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Antimalarial, cytotoxic and antioxidant activities of 14 medicinal plants from Sudan

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ABSTRACT: Fourteen plants endogenous to Sudan were selected to evaluate their total phenolic content, antioxidant, antimalarial and cytotoxicity potential in the present work. Extracts were prepared by maceration of each plant material in chloroform: methanol (C: M; 1:1 v/v) mixture. The antioxidant activity was determined by measuring the radical scavenging effects against 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), and ferric-reducing (FRAP) capacity. The antiplasmodial activity was determined using the NF54 strain of *Plasmodium falciparum*. Cytotoxicity was evaluated towards human colorectal carcinoma cell line (HCT-116), human hormone-sensitive and invasive breast cancer cell line (MCF-7), and human hormone-resistant breast cancer cell line (MDA-MB-231), in addition to endothelial normal EAhy-296 cell line. Results showed that the plants' total phenolic and flavonoid contents were variable. Of the 14 plant species, only *Burnatia enneandra* showed high *in vitro* antiplasmodial activity (IC_{50} 5758 ng/mL). Some plants possessed considerable free radical scavenging ability and reducing power. *Coccinia grandis* fruit extract (IC_{50} 13.23 $\pm$ 0.51 μg/mL) and Geigeria alata root extract (IC_{50} 35.54 $\pm$ 0.27 μg/mL) displayed the highest DPPH and ABTS scavenging activity, respectively. *Striga hermonthica* whole plant extract exhibited the highest FRAP reducing power (107.15 $\pm$ 0.11 nmol Fe^{+2}eq./mg). At a 100 μg/mL concentration, *Dioscorea hirtiflora* bulb extract displayed the highest cytotoxicity (74.23 $\pm$ 03.72%), followed by *Mitragyna inermis* fruit extract (65.28 $\pm$ 04.60%) against HCT-116 cell line. *Aerva javanica* leaf extract showed toxicity to the MDA-MB-231 cell line (50.82 $\pm$ 07.46%) at 100 μg/mL. The current study results showed that endogenous medicinal plants might represent a rich source of natural antioxidant, antimalarial and antitumor agents.

1. INTRODUCTION

Chronic diseases represent a significant cause of increased mortality and morbidity cases worldwide. The number of cancer patients is expected to reach 24 million in 2035, as estimated by the International Agency for Research on Cancer (IARC) (Bray et al., 2013). In Sudan, although there is no national, systematic screening programme for cancer registry, the number of diagnosed cancer cases is increasing (Elamin et al., 2015; Elebead et al., 2012). Furthermore, the number of malaria patients was estimated by the WHO as 229 million cases worldwide in 2019, with more than 1.8 million cases from Sudan (OCHA, 2019; WHO, 2020) (WHO, 2020; OCHA, 2019). Several oxidative stress-induced pathological disorders and disease conditions, including diabetes, cancers,

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Table 1
Profile of the investigated plants

Name of Plant	Family	Voucher No	Ailment treated in traditional medicine	References
Aerva javanica (Burm.f.) Juss. ex Schult.	Amaranthaceae	94/19	Wounds, cough, diarrhoea, ulcer, hyperglycaemia	(Ghazali et al., 1997)
Burnatia enneandra Micheli	Alismataceae	2011/BE	Wounds, intestinal parasites	(I.G. Doka, 2012)
Cissus quadrangularis L.	Vitaceae	2014/CQ	Syphilis, dandruff, back pain, wound, rheumatism	(Ghazali et al., 1997; Issa et al., 2018)
Coccinia grandis (L.) Voigt	Cucurbitaceae	1109KD7	Diabetes, cataracts, skin eruptions	(I.G. Doka, 2012)
Dioscorea dumetorum (Kunth) Pax	Dioscoreaceae	1109KD3	Rheumatoid, arthritis	(I.G. Doka, 2012)
Dioscorea hirtiflora Benth.	Dioscoreaceae	1109KD4	Malaria, stomach troubles	(I.G. Doka, 2012)
Fagonia arabica L.	Zygophyllaceae	95/13	Skin allergy	(Issa et al., 2018)
Geigeria alata Benth. & Hook.f. ex Oliv. & Hiern	Compositae	41935/HNC	Diabetes	(Issa et al., 2018)
Leptadenia arborea (Forssk.) Schweinf.	Apocynaceae	99/8	Snake bits	(Ghazali et al., 1997)
Maerua pseudopetalosa (Gilg & Gilg-Ben.) DeWolf	Capparaceae	83/107	Diabetes, sexual debility, hypertension, kidney disorders	(Issa et al., 2018)
Mitragyna inermis (Willd.) Kuntze	Rubiaceae	2013-12/HBD	Diabetes	(Alamin et al., 2015)
Raphionacme splendens Schltr.	Apocynaceae	1109KR6	Famine food	(I. Doka & Yagi, 2009)
Striga hermonthica (Delile) Benth.	Orobanchaceae	2013-16/HBD	Menstrual cramps, diabetes	(Issa et al., 2018)
Tephrosia apollinea (Delile) DC.	Leguminosae	94/16	Swelling, bone fracture, cough, earache, wounds	(Hassan et al., 2014)

