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A review on ethnobotany, phytochemistry, and pharmacology of the genus *Didymocarpus* wall. (Gesneriaceae)

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ABSTRACT

Ethnopharmacological relevance: Medicinal plants have been extensively used to treat various illnesses since the dawn of civilization. The genus *Didymorcapus* Wall. comprises 100 species widely distributed in the tropical regions of Asia, with a few found scattered in Africa and Australia. Species in this genus have long been used in folk medicine to treat various illnesses, including wounds, kidney stones, inflammations, asthma, flu, eczema, dysentery, fractures, colic etc. Some species have applications as weight loss agents, laxatives, and protective medication after childbirth.

Aim: To provide comprehensive information on the current knowledge of the ethnobotanical uses, phytochemical compounds, pharmacological applications, and toxicology of genus *Didymocarpus* to reveal its therapeutic potential, offering insights into future research opportunities.

Materials and methods: Data were systematically obtained from books and online databases such as PubMed, Web of Science, Scopus, Sci Finder, Google Scholar, Science direct, ACS Publications, Elsevier, Wiley Online Library.

Results: Seventeen *Didymocarpus* species have applications in traditional medicine in different Asian countries. A total of 166 compounds have been isolated from the genus *Didymocarpus* including terpenoids, flavonoids, phenolic compounds, fatty acids, chalcones, steroids, and others. Among these constituents, terpenoids, flavonoids, chalcones, and phenolics are the significant contributors to pharmacological activities of the genus *Didymocarpus*, possessing wide-reaching biological activities both *in vivo* and *in vitro*. The crude extracts and isolated phytochemical compounds from this genus have been shown to exhibit various pharmacological activities, including antiurolithiatic, nephro-protective, antimicrobial, anticancer, antidiabetic, cytotoxic, wound healing, and antioxidant activities.

Conclusions: Traditional uses and scientific evaluation of *Didymocarpus* indicate that *Didymocarpus pedicellata* is one of the most widely used species in some parts of the world. Although substantial progress on the chemical and pharmacological properties of *Didymocarpus* species has been made, further studies on the pharmacology and toxicology of these species are needed to ensure safety, efficacy, and quality. Also, further research on the structure-activity relationship of some of the isolated phytocompounds may improve their biological potency and scientific exploitation of traditional uses of the *Didymocarpus* taxa.

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1. Introduction

Gesneriaceae (African Violet Family) consists of 150 genera and about 3400 species, mainly tropical herbs and shrubs (Weber et al., 2013). The genus *Didymocarpus* comprises over 100 species, widely distributed from the Himalayas to the Malay Peninsula (Nong et al., 2021; Souvannakhoummane et al., 2019). China and India are the highest centers of diversity of this genus, with 34 species and five varieties, 23 species and two varieties, respectively (Michael et al., 2016; Möller et al., 2017). *Didymocarpus* species are lithophytic perennials characterized by ovate to ovate-cordate lamina, predominantly glandular and hairy, oblique limbs on tube-like corollas, a couple of fertile staminate having three staminodes, a capitate stigma, an orthocarpic ovary and a bivalve capsule which dehisces in a loculicidal direction (Weber et al., 2000).

Species in the genus *Didymocarpus* are traditionally used for the treatment of various diseases, including kidney stones, fever, skin allergy, inflammation, chronic asthma, flu, wounds, dysentery, diarrhea, urticaria, psoriasis, bone fracture, and traumatic injuries (Das, 1995; Hinsley et al., 2018; Kottaimuthu, 2008; Kunwar and Bussmann, 2009; Sarwar, 2015; Taylor et al., 1996). Also, *Didymocarpus* species have applications as laxatives, weight loss agents, pain relievers, and as protective medicine after childbirth (Kunwar et al., 2010; Kunwar and Bussmann, 2009; Limbu and Rai, 2013).

