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Bioactivities of *Anacyclus pyrethrum* (L.) Lag. extracts and natural products

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Abstract

Anacyclus pyrethrum (L.) Lag. is an herb that fits into the *Asteraceae* family. It has been using to treat several disorders include lung infections, liver diseases, nervous system diseases, and rheumatism in ethnomedicines. Compounds including pellitorine, anacycline, spilanthol, pyracyclumine A, and agrocybenine have been isolated from this plant species. Thus, this overview work intends to scrutinize, sum up, and record the available scientific evidence of bioactivity of *A. pyrethrum*. This work would be very convenient for future bioactivity and phytochemical studies of this plant species. Electronic databases such as the Web of Science, Scopus, ScienceDirect, and PubMed were applied to identify appropriate published articles associated with bioactivities of *A. pyrethrum* from 1900 to November 2020. Until now, scientific evidence of bioactivity for various parts of this plant species are existing in clinical, *in vivo*, and *in vitro* studies. Bioactivities are including anesthetic, anti-depressant, anti-epileptic, anti-convulsive, and blood circulatory activities in diverse assays and models. Seven antiprotozoal active compounds and an anti-inflammatory active compound have been identified in *A. pyrethrum*. More bioactivities and phytochemical linked researches should be conducted to generate more scientific evidence for the ethnomedicinal uses. This work scrutinized, summed up, and recorded the currently available scientific evidence of bioactivity of *A. pyrethrum*.

Keywords: *Anacyclus pyrethrum*, *Asteraceae*, Sri Lanka, Siddha Medicine, bioactivities

1. Introduction

Anacyclus pyrethrum (L.) Lag. is an herb that fits into the *Asteraceae* family. It is native to Spain, Morocco, and Algeria and it has been introduced into Sri Lanka, India, Ukraine, Germany, Myanmar, France, and Poland [1]. *A. pyrethrum* has been using to treat several disorders include lung infections, liver diseases, nervous system diseases, sciatica, fever, malaria, paralysis, epilepsy, sore throat, rheumatism, colds, neuralgia, toothache, sleep apnea, diaphoresis, poor blood circulation, salivary gland illnesses, head catarrh, nostril catarrh, and urinary tract infections in ethnomedicines [2-12]. It is also utilized for revitalization and vivacity in Ayurveda [11,13]. *A. pyrethrum* is called Akkarahaaram (அக்கரகாரம்) in Tamil and its root are applied to prepare antidiabetic preparations in Sri Lankan Siddha Medicine [14,15]. Compounds including squalene, stigmasterol, γ-stigmasterol, octadecanoic acid, palmitic acid, pellitorine, N-propylnona-2,5-dienamide, anacycline, N-Methyanacycline, dehydro-anacycline, dehydro-matricaric acid, spilanthol, pyracyclumine A, pyracyclumine B, pyracyclumine C, pyracyclumine D, pyracyclumine E, pyracyclumine F, pyracyclumine G, pyracyclumine H, dodeca-2E,4E-dienoic acid 4-hydroxyphenylethylamide, pyracyclumine I, pyracyclumine J, deca-2E,4E-dienoic acid 4-hydroxyphenylethylamide, tetradeca-2E,4E-dienoic acid 4-hydroxyphenylethyl amide, undeca-2E,4E-diene-8,10-diynoic acid 2-phenylethyl amide, and agrocybenine have been isolated from this plant species using analytical chemistry techniques like liquid chromatography-mass spectrometry (LC-MS), gas chromatography-mass spectrometry (GC-MS), nuclear magnetic resonance spectroscopy (NMR), ultraviolet-visible (UV-Vis.) spectroscopy, and infrared (IR) spectroscopy [16-22].

2. Aims and objectives

Thus far, there is no systematic comprehensive review of bioactivities of *A. pyrethrum*. Thus, this overview work intends to scrutinize, sum up, and record the available bioactive scientific evidence of *A. pyrethrum*. This work would be very convenient for future bioactivity and phytochemical studies of this plant species.