aging, neurological, and cardiovascular disorders, generate free radicals (Ramana et al., 2018). Antioxidants play key roles in counteracting oxidative stress by protecting cells against the effects of free radicles. Natural antioxidants are generally categorized into dietary sources, including vegetables, fruits, cereals, and beans and those from medicinal plants and wild herbs (Wilson et al., 2017). Studies have indicated that antioxidants have a high potential to inhibit the development of many diseases, including cancer (Ramana et al., 2018). Nowadays, the pharmaceutical industries are searching for potential natural and safe raw materials to overcome the side effects of synthetic drugs and problems related to drug-resistant (Abdin et al., 2020). Many investigated plant extracts and isolated phyto-components have a wide range of pharmacological properties and could be used as the safest, most effective and natural source instead of chemical drugs. Karunakaran et al. (2020) isolated two anticancer compounds (ananixanthone and trapezifolixanthone) from *Calophyllum macrocarpum* and proved their cytotoxicity against HeLa Chang liver and HEK-293 cell lines. Also, some Omani *Hapllophyllum tuberculatum* species recorded potent antioxidant and intense cytotoxic activities (Al-Muniri & Hossain, 2017). Furthermore, several examined plant extracts exhibited considerable effect against Plasmodium parasites, as displayed by *Syzygium guineense* and *Parinari congensis* extracts (Laryea and Borquaye, 2019) and evaluated by leaf extract of *Fadogia cienkowskii* (Orabueze et al., 2019). Therefore, plants are considered a potential natural source for new lead antimalarial and antitumor compounds and antioxidant agents. The diversity of climates in Sudan results in a wide variety of flora species which comprises about 3137 plant species belonging to 170 families and 1280 genera (H. Khalid et al., 2012). Considering all the issues mentioned above and in an attempt to explore plant-based alternative solutions in promoting health, the objective of this study was to examine 14 medicinal plants, traditionally used in Sudan to cure different diseases, for their antioxidant, antimalarial, and cytotoxic potential and to determine their total phenolic and flavonoid contents. These plants are; *Aerva javanica* (Burm.f.) Juss. ex Schult., *Burnatia enneandra* Micheli, *Cissus quadrangularis* L., *Coccinia grandis* (L.) Voigt, *Dioscorea dumetorum* (Kunth) Pax, *Dioscorea hirtiflora* Benth., *Fagonia arabica* L., Geigeria alata Benth. & Hook.f. ex Oliv. & Hiern, *Leptadenia arborea* (Forssk.) Schweinf., *Maerua pseudopetalosa* (Gilg & Gilg-Ben.) DeWolf, *Mitragyna inermis* (Willd.) Kuntze, *Raphionacme splendens* Schltr., *Striga hermonthica* (Delile) Benth., and *Tephrosia apollinea* (Delile) DC. The identities and traditional medicinal uses of the investigated plants are compiled in Table 1.

2. MATERIALS AND METHODS

2.1. Plant materials

Samples of the selected plants were collected from different regions in Sudan. The plants were identified and authenticated at the Department of Botany, Faculty of Science, University of Khartoum, by Maha Y. Kordofani. Voucher numbers are given in Table 1.

2.2. Preparation of extracts

Samples were dried in the shade at ambient temperature and then grounded into fine powder. Fifty grams of each plant material was macerated in chloroform: methanol (1:1 v/v) solvent for 24 hours, then filtrated and concentrated using a rotary evaporator under reduced pressure and weighed.

