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Bioactivities of *Merremia emarginata* (Burm.f.) Hallier f. extracts and isolated compounds

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Abstract: *Merremia emarginata* (Burm.f.) Hallier f. is a wild herb that belongs to the *Convolvulaceae* family. It is used to treat diabetes, epilepsy, rheumatism, kidney and liver disorders in various traditional medicines. Compounds including caffeic acid, rosmeric acid, scopoletin, tetritol, and vanillic acid have been isolated from various parts of this plant species. This comprehensive review work aims to analyze, summarize, and document the bioactivities related to published studies involving *M. emarginata*. PubMed, ScienceDirect, Scopus, Semantic Scholar, and Web of Science electronic databases were used to obtain the relevant published articles from 1900 to May 2021. There is *in vivo* and *in vitro* scientific evidence is currently available for various bioactivities. So far, there is scientific evidence available for analgesic, antiarthritic, antibacterial, anticancer, antidiabetic, antifungal, antiinflammatory, antioxidant, antipyretic, diuretic, antiurolithiatic, and nephroprotective activities and four bioactive compounds (cynarin, diacetyl, scopoletin, and tetritol) have been identified in this plant species. This work provides the basis for future researches involving this plant species.

Keywords: Bioactivity; *Convolvulaceae; Merremia emarginata;* Siddha Medicine; Sri Lanka.

1. Introduction

Merremia emarginata (Burm.f.) Hallier f. [synonym: *Convolvulus excisus* Zipp. ex Span.; *C. reniformis* Roxb.; *Evolvulus emarginatus* Burm.f.; *E. glechoma* Welw.; *Ipomoea cymbalaria* Fenzl; *I. emarginata* (Burm.f.) Kuntze; *I. gangetica* Voigt; *I. reniformis* (Roxb.) Sweet; and *Lepistemon reniformis* (Roxb.) Hassk.] is a wild herb that belongs to the *Convolvulaceae* family. It is called பூமிசக்கரை (Poomisakkarai) in Tamil / Siddha Medicine and Aakhukarni, Aakhuparni, Aakhuparnika, Muusaakarni, and Undurukarnikaa in Ayurveda Medicine. This plant species is native to Asia (Sri Lanka, India, Nepal, Bangladesh, Malaysia, China, Indonesia, Myanmar, Philippines, and Thailand), Oceania (New Guinea), and Africa (Mauritania, Angola, Cameroon, Burkina, Burundi, Sudan, Chad, Uganda, Ethiopia, Tanzania, and Zaïre) and it has been introduced into Madagascar (Africa) (Kew Science, 2021). Moreover, *M. emarginata* is used as a food and medicinal plant. It is used to treat abscesses, cough, diabetes, ear sores, epilepsy, fever, headache, migraine, neuralgia, rheumatism, worms, wounds, cutaneous, eye, gum, kidney, liver, nasal, and

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skin disorders in various traditional medicines (Khare, 2007; Sathasivampillai et al., 2017, 2018, 2016, 2015). Compounds including1,3-dicaffeoylquinic acid; 3,5-dicaffeoylquinic acid; 3-carboxyl-2-(3,4-dihydroxyphenyl)-2,3-dihydro-7-hydroxy-,4-methyl ester,-4 benzofurancarboxyethenylic acid; 3-O-caffeolquinic acid; 4,5-dicaffeoylquinic acid; 4-feruoyl-5-caffeoylquinic acid; 4-myricetin 3-O-galactoside; 4-O-caffeoylquinic acid; 5-O-caffeoylquinic acid; 5-O-coumaroylquinic acid; 5-O-feruloylquinic acid; caffeic acid; caffeine; chlorogenic acid; cynarin; diacetyltetritol; ferulic acid; hippuric acid; myricetin hexoside; protocatechuic acid; quinic acid; rosmeric acid; scopoletin; tetritol; trihydroxy benzenepro panoic acid; and vanillic acid have been isolated from various parts of this plant species (Angappan et al., 2018; Babu et al., 2013; Rameshkumar et al., 2013).

This comprehensive review work aims to analyze, summarize, and document the bioactivities related to published studies involving *M. emarginata*. This work will be useful for the researchers who are interested to conduct future bioactivities and phytochemical-related studies using this plant species.

