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(54) HEPATOPROTECTIVE ACTIVITY OF 2 -P-HYDROXYBENZOYLMUSSAENOSIDIC ACID

HEPATOPROTEKTOR AKTIVITÄT VON 2'-P-HYDROXYBENZOYLMUSSAENOSIDSÄURE

ACTIVITE HEPATOPROTECTRICE DE L'ACIDE 2'-P-HYDROXYBENZOYLMUSSAENOSIDIQUE

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(73) Proprietor: **Council of Scientific and Industrial Research**
New Delhi 110 001 (IN)

(72) Inventors:
- **PRABHAKAR, Anil,**
  Regional Research Lab. Jammu
  180 001 Jammu (IN)
- **GUPTA, Bishan Datt,**
  Regional Research Lab. Jammu
  180 001 Jammu (IN)
- **SURI, Krishan Avtar,**
  Regional Research Lab. Jammu
  180 001 Jammu (IN)
- **SATTI, Naresh Kumar,**
  Regional Research Lab. Jammu
  180 001 Jammu (IN)
- **MALHOTRA, Swadesh,**
  Regional Research Lab. Jammu
  180 001 Jammu (IN)
- **GUPTA, Kuldip Kumar,**
  Regional Research Lab. Jammu
  180 001 Jammu (IN)
- **SHARMA, Vijay Kumar,**
  Regional Research Lab. Jammu
  180 001 Jammu (IN)
- **JOHRI, Rakesh Kamal,**
  Regional Research Lab. Jammu
  180 001 Jammu (IN)
- **JAGGI, Bupinder S.,**
  Regional Research Lab. Jammu
  180 001 Jammu (IN)
- **CHANDAN, Bal K.,**
  Regional Research Lab. Jammu
  180 001 Jammu (IN)
- **LAL, Shankar,**
  Regional Research Lab. Jammu
  180 001 Jammu (IN)
- **BEDI, Kasturi Lal,**
  Regional Research Lab. Jammu
  180 001 Jammu (IN)
- **SURI, Om Parkash,**
  Regional Research Lab. Jammu
  180 001 Jammu (IN)
- **QAZI, Gulam Nabi,**
  Regional Research Lab. Jammu
  180 001 Jammu (IN)

Printed by Jouve, 75001 PARIS (FR)

(Cont. next page)

(74) Representative: **Pizzoli, Pasquale Vincenzo et al**
Società Italiana Brevetti S.p.A
Via G. Carducci 8
20123 Milano (MI) (IT)

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- **SEHGAL C K; TANEJA S C; DHAR K L; ATAL C K : "2'-P HYDROXYBENZOYL MUSSAENOSIDIC-ACID: A NEW IRIDOID FROM VITEX-NEGUNDO" PHYTOCHEMISTRY., vol. 21, no. 2, 1982, pages 363-366, XP008020945 PERGAMON PRESS., GB ISSN: 0031-9422**

Description

Field of the invention

[0001] This invention relates to the hepatoprotective activity of an iridoid glycoside, 2'-p-hydroxybenzoylmussaenosidic acid (negundoside) of the formula 1 isolated from *Vitex negundo* by extracting the aerial parts/whole plant with polar solvents like methanol, ethanol, aqueous ethanol or water, after removing fatty non polar constituents by triturating the extracts solvents such as hexane, ethylene chloride, methylene chloride, chloroform or ethyl acetate to get a fraction from which negundoside is separated by column chromatograph.

Background Art

[0002] The hepatoprotective activity of negundoside has been confirmed by evaluation of its protective action against CCU and galactosamine induced liver damage models. Background and Prior art references *Vitex negundo* Linn (family: Verbenaceae) is widely used in the indigenous system of medicine in India. The leaves of the plant are constituents of several preparations used in Ayurvedic system of medicine. The roots and leaves of the plant are used as expectorant, febrifuge, vermifuge tonic and aromatic [Chopra, R N. Nayar, S. L. and Chopra I. C ; Glossary of Indian Medicinal Plants, CSIR, New Delhi, 1956, p. 256].

[0003] The plant is reported to have anti-inflammatory and antiarthritic properties. [Wealth of India: Raw Materials, CSIR, New Delhi, 1976, vol. X, p. 522]. A variety of constituents have been reported from this plant. From the leaves Ghosh and Krishna isolated glucononitol, p-hydroxybenzoic acid, 5-hydroxyisophthalic acid and 3,4-dihydroxybenzoic acid along with two glucosides and an amorphous alkaloid [Ghosh, T. P. and Krishna, S., Indian Chem. 1936,13, 634] In the essential oil of leaves a-pinene, camphene, citral and 3-caryophyllene have been reported [Masilungan, V. A., Philip. J. Sci, 1955,84, 275].