2.3. Determination of total phenolic (TPC) and (total flavonoids (TFC) contents

The TPC and TFC were determined by adopting the method described by Wolfe et al. (2003) and Ordoñez et al. (2006). The detailed procedures were given in the Appendix A.

2.4. Pharmacological evaluation

Antioxidant activity of the extracts was estimated using DPPH in vitro method (K.J. Wang et al., 2007), ABTS radical-scavenging activity (Re et al. (1999) Re et al. (1999) and Ferric reducing antioxidant power (FRAP) (Benzie and Strain (1996) Benzie and Strain (1996). The antiplasmodial activity was determined by the in vitro microplate assay against the NF54 strain of *Plasmodium falciparum* (sensitive to all known drugs). A modification of the [3H] hypoxanthine incorporation assay was used (Witschel et al., 2012). Cytotoxicity of the extracts, at concentrations of 50 and 100 μg/mL, was performed as described by Mosmann (1983) using the thiazolyl blue tetrazolium bromide (MTT) procedure. The detailed pharmacological procedures were given in the Appendix A.

2.5. Statistical Analysis

All experiments were performed in triplicate, and the results were expressed as mean $\pm$ standard deviation (SD) values. Significant differences between samples were analyzed using analysis of variance (ANOVA) and Duncan's multiple range test ($P< 0.05$).

3. RESULTS AND DISCUSSION

Plant bioactivity and medicinal aspects are usually linked with various classes of secondary phytochemicals such as phenols, flavonoids, terpenes, etc. Their presence and concentration vary from one plant to another and even from part to another in the same plant, mainly used in Ethnobotany (Kumar et al., 2019).

3.1. Phenolic content

Phenolics are well recognized to exert several biological properties, including antioxidant, antiproliferation, and anti-carcinogenic activities (Wilson et al., 2017). Accordingly, the total polyphenolics and flavonoids contents of the studied plant's extracts were determined (Table 2). The values of total polyphenolic content were ranged between 11.78 $\pm$ 0.07 to 94.43 $\pm$ 0.63 μg gallic acid eq/mg extract. *G. alata* exhibited the highest phenolic content, followed by *D. hirtiflora* (66.45 $\pm$ 0.30 μg gallic acid eq./mg), *L. arborea* (stem) (57.25 $\pm$ 1.37 μg gallic acid eq./mg), *C. quadrangularis* (56.01 $\pm$ 0.64 μg gallic acid eq./mg), *M. inermis* (51.25 $\pm$ 0.51 μg gallic acid eq./mg) and *S. hermonthica* (51.05 $\pm$ 0.07 μg gallic acid eq./mg). Other species extracts had total polyphenolic content of less than 40 μg gallic acid eq./mg.

The total flavonoid content values in the extracts ranged between 2.63 $\pm$ 0.03 to 31.81 $\pm$ 0.74 μg quercetin eq./mg extract. The extract of *S. hermonthica* showed the highest flavonoid content followed by that of *G. alata* (30.20 $\pm$ 0.79 μg quercetin eq./mg extract), *L. arborea* (stem) (25.32$\pm$1.66 μg quercetin eq./mg extract), *L. arborea* (leaf) (24.88$\pm$0.41 μg quercetin eq./mg extract), *C. quadrangularis* (24.52$\pm$0.65 μg quercetin eq./mg extract), *Aerva javanica* (22.86$\pm$0.95 μg quercetin eq./mg extract) and *D. dumetorum* (19.92$\pm$0.26 μg quercetin eq./mg extract) respectively. Other species extracts showed total flavonoid content < 11 μg quercetin eq./mg extract.