2. Materials and methods

PubMed (https://pubmed.ncbi.nlm.nih.gov), ScienceDirect (https://www.sciencedirect.com), Scopus (https://www.scopus.com), Semantic Scholar (https://www.semanticscholar.org), and Web of Science (http://www.webofknowledge.com) electronic databases were used to obtain the relevant published articles from 1900 to May 2021. "*Merremia emarginata"* was employed as a search term, and only bioactivities related to published articles were considered in this work.

3. Reported bioactivities of *M. emarginata*

Level of scientific evidence, bioactivity, part used, extract / fraction / compound, assay / model, dose / concentration, and reference of published bioactivities related studies are presented in Table 1. There are *in vivo* and *in vitro* scientific evidence is currently available for various bioactivities. However, the majority of the studies provide *in vitro* scientific evidence. So far, there is scientific evidence available for analgesic, antiarthritic, antibacterial, anticancer, antidiabetic, antifungal, antiinflammatory, antioxidant, antipyretic, diuretic, antiurolithiatic, and nephroprotective activities (Angappan et al., 2018; Babu et al., 2013, 2009; Baskar et al., 2012; Devadasu et al., 2017; Elumalai et al., 2011; Gandhi and Sasikumar, 2012; Indumathy et al., 2011; Kamakshi et al., 2017, 2017; Parkavi et al., 2020; Prabhu et al., 2019, 2011, 2012; Priya et al., 2012; Purushoth Prabhu et al., 2012; Rameshkumar, 2012; Rameshkumar et al., 2013, 2012). Anyway, antioxidant activity has the highest number of studies. There is *in vivo* evidence for analgesic, antiarthritic, antidiabetic, antiinflammatory, antipyretic, diuretic, and nephroprotective activities and *in vitro* evidence for antiarthritic, antibacterial, anticancer, antidiabetic, antifungal, antiinflammatory, and antioxidant activities. Leaves and whole plant of *M. emarginata* showed various bioactivities while leaves were used in more studies. Up to now, four bioactive compounds (cynarin, diacetyl, scopoletin, and tetritol) have been identified in this plant species (Babu et al., 2013). Presently, traditional medicinal uses to treat such as diabetes, rheumatism, fever, and kidney diseases have scientific evidence (Gandhi and Sasikumar, 2012; Indumathy et al., 2011; Purushoth Prabhu et al., 2012; Rameshkumar et al., 2013). However, the traditional medicinal uses to treat disorders like epilepsy, headache, and migraine have no scientific evidence. Only significant studies which involve the highest level of scientific evidence available, the lowest concentration / dose used and active compounds identified are deliberated in detail beneath.

3.1. Reported *in vivo* studies

3.1.1. Analgesic activity

Ethanol (80%) extract of the leaf (200 mg/kg) intraperitoneally administered to acetic acid-induced writhing and tail immersion mice. After 45 minutes, there was a significant reduction in the writhing count in acetic acid-induced writhing mice and there was a significant increase in the reaction time in tail immersion mice. Pethidine (30 mg/kg) was used as a standard drug in this study (Priya et al., 2012).

3.1.2. Antiarthritic activity

Purushoth Prabhu et al. (2012), ethanol extract prepared using the whole plant administered to complete Freund's adjuvant-induced arthritic rats at a dose of 400 mg/kg for 21 days exhibited antiarthritic activity. Methotrexate was used as a standard drug at 10 mg/kg in this study (Purushoth Prabhu et al., 2012).

3.1.3. Antidiabetic activity

Whole plant methanol extract at a dose of 100 mg/kg was orally administered to Streptozotocin-induced diabetic rats for 28 days. The results showed that there was a significant reduction in the elevated blood glucose level. Glibenclamide (2.5 mg/kg) was used as a standard drug in this research (Gandhi and Sasikumar, 2012).

3.1.4. Antiinflammatory activity

Purushoth Prabhu et al. (2012) studied the antiinflammatory activity of whole plant ethanol extract (400 mg/kg) in Carrageenan-induced rat paw edema rats. After 5 hours, it was noticed that there was a decrease of 74% inhibition. Indomethacin was used as a standard drug in this study. However, the authors did not state the dose of the standard drug they used in this study (Purushoth Prabhu et al., 2012).