[0004] A large number of flavonoids viz., casticin, orientin, isoorientin, luteolin, luteolin-7-0-glucoside, corymbosin, gardenins A and B, 3-0-desmethylartemetin, 5-0-desmethylnobiletin,3\4\5,5\6J,8-heptamethoxyflavone,3\5-dihydroxy-4',7,8-trimethoxy flavanone and 3',5-dihydroxy-4',6,7-trimethoxyflavanone have been reported from this plant [Sirait, L.M., Rimpler, H. and Haensal, R., Experientia 1962,18, 72; Haensal, R. et al. Phytochemistry 1965, 4, 19; Banerji A. et al. Phytochemistry 1969,8, 511; Ferdous, A. J. et al. Bangladesh Acad.Sci. 1984,8, 23; Dayrit, F. M.. et al. Philip. J. Sci. 1987,116, 403; Banerji, J. et al. Indian J. Chem. 1988; 27B, 597; Achari, B. et al. Phytochemistry. 1984,23, 703]. Stem-bark afforded five new flavone glycosides along with luteolin and acerosin. The new flavone glycosides are 6p-glucopyranosyl -7-hydroxy-3',4',5',8-tetramethoxyflavone-5-O-α-L-rhamnopyranoside, 3', 7-dihydroxy-4',6, 8-trimethoxyflavone-5-O-(6"-O-acetyl-p-D-glucopyranoside),3,3',4',6,7-pentamethoxyflavone 5'-O-(4"-O-β-D-glucopyranosyl-cc-rhamnopyranoside, 4',5, 7-tri-hydroxyflavone-8-(2"-caffeoyl-a-glucopyranoside) and 3', 5, 5',7-tetrahydroxy-4-methoxyflavone -3'-O-(4"-O-α-D-galactopyranosyl) galactopyranoside [Rao, V.K.et al. Indian J. Pharm. 1977,39, 41; Subramamian, P.M. and Misra, G.S. Indian J. Chem. 1978, 16B, 615; Subramaniam, P.M. and Misra, G.S.J. Nat. Prod. 1979,42,540]. A diterpenoid, 5 β-hydro-8,11,13-abietatrien-6a-ol and three triterpenoids, 2cc, 3a-dihydroxyoleana-5 12-dien-28-oic acid, 2a, 3a-diacetoxyoleana-5, 12-dien-28-oic acid, 2,3 a-diacetoxy-18-hydroxyoleana-5,12-dien-28-oic acid have been isolated from the seeds. These compounds exhibited antiinflammatory activity [Chawla, A.S., Sharma, A.K., Handa, S.S. and Dhar, K.L. Indian J. Chem. 1991, 30B, 773 and J. Nat. Prod. 1992,55,163]. From the roots acetyloleanolic acid was isolated [Vishnol, S.P., Shoeb, A., Kapil, R.S. and Popli, S.P. Phytochemistry 1983,22, 597].

[0005] Five Iridoid glycosides have been reported from the leaves of V. *negundo.* These are aucubin, agnuside (Hansal et al. Phytochemistry 4, 1965, 9), negundoside, 6'-hydroxyhenzoylmussaenosidic acid (Sehgal et al. Phytochemistry, 21, 1982, 363) and nishindaside (Datta et al. Tetrahedron 39, 1983, 3067).

[0006] Liver disorders are still the major hazard both in urban and rural population. Despite scientific advances in our understandings in the management of liver disorders and the leads provided by traditional system of medicine, no specific treatment of liver ailments is available except chemically undefined a few herbal formulations [Subramoniam and Pushpangadan, Indian Journal of Pharmacology, 31, 166-175 (1999)]. During our search for hepatoprotective agents of plant origin, the aqueous alcoholic extract of V. *negundo* and a fraction isolated from it exhibited strong hepatoprotective and immunostimulating activities. A process has been developed for isolation of fraction possessing immuno-stimulating activity from the leaves of V. *negundo* for which a patent has been ganted to Regional Research Laboratory, Jammu [Sun, J.L. et al. *Indian Patent No.* 178388 dt. 19-03-97). Another patent application has been submitted by Regional Research Laboratory, Jammu for a process for isolation of a bioactive composition possessing hepatoprotective and immuno-stimulating activity (Application no. 116/DEL98 dt. 16.1.98). Iridoid *glycosides of Picrorhizu kurrou* exhibit strong hepatoprotective activity (Ansari, R.A. et al., Indian J. Med. Research 1988, 87, 401). V. *negundo* has also been found to contain a number of iridoid glycosides. An iridoid glycoside, 2'-p-hydroxybenzoylmussaenosidic acid (negundoside) was isolated and evaluated for its hepatoprotective activity along with the alcoholic extract of the plant. Both alcoholic extract (coded as 033) and negundoside (coded as 033 (2)) showed marked hepatoprotective activity in experimentally