3.2. Antioxidant activity

The antioxidant capacity for the selected 14 plant extracts was evaluated using three complementary assays; DPPH, ABTS and FRAP (Table 2). Different extracts exhibited various free radical scavenging activities, as indicated by their IC_{50} values. In the DPPH assay, the IC_{50} values of plants extracts ranged from 13.23 to 1233.24 μg/mL. *C. grandis* displayed the highest DPPH scavenging activity, followed by *S. hermonthica* (IC_{50} 28.14$\pm$0.25 μg/mL), *D. hirtiflora* (IC_{50} 47.28$\pm$3.24 μg/mL), M. inermis (IC_{50} 66.69$\pm$1.12 μg/mL), *G. alata* (IC_{50} 68.54$\pm$0.71 μg/mL) respectively. The IC_{50} values of different plant extracts ranged from 35.54 to 712.72 μg/mL from the ABTS assay. The highest ABTS scavenging activity was obtained from G. alata, followed by *D. hirtiflora* (IC_{50} 59.9 μg/mL), *S. hermonthica* (IC_{50} 71.21 μg/mL) and *M. inermis* (IC_{50} 73.19 μg/mL) respectively. From the FRAP assay values (were ranged from 43.24 $\pm$0.62 to 107.15$\pm$0.11 nmol Fe^{+2} eq./mg where *S. hermonthica* exhibited the highest FRAP reducing power (107.15 $\pm$ 0.11 nmol Fe^{+2} eq./mg), followed by *B. enneandra* (106.31 $\pm$ 0.92 nmol Fe^{+2} eq./mg), *A. javanica* (100.71 $\pm$ 0.4992 nmol Fe^{+2}eq./mg), *L. arborea* (stem) (99.76 $\pm$ 3.42 nmol Fe^{+2} eq./mg), *C. quadrangularis* (96.38 $\pm$ 2.69 nmol Fe^{+2} eq./mg), *G. alata* (83.13 $\pm$ 0.86 nmol Fe^{+2} eq./mg) and *M. inermis* (82.69 $\pm$ 1.18 nmol Fe^{+2} eq./mg) respectively.

It was clear that extracts displayed variable antioxidant capacity in different assays. Although both ABTS and DPPH assays are associated with electron and radical scavenging, the studied extracts revealed variable capacity in both assays. This observation has been reported previously, where it was suggested that factors like stereo-selectivity of the radicals or the solubility of the extracts in different testing systems affect the capacity of extracts to react and quench other radicals (Jimoh et al., 2010). The observed high antioxidant activity of some plant extracts may be attributed to high concentrations of phenolic compounds with potential protective effects (Spanou et al., 2010). Furthermore, these findings supported previous results on the antioxidant activity of *S. hermonthica* (Kiendrebeogo

Table 2
Phenolic contents and antioxidant activity of extracts of the investigated plants.

Name of Plant	Part used	TPC ^{A}	TFC ^{B}	DPPH ^{C}	ABTS ^{C}	FRAP ^{D}
Aerva javanica	leaf	39.96 ± 0.36^d	22.86 ± 0.95^b	154.09 ± 4.49^d	133.67 ± 7.50^e	100.71 ± 0.49^b
Burnatia enneandra	Fruit	32.01 ± 0.30^d	10.88 ± 6.60^d	183.05 ± 4.32^d	162.26 ± 14.94^e	106.31 ± 0.92^a
Cissus quadrangularis	Whole plant	56.01 ± 0.64^b	24.52 ± 0.65^b	89.02 ± 2.80^c	82.72 ± 4.12^c	96.38 ± 2.69^b
Coccinia grandis	Fruit	31.35 ± 0.47^d	04.95 ± 0.10^e	$13.\ 23 \pm 0.51^a$	181.81 ± 12.80^f	60.44 ± 1.49^e
Dioscorea dumetorum	Tuber	22.94 ± 0.24^e	19.92 ± 0.26^c	215.15 ± 16.03^e	299.84 ± 24.87^g	69.15 ± 0.16^d
Dioscorea hirtiflora	Tuber	66.45 ± 0.30^b	08.32 ± 0.57^d	47.28 ± 3.24^b	59.90 ± 7.50^b	78.61 ± 1.32^c
Fagonia arabica	Whole plant	39.18 ± 1.14^d	09.43 ± 0.13^d	272.67 ± 6.82^e	98.95 ± 4.32^d	55.96 ± 0.33^e
Geigeria alata	Root	94.43 ± 0.63^a	30.20 ± 0.79^a	68.54 ± 0.71^b	35.54 ± 0.27^a	83.13 ± 0.86^c
Leptadenia arborea	Stem	57.25 ± 1.37^b	25.32 ± 1.66^b	88.28 ± 1.70^c	94.85 ± 3.41^d	99.76 ± 3.42^b
	leaf	30.57 ± 0.07^d	24.88 ± 0.41^b	127.78 ± 3.89^d	137.07 ± 1.67^e	71.50 ± 1.40^d
Maerua pseudopetalosa	Seed	11.78 ± 0.07^f	8.84 ± 0.20^d	1233.24 ± 28.3^g	482.24 ± 136.9^h	43.24 ± 0.62^f
Mitragyna inermis	Leaf	51.25 ± 0.51^c	10.94 ± 0.97^d	66.69 ± 1.12^b	73.19 ± 1.90^c	82.69 ± 1.18^c
Raphionacme splendens	Root	27.31 ± 0.30^e	02.63 ± 0.03^e	197.35 ± 26.02^d	182.41 ± 4.72^f	61.98 ± 0.23^e
Striga hermonthica	Whole plant	51.05 ± 0.07^c	31.81 ± 0.74^a	28.14 ± 0.25^a	71.21 ± 1.28^c	107.15 ± 0.11^a
Tephrosia apollinea	Seed	12.89 ± 0.26^f	01.54 ± 0.01^f	423.73 ± 9.11^f	712.72 ± 185.1^i	51.01 ± 0.57^e