3.1.5. Antipyretic activity

Leaves were used to prepare ethanol (80%) extract and this extract was injected at a dose of 200 mg/kg to cow's milk-induced pyrexia rats. After 3 hours, remarkable antipyretic activity was observed. Paracetamol (150 mg/kg) was used as a standard drug in this study (Indumathy et al., 2011).

3.1.6. Diuretic activity

Aqueous extract of leaves (200 mg/kg) was orally administered to rats. After 5 hours, it was observed that diuretic effects were induced without any side effects. Furosemide (20 mg/kg) was used as a standard drug (Angappan et al., 2018).

3.1.7. Nephroprotective activity

Rameshkumar et al. (2013) studied the nephroprotective activity of leaf ethanol (70%) extract in gentamicin-induced nephrotoxic rats at a dose of 150 mg/kg. After fifteen days, the histopathology studies exhibited that there was a significant regeneration in tubular epithelial and glomerular cells in the damaged kidney (Rameshkumar et al., 2013).

3.2. Reported *in vitro* studies

3.2.1. Antibacterial activity

Aqueous, methanol, and petroleum ether extracts prepared using leaves exhibited antibacterial activities at a concentration of 10 µg/ml in *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus,* and *Bacillus cereus* assays in agar well diffusion method. Penicillin (10 µg/ml) was utilized as a positive control in this investigation (Elumalai et al., 2011).

3.2.2. Anticancer activity

In a study performed by Prabhu et al. (2012), ethyl acetate fraction of whole plant ethanol extract showed the anticancer activity in human breast carcinoma MCF cell line assay at IC_{50} of 39.6 µg/ml. 5-Fluorouracil was used as a positive control had an IC_{50} of 15.3 µg/ml (Prabhu et al., 2012).

3.2.3. Antifungal activity

Ethyl acetate extract at 25 µg/ml concentration revealed antifungal activities in *Aspergillus niger* and *Candida albicans* assays. However, the authors did not mention the part used in their study. Fluconazole (75 µg/ml) was used a positive control in this investigation (Devadasu et al., 2017).

3.2.4. Antiinflammatory activity

Thus far, three antiinflammatory compounds (Diacetyl tetrytol, Scopoletin, and Tetritol) have been isolated from the whole plant of this plant species. Within these three compounds, Scopoletin showed the antiinflammatory activity at IC_{50} of 2.2 µg/ml in 5-lipoxygenase inhibitory assay (Babu et al., 2013).

3.2.5. Antioxidant activity

So far, three antioxidant compounds (Cynarin, Scopoletin, and Tetritol) have been identified in the whole plant of *M. emarginata.* Among them, Cynarin (IC_{50} 3.7 µg/ml) showed the best antioxidant activity in superoxide scavenging assay. Vitamin C (IC_{50} 3.71 µg/ml) was used as a positive control in this study (Babu et al., 2013).

3.2.6. Antiurolithiatic activity

Methanol extract unveiled antiurolithiatic activity in Calcium oxalate dissolution and Calcium phosphate dissolution assays. Anyway, the authors did not state the part used and the concentrations used in this study (Kamakshi et al., 2017).

3.3. Toxicity studies

Methanol extract of the whole plant at a dose of 4000 mg/kg orally administered to rats for 3 days showed no mortality or toxic effects (Gandhi and Sasikumar, 2012). In another study carried out by Purushoth Prabhu et al. (2012), 2000 mg/kg of ethanol whole plant extract was orally administered to rats for 7 days also, did not show any adverse effect or mortality (Purushoth Prabhu et al., 2012).

Table 1. Reported bioactivities of *M. emarginata*.

