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In-vitro Promising Anticancer activity of *Murraya paniculata* L. Leaves extract against three cell lines and isolation of two new major compounds from the extract

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Abstract

Oxidative stress plays a major part in the development of cancer. While cancer is now recognized as one of the leading causes of death in the world. This study has been undertaken to evaluate the possible potential antioxidant effect of different fractions of *Murraya Paniculata* L. leaves cultivated in Egypt in different seasons using the DPPH scavenging method and to assess their anticancer potential. Also, to determine the total flavonoidal content and isolate the major compounds in the fraction of the alcoholic extract showed the higher activity. Results of screening antioxidant activity showed that the highest antioxidant activity of the alcoholic extracts was noticed during summer season compared with the reference standard; gallic acid. Among all tested fractions, ethyl acetate fraction showed high activity in all seasons. From the ethylacetate fraction of the summer season alcoholic extract, two flavonoids were isolated. These flavonoids are: 5-Hydroxy-6, 7, 3`, 4`, 5`-penta methoxy flavanone and Hexamethoxy flavanone-*O*-[rhamnopyranosyl- (1 → 4)-rhamnopyranoside]. Cytotoxic activity of the alcoholic extract was tested using Staurosporine as a positive control. It was found to possess antiproliferative activity against MCF7, PC3 and Huh7 cancer cells with IC_{50} values of 33.5, 58.6 and 68.8 µg/ml, respectively. This indicates that *Murraya paniculata* L. cultivated in Egypt possess very good antioxidant and anticancer properties.

Keywords: Antioxidant, DPPH, anticancer, MTT assay, Flavonoids, *Murraya paniculata*

1. Introduction

Murraya paniculata L. Jack (formerly *Murraya exotica* L.) (1), known as orange jasmine (2), belongs to Rutaceae, a botanic family that has about 150 genera and 1,600 species distributed in tropical, subtropical and temperate regions all over the world. Oxidative stress plays a major part in the development of chronic and degenerative ailments such as cancer, arthritis, aging, autoimmune disorders, cardiovascular and neurodegenerative diseases. The human body has several mechanisms to counteract oxidative stress by producing antioxidants, which are either naturally produced in situ, or externally supplied through foods and/or supplements. Endogenous and exogenous antioxidants act as "free radical scavengers" by preventing and repairing damages caused by reactive oxygen species (ROS) and reactive nitrogen species (RNS), and therefore can enhance the immune defense and lower the risk of cancer and degenerative diseases (3-7). The DPPH method is one of the most common used methods to evaluate the ability of compounds to scavenge free radicals or to donate hydrogen, as well as determining the antioxidant capacity of various plant extracts at a time (8). A previous study showed that the ethyl acetate fraction of the plant exhibited the most potent antioxidant activity (9). Cancer has been recognized as the most deadly human enemy for a long time. Furthermore, the chemotherapeutic agents currently available for clinical use have failed to fulfill expectations despite the considerable cost and effort for their development (10). *Murraya paniculata* 'kemuning' with several extraction methods possess antioxidant activity. Using linoleic-thiocyanate method the ethanolic extract of "kemuning" leaves showed antioxidant strength in the following sequence: 10% "kemuning" > 1% vitamin E > 5% "kemuning" > 1% of "kemuning" extract. Using 2,2-diphenyl-l-picryl hydrazyl (DPPH) method, the IC_{50} of "kemuning" extract was 126.17 µg/ ml which is 15 times lower than the vitamin E (positive control) 8.27 µg/ml (11). Therefore, the aim of this study has been undertaken to evaluate the possible potential antioxidant effect of different fractions of *Murraya Paniculata* L. leaves cultivated in Egypt in different seasons using the DPPH scavenging method, to assess their anticancer activity and also to isolate the major compounds may be responsible for the plant activities.

