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From wandering weeds to pharmacy: An insight into traditional uses, phytochemicals and pharmacology of genus *Chromolaena* (Asteraceae)

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A R T I C L E I N F O

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A B S T R A C T

Ethnopharmacological relevance: Chromolaena species, of the Asteraceae family, are distributed across the tropical and the temperate regions of Africa, the Americas, southern Asia, and Australia. Despite "falling out of favour" among the people because of their "weedy" nature, *Chromolaena* species have indisputable long medicinal history in the treatment of malaria, nasal congestion, inflammation, eye disorders, asthma, cough, flu, headache, and cold.

Aim of the review: The aim of this review is to systematically summarize the current knowledge on ethnopharmacology, phytochemistry, pharmacology, toxicology, and real-time scientific applications of the genus *Chromolaena* after its re-classification from genus *Eupatorium*, as well as to proffer integrated approaches in maximizing their therapeutic values despite their "weedy" nature.

Materials and methods: First, the current species in the genus were verified by "The Plant List" (http://www.theplantlist.org) and "Royal Botanic Gardens, Kew/Missouri Botanical Garden" (http://mpns.kew.org/mpns-portal/). Second, the relevant information on each of the identified species was gathered from following databases: Google Scholar, Online Wiley library, ScienceDirect, SciFinder, Scopus, PubMed. Scientific literature was searched from inception till August 2021.

Results: More than 190 phytochemicals have been isolated and identified from 27 species of the genus, including flavonoids, alkaloids, triterpenoids, diterpenoids, sesquiterpenoids, steroids, fatty acids, and coumarins among others. Pharmacological investigations, both *in vitro* and *in vivo*, have shown that the extracts and the compounds have antimicrobial, anticancer, antioxidant, insecticidal, anti-inflammatory, and anti-diabetic activities among others.

Conclusions: Many species of genus have potential therapeutic values, and hence they are more than "wandering" weeds. In addition, there is growing interest in the real-time scientific applications of the genus in the production of pharmacological polyherbal products, and this should serve as a stimulus to strategically develop integrated control approaches for preserving these species, with a view of maximizing their therapeutic values and reducing their cost of eradication.

1. Introduction

The genus *Chromolaena* (family Asteraceae) is one of the oldest species of plants ever known to mankind. It was previously and taxonomically classified under the genus *Eupatorium*. It is regarded as one of the largest genera in the family Asteraceae. The genus comprises of

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C. odorata *C. laevigata* (Oliveira et al. 2020)

Fig. 1. Images of *Chromolaena* species, showing leaves and flowers. The photo of *C. odorata* was taken by the first author in Nigeria. Permission was obtained for using photo of *C. laevigata*.

approximately 175 accepted species of shrubs and herbs distributed across the tropical and the temperate regions of Africa, the Americas, southern Asia, and Australia (http://www.theplantlist.org) (King and Robinson, 1987), although majority of the species diversity occurs in South America region, especially Brazil (Oliveira, 2015). They are mostly terrestrial invasive weed species (Fig. 1). In the recent time, many of the *Chromolaena* species are "falling out of favour" among the people because of their invasive nature and the threat they pose to cropping and pastoral farming (McWilliam, 2000), natural ecosystem (Cronk and Fuller, 2014), fire hazard prevention, biodiversity (Adair and Groves, 1998) and environmental quality (Fandohan et al., 2015). Despite the invasive tendency of members of genus *Chromolaena* and the threat they pose worldwide, several *Chromolaena* species have been widely and frequently used by the traditional healers in many nations of the world for treating malaria, nasal congestion, inflammation, eye disorders, asthma, cough, flu, headache, and cold. Moreover, many species of the genus, including *Chromolaena laevigata* (Lam.) R. M. King & H. Rob., *Chromolaena odorata* (L.) R. M. King & H. Rob. and *Chromolaena hirsuta* (Hook. & Arn.) R. M. King & H. Rob. have received considerable attention and scientific research in recent time due to their medicinal potential (Herrera-Calderon et al., 2017; Játem-Lásser et al., 1998; Rodríguez and Torrenegra, 2017; Taleb-Contini et al., 2004).

With the exception of the previous review on wound-healing effect by Sirinthipaporn and Jiraungkoorskul (2017), and other phytochemical and pharmacological reviews by Omokhua et al., (2016) and Vaisakh and Pandey (2012) on the species *C. odorata*, no attempt has been made to explore and holistically synthesize the available literature on the current knowledge on genus *Chromolaena* after its re-classification from genus *Eupatorium*. Moreover, this genus needs to be studied systematically and comprehensively so that potential species can be documented and exploited as therapeutic agents. Thus, this present work provides an overview, for the first time, about the medicinal potential of genus *Chromolaena* and discusses the ethnopharmacology, phytochemistry, pharmacology, toxicology as well as preservation of indigenous knowledge of the genus to identify opportunities for future research on the genus. Besides, translational research involving *Chromolaena* species, and their clinical applications are also examined among others.

2. Review methodology

The websites of Royal Botanic Gardens, Kew/Missouri Botanical Garden (http://mpns.kew.org/mpns-portal/) as well as 'The Plant List' initiative (www.theplantlist.org) were initially employed to identify the names of all the species included in the genus *Chromolaena* using the search word "*Chromolaena*". Scientific publications on each *Chromolaena* species were searched from their inception till August 2021 using the following databases: Google Scholar, Online Wiley library, ScienceDirect, SciFinder, Scopus and PubMed. All publications that mention *Chromolaena* species and their medicinal properties were included in the literature search. Various combinations of keywords used during the literature search are: "*Chromolaena*", "traditional uses", "phytochemistry", "biological activities", and "toxicology". All published papers resulting from different databases search were thoroughly screened and relevant papers were collated using Zotero (https://www.zotero.org/), a web-based reference manager. Chemical structures were drawn using CS ChemDraw® (Ultra version 12.0) software after their structures were confirmed using the databases of PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and SciFinder (www.scifinder.cas.org). Information gathered was analyzed and summarized in table forms where appropriate.

3. Ethnopharmacological uses of *Chromolaena* species

Various ethnopharmacological practices have been linked with genus *Chromolaena*. Members of the genus are well known in the traditional clinical medicine in different local communities across the globe, not as field weeds but as medicinal plants, especially in the treatment of wounds and skin infections. Table 1 shows the ethnopharmacological uses of *Chromolaena* species, along with the part(s) used and modes of preparation. The main part used is the leaves. Others are the stem-bark, roots, aerial part, and flowers. The methods of herbal preparation often involve decoction, infusion, maceration, and pounding. Among all the *Chromolaena* species, *C. odorata*, which is an invasive shrub, has received global relevance in the treatment of tropical diseases and skin problems (Phumthum et al., 2020; Inta et al., 2013) (Table 1). It is reported that traditional medicine practitioners in Nigeria (Fredrick and Oluomachi, 2019) and Cameroon (Lagarde et al., 2013) rely on the decoction of *C. odorata* as their herbal remedy for the treatment of malaria fever, an endemic parasitic infection in Africa. *Chromolaena collina* (DC.) R. M. King & H. Rob. is used for the treatment of gastrointestinal diseases caused by parasitic worms among the Chiapia people of Mexico (De la Cruz et al., 2014). In Brazil, the stems, roots and leaves of *Chromolaena maximilianii* (Schrad. ex DC.) R. M. King & H. Rob. are employed for regulating the women's menstrual cycle and virginal discharge (Ribeiro et al., 2017). In Thailand, *Chromolaena adenophorum* (Spreng.) R. M. King & H. Rob. is employed in the primary healthcare of postpartum women (Panyaphu et al., 2011). Meanwhile, the use of *Chromolaena* species is rather limited in the clinical traditional medicine because only few species have been documented for their use in the traditional medicine (Table 1). A number of speculations could be responsible for this. First, this might partly be due to the general conception that *Chromolaena* species are associated with disturbed

Table 1
Ethnopharmacological uses reported for *Chromolaena* species.

Chromolaena species	Ethnopharmalogical uses	Part(s)	Modes of preparation	Continent/ Country	References
Chromolaena arnottiana (Griseb.) R. M. King & H. Rob.	Cold, gastric pains, asthma, bronchitis, bone fractures and dislocations	Leaves, stems	Infusion	South America/ Argentina, Bolivia	Clavin et al. (2007)
C. collina	gastrointestinal diseases	Leaves	Infusion	North America/ Mexico	(De la Cruz et al., 2014)
Chromolaena christieana (Baker) R. M. King & H. Rob.	Aromatic	Roots		South America	Rojas de Arias et al. (1995)
C. odorata	Wounds, soft-tissue burns and skin infections	Leaves	The leaves are squeezed and topically applied to the wounds	Asia, Africa/ Ivory Coast, Nigeria	Sirinthipaporn and Jiraungkoorskul (2017)
	Fevers, blood clotting	NS	NS	Africa/Ghana	Aigbedion-Atalor (2020)
	Anuria, asthma, athlete's foot, back and waist pain, bone fractures, cough, diarrhoea, epilepsy, fever, gastritis, haemostasis, malaria, diabetes, insect repellent, wounds	Leaves	Pounding, decoction, water infusion	Asia/Thailand	(Phumthum et al., 2020; Inta et al., 2013)
	Malaria	Leaves	Decoction of the leaves	Africa/Nigeria	Fredrick and Oluomachi (2019)
	Haemostasis/Fresh cut bleeding	Leaves	Leaves are crushed and applied externally as poultice	Asia/India	Chetri (2019)
	Cuts and wounds	Leaves sap	Leaf sap is applied onto cuts and wounds	Asia/ Philippines	Dapar et al. (2020)
	Menstruation irregular, genital disease female	Leaves	Decoction /bath	Asia/Vietnam	Lee et al. (2019)
	Malaria	Fresh leaves	Decoction	Africa/ Cameroon	Lagarde et al. (2013)
	Cuts and wounds	Leaves	Leaf juice and paste is applied to fresh cuts and wounds to stop bleeding and to relieve pain	Asia/India	Thomas et al. (2014)
	Malaria fever, headache, tooth problem, skin problem, typhoid fever	NS	NS	Africa/Nigeria	Abiolu (2018)
	Peptic ulcer, stop bleeding, accelerates healing, refreshing	Root, Stem-bark, Leaves	Decoction	Asia/Thailand	Panyaphu et al. (2011)
Chromolaena barranquillensis (Hieron.) R. M. King & H. Rob.	Rashes, insect bites, and colics	NS	NS	South America/ Colombia	Rodríguez et al. (2014)
Chromolaena moritziana (Sch.Bip. ex Hieron.) R. M. King & H. Rob.	Catarrh, ulcer and skin eruption	Leaves, Flowers	Decoction	North America/ Mexico	Hidalgo-Báez et al. (1998)
Chromolaena leivensis (Hieron.) R. M. King & H. Rob.	Anticancer and febrifuge	Aerial part	NS	South America/ Colombia	(García-Barriga, 1975; Calderón et al., 2010)
Chromolaena tacotana (Klatt) R. M. King & H. Rob.	Inflammation and fractures	NS	NS	South America/ Colombia	(Marín and Gómez, 2015)
C. laevigata	Lesions, oral thrush	Aerial part		South America/ Brazil	(Clavin et al., 1999; Murakami et al., 2013)
C. maximilianii	Vaginal discharges, diabetes, swelling, rheumatism, menopause disorders, wounds	Root, stem, leaves	Decoction, infusion, maceration	South America/ Brazil	Ribeiro et al. (2017)
Chromolaena squalida (DC.) R. M. King & H. Rob.	Infections	Leaves	Infusion, maceration	South America/ Brazil	Ribeiro et al. (2017)
Chromolaena tequandamensis (Hieron.) R. M. King & H. Rob.	Alzheimer's disease	NS	NS	South America/ Colombia	Raghunath et al. (2018)
C. adenophorum	Cancer	Leaves, stem-bark	Decoction	Asia/Thailand	Panyaphu et al. (2011)
Chromolaena pulchella (Kunth) R. M. King & H. Rob.	pain, gastrointestinal diseases, respiratory, renal disorders associated with bacterial infections	Leaves, flowers, stem		North America/ Mexico	García-Sánchez et al. (2015)

NS, Not stated.

ecosystem. Second, there might be lack of adequate information on their medicinal values among the rural dwellers who view them as ordinary field weeds.

4. Phytochemistry of *Chromolaena* species

Chromolaena species are, undoubtedly, indispensable source of bioactive phytochemical constituents with potential pharmaceutical, cosmetic, and agro-industrial applications. A thorough literature search on the genus *Chromolaena* revealed that 27 species have been

Table 2
Flavonoids and phenolic acids isolated from genus *Chromolaena*.

