Original Article

Cytotoxic Sulfoquinovosyl Glycerols from the Seaweed *Sargassum Angustifolium* from Persian Gulf

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Abstract

Backgrounds: Seaweeds are an important source of marine organisms that produce a lot of bioactive compounds.

Materials and Methods: In this research, the seaweed *Sargassum angustifolium* was collected from Bushehr province of Persian Gulf of Iran. The seaweed was extracted by methanol:ethyl acetate (1:1) using maceration method. The compounds were isolated with different column chromatography and HPLC(High Performance Liquid Chromatography) by silica gel and hexane:ethyl acetate as mobile phase.

Results: The isolated compounds were elucidated structurally by various 1 and 2 D-NMR and MS spectra. Besides the cytotoxicity test was done against HeLa using standard MTT assay and normal cells.

Conclusion: It afforded four known sulfoquinovosyl diacylglycerides and fucosterol. Compounds 1-5 showed cytotoxic effects against HeLa and HUVEC cell lines, with IC50 values of 12.2 ± 2.3, 25.8 ± 3.7, 14.9 ± 2.6, 9.8 ± 1.2 μM, and 5.6 ± 1.2, respectively.

Keywords: Cytotoxicity test, monogalactosyldiacylglycerol, Persian gulf, seaweed, sulfoquinovosyl diglyceride

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Introduction

Marine environment is a unique source of biologically active secondary metabolites. Isolated compounds from marine resources are different from terrestrial metabolites because of special physical and chemical conditions in the marine habitat.[1] So marine organisms such as algae, sponges, fungi, corals, and ascidians contain potentially active metabolites with characteristic chemical structures. There are more than 2,400 compounds in the field of marine natural plants isolated only from seaweeds of different regions of oceans.[2]

A number of research showed that marine seaweeds are potent resources for drug development. They contain important kinds of secondary metabolites such as steroids, terpenoids, phlorotannins, amino acids, phenolic compounds, and halogenated structures particularly ketones, glycolipids, and cyclic polysulphides.[3-5] New structures and unique mechanisms of action of marine natural products have led to the identufucation and structure elucidation of substances with, antimicrobial, antiviral, antioxidant, antitumor, antidepression, anti-inflammatory, and anti-Alzheimer activities.[6-9]

Glycoglycerolipids are one of the important groups of lipid compounds present in the marine seaweeds. These compounds are famous because of their especial activities, such as antitumor and anti-inflammatory activities along with improving the intestinal condition.[10,11] Marine algae synthesize three important types of glycolipids: monogalactosyldiacylglycerides, digalactosyldiacylglycerides, and sulfoquinovosyldiacylglycerides (SQDG). A number of

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seaweeds can convert simple polyunsaturated fatty acids into complex oxylipins[12] and these derivatives are extremely useful to keep homeostasis in mammalian systems. Besides glycolipids are abnormally produced in diseases such as psoriasis, asthma, arteriosclerosis, ulcers, and cancer.[13] Therefore, it is an interesting area to elucidate the structures of glycoglycerolipid molecules from seaweeds resources.

Sargassum is a genus of more than 250 species in Sargassaceae family that is widespread in different tropical and temperate oceans geographically. Until now, different glycerolipids have been isolated from *sargassum* species worldwide. Recent data have exhibited that more than 150 species of marine algae are present in the coastal area of Persian Gulf and Oman Sea of Iran.[14] There are only limited studies on the phytochemistry of the marine seaweeds of Iran, especially *sargassum* species. So, in this study, we have selected the brown seaweed *Sargassum angustifolium* to isolate its glycolipids.

Materials and Methods

General

TLC: GF254 silica gel plates (Merck, Germany, 20 × 20 cm); detection by spraying with 10% cerium sulphate and heating. Column chromatography (CC): silica gel 63-200 μm. HPLC: Agilent 1100 Series with a silica column (YMC Co., Ltd., Kyoto, Japan) and UV-Vis detector. NMR: Bruker AV-400 (^{1}H) and AV-100 (^{13}C), EI-MS spectra: Varian MAT 112 or MAT 312 spectrometers. The GC-MS was Agilent Technologies 6890N GC with a mass-selective detector 5973 Network MSD and a silica-capillary GC column HP-5MS (30 m × 0.25 mm; i.d. 0.25 μm film, Agilent Technologies, Inc.).

