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Drymaria cordata (Linn.) Willd (Caryophyllaceae): Ethnobotany, Pharmacology and Phytochemistry

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Abstract

In the present paper the isolation and characterization of seven major glycolipid classes (stigmasterol, acylated stigmasteryl glucoside, stigmasteryl glucoside, monogalactosyldiacylglycerol, digalactosyldiacylglycerol, cerebroside and glucocerebroside) from *Drymaria cordata* (Linn.) Willd (Caryophyllaceae Family) are reported after an attempt has been made to congregate the traditional and pharmacological studies done on this important medicinal plant. *Drymaria cordata* is a weak spreading herb found widely dispersed in damp places all over the tropics of Africa, Asia and the Americas. There are many reports on its folk and traditional uses that include snake bite, skin diseases, peptic ulcer, headaches or nephritis, female infertility, sleeping disorders, convulsions, and febrile conditions in children. The plant has been examined on the basis of scientific *in vitro* and *in vivo* evaluations possessing the major pharmacological activities that include analgesic activity, antitussive activity, anxiolytic activity, antipyretic activity, antinociceptive activity, anti-inflammatory and antibacterial activities. The information summarized here is intended to serve as a reference tool for practitioners in the fields of ethnopharmacology, natural product chemistry and drug discovery related research.

Keywords

***Drymaria cordata*; Caryophyllaceae; Stigmasteryl Glucoside; Glyceroglycolipid; Sphingoglycolipid**

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1. Introduction

Drymaria cordata (Linn.) Willd. (Caryophyllaceae) is a creeping herb growing in dense patches in moist shady places and also in dry sun-exposed areas. Stems are green and slender, leaves are opposite, cordate, with short petiole and the flowers are small and green. It has been noticed that the size of the plant as well as the leaf varies in different habitats. Leaves of the plants growing in moist and shady places are large up to 2 cm and succulent, while those growing on exposed rocks and sunny places have thin and smaller leaves up to 5 - 7 mm [1]. The plant is found widely dispersed in damp places all over the tropics of Africa, Asia and the Americas where its various uses for agriculture and traditional medicine have been reported [2]-[8]. It appears to be a good soil binder [1]. The anti-inflammatory [9] [7] [10], antitussive [11], antibacterial [12], cytotoxic [13], anxiolytic [14] activity, analgesic, anti-nociceptive and antipyretic properties [15]-[17] of *Drymaria cordata* extract have been reported. Although several secondary metabolites have been reported from a closely related species, namely *Drymaria diandra* [18] [19] and in spite of the different folks and traditional uses of *D. cordata* coupled to its broad range of pharmacological activities, only preliminary phytochemical screenings indicating the presence of some chemical classes of compounds in this plant have been reported [4] [7] [20], and very few is known concerning its real chemical constituents. The present research work is aimed to summarize the ethnobotanical and pharmacological aspects of *D. cordata*, and further to proceed on the isolation and chemical characterization of the phytoconstituents of this plant growing in the western highlands of Cameroon.

2. Ethnobotanical and Traditional Uses of *Drymaria cordata*

Drymaria cordata has been traditionally used in various parts of the world like Africa, and Asia as folk medicine. In tropical Africa, its preparations are used for the treatment of diverse ailments including cold, headache, coryza, bronchitis, as poultice on sore (to treat aching, inflamed or painful parts), leprosy, tumors, as fumigant for eye troubles, as cerebral stimulant and antifebrile agent [2]. In west Cameroon, the plant is called “Ton tchikou or Ndougo” (Bangangté) and “Mtokia” (Baham) where it is respectively used to cure peptic ulcer, headaches or nephritis [5] and female infertility [6]. *D. cordata* is used in Nigerian folk medicine to treat sleeping disorders, convulsions, and febrile conditions in children [7]. It has been found that the local tribes from Garohills and Khasia of Meghalaya, India, use this herb as an antitussive. The herb is kept on some big leaves, folded, tied and put over fire and the inside material is heated, the vapour is then inhaled for the relief of cough and sinusitis or in acute cold attack.This herb is also used for snake bite, and is applied topically for burns and skin diseases [3] [4]. In North East India, the plant has been traditionally used as an antidote, appetizer, depurative, emollient, febrifuge, laxative and stimulant in both human and animals [8].