induced hepatic damage with CCl_4 and galactosamine (GaIN) in rats. A comparison with the known hepatoprotective agent silymarin revealed that 033 and 033 (2) exhibited higher hepatoprotective potential in most of the parameters with respect to their effect on elevated levels of serum and liver homogenate parameters (Table 1 and 2). Thus the main objective of the present invention is to provide a bioactive molecule having hepatoprotective activity isolated from leaves of V. *negundo* viz., negundoside of formula 1.

Detailed description of the invention

[0007] The present invention provides a compound for use in treating and/or preventing hepatic disease conditions in a subject mammals including human beings, said compound comprising an effective dosage of composition comprising 2'-p-Hydroxy benzoyl mussaenosidic acid from plant *Vitex negundo* optionally as individual or in combination with one or more pharmaceutically additives wherein the said composition reduces the elevated levels of serum glutamin-pyruvic transaminase (GPT) about 70%.

[0008] Another embodiment of the present invention is that the said compound reduces the elevated levels of serum glutamin-oxalo acetic transaminase (GOT) about 60%.

[0009] In yet another embodiment of the present invention said compound reduces the elevated levels of serum alkaline phosphatase (ALP) about 60%.

[0010] In still another embodiment of the present invention said compound reduces the elevated levels of serum tryglycerides about 58%.

[0011] In yet another embodiment of the present invention said compound is against the elevated level of bilirubin up to about 66%.

[0012] In yet another embodiment of the present invention the compound 2'-p-Hydroxy benzoyl mussaenosidic acid is of concentration ranging between about 20 to 200 mg/kg-body weight.

[0013] In still another embodiment of the present invention the compound 2'-p-Hydroxy benzoyl mussaenosidic acid is of concentration of about 50 mg/kg-body weight.

[0014] In yet another embodiment of the present invention the compound is used in mammal preferably humans.

[0015] In still another embodiment of the present invention said compound is used singly or in combination with pharmaceutically acceptable carriers.

[0016] In yet another embodiment of the present invention said compound is administered to subject in combination with pharmaceutically acceptable additives, carriers, diluents, solvents, filters, lubricants, excipients, binder or stabilizers.

[0017] In still another embodiment of the present invention the desired dosage is administered for both preventive and curative properties.

[0018] In yet another embodiment of the present invention said compound is administered, orally or by any clinically/ medically accepted methods.

[0019] In still another embodiment of the present invention the preferred dosage for human beings is about 5 mg/Kg of body weight.

[0020] In yet another embodiment of the present invention the dosage is safe for consumption and free of any side effects.

[0021] In still another embodiment of the present invention state the various physical forms in which the composition is available, e. g. powder, tablet, capsule, syrup, granules, emulsion, aerosol or beads.

[0022] In yet another embodiment of the present invention the compound is used for Liver cirrhosis, Galactosemia, Hemoanigoma, Hemochromatosis, Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D. Hepatitis E, Hepatitis G, Alcholic Liver disease, Autoimmune hepatitis, Cancer of Liver, Biliary Atresia, Glycogen Storage Disease 1, Alpha-1-antitrypsin deficiency, Alagille syndrome, Byler Disease, Caroli disease, Fatty liver, Itching in Liver, Primar Biliary Cirrhosis, Sclerosing Cholangitis or Protoporphyria Erythroepatic.

[0023] A process is described for the isolation of the compound 2'-p-Hydroxy benzoyl mussaenosidic acid of formula 1, said compound being isolated from aerial part/whole body with a process comprising the steps of:

1. powdering the plant material by known methods
2. preparing the aqueous alcoholic extract by percolation
3. concentrating the alcoholic extract by conventional method
4. removing fatty non-polar constituents by triturating the extract with solvents such as ethylene chloride, methylene chloride, chloroform or ethyl acetate
5. adsorbing the residue extract over silica gel
6. isolating of 2'-p-Hydroxy benzoyl mussaenosidic acid from the adsorbed extract by column chromatography.