Didymocarpus species are rich in terpenoids, flavonoids, phenolic compounds, fatty acids, chalcones, steroids, and various esters, which authenticate their medicinal importance (Gowda et al., 2012; Lowry, 1972; Prameela et al., 2015). Antiurolithiatic, nephro-protective, antimicrobial, anticancer, antidiabetic, cytotoxicity, wound healing, and antioxidant activities properties exhibited by various extracts and compounds isolated from the genus *Didymocarpus* showed its pharmacological importance (Baheti and Kadam, 2013; Biswas et al., 1981; Gowda et al., 2012; Kaur et al., 2007; Lone et al., 2016; Mittal et al., 2020). *Didymocarpus pedicellatus* R. Br. is the most popular, widely utilized and highly investigated species in the genus despite the relatively high number of other species within the genus, which are more or less underexplored. This species is an important medicinal species extensively used in Asian countries to treat kidney stones and renal diseases (Bhongade et al., 2021; Devkota et al., 2017; Hinsley et al., 2018; Kapoor and Kapoor, 1976; Khare, 2007; Sarin, 2008; Saklani et al., 2015).

This review aims to establish a relationship between traditional uses and scientific studies by critically assessing the available literature on phytochemistry, ethnobotanical and pharmacological uses, possible mechanisms of action, and toxicology of the plant species from the genus *Didymocarpus*. Further, this review also highlights the various research gaps for better exploitation of this genus and provides a baseline for future research studies.

2. Methodology

This review highlights the phytochemistry, ethnobotanical, and pharmacological uses of the genus *Didymocarpus* from 1948 to 2022. Data were obtained by searching various scientific online databases, including Google Scholar, PubMed, Web of Science, SciFinder, Science Direct, ACS Publications, Elsevier, and Wiley Online Library using keywords such as *Didymocarpus*, morphology or botany, distribution, ethnobotany, phytochemistry, pharmacology, and toxicity. Additional information was obtained from other literature sources such as books and journals. English and non-English reference books containing important properties of *Didymocarpus* species were systematically reviewed. Species names were verified using the World Flora Online (http://www.worldfloraonline.org/) database, while the chemical structures of the compounds were drawn using the ChemDraw software and confirmed using the PubChem (https://pubchem.ncbi.nlm.nih.gov/) database.

3. Distribution, habitat and ecology

Didymocarpus species are distributed across northwest regions of India, eastern parts of Nepal, Bhutan, northeast India, Burma (Myanmar), Vietnam, Laos, Thailand, the Malay Peninsula, China (southern and southeastern Xizang, Yunnan, western and southwestern Sichuan, eastern and southern Guangxi, and western Guangdong), and Cambodia (Michael et al., 2016; Nangngam and Maxwell, 2013; Nangngam and Middleton, 2014; Zhang et al., 2020). Only a single species, *Didymocarpus cordatus* Wall. ex A. DC. extends up to the northern regions of Sumatra (Palee et al., 2006). Recent phylogenetic studies proposed the origin of *Didymocarpus* to be the Malay Peninsula (Palee et al., 2006), even though the northeast region of India and southern China consists of more than half of all known *Didymocarpus* species (Möller, 2019; Möller et al., 2017). Species of this genus occur in shaded and moist regions, terrestrial, on trees, bedrocks, and seasonal rainfall areas (Nangngam and Middleton, 2014). Many *Didymocarpus* species are found between 500 and 1800m elevations in primary forests, including mixed evergreen, pine forest and deciduous dipterocarp-oak seasonal hardwood forest (Nangngam and Maxwell, 2013).