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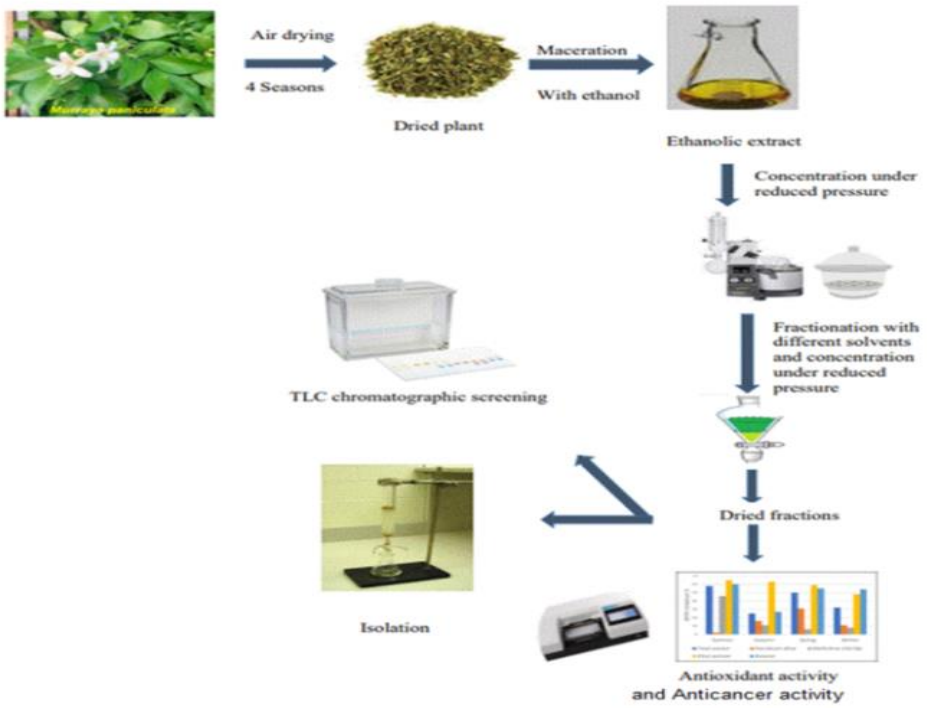


Figure (1): Graphical abstract

2. Experimental

2.1. Plant material

Murraya paniculata L. leaves were collected from ornamental plant garden at Shbeen El Koom, Menoufia, Egypt in different seasons (Summer in July 2019, Autumn in November 2019, Winter in February 2020 and Spring in May 2020). Plant identification was confirmed by Prof. Dr. Sliem Zeidan Heneidy and Prof. Dr. Sania Ahmed Kamal at Botany Department, Faculty of Science, Alexandria university, Egypt. The voucher specimen was kept in the herbarium there, under number 10802.

2.2. General experimental procedure

Melting points were determined using Fisher- Johns melting point apparatus. Solvent evaporation and concentration was performed on Rotavapor Heidolphvv 2000 and measurement of UV spectra in methanol as well as determination of flavonoidal content were done using Spectrophotometer (Optima SP-300, Japan). The 1H- NMR spectra were recorded in DMSO-d_6 using TMS as internal standard, on Varian- Mercury BB 400 NMR. Mass spectral analysis of the flavonoids were recorded on electrospray ionization mass spectroscopy; using Advion compact mass spectrometer in the negative electrospray mode .Cytotoxicity assays were measured in an ELISA reader spectrophotometer (Tecan Group Ltd.-Sunrise). Germany. TLC analysis was done on precoated silica gel 60 F254 plates, (Germany). UV detection of the TLC plates was done using Camag, Switzerl and UV Lamp. Column chromatographic separations were performed on silica gel (70-230 mesh).

2.3. Extraction and fractionation of plant material

Air dried leaves (625 g for each of the four seasons; Summer, Autumn, Winter and Spring were extracted separately by maceration with 70% ethyl alcohol. The ethanolic extracts were concentrated under reduced pressure using a rotary evaporator to give solid residues then each extract was fractionated successively with petroleum ether, methylene chloride, ethyl acetate and *n*-butanol. These fractions of each extract were freed from solvents under reduced pressure yielding dried residues of different weights. The ethanolic extracts and their fractions were evaluated for their *in-vitro* antioxidant and anticancer activities.

