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Review

A review on genus *Millettia*: Traditional uses, phytochemicals and pharmacological activities

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ABSTRACT

The genus Millettia belongs to Fabaceae includes 200 species which are distributed in tropical and subtropical regions of the world. Plants belong to this genus are used as folkloric medicine, for the treatment of different ailments like in wound healing, boil, sores, skin diseases, snake bite, muscle aches, pains, rheumatic arthritis, and gynaecological diseases. The aim of the review is to provide updated, comprehensive and categorized information on the aspects of ethnobotanical, phytochemical, pharmacological uses and toxicity of genus Millettia in order to identify their therapeutic potential and generate space for future research opportunities. The present study comprises of isolated flavonoids, phenolic compounds, phytosterols, saponins, alkaloids, polysaccharides, terpenoids and resins and pharmacological activities of various Millettia species. The relevant data were searched by using the keyword "Millettia" in different scientific databases like, "Google Scholar"; "NISCAIR repository"; "Pub Med"; "Science Direct"; "Scopus" and the taxonomy is validated by "The Plant List". This review discusses the existing information of the traditional evaluation as well as phytochemical and pharmacological evaluation of the extract and active constituents of the genus "Millettia". This review confirms that several Millettia species have emerged as a high-quality medicine in a traditional system for arthritis, wound healing, inflammation, skin diseases. Numerous conventional uses of Millettia species have been validated by modern pharmacology research. Intensive investigations of the genus Millettia relating to phytochemistry and pharmacology, especially their mechanism of action, safety, and efficacy could be the future research interests by the researcher in the area of phytomedicine.

Contents

Abbreviations: EtOAc, ethyl acetate; MeOH, CH_3OH, methanol; *n*-BuoH, *n*-butanol; CH_2Cl_2, dichloromethane; MDR, multidrug resistance; CNS, central nervous system; MIC, minimum inhibitory concentration; DPPH, 2,2-diphenyl-picyrlhydrazyl; NO, nitric oxide; TNF-α, tumour necrosis factor; IL-6, interleukin; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; LPS, lipopolysaccharide; HepG2, hepatocellular carcinoma; MCF7, breast cancer cell line; HCT116, colon cancer; KG-1, acute myelogenous leukemia cell line; Raji, lymphoma cell line; MTT assay, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; ORAC assay, oxygen radical absorption capacity; TLR4, toll-like receptor4; SRA, scavenger receptor type A and GR, glucagon receptor; COX, cycloxygenase.

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1. Introduction

The genus *Millettia* belongs to family Fabaceae consists of more than 200 species plants which are grown in tropical and subtropical regions of the world (Chen et al., 2018). The family Fabaceae is positioned as the major group of angiosperms and the genus was earlier known as *Pongamia*, which is a large distributed genus of flowering plants. The plant list includes 363 scientific plant names of species rank, for the genus *Millettia*, out of which 202 are acknowledged species (www.theplantlist.org).

The traditional use of *Millettia* species includes antibacterial, anti-tumour, insecticidal, pesticidal, piscicidal (Sritularak and Likhitwitayawuid, 2006), antispasmodial, chemopreventive (Marco et al., 2017) joint pain, rheumatoid arthritis, amenorrhea, tuberculosis, etc. Most of them are used in the production of biodiesel (Madhu et al., 2016).

A number of distinctive studies have been performed by validating the usefulness in conventional medicine during the past few years by putting efforts to characterize both the chemical and pharmacological properties of *Millettia* species. A variety of phytochemicals have been identified from different species of *Millettia* such as flavonoids, phenolic compounds, phytosterols, saponins, alkaloids, polysaccharides, terpenoids and resins, etc as its secondary metabolites (Manikandan et al., 2017).

Some of the well-known species of the genus *Millettia* are *Millettia extensa* (Benth.) Baker, *Millettia pinnata* (L.) Panigrahi, *Millettia ovalifolia* Kurz, *Millettia auriculata* Brandis, *Millettia speciosa* Champ., *Millettia laurentii* De Wild. as per report collected from electronic search (using Pub med, Science Direct, Google Scholar, Scopus and NISCAIR repository) by using the keyword *Millettia*. A complete library search was done for the available data in different published articles and also in locally surveyed folkloric claims.

This review targets a comprehensive and significant assessment based on the existing access data in the area of the ethnomedicinal uses, phytochemistry, biological activities and toxicological research of different *Millettia* species in order to analyze their therapeutic potential and help the researchers in marking out of the strength and opportunities present in the plant species.

2. Distribution and botanical description

The genus *Millettia* belongs to the family Fabaceae (Leguminosae) which is comprised of more than 200 species (Chen et al., 2018). These include mostly trees, shrubs and woody climbers having cultured distribution. All the species are distributed broadly all over the tropical parts of the globe i.e. continents like Asia, Africa, and Australia are presented in Table 1 (Dat et al., 2019). African *Millettia* contributes about 24% and is found in East Africa and more than 25 species of *Millettia* available in Tanzania and also available in Republic of Congo, Cameroon, and Pacific Islands. From the literature, it is found that near about 30 different species of *Millettia* are found in a different region of India. Most of the species are found in eastern India, Western Ghats, and Himalayan foot hills. In tropical South-East Asia, this genus is distributed from Bhutan, China, India, Pakistan, Nepal, Myanmar, Bangladesh, Thailand, and Taiwan to Malaysia.

The leaves are opposite and imparipennates, stipellae. The inflorescence is paniculate with different colour flowers; the calyx is campanulate, adherent stamen, vexillary filament, ovate and dorsifixed anther, pubescent and sessile ovary. The seeds are kidney-shaped having funicle. The pod is flat, coriaceous and woody (Banzouzi et al., 2008).

3. Traditional uses and ethnopharmacology

A few species of *Millettia* has evidence of values as a drug in the indigenous system of medicine for a number of ailments. In different countries of Asia, Africa and Australia such as India, Pakistan, Burma, China, Thailand, France, Kenya, etc in which *Millettia* species are also grown naturally and used as ethnomedicine by local people (Dat et al., 2019). These species have been accessed for the treatment of various ailments. A number of studies have reported their use as traditional medicine by local people and have been widely used to treat the infected wounds, skin disorders, cough, rheumatoid pain, ulcer, menstrual disorder, inflammation, bronchititis, toothache, muscle ache, tuberculosis, hepatitis and bruises, etc presented in Table 1. The roots of *M. auriculata* Brandis, *M. racemosa* (Roxb.) Benth., *M. pachycarpa* Benth. and *M. piscidia* (Roxb.) Wight were reported to have insect repellent, larvicidal activity, antitumor, anti-inflammatory, antiviral, and antibacterial and pest destroying activity. These are also used as a fish poison and applied to sores of cattle to kill vermin. A different community of Cameroon has used this *Millettia* species for the treatment of intestinal parasites in case of children as a potent inhibitor (Rahman et al., 2015). In India, the Gujjar tribe follows the use of *M. extensa* (Benth.) Baker barks paste for the treatment of wound (Sharma et al., 2013). The Bhilla tribe in Maharashtra, India also used its bark juice for the wound by applying it once a day for a time period of 4–5 days (Kamble et al., 2010). The tribal community of Odisha (Kalahandi District) used the root paste of *M. extensa* (Benth.) Baker with liquor

Table 1
Traditional uses of plant parts belonging to *Millettia* species.

Plant Species	Plant parts	Traditional uses and method of preparation/administration	Geographical distribution	References
M. extensa (Benth.) Baker	Stem, root, leaves, bark	Infected wound, tonic, skin infection, cough, boils, sores The juice of bark is applied over the wounded area.	India	(Sharma et al., 2014)
M. ovalifolia Kurz	Bark	Hypotension, malaria	Pakistan	(Rahman et al., 2015)
M. conraui Harms	Stem, bark	Insecticidal, molluscicidal, pesticidal	France, Cameroon, Nigeria	(Fuendjiep et al., 1998)
M. pachycarpa Benth.	Seed	Pain, bruises, skin disorders, anthelmintic. The seeds are useful for the treatment of worm infection.	South-East Asia, China, India, Bhutan, Nepal, Myanmar, Bangladesh, Thailand, Taiwan	(Tu et al., 2019)
M. auriculata Brandis	Leaves, stem	Toothache, insecticide, vermifuge, fishing poison The stem and leaves are boiled with water and used in bath for its tonic property.	India	(Das and Ganapaty, 2014)
M. dielsiana Harms ex Diels	Leaves, stem	Muscle ache, pain, rheumatoid arthritis	China, Vietnam, Laos	(Dat et al., 2019)
M. dura Dunn	Stem bark, seed pod, root	Insecticidal, pesticidal, larvicidal, diarrhoea, hernia, wound healing, menstrual irregularities	Kenya	(Marco et al., 2017)
M. pachyloba Drake	Vine stem, leaves	Pain, relieving stasis, promoting blood circulation, irregular menstruation	China	(Yan et al., 2019)
M. pervilleana	Root bark	Cancer	Italy	(Palazzino et al., 2003)
M. laurentii De Wild.	Stem bark	Commercial timber	France, Africa, Republic of Congo, Cameroon	(Kamnaing et al., 1994)
M. pinnata (L.) Panigrahi	Seed, flower	Diarrhoea, ulcer, diabetes The flower is used for the treatment of piles as well as bleeding disorders. Fruits are meant for the treatment of abdominal ulcer and tumour. Leaf juice is meant for the treatment of cough, colds leprosy, diarrhoea and whole leaves are used as digestive and also for inflammation and wounds. Stem extract is used as a sedative in CNS. The root juice is mixed with coconut milk and lime water for the treatment of gonorrhoea.	Australia, Pacific islands. In Tropical Asia it extends from India, Japan, and Thailand to Malaysia including Himalayan foothills.	(Bora et al., 2014)
M. speciosa Champ.	Root	Joint pain, rheumatoid arthritis, amenorrhea, hepatitis, tuberculosis, chronic bronchitis	China	(Fu et al., 2016)
M. brandisianai Kurz	Root	Haematonic, inflammation, ulcer	Thailand	(Pailee et al., 2019)
M. dorwardii Collett & Hemsl.	Vine stem	Cancer, inflammation	China	(Chen et al., 2018)
M. duchesnei De Wild.	Twig	Fish poison, insecticide	Cameroon	(Ngandeu et al., 2008)
M. griffithii Dunn	Stem	Inflammation, joint pain, skin disease	China	(Tang et al., 2016)
M. nitita Var. *hirsutissima*	Vine stem	Promotes blood circulation, relieving stasis	China	(Zhang et al., 2009)
M. pulchra Kurz	Whole plant	Memory improvement, anti-ageing	China	(Lin et al., 2014)
M. barteri (Benth.) Dunn	Stem, bark root, twig	Vermifuge, purgative, feverish aches, cough, dysmenorrheal, cardiac pain As a rectal formulation, the macerated twigs are used to treat the purgative disorder. The stem bark (decoction) extract is taken for feverish aches, cough, and dysmenorrhea. The decoction of bark root helps to lower the cardiac pains.	Cameroon	(Havyarimana et al., 2012)
M. versicolor Baker	Stem bark, leaves	Relieve pain, parasitosis, cough, female sterility, headache, rheumatism In Congo, the aqueous decoction of leaves and stem bark is taken to treat intestinal parasitoses, feverish aches, kidney pains, cough, and female sterility. For the treatment of the syphilitic wounds, the infusion of stem bark is used on the bath. The trunk barks having potent anthelmintic property.	Congo	(Ongoka et al., 2008)