S/N	Compound name	Species	Extract	Part(s)	Reference
1	5,3'-dihydroxy-7,6'-dimethoxyflavanone (odoratenin)	*C. odorata*	Methanol	Leaves	Putri and Fatmawati (2019)
2	5,3′-dihydroxy-7,4′-dimethoxyflavanone (persicogenin)	*C. odorata*	Chloroform	Flowers	Suksamrarn et al. (2004)
		C. farinosa	Ethyl acetate	Aerial parts	Triana et al. (1995)
3	Naringenin-4′-methyl ether (Isosakuranetin) or (5,7-dihydroxy-4′-methoxyflavanone)	*C. odorata*	Chloroform	Flowers	Suksamrarn et al. (2004)
			Chloroform	Aerial part	Pel et al. (2020)
			Methanol	Leaves	Putri and Fatmawati (2019)
			Acetone	Leaves	Wollenweber et al. (1995)
4	Naringenin-7-methyl ether (sakuranetin)	*C. odorata*	Acetone	Leaves	Wollenweber et al. (1995)
		C. subscandens	Dichloromethane	Leaves, flowers	(Antonio et al., 2007a; Guzmán, 2008)
		C. connivens	Petroleum ether	Aerial parts	Tamayo-Castillo et al. (1989)
		C. tyleri	Ethanol	Aerial parts	De Perez (1999)
5	Subscandenin	*C. odorata*	Methanol	Leaves	Putri and Fatmawati (2019)
		C. subscandens	Dichloromethane	Leaves, flowers	Antonio et al. (2007b)
6	5,7-dihydroxy-6,4′-dimethoxy flavanone	*C. odorata*	Methanol	Aerial parts	Pisutthanan et al. (2006)
7	6,4'-dimethyl ether quercetagetin (laciniatin)	*C. odorata*	Acetone	Leaves	Wollenweber and Roitman (1996)
8	3,5,7,3'-tetramethyl ether quercetagetin	*C. odorata*	Acetone	Leaves	Wollenweber and Roitman (1996)
9	5,6,7,3',4'-pentamethyl ether quercetagetin	*C. odorata*	Acetone	Leaves	Wollenweber and Roitman (1996)
10	(Z)-*p*-coumaric acid	*C. odorata*	Chloroform	Aerial part	Pel et al. (2020)
11	caffeic acid	*C. odorata*	Ethyl acetate	Aerial part	Pel et al. (2020)
		C. arnottiana	Ethanol	Aerial parts	Clavin et al. (2007)
12	caffeic acid methyl ester	*C. odorata*	Ethyl acetate	Aerial part	Pel et al. (2020)
13	gallic acid	*C. odorata*	Ethyl acetate	Aerial part	Pel et al. (2020)
		C. laevigata	Ethyl acetate fraction	Aerial parts	Oliveira et al. (2020)
14	4-hydroxybenzoic acid	*C. odorata*	Chloroform	Aerial part	Pel et al. (2020)
15	protocatechuic acid	*C. odorata*	Ethyl acetate	Aerial part	Pel et al. (2020)
16	protocatechuic acid methyl ester	*C. odorata*	Chloroform	Aerial part	Pel et al. (2020)
17	epitaxifolin	*C. odorata*	Chloroform	Aerial part	Pel et al. (2020)
18	epiaromadendrin	*C. odorata*	Ethyl acetate	Aerial part	Pel et al. (2020)
19	5,7,4′-trihydroxy-6,3′-dimethoxy flavone (jaceosidin)	*C. odorata*	Chloroform	Aerial part	Pel et al. (2020)
		C. arnottiana	Dichloromethane	Aerial parts	Clavin et al. (2007)
		C. hirsuta	Dichloromethane	Leaves	(Taleb-Contini et al., 2003, 2004, 2007)
20	5,7-dihydroxy-4'-methoxyflavone (acacetin)	*C. odorata*	Methanol	Flowers	Suksamrarn et al. (2004)
			Chloroform	Aerial part	Pel et al. (2020)
		C. congesta	Chloroform fraction	Whole plants	de Oliveira et al. (2017)
		C. farinosa	Ethyl acetate	Aerial parts	Triana et al. (1995)
21	5,7,3′,4′-tetrahydroxyflavone (luteolin)	*C. odorata*	Methanol	Flowers	Suksamrarn et al. (2004)
		C. hirsuta	Dichloromethane	Leaves	(Taleb-Contini et al., 2003, 2004, 2007)
		C. congesta	Chloroform fraction	Whole plants	de Oliveira et al. (2017)
22	4',5,6,7-tetramethoxyflavone (scutellarein tetramethyl ether)	*C. odorata*	Acetone	Leaves	Wollenweber et al. (1995)
			Cyclohexane	Leaves	Atindehou et al. (2013)
23	4′-hydroxy-5,6,7-trimethoxyflavanone	*C. odorata*	Methanol	Flowers	Suksamrarn et al. (2004)
			Ethyl acetate	Aerial part	Pel et al. (2020)
24	5-hydroxy-7,4′-dimethoxylflavanone	*C. odorata*	Chloroform	Aerial part	Pel et al. (2020)
25	5,6,7,4′-tetramethoxyflavanone	*C. odorata*	Chloroform	Flowers	Suksamrarn et al. (2004)
			Chloroform	Aerial part	Pel et al. (2020)
26	Apigenin	*C. odorata*	Chloroform	Aerial part	Pel et al. (2020)
		C. congesta	Chloroform fraction	Whole plants	de Oliveira et al. (2017)
		C. laevigata	Hexane fraction	Aerial parts	Oliveira et al. (2020)
27	eriodictyol	*C. odorata*	Ethyl acetate	Aerial part	Pel et al. (2020)
		C. arnottiana	Ethanol	Aerial parts	Clavin et al. (2007)
		C. tyleri	Ethanol	Aerial parts	De Perez (1999)
28	Diosmetin	*C. odorata*	Ethyl acetate	Aerial part	Pel et al. (2020)
		C. farinosa	Ethyl acetate	Aerial parts	Triana et al. (1995)
29	kaempferol	*C. odorata*	Ethyl acetate	Aerial part	Pel et al. (2020)
		C. moritziana	Ethyl acetate fraction	Leaves	Hidalgo-Báez et al. (1998)
		C. laevigata	Ethyl acetate fraction	Aerial parts	Oliveira et al. (2020)
		C. congesta	Chloroform fraction	Whole plants	de Oliveira et al. (2017)
30	Quercetin	*C. odorata*	Chloroform	Aerial part	Pel et al. (2020)
		C. squalida	Dichloromethane	Stem	(Taleb-Contini et al., 2003, 2007)
		C. hirsuta	Dichloromethane	Leaves	(Taleb-Contini et al., 2003, 2004, 2007)
		C. laevigata	Ethyl acetate fraction	Aerial parts	Oliveira et al. (2020)
31	aromadendrin-4'-methyl ether	*C. odorata*	Chloroform	Leaves	Saiful (2012)
32	eriodictyol-7,4′-dimethyl ether	*C. odorata*	Chloroform	Leaves	Saiful (2012)
33	kaempferol-4'-methyl ether (kaempferid)	*C. odorata*	Chloroform	Leaves	Saiful (2012)
			Acetone	Leaves	Wollenweber et al. (1995)
			Ethyl acetate	Leaves	(Kumkarnjana et al., 2018, 2019)
34	kaempferol-7-methyl ether (rhamnocitrin)	*C. odorata*	Acetone	Leaves	Wollenweber et al. (1995)

(*continued on next page*)

Table 2 (*continued*)

S/N	Compound name	Species	Extract	Part(s)	Reference
		C. subscandens	Dichloromethane	Aerial parts	Antonio et al. (2007a)
			Dichloromethane fraction	Leaves	(Guzmán, 2008)
		C. bullata	Ethanol	Leaves	Sánchez et al. (2008)
35	kaempferol-7,4′-dimethyl ether	*C. odorata*	Acetone	Leaves	Wollenweber et al. (1995)
36	quercetin-7,4'-dimethyl ether (ombuin)	*C. odorata*	Chloroform, acetone	Leaves	(Saiful, 2012; Wollenweber et al., 1995)
		C. farinosa	Ethyl acetate	Aerial parts	Triana et al. (1995)
37	quercetin-4'-methyl ether (tamarixetin)	*C. odorata*	Chloroform, acetone	Leaves	(Saiful, 2012; Wollenweber et al., 1995)
38	quercetin-7-methyl ether (rhamnetin)	*C. odorata*	Chloroform, acetone	Leaves	(Saiful, 2012; Wollenweber et al., 1995)
		C. meridensis	Dichloromethane	Aerial parts	Amaro and Morales-Mendez (1983)
39	quercetin-7,3′,4′-trimethyl ether	*C. odorata*	Acetone,	Leaves	Wollenweber et al. (1995)
40	quercetin-3′,4′-dimethyl ether (dillenetin)	*C. odorata*	Acetone, Ethyl acetate	Leaves	(Wollenweber et al., 1995; Kumkarnjana et al., 2018, 2019)
41	taxifolin-4'-methyl ether	*C. odorata*	Chloroform	Leaves	Saiful (2012)
42	taxifolin-7-methyl ether (padmatin)	*C. odorata*	Chloroform, Acetone	Leaves	(Saiful, 2012; Wollenweber et al., 1995)
43	3', 4', 5, 6, 7-pentamethoxyflavone (Sinensetin)	*C. odorata*	Cyclohexane	Leaves	Atindehou et al. (2013)
44	kaempferol-3-*O*-rutinoside	*C. moritziana*	Ethyl acetate fraction	Leaves	Hidalgo-Báez et al. (1998)
45	Rutin	*C. moritziana*	Ethyl acetate fraction	Leaves	Hidalgo-Báez et al. (1998)
		C. arnottiana	Ethanol	Aerial parts	Clavin et al. (2007)
46	isoquercitrin	*C. moritziana*	Aqueous fraction	Leaves	Hidalgo-Báez et al. (1998)
47	(2R)-5,7-dihydroxy flavanone or (R) pinocembrin	*C. leivensis*	Ethanol	Leaves	Rodriguez et al. (2018)
		C. chaseae	Petroleum ether	Aerial parts	Bohlmann et al. (1982)
48	3,5-dihydroxy-7-methoxyflavone	*C. leivensis*	Toluene fraction	Leaves	(Ruben et al., 2011; Whitted et al., 2016)
		C. perglabra	Ethyl acetate	Leaves, stem	Antonio et al. (2007b)
49	3,5,7-trihydroxy-6-methoxyflavone	*C. leivensis*	Toluene fraction	Leaves	Ruben et al. (2011)
		C. chaseae	Petroleum ether	Aerial parts	Bohlmann et al. (1982)
50	3,5-dihydroxy-7-methoxyflavanone	*C. leivensis*	Toluene fraction	Leaves	(Ruben et al., 2011; Whitted et al., 2016)
51	kaempferitrina	*C. subscandens*	Dichloromethane	Leaves, flowers	(Antonio et al., 2007a; Amaro-Luis and Delgado-Méndez, 1993)
52	*p*-methoxybenzoic acid	*C. subscandens*	Dichloromethane	Leaves, flowers	Antonio et al. (2007a)
53	5,4′-dihydroxy-6,7-dimethoxyflavanone	*C. subscandens*	Dichloromethane	Leaves, flowers	Antonio et al. (2007a)
			Dichloromethane	Leaves	Amaro-Luis and Delgado-Méndez (1993)
54	7- α - (L) -rhamnosyl-kaempferol	*C. subscandens*	Dichloromethane	Leaves, flowers	(Antonio et al., 2007a; Amaro-Luis and Delgado-Méndez, 1993)
55	3,8-dimethoxy-gossypetin (5,7,3',4'-tetrahydroxy-3,8-dimethoxyflavone)	*C. subscandens*	Dichloromethane fraction	Leaves	(Guzmán, 2008)
56	Nepetin	*C. arnottiana*	Dichloromethane	Aerial parts	Clavin et al. (2007)
57	hyperoside	*C. arnottiana*	Ethanol	Aerial parts	Clavin et al. (2007)
		C. laevigata	Ethyl acetate, butanol, dichloromethane fractions	Aerial parts	Oliveira et al. (2020)
58	Hispidulin	*C. arnottiana*	Dichloromethane	Aerial parts	Clavin et al. (2007)
59	eupatilin (5,7-dihydroxy-3′,4′,6-trimethoxyflavone)	*C. arnottiana*	Ethanol	Aerial parts	Clavin et al. (2007)
			Chloroform fraction	Leaves, flowers	de Gutiérrez et al. (1995)
60	5-hydroxy-3',4′,5′,6,7-pentamethoxyflavone	*C. arnottiana*	Chloroform fraction	Leaves, flowers	de Gutiérrez et al. (1995)
61	eupatorin (5,3'-dihydroxy-6,7,4′-trimethoxyflavone)	*C. arnottiana*	Chloroform fraction	Leaves, flowers	de Gutiérrez et al. (1995)
62	4',5,6-trihydroxy-7-methoxyflavone	*C. squalida*	Dichloromethane	Leaves	(Taleb-Contini et al., 2003, 2007)
		C. hirsuta	Dichloromethane	Leaves	(Taleb-Contini et al., 2003, 2004, 2007)
63	3',4',5,6-tetrahydroxy-7-methoxyflavone	*C. squalida*	Ethanol	Leaves	(Taleb-Contini et al., 2003, 2007)
64	3',4',5,7-tetrahydroxy-3,6-dimethoxyflavone	*C. squalida*	Methanol	Leaves	Taleb-Contini et al. (2007)
		C. hirsuta	Dichloromethane	Leaves	(Taleb-Contini et al., 2003, 2004, 2007)
65	5-hydroxy-2-(4-hydroxy-3-methoxyphenyl) −3,7-dimethoxy-8-ethyl-4H-chromen-4-one	*C. morii*	Petroleum ether	Aerial parts	Bohlmann et al. (1981)
66	quercetin 3-*O*-α-L-rhamnosyl-(1–6)-β-D-galactoside	*C. squalida*	Methanol	Leaves	Taleb-Contini et al. (2007)
		C. hirsuta	Dichloromethane	Leaves	(Taleb-Contini et al., 2003, 2004, 2007)
67	quercetagetin 3,6,7-trimethyl ether	*C. hirsuta*	Dichloromethane	Leaves	(Taleb-Contini et al., 2003, 2004, 2007)
68	quercetin 3-*O*-α-L-rhamnoside	*C. hirsuta*	Dichloromethane	Leaves	(Taleb-Contini et al., 2003, 2004, 2007)
69	4',5-dihydroxy-3',3,6,7-tetramethoxyflavone	*C. hirsuta*	Dichloromethane	Leaves	(Taleb-Contini et al., 2003, 2004, 2007)
		C. squalida	Methanol	Leaves	Taleb-Contini et al. (2007)
70	4',5,7-trihydroxy-3',3,6-trimethoxyflavone	*C. hirsuta*	Dichloromethane	Leaves	(Taleb-Contini et al., 2003, 2004, 2007)
71	3',4',5,7-tetrahydroxy-3-methoxyflavone	*C. hirsuta*	Dichloromethane	Leaves	(Taleb-Contini et al., 2003, 2004, 2007)
		C. tacotana	Dichloromethane	Leaves	Torrenegra et al. (2018)
72	3',4',5,7-tetrahydroxy-6-methoxyflavone	*C. hirsuta*	Dichloromethane	Leaves	(Taleb-Contini et al., 2003, 2004, 2007)
73	4',5-dihydroxy-3',7-dimethoxyflavone	*C. hirsuta*	Dichloromethane	Leaves	(Taleb-Contini et al., 2003, 2004, 2007)
74	5-hydroxy-3',4',6,7-tetramethoxyflavone	*C. hirsuta*	Dichloromethane	Leaves	(Taleb-Contini et al., 2003, 2004, 2007)
75	gonzalitosin I	*C. laevigata*	Dichloromethane fraction	Aerial parts	Oliveira et al. (2020)
76	quercetin-3-O-α-rhamnopyranoside	*C. laevigata*	Ethyl acetate fraction	Aerial parts	Oliveira et al. (2020)
77	Pillion	*C. laevigata*	Hexane fraction	Aerial parts	Oliveira et al. (2020)
		C. farinosa	Ethyl acetate	Aerial parts	Triana et al. (1995)
78	apigenin 5-methyl ether	*C. congesta*	Chloroform fraction	Whole plants	de Oliveira et al. (2017)

(*continued on next page*)

Table 2 (*continued*)

S/N	Compound name	Species	Extract	Part(s)	Reference
79	apigenin 5,7-dimethyl ether	*C. congesta*	Chloroform fraction	Whole plants	de Oliveira et al. (2017)
80	kumatakenin	*C. congesta*	Chloroform fraction	Whole plants	de Oliveira et al. (2017)
81	genkwanin	*C. congesta*	Chloroform fraction	Whole plants	de Oliveira et al. (2017)
		C. perglabra	Ethyl acetate	Leaves, stem	Antonio et al. (2007b)
82	kaempferol-3-methyl ether	*C. congesta*	Chloroform fraction	Whole plants	de Oliveira et al. (2017)
83	5,7-dihydroxy- 3',4′–dimethoxyflavone	*C. farinosa*	Ethyl acetate	Aerial parts	Triana et al. (1995)
84	5,3′,4′-trihydroxy-7-methoxy-flavanone	*C. farinosa*	Ethyl acetate	Aerial parts	Triana et al. (1995)
85	3,5,7-trihydroxyflavone or (3,5,7-trihydroxy-2-phenyl-4H-chromen-4-one)	*C. chaseae*	Petroleum ether	Aerial parts	Bohlmann et al. (1982)
86	(E)-3-phenyl-1-(2,4,6 trihydroxyphenyl) prop-2-en-1-one or (Pinocembrin chalcone)	*C. chaseae*	Petroleum ether	Aerial parts	Bohlmann et al. (1982)
87	4',5,7-trihydroxyflavanone (naringenin)	*C. connivens*	Petroleum ether	Aerial parts	Tamayo-Castillo et al. (1989)

Table 3
Steroids and triterpenoids isolated from genus *Chromolaena*.