Characterisation of negundoside 1

[0024] 1 obtained as crystalline compound, mp 148-50°C M^+ : 496, UV-260 nm (MeOH) nm, (KBr) spectrum showed absorptions at 3400, 1700, 1640 and 1610 cm'1 'H NMR (200 MHz, CD_3OD) 5 5.48 (*J* 3, H-1) 7.09 (s, H-3) 25 (m-H-5) 2.19 (m, H-9) 1.25 (s, H-10) 6.80 (dd, 2, 7, H-3", H-5"), 7.83 (d, 2,7, H-2", 6") 4.99 (d,7, H-1') 4.69 (d, *J*, 7, H-2") ^{13}C NMR, 122.99 (C-1), 133.67, (C-2",6") 116.92 (C-3",5"), 164.11 (C-4") 168.08 (CO) (95.83 (C-1), 151.98 (C-3), 116.92 (C-4), 30.96 (C-5) 31.98 (C-6) 42.04 (C-7), 80.64 (C-8). 53.19 (C-9) 25.15 (C-10), 170.71 (C-11) 98.64 (C-1'), 76-85 (C-2') 75.70 (C-3'), 72.55 (C-4') 79.30 (C-5') 63.54 (C-6').

Brief description of the accompanying drawings

[0025]

Fig. 1 shows the negundoside; and
Fig. 2 shows the flow sheet for isolation of 2'-p-hydroxybenzoylmussaenosidic acid (negundoside).

[0026] The following examples are intended to demonstrate some of the preferred embodiments and in no way should be construed so as to limit the scope of the invention. Any person skilled in the art can design more formulations, which may be considered as part of the present invention.

Example 1

[0027] The shade dried and powdered leaves of V. *negundo* were extracted with 80% ethanol (4+x-3L) by percolation. The pooled extract was concentrated under reduced pressure at below to 1 litre of aqueous concentrate. The aqueous concentrate was washed with ethyl acetate (3 x 500 ml) and further concentrated to 400 ml. The syrupy residue was adsorbed over silica gel 400 g and allowed to dry at room temperature. The slurry was put on silica gel column and eluted with mixture of chloroform-methane (9:1), furnished 1 (1.5g) (coded as 033 (2)).

Example 2

[0028] The finely ground leaves (200 g) of *Vitex negundo* were extracted thrice with petroleum (60-80°) (1 litre for the first extraction and 600 ml each for two subsequent extractions) The drug was freed of solvent at room temperature. It was then extracted with ethanol (1 litre for the first extraction and then thrice with the same solvent 600 ml each time). Evaporation of ethanol in a rotary film evaporator yielded 30 g of extract (coded as 033).

Example 3

[0029] 033 and 033 (2) showed marked hepatoprotective activity in experimentally induced hepatic damage in rodents using CCU as hepatoxin. 033 and 033 (2) reduced the elevated levels of serum OPT, GOT, ALP, bilirubin, TG and liver homogenate lipid peroxidation and increased the GSH level. 033 and 033 (2) were almost as effective as silymarin, reducing the elevated level of GPT by 67.52 & 60.34%, GOT- 58.91 'ft 58.05%, ALP-58.26 & 53.95%, Bilirubin- 60.00 & 66.66%, TG- 46.47 & 44.19% and in liver homogenate LP- 55:71 & 45.85% and GSH- G1.42 & 45.56% respectively. The same with silymarin was : 58.44, 51:63, 52, 26,57.50,41.30,62.05 & 60.15% respectively. (Table-1).

Example 4

[0030] On treatment of experimental animals with galactosamine (GAIN) induced hepatic damage the hepatoprotective activity observed with 033 and 033 (2) was 59.58 & 50.75. 56.62 & 43.64, 54.28 & 50.11, 57.71 & 57.57, 57.89 & 44.76 percent in serum GPT, GOT, Bilirubin, ALP, and TG respectively and 67.51 & 38.65, 66-56 & 48.10 percent in liver homogenate lipid peroxidation (LP) and GSH respectively. The same with silymarin was 57.38, 55.40, 60.00. 53.54, 46-17, 69.59, 67.18 percent respectively (Table-2). Advantages of the present invention over currently used plant based hepatoprotectives:

1. Negundoside is more potent than the commercially available herbal hepatoprotective agent silymarin.
2. Silymarin is a mixture of three constituents whose relative proportion varies from batch to batch while negundoside is a pure compound.

Table 1: Hepatoprotective activity (in vivo) of 033, 033 (2) and Silymarin fed at 48h, 24h, 2h before and 6h after CCU (1 ml/kg, p.o.) induced hepatic injury in rats[a].