Authentication of plant material

The algae was collected from Bushehr Province in 2012 and identified by Agricultural and Natural Resources Research Center of Bushehr (voucher specimens coded as 2662).

Extraction and fractionation of lipids

The powder of dried *S. angustifolium* was extracted with EtOAc/methanol 1:1 (v/v) solvent at room temperature. The extracts were filtered and dried and partitioned to hexane, dichloromethane, butanol, and water through Kupchan method. The Hexane partition was fractionated by normal phase MPLC with a gradient solvent system from pure hexane to 100% EtOAc. The eluates were monitored by ^{1}HNMR and TLC and divided into 14 fractions (Frs. 1-14). Fraction F14 was purified on a silica gel columnand chloroform/methanol solvent with increasing amounts of methanol (95:5, 90:10, 80:20, 50:50 v/v) and 100% methanol. The eluates were combined into 12 final fractions. Fractions F14i, F14j, F14k, and F14l were further isolated by HPLC separation yielded the pure compounds 1, 2, 3, 4, and 5.

Alkaline hydrolysis

A 12% solution of each compounds (2-5) was treated with NaOMe (0.5M in MeOH) and stirred for 5 h at room temperature. After this time, the mixture was further neutralized with Dowex 50 W × 4 and the resin filtered. The filtrate was dissolved in hexane, concentrated and analyzed by GC-MS. The column oven temperature was 80°C for 1 min and then increased up to 310°C with a rate of 15°C/min (flow rate 0.8 mL/min).

In vitro cytotoxicity assay

The HeLa (epitheloid cervix carcinoma) cell line and HUVEC (and human umbilical vein endothelial cells) were obtained from the Pasteur Institute of Iran. Cells were incubated in an incubator with 5% CO_2 at 37°C. The cells were fed with Roswell Park Memorial Institute medium and Dulbecco's Modified Eagle's medium, supplemented with FBS (10%) and penicillin-streptomycin (100 IU/mL and 100 μg/mL).

Compounds 2-5 were tested about cytotoxic effects using MTT [3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide] against HeLa as well as HUVEC cells. Briefly, a cell suspension of 2 × 10^5 cells/mL in 96-well plates were incubated overnight. The dried samples were dissolved in dimethyl sulfoxide (DMSO) (less than 1% final concentration of DMSO in the palate). 20 μL of various concentrations of compounds or partitions were added and incubated at 37°C in a humidified atmosphere for 72 h. After that cells were incubated with 20 μL of MTT solution (5 mg/mL) at 37°C for 3 h. The medium was removed and 150 μL of DMSO was added to dissolve MTT-formazan crystals. Finally, the absorbance at 570 nm was measured by a plate reader. Following equation was used to calculate the cell survival:[15-17]

% Cell survival = (Absorbance in treated wells - Absorbance in blank well)/(Absorbance in negative control or untreated well – Absorbance in blank well).

Results

Compound 1

White powder, MW (g/mol): 412 (M + H); ^{1}H NMR (400 MHz, CDCl3): 5.38 (1H, br. d, J = 5.3 Hz, H-6), 5.2 (1H, q, J = 6.7 Hz, H-28), 3.58 (1H, m, H-3), 1.52 (3H, br s, H-21), 1.05 (3H, s, H-19), 1.03 (3H, br s, H-21),1.02 (3H, d, J = 1.2 Hz, H-27), 0.99 (3H, d, J = 1.2 Hz, H-26), 0.75 (3H, s, H-18). ^{13}C-NMR (100 MHz, CDCl3): 146.5 (C-24), 140.6 (C-5),121.3 (C-6), 115.8 (C-28), 71.4 (C-3), 56.8 (C-14), 55.2 (C-17), 50.6 (C-9), 42.7 (C-13), 42.1 (C-4), 39.5 (C-12), 37.5(C-1), 36.4 (C-10), 36.3 (C-20), 35.5 (C-22), 34.8 (C-25),31.6 (C-7,8), 31.7 (C-2), 28.1 (C-16), 25.5 (C-23), 24.2 (C-15), 22.1 (C-26), 22.0 (C-27), 21.3 (C-11), 19.5 (C-19), 18.7(C-21), 131.2 (C-29), 11.8 (C-18).