S/N	Compound name	Species	Extract	Part(s)	Reference
88	poriferasterol	*C. odorata*	Chloroform	Aerial part	Pel et al. (2020)
89	stigmasterol	*C. odorata*	Chloroform	Aerial part	Pel et al. (2020)
		C. pulchella	Dichloromethane	Flowers	Gómez-Hurtado et al. (2011)
		C. subscandens	Dichloromethane	Aerial parts	Antonio et al. (2007a)
		C. chaseae	Petroleum ether	Roots	Bohlmann et al. (1982)
		C. arnottiana	Hexane fraction	Leaves, flowers	de Gutiérrez et al. (1995)
		C. squalida	Dichloromethane	Stem	(Taleb-Contini et al., 2003, 2007)
		C. perglabra	Ethyl acetate	Leaves, stem	Antonio et al. (2007b)
		C. laevigata	Hexane fraction	Aerial parts	Oliveira et al. (2020)
90	stigmastenol	*C. pulchella*	Hexane	Leaves	Gómez-Hurtado et al. (2011)
		C. squalida	Dichloromethane	Stem	(Taleb-Contini et al., 2003, 2007)
91	campesterol	*C. squalida*	Dichloromethane	Stem	(Taleb-Contini et al., 2003, 2007)
92	α-spinasterol	*C. squalida*	Dichloromethane	Stem	(Taleb-Contini et al., 2003, 2007)
93	β-sitosterol 3-O-β-D-glucoside	*C. pulchella*	Dichloromethane	Flowers	Gómez-Hurtado et al. (2011)
		C. laevigata	Hexane fraction	Aerial parts	Oliveira et al. (2020)
94	stigmasterol 3-O-β-D-glucoside	*C. pulchella*	Dichloromethane	Flowers	Gómez-Hurtado et al. (2011)
		C. laevigata	Hexane fraction	Aerial parts	Oliveira et al. (2020)
95	β-sitosterol	*C. pulchella*	Dichloromethane	Flowers	Gómez-Hurtado et al. (2011)
		C. subscandens	Dichloromethane	Leaves	Amaro-Luis and Delgado-Méndez (1993)
		C. arnottiana	Hexane fraction	Leaves, flowers	de Gutiérrez et al. (1995)
		C. chaseae	Petroleum ether	Roots	Bohlmann et al. (1982)
		C. squalida	Dichloromethane	Stem	(Taleb-Contini et al., 2003, 2007)
		C. perglabra	Ethyl acetate	Leaves, stem	(Antonio et al., 2007a)
		C. laevigata	Hexane fraction	Aerial parts	Oliveira et al. (2020)
96	19-hydroxy amyrin derivative	*C. odorata*	Aqueous	Leaves	Prabhu (2012)
97	acetyloleanolic acid	*C. odorata*	Dichloromethane	Whole plant	Zhang et al. (2012)
98	ursolic acid	*C. odorata*	Dichloromethane	Whole plant	Zhang et al. (2012)
99	α-amyrin stearate	*C. pulchella*	Hexane	Leaves	Gómez-Hurtado et al. (2011)
100	β-amyrin stearate	*C. pulchella*	Hexane	Leaves	Gómez-Hurtado et al. (2011)
101	lupeoyl stearate	*C. pulchella*	Hexane	Leaves	Gómez-Hurtado et al. (2011)
102	α-amyrin	*C. moritziana*	Dichloromethane fraction	Flowers	Hidalgo-Báez et al. (1998)
		C. arnottiana	Hexane fraction	Leaves, flowers	de Gutiérrez et al. (1995)
103	β-amyrin	*C. arnottiana*	Hexane fraction	Leaves, flowers	de Gutiérrez et al. (1995)
104	squalene	*C. chaseae*	Petroleum ether	Aerial parts	Bohlmann et al. (1982)
		C. morii	Petroleum ether	Aerial parts	Bohlmann et al. (1981)

phytochemically studied for their chemical constituents in the past two decades. These include *C. odorata*, *C. collina*, *C. adenophorum*, *C. tacotana*, *C. pulchella*, *C. arnottiana*, *C. squalida*, *C. moritziana*, *C. leivensis*, *C. tequandamensis*, *C. laevigata*, *C. barranquillensis*, *C. subscandens* (Hieron.) R. M. King & H. Rob., *C. hirsuta* (Hook. & Arn.) R. M. King & H. Rob., *C. glaberrima* (DC.) R. M. King & H. Rob., *C. congesta* (Hook. & Arn.) R. M. King & H. Rob., *C. farinosa* (B. L. Rob.) R. M. King & H. Rob., *C. bullata* (Klatt) R. M. King & H. Rob., *C. perglabra* (B. L. Rob.) R. M. King & H. Rob., *C. opadoclinia* (S. F. Blake) R. M. King & H. Rob., *C. chaseae* (B. L. Rob.) R. M. King & H. Rob., *C. pseudinsignis* R. M. King & H. Rob., *C. connivens* (Rusby) R. M. King & H. Rob., *C. tunariensis* (Hieron.) R. M. King & H. Rob., *C. morii* R. M. King & H. Rob., *C. meridensis* (B. L. Rob.) R. M. King & H. Rob., and *C. tyleri* (B. L. Rob.) R. M. King & H. Rob.

Phytochemically, more than 190 compounds have been isolated and identified from the studied species. These include flavonoids, alkaloids, anthraquinone derivatives, fatty acids, triterpenoids, diterpenes, sesquiterpenes, essential oils, steroids, prostaglandins, and stilbenes among others. Various phytochemicals isolated from the *Chromolaena* species reported in the literature are shown in Tables 2–7, with some of their chemical structures in Figs. 2–7.

Table 4
Alkaloids and anthraquinones reported from genus *Chromolaena*.

S/N	Compound name	Species	Extract	Part(s)	Reference
105	7-angeloylretronecine	*C. odorata*	Dichloromethane	Flowers	Biller et al. (1994)
106	9-angeloylretronecine	*C. odorata*	Dichloromethane	Flowers	Biller et al. (1994)
107	intermedine	*C. odorata*	Dichloromethane	Flowers	Biller et al. (1994)
108	rinderine	*C. odorata*	Dichloromethane	Flowers	Biller et al. (1994)
109	3'-acetylrinderine	*C. odorata*	Dichloromethane	Flowers	Biller et al. (1994)
110	3-hydroxy-1,2,4-trimethoxy-6-methylanthraquinone	*C. odorata*	Dichloromethane	Whole plant	Zhang et al. (2012)
111	3-hydroxy-1,2-dimethoxy-6-methylanthraquinone	*C. odorata*	Dichloromethane	Whole plant	Zhang et al. (2012)
112	1,2-methylenedioxy-6-methylanthraquinone	*C. odorata*	Dichloromethane	Whole plant	Zhang et al. (2012)
113	5aα, 6, 9, 9aβ, 10-pentahydro-10β-hydroxy-7-methylanthra[1,2-*d*][1,3]dioxol-5-one	*C. odorata*	Dichloromethane	Whole plant	Zhang et al. (2012)
114	austrocortinin	*C. odorata*	Dichloromethane	Whole plant	Zhang et al. (2012)

Table 5
Straight chain alkanes and fatty acids reported from genus *Chromolaena*.

S/N	Compound name	Species	Extract	Part(s)	Reference
115	(S)-coriolic acid	*C. odorata*	Chloroform	Aerial part	Hanh et al. (2011)
116	(S)-coriolic acid methyl ester	*C. odorata*	Chloroform	Aerial part	Hanh et al. (2011)
117	(S)-15,16-didehydrocoriolic acid	*C. odorata*	Chloroform	Aerial part	Hanh et al. (2011)
118	(S)-15,16-didehydrocoriolic acid methyl ester	*C. odorata*	Chloroform	Aerial part	Hanh et al. (2011)
119	linoleamide	*C. odorata*	Chloroform	Aerial part	Hanh et al. (2011)
120	linolenamide	*C. odorata*	Chloroform	Aerial part	Hanh et al. (2011)
121	tianshic acid	*C. odorata*	Dichloromethane	Whole plant	Zhang et al. (2012)
122	hexacosanol	*C. odorata*	Whole plant (excluding roots)	Methanol	Gade et al. (2017)
123	Eicosanol	*C. subscandens*	Dichloromethane	Leaves, flowers	Antonio et al. (2007a)
		C. perglabra	Ethyl acetate	Leaves, stem	Antonio et al. (2007b)
124	Prostaglandins	*C. morrii*	Petroleum ether	Aerial parts	Bohlmann et al. (1981)
		C. chaseae	Petroleum ether	Aerial parts	Bohlmann et al. (1982)
		C. tequandamensis	Petroleum ether	Aerial parts	Sanabria-Galindo et al. (1989)
125	heptacosane	*C. perglabra*	Ethyl acetate	Leaves, stem	Antonio et al. (2007b)
126	hexatriacontane	*C. perglabra*	Ethyl acetate	Leaves, stem	Antonio et al. (2007b)
127	tetratetracontane	*C. perglabra*	Ethyl acetate	Leaves, stem	Antonio et al. (2007b)
128	tetratriacontane	*C. perglabra*	Ethyl acetate	Leaves, stem	Antonio et al. (2007b)

4.1. Flavonoids and phenolic acids

Flavonoids are well distributed in the plant kingdom and have been reported to show diverse biological activities. Structurally, flavonoids are made up of 15 carbon atoms arranged in a C_6–C_3–C_6 pattern. This class of compound can be grouped into six, namely flavones, isoflavones, flavanols, flavanones, anthocyanidins, and flavonols based on the nature of hydroxylation on the ring systems (Nijveldt et al., 2001). As regards the *Chromolaena* genus, flavonoids and their derivatives are the most diverse group of specialized phytochemicals isolated from its species, and they have been utilized in the chemotaxonomic classification of the genus (de Oliveira et al., 2017; Baldoqui et al., 2019). A systematic analysis of the available literature showed that 79 flavonoids have been identified from the *Chromolaena* species so far. Meanwhile, only few phenolic acids such as (Z)-*p*-coumaric acid, caffeic acid, caffeic acid methyl ester, gallic acid, 4-hydroxybenzoic acid, protocatechuic acid, protocatechuic acid methyl ester, and *p*-methoxybenzoic acid **[10–16, 52]** have been reported from the genus (Table 2).

4.2. Steroids and triterpenoids

Steroids and triterpenoids, though few, are components of *Chromolaena* species as revealed in the data available. A total of 8 steroids have been isolated from the *Chromolaena* species. These include poriferasterol, stigmasterol, stigmastenol, campesterol, α-spinasterol, β-sitosterol 3-O-β-D-glucoside, stigmasterol 3-O-β-D-glucoside, and β-sitosterol **[88–95]**. In addition to the steroids, 19-hydroxy amyrin, 3β-acetyloleanolic acid, ursolic acid, α-amyrin stearate, β-amyrin stearate, lupeoyl stearate, α-amyrin and β-amyrin **[96–104]** are the main reported triterpenoids or derivatives from the genus (Table 3 and Fig. 3).

4.3. Alkaloids and anthraquinones

To the best of our knowledge, the presence of alkaloids and anthraquinone derivatives has been identified from only one species so far. Five pyrrolizidine-type alkaloids **[105–109]** have been found in *C. odorata* (Biller et al., 1994). Similarly, anthraquinone derivatives **[110–114]** were reported from *C. odorata* (Zhang et al., 2012) (Table 4 and Fig. 4).

4.4. Straight-chain alkanes and fatty acids

A review of available literature revealed that fatty acids and the derivatives - fatty alcohols and amides **[115–124]** have been identified from genus *Chromoleana,* along with four long-chain alkanes **[125–128]** (Antonio et al., 2007b) (Table 5 and Fig. 5).

4.5. Sesquiterpenoids and diterpenoids

Chromolaena genus is rich in sesquiterpenoids, such cadinenes, azulenoid, germacranolides, acyclic sesquiterpenes and others. Notably, azulenoid-sesquiterpenoids **[129–130]**, cadinene-sesquiterpenoids **[131–134]**, carotane-sesquiterpenoids **[135–136]**, chromolaevanedione **[137]** and eudesm-4(15)-ene-1β,6α-diol [**138**]. Others are germacranolide-type sesquiterpenes **[139–143]** from *C. glaberrima* and *C. opadoclinia* (El-Sayed et al., 1988), acyclic sesquiterpene **[144]**, bisabolene [**145**] from *C. pseudinsignis,* and trinorguaiane- and cadalene-type sesquiterpenes [**146–148**]. In addition to this type of terpenoids, a number of diterpenoids has been identified from *Chromolaena* species, including *C. odorata*, *C. pulchella*, *C. collina* and *C. connivens*. These diterpenoids could be grouped as *ent*-kaurane-type diterpenoids **[149–150]**, clerodane-skeleton diterpenoids **[151–159]** and labdane-type diterpenoids **[160–163]** (Table 6 *and* Fig. 6).

Table 6
Sesquiterpenoids and diterpenoids isolated from genus *Chromolaena*.