3. Pharmacological Properties of *Drymaria cordata*

3.1. Anti-Inflammatory Activity

Carrageenan induced paw oedema model in rats and mice, formalin-induced paw licking in mice were used to evaluate the anti-inflammatory effects of *Drymaria cordata* methanolic extract (DCME) at the doses 300 to 900 mg/kg body wt. *p.o.* in comparison with control and standard drug indomethacin (10 mg/kg body wt. *p.o.*). The effect was dose dependent and comparable with the standard drug indomethacin in carrageenan induced paw oedema in rat and mice. In formalin-induced paw licking model, there was significant reduction in duration of paw licking in early and late phase as well, thus indicating the anti-inflammatory property of DCME [10]. Furthermore the anti-inflammatory activity of the aqueous extract of *Drymaria cordata* (100 - 800 mg/kg) was also evaluated using the carrageenan, egg albumin, xylene induced oedema models and pleurisy test with indomethacin (10 mg/kg; *p.o.*) as standard drug. The results obtained in this study suggest that the aqueous extract of *Drymaria cordata* possesses anti-inflammatory activity mediated possibly by the inhibition of one or a combination of mediators like histamine, serotonin, kinins and prostaglandins [7].

3.2. Analgesic and Anti-Nociceptive Activities

The acetic acid-induced writhing, formalin, and tail clip tests were used to evaluate analgesic activity while the 2,4-dinitrophenol (DNP)-, *d*-amphetamine-, and yeast-induced hyperthermia tests were used to investigate antipyretic activity in rodents. The aqueous whole plant extract of *Drymaria cordata* (100, 200, and 400 mg/kg;

p.o.) produced significant ($p < 0.05$) analgesic activity in the mouse writhing, formalin (second phase), and tail clip tests and the effects were generally comparable to those of acetylsalicylic acid (ASA, 100 mg/kg; *p.o.*) and morphine (2 mg/kg; *s.c*) [15]. The effect of *Drymaria cordata* hydroethanolic extract (DCHE) in acetic acid induced writhing model was better than the standard drug indomethacin (10 mg/kg; *p.o.*). In the hot plate model, the maximum effect was observed at 60 min at a dose of 200 mg/kg; *p.o.*, which was higher than the standard drug morphine sulfate (1.5 mg/kg; *i.p.*), whereas in the tail flick model, effect was comparable with morphine sulfate. In formalin-induced paw licking model, administration of DCHE completely abolished the early phase at 100 and 200 mg/kg; *p.o.* and in the late phase, the effect of DCHE (200 mg/kg; *p.o.*) was higher than indomethacin (10 mg/kg; *p.o.*) [16].

3.3. Antipyretic Activity

The aqueous whole plant extract of *Drymaria cordata* (100, 200, and 400 mg/kg; *p.o.*) produced significant ($p < 0.05$) dose-dependent inhibition of temperature elevation in the 2,4-DNP and yeast-induced hyperthermia models with peak effects produced at the dose of 400 mg/kg. The effect at this dose was comparable to that of acetylsalicylic acid (ASA) in the two models. In the *d*-amphetamine method, this extract produced significant ($p < 0.05$) dose- and time-dependent reduction of temperature elevation with peak effect produced at the dose of 200 mg/kg. The effect of the extract at this dose was greater than that of ASA. The results obtained in this study demonstrate that the aqueous whole plant extract of *Drymaria cordata* possesses analgesic and antipyretic properties mediated through peripheral and central mechanisms [15].

3.4. Anti-Bacterial Activity

The aerial parts of different extracts of *Drymaria cordata* Willd were tested for antibacterial efficacy against *Staphylococcus aureus* ATCC 29737, *Escherichia coli* ATCC 10536, *Bacillus subtilis* ATCC 6633, *Bacillus pumilis* ATCC 14884 and *Pseudomonas aeruginosa* ATCC 25619. The methanol extract was found to be the most effective one and the effects produced by all the extracts were found to have significant activities against all the tested organisms and the effects so produced were compared with those of chloramphenicol [12].

3.5. Antitussive Activity

The antitussive effect of the methanol extract of *D. cordata* was investigated on a cough model induced by sulfur dioxide gas in mice. The activity of the extract was dose-dependent and comparable to that of codeine phosphate, a prototype antitussive agent. The *D. cordata* extract (100, 200, 400 mg/kg) showed 11.6%, 31.6% and 51.5% inhibition of cough with respect to the control group [11].