Treatment	Dose	Serum parameters					Hepatic parameters	
	Mg/kg p.o.	OPT (Units)	GOT (Units)	ALP[b]	Bilirubin (mg%)	Triglycerides (mg %)	Lipid peroxidation[c]	Glutathione[d]
033+ CCl_4	400	67.52	58.91	58.26	60.00	46.47	55.71	61.42
033(2)+CCl_4	50	60.34	58.05	53.95	66.66	44.19	45.85	45.56
Silymarin+CCU	50	58.44	51.63	52.26	57.50	41.30	62.05	60.15

a: Values represent the mean percent hepatoprotective activity of six animals in each group.
H: Hepatoprotective activity was calculated as {1- (T - V / C - V)} x 100 where "T" is mean value of drug and CCl_4, "C" is mean value of CCU alone and "V "is the mean value of vehicle treated animals.
Unit: each unit is μ mole pyruvate/min/L.
b: is n mole of *p*-nitrophenol formed/min/L,
c: is n moles MDA/g liver,
d: is m mole GSH/g liver.

Table 2: Hepatoprotective activity *(in vivo)* of 033,033 (2) and Silymarin fed at 48 h, 24h, 2h before and 6h after GalN (300 mg/kg, s.c.) induced hepatic injury in rats[a].

Treament	Dose	Serum parameters			Hepatic parameters			
	mg/kg, p.o	OPT (Units)	GOT (Units)	Dilirubin (mg%)	ALP[b]	Triglycerides (mg%)	Lipid peroxidation[c]	Glutathione[d]
033 + GalN	400	59.58	56.62	54.28	57.71	57.89	67.51	66.56
033 (2) + GalN	50	50.75	43.64	50.11	57.57	44.76	38.65	48.10
Silymarin + GalN	50	57.38	55.40	60.00	53.54	46.17	69.59	67.18

a: Values represent the mean percent hepatoprotective activity of six animals in each group.
H: Hepatoprotective activity was calculated as {1- (T - V / C - V)} x 100 where "T" is mean value of drug and GalN, 'C' is mean value of GalN alone and "V" is the mean value of vehicle treated animals.
Unit: each unit is nmole pyruvate/min/L.
b: is u, mole of p-nitrophenol formed/min/L,
c: is n moles MDA/g liver,
d: is n mole GSH/g liver.

Claims

1. A composition comprising 2'-p-Hydroxy benzoyl mussaenosidic acid obtained from plant *Vitex negundo* by a process comprising a step of isolation of 2'-p-Hydroxy benzoyl mussaenosidic acid, wherein said 2'-p-Hydroxy benzoyl mussaenosidic acid is comprised optionally as individual or in combination with one or more pharmaceutical additives, for use in the treatment and/or prevention of hepatic disease conditions in a subject mammals including human beings.

2. A composition for the use as claimed in claim 1, capable to reduce the elevated levels of serum glutamin-pyruvic transaminase (GPT) by about 70%.

3. A composition for the use as claimed in claim 1, capable to reduce the elevated levels of serum glutamin-oxalo acetic transaminase (GOT) by about 60%.

4. A composition for the use as claimed in claim 1, capable to reduce the elevated levels of serum alkaline phosphatase (ALP) to about 60%.

5. A composition for the use as claimed in claim 1, capable to reduce the elevated levels of serum tryglycerides by about 58%.

6. A composition for the use as claimed in claim 1, capable to reduce the elevated level of bilirubin up to about 66%.

7. A composition for the use as claimed in claim 1, wherein the concentration of 2'-p-Hydroxy benzoyl mussaenosidic acid is ranging between about 20 to 200 mg/kg-body weight.

8. A composition for the use as claimed in claim 7, wherein the concentration of 2'-p-Hydroxy benzoyl mussaenosidic is of about 50 mg/kg-body weight.

9. A composition for the use as claimed in claim 1, wherein the subject of the treatment is a mammal preferably humans.

10. A composition for the use as claimed in claim 1, wherein said composition is used singly or in combination with pharmaceutically acceptable carriers.

11. A composition for the use as claimed in claim 1 wherein said composition is to be administered to subject in combination with pharmaceutically acceptable additives, carriers, diluents, solvents, filters, lubricants, excipients, binder or stabilizers.

12. A composition for the use as claimed in claim 1, wherein the desired dosage is to be administered for both preventive and curative properties.

13. A composition for the use as claimed in claim 1, wherein said composition is to be administered, orally or by any clinically/medically accepted methods.

14. A composition for the use as claimed in claim 1, wherein the preferred dosage for human beings is about 5 mg/Kg of body weight.