S/N	Compound name	Species	Extract	Part(s)	Reference
129	dehydrochromolaenin	*C. laevigata*	Ethanol-ether	Aerial parts	Misra et al. (1985)
130	sphatulenol	*C. pulchella*	Hexane	Leaves	Gómez-Hurtado et al. (2011)
131	7,7-dihydroxycalamen-12-oic acid lactone	*C. laevigata*	Ethanol-ether, Dichloromethane fraction	Aerial parts	Misra et al. (1985) Oliveira et al. (2020)
132	7-hydroxy-7-methoxycalamen-12-oic acid lactone	*C. laevigata*	Ethanol-ether	Aerial parts	Misra et al. (1985)
133	chromolaevigone glucoside	*C. laevigata*	Butanol fraction	Aerial parts	Oliveira et al. (2020)
134	6α, 12-didydroxy-cadin-3-en-2-one	*C. pseudinsignis*	Petroleum ether	Roots	Bohlmann et al. (1982)
135	10-oxo-isodauc-3-en-15-al	*C. laevigata*	Ethanol-ether	Aerial parts	Misra et al. (1985)
136	10α-hydroxyisodauc-3-en-15-al	*C. laevigata*	Ethanol-ether	Aerial parts	Misra et al. (1985)
137	chromolaevanedione	*C. laevigata*	Ethanol-ether	Aerial parts	Misra et al. (1985)
138	eudesm-4(15)-ene-1β,6α-diol	*C. pulchella*	Hexane	Leaves	Gómez-Hurtado et al. (2011)
139	Heliangolide chromolaenide	*C. glaberrima*	Organic solvent	Aerial part	Çalzada et al. (1980)
140	deltoidin A	*C. opadoclinia*	Dichloromethane	Aerial parts	El-Sayed et al. (1988)
141	8-*β*-[5'-angeloyloxy]-tigloyloxyparthenolide	*C. opadoclinia*	Dichloromethane	Aerial parts	El-Sayed et al. (1988)
142	8-*β*-[4'-angeloyloxy]-5'-hydroxytigloyloxyparthenolide	*C. opadoclinia*	Dichloromethane	Aerial parts	El-Sayed et al. (1988)
143	8-*β*-[3'-angeloyloxy]-4'-hydroxyethacryloyloxyparthenolide	*C. opadoclinia*	Dichloromethane	Aerial parts	El-Sayed et al. (1988)
144	*β*-farnesene	*C. pseudinsignis*	Petroleum ether	Roots	Bohlmann et al. (1982)
145	bisabolene	*C. pseudinsignis*	Petroleum ether	Roots	Bohlmann et al. (1982)
146	radicol	*C. odorata*	Chloroform	Aerial part	Pel et al. (2020)
147	1,6-dimethyl-4-(1-methylethyl) naphthalene (cadalene)	*C. odorata*	Hexane	Leaves	Kouamé et al. (2013)
148	tetradehydrochromoarnottione	*C. laevigata*	Ethanol-ether	Aerial parts	Misra et al. (1985)
149	15-angeloyloxy-16,17-epoxy-19-kauronic acid	*C. odorata*	Hexane fraction	Roots	Wafo et al. (2011)
150	16-kauren-19-oic acid	*C. odorata*	Hexane fraction	Roots	Wafo et al. (2011)
151	(5*R*,8*R*,9*S*,10*R*)-(−)-hardwikiic acid	*C. pulchella*	Dichloromethane	Flowers	Gómez-Hurtado et al. (2011)
152	(5*R*,8*R*,9*S*,10*R*)-(−)-hardwikiate	*C. pulchella*	Dichloromethane	Flowers	Gómez-Hurtado et al. (2011)
153	(5*S*,8*R*,9*S*,10*R*)-(−)-hautriwaic acid lactone	*C. pulchella*	Hexane	Leaves	Gómez-Hurtado et al. (2011)
154	methyl (5*R*,8*R*,9*S*,10*R*)-(−)-nidoresedate	*C. pulchella*	Dichloromethane	Flowers	Gómez-Hurtado et al. (2011)
155	methyl (8*R*,9*R*)-(−)-strictate	*C. pulchella*	Dichloromethane	Flowers	Gómez-Hurtado et al. (2011)
156	6α-isobutyryloxy-7β-acetoxy-13-Z-kolavenic acid	*C. laevigata*	Ethanol-ether	Aerial parts	Misra et al. (1985)
157	6α,7β-diacetoxy-13-Z-kolavenic acid	*C. laevigata*	Ethanol-ether	Aerial parts	Misra et al. (1985)
158	6α-isobutyryloxy-7β-angeloyloxy-13, 14-dihydrokolavenic acid	*C. laevigata*	Ethanol-ether	Aerial parts	Misra et al. (1985)
		C. connivens	Petroleum ether	Aerial parts	Tamayo-Castillo et al. (1989)
159	6α,7β-dihydroxy-norkolavenic acid	*C. laevigata*	Ethanol-ether	Aerial parts	Misra et al. (1985)
160	trans-communic acid	*C. collina*	Petroleum ether	Aerial part	(Bohlmann et al., 1980)
		C. laevigata	Dichloromethane fraction	Aerial parts	Oliveira et al. (2020)
161	7α-acetoxy-trans-communic acid	*C. collina*	Petroleum ether	Aerial part	(Bohlmann et al., 1980)
162	*ent*-labd-13-ene-8,15-diol	*C. pulchella*	Hexane	Leaves	Gómez-Hurtado et al. (2011)
		C. connivens	Petroleum ether	Aerial parts	Tamayo-Castillo et al. (1989)
163	(+)-isoabienol	*C. pulchella*	Hexane	Leaves	Gómez-Hurtado et al. (2011)

4.6. Essential oils and other phytochemical compounds

Essential oils/volatile oils are invaluable ingredients in insecticides, cosmetics, and foods. A number of essential oils/volatile compounds have been identified from *Chromolaena* species, including *C. barranquillensis* (Acevedo et al., 2011), *C. odorata* (Koba et al., 2011), *C. collina* (Bohlmann et al., 1981b), *C. laevigata* (Valarezo et al., 2016; Murakami et al., 2013), *C. chaseae* (Bohlmann et al., 1982), *C. morii* (Bohlmann et al., 1981a), *C. adenophorum* (Chen et al., 2018) and *C. connivens* (Tamayo-Castillo et al., 1989) among others. The notable essential oils are germacrene D **[164]**, laevigatin **[165]**, α-pinene **[166]**, bicyclogermacrene **[167]**, limonene **[167]**, and viridiflorol **[169]**. Besides these constituents, there are other phytochemical compounds reported from genus *Chromolaena*. These include the lignans **[170–174]**, along with coumarino-lignoid compounds cleomiscosin A and D **[175–176]** from *C. odorata* (Zhang et al., 2012). The presence of stilbene **[177]**, bergenin [**178**], uridine [**179**], chlorogenic acid [**180**], acetophenone derivative [**181**] and monoterpene lactone [**182**] have also been reported from the genus. Hydroquinone **[183]**, a benzenediol, was isolated from *C. subscandens* (Antonio et al., 2007a). Monocarboxylic acid, trachelanthis acid **[184]** was present in *C. laevigata*. The derivatives of chalcones **[185–190]** and coumarins **[191–194]** were also identified from the genus (Table 7 and Fig. 7).

5. Pharmacological activities of *Chromolaena* species

Biological activities of the crude extracts, essential oils, and those of the pure isolates from the species in the genus *Chromolaena* have been investigated by different researchers. In the following sections, some of the important biological activities are discussed.

5.1. Antibacterial activity

5.1.1. Crude extracts and essential oils

Recently, studies have shown that herbal medicines offer good sources of finding antibacterial drugs (Chandra et al., 2020; Garg and Roy, 2020). Interestingly, different extracts of the genus *Chromolaena* have been documented in the literature to exhibit antibacterial actions against a wide range of both Gram-positive and Gram-negative bacteria. The most investigated part has been the leaves using different organic solvents, including dichloromethane, ethyl acetate, ethanol, methanol, butanol, and aqueous solution (Natheer, 2012; Naidoo et al., 2011; Mondal et al., 2012; Vital and Rivera, 2009; Vijayaraghavan et al., 2018; Arief-Prajitno and Happy-Nursyam, 2015) (Table 8). While the *C. odorata* extracts showed appreciable antibacterial activities, other species displayed lesser activity when compared with the positive controls used (Table 8). Notably, hexane, ethyl acetate and methanol leaves extract of *C. odorata* exhibited better inhibitory activity against *Vibrio harveyi*, with zone of inhibition ranging from 7.0 to 19.0 mm when compared with known antibacterial drug, streptomycin (28.0 mm) (Arief-Prajitno and Happy-Nursyam, 2015). Methanol leaves extract of *C. odorata* inhibited the growth of *Escherichia coli*, *Shigella flexneri*, *Proteus mirabilis*, *Pseudomonas diminuta*, *Enterobacter cloacae*, and *Staphylococcus aureus*, with MICs ranging from 12.5 to 50 mg/ml (Natheer, 2012).

Table 7
Essential oils and other phytochemical compounds isolated from genus *Chromolaena*.

S/N	Compound name	Species	Extract	Part(s)	Reference
164	germacrene D	*C. odorata*	Steam-distillation	Leaves	Koba et al. (2011)
		C. collina	Petroleum ether	Roots, aerial parts	(Bohlmann et al., 1980)
		C. pseudinsignis	Petroleum ether	Roots	Bohlmann et al. (1982)
		C. chaseae	Petroleum ether	Roots	Bohlmann et al. (1982)
		C. laevigata	Hydro-distillation	Aerial part	Valarezo et al. (2016)
165	laevigatin	*C. laevigata*	Hydro-distillation	Leaves, capitulum, and cypsela	(Valarezo et al., 2016; Murakami et al., 2013)
166	α-pinene	*C. laevigata*	Hydro-distillation	Aerial part	Valarezo et al. (2016)
167	bicyclogermacrene	*C. laevigata*	Hydro-distillation	Aerial part	Valarezo et al. (2016)
		C. morii	Petroleum ether	Aerial parts	Bohlmann et al. (1981)
168	limonene	*C. laevigata*	Hydro-distillation	Aerial part	Valarezo et al. (2016)
169	viridiflorol	*C. laevigata*	Hydro-distillation	Aerial part	Valarezo et al. (2016)
170	(−)-syringaresinol	*C. odorata*	Dichloromethane	Whole plant	Zhang et al. (2012)
171	(−)-pinoresinol	*C. odorata*	Dichloromethane	Whole plant	Zhang et al. (2012)
172	7-methoxy-7-*epi*-medioresinol	*C. odorata*	Dichloromethane	Whole plant	Zhang et al. (2012)
173	(−)-medioresinol	*C. odorata*	Dichloromethane	Whole plant	Zhang et al. (2012)
174	citrusin	*C. odorata*	Ethyl acetate	Aerial part	Pel et al. (2020)
175	cleomiscosin A	*C. odorata*	Dichloromethane	Whole plant	Zhang et al. (2012)
176	cleomiscosin D	*C. odorata*	Dichloromethane	Whole plant	Zhang et al. (2012)
177	(+)-8b-*epi*-ampelopsin A	*C. odorata*	Chloroform	Aerial part	Pel et al. (2020)
178	bergenin	*C. odorata*	Ethyl acetate	Aerial part	Pel et al. (2020)
179	uridine	*C. odorata*	Ethyl acetate	Aerial part	Pel et al. (2020)
180	chlorogenic acid	*C. arnottiana*	Ethanol	Aerial parts	Clavin et al. (2007)
181	2-hydroxy-4-(2′-hydroxypropoxy)-acetophenone	*C. arnottiana*	Chloroform fraction	Leaves, flowers	de Gutiérrez et al. (1995)
182	loliolide	*C. arnottiana*	Chloroform fraction	Leaves, flowers	de Gutiérrez et al. (1995)
183	hydroquinone	*C. subscandens*	Dichloromethane	Leaves, flowers	Antonio et al., 2007a
184	trachelanthic acid	*C. laevigata*	Butanol fraction	Aerial parts	Oliveira et al. (2020)
185	2',4-dihydroxy-4',5',6'-trimethoxychalcone	*C. odorata*	Chloroform	Leaves	Saiful (2012)
			Chloroform	Flowers	Suksamrarn et al. (2004)
			Ethyl acetate	Leaves	Kumkarnjana et al. (2018)
			Dichloromethane	Whole plant	Zhang et al. (2012)
186	2'-hydroxy-3',4,4',5',6'-pentamethoxychalcone	*C. odorata*	Acetone	Leaves	Wollenweber et al. (1995)
187	2'-hydroxy-4,4',5',6'-tetramethoxychalcone	*C. odorata*	Chloroform, Acetone, Hexane	Flowers, Leaves, Leaves	(Suksamrarn et al., 2004; Wollenweber et al., 1995; Kouamé et al., 2013)
188	2′,4-dihydroxy-4′,5′,6′-trihydroxy chalcone	*C. odorata*	Acetone	Leaves	Wollenweber et al. (1995)
189	4,6′-dihydroxy-2′,3′,4′-trimethoxychalcone	*C. odorata*	Chloroform	Aerial part	Pel et al. (2020)
190	6′-hydroxy-4,2′,3′,4′tetramethoxychalcone	*C. odorata*	Chloroform	Aerial part	Pel et al. (2020)
191	umbelliferone	*C. subscandens*	Dichloromethane	Leaves, flowers	Antonio et al. (2007b)
192	7-methoxycoumarin	*C. pseudinsignis*	Petroleum ether	Roots	Bohlmann et al. (1982)
193	coumarin	*C. tunariensis*	Petroleum ether	Aerial parts	Tamayo-Castillo et al. (1989)
194	*O*-hydroxycinnamic acid	*C. tunariensis*	Petroleum ether	Aerial parts	(Tamayo-Castillo et al. 1989)

5.1.2. Pure compounds

The antibacterial activities of the *Chromolaena* species are due to their chemical constituents. Besides the sesquiterpenoid **[139]** isolated from the aerial part of *C. glaberrima* (Çalzada et al., 1980), the reported antibacterial compounds are mainly the flavonoids isolated from the genus (Table 8) whose activities may be due to the hydroxyl groups at different sites on the benzene ring of the flavonoids and the lipophilicity of chalcone's ring A (Xie et al., 2015). Notably, flavonoids **[3]** and **[32]**, as well as chalcone **[185]** exhibited stronger efflux inhibitory action against methicilline-resistant *S. aurues* strains than the positive control (Saiful, 2012). Similarly, scutellarein tetramethyl ether **[22]** and sinensetin **[43]** were reported to inhibit diarrhoeal-causing strains of *Vibrio cholera*, *Salmonella enterica*, *Klebsiella oxytoca*, and *Shigella sonnei* (MICs = 0.156–1.25 mg/mL) (Atindehou et al., 2013).

5.2. Anticancer activity

5.2.1. Crude extracts and essential oils

Cancers and tumours remain a heavy burden globally. Meanwhile, the uses of *Chromolaena* species in the fight against cancers have been documented (Table 1). Moreover, evidence abounds of drugs from medicinal plants currently used in cancer and tumour chemotherapy. For instance, the anti-cancer agent, Paclitaxel, was commercially introduced in the U.S. for clinical use in the 1990s. It was isolated from *Taxus brevifolia* (Zhu and Chen, 2019). Camptothecin, a topoisomerase inhibitor, was isolated from *Camptotheca acuminate*. It was discovered in 1966 (Wall, 1998). Although there is improvement in cancer diagnosis and chemotherapy in recent time, successful commercialization of these drugs and many others from natural source affirms that medicinal plants remain solution or part of the solution to our common enemy, cancers. Thus, given the need for new and more anticancer agents, the roles of extracts and constituents of *Chromolaena* species in fighting different forms of cancer, including lung cancer, colon cancer, breast cancer, liver cancer, and leukemia have been investigated by different researchers (Table 9).