for the treatment of piles. They used this herbal formulation by applying it over the piles for 5 min in a time period of 2 days and also the root paste is used for the treatment of patient bitten by a mad dog (Panda and Padhy, 2008). It is also used for the treatment of cough and skin infection (Padhi et al., 2017). The Tai Yai community in Northern Thailand used the leaves and stem of *M. auriculata* Brandis by boiling it with water and used in the bath due to its tonic property (Khuankaew et al., 2014). *M. pachycarpa* Benth. seeds are promptly used for the treatment of worm infection, pain and bruises (Tu et al., 2019). As a rectal formulation the macerated twigs of *M. barteri* (Benth.) Dunn is used to treating the purgative disorder. The stem bark (decoction) extract is taken for feverish aches, cough, and dysmenorrhea. Also, the decoction of bark root is taken to lower the cardiac pains (Havyarimana et al., 2012). In Congo, the aqueous decoction of *M. versicolor* Baker leaves and stem bark is taken to treat intestinal parasitoses, feverish aches, kidney pains,

cough, and female sterility. For the treatment of the syphilitic wounds, the infusion of stem bark is used on the bath. The trunk barks having potent anthelmintic property (Ongoka et al., 2008). *M. pinnata* (L.) Panigrahi flower is used for the treatment of piles as well as bleeding disorders. Its fruits are meant for the treatment of abdominal ulcer and tumor. The leaf juice is meant for the treatment of cough, colds, leprosy, diarrhoea. The whole leaves are used as digestive, inflammation and also for wounds. Stem extract is used as sedative for CNS. The root juice is mixed with coconut milk and lime water for the treatment of gonorrhea (Pulipati et al., 2018). However, to the best of our knowledge, there are a number of traditional uses of the genus *Millettia* are available in the literature as folkloric claims and these findings raised the possibility of researchers to undertake the exploration as well as scientific assessment of the activities.

4. Phytochemical constituents

This genus "*Millettia*" is well recognized for its medicinal priority due to presence of a number of secondary metabolites. An extensive and depth investigations of different *Millettia* species have derived isolation and characterization of various secondary metabolites belongs to alkaloids, triterpenoids, coumarins, flavonoids, isoflavonoids, phenols, and phytosterols (Havyarimana et al., 2012) presented in Table 2 and the important chemical structure are described (Fig. 1).

These flavonoids and isoflavonoids mainly play the important mechanism as wound healing, insecticidal, piscicidal and molluscicidal activity. From *M. ovaifolia* Kurz., flavonoids chalcones were isolated showing antimalarial activity and are also used as hypotensive agent (Rahman et al., 2015). It is reported that the activities of murine retroviral reverse transcriptase and human DNA polymerases are inhibited by *M. pachycarpa* Benth. (Ye et al., 2008).

Phytoconstituents like rotenone and 3α-hydroxyrotenone identified from *M. pervilleana* showed of TPA-induced ornithine decarboxylase inhibition at the level of its m RNA expression and act as a potent cancer chemo-preventive agents (Manikandan et al., 2017). Anticancer agents like prenylated isoflavanone, pervilleanone were screened from *M. pervilleana*. 4- prenyloxyderrone, isoflavones, chalcone, pterocarpan were isolated from *M. dura* Dunn and another compound i.e. 6α, 12α-didehydro-6-oxodeguelin was also screened having an insecticidal activity which inhibits phytotoxins of ornithine decarboxylase (Marco et al., 2017). Isoflavonoids, maximaisoflavone, griffonianone were screened from *M. griffoniana* Baill. showing significant cytotoxicity whereas, another compound i.e. griffonianone C showed promising estrogenic activity (Yankep et al., 1998). An anti-tumour agent, known as millepurone isolated from *M. atropurpurea* (Wall.) Benth. and osajin from *M. auriculata* Brandis showed antioxidant activity (Manikandan et al., 2017). *M. duchusnei* De Wild. contains rotenones, which is a potent insecticide (Ngandeu et al., 2008).

An extensive and thorough review of the various available species of *Millettia* genus have emerged in the isolation and identification of numerous isolates belongs to flavonoids, alkaloids, pterocarpan, phenols, rotenoids and steroids. Approximately 148 phytoconstituents have been isolated from 24 *Millettia* species of which 73 are flavonoids, 29 are phenolics, and 18 are rotenoids thus, making flavonoids and phenolic compounds i.e. the chief phytochemical class of *Millettia* genus.

5. Pharmacological activities

The genus *Millettia* is the target of different pharmacological investigations, which is evaluated for their various ethno-medicinal uses. From the literature, it was found that *Millettia* genus exhibit an extensive variety of biological activities, such as antibacterial, antiviral, anthelmintic, anti-inflammatory, antioxidant, antiplasmodial, anti-allergy, anti-tumour, cognitive activity and cytotoxicity. The active phytoconstituents have been isolated from the solvents like ethanol, butanol, n-hexane, chloroform, acetone, ethyl acetate, dichloromethane, etc. followed by characterization. A summary of the curative activity assessments performed on this *Millettia* has been represented in Table 3. These findings endorse the traditional uses of plants with respect to the pharmacological activity.

5.1. Antimicrobial activity

The antimicrobial activity of various extracts of *Millettia* species viz. *M. extensa* (Benth.) Baker, *M. pachycarpa* Benth., *M. pinnata* (L.) Panigrahi, *M. speciosa* Champ. have been reported against gram-positive, gram-negative and fungal strains. Both agar well diffusion and disk diffusion *in vitro* methods were adopted for the evaluation of the antimicrobial property.

The antimicrobial activity of hexane and EtOAc extract of the stem bark of *M. barteri* (Benth.) Dunn was evaluated by determining the minimum inhibitory concentration against bacterial and fungal strains where, the reported MIC value is 64–512 μg/mL (Havyarimana et al., 2012). The isolates millaurine and milletonine were tested for the first time for its antimicrobial activity. Both of the extracts showed antimicrobial where, EtOAc extract showed a significant result.

The antimicrobial activities of different extracts of leaves of *M. extensa* (Benth.) Baker were evaluated against various multidrug-resistant (MDR) bacterial strains i.e. *Staphylococcus aureus, Escherichia coli, Candida albicans* using the agar cup plate method and MIC. Both aqueous and methanol extracts were evaluated and the methanol extract was shown to have the zone of inhibition $\geq$12 mm whereas, the MIC (minimum inhibitory concentration) is $\leq$1 mg/mL against both gram-positive and gram-negative organisms (Padhi et al., 2017). The root and leaf extract (methanol) of *M. extensa* (Benth.) Baker are having antifungal activity against *Mycobacterium phlei* (Gautam et al., 2007).

The ethyl acetate and petroleum extract of *M. pinnata* (L.) Panigrahi seed, bark and leaves showed good antimicrobial activity against different strains in agar well diffusion method. Extracts showed maximum zone of inhibition against *Bacillus subtilis.* The presence of triterpenes, chalcones, flavones and carboxylic acid may be responsible for the antimicrobial activity. The oil extracted from its seed showed significant antifungal activity against *Aspergillus niger.* Ethanol extract of stem of *M. pinnata* (L.) Panigrahi also showed significant antimicrobial activity against selected gram-positive and gram-negative organism by agar diffusion method at a concentration ranging from 250 to 1000 μg (Pulipati et al., 2018).

The leaf extract of *M. pinnata* (L.) Panigrahi and green synthesized silver nanoparticles possessed potent antibacterial activity in disc diffusion method against different microbial strains where, it showed maximum inhibition against the *E. coli* (Rajakumar et al., 2017). This inhibitory activity may be due to the presence of silver cations which is responsible for the structural changes of the membrane of microbes and alteration of membrane permeability leading to cell death.