3.6. Anxiolytic Activity

Different models for anxiolytic activity like Hole board, Open field, Elevated plus maze, Light/dark exploration model were used to evaluate the effect of *Drymaria cordata* hydroethanolic extract (DCHE) administered at 25, 50, and 100 mg/kg (*p.o.*). In the hole board model, there was dose-dependent and significant increase in the numbers of head pokes and the time of head dipping in the treated groups in comparison to the vehicle. In open field test, the number of rearing assisted rearing and numbers of squares traversed increased significantly. Similarly, in elevated plus maze test, there was significant increase in the time spent and number of entries in open arm as compared to the time spent and number of entries in closed arm in dose dependent manner. In light/dark exploration test, another model for anxiolytic activity, the time spent in lit box, number of crossing and the latency period increased significantly with reduction in time spent in dark box after treatment with DCHE. It could therefore be concluded that the DCHE might affect certain mediators to reduce anxiety [14].

3.7. Cytotoxic Activity

The cytotoxic effect of *Drymaria cordata* hydroethanolic extract on HeLa (cervix adenocarcinoma) cell line was determined using a modification [21] of the MTT assay [22]. It was potentially cytotoxic showing over 50% activity at 500 µg/ml [13]. Moreover one anti leukemic compound ($C_{17}H_{22}O_2$) which is effective as inhibitory to primary cultures of human encomia cells has been isolated from this plant [4].

4. Phytochemical Study

4.1. Experimental

4.1.1. Plant Materials

The fresh aerial parts of *D. cordata* were collected in Bangoua village, near Bangangté (West Cameroon) in November 2010 and identified by Mr Victor Nana at the National Herbarium of Cameroon; Yaoundé, Cameroon by comparison to an existing voucher specimen (N˚ 20550/SRF/CAM).

4.1.2. Extraction and Isolation

The dried and pulverized plant material (3 kg) was extracted at room temperature three times (each for 24 h) with MeOH (95%). The filtrate obtained was concentrated under reduced pressure to yield a dark residual solution (372 g). This solution was constituted by two main phases, an oily upper phase (18 g) and a brown residue (350 g) and these two phases were separated by decantation. Part of the brown residue (120 g) was suspended in water (250 ml) and successively extracted with EtOAc and n-BuOH, yielding 63.4 and 11 g of extracts after evaporation to dryness, respectively. One part of the EtOAc extract (53 g) and the n-BuOH extract were subjected to silica gel column chromatography using the mixture Hex-EtOAc in increase polarity for the EtOAc extract, and EtOAc-MeOH in increase polarity for the n-BuOH extract to yield compound **1** (7 mg), **2** (14 mg), **3** (10 mg), **4** (50 mg), **5** (180 mg), **6** (6 mg) and **7** (8 mg). The oily upper phase was mainly constituted of phenolics as revealed from visualization of TLC on UV lamps (254 and 365 nm) follow by spraying with 50% H_2SO_4, and their purification has been unsuccessful.

5. General Experimental Procedure

ESI mass spectra were carried out on an Agilent Technologies LC/MSD Trap SL (G2445D SL). ^{1}H NMR, ^{13}C NMR, COSY, HSQC and HMBC spectra were performed in deuterated MeOH, $CHCl_3$, Acetone, on a varian Mercury plus Spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C). Column chromatography was performed on silica gel (60 merck) and sephadex gel (LH-20). Fractions were monitored by TLC using Merck pre-coated silica gel sheets (60 F254), and spots were visualized under UV lamps (254 and 365 nm) and by spraying with 50% H_2SO_4 and heating at 110˚C.

Methanolysis of Compound 5

Compound **5** (20 mg) was refluxed with 0.9 N HCl in 82% aqueous MeOH (10 mL) for 18 h [23]. The resulting solution was extracted with n-hexane. The n-hexane layer was dried with Nitrogen to give the fatty acid methyl ester (**5'**) which was analyzed by GC.

6. Results

Identification of Purified Compounds

The identification of compounds **1**-**7** was proposed from their spectral data mainly 1D and 2D NMR techniques (^{1}H, ^{13}C, DEPT, COSY, HMBC, HMQC and NOESY) and by comparison with literature data as: 24-ethyl-cholesta-5,22*E*-diene (Stigmasterol) (**1**) [23], [(2*S*,3*S*,4*R*,8*E*)-2N-[(2')-2'-hydroxylpentaeicosanoyl]-8(*E*)-tetraeicosanoyl-1,3,4-triol] (**2**) [24], 24-ethyl-cholesta-5,22*E*-dien-3*β*-*O*-*β*-D-pyranoglucosyl-6'-*O*-palmitate (**3**) [23], 24-ethyl-cholesta-5,22*E*-dien-3*β*-*O*-*β*-D-pyranoglucosyle (**4**) [23], (2*S*,3*R*,4*E*,8*E*,2'*R*)-1-*O*-*β*-*D*-glucopyranosyl-2-(2-hydroxypalmitoyl)-amino-4,8-octadecadien-1,3-diol (**5**) [24], monogalactopyranosyldiacylglycerol (**6**) and digalactopyranosyldiacyglycerol (**7**) [25] [26] (**Figure 1**).