5.2.2. Pure compounds

The compound **[48]** from *C. leivensis* induced apoptosis against colon (HCT116), pancreas (MIA PaCa-2, Panc28) and lung (A549) cancer cells. The isolate **[50]** displayed mild cytotoxicity against colon cell line (CaCo-2). It also showed proliferative effects in A549, Panc 28, MIA PaCa, and HCT116 cells. None of the compounds displayed inhibitory effect towards breast (SKBr3) and liver (HepG2) cancer cell lines at the studied concentration (5–80 μM). However, there was synergetic

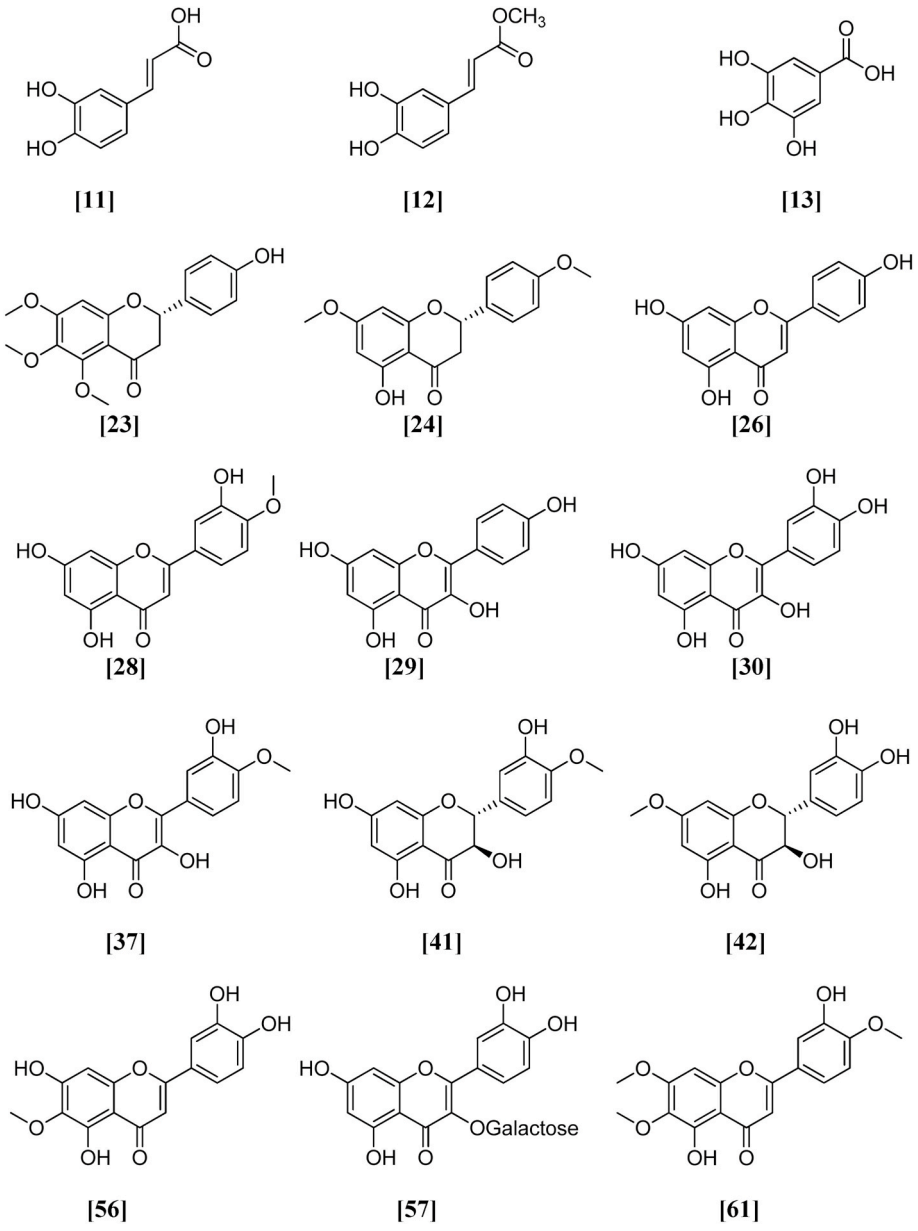

Fig. 2. Chemical structures of some flavonoids and phenolic acids isolated from the genus *Chromolaena*.

increase in inhibition of compound **[50]** against MIA PaCa-2 and Panc28 after 48 h when used in combination with flavonoid **[48]** (Whitted et al., 2016). Cytotoxic activity of flavonoid (R)-pinocembrin **[47]** isolated from the ethanol leaves extract of *C. leivensis* has been reported. The study showed that the isolate reduced cell proliferation against cervix SiHa, prostate PC-3, colon HT29, breast MDA-MB-231, and lung A549 cancer cell lines (IC_{50} = 30.9–58.9 mg/L) (Rodriguez et al., 2018). Compound **[187]** isolated from the hexane-soluble portion of ethanol leaves extract of *C. odorata* reportedly showed cytotoxic and anticlonogenic properties (Kouamé et al., 2013). Constituent **[20]** from *C. odorata* exerted moderate cytotoxic effect against human lung cancer cell (NCI–H187), with the MIC value of 24.6 μM, while luteolin **[21]** showed moderate toxicity against NCI–H187 cells (MIC, 19.2 μM) and weak toxicity against human breast cancer cells (MIC, 38.4 μM). (Suksamrarn et al., 2004). Similarly, compounds **[185]** and **[111]** isolated from *C. odorata* displayed weak cytotoxic activity against U251-SP and PC-6 human tumour cell lines (Zhang et al., 2012). Flavonoids **[48]** and **[50]** isolated from *C. leivensis* exhibited cytotoxicity via 3-(4, 5-Dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay against some cancer cell lines (Ruben et al., 2011).

5.3. Antiprotozoal activity

5.3.1. Crude extracts

An earliest study on the antiprotozoal activity of the genus showed that the ethanol crude extract of *C. christieana* exhibited trypanocidal activity against *Trypanosoma cruzi* at a concentration of 250 μg/ml (Rojas de Arias et al., 1995). The aerial part of ethanol crude extract of *C. leivensis* inhibited *T. cruzi,* with IC_{50} of 8 μg/mL when compared with a drug used to treat trypanosomiasis - Nifurtimox, IC_{50} = 10 μM (Calderón et al., 2010) (Table 10). Antiprotozoal activity of the stem and leaves of *C. perglabra* has been reported against the causative agents of chagas and leishmaniosis (Antonio et al., 2007b). Ethanol leaves extract of *C. odorata* was found to exhibit *in vivo* antimalarial activity against chloroquine-sensitive strain of *Plasmodium berghei* at a concentration of 500 mg/kg (Omoya and Momoh, 2014). The ethanol and dichloromethane extracts of *C. hirsuta* exerted considerable antiprotozoal effect against *T. cruzi* and *Leishmania amazonensis* (Taleb-Contini et al., 2004).

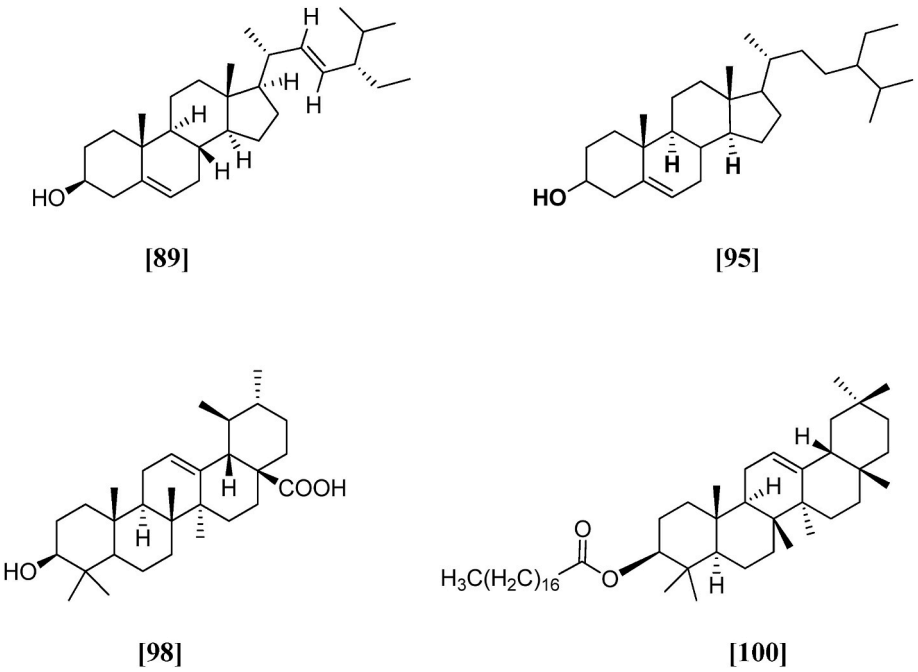

Fig. 3. Chemical structures of some steroids and triterpenoids isolated from the genus *Chromolaena*.

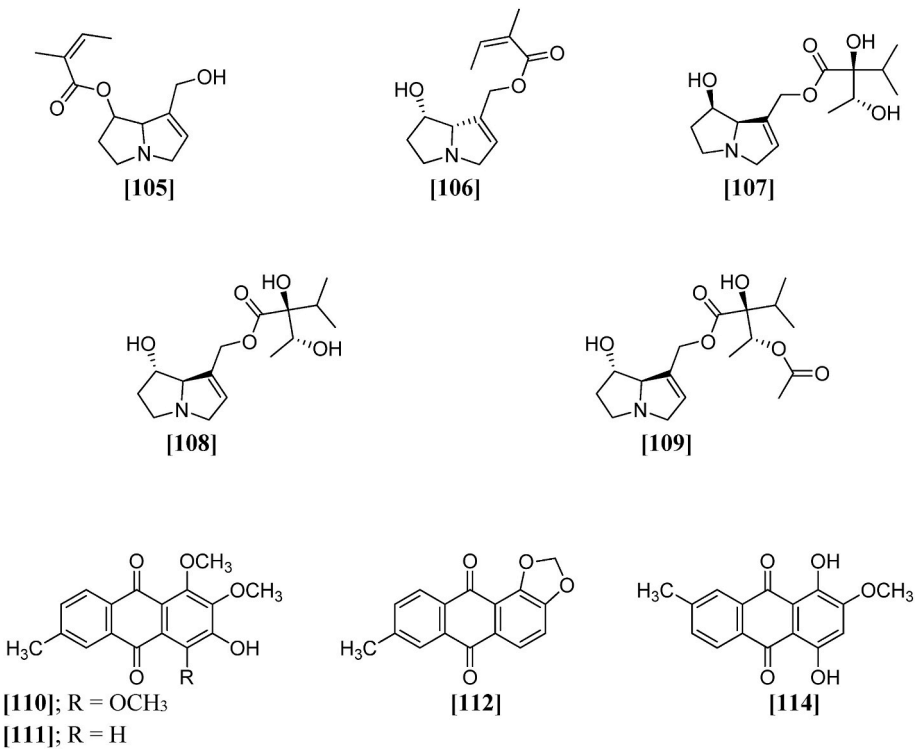

Fig. 4. Chemical structures of some alkaloids and anthraquinones isolated from the genus *Chromolaena*.

5.3.2. Pure compounds

Compounds **[89]** and **[122]** isolated from *C. odorata* showed larvicidal and repellant activity against *Culex quinquefasciatus* via the inhibition of acetylcholinesterase, with **[122]** showing significant activity (LC_{50} = 3.56 μg/ml) (Gade et al., 2017). Flavonoids **[30]**, **[64]**, **[69–70]** and **[73]** isolated from *C. hirsuta* had considerable antiprotozoal activity on the growth of *T. cruzi* and *L. amazonensis,* with IC_{50} between 102.4 and 352.6 μg/ml against *T. cruzi* (Taleb-Contini et al., 2004) (Table 10).

5.4. Antioxidant and anti-inflammatory activities

5.4.1. Crude extracts

Previous studies have shown that extracts and active constituents of *Chromolaena* spp have promising scavenging potential against a number of radical ions (Table 11). Antioxidant activity of the methanol leaves and flowers extracts of *C. bullata* has been studied using 2, 2-diphenyl-1-picrylhydrazyl (DPPH) and 2, 2'-azino-bis-(3-ethylbenzothiazoline6-sulphonic acid) (ABTS) (Rodríguez and Torrenegra, 2017). Free radicals

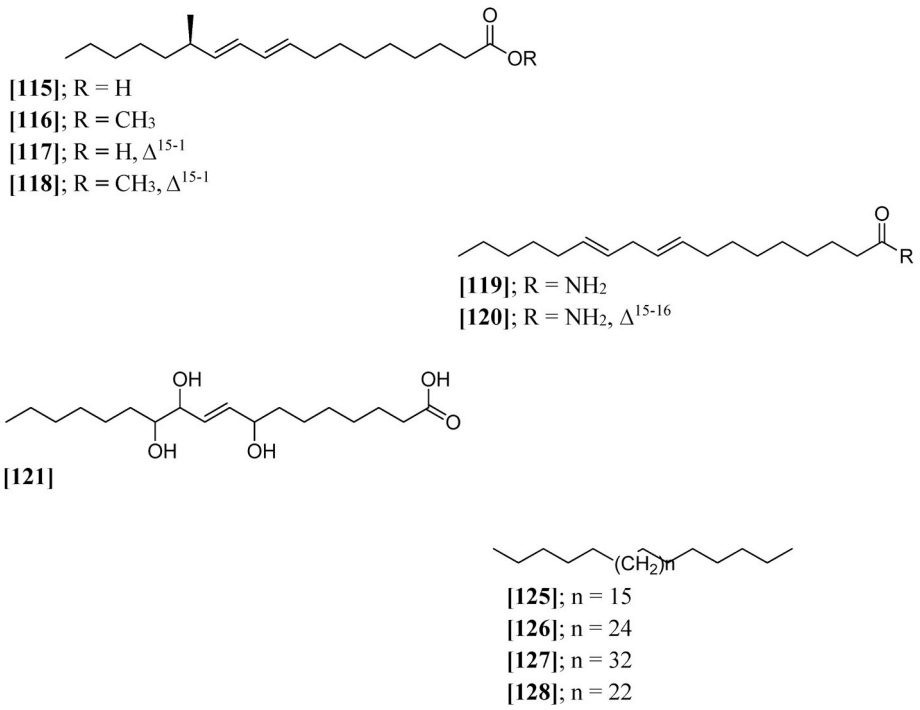

Fig. 5. Chemical structures of some straight-chain alkanes, fatty acids and their derivatives isolated from the genus *Chromolaena*.

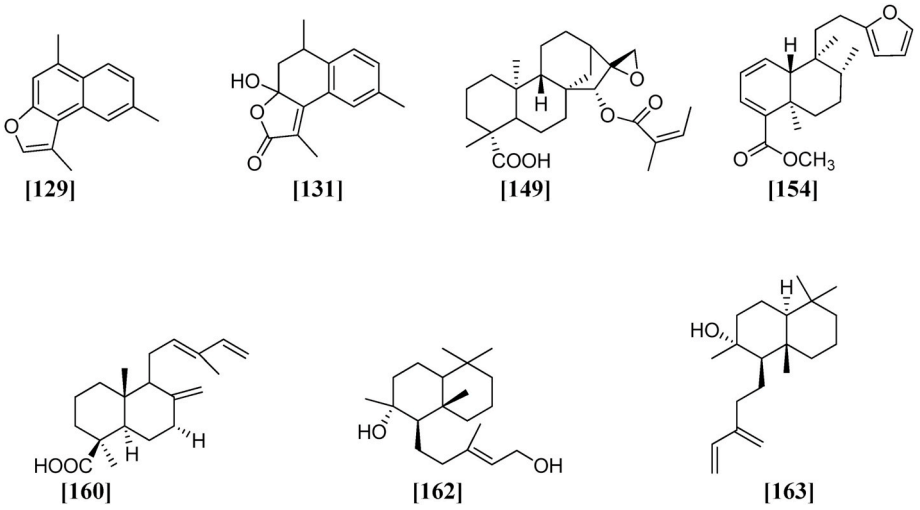

Fig. 6. Chemical structures of some sesquiterpenoids and diterpenoids isolated from the genus *Chromolaena*.

scavenging activity of the flavonoids from *C. tacotana* leaves extract have been reported (Torrenegra et al., 2018). The antioxidant activity of *C. laevigata* ethanol leaves extract was evaluated against DPPH and ABTS. The highest free radical scavenging activities were IC_{50} of 11.66 ± 1.0 μg/mL for DPPH and IC_{50} of 12.45 ± 0.50 μg/mL for ABTS (Herrera-Calderon et al., 2017). Antioxidant activities of various extracts of *C. odorata* have been reported using different assays, including DPPH, ABTS, nitric oxide and hydroxyl radicals (Alisi and Onyeze, 2008; Bhargava et al., 2013; Melinda et al., 2010; Putri and Fatmawati, 2019; Thang et al., 2001; Srinivasa et al., 2010) (Table 11). In all these studies, the leaves' part has received the most considerable attention. The leaves methanol extract of *C. odorata* inhibited the occurrence of inflammation in carrageenan-induced rat paw edema at a concentration of 50, 100 and 200 mg/kg (Taiwo et al., 2000). Anti-inflammatory effect of ethanol extract of *C. leptocephala* has also been reported (Rebaza et al., 2017).