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3. Materials and methods

Electronic databases the Web of Science, Scopus, ScienceDirect, and PubMed were applied to identify appropriate published articles related to bioactivities of *A. pyrethrum* from 1900 to November 2020. The databases used in this review work have greater advantages than Google Scholar. These databases contain multiple organizing functions like categorizing the document type, subject, country, affiliation, and year. Anyhow, not all the abstracts, full articles, and journals obtained from Google Scholar search results are available at the moment for analysis. *"Anacyclus pyrethrum"* (in double quotation marks) was employed as an exploration term and the results were limited to subjects like Pharmacology, Toxicology and Pharmaceutics, Medicine, Biochemistry, Genetics and Molecular Biology, Chemistry, Agricultural and Biological Sciences, and Multidisciplinary and then the reviews were excluded from the document type.

4. Results and discussions

4.1. Bioactivities of *A. pyrethrum*

Search results obtained from the literature review are presented in Table 1. Until now, scientific evidence related to the bioactivity of various parts of this plant species exists for clinical, in vivo, and in vitro studies. However, most of them are in vivo studies. Anesthetic [23,24], antibacterial [17,21,25], anticancer [26], antidementia [27], antidiabetic [28,29], antifungal [21], anti-inflammatory [20,30,31], antilipidemic [28], antimutagenic [32], antioxidant [28,30,33-35], antiprotozoal [36], blood circulatory [37], oxidative DNA damage preventive [33], anabolic [38], androgenic [39], anticonvulsive [30,40-43], antidepressant [44], anti-epileptic [45], aphrodisiac [38,46], fertility improvement [47], hepatoprotective [48], immunomodulatory [4,49,50], neuroprotective [30], reproductive tract [38], and spermatogenic [39] activities in diverse assays and models are available. Anyhow, the majority of the scientific evidence is existing for antioxidant activities and roots revealed a greater number of bioactivities. Further, water has been used in the majority of the studies to prepare the extracts. Seven bioactive compounds such 9,10-dehydropellitorine, deca-2E,4E-dienoic acid 2-phenylethylamide, deca-2E,4E-dienoic acid tyramide, dodeca-2E,4E-dienoic acid 4-hydroxy-2-phenylethylamide, pellitorine, tetradeca-2E,4E,12Z-trien-8,10-diynoic acid isobutylamide, and undeca-2E,4E-dien-8,10-diynoic acid isopentylamide have been identified in A. pyrethrum. Except for deca-2E,4E-dienoic acid tyramide all other compounds have shown antiprotozoal activities in a variety of in vitro assays [36]. Whereas deca-2E,4E-dienoic acid tyramide has been unveiled anti-inflammatory activity [20]. Pellitorine has exhibited both blood circulatory and antiprotozoal activities [36,37]. Hitherto, exclusively scientific evidence is existing for liver diseases, nervous system diseases, sciatica, epilepsy, rheumatism, neuralgia, sleep apnea, and poor blood circulation remedies. Significant studies based on the available lowest concentration/dose of treatment are conferred underneath.

4.2. Clinical trial

4.2.1. *Anesthetic activity*

A solution containing 2% of root alcohol extract (freshly dissolved in sterile distilled water) was administered to 200 dental patients and it exhibited anesthetic activity in extended oral reconstructive surgeries. The extract did not show any side effect and seemed safer at a lower dose. Xylocaine was used as a positive control in this clinical trial [24].

4.3. *In vivo* studies

4.3.1. *Androgenic activity*

A dose of 50 mg/kg of root aqueous and ethanolic extracts was orally administered to rats and noticeable anabolic effects in two different studies were observed [38,39].

4.3.2. *Anticonvulsive activity*

Root ethanolic extract (200 mg/kg) was orally administered to mice and it showed anticonvulsive properties by curative effects in maximal electroshock seizures [41].

4.3.3. *Antidepressant activity*

Badhe et al. (2010) studied the antidepressant effects of root aqueous extract (50 mg/kg) in both clonidine-induced hypothermia and reserpine-induced hypothermia mice [44]. In this study, they performed various methods like haloperidol-induced catalepsy, locomotor activity, tail suspension test, and forced swim test. It has been observed that there was a rise in ambulatory behavior representing a stimulant outcome and increased movability.

4.3.4. *Antiepileptic activity*

Root hydroalcoholic extract at doses of 250 and 500 mg/kg was injected into pentylenetetrazole-induced kindling mice and it protected cognitive diminishing by reducing oxidative stress [45].