Compound 2

White powder, MW (g/mol): 792 (M + H); ^{1}H NMR (400 MHz, DMSO): 4.32 (1H, dd, J = 2.4,12 Hz, H-1), 4.12 (1H, dd, J = 7.6,12 Hz, H-1), 5.12 (1H, m, H-2), 3.86 (1H, dd, J = 6,10.8 Hz, H-3), 3.41 (1H, dd, J = 6,10.8 Hz, H-3), 4.56 (1H, d, J = 3.6 Hz, H-1‴), 3.18 (1H, dd, J = 6,9.6 Hz, H-2‴), 3.36 (1H, t, J = 9.2 Hz, H-3‴), 2.92 (1H, t, J = 9.2 Hz, H-4‴), 3.75 (1H, ddd, J = 4.8,5.6,10.4 Hz, H-5‴), 2.58 (1H, dd, J = 6,14 Hz, H-6‴), 2.57 (1H, dd, J = 6.2,13.9 Hz, H-6‴),

2.25 (4H, m, H-2′,2″), 1.49 (4H, m, H-3′,3″), 1.2-1.3 (m, H-4′-7′, 12′-15′, 4″-15″), 5.31 (2H, t, J = 4.8 Hz, H-9′,10′), 0.84 (6H, t, J = 6.8 Hz, H-16′,16″), 1.97 (4H, m, H-8′,11′).

^{13}C-NMR (100 MHz, DMSO): 172.3,173.5 (C-1′,1″), 129.5 (C-9′,10′), 98.2 (C-1‴), 74.2 (C-5‴), 72.8 (C-4‴), 71.5 (C-3‴), 69.6 (C-2‴), 68.5 (C-2), 64.5 (C-3), 62.5 (C-1), 54.6 (C-6‴), 33.4,33.5 (C-14′,14″), 31.2 (C-2′,2″), 28.9-29 (C-4′-7′,12′,13′,4″-13″), 28.4 (C-8′,11′), 24.4 (C-3′,3″), 22.0 (C-15′,15″), 13.9 (C-16′,16″).

Compound 3

White powder, MW (g/mol): 826 (M + H); ^{1}H NMR (400 MHz, MeOH): 4.32 (1H, dd, J = 2.8, 12 Hz, H-1), 4.12 (1H, dd, J = 2.8, 12 Hz, H-1), 5.17 (1H, m, H-2), 3.86 (1H, dd, J = 5.6, 10.8 Hz, H-3), 3.63 (1H, dd, J = 5.2, 10.8 Hz, H-3), 4.12 (1H, d, J = 7.6 Hz, H-1‴), 3.62 (1H, dd, J = 7.2, 9.6 Hz, H-2‴), 3.36 (1H, t, J = 9.2 Hz, H-3‴), 2.92 (1H, t, J = 9.2 Hz, H-4‴), 3.75 (1H, ddd, J = 4.8, 5.6, 10.4 Hz, H-5‴), 2.58 (1H, dd, J = 6, 14 Hz, H-6‴), 2.57 (1H, dd, J = 6.2,13.9 Hz, H-6‴), 2.21 (4H, m, H-2′,2″), 1.50 (4H, m, H-3′,3″), 1.2-1.3 (m, H-1′,1″,4′-7′,12′-17′, 4″-15″), 5.23 (2H, t, J = 4.8 Hz, H-9′,10′), 0.84 (6H, t, J = 6.8 Hz, H-18′,16″), 1.97 (4H, m, H-8′,11′). ^{13}C NMR (100 MHz, MeOH): 174.7,175 (C-1′,1″), 130.9,130.8 (C-9′,10′), 105.3 (C-1‴), 76.8 (C-5‴), 74.8 (C-4‴), 72.4 (C-3‴), 71.8 (C-2‴), 70.2 (C-2), 68.7 (C-3), 64.0 (C-1), 62.4 (C-6‴), 35,35.1 (C-16′,14″), 33.1 (C-2′,2″), 30.8 (C-8′,11′), 30.2-30.6 (C-4′-7′, 12′-15′, 4″-13″), 26.0 (C-3′,3″), 23.7 (C-17′,15″), 14.5 (C-18′,16″).