Level of scientific evidence	Bioactivity	Part used	Extract / fraction / compound	Assay / model	Dose / concentration	Reference
In vivo	Analgesic	Leaf	Ethanol (80%)	Acetic acid-induced writhing, Tail immersion	200 mg/kg	Priya et al. (2012)
In vivo	Analgesic	Whole plant	Ethanol	Hot plate analgesia	400 mg/kg	Purushoth Prabhu et al. (2012)
In vivo	Antiarthritic	Whole plant	Ethanol	Complete Freund's adjuvant	400 mg/kg	Purushoth Prabhu et al. (2012)
In vivo	Antidiabetic	Whole plant	Methanol	Streptozotocin-induced diabetic	100 mg/kg	Gandhi and Sasikumar (2012)
In vivo	Antiinflammatory	Whole plant	Ethanol	Carrageenan-induced rat paw edema	400 mg/kg	Purushoth Prabhu et al. (2012)
In vivo	Antipyretic	Leaf	Ethanol (80%)	Milk-induced pyrexia	200 mg/kg	Indumathy et al. (2011)
In vivo	Diuretic	Leaf	Aqueous	Rat	200 mg/kg	Angappan et al. (2018)
In vivo	Nephroprotective	Leaf	Ethanol (70%)	Gentamicin-induced nephrotoxic	150 mg/kg	Rameshkumar et al. (2013)
In vivo	Nephroprotective	NS	NS	Gentamicin-induced nephrotoxic	150 mg/kg	Rameshkumar (2012)
In vitro	Antiarthritic	Whole plant	Ethanol, Ethanol (Chloroform, Ethyl acetate, Hexane, and Methanol fractions)	Protein denaturation inhibitory	250 µg/ml	Prabhu et al. (2019)
In vitro	Antibacterial	Leaf	Aqueous, Methanol, Petroleum ether	*Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*	10 µg/ml	Elumalai et al. (2011)
In vitro	Antibacterial	Leaf	Methanol, Petroleum ether	*Bacillus cereus*	10 µg/ml	Elumalai et al. (2011)
In vitro	Antibacterial	Leaf	Aqueous	*Escherichia coli*	100 µg	Rameshkumar et al. (2012)

Level of scientific evidence	Bioactivity	Part used	Extract / fraction / compound	Assay / model	Dose / concentration	Reference
In vitro	Antibacterial	NS	Ethyl acetate	*Escherichia coli, Staphylococcus aureus*	800 µg/ml	Devadasu et al. (2017)
In vitro	Antibacterial	Leaf	Methanol	*Acinetobacter baumannii, Enterococcus faecalis, Escherichia coli, Klebsiella pneumonia, Proteus mirabilis, Pseudomonas aeruginosa, Pseudomonas otitidis, Salmonella paratyphi* B, *Staphylococcus aureus*	100 mg/ml	Parkavi et al. (2020)
In vitro	Anticancer	Whole plant	Ethanol (Chloroform fraction)	Human breast carcinoma MCF cell	211.7 µg/ml (IC_{50})	Prabhu et al. (2012)
In vitro	Anticancer	Whole plant	Ethanol (Chloroform fraction)	Human cervical carcinoma Hela cell	235.8 µg/ml (IC_{50})	Prabhu et al. (2012)
In vitro	Anticancer	Whole plant	Ethanol (Ethyl acetate fraction)	Human breast carcinoma MCF cell	39.6 µg/ml (IC_{50})	Prabhu et al. (2012)
In vitro	Anticancer	Whole plant	Ethanol (Ethyl acetate fraction)	Human cervical carcinoma Hela cell	57.6 µg/ml (IC_{50})	Prabhu et al. (2012)
In vitro	Anticancer	Whole plant	Ethanol (Hexane fraction)	Human breast carcinoma MCF cell	434.5 µg/ml (IC_{50})	Prabhu et al. (2012)
In vitro	Anticancer	Whole plant	Ethanol (Hexane fraction)	Human cervical carcinoma Hela cell	418.3 µg/ml (IC_{50})	Prabhu et al. (2012)
In vitro	Anticancer	Whole plant	Ethanol (Methanol fraction)	Human breast carcinoma MCF cell	46.3 µg/ml (IC_{50})	Prabhu et al. (2012)
In vitro	Anticancer	Whole plant	Ethanol (Methanol fraction)	Human cervical carcinoma Hela cell	71.5 µg/ml (IC_{50})	Prabhu et al. (2012)
In vitro	Antidiabetic	NS	Hexane	α-Amylase inhibitory	133.4 µg/ml (IC_{50})	Babu et al. (2009)
In vitro	Antidiabetic	NS	Methanol	α-Amylase inhibitory	104.5 µg/ml (IC_{50})	Babu et al. (2009)
In vitro	Antifungal	NS	Ethyl acetate	*Aspergillus niger, Candida albicans*	25 µg/ml	Devadasu et al. (2017)
In vitro	Antiinflammatory	Whole plant	Diacetyl tetritol	5-Lipoxygenase inhibitory	25.4 µg/ml (IC_{50})	Babu et al. (2013)
In vitro	Antiinflammatory	Whole plant	Scopoletin	5-Lipoxygenase inhibitory	2.2 µg/ml (IC_{50})	Babu et al. (2013)
In vitro	Antiinflammatory	Whole plant	Tetritol	5-Lipoxygenase inhibitory	17.4 µg/ml (IC_{50})	Babu et al. (2013)
In vitro	Antioxidant	Leaf	Aqueous	ABTS scavenging	30.1 µg/ml (IC_{50})	Rameshkumar et al. (2012)
In vitro	Antioxidant	Leaf	Aqueous	DPPH scavenging	86.5 µg/ml (IC_{50})	Rameshkumar et al. (2012)
In vitro	Antioxidant	Leaf	Aqueous	Lipid peroxidation inhibitory (rat liver homogenate)	325 µg/ml (IC_{50})	Rameshkumar et al. (2012)
In vitro	Antioxidant	Leaf	Aqueous	Superoxide anion scavenging	40.3 µg/ml (IC_{50})	Rameshkumar et al. (2012)