4.3.5. *Anti-inflammatory activity*

Extracts prepared from roots (3 mg) in water, chloroform, and ethanol were topically applied separately on arachidonic acid-induced ear edema in mice inhibited the inflammation. Indomethacin was used as a positive control in this research [31].

Table 1. Reported bioactivities of *A. pyrethrum*

Level of scientific evidence	Bioactivity	Part used	Extract / compound	Assay / model / subject	Dose / concentration	Ref.
Clinical	Anesthetic	Root	Alcohol	Dental patient	2% freshly dissolved in sterile distilled water	[24]
In vivo	Anesthetic	Root	Aqueous	Guinea pig	1%	[23]
		Root	Ethanol	Guinea pig	2%	
In vivo	Androgenic	Root	Aqueous, ethanol	Rat	50 mg/kg	[38,39]
In vivo	Androgenic	Root	Ethanol	Rat	100 mg/kg	[47]
In vivo	Anticonvulsive	Root	Ethanol	Pilocarpine-induced epilepsy	200, 400 mg/kg	[40]
In vivo	Anticonvulsive	Root	Ethanol	Maximal electroshock seizure	200, 400, 600 mg/kg	[41]
In vivo	Anticonvulsive	Root	Methanol (50%)	Cognitive impairment	250, 500, 1000 mg/kg	[42]
In vivo	Anticonvulsive	Root	Aqueous, methanol	Kainic acid-induced-status epilepticus	5 g/L	[43]
In vivo	Antidepressant	Root	Aqueous	Clonidine-induced hypothermia, reserpine-induced hypothermia	50, 100, 200 mg/kg	[44]
In vivo	Antiepileptic	Root	Hydroalcoholic	Pentylenetetrazole-induced kindling	250, 500 mg/kg	[45]
In vivo	Anti-inflammatory	Root	Aqueous, methanol	Complete Freund's Adjuvant-induced paw edema, xylene-induced ear edema	125 mg/kg	[30]
In vivo	Anti-inflammatory	Root	Aqueous	Arachidonic acid-induced ear oedema	3 mg	[31]
		Root	Aqueous, chloroform, ethanol	Carrageenan-induced sub plantar oedema	100 mg/kg	
		Root	Chloroform, ethanol	Arachidonic acid-induced ear oedema	3 mg	
In vivo	Aphrodisiac	Root	Petroleum ether	Rat	50, 100 mg/kg	[46]
In vivo	Blood circulatory	Root	Pellitorine	Rat	5 mg/mL	[37]
In vivo	Antihepatotoxic	Root	Ethanol (50%)	Antitubercular drug-induced hepatotoxic	200, 400 mg/kg	[48]
In vivo	Immunomodulatory	Root	Aqueous	Mouse	10 mg/kg	[4]
In vivo	Immunomodulatory	Root	Petroleum ether	Cyclophosphamide-induced Immunosuppression	50, 100 mg/kg	[50]
In vivo	Immunomodulatory	Root	Methanol	Rat	50, 100, 200 mg/kg	[49]
In vivo	Antineurotoxic	Root	Aqueous, methanol	Kainic acid-induced-status epilepticus	5 g/L	[43]
In vitro	Antibacterial	Root	Ethanol	*Bacillus subtilis*, *Enterobacter aerogenes*, *Enterecoccus faecalis*, *Enterococcus durans*, *Escherichia coli*, *Klebsiella pneumoniae*, *Listeria innocua*, *Listeria monocytogenes*, *Pseudomonas aeruginosa*, *Pseudomonas fluorescens*, *Salmonella enteritidis*, *Salmonella infantis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*	NS	[17]
In vitro	Antibacterial	Root	Methanol	*Escherichia coli*	1000 mg/mL (MIC), 800 mg/mL (MBC)	[25]
In vitro	Antibacterial	Aerial	Essential oil	*Staphylococcus aureus*	1.25 mg/mL	[21]
In vitro	Anticancer	Aerial	Ethanol	Human colorectal cancer cell	64.75 µg/mL (IC_{50}) for 24 h; 105.9 µg/mL (IC_{50}) for 48 h	[26]
In vitro	Antidementia	Root	Chloroform	Acetylcholinesterase inhibitory	150 mg/mL (IC_{50})	[27]
		Root	Ethanol	Acetylcholinesterase inhibitory	70 mg/mL (IC_{50})	
In vitro	Antidiabetic	NS	Aqueous	α-Amylase inhibitory	39.1 µg/mL (IC_{50})	[28]
In vitro	Antidiabetic	Root	Acetone	α-Amylase inhibitory	57.29 µg/mL (IC_{50})	[29]
		Root	Aqueous	α-Amylase inhibitory	49.36 µg/mL (IC_{50})	
		Root	Chloroform	α-Amylase inhibitory	40.34 µg/mL (IC_{50})	
		Root	Ethanol	α-Amylase inhibitory	29.25 µg/mL (IC_{50})	
		Root	Ethyl acetate	α-Amylase inhibitory	52.52 µg/mL (IC_{50})	
In vitro	Antifungal	Root	Ethanol	*Candida albicans*	NS	[17]
In vitro	Antifungal	Aerial	Essential oil	*Candida albicans*	0.72 mg/mL	[21]
In vitro	Anti-inflammatory	Root	Deca-2E,4E-dienoic acid tyramide	5-lipoxygenase inhibitory, cyclooxygenase inhibitory	50 µg/mL	[20]
		Root	Hexane	5-lipoxygenase inhibitory, cyclooxygenase inhibitory	11.5 g/mL	
In vitro	Antilipidemic	NS	Aqueous	Rat intestinal disaccharidases inhibitory (Lipase)	NS	[28]
In vitro	Antimutagenic	Root	Chloroform	*Ames Salmonella* / microsome	1 mg/plate	[32]
In vitro	Antioxidant	NS	Aqueous	ABTS radical scavenging	NS	[28]
In vitro	Antioxidant	Root	Methanol (50%)	ABTS radical scavenging	31.76 µg/mL (IC_{50})	[33]