Compound 4

Crystallin, MW (g/mol): 302 (M + H); ^{1}H NMR (400 MHz, CDCl3): 3.54 (1H, dd, J = 2.8, 11.2 Hz, H-1), 3.65 (1H, dd, J = 2.8, 11.2 Hz, H-1), 5.24 (1H, m, H-2), 4.13 (1H, ddd, J = 5.2, 11.6, 12.4 Hz, H-3), 2.2 (2H, t, J = 7.6 Hz, H-2′), 1.47 (2H, m, H-3′), 1.2-1.3 (m, H-4′-13′), 0.83 (6H, t, J = 6.8 Hz, H-14′), 1.58 (2H, m, H-1′). ^{13}C NMR (100 MHz, CDCl3): 174.4 (C-1′), 70.1 (C-2), 65.5 (C-3), 63.4 (C-1), 34.2 (C-12′), 31.8 (C-2′), 29.6-29.8 (C-4′-11′), 24.8 (C-3′), 22.7 (C-13′), 14.1 (C-14′).

Compound 5

White powder, MW (g/mol): 836 (M + H); ^{1}H NMR (400 MHz, DMSO): 4.26 (1H, dd, J = 2.8, 12 Hz, H-1), 4.0 (1H, dd, J = 7.6, 12 Hz, H-1), 5.04 (1H, m, H-2), 3.3 (1H, dd, J = 6, 16 Hz, H-3), 3.80 (1H, dd, J = 6,10.6, H-3), 4.48 (1H, d, J = 4 Hz, H-1‴), 3.10 (1H, dd, J = 6,9.6, H-2‴), 3.21 (1H, t, J = 9.6, H-3‴), 2.82 (1H, t, J = 9.2 Hz, H-4‴), 2.90 (1H, s, H-11′), 3.68 (1H, ddd, J = 4.8, 5.6, 10.4 Hz, H-5‴), 2.41, 2.47, 2.19 (4H, m, H-2′,2″), 1.40 (4H, m, H-3′,3″), 1.1-1.2 (m, H-4′-18′,4″-15″), 0.76 (6H, t, J = 6.8 Hz, H-19′,16″). ^{13}C NMR (100 MHz, DMSO): 172.3, 172.5 (C-1′,1″), 98.2 (C-1‴), 74.2 (C-5‴), 72.8 (C-4‴), 71.5 (C-3‴), 69.6 (C-2‴), 68.5 (C-2), 64.5 (C-3), 62.6 (C-1), 54.5 (C-6‴), 42.07 (C11′), 33.4, 33.5 (C-14″,16′), 31.2 (C-2′,2″), 29 (C-4′-7′, 12′-15′, 4″-13″), 28.4 (C-8′), 24.4 (C-3′,3″), 22.0 (C-17′,15″), 13.9 (C-19′,16″).

Cytotoxic activity

The cytotoxic activities of all compounds was shown in table 1.

Discussion

Sargassum species are rich sources of different primary and secondary metabolites.[18-20] Assignment of all ^{13}C- and ^{1}H-NMR signals was done by careful analysis of 1H-1H COSY, DEPTHMBC, and HSQC spectra [Figure 1]. About compound 2, a glycerol one spin moiety [δ_H 4.32 and 4.14 (δ_C 62.7); δ_H 5.18 (δ_C70.2); δ_H 3.88 and 3.64 (δ_C 68.7)] was recognized.

The presence of acyl groups on the sn-1 and sn-2 positions of the glycerol moiety was identified by HMBC (Heteronuclear Multiple Bond Coherence) cross-peaks [δ_H/δ_C: 5.18 (Hsn-2)/173.5, 175 (COO); 4.34 and 4.13 (Hsn-1)/172.5, 172.6 (COO); 2.29 (α-CH2)/172.5, 172.6 (COO)]. Therefore, terminal methyl signals of two

Table 1: Cytotoxic activity of isolated compounds

Sample	Compound 1	Compound 2	Compound 3	Compound 4	Compound 5
IC_{50} (μg/ml)	12.2±2.3	25.8±3.7	14.9±2.6	9.8±1.2	5.6±1.2