15. A composition for the use as claimed in claim 1, wherein the dosage is safe for consumption and free of any side effects.

16. A composition for the use according to one or more of the preceding claims in the various physical forms in which the composition is available, e.g. powder, tablet, capsule, syrup, granules, emulsion, aerosoal, or beads.

17. A composition for the use according to claim 1, useful to be used against Liver cirrhosis, Galactosemia, Hemoangioma, Hemochromatosis, Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D, Hepatitis E. Hepatitis G, Alcholio Liver disease, Autoimmune hepatitis, Cancer of Liver, Biliary Atresia, Glycogen Storage Disease 1, Alpha-1-antitrypsin deficiency, Alagille syndrome, Byler Disease, Caroli disease, Fatty liver, Itching in Liver, Primer Biliary Cirrhosis, Sclerosing Cholangitis or Protoporphyria Erythroepatic.

Patentansprüche

1. Eine Verbindung, welche 2'-p-Hydroxy-Benzoyl-Mussaenosid-Säure enthält, und aus der Pflanze *Vitex negundo* mittels eines Prozesses erhalten wird, welcher einen Schritt zum Isolieren von 2'-p-Hydroxy-Benzoyl-Mussaenosid-Säure umfasst, wobei die genannte 2'-p-Hydroxy-Benzoyl-Mussaenosid-Säure optional einzeln oder in Kombination mit einem oder mehreren pharmazeutischen Additiven enthalten ist, zur Verwendung in der Behandlung und/oder Prävention von Leber-Krankheits-Zuständen eines Säugetier-Subjektes, einschließlich Menschen.

2. Eine Verbindung zur Verwendung gemäß Anspruch 1, welche dazu geeignet ist, die erhöhten Werte von Serum Glutamin-Pyruvat-Transaminase (GPT) um ungefähr 70% zu reduzieren.

3. Eine Verbindung zur Verwendung gemäß Anspruch 1, welche dazu geeignet ist, die erhöhten Serum-Werte von Glutamin-Oxalessigsäure-Transaminase (GOT) um ungefähr 60% zu reduzieren.

4. Eine Verbindung zur Verwendung gemäß Anspruch 1, welche dazu geeignet ist, die erhöhten Werte von Serum-Alkali-Phosphatase (ALP) auf ungefähr 60% zu reduzieren.

5. Eine Verbindung zur Verwendung gemäß Anspruch 1, welche dazu geeignet ist, die erhöhten Werte von Serum-Triglyceriden um 58% zu reduzieren.

6. Eine Verbindung zur Verwendung gemäß Anspruch 1, welche dazu geeignet ist, die erhöhten Werte von Bilirubin um bis zu ungefähr 66% zu reduzieren.

7. Eine Verbindung zur Verwendung gemäß Anspruch 1, wobei die Konzentration von 2'-p-Hydroxy-Benzoyl-Mussaenosid-Säure sich im Bereich von zwischen ungefähr 20 bis 200 mg/kg-Körpergewicht bewegt.

8. Eine Verbindung zur Verwendung gemäß Anspruch 7, wobei die Konzentration von 2'-p-Hydroxy-Benzoyl-Mussaenosid ungefähr 50 mg/ kg-Körpergewicht beträgt.

9. Eine Verbindung zur Verwendung gemäß Anspruch 1, wobei das behandelte Subjekt ein Säugetier, bevorzugt ein Mensch ist.

10. Eine Verbindung zur Verwendung gemäß Anspruch 1, wobei die genannte Verbindung einzeln oder in Kombination mit pharmazeutisch akzeptablen Trägern verwendet wird.

11. Eine Verbindung zur Verwendung gemäß Anspruch 1 wobei die genannte Verbindung zur Verabreichung an (das) Subjekt in Kombination mit pharmazeutisch akzeptablen Additiven, Trägern, Verdünnern, Lösungsmitteln, Filtern, Gleitmitteln, Arzneimittelträgern, Bindemitteln oder Stabilisatoren vorgesehen ist.

12. Eine Verbindung zur Verwendung gemäß Anspruch 1, wobei die gewünschte Dosierung sowohl für präventive wie kurative Eigenschaften zu verabreichen ist.

13. Eine Verbindung zur Verwendung gemäß Anspruch 1, wobei die genannte Verbindung oral oder mittels irgendwelcher klinisch/medizinisch akzeptierter Methoden zu verabreichen ist.

14. Eine Verbindung zur Verwendung gemäß Anspruch 1, wobei die bevorzugte Dosierung für Menschen ungefähr 5 mg/kg-Körpergewicht beträgt.