Level of scientific evidence	Bioactivity	Part used	Extract / fraction / compound	Assay / model	Dose / concentration	Reference
In vitro	Antioxidant	Leaf	Methanol	DPPH scavenging	200 µg/ml	Parkavi et al. (2020)
In vitro	Antioxidant	NS	Ethanol	DPPH scavenging	12.5 µg/ml	Devadasu et al. (2017)
In vitro	Antioxidant	NS	Methanol	DPPH scavenging	8.6 µg/ml (IC_{50})	Babu et al. (2009)
In vitro	Antioxidant	Whole plant	Cynarin	DPPH scavenging	3.7 µg/ml (IC_{50})	Babu et al. (2013)
In vitro	Antioxidant	Whole plant	Ethanol	ABTS scavenging	14.6 µg/ml (IC_{50})	Prabhu et al. (2019)
In vitro	Antioxidant	Whole plant	Ethanol	DPPH scavenging	26.5 µg/ml (IC_{50})	Prabhu et al. (2019)
In vitro	Antioxidant	Whole plant	Ethanol	H_2O_2 scavenging	77.6 µg/ml (IC_{50})	Prabhu et al. (2019)
In vitro	Antioxidant	Whole plant	Ethanol	OH scavenging	100 µg/ml (IC_{50})	Prabhu et al. (2019)
In vitro	Antioxidant	Whole plant	Ethanol (Chloroform fraction)	ABTS scavenging	36.7 µg/ml (IC_{50})	Prabhu et al. (2019)
In vitro	Antioxidant	Whole plant	Ethanol (Chloroform fraction)	DPPH scavenging	67.7 µg/ml (IC_{50})	Prabhu et al. (2019)
In vitro	Antioxidant	Whole plant	Ethanol (Chloroform fraction)	H_2O_2 scavenging	100 µg/ml (IC_{50})	Prabhu et al. (2019)
In vitro	Antioxidant	Whole plant	Ethanol (Chloroform fraction)	OH scavenging	100 µg/ml (IC_{50})	Prabhu et al. (2019)
In vitro	Antioxidant	Whole plant	Ethanol (Ethyl acetate fraction)	ABTS scavenging	23.8 µg/ml (IC_{50})	Prabhu et al. (2019)
In vitro	Antioxidant	Whole plant	Ethanol (Ethyl acetate fraction)	DPPH scavenging	45.7 µg/ml (IC_{50})	Prabhu et al. (2019)
In vitro	Antioxidant	Whole plant	Ethanol (Ethyl acetate fraction)	H_2O_2 scavenging	100 µg/ml (IC_{50})	Prabhu et al. (2019)
In vitro	Antioxidant	Whole plant	Ethanol (Ethyl acetate fraction)	OH scavenging	100 µg/ml (IC_{50})	Prabhu et al. (2019)
In vitro	Antioxidant	Whole plant	Ethanol (Hexane fraction)	ABTS scavenging	37.8 µg/ml (IC_{50})	Prabhu et al. (2019)
In vitro	Antioxidant	Whole plant	Ethanol (Hexane fraction)	DPPH scavenging	78.7 µg/ml (IC_{50})	Prabhu et al. (2019)
In vitro	Antioxidant	Whole plant	Ethanol (Hexane fraction)	H_2O_2 scavenging	100 µg/ml (IC_{50})	Prabhu et al. (2019)
In vitro	Antioxidant	Whole plant	Ethanol (Hexane fraction)	OH scavenging	100 µg/ml (IC_{50})	Prabhu et al. (2019)
In vitro	Antioxidant	Whole plant	Ethanol (Methanol fraction)	ABTS scavenging	18.6 µg/ml (IC_{50})	Prabhu et al. (2019)
In vitro	Antioxidant	Whole plant	Ethanol (Methanol fraction)	DPPH scavenging	27.5 µg/ml (IC_{50})	Prabhu et al. (2019)
In vitro	Antioxidant	Whole plant	Ethanol (Methanol fraction)	H_2O_2 scavenging	85.6 µg/ml (IC_{50})	Prabhu et al. (2019)