2.4. Determination of antioxidant activities

The free radical scavenging activity of the different extracts of *Murraya paniculata* were measured by 1, 1-diphenyl-2-picrylhydrazyl (DPPH) (Sigma-Aldrich) scavenging method (8). Briefly, 0.04 mg/ml solution of DPPH in methanol was prepared and 10 mg/ml solution of samples in methanol was prepared. In 96 well microplate, ten microliters of each sample, standard Gallic acid (Sigma-Aldrich) (0.4 mg/ml) (positive control) and methanol (negative control) were added in the microplate in triplicate, Afterwards, 190 µl of DPPH solution were added to each well. After shaking, the mixture was allowed to stand in dark at room temperature for 30 min, and absorbance was measured at 517 nm. The following equation was used to calculate the % DPPH scavenging effect.

$$\% \text{ DPPH inhibition} = A_0\text{-}A_1/A_0 \times 100$$

Where : A_0 **=** the absorbance of control reaction, A_1 = the absorbance of the test or standard reaction

2.5. Determination of anticancer activities

2.5.1. Cancer cell lines and culture

The human cancer cell lines PC3 (prostate cancer), MCF7 (breast cancer) and Huh7 (hepatocellular carcinoma) were recognized from ATCC. PC3, MCF7 and Huh7 cells were cultured using Dulbecco's Modified Eagle's Medium (DMEM)

(Lonza®, Basel, Switzerland). The medium was supplemented with 10% fetal bovine serum, 10 µg/ml of insulin and 1% penicillin-streptomycin (Sigma–Aldrich, St. Louis, USA).

2.5.2. *In vitro* cytotoxic activity by MTT test

The cytotoxic activity of the summer ethanolic extract was evaluated on cell viability using MTT-assay (12, 13) with some modifications. MTT was purchased from Serva, Heidelberg, Germany. Cells were seeded (1 × 104 cells/well) in growth medium (DMEM) into 96-well plates and incubated at 37 °C for 24h in a 5% CO2 incubator. The sample was added at different concentrations to each well (0.4, 1.6, 6.3, 25 and 100 µg/ml) whereas the medium in control wells was substituted by serum free medium (SFM) containing an equivalent volume of dimethyl sulfoxide (DMSO) and incubated for another 24h. SFM was then removed and MTT was added to each well. MTT solution was removed and 100 µL isopropanol was added to each well to dissolve the produced purple formazan crystals (MTT byproduct). The plates were read using the plate reader at 570 nm wavelength (Bio-Rad, USA). The treated samples and the control were compared. The percent viabilities of cells were calculated using the following equation: (AT/AC) ×100 Where, AT stands for the average absorbance of cells treated with different extract concentrations and AC stands for the average absorbance of untreated cells in culture medium (control). Cytotoxicity was expressed as IC50- value which was calculated as the concentration of the extract inhibiting cell viability by 50%. Staurosporine was utilized as a positive control. All measurements were performed in triplicate. The means and standard deviations were calculated. Data are presented as mean ± standard deviation (SD) (MS Excel 2010).

2.6. Determination of total flavonoid concentration in the alcoholic extract of *Murraya paniculata*

The content of flavonoids in the total ethanolic summer extract of *Murraya paniculata* L. was determined using spectrophotometric method (14).

2.7. Isolation of two flavonoidal compounds from ethyl acetate fraction of leaves extract of summer season

0.5 gm of ethyl acetate fraction of leaves extract was chromatographed on 90 gm silica gel column (2.7 cm ×40 cm length). Elution was occurred using ethyl acetate: methanol: water (60:5:4). Ninteen fractions (50 ml each) were collected and monitored by TLC. TLC plates were revealed by UV, ammonia exposure, aluminum chloride and anisaldehyde/ sulfuric acid spray reagent.

2.7.1. Isolation of compound "A1"

Fraction 12 (45 mg) showed a major yellow spot upon exposure to ammonia and AlCl3 and giving orange color upon using anisaldehyde/sulphric acid spray reagent, in addition to other minor spots. It was rechromatographed on 20 gm Sephadex LH 20 (pharmazie) column for purification to obtain compound A1. compound A1 (10 mg) has m.p. 177-178 showed one yellow spot of Rf value 0.38 and 0.79 in solvent system Ethyl acetate: methanol: water (30:5:4 V/V/V) and Methylene chloride: methanol (7:3 V/V) respectively.

2.7.2. Isolation of compound "A2"

Fraction 16 (30 mg) showed a major yellow spot with other dark spots. It was rechromatographed on 20 gm Sephadex LH 20 column several times for purification. Compound A2 (5 mg) has m.p. 251-254 and showed one yellow spot of Rf value 0.375 and 0.857 in solvent system Ethyl acetate: methanol: water (30:5:4 V/V/V) and Methylene chloride: methanol (7:3 V/V) respectively.