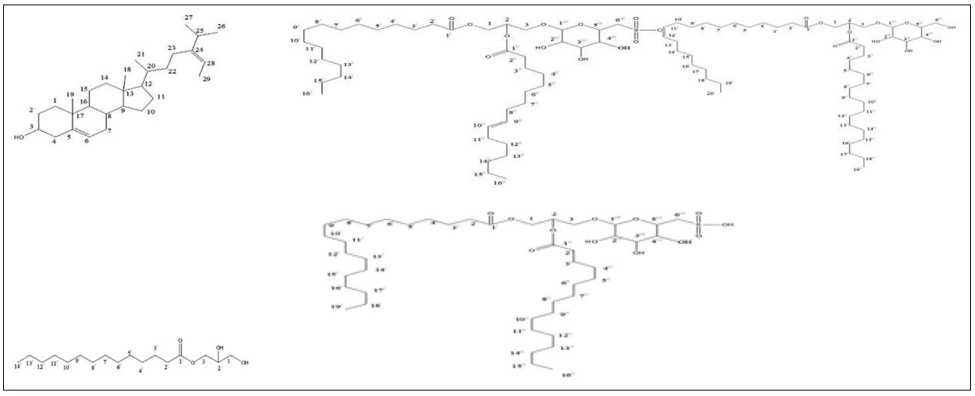

Figure 1: Structure of compounds 1-5

fatty acyl groups were shown by the second spin system signals (6H, t, J = 6.8 Hz, δ_C 14.6).

The relatively small coupling constant of the anomeric proton (H-1‴), J = 3.7 Hz, presented the α orientation of the glycosidic part, and the large vicinal coupling constants between H-2‴/H-3‴, H-3‴/H-4‴, and H-4‴/H-5‴ (J = 9.6 Hz), showed the glucopyranosyl structure of the sugar unit.

Besides, the ^{1}H- and ^{13}C-NMR characteristic chemical shifts of carbon C-6‴(δc 54.6) and methylene protons H-6‴ (δ 2.91 and 2.55) indicated the presence of a sulphonyl group attach to the sugar (C-6‴), instead of glucose.[21-23]

All ^{1}H- and ^{13}C-NMR characteristic data are in agreement with the structure of 6-deoxy-6-sulpho-α-D-glucopyranosyl-1,2-O-diacyl-glycerols. Alkaline hydrolysis with NaOMe in MeOH was done for identification of acyl substituents at sn-1 and sn-2. The hydrolysis was followed by GC/MS analysis. The composition of the fatty acid methyl esters was elucidated as methyl myristate, methyl oleate, and methyl palmitate, being the last in greater proportion.

Compound 5 was the most potent isolated compound as shown in Table 1. Comparing the structures and cytotoxic activity of isolated compounds shows that presence of a double bond in the side chains of fatty acid may reduce the cytotoxic activity. Structure activity relationship studies of SQDG has shown that the cytotoxicity is probably dependent on the fatty acid chain, besides each of the SQMG/SQDG was a stronger inhibitor than the fatty acid alone. The inhibitory effect could be influenced by the chain size of fatty acids too. The sulfate moiety in the quinovose is also important for the inhibition.[24]

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Conflicts of interest

There are no conflicts of interest.