7. Discussion

In all, seven secondary metabolites mainly belonging to glycolipid chemical group and including one ceramide, one cerebroside, tree stigmasterol derivatives and two galactosyl-di-acyl-glyceride derivatives have isolated and characterized from this plant. This chemical composition is quite close to that of the red Bell Pepper (*Capsicum annuum*) [26]. Edible plant glycolipids are believed to play a role in human diet as nutrients. The average daily intake of glycolipids in humans has been reported to be 140 mg of acylated steryl glucoside, 65 mg of steryl

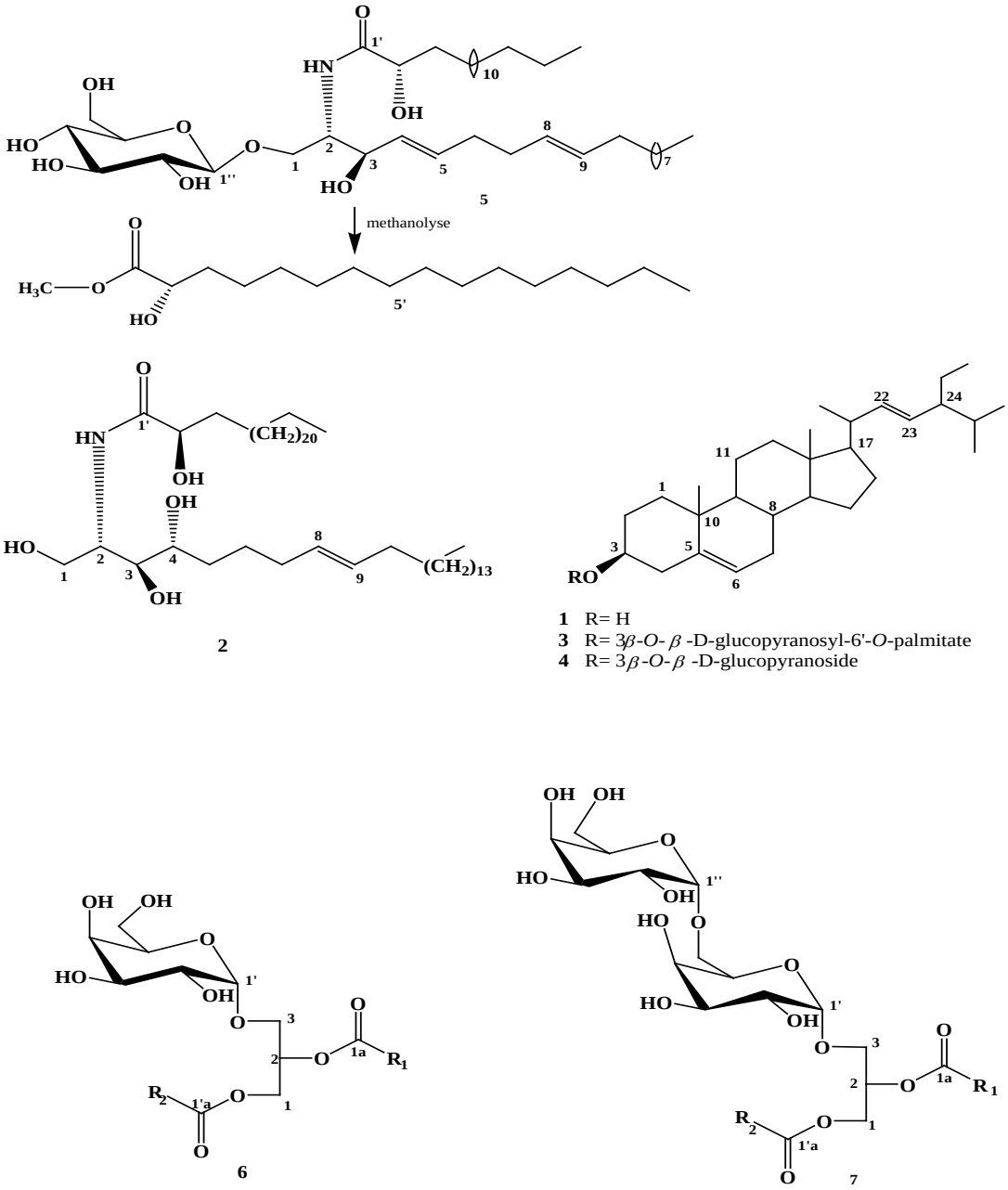

Figure 1. Structures of Stigmasterol (**1**), cerebroside (**2**), acylated stigmasteryl glucoside (**3**), stigmasteryl glucoside (**4**), glucocerebroside (**5**), monogalactosyldiacylglycerol (**6**) and digalactosyldiacylglycerol (**7**) isolated from the aerial parts of *Drymaria cordata.*

glucoside, 50 mg of cerebroside, 90 mg of monogalactosyldiacylglycerol, and 220 mg of digalactosyldiacylglycerol [27]. Aerial parts of *D. cordata* appear to be a rich source of such glycolipids.

Moreover literature survey shows that Glycolipids have been implicated in cell development, differentiation, and carcinogenic transformation [28]. Ceramide plays the role of a lipid second messenger in cell signaling transductions [29]-[31] such as cell growth, differentiation [32], proliferation [33], senescence [34] and necrosis [35]. In recent years several different types of biological activities have been found for these compounds, including antifungal, antitumor, antiviral, cytotoxicity and immunomodulatory properties, anti-inflammatory and anti-microbial activities [36] [37]. Stigmasterol possesses analgesic and anti-inflammatory activities [38]. One or a combination of the phytoconstituents of *D. cordata* may be responsible for its different activities observedin