The probable mechanism behind the antimicrobial activity is somehow linked with the presence of prenylated isoflavones, chalcones, and pterocarpans. The prenyl groups help in the attachment to the outer membrane of the cell of the bacteria resulting in membrane apoptosis.

5.2. Antioxidant activity

The antioxidant activity of ethanol extract of leaves of *M. pinnata* (L.) Panigrahi may be due to the presence of polyphenols

Table 2
Isolated phytoconstituents of evaluated extracts from *Millettia* species.

Plant Species	Phytoconstituents	Chemical class	Extracts	References
M. extensa (Benth.) Baker	Millexatins A, Millexatins B, Millexatins C, Millexatins D, Millexatins E, Millexatins F, Auriculatin, Scandenone, Elongatin, Auriculasin, Isoauriculasin, isoauriculatin, 3′-methylorobol, 7,4′-di-*O*-prenylgenistein, 2′-deoxyisoauriculatin, 2′-*O*-methylisoauriculatin, 4′-methylalpinumisofiauone, 5-O-methyl-4′-*O*-(3-methyl-2-utenyl)alpinumisoflavone, 5-hydroxy-7-methoxy-4′-*O*-(3-methylbut-2-enyl) isoflavones	Isoflavones	Acetone	(Padhi et al., 2017; Raksat et al., 2018)
	(−)-maackiain	Pterocarpan		
	(−)-sumatrol	Rotenoids		
	(−)-6a,12a-dehydrotoxicarol			
M. ovalifolia Kurz	7-(4 methoxyphenyl)-9H-furo[2,3-f]chromen-9-one,	Flavonoids	Chloroform fraction of methanol extract	(Rahman et al., 2015)
	Pervilleanone (Potent hypotensiveagent)	Prenylated isoflavanone		
M. pachycarpa Benth.	4-methoxylonchocarpin, dorspoinsettifolin, isobavachromene, deguelin, tephrosin, barbigerone, 4′,5′-dimethoxy-6,6-dimethylpyrano isoflavones, 4′-hydroxyisolonchocarpin, 12a-hydroxyrotennone	Flavonoids	EtOAc extract	(Y. Tu et al., 2019; Su et al., 2012)
	3-hydroxy4-methoxylonchocarpin	Prenylated chalcone	Petroleum ether fraction of ethanol extract	
	4-methoxylonchocarpin	Flavonoids	Petroleum ether fraction of ethanol extract	
	Isobarachromene			
	Dorspoinsettifolin			
M. dielsiana Harms ex Diels	Mildiside-A	Isoflavonoe glycoside	Chloroform and EtOAc fraction of ethanol extract	(Dat et al., 2019)
	Formononetin, ononin, isoliquiritigenin, liquiritigenin, naringenin, gallocatechin, catechin, (3*S*)-vestitol, tupichinol C, (+)-epicatechin, (−)-epicatechin, protocatechuic acid, *trans*-ferulic acid, *trans*-3-O-*p*-hydroxycinnamoyl ursolic acid	Phenolic derivatives		
M. dura Dunn	3-*O*-prenylmaackiain	Pterocarpan	Chloroform: methanol (1:1)	(Marco et al., 2017)
	Calopogonium isoflavone B, Maximaisoflavone B, durmillone, isoerythrin A-4′-(3-methylbut-2-enyl) ether, 7-hydroxy-8,3′,4′-trimethoxyisoflavone, 7,2′-dimethoxy-4′,5′-methylenedioxyisoflavone	Isoflavones		
	Butein	Chalcone		
M. pervilleana	3-phenylcoumarin or pervilleanine	Prenylated isoflavanone	Chloroform	(Palazzino et al., 2003)
	Pervilline, Pervillinine	Pterocarpans		
	3α-hydroxyrotenone	Rotenone		
	Pervilleanone, 3′-*O*-demethylpervilleanone	Isoflavanones		
M. griffoniana Baill.	4′-methoxy-7-*O*-[(*E*)-3-methyl-7-hydroxymethyl-2,6-octadienyl]isoflavone, 3′,4′-dihydroxy-7-*O*-[(*E*)-3,7-dimethyl-2,6-octadienyl]isoflavone,	*O*-geranylated isoflavones	n-hexane, chloroform	(Yankep et al., 1998)
	4-hydroxy-5,6,7-trimethoxy-3-(3′,4′-methylenedioxy) phenylcoumarin	3-phenylcoumarin		
M. erythrocalyx Gagnep.	6-methoxy-[2″,3″:7,8]-furanoflavanone, 2,5-dimethoxy-4-hydroxy-[2″,3″:7,8]-furanoflavan	Flavonoid	n-hexane, chloroform, methanol	(Sritularak and Likhitwitayawuid, 2006)
	3,4-methylenedioxy-2′,4′-dimethoxychalcone	Chalcone		
M. laurentii De Wild.	3′, 6 '-diketo-7-hydroxy-8,2′,4′-trimethoxyisoflavan or laurentiquinone	Isoflavan-quinone	n-hexane, chloroform, EtOAc, methanol	(Kamnaing et al., 1994; Kamnaing et al., 1999)
	3,7,4 '-trihydroxy-3′,5′-dimethoxyflavone or laurentinol	Flavonol		
	Calycosin, Glyricidin	Isoflavones		
M. oblate ssp. *teitensis*	4- prenyloxyderrone, durmilone, 8-*O*-methylretusin, Maximaisoflavone B, Maximaisoflavone H, Maximaisoflavone J	Isoflavone	CH_2Cl_2:MeOH (1:1)	(Derese et al., 2014)
	Tephrosin	Rotenoid		
	Lupeol	Triterpene		
M. leucantha Kurz	1-(3-hydroxy-4-methoxyphenyl)-3-(2,4-dihydroxy-5-methoxyphenyl)propan-1-ol (millettinol) physcion, (*R*)-(-)-mellein, isoliquiritigenin	Phenolic compound	n-BuOH, EtOAc fraction of ethanol extract	(Rayanil et al., 2011)
	4-hydroxy-3-methoxy-8,9-methylenedioxypterocarpan	Pterocarpan		
	3-hydroxy-9-methoxypterocarpan or medicarpin			
	5,4′-dihydroxy-7,8-dimethoxyisoflavone	Isoflavone		
M. pinnata (L.) Panigrahi	Resin, flavonoids, terpenoids, phenols, saponins, alkaloids, alkyd resin			(Bora et al., 2014)
	Palmitic acid, stearic acid, oleic acid, linoleic acid, lignoceric acid, arachidic acid and behenic acid	Fatty acid	Oil extract	
M. speciosa Champ.	Naringenin, liquiritigenin, garbanzol	Flavonoid	n-BuOH, EtOAc fraction of ethanol extract	(Fu et al., 2016)
	Calycosin, 2′-hydrroxybiochanin	Isoflavones		
	7-hydroxy-6,4′-dimethoxyisoflavone, 2′5′7-trihydroxy-4′-methoxyisoflavone, 6-methoxycalopogonium isoflavones A			
	Secoisolariciresinol, polystachyol	Lignan		
	4,4′-dihydroxy-2′-methoxychalcone, 2,4′-dihydroxy-4-methoxychalcone	Chalcones		
	Rhododendrol	Phenolic		

Table 2 (*continued*)

Plant Species	Phytoconstituents	Chemical class	Extracts	References
		compound		
	Polysaccharide(MSCP2)		Aqueous	(Huang et al., 2020)
M. brandisiana Kurz	Brandisianones A, Brandisianones B, Brandisianones C, Brandisianones D, Brandisianones E	Flavonoids	Dichloromethane	(Pailee et al., 2019)
M. conraui Harms	Conrauinones C, Conrauinones D, 7- hydroxyl-6-methoxy-3′,4′-methylenedioxy isoflavone	O-geranylated isoflavones	Benzene	(Fuendjiep et al., 1998)
M. duchesnei De Wild.	Elliptol, 12-deoxo-12-α-methoxyelliptone, 6-methoxy-6a,12a-dehydrodeguelin, 6a,12a-dehydrodeguelin, 6-hydroxy-6a,12a-dehydrodeguelin, 6-oxo-6a,12a-dehydrodeguelin, elliptone, 12a-hydroxyelliptone, eriodictyol	Prenylated rotenoids	CH_2Cl_2:MeOH (1:1)	(Ngandeu et al., 2008)
M. micans Taub.	Micanspterocarpan	Pterocarpan	CH_2Cl_2:MeOH (1:1)	(Marco et al., 2017)
M. griffithii Dunn	Griffinones A, Griffinones B, Griffinones C, Griffinones D, Griffinones E	Flavonoids	n-hexane, EtOAc	(Tang et al., 2016)
	Griffiliganan A	Biphenylneolignan		
M. manni Baker	5-hydroxy-4,7′-dimethoxyisoflavone	Isoflavones	Methanol	(Kamto et al., 2012)
	Furanonaphthoquinone	Naphthalene		
M. pachyloba Drake	Pachyloisoflavone A, Pachyloisoflavone B	Prenylated isoflavones	Ethanol	(Na et al., 2017)
	Pachylobin A	Pterocarpan		
	6-methoxycalogonium isoflavones A, durallone, genistein, millesianin C, millesianin D, afromosin, hernancorizin, ichthynone, 5-hydroxy-2′,4′,5′,7-tetramethoxyflavone	Flavonoids		
M. pulchra Kurz	(2*S*)-5,7,4′-trihydroxy-8,3′,5′-triprenylflavanone, (2*R*,3*R*)-7,4′dihydroxy-8,3′,5′-triprenyldihydroflavanol, 5,7,2′,4′-tetrahydroxy-6,3′-diprenylisoflavone, 5,7,4′-trihydroxy-2′-methoxy-6,3′-diprenylisoflavone.	Isoflavones	Chloroform, methanol	(Baruah et al., 1984)
	(6*S*, 6a*S*, 11a*R*)-6a-methoxypterorpin, (6*S*, 6a*S*,l1a*R*)-6α-methoxyhomopterocarpin	Pterocarpan		
M. usaramensis Taub.	(6a*R*,12a*S*)-2,3-methylenedioxy-9-methoxy-8-(3,3-dimethylallyl)-12a-hydroxyrotenoid (usararotenoid C)	Rotenoids	Dichloromethane	(Yenesew et al., 2003)
	12a-epimillettosin, 6a,12a-dehydromillettone, barbigerone, 4′-*O*-geranylisoliquiritigenin	Flavonoids		
M. barteri (Benth.) Dunn	Millaurine, milletonine	Guanidine alkaloids	Methanol	(Havyarimana et al., 2012)
	Afzelin	Flavonoid		
	β-sitosterol, β-sitosterol glucoside, a mixture of stigmasterol and β-sitosterol, palmitates	Sterols		
M. peguensis Ali	Pentadecane, Tetradecane, Octadecane, Undecane, 9-methylheptadecane, Heptadecane, 2,6,10,15-tetramethyl- 2-Bromo dodecane	Alkane hydrocarbon	Petroleum ether	(Manikandan et al., 2017)
	Eicosane, Heneicosane	Acyclic alkane		