4. Botanical traits

Didymocarpus species are characterized by a perennial deciduous herb having annual or monocarpic flowering stems with innovation and resting shoots that develop during the rainy season and turn into flowering shoots during the subsequent season (Weber et al., 2000). The leaves are opposite and decussate and show anisophylly, while the inflorescence is cymose pedunculate, having several flowers with a pair of oval wine-colored bracts (Fig. 1). The calyx appears either merged for more than half of its length or free to the base, while the corolla is salverform, funnelform or personate, opening widely towards the mouth with a bilabiate limb, circular lobes that may be mauve, claret, violet or yellow/white (Burtt and Wiehler, 1995). The flower has a pair of stamens with cohering anthers, thin filaments, two or three tiny staminodes, a cup-like disc with an unevenly lobed rim, and a cylindrical ovary with a capitate stigma. The capsules dehisce loculicidally are usually straight, orthocarpic, and bivalved, whereas some species have a dense cover of pigment glands on the lower side of leaf blades. The morphology of the *Didymocarpus* species is varied from single-celled and globose or conoid, with a double-celled head, to four-celled conoid (Weber et al., 2000).

5. Herbal uses

Herbal medicine has been used to treat an array of conditions by humans since ancient days (Schulz et al., 2001). A report by the World Health Organization indicates that indigenous or native populations still practice traditional medicine, and more than 80% of the people in Asian and African countries rely on it for primary health care (Chan, 2008; Alam et al., 2012). Although herbs have been used as potent medicine since ancient history, most lack scientific validation and are underexplored (O'Connor and Hufford, 2001).

Didymocarpus species have a long application history in traditional medicine (Lama et al., 2001; Sarwar, 2015). *Didymocarpus pedicellata*, also known as the black stone flower, is native to tropical Asia and commonly referred to as shilapushpa, shantapushp, and sometimes pasanbheda in Ayurveda (Goyal and Ikshit Sharma, 2015). The whole plant is usually sun-dried and used as a spice. In contrast, flowers have numerous medicinal properties, including wound healing, digestion, suppression of respiratory disorders, and pain relievers (Ramsay and Stewart, 1998). In Ayurveda formulations, *D. pedicellata* is used to treat kidney conditions, including stones, urolithiasis, neuro-ureterolithiasis, burning micturition, and other renal disorders (Goyal and Ikshit Sharma, 2015). The power of the root and rhizome of this species is used as incense (Devkota et al., 2017). Furthermore, the roots of this species

Fig. 1. Didymocarpus longicalyx G.W. Hu & Q.F. Wang.

are used as an alternative to *Bergenia ligulata* Engl. for its therapeutic application in kidney stones (Prasad and Chandra, 2017). Previous studies have attributed the biological properties of this plant to its ability to regulate calcium absorption in the body, thus its diuretic effect in maintaining a healthy urinary tract (Kapoor and Kapoor, 1976; Sarin, 2008). In India, the local people of Pithoragarh use *D. pedicellata* buds as pain relievers for stomach pain and to eliminate stomach *Ascaris lumbricoides* (Prasad and Chandra, 2017).

In the Himalayas (Uttar Pradesh to Bhutan), North-Eastern India and Nepal, *Didymocarpus lanuginosus* Wall. ex DC., has extensive usage in treating kidney conditions (Lama et al., 2001). This species is used to treat poisoning, diarrhea, and chronic wounds (Ayyanar and Ignacimuthu, 2009; Lama et al., 2001). *Didymocarpus tomentosus* Wight., a herb widely distributed in India, has been used in herbal medicine to manage various conditions, including fever, skin allergy, and inflammation (Kottaimuthu, 2008; Sathyavathi and Janardhan, 2011). The leaf juices of this species are also used as a tonic (Kottaimuthu, 2008). *Didymocarpus leucocalyx* C.B. Clarke has been used as an aromatic stomachic and carminative for diseases caused by vata dosha imbalance in Indian Ayurveda (Segawa et al., 1999). Additionally, *Didymocarpus gambleanus* C.E.C.Fisch. leaf paste is used for wound healing, particularly on pimples and external cracks, by the tribes of Sirumalai hills in India (Karuppusamy, 2007).