^{A}, Total polyphenolic content (μg gallic acid eq/mg extract); ^{B}, Total flavonoid content (μg quercetin eq./mg extract); ^{C}, IC_{50} (μg/mL); ^{D}, nmol Fe^{+2} eq./mg extract. Extract: chloroform:methanol (1:1). Different superscript letters in the same column indicate significant difference ($p < 0.05$).

et al., 2005), *C. grandis* (Deshpande et al., 2011), *C. quadrangularis* (Prabhavathi et al., 2016; Tiwari et al., 2021), *D. hirtiflora* (Adeniran et al., 2020; Sonibare & Abegunde, 2012), G. alata (Zheleva-Dimitrova et al., 2017) and M. inermis (Ouédraogo et al., 2020) using different extraction solvents.

3.3. Antimalarial activity

In vitro antimalarial activity was measured using the chloroquine-sensitive NF54 strains of *Plasmodium falciparum* (Table 3). Of the 14 plant species, only B. enneandra showed considerable *in vitro* antiplasmodial activity with an IC_{50} value of 5758 ng/mL. However, except for determining total phenolic content, this plant has never been investigated for its secondary metabolite content. Other plants extract showed IC_{50} value >10 000 ng/mL. However, some of these plant species are reported to be used to treat malaria in other countries and were found to exert antiplasmodial activity in other plasmodial strains (Philip et al., 2017; Tefera & Kim, 2019).

For example, leaves of *M. inermis* is used to treat malaria in Guinea, and an antiplasmodial activity test on strain W2 showed that it has potent activity with an IC_{50} value of 4.32 μg/mL (Traoré et al., 2015). Leaf of *C. grandis* possessed antiplasmodial activity against *P. falciparum* with an inhibition value of 69 % (Ravikumar et al., 2012). *S. hermonthica* exhibited a high intrinsic antimalarial activity (68.5% suppression of parasitaemia) against *P. berghei* in mice (Okpako & Ajaiyeoba, 2004). Dichloromethane extract of C. quadrangularis whole plant had moderate (IC_{50} 23.9 μg/mL) antiplasmodial activity against *P. falciparum* chloroquine-sensitive strain 3D7 (Bah et al., 2007). Leaves and roots of *D. dumetorum* are commonly used to treat malarias in Southwest Negeria (Dike et al., 2012), but no scientific evidence was found. Moreover, pure compounds, tephroglabrin, (-)-semiglabrin, semiglabrinone, (+)-glabratephrin isolated from T. apollinea were found to be inactive against P. falciparum (S.A. Khalid et al., 1986). Thus, it could be concluded that the antimalarial activity of plant extracts depends on many factors, among them the type of extract and plasmodial strains.

Table 3
In vitro inhibition of plant species extracts under the study against *Plasmodium falciparum* strain NF54.