and flavonoid contents which was performed upon the oral administration of the extract (300 mg/kg body mass) in the albino rat. There was a significant increase in the reduced glutathione, glutathione peroxidase, catalase, superoxide dismutase levels whereas, a decrease in the levels of conjugative dines, hydrooxyperoxide, thiobarbituric acid reactive substances were found. This results showed a protective role of the extract against lipid peroxidation which draws a probable mechanism for antioxidant activity (Pulipati et al., 2018).

The evaluation of the antioxidant activity of hexane and EtOAc extract of the stem bark of *M. barteri* (Benth.) Dunn was done by using the DPPH assay technique and revealed that millaurine showed maximum activity in comparison with other compounds (Havyarimana et al., 2012).

Ethyl acetate and ethanol extracts/fractions contain most of the free radical scavenger and in other hands the phenolic contents directly related to the antioxidant effect, which may be a possible mechanism for this activity.

5.3. Antiplasmodial activity

It was investigated on the antiplasmodial activity of isolated rotenoid and flavonoids which was extracted from the stem bark of *M. usaramensis* Taub. using dichloromethane. This study was carried out against the chloroquine-sensitive (D6) and chloroquine-resistant (W2) strains of *P. falciparum* with an IC_{50} value of 21.1 and 28 μg/mL each (Yenesew et al., 2003).

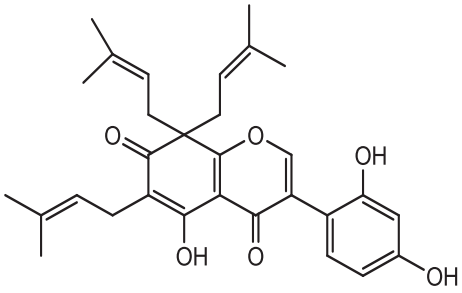
The CH_2Cl_2/MeOH (1:1) extract of the stem bark of *M. oblate* ssp. *teitensis* was evaluated, which confirmed about the *in vitro* antiplasmodial activity using non-radioactive assay against the chloroquine-sensitive Sierra Leone 1 (D6) and chloroquine-resistant Indochina 1 (W2) strains of *P. falciparum* with an IC_{50} value of 12.0 ± 1.2 and 10.0 ± 2.3 μM each (Derese et al., 2014).

The antiplasmodial activity of CH_2Cl_2/CH_3OH (1:1) extract of the root bark of *M. dura* Dunn was investigated and the minimal activity was found for compounds viz. calopogonium isoflavone B, maximaisoflavone B and 7, 2′-dimethoxy-4′, 5′-methylenedioxyi soflavone against the chloroquine-sensitive 3D7 and the chloroquine-resistant Dd2 *P. falciparum* strain where the activity found in between 70 and 90% inhibition at 40 μM (Marco et al., 2017).

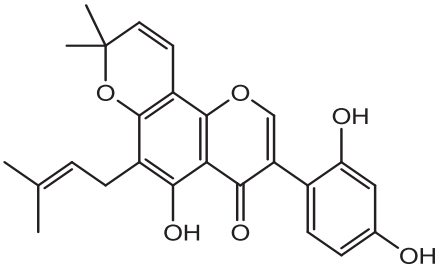
5.4. Immunomodulatory activity

A novel polysaccharide fraction (MSCP2) was extracted and isolated from the roots of *M. Speciosa* Champ. MSCP2 (molecular weight = 2.85 × 104 Da) was purified from the aqueous root extract and confirmed to have significant immunomodulatory activity by improving the pinocytic capacity and increasing the levels of NO, TNF-α, and IL-6. TLR4, SRA and GR were found to be the major PRRs for MSCP2 to trigger signalling transcription and

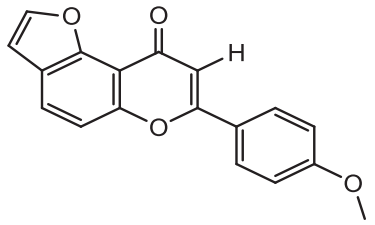
Isolated flavonoids from different *Millettia* species



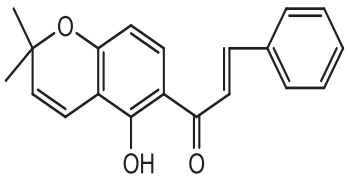
Millexatins A



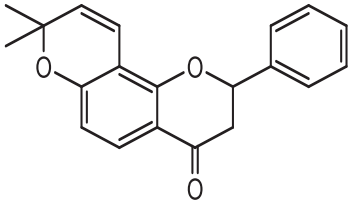
Millexatins F



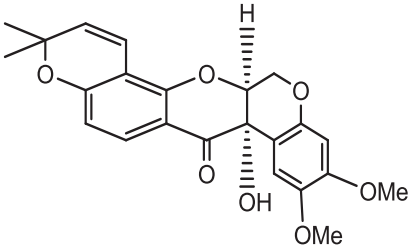
7-(4-methoxyphenyl)-9H-furo[2,3-f] chromen-9-one



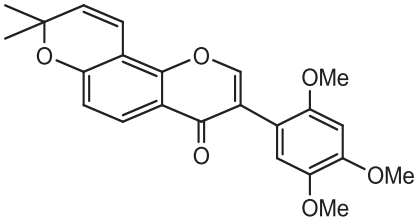
Isobavachromene



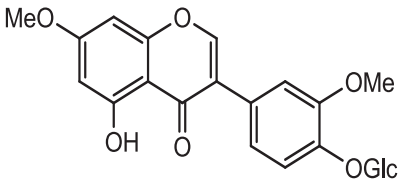
4'-hydoxyisolonchocarpin



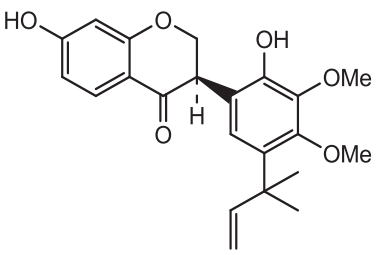
Tephrosin



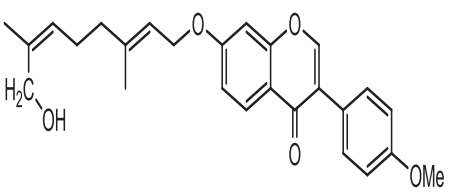
Barbigerone



Milldiside-A

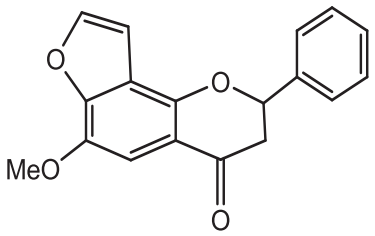


Pervilleanone

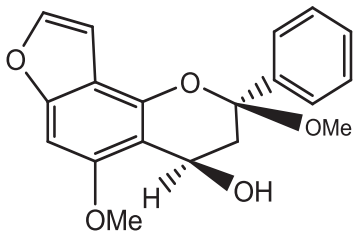


4'-methoxy-7-*O*-[(*E*)-3-methyl-7-hydroxymethyl-2,6-octadienyl]isoflavones

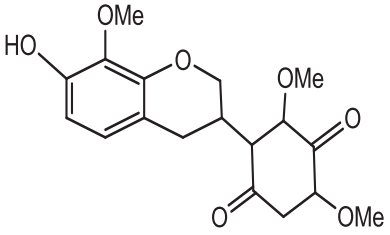
Fig. 1. Chemical structure of isolated compounds from various *Millettia* species.