this study, especially as synergy is an important concept in the pharmacology of phytochemicals of botanical medicines [39]. Furthermore Previous study reported the safety of oral administration of the aqueous extract of *D. cordata* based on the fact that no mortality and visible signs of toxicity were recorded on rats given up to 2 g/kg. The LD_{50} administered intraperitoneally was estimated to be 133.35 mg/kg [7].

Knowing that plant species such as *Ginkgo biloba*, *Salvia officinalis* and *Melissa officinalis* which have currently being used for the management of Alzheimer's disease and other cognitive disorders usually cumulate plethora of relevant bioactivities [40] [41], *D. cordata* extracts could be good candidates against such diseases.

8. Spectroscopic Data of Isolated Compounds

24-ethyl-cholesta-5,22*E*-diene (Stigmasterol) (1): White powder; ^{13}C (Acetone-d_6) δ 30.7 (C_2); 71.2 (C_3); 140.6 (C_5); 118.7 (C_6); 35.4 (C_7); 31.6 (C_8); 51.2 (C_9); 21.4 (C_{11}); 39.4 (C_{12}); 42.0 (C_{14}); 56.1 (C_{17}); 139.5 (C_{22}); 130.7 (C_{23}); 50.9 (C_{24}).

[(2*S*,3*S*,4*R*,8*E*)-2N-[(2')-2'-hydroxylpentaeicosanoyl]-8(*E*)-tetraeicosanoyl-1, 3, 4-triol] (2): White crystal; ESI-MS (positive mode): *m/z* 682 $[M + H]^+$, 399 $[C_{24}H_{48}NO_3 + H]^+$ in negative-ion mode, we observed a peak ion mass *m/z* 680 $[M-H]^-$, *m/z* 716 $[M + Cl]^-$. ^{13}C (MeOH-d_4) δ 60.7 (C_1); 51.7 (C_2); 74.5 (C_3); 72.0 (C_4); 31.4 (C_5); 29.2 (C_6); 32.2 (C_7); 130.0 (C_8); 130.0 (C_9); 32.2 (C_{10}); 28.8 - 31.5 ($C_{11\text{-}23}$); 12.5 (C_{24}); 188.6 ($C_{1'}$); 71.6 ($C_{2'}$); 31.7 ($C_{3'}$); 34.3 - 28 ($C_{4'\text{-}24'}$); 12.5 ($C_{25'}$).