The whole plant of *Didymocarpus albicalyx* C.B. Clarke has been reported to have veterinary uses in herbal medicine among the Temang people in central Nepal (Luitel et al., 2014). It is administered orally to weak animals to energize them. This species was also used to treat respiratory conditions and chronic asthma in children (Burlakoti and Kunwar, 2008). *Didymocarpus primulifolius* D. Don commonly referred to as "Paharo ko kan" in Nepalese, is used as an antiviral to treat flu (Taylor et al., 1996). Both *Didymocarpus aromatica* D. Don and *Didymocarpus villosus* D. Don have a long history of application in treating respiratory problems in children, chronic asthma, and are also used as disinfectants (Kunwar and Bussmann, 2009). Moreover, the essential oils of *D. villosus* have applications in weight loss (Kunwar et al., 2010). Additionally, *Didymocarpus humboldtiana* Gardner, is used to treat wounds in Nepal (Ayyanar and Ignacimuthu, 2009; Karuppusamy, 2007; Lama et al., 2001).

Didymocarpus hedyotideus Chun and *Didymocarpus hancei* Hemsl. have been used in Traditional Chinese Medicine (TCM) to treat eczema, urticaria psoriasis, bone fracture, traumatic injuries, and gastric mucosal injury (Guo, 2020; Medica, 1999; Xiao et al., 2011). In Bangladesh, *Didymocarpus mollis* Wall. ex C.B.Clarke has long been used as a pain reliever in swellings, ankle, and wrist pain (Sarwar, 2015).

In Malaysia, *Didymocarpus reptans* Jack has been used to alleviate colic, constipation, and dysentery (Uphof, 1968). Moreover, in the Malay Peninsula, *Didymocarpus atrosanguineus* Ridl. and *Didymocarpus crinitus* Jack have been used traditionally as protective medicine after childbirth. *Didymocarpus platypus* C.B. Clarke on the other hand has been used in the treatment of chronic coughs (Miller, 2000).

The ethnopharmacological applications of *Didymocarpus* species reveal that they present a significant number of indications in Asian countries where they are widely distributed. Generally, widespread knowledge can facilitate the exploration and probing of medicinal plants, which usually results in the discovery of pharmacologically active compounds (Maciel et al., 2002). Therefore, species of the genus *Didymocarpus* can be studied for activities such as nephro-protective, antiurolithiatic, and wound healing activities. The herbal uses of *Didymocarpus* species have been summarized in Table 1 below.

6. Phytochemistry

6.1. Preliminary phytochemical screening

Early phytochemical studies of *Didymocarpus platypus* occurred in the '80s and revealed the presence of saponins in the leaves of this species (Othman and Toia, 1985). Saponins were also recently identified in the hexane extract of *D. tometonsa* (Juliet et al., 2012). Later, preliminary phytochemical investigation on the hexane extract of *Didymocarpus Oblong*us Wall. ex D. Don led to the isolation of diterpenes (Mitra et al., 1987). Other studies in subsequent years have led to the isolation and identification of reducing sugars, flavonoids, glycosides, phenolic compounds, tannins, terpenoids, quinones, triterpenoids, fats and oils from petroleum ether, hexane, chloroform, ethyl acetate, and ethanol extracts of *D. tomentosa* (Juliet et al., 2012). Moreover, a study on the antioxidant activity, phytochemicals, and nutrients of *D. pedicellata* resulted in the extraction and characterization of phenolic compounds from this species (Prasad and Chandra, 2017).

6.2. Chemical composition

Detailed phytochemical studies on the genus *Didymocarpus* have

Table 1
Summary of the ethnobotanical uses of the genus *Didymocarpus* (species name, plant part, country, uses, mode of administration, and associated references).