5.4.2. Pure compounds

Odoratenin **[1]** isolated from the methanol extract of the leaves of *C. odorata* was reported to exhibit potent antioxidant activity (IC_{50} = 23.74 μM) than the control trolox (IC_{50} = 31.32 μM) (Putri and Fatmawati, 2019). Six fatty acids **[115–120]** isolated from the aerial part of the *C. odorata* methanol extract reportedly showed anti-inflammatory activity, with compounds **116** and **118** exhibited better activity than the positive control, Resveratrol (Hanh et al., 2011). Nepetin **[56]**, jaceosidin **[19]** and hispidulin **[58]** from the dichloromethane aerial part extract of the *C. arnottiana* have been reported to possess anti-inflammatory activity (Clavin et al., 2007).

5.5. Anti-diabetic and anti-adipogenic activities

5.5.1. Crude extracts

The mild α-glucosidase inhibitory activity of the methanol, hexane,

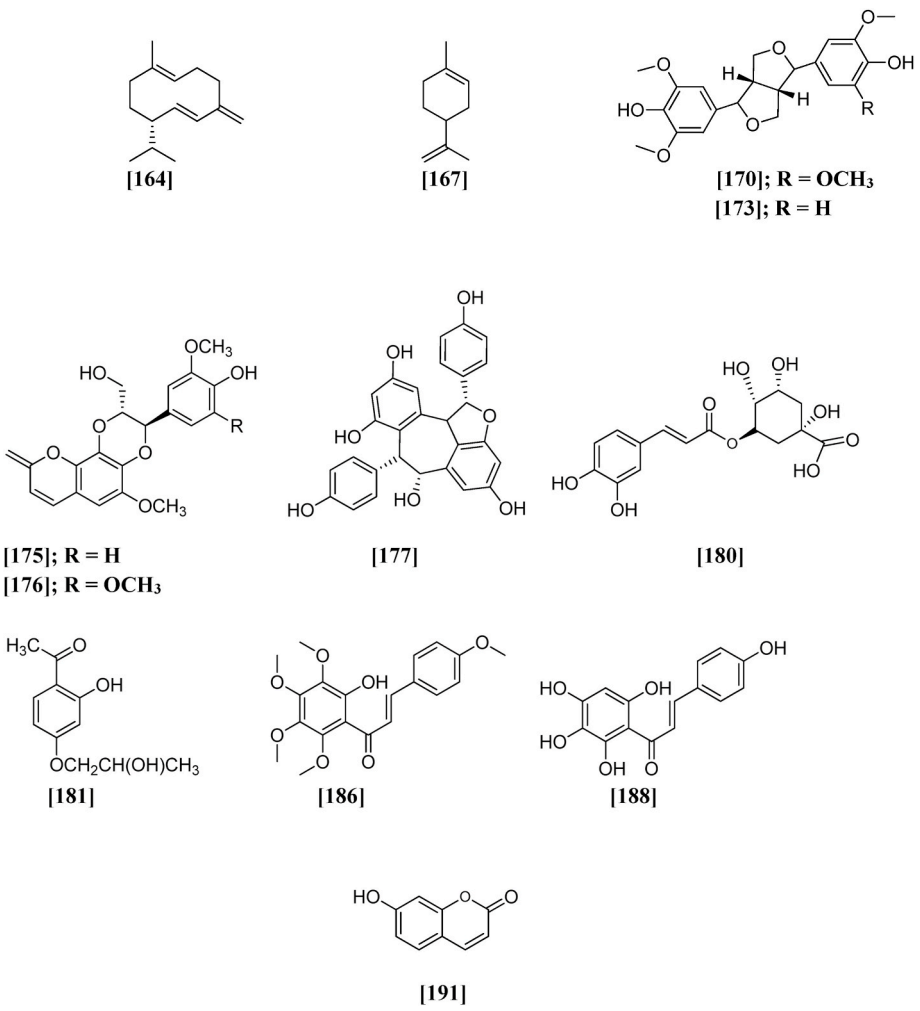

Fig. 7. Chemical structures of some essential oils, lignans, chalcones, and other phytochemicals isolated from the genus *Chromolaena*.

aqueous, dichloromethane and ethanol leaves extract of *C. odorata* have been reported, with ethanol extract showing best activity at IC_{50} of 779.54 μg/mL (Putri and Fatmawati, 2019). In another study, ethanol leaves extract of *C. odorata* reduced the serum glucose level in streptozotocin-induced diabetic rats in a dose-dependent concentrations at 200 and 400 mg/kg, p.o. (Onkaramurthy et al., 2013). The anti-obesity activities of the methanol, ethanol, and hexane extracts of the leaves of *C. odorata* have been reported. It was revealed that the ethanol extract showed significant suppression and inhibition of lipid accumulation in 3T3-L1 adipocytes at 20 and 40 mg/ml (Kumkarnjana et al., 2018).

5.6. Antifungal activity

5.6.1. Crude extracts and essential oils

Essential oils from *C. laevigata* aerial parts exhibited antifungal activity against *Trichophyton rubrum* (ATCC 28188) and *Trichophyton mentagrophytes* (ATCC 28185), with MICs of 125 and 250 μg/ml respectively (Valarezo et al., 2016). Antifungal activity of *C. adenophorum* has also been documented (Katoch et al., 2012; Bhattarai and Shrestha, 2009). The aerial part of the hexane fraction of *C. laevigata* exhibited moderate inhibition *Trichophyton rubrum* (ATCC 28289), *Trichophyton mentagrophytes* (ATCC 11480) and *Microsporum gypseum* (ATCC 14683), with MICs ranging from 125 to 500 μg/ml (Oliveira et al., 2020). The aqueous ethanol leaves extract of *C. odorata* inhibited the growth of *Cryptococcus neoformans*, *Microsporum gypseum, Trichophyton mentagrophytes* and *Trichophyton rubrum,* with MICs ranging from 62.5 to 500 μg/ml (Ngane et al., 2006). Ethanol and aqueous leaves extract of *C. odorata* exhibited varying degree of inhibition against *Phytophthora megakarya* (Adeyemi et al., 2018; Chuyong et al., 2019).

5.7. Insecticidal and molluscicidal activity

5.7.1. Crude extracts

Methanol leaves extract of *C. odorata* showed *in vitro* insecticidal activities against *Anopheles gambiae* larvae, with LC_{50} and LC_{90} values of 31.33 and 95.73 mg/L respectively (Ileke Kayode and Olabimi Isaac, 2019). The aqueous leaves extract of *C. odorata* exhibited *in vitro* larvicidal activity against the larva of *Simulium* spp (blackflies), with LC_{50} of 0.001 mg/mL (Matur and Davou, 2007). The ethanol and the aqueous leaves extracts of *C. odorata* have been reported to exhibit molluscicidal activity against the adult form of *Biomphalaria pfeifferi,* with LC_{50} of 217.57 and 288.96 ppm respectively (Otarigho and Morenikeji, 2013).

5.8. Anti-diarrhoeal and spasmolytic activity

5.8.1. Crude extracts

The *in vitro* anti-diarrhoeal activity of the cyclohexane, dichloromethane, ethyl acetate, and butanol extracts of *C. odorata* leaves against diarrhoeal-causing pathogens have been reported, with dichloromethane and butanol extracts showing the best activity against *Vibro cholerae* at an MICs of 0.156 and 0.312 mg/ml respectively (Atindehou et al., 2013). In a previous animal model experiment, methanol leaves

Table 8
Antibacterial activities of *Chromolaena* species.

Chromolaena species	Extract/compound	Testing model/ concentration	MICs	Control	Experimental results	Reference
C. moritziana	Aqueous leaves extract	Disc diffusion method	Zones of inhibition (22 and 35 mm)	No report	Inhibition of *S. aureus* and *B. cereus*.	Hidalgo-Báez et al. (1998)
C. moritziana	DCM leaves and EA flower extracts	Disc diffusion method	Zone of inhibition (22 and 25 mm)	No report	Inhibition of *S. aureus* and *B. cereus*	Hidalgo-Báez et al. (1998)
C. laevigata	Essential oils	Broth microdilution method	MIC = >1000 μg/ml	Gentamicine, (MIC, 0.39 μg/ml) Ampicilline, (MIC, 3.125 μg/ml)	Inactive against *P. aeruginosa*, *K. pneumonia*, *P. vulgaris*, *E. coli*, *S. typhimurium*, *E. faecalis* and *S. aureus*	Valarezo et al. (2016)
C. laevigata	Essential oils (at flowering stage)	Broth microdilution method	MICs = 62.5–500 μg/ml	Chloramphenicol, MIC = 4.0 μg/ml	Inhibition of *E. coli, S. aureus* and *P. aeruginosa*, with best activity against *S. aureus* (MIC, 62.5 μg/ml)	Murakami et al. (2013)
C. glaberrima	Chromolaenide **[139]**	Microdilution method	MIC = 200 – >1000 μg/ml	No report	Inhibition of *S. aureus*. However, *E. coli* and *K. pneumonia* were inactive (MIC >1000 μg/ml)	Çalzada et al. (1980)
C. laevigata	HEX, BuOH, DCM, EA and Hydromethanolic fractions	Microdilution method	MICs = 125 – >1000 μg/ml	No report	HEX and DCM fractions had mild inhibition of *B. subtilis*, with MIC of 125 and 500 μg/ml respectively. However, no appreciable inhibition by all the fractions against *E. coli*, *P. aeruginosa*, and *S. aureus*, with MIC >1000 μg/ml.	Oliveira et al. (2020)
C. odorata	MeOH leaves extract	Disc diffusion and serial dilution methods	MICs = 12.5–50.0 mg/ml	Chloramphenicol (MIC <2.0 μg/ml) Streptomycin sulfate (MIC <2.0 μg/ml)	Inhibition of *E. coli*, *S. flexneri*, *P. mirabilis*, *P. diminuta, E. cloacae* and *S. aureus*	Natheer (2012)
C. odorata	ET and aqueous leaves extracts	Agar diffusion method/ 10, 20, and 30 mg/ml	Zones of inhibition, ranging from 4.0 to 25.0 mm	Streptomycin, 9.0–12.1 mg/ml	Inhibition of *P. aeruginosa*, *S. aureus*, *E. coli*, *B. subtilis* and *B. cereus*	Vijayaraghavan et al. (2018)
C. odorata	Water leaves & stem extracts	Serial dilution method	Nil		Inactive against *B. subtilis*, *B. cereus*, *S. aureus*, *S. epidermidis* *E. coli*, *P. vulgaris*, *E. aerogenes* and *S. sonnei*	Naidoo et al. (2011)
	EA leaves and stem extracts		7.0–9.0 μg/ml		Inhibition of *B. subtilis*, *B. cereus*, *S. aureus* and S. *epidermidis*	
	MeOH leaves and stem extracts		7.5–9.0 μg/ml		Inhibition of *B. subtilis*, *B. cereus*, *S. aureus*, *S. epidermidis* and *E. coli*	
C. odorata	95% ET leaves extract	Disc diffusion assay	Zones of inhibition, 8.33 ± 0.58–10.00 ± 0.00 mm	Ampicillin (10 μg/ml) Gentamicin (10 μg/ml)	Inhibition of *S. typhimurium*, *B. subtilis* and *S. aureus*	Vital and Rivera (2009)
C. odorata	ET and MeOH leaves extracts	Agar diffusion and test tube dilution methods	90.0–1000 μg/m	Ciprofloxacin (1.0–7.0 μg/ml) Tetracycline (2.0–5.0 μg/ml)	Inhibition of strains of *N. gonorrhoeae*	Mondal et al. (2012)
C. odorata	MeOH, HEX, EA, and aqueous leaves extracts	Agar well diffusion technique	Zones of inhibition ranging from 7.0 to 19.0 mm	Streptomycin, zone of inhibition (28.0 mm)	Inhibition of *Vibrio harveyi* by MeOH extract (19.0 mm), EA extract (9.0 mm), Aqueous extract (7.0 mm).	Arief-Prajitno and Happy-Nursyam (2015)
C. odorata	Naringenin-4'-methyl ether **[3]** Eriodictyol-7,4'-dimethyl ether **[32]** 2',4-dihydroxy-4',5',6'-trimethoxychalcone **[185]**	Microdilution efflux bioassay	MIC = 1.95–125.0 μg/ml MIC = 1.95–62.5 μg/ml MIC = 3.9–62.5 μg/ml	Ethidium bromide (EtBr): MICs = 7.8–250 μg/ml. Reserpine: MICs = 3.9–125 μg/ml.	Efflux inhibitory activity against *MRSA* clinical isolates (N441), (U949), and *MSSA* isolate (ATCC 25923) and *MRSA* (ATCC 33591)	Saiful (2012)
C. odorata	Naringenin-4'-methyl ether **[3]** 4′-hydroxy-5,6,7-trimethoxyflavanone **[23]** 5,7-dihydroxy-4'-methoxyflavone **[20]** 5,7,3′,4′-tetrahydroxyflavone (luteolin) **[21]**	Microplate Alamar Blue Assay	MIC = 174.8 μg/ml MIC = 606.0 μg/ml MIC = 704.2 μg/ml MIC = 699.3 μg/ml	Isoniazid, MIC = 0.44 Kanamycin sulfate, MIC = 4.29	Moderate to weak inhibition of *Mycobacterium tuberculosis*	Suksamrarn et al. (2004)
C. squalida	DCM leaves and stem extracts	Well diffusion method		Bacitracine (0.2 μl/ml), gentamicine (10 mg)	All the crude extracts exhibited antibacterial activity, mainly against Gram-positive (*Staphylococcus* and *Streptococcus*) bacteria, at 1000 mg/mL	Taleb-Contini et al. (2003)
C. scabra	ET leaves and flower extracts	Agar diffusion method		Rifampicin	Inhibition of *S. aureus*, with MIC values of 85.8 and 50.3 mg/ml respectively	Arias et al. (2020)

Solvent: DCM – Dichloromethane; EA - Ethyl acetate; ET – Ethanol; HEX – Hexane; MeOH – Methanol; BUOH – Butanol **Concentration**: MIC - minimum inhibitory concentration **Organism**: *S. aureus - Staphylococcus aureus; S. epidermidis - Staphylococcus epidermidis*; *S. typhimurium - Salmonella typhimurium; E. coli - Escherichia coli; E. cloacae – Enterobacter cloacae; E. aerogenes - Enterobacter aerogenes*; *P. mirabilis - Proteus mirabilis; P. diminuta - Pseudomonas diminuta; P. aeruginosa - Pseudomonas aeruginosa; P. vulgaris - Proteus vulgaris*; *S. flexneri - Shigella flexneri; S. sonnei - Shigella sonnei*; *S. typhi - Salmonella typhi; B. cereus - Bacillus cereus; B. subtilis - Bacillus subtilis; K. pneumonia - Klebsiella pneumonia; N. gonorrhoeae - Neisseria gonorrhoeae*.

extract of *C. odorata* exhibited dose-dependent anti-diarrhoeal activity in castor oil-induced diarrhoea in mice at 50, 100,150 and 200 mg/kg, p. o (Taiwo et al., 2000). Similarly, in a recent study, ethanol leaves extract of *C. odorata* exhibited dose-dependent inhibition of diarrhoea in castor oil-induced diarrhoea rats' models at dose of 200 and 400 mg/kg body weight (Aba et al., 2015). The leaves methanol extract of *C. collina* reportedly showed spasmolytic activity (Tortoriello et al., 1995).