24-ethyl-cholesta-5,22*E*-dien-3*β*-*O*-*β*-D-pyranoglucosyl-6'-*O*-palmitate (3): ESIMS (negative-ion mode) *m/z* 847 $[M + Cl]^-$, ^{13}C (MeOH-d_4) δ 37.1 (C_1); 31.4 (C_2); 78.2 (C_3); 42.3 (C_4); 139.0 (C_5); 117.0 (C_6); 31.4 (C_7); 31 (C_8); 49.2 (C_9); 36.0 (C_{10}); 21.0 (C_{11}); 39.7 (C_{12}); 43.8 (C_{13}); 56.0 (C_{14}); 24.8 (C_{15}); 28.4 (C_{16}); 56.0 (C_{17}); 11.1 (C_{18}); 21.2 (C_{19}); 40.5 (C_{20}); 21.4 (C_{21}); 138.4 (C_{22}); 129.6 (C_{23}); 49.1 (C_{24}); 31.4 (C_{25}); 21.2 (C_{26}); 20.0 (C_{27}); 25.0 (C_{28}); 12.0 (C_{29}); 101.2 ($C_{1'}$); 73.6 ($C_{2'}$); 76.7 ($C_{3'}$); 70.7 ($C_{4'}$); 73.6 ($C_{5'}$); 63.4 ($C_{6'}$).

24-ethyl-cholesta-5,22*E*-dien-3*β*-*O*-*β*-D-glucopyranosyle (4): identified by co-TLC comparison with an authentic sample available in the laboratory.

(2*S*,3*R*,4*E*,8*E*,2'*R*)-1-*O*-*β*-*D*-glucopyranosyl-2-(2-hydroxypalmitoyl)-amino-4,8-octadecadien-1,3-diol (5): White amorphous powder. ESIMS (negative-ion mode) *m/z* 712.7 $[M-H]^-$, *m/z* 550 $[M-162]^-$, *m/z* 463 $[M-162-18-70]^-$, ^{13}C (MeOH-d_4) δ 68.3 (C_1); 53.1 (C_2); 71.37 (C_3); 133.0 (C_4); 133.0 (C_5); 32.0 (C_6); 32.4 (C_7); 133.5 (C_8); 129.4 (C_9); 32.7 (C_{10}); 30.32 - 30.86 ($C_{11\text{-}17}$); 14.4 (C_{18}); 177.3 ($C_{1'}$); 71.6 ($C_{2'}$); 23.7-33.3 ($C_{3'\text{-}15'}$); 14.4 ($C_{16'}$); Sugar moiety: δ 103.8 (C_1); 73.6 (C_2); 76.0 (C_3); 70.0 (C_4); 76.0 (C_5); 61.2 (C_6).

Compound 5': White amorphous powder: GC, the retention time (t_R) of the peak was 15.202 min for fatty acid methyl ester, thus it was then identified as 2-hydroxy hexadecanoic acid methyl ester (**5'**).

monogalactosyldiacylglycerol (6): ESIMS (negative ion mode) *m/z* 793 $[M-H]^-$. ^{13}C (MeOH-d_4) Glycerol: 62.6 (C_1); 69.4 (C_2); 63.2 (C_3). Galactosyl moiety: 98.4 ($C_{1'}$); 73.6 ($C_{2'}$); 72.0 ($C_{3'}$); 73.6 ($C_{4'}$); 68.8 ($C_{5'}$); 52.8 ($C_{6'}$). Acid moiety: 173.6 ($C_{1a\text{-}1'a}$).

digalactosyldiacylglycerol (7): ESIMS (negative ion mode) *m/z* 823 $[M-H]^-$, 210.9 $[C_{14}H_{27}O]^-$, 636 $[C_{21}H_{75}O_{14}]^-$, and in positive ion mode *m/z* 847 $[M+Na]^+$, 499 $[CH_2(OCOR_1)CH(COCOR_2)CH_2OH]^+$ diacylglycerol, 303 $[CH_2(OH)CH(OCOR^1)CH_2O]^+$ monoacylglycerol. ^{13}C (MeOH-d_4) Glycerol: 63.9 (C_1); 71.5 (C_2); 68.7 (C_3). Acid moiety: 174.7 and 175.0 ($C_{1a\ or\ 1'a}$). Galactosyl moiety: 105.1 ($C_{1'}$); 72.2 ($C_{2'}$); 74.7 ($C_{3'}$); 71.1 ($C_{4'}$); 74.7 ($C_{5'}$); 67.7 ($C_{6'}$); 100.4 ($C_{1''}$); 70.2 ($C_{2''}$); 74.7 ($C_{3''}$); 70.0 ($C_{4''}$); 74.7 ($_{5''}$); 62.6 ($C_{6''}$).

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