15. Eine Verbindung zur Verwendung gemäß Anspruch 1, wobei die Dosierung sicher in der Aufnahme und frei von irgendwelchen Nebenwirkungen ist.

16. Eine Verbindung zur Verwendung gemäß einem oder mehreren vorhergehenden Ansprüchen in den verschiedenen physischen Formen, in welchen die Verbindung verfügbar ist, beispielsweise als Pulver, Tablette, Kapsel, Sirup, Granulat, Emulsion, Aerosoal oder Kügelchen.

17. Eine Verbindung zur Verwendung gemäß Anspruch 1, welche zur Verwendung gegen Leberzirrhose, Galactosämie, Hämoanigomie, Hämochromatose, Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D, Hepatitis E, Hepatitis G, Alkoholische Lebererkrankung, Autoimmun-Hepatitis, Leberkrebs, Biliär-Atresie, Glykogen-Speicher-Krankheit 1, Alpha-1-Antitrypsin-Störung, Alagille-Syndrom, Byler-Krankheit, Caroli-Krankheit, Fettleber, Leber-Reizung, Primär-Biliär-Zirrhose, Sklerosierende Cholangitis oder Erythroepatische Protoporphyrie verwendbar ist.

Revendications

1. Composition comprenant de l'acide 2'-p-hydroxy-benzoylmussaenosidique obtenu à partir de la plante *Vitex negundo* par un procédé comprenant une étape d'isolation de l'acide 2'-p-hydroxy-benzoylmussaenosidique, dans laquelle ledit acide 2'-p-hydroxy-benzoylmussaenosidique est compris éventuellement seul ou en combinaison avec un ou plusieurs additifs pharmaceutiques, destinée à être utilisée pour traiter et/ou prévenir les pathologies hépatiques chez un sujet mammifère comprenant l'homme.

2. Composition destinée à être utilisée selon la revendication 1, capable de réduire les taux élevés de transaminase glutamique-pyruvique (TGP) sérique d'environ 70 %.

3. Composition destinée à être utilisée selon la revendication 1, capable de réduire les taux élevés de transaminase glutamique-oxaloacétique (TGO) sérique d'environ 60 %.

4. Composition destinée à être utilisée selon la revendication 1, capable de réduire les taux élevés de phosphatase alcaline (PAL) sérique jusqu'à environ 60 %.

5. Composition destinée à être utilisée selon la revendication 1, capable de réduire les taux élevés de triglycérides sériques d'environ 58 %.

6. Composition destinée à être utilisée selon la revendication 1, capable de réduire les taux élevés de bilirubine jusqu'à environ 66 %.

7. Composition destinée à être utilisée selon la revendication 1, dans laquelle la concentration d'acide 2'-p-hydroxybenzoylmussaenosidique varie entre environ 20 et 200 mg/kg de poids corporel.

8. Composition destinée à être utilisée selon la revendication 7, dans laquelle la concentration d'acide 2'-p-hydroxybenzoylmussaenosidique est d'environ 50 mg/kg de poids corporel.

9. Composition destinée à être utilisée selon la revendication 1, dans laquelle le sujet du traitement est un mammifère, de préférence, l'homme.

10. Composition destinée à être utilisée selon la revendication 1, dans laquelle ladite composition est utilisée seule ou en combinaison avec des véhicules pharmaceutiquement acceptables.

11. Composition destinée à être utilisée selon la revendication 1, dans laquelle ladite composition doit être administrée au sujet en combinaison avec des additifs, des véhicules, des diluants, des solvants, des filtres, des lubrifiants, des excipients, un liant ou des stabilisants pharmaceutiquement acceptables.

12. Composition destinée à être utilisée selon la revendication 1, dans laquelle la dose souhaitée doit être administrée à la fois pour ses propriétés préventives et curatives.

13. Composition destinée à être utilisée selon la revendication 1, dans laquelle ladite composition doit être administrée par voie orale ou par tout procédé cliniquement/médicalement admis.