5.9. Immunomodulatory effects

5.9.1. Crude extracts

The *C. arnottiana* has been shown to exhibit immune-modulatory effect (Fernández et al., 2002).

5.9.2. Pure compounds

Methoxylated flavonoids, including 4', 5-dihydroxy-3', 3, 6, 7-tetramethoxyflavone **[69]**, 3',4',5,7-tetrahydroxy-3,6-dimethoxyflavone **[64]**, and 4',5,7-trihydroxy-3',3,6-trimethoxyflavone **[70]** from *C. hirsuta* displayed inhibitory effect on the oxidative metabolism of polymorphonuclear leukocytes (PMNL), with IC_{50} of >100, 78.0 and 18.0 μmol/L respectively (Taleb-Contini et al., 2006).

5.10. Miscellaneous activities

5.10.1. Crude extracts

Besides these pharmacological activities, the ethanol crude extract of *C. christieana* was found to show mutagenic effects at all tested concentrations. However, concentration above 10 μg/ml is statistically significant (Rojas de Arias et al., 1995). Anthelmintic (Panda et al., 2010), CNS-stimulant (Kamat and Joshi, 2013) and wound-healing activities (Sirinthipaporn and Jiraungkoorskul, 2017; Panda et al., 2010) of *C. odorata* extracts have also been reported.

5.10.2. Pure compounds

Odoratin **[187]** isolated from *C. odorata* showed significant transactivation effect on peroxisome proliferator-activated receptor (PPAR) agonistic (Zhang et al., 2012). Compounds **[3]**, **[31–33]**, **[36–38]**, **[41–42]**, and **[44]** exhibited strong to weak platelet-activating factor (PAF) receptor binding antagonist activity, with IC_{50} values ranging from 19.5 to 79.7 μM (Ling et al., 2007).

6. Toxicity

It has been stressed that the safety and toxicity of herbal drugs or new drugs is one of the important parameters for new drug discovery. Meanwhile, toxicity and safety evaluation of *Chromolaena* species are still lacking as only limited studies have been documented in the literature (Table 12). Acute toxicity of leaves and flower ethanol extract of *C. perglabra* in rat model has been investigated (Centanaro et al., 2018). Animals were administered with different concentrations of the extracts. Histopathological examination after 72 h revealed enlargement in size with mild lymphoid hyperplasia in the spleen and toxic hepatitis in all studied rats. Methanol aerial part of *C. odorata*, at a concentration of 250 and 500 mg/kg for 14 days showed no mortality in the studied rats. However, observable signs of sedation, loss of appetite, enteritis and decreased weight gain in treated mice were noticed (Paulose et al., 2016). The adverse effects of the ethanol leaves extract of *C. odorata* on the kidney functions and the histology of the intestine of the studied rats have also been reported at the highest tested concentration (250 mg/kg) (Anyanwu et al., 2017). These adverse effects could be associated with the pyrrolizidine alkaloids in *C. odorata* (Biller et al., 1994) (Table 4), since these compounds constitute a group of plant toxin linked to diseases in man and animals.

7. Translational research or inventions involving *Chromolaena* species

In order to assess the degree of real-time scientific applications or translation research on *Chromolaena* species, a patent web search was conducted in September 2021 on all the reported *Chromolaena* species using the patent database of Espacenet (http://worldwide.espacenet.com) of the European Patent Office, which contains over 120 million patent documents. The patent web search revealed that there is an increasing awareness in the pharmacological and scientific applications of the species *C. odorata*, suggesting the potential future herbal products and other allied products from this noxious weed. However, no relevant patents were found on other species of the genus. The search queries used consist of "*Chromolaena*" (104 hits), "Siam weed" (2 hits), and "*Chromolaena odorata*" (88 hits). Below are some of the patent lists or inventions that include *C. odorata* (**in bold**) alone or with other plants, and their pharmacological applications.

A medicament for treating Acquired Immuno-Deficiency Syndrome (AIDS), a deadly and infectious disease, and for improving human immunologic function was patented in 2010 by Junsong Zhang. The medicament composition comprised, by weight, 5–50 g each of ***Chromolaena odorata***, *Clerodendrum thomsonae*, *Gynostemma pentaphyllum*, common *Andrographis* herb, and *Paris polyphylla*. One year after, Kadir Nurul Huda Binti Abdul and Mamat Awang Soh Yusoff Bin were granted a patent on an anti-microbial lotion for wound healing. The invention comprised of essential oil of ***Chromolaena odorata***, non-ionic surfactant, and at least one pharmaceutically acceptable solvent.

Recently, a foot bath powder for promoting blood circulation, relieving pain, and regulating menstruation was granted the patent. Yin Haiquan filed the patent. The foot bath powder was prepared from the raw materials, including ***Chromolaena odorata***, *Corydalis* tuber, *Radix paeoniae alba*, *Angelica sinensis*, cortex *Cinnamomi*, honeysuckle, *Notopterygium* root, *Magnolia* flower, *Bletilla hyacinthina* Reichb., *Acorus calamus*, *Monkshood*, *Achyranthes* root, *Cortex pseudolaricis*, *Ramie* root, fresh *Rehmannia* root, parasitic *Loranthus*, *Plumeria rubra*, *Schizonepeta* and *Kadsura* pepper stem. Similarly, in 2015, Yu Zhiqiu was honoured for the invention – a Chinese herbal capsule for preventing and curing presenile dementia. The invented product was made from several Chinese herbal materials, including ***Chromolaena odorata***, *Rehmannia* root, *Acorus calamus*, *Polygonum multiflorum*, *Savia miltiorrhiza*, *Ligusticum wallichii*, *Corylus avellana*, *Colocynth*, snow frog fat, *Pine* pollen disruption powder, *Radix bupleuri*, oyster, *Fructus chebulae immaturus*, *Astragali radix*, milk peach, tobacco, *Sapium baccatum*, wild sword bean and *Aizoon stonecrop* herb in different weight proportions.

Likewise, a patent traditional Chinese medicinal enema for treating acute pancreatitis was granted to Bian Yongxing in 2015. The herbal product was made from a combination of ***Chromolaena odorata***, *Gypsophila oldhamiana*, *Radix paeoniae alba*, immature bitter oranges, *Scutellaria baicalensis*, *Cortex magnoliae officinalis*, purple flower *holly* leaves, licorice, yellow soya beans, raw *Rhubarb*, *Radish* seeds, *Dandelions*, *Virgate wormwood* herb, *Tibet vicatia coniifolia* roots, *Hydnocarpus annamensis*, *Semen nigellae*, *Erigeron breviscapus*, *Troscart maritime*, *Piptostegia* roots, *Sapium baccatum*, wild string beans, *Aizoon stonecrop* herb and *Pine* pollen disruption powder in different weight proportions.

8. *Chromolaena* species: Preservation of indigenous knowledge of the genus for therapeutic use

Chromolaena species, undoubtedly, possess enormous medicinal potential. They are means of finding new drug-like compounds from nature. However, different government policies on them have been a serious challenge. This has negatively affected the rural dwellers who use them in folklore medicine as well as the researchers in the field of drugs discovery from plant source. For instance, *C. odorata*, a well-known invasive species, has been shown in this review to possess potential medicinal values and its phytochemicals have been linked with

Table 9
Anticancer activity of *Chromolaena* species.

Chromolaena species	Extract/compound	Testing model/ concentration	MICs	Control	Experimental results	Reference
C. odorata	essential oils	*In vitro* MTT assay/ 50–3000 mg/mL		β-caryophyllene and germacrene D	No observable cytotoxic activity against human skin cell line HaCat at lower conc. (50–100 mg/ml). Significant increase in cell viability (up to 156 %)	Koba et al. (2011)
C. odorata	95% ET leaves extract	*In Situ* Cell Death Detection Kit (Fluorescein)		Metronidazole (Positive control) Ethanol and ethyl acetate (Negative control)	Induction of apoptotic-like changes to *T. vaginalis* trophozoites	Vital and Rivera (2009)
C. odorata	2',4-dihydroxy-4',5',6'-trimethoxychalcone **[185]** 3-hydroxy-1,2-dimethoxy-6-methylanthraquinone **[111]**	MTT assay/1–100 μM	**[185]**, IC_{50} = 92.72 μM **[111]**, IC_{50} = 52.21 μM	Cisplatin	Compounds **[185]** and **[111]** displayed weak cytostatic activity against U251-SP and PC-6 human tumour cell lines.	Zhang et al. (2012)
C. odorata	5,7-dihydroxy-4'-methoxyflavone (acacetin) **[20]** 5,7,3′,4′-tetrahydroxyflavone (luteolin) **[21]**	Cytotoxicity assays	MIC = 24.6 μM MIC = 19.2 μM and 38.4 μM	Ellipticine, MICs = 1.58 μM (NCI–H187) MICs = 5.93 μM (BC)	Compounds **[20]** and **[21]** exhibited moderate cytotoxicity against human lung cancer cell (NCI–H187), while **[21]** had weak toxicity against human breast cancer cells (BC) (MIC, 38.4 μM).	Suksamrarn et al. (2004)
C. odorata	2′-Hydroxy-4, 4′, 5′, 6′-tetramethoxychalcone (odoratin) **[187]**	Viability assay/20 μM for 48 h Clonogenicity assay/10, 20 or 50 μM		Resveratrol	Decrease in cell viability of breast cancer cell lines - Cal51, MCF7 and HeLa cells respectively in all three lines in a dose-dependent manner.	Kouamé et al. (2013)
C. leivensis	3, 5 dihydroxy-7-methoxyflavone **[48]** 3, 5 dihydroxy-7-methoxyflavanone **[50]**	MTT assay/5, 10, 20, 40, and 80 μM	EC_{50} = 24.19 μM EC_{50} = 120.80 μM	Negative control (DMSO)	**[48]** exhibited cytotoxicity against colon (HCT116), pancreas (MIA PaCa-2, Panc28) and lung (A549) cancer cells while **[50]** showed mild cytotoxicity against colon cell line (CaCo-2)	Whitted et al. (2016)
C. laevigata	ET aerial part extract, HEX, BuOH, DCM, EA and Hydromethanolic fractions	Antiproliferative assay	GI_{50} = 1.9 - >250 μg/ml	Doxorubicin	HEX fraction exhibited antiproliferative activity against all the nine human cancer cell lines and one human non-tumour cell: U251 (glioma), MCF-7 (breast), NCI-ADR /RES (ovary), 786–0 (kidney), NCI–H460 (lung), PC-3 (prostate), OVCAR-03 (ovary), HT-29 (colon), K562 (leukemia), and HaCaT (keratinocyte), with best activities were against OVCAR-03 at GI_{50} of 1.9 μg/ml, and 786–0 at GI_{50} of 2.5 μg/ml.	Oliveira et al. (2020)
C. laevigata	ET aerial part extract, HEX, BuOH, DCM, EA and Hydromethanolic fractions	31.25, 62.5, 125, 250, 500 and 1000 μg/ml	CC_{50} = 19.0–116.2 μg/ml	No report	HEX soluble fraction exhibited significant cytotoxicity, with CC_{50} of 19.0 μg/ml.	Oliveira et al. (2020)
C. laevigata	ET leaves extract	Cytotoxicity assay	IC_{50} = 7.34–112.3 μg/mL		Low cytotoxicity against human tumor cell lines (IC_{50} > 20 μg/mL) for DU-145 (prostate carcinoma), HT-29 (colon adenocarcinoma), MCF-7 (breast cancer) and M-14 (human amelanotic melanoma). High cytotoxicity against H-460 (lung large cell carcinoma) and K562 (chronic myelogenous leukemia) tumor cell lines	Herrera-Calderon et al. (2017)
C. leivensis	3, 5 dihydroxy-7-methoxyflavone **[48]** 3, 5 dihydroxy-7-methoxyflavanone **[50]**	Cell viability assay/100 μg/mL		No report	The flavonoid 3,5-dihydroxy-7-methoxyflavone **[48]** had activity on the mitochondrial membrane at varying concentrations (25, 50 and 100 μg/mL)	Ruben et al. (2011)
C. leivensis	5, 7-dihydroxy flavanone **[47]**	MTT assay/5, 10, 25, 50, 100, 150 and 200 mg/L	IC_{50} (A549) = 30.0 μg/ml IC_{50} (SiHa) = 58.0 μg/ml IC_{50} (MDA-MB-231) = 42.0 μg/ml IC_{50} (HT29) = 50.0 μg/ml IC_{50} (PC-3) = 48.0 μg/ml	Vincristine	Significantly inhibited cell viability and proliferation of colon adenocarcinoma (HT29), prostate cancer (PC-3), adenocarcinomic human alveolar basal epithelial (A549), breast adenocarcinoma (MDA-MB-231), and cervical squamous carcinoma (SiHa) cell lines	Rodriguez et al. (2018)

Solvent: DCM – Dichloromethane; EA - Ethyl acetate; ET – Ethanol; HEX – Hexane; BUOH – Butanol; **Concentration**: IC_{50} – half maximal inhibitory concentration; CC_{50} – 50% cytotoxic concentration; GI_{50} – 50% of maximal inhibition of cell proliferation; EC_{50} – half maximal effect concentration; **Activity:** MTT – 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; **Chemical**: DMSO – Dimethyl sulphoxide.

Table 10
Antiprotozoal activity of *Chromolaena* species.