3. Results

3.1. Antioxidant activities

Results of antioxidant activity showed that the highest antioxidant activity of tested hydro-alcoholic extracts was noticed during summer season compared with the standard; gallic acid. Among all tested fractions, ethyl acetate fraction showed high activity in all seasons as shown in F Table 1 & Figure 2.

Table 1: Average of DPPH absorbance and % inhibition values of tested samples compared to Gallic acid as standard reference and methanol as negative control

Type	Summer		Autumn		Spring		Winter	
		% Inhibition	A	% Inhibition	A	% Inhibition	A	% Inhibition
Hydro-alcoholic extract	0.25	58	0.448	25	0.297	50	0.404	32
Pet. ether fraction	0.581	2	0.499	16	0.409	31	0.530	11
DCM fraction	0.32	46	0.527	11	0.561	6	0.543	8
Ethyl acetate fraction	0.210	65	0.222	63	0.242	59	0.309	48
Butanol fraction	0.237	60	0.433	27	0.27	55	0.271	54
Methanol (A= 0.593)								
% Inhibition of Gallic acid (0.4 mg/ml) 70%								

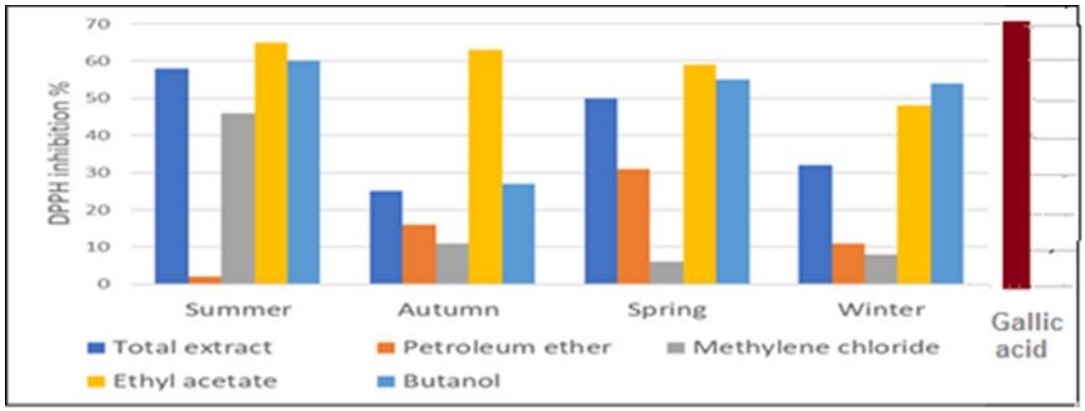


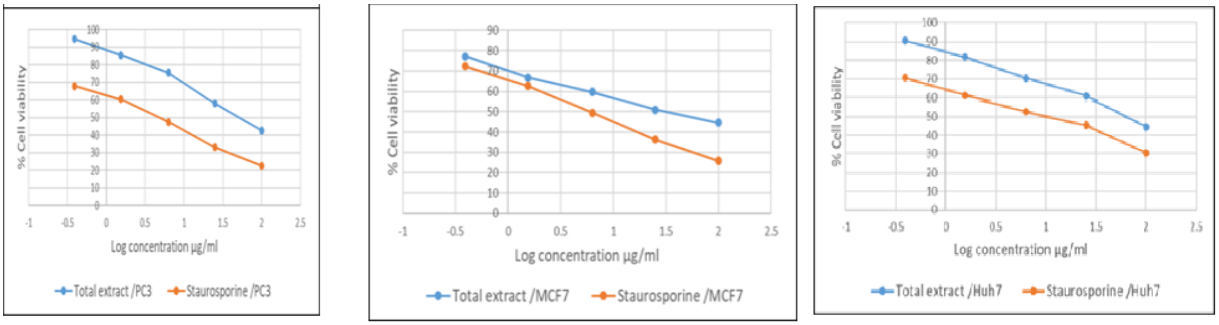
Figure 2: DPPH Scavenging Effect (%) for different extracts and their fractions of *Murraya paniculata L.* (10 mg/ml concentration of each is used) collected during the four seasons

3.2. Anticancer activities

Figure 3 shows a concentration-dependent cytotoxic effects on treating cells with sample concentrations of 0.4, 1.6, 6.3, 25 and 100 µg/ml. Figure 4 illustrate IC50 values of ehanolic extract and the positive standard; Staurosporine on PC3, MCF7 and Huh7 cells. The resulted IC_{50} values are 58.6, 33.5 and 68.8 µg/ml, respectively. The positive standard; Staurosporine showed IC50 values of 4.02, 5.75 and 8.31 µg ml-1, respectively against the same cancer cell line as shown in (Figure 4).