Name of Plant	Part used	IC_{50} NF54 (ng/mL)
Aerva javanica	leaf	> 10 000
Burnatia enneandra	Fruit	5758
Cissus quadrangularis	Whole plant	> 10 000
Coccinia grandis	Fruit	> 10 000
Dioscorea dumetorum	Tuber	> 10 000
Dioscorea hirtiflora	Tuber	> 10 000
Fagonia arabica	Whole plant	> 10 000
Geigeria alata	Root	> 10 000
Leptadenia arborea	Stem	> 10 000
	leaf	> 10 000
Maerua pseudopetalosa	Seed	> 10 000
Mitragyna inermis	Leaf	> 10 000
Raphionacme splendens	Root	> 10 000
Striga hermonthica	Whole plant	> 10 000
Tephrosia apollinea	Seed	> 10 000
Chloroquine	Standard	2500
Artesunate	Standard	1400

*Extract: chloroform:methanol (1:1).

3.4. Cytotoxicity

The cytotoxicity of the 15 plant extracts against three cancerous cell lines, HCT 116, MCF 7 and MDA-MB-231, in addition, to one human normal cell line, EAhy 926, were determined after treatment with 50 and 100 μg/mL of extracts for 48 hours (Figure 1). Cytotoxicity of extracts against HCT 116 showed that at 50 μg/mL, *D. hirtiflora* displayed

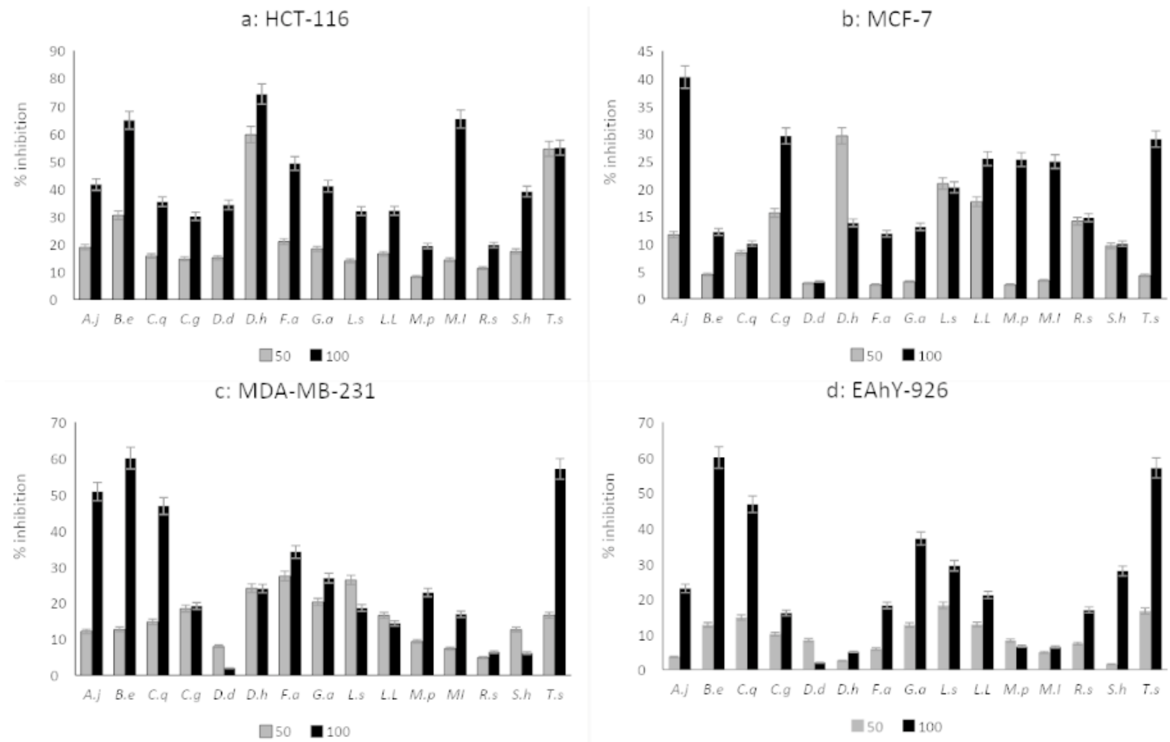

Figure 1. Cytotoxicity of 15crude extracts of investigated plants towards HCT-116, MCF-7, MDA-MB-231 andEAhy-296 cells lines at concentrations 50 and 100 μg/mL for 48 hours. A.j, *Aerva javanica*; B.e, *Burnatia enneandra*; C.q, *Cissus quadrangulari*;C.g, *Coccinia grandes*; D.d, *Dioscorea dumetorum*; D.h, *Dioscorea hirtiflora*; F.a, *Fagonia arabica*; G.a, Geigeria alata; L.s & L.l, *Leptadenia arborea* (s:stem, l:leaf);M.p, *Maerua pseudopetalosa*; M.i, *Mitragyna inermis*; R.s, *Raphionacme splendens*; S.h, *Striga hermonthica*; T.a, *Tephrosia apollinea*.
Different superscript letters indicate significant difference ($p<0.05$).