Chromolaena species	Extract/compound	Testing model/ concentration	MICs	Control	Experimental results	Reference
C. odorata	95% ET leaves extract	*In vitro* antiprotozoal assay at extract concentrations of 0.1, 0.5 and 1.0%		metronidazole	Growth inhibition of *Trichomonas vaginalis* at the highest extract concentration within 24 h, and *Blastocystis hominis* (SVM ATCC 50613) at 144 h	Vital and Rivera (2009)
C. odorata	95% ET leaves extract	*In vivo* curative test assay in mice/500 mg/kg		Chloroquine, 10 mg/kg	*in vivo* antimalarial activity against chloroquine-sensitive strain of *Plasmodium berghei*	Omoya and Momoh (2014)
C. odorata	Stigmasterol **[89]** Hexacosanol **[112]**	Acetylcholinesterase (AChE) assay	LC_{50} = 70.84 μg/ml LC_{50} = 3.56 μg/ml	Galantamine hydrobromide (GHB)	Larvicidal and repellant action against *Culex quinquefasciatus via* inhibition of acetylcholinesterase activity	Gade et al. (2017)
C. christieana	ET root extract	4.0, 20.0, 40.0, 100.0 and 250.0 μg/ml	% inhibition = 91.9	Gentian violet (Negative control)	The extract exhibited highest percentage of lysis on bloodstream of *Trypanosoma cruzi* at a concentration of 250 μg/ml	Rojas de Arias et al. (1995)
C. leivensis	ET aerial part extract	Antitrypanosomal assay (β-galactosidase (βGal) Antiplasmodial assay (microfluorimetric assay) Antileishmanial assay (axenic amastigote assay)	IC_{50} = 8 μg/ml IC_{50} = >50 μg/ml IC_{50} = >50 μg/ml	Nifurtimox, IC_{50} = 10 μM Chloroquine, IC_{50} = 65–100 μM Amphotericin B, IC_{50} = 10 μM	Inhibited the growth of trypomastigote, the bloodstream form of the parasite *Trypanosoma cruzi* with IC_{50} = 8 μg/ml. Chloroquine-resistant *Plasmodium falciparum* strain (W2 Indochina), IC_{50} = >50 μg/ml *Leishmania mexicana,* IC_{50} = >50 μg/ml	Calderón et al. (2010)
C. hirsuta	ET leaves and flower extracts DCM leaves and flower extracts	Trypanocidal assay *in vitro* *Leishmania amazonensis* assay *in vitro*		Gentian violet Glucantime	Exhibited considerable activity, with % viability of *T. cruzi* (trypomastigotes) was 20.27 and 38.72 at 4000 μg/ml for DCM leaves and flower extracts respectively, while ET extracts had 17.0% viability	Taleb-Contini et al. (2004)
C. hirsuta	4',5-dihydroxy-3',7-dimethoxyflavone **[73]** 4',5-dihydroxy-3',3,6,7-tetramethoxyflavone **[69]** 4',5,7-trihydroxy-3',3,6-trimethoxyflavone **[70]** 3',4',5,7-tetrahydroxy-3,6-dimethoxyflavone **[64]** Quercetin **[30]**	Trypanocidal assay *in vitro*	IC_{50} **[73]** = 144.6 μg/ml IC_{50} **[69]** = 102.4 μg/ml IC_{50} **[70]** = 352.6 μg/ml IC_{50} **[64]** = 138.1 μg/ml IC_{50} **[30]** = 233.2 μg/ml		Exhibited trypanocidal activity against *T. cruzi*-trypomastigote by reducing the viability of trypomastigote with IC_{50} between 102.4 and 352.6 μg/ml	Taleb-Contini et al. (2004)

Solvent: DCM – Dichloromethane; ET – Ethanol **Concentration**: IC_{50} – half maximal inhibitory concentration; LC_{50} – lethal concentration 50.

many biological activities. This species, and many others are very scarce to find in recent time in many countries, especially developed nations of the world owing to different government policies towards their eradication. Some African nations are not left out despite the fact that majority of their population relies on these medicinal plants for treating several kinds of diseases (Table 1). This development has led to the extinction of many of these species, and consequently threatens drug discovery from medicinal plants. Although, it has been identified that invasive weeds, such as those in genus *Chromolaena* adversely affect human livelihood, reduce agricultural productivity, deplete water supply, promote wildfire, and endanger biodiversity (Richardson and van Wilgen, 2004), Máximo et al., (2020) are of the opinion that they could be channeled for positive utility values in the area of drugs discovery as revealed in their recent study entitled, "Invasive Plants: Turning Enemies into Value". Thus, studying the better ways of managing these plants, if not for anything else but for pharmaceutical purposes, calls for a better integrated control and management strategies. We, therefore, put forward some of the following ways of maximizing potential therapeutic values of these species:

- Dedicating special fields for growing some notable *Chromolaena* species for medicinal purposes.
- Cultivating and processing them into pharmaceutical herbal products, thereby generating income, and reducing costs of eradication.
- Regulating the rates of urbanization which could adversely affect some notable *Chromolaena* species endemic to some rural parts of the country.
- Empowering the traditional healers with the basic skills of reading and writing. This would widen their horizons on documenting and conserving these floras for coming generations.
- Channeling some notable species with evergreen leaves and bright flowers for horticultural purposes.

9. Concluding remarks and future perspectives

The species of the genus *Chromolaena* are particularly regarded as field weeds. Interestingly, many of these species, including *C. odorata*, *C. maximilianii*, and *C. squalida* have found applications in the traditional medicine for preventing and curing sickness and diseases, such as malaria, wounds and skin infections, typhoid, diabetes, gastrointestinal diseases, cough, diarrhoea and cancer in many countries. The modes of herbal preparations usually involved infusion, maceration, or decoction of the plant's part(s), and sometimes they are crushed and applied topically. Within the past three decades, phytochemistry and pharmacology of the genus had received considerable attention from the scientific community, and were considered as an active and promising area for new lead drugs. As a result, 27 species, out of 175 accepted species of the genus, have been investigated for their phytochemical constituents.

Table 11
Antioxidant and anti-inflammatory activity of *Chromolaena* species.

Activity	*Chromolaena* species	Extract/compound	Testing model/concentration	MICs	Control	Experimental results	Reference
Antioxidant	*C. bullata*	MeOH leaves and flower extracts	DPPH and ABTS assays/1, 10, 62.5, 100 and 250 mg	46.16 ± 0.7–92.21 ± 0.2 at 250 mg/l (leaves) 46.19 ± 3.1–91.13 ± 0.3 at 250 mg/l (flowers)	Trolox, Quercetin, Ascorbic acid	Antioxidant activity against DPPH and ABTS radicals	Rodríguez and Torrenegra (2017)
	C. laevigata	ET leaves extract	DPPH and ABTS assays/1.0, 5.0, 10.0, 25.0 and 50.0 µg/ml	IC_{50} = 11.66 µg/ml for DPPH assay IC_{50} = 12.45 µg/ml for ABTS	Trolox	Antioxidant activity against DPPH and ABTS radicals	Herrera-Calderon et al. (2017)
	C. odorata	EA leaves fraction	Nitric oxide scavenging assay	IC_{50} = 380 µg/ml IC_{100} = 2800 µg/ml	Quercetin: IC_{50} = 50 µg/ml IC_{100} = 2000 µg/ml	*in vitro* nitric oxide radicals scavenging activity	(Alisi and Onyeze, 2008)
	C. odorata	MeOH and ET leaves extracts	DPPH assay/Extract conc. of 300.0 µg/ml		Ascorbic acid	DPPH radical's inhibition	Bhargava et al. (2013)
	C. odorata	MeOH, ET, DCM, HEX and Water leaves extracts	DPPH and ABTS assays	DPPH: IC_{50} = 188.61 IC_{50} = 57.26 IC_{50} = 90.83 IC_{50} = >319 IC_{50} = >319 (µg/ml) respectively ABTS: IC_{50} = 46.80 IC_{50} = 24.43 IC_{50} = 13.97 IC_{50} = >99.0 IC_{50} = 21.37 (µg/ml) respectively	Gallic acid, IC_{50} = 1.11 Trolox, IC_{50} = 7.84	ET extract had highest inhibitory activity against DPPH radicals. Most of the extracts had potential activity against ABTS radical cations	Putri and Fatmawati (2019)
	C. odorata	Chloroform leaves extract	DPPH, ABTS Nitric oxide and Hydroxyl radical assays/0.1, 0.5, 0.75, 1.0, 2.50 and 5.0 mg/ml	IC_{50} = 0.28–1.32 µg/ml	Ascorbic acid, IC_{50} = 0.23–1.0 µg/ml	Dose-dependent inhibition of different radical ions	Srinivasa et al. (2010)
	C. odorata	MeOH leaves extract	DPPH assay/20.0 mg/ml		BHT, % inhibition of 90.0	DPPH radical's inhibition (%) of 88.0	Melinda et al. (2010)
	C. odorata	Odoratenin **[1]**	ABTS assay	IC_{50} = 23.74 μM	Trolox (IC_{50}, 31.32 μM)	Potent ABTS radical inhibition	Putri and Fatmawati (2019)
	C. leivensis	3, 5 dihydroxy-7-methoxyflavone **[48]** 3, 5 dihydroxy-7-methoxyflavanone **[50]**	DPPH assay/16.7, 33.4 and 66.8 mg/ml		No report	Compound **[48]** had, in a dose-dependent conc., significant radical scavenging activity while compound **[50]** exhibited antioxidant at the highest tested concentration.	Whitted et al. (2016)
Anti-inflammatory	*C. odorata*	MeOH leaves extract	Carrageenan-induced rat paw edema model/50, 100 and 200 mg/kg	% Inhibition of Edema; 40.7, 64.0 and 59.3 respectively	Indomethacin, 65.1 % inhibition at a dose of 5.0 mg/kg	Inhibition of paw edema in rats	Taiwo et al. (2000)
	C. arnottiana	DCM and ET aerial parts	Carrageenan-induced edema in rats/200 mg/kg		Indomethacin (10 mg/kg)	DCM extract showed activity in the topical ear test, inducing an edema inhibition	Clavin et al. (2007)
	C. odorata	(S)-coriolic acid **[115]** (S)-coriolic acid methyl ester **[116]** (S)-15,16-didehydrocoriolic acid **[117]** (S)-15,16-didehydrocoriolic acid methyl ester **[118]** Linoleamide **[119]** Linolenamide **[120]**	NF – κB reporter and MTT assays	IC_{50} = 30.60 and 34.10 μM IC_{50} = 5.22 and 5.73 μM IC_{50} = 41.2 and 47.6 μM IC_{50} = 10.6 and 12.4 μM IC_{50} = 25.1 and 24.0 μM	Resveratrol, MIC = 12.5 (NF – κB) and 10.90 μm (NO)	Inhibition of NF – κB and the nitric oxide (NO) radical production. No significant toxicity at the effective doses for NO inhibition	Hanh et al. (2011)

(*continued on next page*)

Table 11 (*continued*)

Activity	*Chromolaena* species	Extract/compound	Testing model/concentration	MICs	Control	Experimental results	Reference
	C. arnottiana	Jaceosidin **[19]** Nepetin **[56]** Hispidulin **[58]**	12-*O*-tetradecanoylphorbol-13 acetate (TPA)-induced ear edema in mice/(1 mg/ear)	IC_{50} = 42.3 and 36.4 μM respectively	Indomethacin (0.5 mg/ear); 60.4% inhibition	**[56]** and **[19]** reduced the TPA mouse ear edema by 46.9% and 23.2%, and inhibited the NF – κB induction by 91 and 77%, respectively	Clavin et al. (2007)

Solvent: DCM – Dichloromethane; EA - Ethyl acetate; ET – Ethanol; HEX – Hexane; MeOH – Methanol; **Concentration:** IC_{50} – half maximal inhibitory concentration; IC_{100} – maximal inhibitory concentration; **Activity:** MTT – 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; DPPH – 2,2-diphenyl-1-picrylhydrazyl; ABTS – (2,20-Azinobis-(3-Ethylbenzthiazolin-6-Sulfonic Acid)); **Enzyme/protein:** NF-κB – nuclear factor kappa-light-chain-enhancer of activated B cells.

Phytochemically, more than 190 compounds have been reported from the genus. Essential oils, flavonoids, phenolic acids, triterpenoids, sesquiterpenoids, stilbene, straight-chain alkanes, fatty acids, diterpenoids, steroids, anthraquinones, and alkaloids constitute the main classes of chemical constituents of the genus *Chromolaena*. As regards the genus, flavonoids and their derivatives are the most predominant group of phytochemicals isolated. The bulk of the flavonoids were reported from the aerial parts, mainly leaves using different organic solvents. The aerial parts similarly afford most of the sesquiterpenoids, diterpenoids, and fatty acids. The leaves were also rich in essential oils, containing mainly germacrene D. However, the roots have not received much attention as only few phytochemicals have been reported. Therefore, more phytochemical studies are needed on the root part and other yet-to-be-investigated species.

Crude extracts and chemical constituents of *Chromolaena* species have been shown to exhibit pharmacological activities. These include antibacterial, anticancer, antiproliferative, antifungal, antioxidant, cytotoxicity, anti-diabetic, insecticidal, anti-inflammatory, and anti-protozoal activities. Some of the biological activities with significant results better or equal to the positive controls are: (i) antibacterial effects of hexane, ethyl acetate and methanol leaves extract of *C. odorata*, (ii) antioxidant activity of the compounds 5, 3'-dihydroxy-7, 6'-dimethoxy-flavanone, (S)-15,16-didehydrocoriolic acid methyl ester and (S)-coriolic acid methyl ester, (iii) antiprotozoal activity of ethanol aerial part of *C., leivensis* (iv) anti-inflammatory activity of methanol leaves extract of *C. odorata*, and (v) anti-cancer activity of hexane fraction of *C. laevigata* aerial part. However, many of them still lack appropriate, adequate testing models and positive controls, and this calls for further research to re-assess their biological activities coupled with mechanisms of actions to ascertain their pharmacological relevance. Similarly, as for other un-investigated species, they may also be assumed as promising research gaps for future studies both *in vitro* and *in vivo*.

The toxicity and safety evaluation of *Chromolaena* species are still lacking as reviewed in this paper. Although one of the species, *C. odorata*, has gained real-time scientific applications in pharmaceutical herbal products, there is need to generate robust toxicological data concerning the safety of members of the genus and their isolated compounds in animal experiments or clinical trials. This will afford us to have better information as regards their safety for human consumption by the locals. Lastly, the genus possesses promising potential to be considered for pharmacological interest in the face of myriad of diseases and infections ravaging our world nowadays. We, thus, proffer that despite the invasive nature of some *Chromolaena* species, notable ones with remarkable medicinal potential could be channeled for positive utility by processing them into pharmaceutical herbal products and other allied goods after ascertaining their safety, thereby reducing cost of eradication, creating jobs for the citizens, and generating revenue for the government.

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CRediT authorship contribution statement

Olusesan Ojo: Conceptualization, Project administration, Methodology, Data curation, Formal analysis, Writing – original draft. **Mokgadi P. Mphahlele:** Methodology, Data curation, Formal analysis, Writing – review & editing. **Olatunde S. Oladeji:** Methodology, Data curation, Formal analysis, Writing – review & editing. **Edwin M. Mmutlane:** Data curation, Writing – review & editing, Supervision. **Derek T. Ndinteh:** Conceptualization, Project administration, Supervision, Writing – review & editing, Funding acquisition.

Table 12
Toxicity of *Chromolaena* species.

Chromolaena species	Extract/ compound	Testing model/concentration	Control	Experimental results	Reference
C. odorata	MeOH aerial part extract	250 and 500 mg/kg orally for 14 days	Distilled water (negative control)	No mortality in the studied rats. However, observable signs of sedation, loss of appetite, enteritis and decreased weight gain in treated mice were noticed	Paulose et al. (2016)
C. odorata	ET leaves extract	50,100, and 250 mg/kg	Distilled water (negative control)	Observable adverse effect on the kidney functions and the histology of the intestine of the studied rats at the highest concentration	Anyanwu et al. (2017)
C. perglabra	ET leaves extract ET flower extract	*in vivo* acute toxicity assay in mice/125, 250, 500, 1000 and 2000 mg/kg	Vehicle (control group)	Histopathological examination showed enlargement in size with mild lymphoid hyperplasia in the spleen and toxic hepatitis in all studied rats after 72 h	Centanaro et al. (2018)

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

ATCC	American type culture collection
CNS	Central nervous system
conc	concentration
IC_{50}	half maximal inhibitory concentration
LC_{50}	Half minimum lethal concentration
EC_{50}	Half maximal effective concentration
MIC	Minimum inhibitory concentration
DPPH	2, 2-diphenyl-1-picrylhydrazyl
ABTS	2, 2'-azino-bis-(3-ethylbenzothiazoline6-sulphonic
NO	Nitric oxide;
MTT	3-(4, 5-Dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide;
PPAR	Peroxisome proliferator-activated receptor (PPAR)
PAF	Platelet-activating factor
PMNL	Polymorphonuclear leukocytes
STZ	streptozotocin
ND	Not done
CL-lum	chemiluminescence

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