3.3 Total flavonoidal content of the alcoholic extract of *Murraya paniculata*

The total content of flavonoids in spring season extract was expressed in terms of quercetin equivalent (1.67 mg of quercetin/g of extract).



a b c

Figure 3: Cytotoxic effects of ethanolic extract (0.4-100 µg/ml) on PC3 (a), MCF7 (b) and Huh7 (c) cell lines compared to Staurosporine

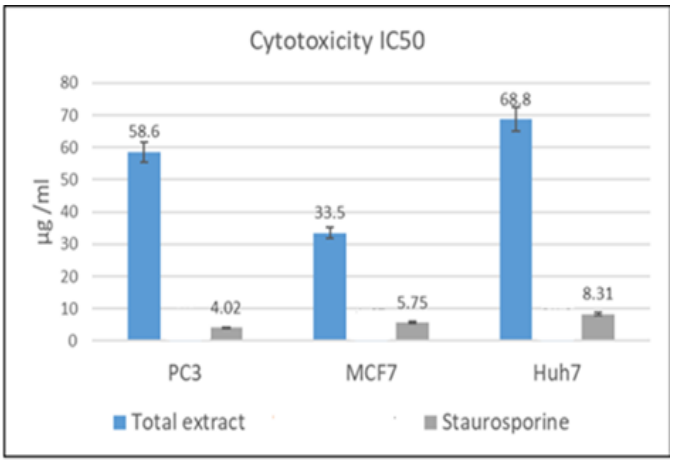


Figure 4: IC_{50} values of the ethanolic extract of Murraya paniculata L. against PC3, MCF7 and Huh7 compared to Staurosporine. Data are expressed as the mean± SD of three experiments each conducted in triplicate.

3.4. Identification of the isolated compound A1

Compound A1 was isolated as a yellow powder (10 mg, methanol) from ethyl acetate fraction of Murraya paniculata leaves extract. Qualitative chemical tests and the UV,1H-NMR Spectral data of the compound pointed to its flavanoidal nature (15). Extensive study of the UV spectra of compound A1 using different shift reagents indicated that it is most probably to be a substituted flavanone since band I of the methanol spectrum appeared at (297 nm shoulder peak, 339 nm). The bathochromic shift in band I with addition of AlCl3/ HCl reagent (16 nm) indicated the absence of an ortho- di hydroxy group and presence of 5-OH (16).

In the 1H-NMR spectrum of Compound A1, characteristic flavanone proton signals for H-2 (δ 5.45, 1H, dd, J= 12, 3.3 Hz), H-3eq (δ 2.7, 1H, dd, J= 17, 3.3 Hz) and H-3ax (δ 3.66, 1H, dd, J= 12, 17 Hz) were recorded (15). Five methoxy signals were observed at δ 3.32-3.79 (Table 1).

MS data of compound A1 showed characteristic peaks at m/z (% rel.int.): 390 [M]- (4), 389 [M-1]- (2), 318 (6), 196 (53), 152 (3), 111 (100) (Figure 5). Structure of compound A1 could be identified as 5-hydroxy-6,7,3`,4`,5`-penta methoxy flavanone (Figure 6). This was compared with the published data (15). It is worth to mention that this is a new compound and to our best of knowledge, it is the first time to isolate this compound from Murraya Paniculata leaves.

Table 2: 1H-NMR spectral data of compound A

Number	δ_H (ppm), m, J (Hz)
H-2	5.45 (1H, *dd*, *J*= 12, 3.3 Hz)
H-3_{eq}	2.7 (1H, *dd*, *J*= 17,3.3 Hz)
H-3_{ax}	3.66 (1H, *dd*, *J*= 12,17 Hz)
H-8	7.2 (1H, *S*)
H-2`	7.78 (1H, *d*, *J*= 3 Hz)
H-6`	7.81 (1H, *d*, *J*= 3 Hz)
O-CH_3 groups	3.32, 3.35, 3.37, 3.38, 3.79