Level of scientific evidence	Bioactivity	Part used	Extract / compound	Assay / model / subject	Dose / concentration	Ref.
		Root	Methanol (50%)	DPPH radical scavenging	467.1 µg/mL (IC_{50})	
		Root	Methanol (50%)	Peroxynitrite scavenging	1.13 µg/mL (IC_{50})	
		Root	Methanol (50%)	OH radical scavenging	41.22 µg/mL (IC_{50})	
		Root	Methanol (50%)	Superoxide radical scavenging	83.49 µg/mL (IC_{50})	
In vitro	Antioxidant	Root	Methanol	DPPH radical scavenging, FRAP	NS	[34]
In vitro	Antioxidant	Seed	Ethanol (70%)	DPPH radical scavenging	0.5, 1.0, 5.0, 10.0 mg/mL	[35]
In vitro	Antioxidant	Root	Aqueous	DPPH radical scavenging	13.41 µg/mL (IC_{50})	[30]
		Root	Aqueous	FRAP	60.17 µg/mL (IC_{50})	
		Root	Aqueous	β-carotene-linoleic acid bleaching	120.66 µg/mL (IC_{50})	
		Root	Methanol	DPPH radical scavenging	12.38 µg/mL (IC_{50})	
		Root	Methanol	FRAP	50.89 µg/mL (IC_{50})	
		Root	Methanol	β-carotene-linoleic acid bleaching	107.07 µg/mL (IC_{50})	
In vitro	Antiprotozoal	Root	9,10-dehydropellitorine	*Leishmania donovani*	21.6 µM (IC_{50})	[36]
		Root	9,10-dehydropellitorine	*Plasmodium falciparum*	32.2 µM (IC_{50})	
		Root	9,10-dehydropellitorine	*Trypanosoma brucei rhodesiense*	13.2 µM (IC_{50})	
		Root	9,10-dehydropellitorine	*Trypanosoma cruzi*	181 µM (IC_{50})	
		Root	Deca-2E,4E-dienoic acid 2-phenylethylamide	*Leishmania donovani*	11 µM (IC_{50})	
		Root	Deca-2E,4E-dienoic acid 2-phenylethylamide	*Plasmodium falciparum*	18 µM (IC_{50})	
		Root	Deca-2E,4E-dienoic acid 2-phenylethylamide	*Trypanosoma brucei rhodesiense*	14.9 µM (IC_{50})	
		Root	Deca-2E,4E-dienoic acid 2-phenylethylamide	*Trypanosoma cruzi*	18.5 µM (IC_{50})	
		Root	Dichloromethane	*Leishmania donovani*	4.22 µg/mL (IC_{50})	
		Root	Dichloromethane	*Plasmodium falciparum*	3.04 µg/mL (IC_{50})	
		Root	Dichloromethane	*Trypanosoma brucei rhodesiense*	10 µg/mL (IC_{50})	
		Root	Dichloromethane	*Trypanosoma cruzi*	8.83 µg/mL (IC_{50})	
		Root	Dodeca-2E,4E-dienoic acid 4-hydroxy-2-phenylethylamide	*Leishmania donovani*	13.3 µM (IC_{50})	
		Root	Dodeca-2E,4E-dienoic acid 4-hydroxy-2-phenylethylamide	*Plasmodium falciparum*	10.1 µM (IC_{50})	
		Root	Dodeca-2E,4E-dienoic acid 4-hydroxy-2-phenylehylamide	*Trypanosoma brucei rhodesiense*	7.17 µM (IC_{50})	
		Root	Dodeca-2E,4E-dienoic acid 4-hydroxy-2-phenylethylamide	*Trypanosoma cruzi*	5.97 µM (IC_{50})	
		Root	Tetradeca-2E,4E,12Z-trien-8,10-diynoic acid isobutylamide	*Leishmania donovani*	18.7 µM (IC_{50})	
		Root	Tetradeca-2E,4E,12Z-trien-8,10-diynoic acid isobutylamide	*Plasmodium falciparum*	26.7 µM (IC_{50})	
		Root	Tetradeca-2E,4E,12Z-trien-8,10-diynoic acid isobutylamide	*Trypanosoma brucei rhodesiense*	23.7 µM (IC_{50})	
		Root	Tetradeca-2E,4E,12Z-trien-8,10-diynoic acid isobutylamide	*Trypanosoma cruzi*	144 µM (IC_{50})	
		Root	Undeca-2E,4E-dien-8,10-diynoic acid isopentylamide	*Leishmania donovani*	16.6 µM (IC_{50})	
		Root	Undeca-2E,4E-dien-8,10-diynoic acid isopentylamide	*Plasmodium falciparum*	42.5 µM (IC_{50})	
		Root	Undeca-2E,4E-dien-8,10-diynoic acid isopentylamide	*Trypanosoma brucei rhodesiense*	18.9 µM (IC_{50})	
		Root	Undeca-2E,4E-dien-8,10-diynoic acid isopentylamide	*Trypanosoma cruzi*	66.9 µM (IC_{50})	
In vitro	Blood circulatory	Root	Pellitorine	Caco-2 cell permeability (human colorectal carcinoma)	0.31 µg	[37]
In vitro	Immunomodulatory	Root	Aqueous	Spleen cell	50 µg/mL	[4]
In vitro	Oxidative DNA damage preventive	Root	Methanol (50%)	Fenton-induced damage of pBluescript II SK (-) supercoiled DNA	1.52 µg/mL	[33]