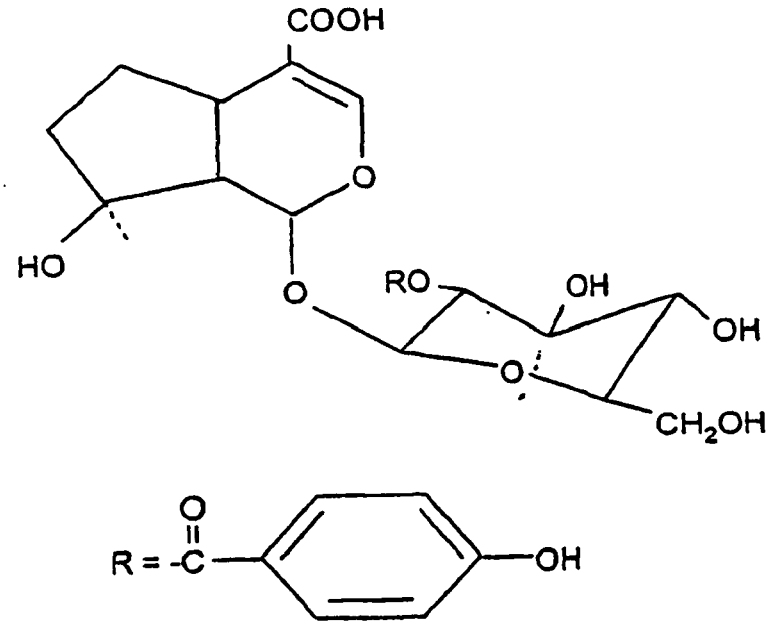
14. Composition destinée à être utilisée selon la revendication 1, dans laquelle la dose préférée pour l'homme est d'environ 5 mg/kg de poids corporel.

15. Composition destinée à être utilisée selon la revendication 1, dans laquelle la dose est apte à la consommation et dépourvue de tout effet secondaire.

16. Composition destinée à être utilisée selon une ou plusieurs des revendications précédentes sous les diverses formes physiques sous lesquelles la composition est disponible, par exemple, poudre, comprimé, capsule, sirop, granules, émulsion, aérosol ou billes.

17. Composition destinée à être utilisée selon la revendication 1, utile pour lutter contre la cirrhose du foie, la galactosémie, l'hémoangiome, l'hémochromatose, l'hépatite A, l'hépatite B, l'hépatite C, l'hépatite D, l'hépatite E, l'hépatite G, les maladies alcooliques du foie, l'hépatite autoimmune, le cancer du foie, l'atrésie des voies biliaires, la glycogénose 1, le déficit en alpha-1-antitrypsine, le syndrome d'Alagille, la maladie de Byler, la maladie de Caroli, la stéatose du foie, le prurit, la cirrhose biliaire primitive, la cholangite sclérosante ou la protoporphyrie érythropoïétique.

Figure 1

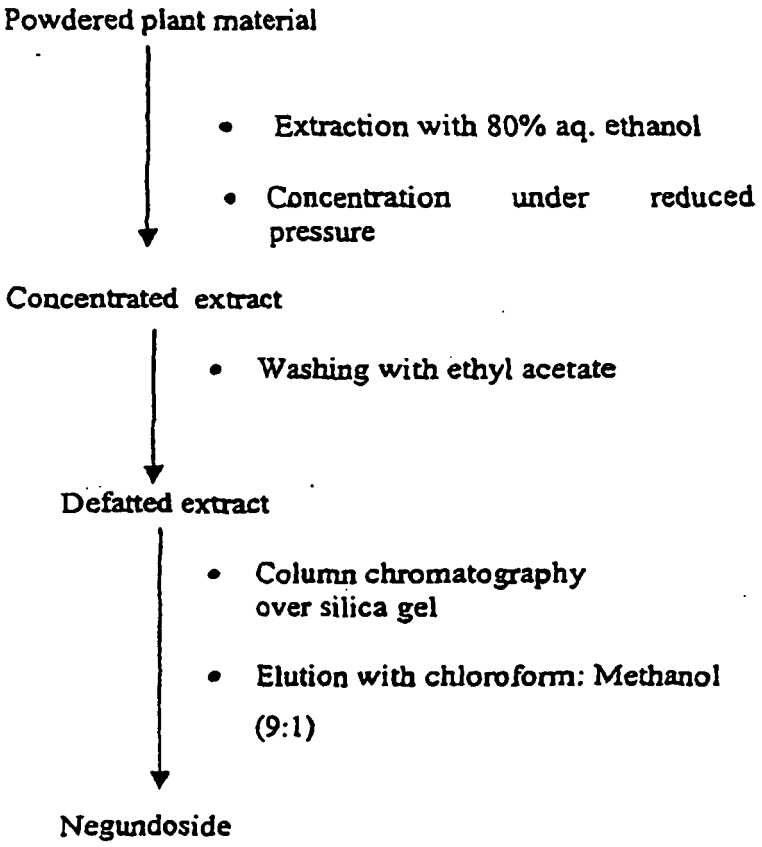


1

Negundoside

Figure 2

Flowsheet for isolation of 2'-p-hydroxybenzoylmussaenosidic (negundoside)



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