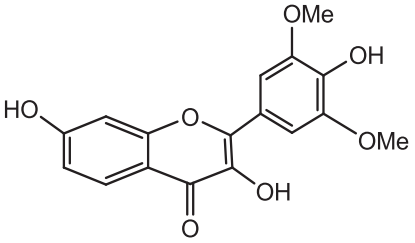
6-methoxy-[2”,3”:7,8]-furanoflavanone



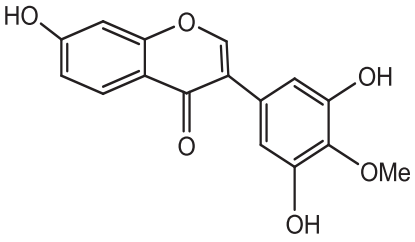
2,5-dimethoxy-4-hydroxy-[2”,3”:7,8]-furanoflavan



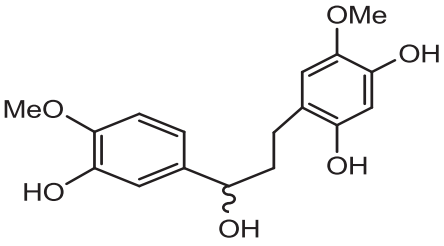
Laurentiquinone



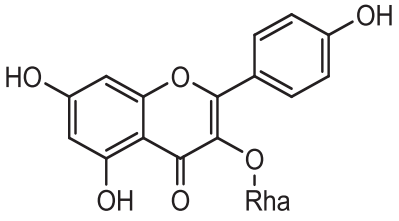
Laurentinol



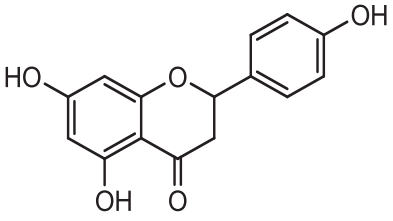
Glyricidin



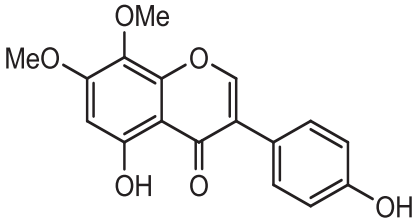
Afzelin



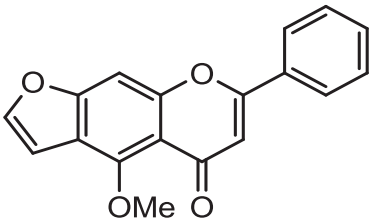
Millettinol



Naringenin

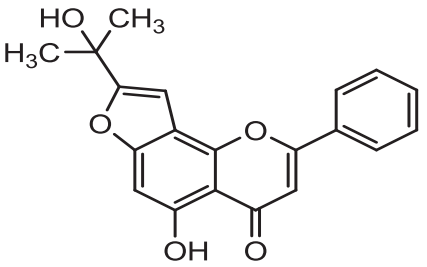


5,4'-dihydroxy-7,8-dimethoxyisoflavone

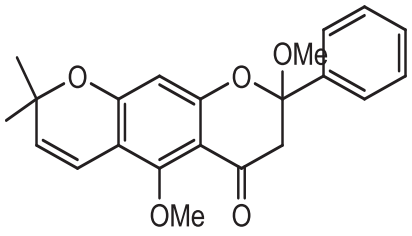


Pinnatin

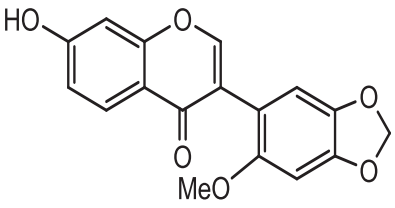
Fig. 1 (*continued*)



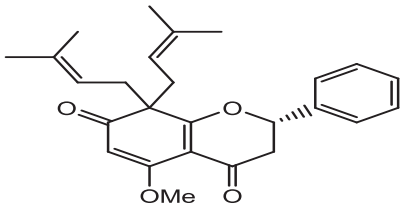
Brandisianones A



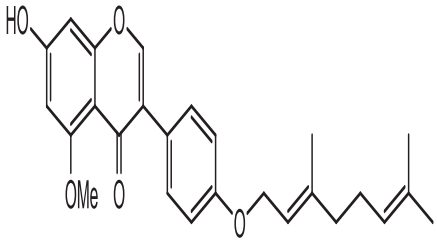
Brandisianones D



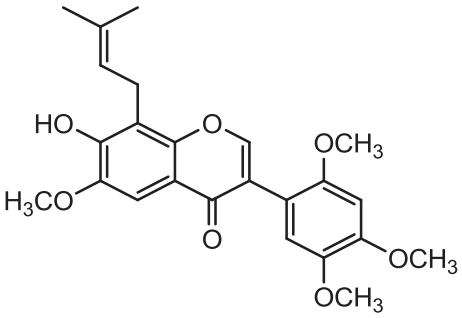
Maximaisoflavone G



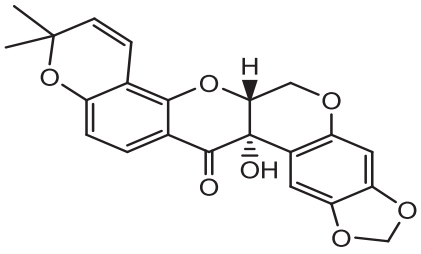
Griffinone A



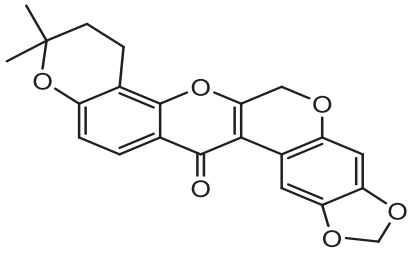
Conrauinones C



Pachyloisoflavone A



12a-epimillettosin



6a,12a-dehydromillettone

Fig. 1 (*continued*)

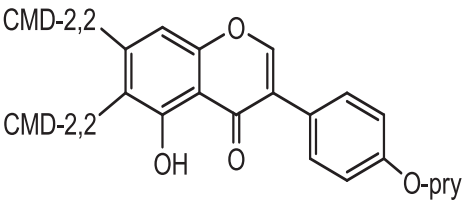
macrophage activation. These results indicated that MSCP2 might be a potent agent in medical science and food industries (Huang et al., 2020).

5.5. Cognitive activity

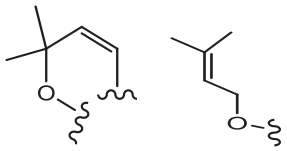
A polysaccharide isolated and purified by DEAE-cellulose and Sephadex G-75 chromatography from *M. pulchra* Kurz was investigated for its cognitive activity. The polysaccharide was evaluated in experimental animals (Kunming mice) by performing the behavioural study (Lin et al., 2014). From this study, it was found that polysaccharide significantly reversed D-galactose induced learning and memory impairments by reducing the oxidative stress along with suppression of inflammatory response. It was also found that polysaccharide distinctly lowers the content and deposition of β-amyloid peptide increase the level of acetylcholine but decreased the cholinesterase activity. These outcomes suggested that polysaccharide may be the active constituent to exert a protective effect on cognitive impairment in mice (Zhang et al., 2018).

5.6. Anti-cholinesterase activity

It was reported that a stronger inhibitory activity of both acetylcholinesterase and butyrylcholinesterase found for the green syn-

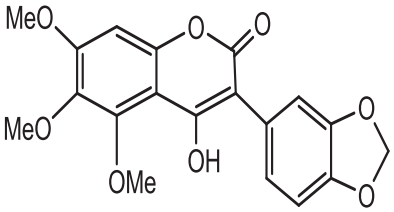


4'- Prenyloxyderrone

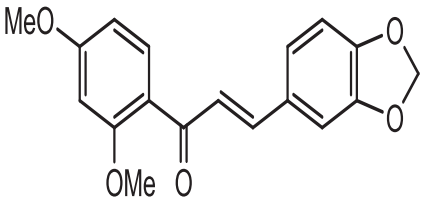


(2,2-DMC) (O-pry)

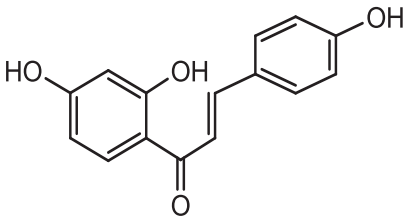
Isolated phenolic compounds from different *Millettia* species



4-hydroxy-5,6,7-trimethoxy-3-(3',4'-methylenedioxy)phenylcoumarin



3,4-methylenedioxy-2',4'-dimethoxy-chalcone



Isoliquiritigenin

Fig. 1 (*continued*)

thesized silver nanoparticles ($AgNP_s$) as compared with flower extract of *M. pinnata* (L.) Panigrahi (Rajakumar et al., 2017).

Studies were carried out to observe the anti-cholinesterase activity of the ethanol n- BuOH extracts of seed of *M. pachycarpa* Benth. which showed potent activity where n- BuOH extract also showed significant anti-cholinesterase activity. The bio-assay guided isolates of EtOAc extract was evaluated by Ellman's methods and also showed better anticholinesterase activity which showed moderate to weak acetylcholinesterase activity with an IC_{50} value ranging from 17.14 to 131.17 μM, which is the future prospect to analyze as a definite agent for Alzheimer's therapy (Tu et al., 2019).

