (I) paste formulation 6:

Components	**Content (mass percentage, %)**
Compound of formula (I)	20
Polyethylene glycol	80

Compound of formula (I) paste formulation 7:

Components	**Content (mass percentage, %)**
Compound of formula (I)	0.0005
Polyethylene glycol	99
other additives	proper amount

[0046] Compound of formula (I) Tablets:

[0047] Tablets: active ingredient compound of formula (I) 10 mg, lactose 180 mg, starch 55 mg, magnesium stearate 5 mg.

[0048] Preparing method：Active ingredient, lactose and starch are mixed and wetted uniformly. The wetted mixture is subjected to sieve and dry, subjected to sieve again and added in magnesium stearate. The mixture is then compressed into tablets, weighing 250 mg each with a content of the active ingredient of 10 mg.

[0049] Compound of formula (I) nasal spray：

Compound of formula (I)	80 mg
sodium chloride	8 mg
EDTA	1 mg
Sodium phosphate buffer (pH6.5)	10 mg
Polyethoxy ether	10 mg
redistilled water	to 2ml

[0050] Preparing method: One ingredient at a time is added into proper volume of redistilled water under stirring until completely dissolved, then another ingredient is

added. After adding water to 2 ml，the solution is filtered on a sterile filter, filled into bottles and separated according to suitable dosage.

[0051] Compound of formula (I) dropping pills：

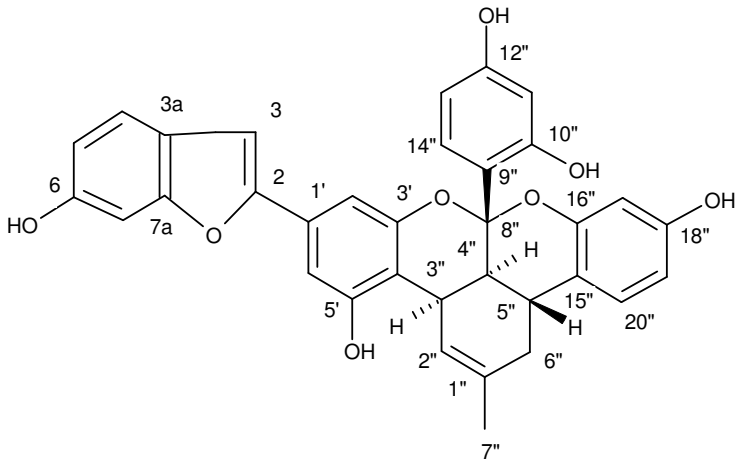
Compound of formula (I)	1g
polyethylene glycol 6000	9g

[0052] Preparing method: preparation of molten liquid of compound of formula (I) and polyethylene glycol 6000: Compound of formula (I) is weighed according to the prescribed amount above, to which a proper amount of dehydrated ethanol is added. After being dissolved by tepefaction, the resultant substances are added into prescribed amount of polyethylene glycol molten liquid (incubated in 60˚C water bath). The mixture is stirred to mix uniformly until ethanol is completely evaporated. The resultant is allowed to stay in 60˚C water bath to incubate for 30min, After bubbles are completely removed, the uniformly mixed molten liquid above in which bubbles are completely removed is transferred into a storing tank. Under a condition that the temperature is maintained at 80-85˚C, the molten liquid is dropped dropwise into a condensing liquid under the controlling the dropping speed. After the condensation being completed, the condensing liquid is decanted and the dropping pills are collected. Condensing liquid on the pills is trickled and removed with filter paper. Then, the pills are placed in a silica gel desiccator or dried naturally.

[0053] The above detailed description of the present invention sets forth a lot of specified details, the object thereof is to give clear and integrated explanation of the invention to facilitate the public to read and understand. However, what will be clear to one skilled in the art is that in some cases, the present invention may also be practiced without these specified details, or by making some non-essential modification or substitution to these specified details. These variations should be all considered to fall into the sprite and scope of the present invention. The scope of the invention should be determined by the plain text of the appended claims, rather than limited to the particular examples provided in the description.

CLAIMS:

1. A compound of formula (I):



(I).

2. The compound of claim 1, wherein the compound is extracted from Cortex Mori.

3. The compound of claim 1, wherein the purity of the compound is 50%-99.9%.

4. The compound of claim 1, wherein the purity of the compound is 75%-99.9%.

5. The compound of claim 1, wherein the purity of the compound is higher than 98%.

6. A method to prepare the compound of claim 1, comprising extracting a plant with an organic solvent and isolating the extract by using gel column chromatography.

7. The method of claim 6, wherein the plant is Cortex Mori.

8. A pharmaceutical composition for treating or preventing oral diseases, comprising an amount of the compound of claim 1 effective for treating or preventing oral diseases, and a pharmaceutically acceptable carrier.

9. A product for oral care, comprising an amount of the compound of claim 1 in an effective for oral care, and an oral care acceptable adjuvant.

10. The pharmaceutical composition for treating or preventing oral diseases or the product for oral care as claimed in claim 8 or 9, wherein the content of the

compound of claim 1 is 0.0005-99% (mass percentage).

11. The pharmaceutical composition for treating or preventing oral diseases or the product for oral care as claimed in claim 10, wherein the content of the compound of claim 1 is 0.001-10% (mass percentage).

12. The pharmaceutical composition for treating or preventing oral diseases or the product for oral care as claimed in claim 10, wherein the content of the compound of claim 1 is 0.025-5% (mass percentage).

13. The pharmaceutical composition for treating or preventing oral diseases or the product for oral care as claimed in claim 11, wherein the content of the compound as claimed in claim 1 is 0.05-0.5% (mass percentage).

14. The pharmaceutical composition for treating or preventing oral diseases or the product for oral care as claimed in claim 11, wherein the content of the compound as claimed in claim 1 is 0.5-90% (mass percentage).

15. Use of the compound as claimed in claim 1 in manufacturing medicaments for treating or preventing oral diseases.

16. Use of the compound as claimed in claim 1 in manufacturing oral care products.