References

1. Yegdaneh A, Putchakarn S, Yuenyongsawad S, Ghannadi A, Plubrukarn A. 3-oxoabolene and 1-oxocurcuphenol, aromatic bisabolanes from the sponge Myrmekioderma sp. Nat Prod Commun 2013;8:1355-7.
2. Blunt JW, Copp BR, Keyzers RA, Munro MHG, Prinsep MR. Marine natural products. Nat Prod Rep 2017;34:235-94.
3. Lopez-Santamarina A, Miranda JM, Mondragon ADC, Lamas A, Cardelle-Cobas A, Franco CM, *et al*. Potential use of marine seaweeds as prebiotics: A review. Molecules 2020;25:1004.
4. Janarthanan M, Senthil Kumar M. The properties of bioactive substances obtained from seaweeds and their applications in textile industries. J Ind Text 2018;48:361-401.
5. Akbari V, Safaiee F, Yegdaneh A. Bioassay-guided fractionation and antimicrobial activities of padina australis extracts. Jundishapur J Nat Pharm Prod 2021;15:e68304.
6. Akbari V, Zafari S, Yegdaneh A. Anti-tuberculosis and cytotoxic evaluation of the seaweed sargassum boveanum. Res Pharm Sci 2018;13:30-7.
7. Ghannadi A, Plubrukarn A, Zandi K, Sartavi K, Yegdaneh A. Screening for antimalarial and acetylcholinesterase inhibitory activities of some Iranian seaweeds. Res Pharm Sci 2013;8:113-8.
8. Sharifi M, Yegdaneh A, Sajjadi SE, Shushizadeh M. Identification and quantification of Phthalate pollution in Holothuria atra: A sea cucumber from the Persian gulf (Iran). Jundishapur J Nat Pharm Prod 2017;12:e65055.
9. Mesripour A, Rabian N, Yegdaneh A. The effect of different partitions of seaweed sargassum plagyophylum on depression behavior in mice model of despair. J Complement Integr Med 2019;16:20180207.
10. Liu J, Luthuli S, Wu Q, Wu M, Choi JI, Tong H. Pharmaceutical and nutraceutical potential applications of sargassum fulvellum. Biomed Res Int 2020;2020:2417410.
11. Hira K, Farhat H, Sohail N, Ansari M, Ara J, Ehteshamul-Haque S. Hepatoprotective activity against acetaminophen-induced liver dysfunction and GC-MS profiling of a brown algae sargassum ilicifolium. Clin Phytoscience 2021;7:1-11.
12. Arguelles EDLR. Evaluation of antioxidant capacity, tyrosinase inhibition, and antibacterial activities of brown seaweed, sargassum ilicifolium (Turner) c. agardh 1820 for cosmeceutical application. J Fisheries Environ 2021;45:64-77.
13. Negara BFSP, Sohn JH, Kim JS, Choi JS. Antifungal and larvicidal activities of phlorotannins from brown seaweeds. Mar Drugs 2021;19:223.
14. Devi RM, Loganathan P, Kalaiarasi J. Pharmacognostical and phytochemical analysis of sargassum cinereum (Turner) C. Agardh J Pharmacogn Phytochem 2018;7:2233-8.
15. Panjehpour, M., Movahedian, A., Sadeghi, H., Eghbali, B., Yekdaneh, A. Adenosine receptor expression in two different human cancer cell lines at molecular level. Iranian Journal of Cancer Prevention. 2010; 3: 111-116.
16. Yegdaneh A, Saeedi A, Shahmiveh T, Vaseghi G. The effect of sargassum glaucescens from the Persian gulf on neuropathy pain induced by paclitaxel in mice. Adv Biomed Res 2020;9:79.
17. Mousavi SE, Hatamipour MS, Yegdaneh A. Ultrasound-assisted extraction of alginic acid from sargassum angustifolium harvested from Persian gulf shores using response surface methodology. Int J Biol Macromol 2023;226:660-9.
18. Savaghebi D, Barzegar M, Mozafari MR. Manufacturing of nanoliposomal extract from sargassum boveanum algae and investigating its release behavior and antioxidant activity. Food Sci Nutr 2020;8:299-310.
19. Mesripour A, Rafieian-Kopaei M, Bahrami B. The effects of *anethum graveolens* essence on scopolamine-induced memory impairment in mice. Res Pharm Sci 2016;11:145-51.
20. Hassanzadeh A, Yegdaneh A, Rabbani M. Effects of hydroalcoholic, methanolic, and hexane extracts of brown algae Sargassum angustifolium on scopolamine-induced memory impairment and learning deficit in rodents. Res Pharm Sci 2023;18:292-302.
21. Yunoki K, Sato M, Seki K, Ohkubo T, Tanaka Y, Ohnishi M. Simultaneous quantification of plant glyceroglycolipids including sulfoquinovosyldiacylglycerol by HPLC-ELSD with binary gradient elution. Lipids 2009;44:77-83.
22, Sadeghi M, Safaeian L, Ghazvini MA, Ramezani M. Evaluation of fibrinolytic and antioxidant effects of Allium affine hydroalcoholic extract. Research in pharmaceutical sciences. 2017;12:299-306
22. Xiao H, Chen C, Li C, Huang Q, Fu X. Physicochemical characterization, antioxidant and hypoglycemic activities of selenized polysaccharides from sargassum pallidum. Int J Biol Macromol 2019;132:308-15.
23. Hanashima S, Mizushina Y, Ohta K, Yamazaki T, Sugawara F, Sakaguchi K. Structure-activity relationship of a novel group of mammalian DNA polymerase inhibitors, synthetic sulfoquinovosylacylglycerols. Jpn J Cancer Res 2000;91:1073-83.
24. MesripourA, Almasi M. Flaxseed prevents interferon-alpha induced depressive behavior in mice: the α-linolenic acid is essential Research Journal of Pharmacognosy 2021;8 :63-71.