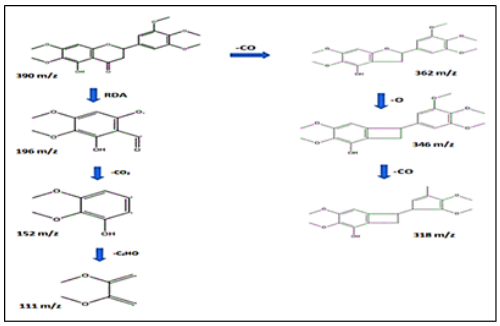


Figure 5: Fragmentation pathways of compound A1 (17)

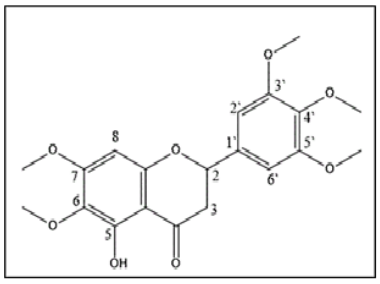


Figure 6: 5-hydroxy- 6, 7, 3`, 4`,5`-penta methoxy flavanone

3.5. Identification of the isolated compound A2

Compound (A2) was isolated from the ethyl acetate fraction of *Murraya paniculata* L. leaves extract. UV spectrum of Compound (A2) showed λ max at 231, 300 sh., 313.1H-NMR: Spectral data; 400 MHZ (methanol-D6) (Table 3). MS data showed characteristic peaks at m/z (% rel.int.): 712 [M]- (4), 402 (20) (aglycone-2H), 304 (38), 210 (2), 196 (5), 147 (base peak) (100) (Figure 7). The structure of compound A2 could be identified as hexamethoxy flavanone-O-[rhamnopyranosyl- (1 → 4)-rhamnopyranoside] (Figure 8)

Table 3: ^{1}H-NMR spectral data of compound A2

Number	δ_H (ppm), m, J (Hz)
H-2	5.45 (1H, *dd*, *J*= 8, 4 Hz)
H-3_{cis}	2.1 (1H, *dd*, *J*= 4, 8 Hz)
H-3_{trans}	2.2 (1H, *dd*, *J*= 4, 8 Hz)
H-2`	7.4 (1H, *d*, *J*= 3 Hz)
H-6`	7 (1H, *d*, *J*= 3 Hz)
Rhamnose C-CH_3 groups	1.3 (3H, br *d*, *J*= 8, 1.4 (3H, br *d*, *J*= 8 Hz)
Rhamnose hydro groups	6.81(2H, *d*),4.2-4.4 (8 H, *m*)
O-CH_3 groups	3.3, 3.85, 3.9, 3.95

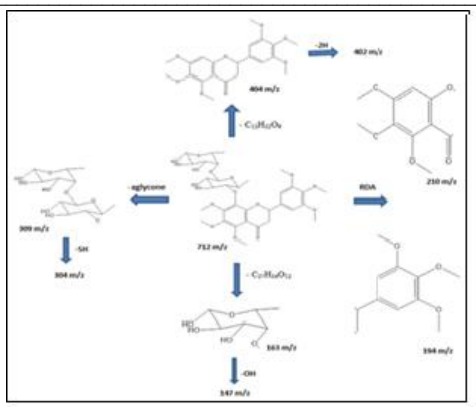


Figure 7: Fragmentation pathways of Compound A2

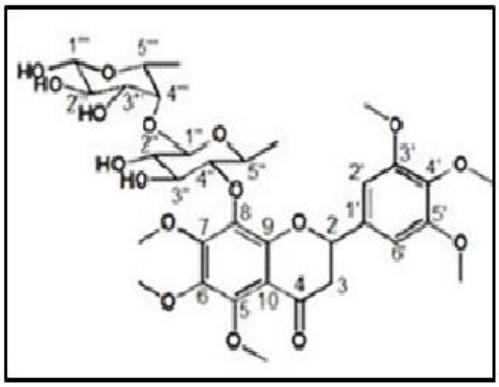


Figure 8: Hexamethoxy flavanone-*O*-[rhamnopyranosyl-(1 → 4)-rhamnopyranoside]