Level of scientific evidence	Bioactivity	Part used	Extract / fraction / compound	Assay / model	Dose / concentration	Reference
In vitro	Antioxidant	Whole plant	Ethanol (Methanol fraction)	OH scavenging	100 µg/ml (IC_{50})	Prabhu et al. (2019)
In vitro	Antioxidant	Whole plant	Scopoletin	DPPH scavenging	89.2 µg/ml (IC_{50})	Babu et al. (2013)
In vitro	Antioxidant	Whole plant	Tetritol	DPPH scavenging	25.1 µg/ml (IC_{50})	Babu et al. (2013)
In vitro	Antioxidant	Whole plant	Tetritol	Superoxide scavenging	7.2 µg/ml (IC_{50})	Babu et al. (2013)
In vitro	Antioxidant	NS	Ethyl acetate	DPPH scavenging	357.1 µg/ml (IC_{50})	Baskar et al. (2012)
In vitro	Antioxidant	NS	Ethyl acetate	NO scavenging	512.8 µg/ml (IC_{50})	Baskar et al. (2012)
In vitro	Antioxidant	NS	Hexane	DPPH scavenging	150.4 µg/ml (IC_{50})	Baskar et al. (2012)
In vitro	Antioxidant	NS	Hexane	NO scavenging	206.1 µg/ml (IC_{50})	Baskar et al. (2012)
In vitro	Antioxidant	NS	Methanol	DPPH scavenging	514.1 µg/ml (IC_{50})	Baskar et al. (2012)
In vitro	Antioxidant	NS	Methanol	NO scavenging	756.1 µg/ml (IC_{50})	Baskar et al. (2012)
In vitro	Antiurolithiatic	NS	Methanol	Calcium oxalate dissolution, Calcium phosphate dissolution	NS	Kamakshi et al. (2017)

Abbreviations: ABTS: 2,2'-azino-bis (3-ethylbenzthiazoline-6-sulphonic acid); DPPH: diphenyl-1-picrylhydrazyl; H_2O_2: Hydrogen peroxide; NO: Nitric oxide; NS: Not stated; OH: Hydroxyl

4. Conclusions

This work analyzed, summarized, and documented the bioactivities related to published work using *M. emarginata.* This plant species has several traditional medicinal uses and at the moment only some of these uses have scientific evidence. Hence, more bioactivities and phytochemical associated researches should be carried out using this plant species for its traditional medicinal uses. Initially, various extracts of different parts of this plant species should be screened for various bioactivities using *in vitro* assays. More consideration should be taken to choose the *in vitro* assays used in the studies and more priority should be given to those illnesses which are challenging at the moment around the world like cancer. Then the extracts showed promising results that should be used to isolate the bioactive compounds from them using the techniques like bioassay guided isolation of the active compounds. Compounds have shown better results could be studied in *in vivo* models and toxicity studies should be conducted for extracts and isolated compounds for safety and efficacy purposes. Extracts and compounds that showed more efficient results should be further studied in clinical trials. These identified bioactive compounds could be lead compounds in future drug discovery researches. Also, the extracts showed better bioactivities should be standardized and make available for everyone to use it. The reaction mechanisms of these extracts should be studies to see the interactions within our bodies. This work provides the basis for future researches involving this plant species.

Conflict of interest

The authors declare that there is no conflict of interest.

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