5.7. Anthelmintic activity

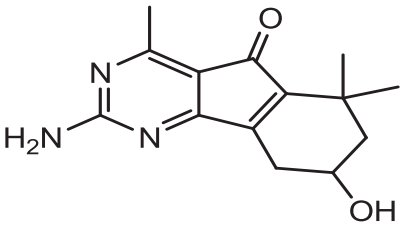
Assessment of the anthelmintic activity of chloroform extract of leaves and stems of *M. auriculata* Brandis was carried out using *Pheretima posthuma* at a dose of 10 mg/mL against the standard drug Albendazole, where, the leaves extracts were found to be more potent as compared with stem extract and standard. Here Albendazole plays an inhibitory mechanism on the helminthic β-tubulin polymerization by interfering with microtubule-dependent functions such as uptake of glucose and depletion of glycogen (Das and Ganapaty, 2014). The probable mechanism behind the anthelmintic activity maybe due to the availability of the rich source like flavonoids, triterpenes, and phenolic contents, which is responsible for the death of parasite by damaging the glycoprotein.

It was observed that different extracts (ethanol, acetone and aqueous) of *M. extensa* (Benth.) Baker leaves (1 μL) were having anthelmintic property against the activity of *C. elegans* where the aqueous extract showed significant result i.e. 80.0 ± 3.0 in terms of % of inhibition of relative movement (Padhi et al., 2017).

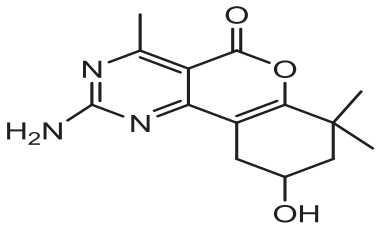
5.8. Anti-ulcer activity

The *in-vivo* assay was performed to investigate the methanol extract of seeds of *M. pinnata* (L.) Panigrahi and observed anti-ulcerogenic activity at a dose of 25 mg/kg in pyloric ligation and aspirin-induced ulcer model (Pulipati et al., 2018). Generally, secondary metabolites like terpenoids, quinines, flavonoids, etc. exhibits some kind of cytoprotective as well as anti-secretory property. Flavonoids play a vital role in anti-ulcer activity by amplifying the mucosal defence system and also improve the capillary resistance

Isolated alkaloid from different *Millettia* species

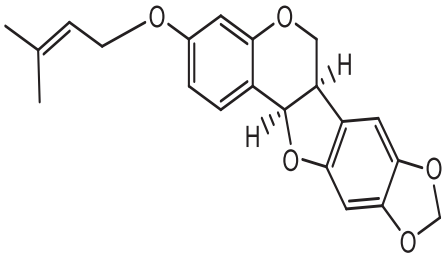


Millaurine

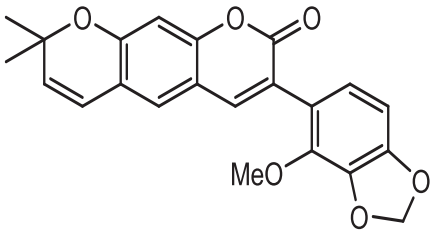


Milletonine

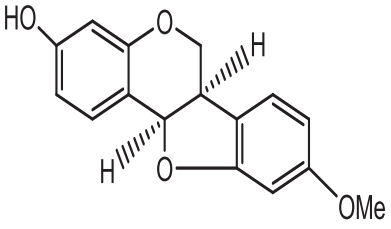
Isolated pterocarpan from different *Millettia* species



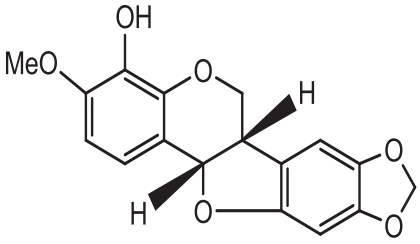
3-*O*-prenylmaackiain



Pervilleanine



Medicarpin



4-hydroxy-3-methoxy-8,9-methylenedioxypterocarpan

Fig. 1 (*continued*)

by raising the gastric defensive factors (Mohod and Bodhankar, 2013).

5.9. Anti-inflammatory activity

Studies were carried out to investigate the *in vitro* anti-inflammatory activity of the isolated compounds of the n-hexane and EtOAc extract of *M. griffithii* Dunn on LPS-induced NO production in RAW 264.7 cell, where, griffinone B showed the best activity. Further, it was selected for the evaluation of iNOS and COX-2 expression with 1400 W and revealed the suppression of iNOS protein and mRNA as the positive control (Tang et al., 2016).

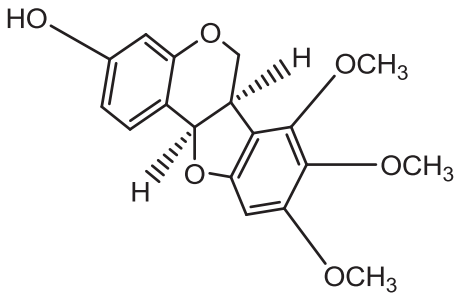
The anti-inflammatory activity of ethanol extracts of stems of *M. dielsiana* Harms ex Diels was evaluated. The nitric oxide (NO) production in lipopolysaccharide (LPS)-stimulated murine RAW264.7 macrophage cells showed the highest inhibitory effect (IC_{50} value 16.0 ± 1.5 μM). Isoliquiritigenin and tupichinol C showed the modest inhibitory effects on NO production having IC_{50} values 31.2 ± 2.5 and 38.4 ± 1.9 μM respectively (Dat et al., 2019).

It was also evaluated that *M. pinnata* (L.) Panigrahi leaves extract (70% ethanol) having potent anti-inflammatory activity in three different models (acute, sub-acute and chronic) in both Wister rat and Swiss mice. There were no signs of gastric lesion as well as ulcerogenic activity in both acute and chronic models which draw a possible mechanism for inflammatory activity (Pulipati et al., 2018).

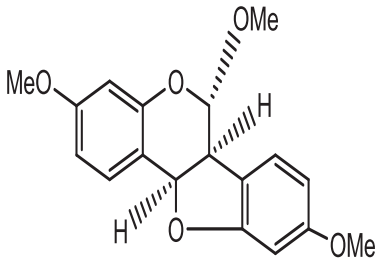
The direct mechanism involved in anti-inflammatory activity is the inhibition of pro inflammatory mediators like keratinocytes, leukocytes endothelial cells and also prostaglandin release and synthesis by flavonoids (inhibit COX-1 and COX-2) (Schäfer et al., 2006), alkaloids (inhibit the metabolic pathway of arachidonic acid) (Ayal et al., 2019) and biphenylneolignans.

5.10. Antidiabetic activity

Different solvent extracts of leaves of *Pongamia piñata* (synonym of *M. pinnata* (L.) Panigrahi) was evaluated for antidiabetic activity in alloxan-induced diabetic rats against standard drug Glibenclamide. It was observed that the aqueous and ethanol extract showed less potential but significant than the standard

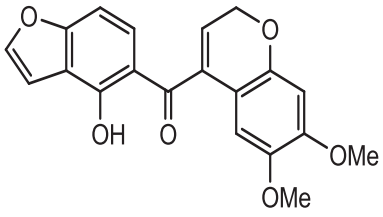


Micanspterocarpan



(6*S*, 6a*S*,11a*R*)-6α-methoxyhomopterocarpin

Isolated rotenoids from different *Millettia* species



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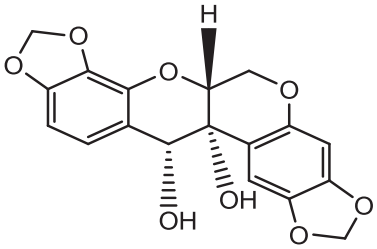
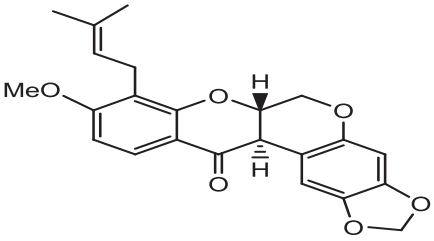
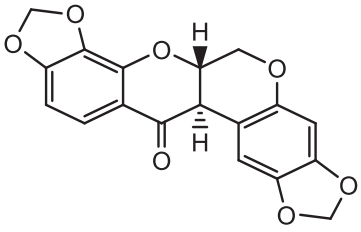


12-dihydrousararotenoid A



Usararotenoid C



Usararotenoid A

Fig. 1 (*continued*)

Glibenclamide at an oral dose of 500 mg/kg. Both of the extracts also decrease blood glucose and increase body weight. So the possible mechanism may be for the increase insulin secretion which improves the rate of glucose utilization. Different bioactive constituents like flavonoids, phenolics and steroids also play an important role in the antidiabetic study (Sikarwar and Patil, 2010).

5.11. Cytotoxicity

The cytotoxicity and anti-cancer activity of the isolates of the wood of *M. leucantha* Kurz was evaluated against NCI-H187, BCA-1and KB tumour cell lines where, physcion showed potent anticancer activity against the NCI-H187 cell lines (IC_{50} value 4.30 μg/mL) and millettinol also showed significant activity against BCA-1 cell lines (IC_{50} value 3.44 μg/mL) (Rayanil et al., 2011).

Studies were carried out to evaluate the cytotoxicity of two new petroleum ether soluble isolates from the ethanol (70%) extract of the root of *M. speciosa* Champ. by using four different human cancer cell lines viz. MCF-7, HCT-116, A549, HepG-2 and showed moderate activity (Chen et al., 2015).