ABTS: 2,22′-azinobis (3-ethyl-benzothiazoline6-sulfonic acid); DPPH: 2,2-diphenyl-1-picrylhydrazyl; FRAP: Ferric Reducing Antioxidant Power; IC50: The half maximal inhibitory concentration; MIC: Minimum Inhibitory Concentration; MBC: Minimum Bactericidal Concentration; NS: Not stated; OH: Hydroxyl; TBARS: Thiobarburic acid reactive substances; Ref.: Reference.

4.3.6. *Aphrodisiac activity*

In an investigation by Sharma et al., 50 and 100 mg/kg of root petroleum ether extract was orally administered to rats. This treatment elevated the precopulatory properties of male rats towards female rats. Also, there was an increase in penile erection index recognized, the mount was elevated four times, and intromission frequency was elevated three times [46].

4.3.7. *Blood circulatory activity*

Pellitorine (5 mg/mL) was isolated from roots was administered intracerebroventricularly and intravenously to rats. The outcomes revealed that pellitorine quickly and seamlessly permeated the gut mucosa and blood-brain barrier [37].

4.3.8. *Antihepatotoxic activity*

Usmani et al. investigated the antihepatotoxic properties of root ethanolic (50%) extract (200 and 400 mg/kg) in antitubercular drug-induced hepatotoxic rats. The results unveiled that the hepatic marker concentrations were reinstated and the root owns hepatoprotective action. Silymarin was utilized as a positive control in this investigation [48].