4. Discussion

This study is a part of the search for useful and promising natural compounds derived from Egyptian plants. In the current study, we discovered that the extracts of *M. paniculata* L. leaves have antioxidant and cytotoxic activities. The DPPH radical-scavenging capacities of all extracts were showed extract dependency and their activity varied among different extracts. Results of antioxidant activity showed that the highest antioxidant activity of tested hydro-alcoholic extracts was noticed during summer season compared with gallic acid with absorbance value of 0.17. Among all tested fractions, ethyl acetate fraction of the alcoholic extract showed high activity in all seasons. The Potency of ethylacetate fractions may be attributed to their content of flavonoids. Thus total flavonoidal content was determined and two major flavonoids had been isolated from the ethyl acetate fraction in summer season. Cytotoxicity was monitored by determining the effect of the test samples on cell viability. It was demonstrated that the tested extracts suppressed the proliferation of human prostate cancer cells (PC3), human breast cancer cells (MCF7) and human hepatocellular carcinoma (Huh7) in a dose dependent manner with different IC50 values and varying degrees of potency. It demonstrated the most potent antiproliferative activity against breast cancer with IC50 value of 1.67 µg ml-1 followed by liver cancer with IC50 of 5.78 µg ml-1 and prostate cancer with IC50 of 6.5 µg ml-1, when compared to Staurosporine (positive control) (18), which had IC50 values of 5.75, 8.31 and 4.02 µg ml-1, respectively while hydro-alcoholic extract was found to possess antiproliferative activity against MCF7, PC3 and Huh7. cancer cells with IC50 values of 33.5, 58.6 and 68.8 µg/ml, respectively. Several studies established the cytotoxic activity of the *Murraya paniculata* L. against various cancer cell lines (19-22). This is the first study to assess the anticancer potential of Murraya paniculata extract against MCF7, PC3 and Huh7.Variations in the activity could be attributed to the differences in the constituents of the extracts.Concerning compound A1, 1H-NMR spectrum showed two aromatic proton signals at δ 7.78 (1H, d, J= 3 Hz) and 7.81 (1H, d, J= 3 Hz) (meta coupling) were characteristic of H-2`, H-6`, respectively, which means the B-ring is 3`, 4`and 5` methoxylated. The aromatic proton signal at δ 7.2 (1H, s) was assigned to H-8 while broad signal observed at δ 7.83 was assigned to OH-5, which means the A ring is 6 ,7- methoxylated. The molecular formula of compound A1 was established as $C_{20}O_8H_{22}$ from the mass spectral analysis that showed a molecular weight [M]- at m/z 390. Other significant peaks were attributed to Retro-Diels-Alder fragmentation which supported a structure of a hexa oxygenated flavanone having one hydroxyl and five methoxy groups.

In the 1H-NMR spectrum, of Compound A_2, the characteristic proton signals for H-2 (δ 5.45, 1H, dd, J= 8, 4 Hz), H-3cis (δ 2.1, 1H, dd, J= 4, 8 Hz) and H-3trans (δ 2.2, 1H,dd, J= 4, 8 Hz) were recorded (23) that verified the compound was a flavanone. The signals at δ 3.3-3.95 could be assigned to methoxy groups. Two aromatic proton signals at δ 7.4 (1H, d, J= 3 Hz) and 7 (1H, d, J= 3 Hz) (meta coupling) were characteristic of H-2`, H-6`, respectively, which means the B-ring is 3`, 4`and 5` methoxylated. The signals at δ 1.3 and δ 1.4 represented rhamnose methyl groups, those at around δ 4.2-4.4 and δ 6.81 corresponded to rhamnose hydro groups, which means the A ring is 5,6 and 7 methoylated.

The molecular formula of compound A2 was established as $C_{33}O_{17}H_{44}$ from the mass spectral analysis that showed a molecular weight [M]- at m/z 712, and significant peaks at m/z 402, 304, 210, 196 and 147 (base peak) were attributed to Retro-Diels-Alder fragmentation (17) which supported a structure of hexa methoxy flavanones.

Based on the previously mentioned discussion, the structure of compound A2 could be identified as hexamethoxy flavanone-O-[rhamnopyranosyl- (1 → 4)-rhamnopyranoside]. This was confirmed by comparison with the published data (23). This is the first isolation of this compound from Murraya paniculata.

5. Conclusion

Murraya paniculata extracts and fractions showed potent antioxidant activity and also promising anticancer activity against three types of human cancer cell lines. Isolation and identification of new flavonoids may be promising for discovery of new antioxidant and anticancer drugs of natural origin.

6. Recommendation

Further in vivo and clinical research investigations are recommended to nominate the plant medicinal applications.

7. Conflicts of interest

Authors have no conflicts of interest.

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