In another research, the cytotoxicity activity of green silver nanoparticles synthesized product of *M. pinnata* (L.) Panigrahi flower extract was evaluated of particular concentration using brine shrimp lethality assay where the LD_{50} value was 36.41 μg/mL. This revealed the presence of toxic constituents in green silver nanoparticles synthesized product which links a mechanism towards an anticancer activity as the nanoparticles are a good substitute for a cancer drug. Anticancer activity is due to the presence of flavonoid which is chemopreventive in nature and plays an important role in the cell signalling (i.e. cell proliferation and angiogenesis phase). It is the fact that phytoconstituents from flavonoid group may show potent anticancer activity (Rajakumar et al., 2017). *Pongamia piñata* (synonym of *M. pinnata* (L.) Panigrahi) was reported earlier for its sub-acute toxicity of its isolated compound "Pongamol" using long Evan's rats at a dose of 300 μg/kg/day for a period of 14 days. Different parameters like biochemical, haematological, body weight and histopathology were evaluated in both the control and experimental group. It was found that Pongamol is safe for clinical trial as it showed no significant changes in any parameters (Baki et al., 2007). Again, the acute oral toxicity study of this same plant was also evaluated by using female Wistar rat. A dose of 2000 mg/kg/day of crude extract were administrated to the animals (100–120 gm, 4–8 week old) for 14 days. As a result, there were no toxicity signs and death found

Table 3
Reported pharmacological activities of plant extracts and compounds of *Millettia* species.

Plant species	Plant parts	Activity studies	*In- vivo*/*in-vitro*	Tested extracts/ active constituent	Observed effect	Mechanism	References
M. barteri (Benth.) Dunn	Stem bark	Antimicrobial	*In-vitro*	Hexane, EtOAc	Both extracts showed a MIC value of 64 to 512 μg/mL.	Not studied	(Havyarimana et al., 2012)
M. extensa (Benth.) Baker	Leaves	Antimicrobial	*In-vitro*	Acetone, ethanol	Both extracts showed significant MIC value i.e. 140 μg/mL and 210 μg/mL against *S. aureus*.	Not studied	(Padhi et al., 2017)
M. pinnata (L.) Panigrahi	Seed, bark, leaves	Antimicrobial	*In-vitro*	EtOAc, petroleum ether,	EtOAc, petroleum ether extract showed maximum zone of inhibition against *B. subtilis*.	Flavones, flavans, chalcone, triterpenes and aromatic carboxylic acids are responsible for the antimicrobial property.	(Pulipati et al., 2018)
				green synthesized silver nanoparticles	A maximum growth inhibition observed i.e the inhibition zone is more than 10 mm (10 mL/disc) particularly against *E. coli* (20.25 ± 0.91 mm), *P. aeruginosa* (17.13 ± 0.80 mm), *S. aureus* (15.09 ± 0.17 mm), *K. pneumonia* (14.81 ± 0.34 mm)		(Rajakumar et al., 2017)
M. pinnata (L.) Panigrahi	Leaves	Antioxidant	*In-vivo*	Ethanol	Upon the oral administration of the extract (300 mg/kg body mass), there was a significant increase in the reduced glutathione, glutathione peroxidase, catalase, superoxide dismutase level and decrease in the level of conjugative dines, hydrooxyperoxide, thiobarbituric acid reactive substances in albino rats by using ammonium chloride-induced model.	Free radical scavenging activity	(Pulipati et al., 2018)
M. barteri (Benth.) Dunn	Stem bark	Antioxidant	*In-vitro*	Hexane, EtOAc, millaurine	Both extracts showed IC50 62.74 and 77.23 μg/mL in DPPH assay.	Free radical scavenging activity	(Havyarimana et al., 2012)
M. usaramensis Taub.	Stem bark	Antiplasmodial	*In-vitro*	Rotenoid, flavonoids	Dichloromethane against the chloroquine-sensitive (D6) and chloroquine-resistant (W2) strains of *P. falciparum* showed potent activity with an IC_{50} value of 21.1 and 28 μg/mL each.	Not studied	(Yenesew et al., 2003)
M. oblate ssp. *teitensis*	Stem bark	Antiplasmodial	*In-vitro*	CH_2Cl_2/CH_3OH (1:1)	The extract showed significant activity against chloroquine-resistant Indochina 1 (W2) and chloroquine-sensitive Sierra Leone 1 (D6) strains of *P. falciparum* with an IC_{50} value of 10.0 ± 2.3 and 12.0 ± 1.2 μM each.	Presence of isoflavones is responsible	(Derese et al., 2014)
M. dura Dunn	Root bark	Antiplasmodial	*In-vitro*	CH_2Cl_2/CH_3OH (1:1)	The minimal activity was found for compounds viz. calopogonium isoflavone B, maximaisoflavone B and 7, 2′-dimethoxy-4′, 5′-methylenedioxyisoflavone against the chloroquine-sensitive 3D7 and the chloroquine-resistant Dd2 *P. falciparum* strain where the activity found in between 70 and 90% inhibition at 40 μM.	Isoflavones like Calopogonium isoflavone B, Maximaisoflavone B are responsible for this activity	(Marco et al., 2017)
M. Speciosa Champ.	Root	Immunomodulatory	*In-vitro*	Polysaccharide fraction (MSCP2)	MSCP2 was confirmed to have significant	The molecular mechanism of MSCP2	(Huang et al., 2020)

Table 3 (*continued*)

Plant species	Plant parts	Activity studies	*In- vivo*/*in-vitro*	Tested extracts/ active constituent	Observed effect	Mechanism	References
					immunomodulatory activity by improving the pinocytic capacity and increasing the levels of NO, TNF-α, and IL-6.	is executed by macrophage activation through TLR4, SRA and GR mediated signalling pathways.	
M. pulchra Kurz	Whole plant	Cognitive	*In-vivo*	Polysaccharide	The animal behavioural study showed that polysaccharide significantly reversed D-galactose induced learning and memory impairments with distinctively decreasing of the content and deposition of β-amyloid peptide increase the level of acetylcholine but decreased the cholinesterase activity.	The mechanisms of this action are the reduction of oxidative stress as well as the suppression of inflammatory responses	(Zhang et al., 2009)
M. pinnata (L.) Panigrahi	Flower	Anti-cholinesterase	*In-vitro*	Green synthesized nanoparticles ($AgNP_s$)	The IC_{50} value of $AgNP_s$ was 24.03 ± 1.01 mg/mL for acetylcholinesterase and 171.69 ± 0.98 mg/mL for butyrylcholinesterase which is comparatively higher than the activity of flower extract.	Not studied	(Rajakumar et al., 2017)
M. pachycarpa Benth.	Seed	Anti-cholinesterase	*In-vitro*	n- BuOH, EtOAc	The isolates were evaluated by Ellman's methods where they result moderate to weak acetylcholinesterase activity with an IC_{50} value ranging from 17.14 to 131.17 μM.	Flavonoids exhibited Anti-cholinesterase activity.	(Y. Tu et al., 2019)
M. auriculata Brandis	Stem, leaves	Anthelmintic	*In-vitro*	Chloroform	Extract possessed a significant anthelmintic activity (*in-vitro*) using *Pheretima posthuma* at a dose of 10 mg/mL against the standard drug albendazole, where the leaves extract was found to be more potent as compared with stem and standard.	Phenolic compounds and flavonoids may have a direct effect on the pre-parasitic stages which hampers the viability of parasite.	(Das and Ganapaty, 2014)
M. extensa (Benth.) Baker	Leaves	Anthelmintic	*In-vitro*	Acetone, ethanol, aqueous	After treatment of 1 μL of extract, the % of inhibition on *C. elegans* was observed where the aqueous extract was found to be more potent (% of inhibition is 88.0 ± 3.0)	Due to the presence of flavonoids as its major phytoconstituents.	(Padhi et al., 2017)
M. pinnata (L.) Panigrahi	Seed, root	Anti-ulcer	*In-vivo*	Methanol	The extract showed optimal effective dose at a dose of 25 mg/kg in pyloric ligation, aspirin and duodenal induced ulcer model.	Not studied	(Pulipati et al., 2018)
M. griffithii Dunn	Whole plant	Anti inflammatory	*In-vitro*	EtOAc, n-hexane, griffinone B	Isolates were evaluated on LPS-induced NO production in RAW 264.7 cell resulting significant activity and 3 isolates showed more than 50% inhibition having IC_{50} value 20.4, 2.1 and 35.7 μM. griffinone B exhibits the best activity.	The possible mechanism is the suppression of the expression of iNOS protein and inhibition of NO production.	(Tang et al., 2016)
M. dielsiana Harms ex Diels	Stem	Anti-inflammatory	*In-vitro*	Ethanol	Isolates were evaluated for nitric oxide (NO) production in lipopolysaccharide (LPS)-	The mechanism is based on a decrease in NO production and TNF-α secretion.	(Dat et al., 2019)

(*continued on next page*)

Table 3 (*continued*)