4.3.9. *Immunomodulatory activity*

A root aqueous extract at a dose of 10 mg/kg was orally administered to mice and it exhibited a better immunoenhancing index [4].

4.3.10. *Antineurotoxic activity*

Antineurotoxic effects of root aqueous and methanolic extracts (5 g/L) were researched in kainic acid-induced-status epileptic mice and it showed neuroprotective property against seizures encouraged by kainic acid [43].

4.4. *In vitro* studies

4.4.1. *Antibacterial activity*

The essential oil distilled from aerial parts applied on *Staphylococcus aureus* assay at a concentration of 1.25 mg/mL unveiled antibacterial activity [21].

4.4.2. *Anticancer activity*

In a study by Mohammadi et al., ethanolic extract of aerial showed time-dependent anticancer effect against human colorectal cancer cells at IC_{50} 64.75 µg/mL for 24 h and IC_{50} 105.9 µg/mL for 48 h [26].

4.4.3. *Antidementia activity*

Root ethanolic extract (IC_{50} 70 mg/mL) inhibited acetylcholinesterase and Rivagistmine was used as a positive control in this investigation [27].

4.4.4. *Antidiabetic activity*

Kumar and Lalitha studied the antidiabetic effects of root ethanolic extract and it was noticed that at IC_{50} 29.25 µg/mL there was inhibition in the α-amylase activity [29].

4.4.5. *Antifungal activity*

The essential oil of aerial showed antifungal activity against *Candida albicans* at a concentration of 0.72 mg/mL [21].

4.4.6. *Anti-inflammatory activity*

Deca-2E,4E-dienoic acid tyramide isolated from roots inhibited 5-lipoxygenase and cyclooxygenase distinctly at a concentration of 50 µg/mL [20].

4.4.7. *Antilipidemic activity*

In an investigation by Huerta et al., the aqueous extract inhibited rat intestinal disaccharidases (lipase). However, the authors did not state the part used and the concentration of the extract used in this investigation [28].

4.4.8. *Antimutagenic activity*

Root chloroform extract (1 mg/plate) generated inhibition in *Ames Salmonella* / microsome assay [32].

4.4.9. *Antioxidant activity*

An extract was prepared using root and methanol (50%) exhibited antioxidant effects in peroxynitrite scavenging assay at IC_{50} 1.13 µg/mL [33].

4.4.10. *Antiprotozoal activity*

Dodeca-2E,4E-dienoic acid 4-hydroxy-2-phenylethylamide (IC_{50} 5.97 µM) was isolated from roots showed antiprotozoal activity in *Trypanosoma cruzi* assay [36].

4.4.11. *Blood circulatory activity*

Pellitorine also isolated from roots (0.31 µg) can cross the Caco-2 cell monolayer from the apical-to-basolateral to basolateral-to-apical side [37].

4.4.12. *Immunomodulatory activity*

Bendjeddou et al. investigated the immunomodulatory effects of root aqueous extract in spleen cells. It was noticed that there was a better stimulation index at a concentration of 50 µg/mL [4].

4.5. Toxicity studies

There are three toxicity studies available regarding *A. pyrethrum* and they are discussed below.

Subchronic toxicity of root ethanolic extract (1000 mg/kg) was (orally administered) evaluated in rats for 90 days. This study revealed that there were no mortalities or adverse effects. Also, this extract had no treatment-associated toxicological irregularities. Therefore, this study suggests the ethanolic extract is safe for chronic treatments [51].

In another study by Manouze et al., 5000 mg/kg of both aqueous and methanolic extracts (root) were separately orally administered to mice for 14 days. The results show that there was no toxicity-related

symptoms, mortality, and weight changes in body and organs were observed after 14 days [30].

5. Conclusion

Several compounds have been isolated from *A. pyrethrum* and there are several ethnomedicinal uses of this plant species. However, only some scientific evidence is available in terms of bioactivities study. Therefore, more bioactivities and phytochemical linked researches should be conducted to generate more scientific evidence for the ethnomedicinal uses and identify more bioactive compounds that might be future lead compounds in drug discovery related researches. This work scrutinized, summed up, and recorded the currently available bioactive scientific evidence of *A. pyrethrum*.

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