cytotoxicity with inhibition values of 59.59 ± 13.03%. At 100 μg/mL, the same extract displayed the highest cytotoxicity (74.23 ± 03.72%), followed by those of *M. inermis* (65.28 ± 04.60%) and *B. enneandra* (64.79 ± 02.05%) respectively (Figure 1-a). All the 15 studied extracts did not exert cytotoxicity against the MCF-7 cells line at both concentrations used (Figure 1-b). Extract of *A. javanica* was the only extract with toxicity against the MDA-MB-231 cell line with an inhibition value equal to 50.82 ± 07.46% at 100 μg/mL (Figure 1-c). Furthermore, all extracts were not toxic to human normal cell line EAhy-926 at 50 μg/mL. Nevertheless, at 100 μg/mL, *B. enneandra* and *T. apollinea* extracts were relatively toxic (60.04 ± 01.21% and 57.07 ± 03.11%, respectively), while all other extracts were not toxic (Figure 1-d).

The results of cytotoxicity screening of the present study revealed that D. hirtiflora and *M. inermis* displayed interesting cytotoxic effects towards HCT -116. Both plant species were not toxic to the normal EAhY-926 cell line. No published data on the antitumor activity of *D. hirtiflora*, *A. javanica* and *B. enneandra* were found. However, the antitumor effect of other Dioscorea spp like *D. bulbifera* (J.M. Wang et al., 2012), *D. esculenta* (Murugan & Mohan, 2012), and *D. opposite* (Liu et al., 2016; Zhang et al., 2016) was reported. A previous study on *M. inermis* showed that the alkaloid rich extract did not exert mutagenic or genotoxic activity (Traore et al., 2000)

4. CONCLUSION

In conclusion, the results obtained in this study showed that total polyphenolic and flavonoid contents and antioxidant activity differ among extracts of the studied medicinal plants. Some of these medicinal plants are promising sources of natural antioxidants. Results of antiplasmodial activity demonstrated that *B. enneandra* could be a potential source of antimalarial agent(s). Cytotoxicity screening suggested that *D. hirtiflora* and *M. inermis* are promising candidates with antitumor activity. It is well known that plant extracts comprise mixtures of complex metabolites, which exert their action on different levels and through several mechanisms. Thus, isolation and determination of bioactive molecule(s) responsible for the antitumor activity of these two species and their mode of action are warranted to evaluate their potential for cancer therapy. Moreover, bioassay-guided fractionation of crude extracts of *B. enneandra* would be interesting to determine and verify whether the same constituents or different ones exert their toxicity towards cancer and normal cells. To the best of our knowledge, this is the first report on the cytotoxicity property of these two plants and the antiplasmodial activity of *B. enneandra*.

CONFLICTS OF INTEREST

Given his role as Associate Editor, Gokhan Zengin has not been involved and has no access to information regarding the peer review of this article. Full responsibility for the editorial process for this article was delegated to Editor-in-Chief Carlos L. Cespedes Acuña. All authors reported that there is no conflict of interest associated to this work.

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A. APPENDIX, SUPPLEMENTARY INFORMATION

Supplementary information to this article can be found online at https://doi.org/10.53365/nrfhh/146223.

AUTHOR CONTRIBUTIONS

IBEEB, SY, AAAA, AMA - Research concept and design; IBEEB, MYK, AAQ, EMAS - Collection and/or assembly of data; MYK, AAAA, AAQ, EMAS - Data analysis and interpretation, SY, AAQ, AMA, MAAM, AMAA - Writing the article; SY, AMA, MAAM, AMAA, GZ - Critical revision of the article, GZ - Final approval of the article.

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