Plant species	Plant parts	Activity studies	*In- vivo*/*in-vitro*	Tested extracts/ active constituent	Observed effect	Mechanism	References
					stimulated murine RAW264.7 macrophage cells where (3S)-vestitol showed the highest inhibitory effect (IC_{50} value 16.0 ± 1.5 μM).		
M. pinnata (L.) Panigrahi	Leaves	Anti-inflammatory	*In-vivo*	70% ethanol	An oral dose of 100, 300 and 1000 mg/kg did not show any gastric lesion and ulcerogenic activity in the both acute and chronic model which implied a significant anti-inflammatory activity.	COX-2 inhibition resulting decrease in PGE-2 synthesis	(Pulipati et al., 2018)
Pongamia piñata (synonym of *M. pinnata* (L.) Panigrahi)	Leaves	Antidiabetic	*In-vivo*	Petroleum ether, chloroform, ethanol, aqueous	An oral dose of 500 mg/kg of extracts was evaluated for in alloxan-induced diabetic rat model against standard drug Glibenclamide. It was observed that the aqueous and ethanol extract showed less potential but significant than the standard Glibenclamide and at the same time both of the extracts decrease the blood glucose and increase the body weight.	The possible mechanism may be for the increase insulin secretion which improves the rate of glucose utilization. Different bioactive constituents like flavonoids, phenolics, steroids also play an important role in antidiabetic study	(Sikarwar and Patil, 2010).
M. leucantha Kurz	Wood	Cytotoxicity, anti-cancer	*In-vitro*	Ethanol	Extracts were evaluated against NCI-H187, BCA-1and KB tumour cell lines resulting physcion and millettinol having potent activity against the NCI-H187 cell lines (IC_{50} value 4.30 μg/mL) and BCA-1 cell lines (IC_{50} value 3.44 μg/mL) respectively.	Not studied	(Rayanil et al., 2011)
M. speciosa Champ.	Root	Cytotoxicity	*In-vitro*	70% ethanol, petroleum ether	The extract showed moderate activity against MCF-7, HCT-116, A549, HepG-2 cell lines.	Not studied	(Chen et al., 2015)
M. pinnata (L.) Panigrahi	Flower	Cytotoxicity, anti-cancer	*In-vitro*	Green synthesized nanoparticles	Several concentrations i.e. 11.11, 33.33, 100, 300 μg/mL of extract were evaluated using brine shrimp lethality assay resulting lowered LD_{50} value of 36.41 μg/mL.	This lowered LD_{50} value suggests the cytotoxicity activity green silver nanoparticles synthesized. This enhanced activity justifies the presence of toxic molecules which is a probable mechanism for anticancer activity.	(Rajakumar et al., 2017)
M. dorwardi Collett & Hemsl.	Vine stem	Cytotoxicity	*In-vitro*	EtOAc, n-BuOH, millepurpan, Medicarpin	Millepurpan showed moderate activity against four cancer cell lines, HepG2, HCT116, Raji and KG-1 cell lines (IC_{50} values 52.03, 68.89, 40.17 and 61.22 μM respectively). Medicarpin exhibited the best cytotoxic activity as compared to other compounds having IC_{50} value 38.07, 46.85, 36.13 and 30.11 μM, respectively.	Not studied	(Chen et al., 2018)
M. brandisiana Kurz	Root	Cytotoxicity, antioxidant, anti-cancer, aromatase inhibition activity,	*In-vitro*	Dichloromethane	MTT assay of the extract showed significant cytotoxicity against HepG2, A549, HuCCA-1,	Bioactive flavonoids like lanceolatin B, isoloncho may be responsible to execute	(Pailee et al., 2019)

Table 3 (*continued*)

Plant species	Plant parts	Activity studies	*In- vivo*/*in-vitro*	Tested extracts/ active constituent	Observed effect	Mechanism	References
					HeLa cell lines. The flavonoid isolates also showed good aromatase inhibition activity.	cytotoxicity as well as anti-cancer activity.	
M. pachyloba Drake	Stem	Cytotoxicity	*In-vitro*	Ethanol, durmillone	Preliminary screening study resulted in 10 compounds having cytotoxicity against HeLa and MCF-7 cells and further evaluation against HeLa, HepG2, MCF-7, Hct116, MDA-MB-231 and HUVEC (normal cell line) showed specific cytotoxicity having an IC_{50} range from 5 to 40 μM among of them durmillone showed potent activity by inducing apoptosis.	The isolates may induce apoptosis and autophagy in a concentration-dependent manner.	(Yan et al., 2019)

in any groups (Aneela et al., 2011). Later, another isolated compound known as "Karanjin" was also isolated from the methanol extract of the same plant and evaluated for its toxicity. Male Wistar rats (180–200 gm) were administered at a dose of 20 mg/kg/day of Karanjin for a time period of 14 days. The result showed no major changes in the biochemical profile indicating no lethal effect (Vismaya et al., 2011). Different solvent extracts like ethanol, aqueous, chloroform, and petroleum ether of *Pongamia piñata* (synonym of *M. pinnata* (L.) Panigrahi) was evaluated for acute oral toxicity for a dose range of 50–5000 mg/kg/day for a period of 14 days. It was observed that there is no significant change in the toxicity parameters of all the extracts (Sikarwar and Patil, 2010).

The seeds, root, and bark extract of *M. ferruginea darasana* were evaluated for *in-vitro* toxicity against *Amblyomma variegatum* Fabricius larvae (both male and female) at a different concentration ranging from 20 to 100% in Petri plates. Based on the mortality rate, it was observed that no toxic constituents were present in leaves extract where, the highest toxicity is observed in seed followed by root extract (Choudhury et al., 2015).

It was reported that different compounds were identified from EtOAc and n-BuOH extracts of vine stems of *M. dorwardi* Collett & Hemsl. and evaluated for the cytotoxicity effect against five cancer cell lines viz. HepG2, HCT116, MCF7, Raji and KG-1. These compounds have no evident activity but one of the compound known as millepurpan showed modest growth inhibitor activity against Raji and KG-1 cell line. From the advance study, it was revealed that millepurpan could induce G1 arrest and apoptosis in KG-1 cells (Chen et al., 2018).

The dichloromethane root extracts of *M. brandisiana* Kurz was reported for having significant cytotoxicity activity against mammalian cancer cell lines such as HepG2, A549, HuCCA-1, HeLa using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT assay). This study revealed the reports about the efficacy of isolated flavonoids having good aromatase inhibition activity and antioxidant activity (ORAC assay) as well. These results draw a probable mechanism that the bioactive flavonoids could be of importance for advance studies as prospective cytotoxicity and cancer chemopreventive agents (Pailee et al., 2019).

Studies were conducted to investigate the cytotoxicity activity of different fractionated isolates of ethanol extracts of stems of *M. pachyloba* Drake on HeLa and MCF-7cell lines by MTT assay. Total of 10 compounds showed potent cytotoxicity activity for which these were again subjected, to study the activity against different cancer cell lines viz. HeLa, HepG2, MCF-7, Hct116, and MDA-MB-231 and one normal cell line HUVEC. This revealed that these compounds have specific cytotoxicity potential in a cancer cell line whereas, there are no such results obtained in case of the normal cell line. Again, the autophagic effect was investigated by using GFP-LC3-HeLa cells and confirmed about the compound known as durmillone, which significantly induces autophagy. From the PI/Annexin V double staining assay, it was confirmed that durmillone, also induces apoptosis in HeLa and MCF-7 cells. These findings suggest the compound, as a potent anti-cancer agent demonstrated by highest cytotoxic activity, through the combined action of apoptosis and autophagy (Yan et al., 2019). Significant cytotoxicity is observed due to the presence of bioactive rotenoids.

6. Conclusions

Millettia species have been used as a conventional medicine across the globe as it a rich source of isoflavonoids, rotenoids, sterols, phenolic compounds, coumarin, terpenoids, resin, saponins, etc (Derese et al., 2014). The present review reports traditional uses, phytochemical constituents and pharmacological activities based on ethnopharmacological claims of genus "*Millettia*". Extensive literature survey revealed that most of the species are used traditionally in different African and Asian countries including India, Pakistan, China, France, Burma, Malaysia, Thailand, Kenya, etc where, only a few species were scientifically evaluated for their phytochemical constituents that could mediate particular pharmacological activities. *M. pinnata* (L.) Panigrahi has been the most investigated species and it plays an important role in biodiesel production (Ruhul et al., 2017; Madhu et al., 2016). The major traditional use of *Millettia* species as reviewed involved in the treatment of joint pain, rheumatoid arthritis, hepatitis amenorrhea, tuberculosis, chronic bronchitis, the fish poison, insecticide, skin disease, vermifuge which have been validated scientifically. It is observed that most of the pharmacological activity studies were limited to both *in-vitro* and *in-vivo* screening where, the mechanisms of action, bioavailability and pharmacokinetics are not explored clearly. Furthermore, a number of studies were done for the bioassay-guided extraction and isolation of phytochemical constituents. Further research should target on the exploration and validation of traditional claims of other species by focusing the bioassay-guided drug discovery along with the formulation and mode of administration of drugs which we found lacking in

most of the reviewed literature. An additional extensive use that requires to be evaluated is in the menstrual irregularities. Even though these species have ethno claims to be used for the female disease but it has not been evaluated significantly. So, further well designed and more clinical in-depth studies are required by focusing on the mechanism-based *in vitro* and *in vivo* studies for understanding the underlying mechanisms linked to ethnopharmacological uses.

7. Future perspective

The feature of this review based on traditional uses, phytochemicals and significant pharmacological activities of different *Millettia* species. Therefore, it would be essential to carry out a comprehensive investigation to identify their individual phytochemicals and possible mechanism of pharmacological activity for the development of new formulations in drug discovery.

Millettia species imply dynamic medicinal as well as pharmacological activity. So researchers should focus on the exploration of these species having potent activity against various ailments to figure out the probable mechanism in the molecular ground. However, the traditional uses are validated by performing different animal studies and the clinical trial is required to measure the safety and efficacy in the human being which is a part of the drug development process.

8. Author's contributions

Rasmita Jena: Collection and compilation of data, writing of the manuscript. Diptirani Rath: Review and editing of the manuscript. Sudhanshu Sekhar Rout: Correction and analysis of chemical compounds. Durga Madhab Kar: Designing, supervising and editing of the manuscript. All authors read and approved the final manuscript.

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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