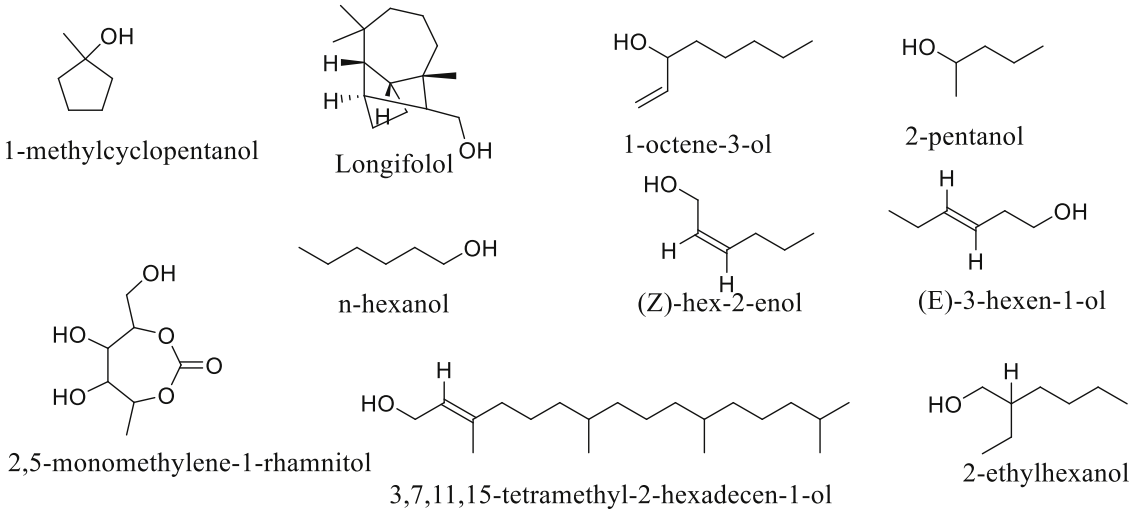
Species	Plant part used	Country	Uses	Mode of administration	References
Didymocarpus pedicellata	Leaves, buds	India	Treatment of renal diseases, particularly kidney stones and stones of the bladder, regulates the absorption of calcium minerals in the body, pain reliever in stomach pains and eliminates *A. lumbricoides* in the stomach	Two spoonfuls of fresh leaves paste for two weeks	Devkota et al. (2017), Hinsley et al. (2018), Kapoor and Kapoor (1976), Khare (2007), Prasad and Chandra (2017), Sarin (2008)
	Whole plant		Used as a diuretic and in the maintenance of a healthy urinary tract		
	Roots		Treatment of kidney stones, power of root and the rhizome is used as incense		
D. tomentosa	Whole plant	India	Treatment of fever, skin allergy and inflammation		Kottaimuthu (2008), Sathyavathi and Janardhan (2011)
	Leaves	India	Tonic	Leaf juice	Kottaimuthu (2008)
D. mollis	–	Bangladesh	Pain reliever in swellings, ankle, and wrist pain		Sarwar (2015)
D. albicalyx	Leaves andrhizomes	Nepal	Treatment of respiratory conditions, chronic asthma in children, and energizing weak animals	Leaf infusion and dust are taken orally	Burlakoti and Kunwar (2008), Luitel et al. (2014)
	Dried leaves	India	Cure of kidney stones and bladder		Das (1995)
D. aromatica	Leaves and whole plant	Nepal	Treatment of respiratory problems in children, chronic asthma, and as an antibacterial agent, and treatment of bovine haematuria in animals	Juice	Kunwar and Bussmann (2009), Manandhar (1995)
D. villosus	Leaves	Nepal	Treatment of respiratory conditions in children, chronic asthma, and as an antibacterial agent, a laxative, and weight loss agent	Leaves are smoked for laxative action; essential oils are taken orally for weight loss	Kunwar et al. (2010), Kunwar and Bussmann (2009), Limbu and Rai (2013)
D. primulifolius	Whole plant	Nepal	Treatment of flu		Taylor et al. (1996)
D. humboldtiana	Whole plant	India	Wound healing		Ayyanar and Ignacimuthu (2009)
D. leucocalyx	Leaves and whole plant	India	An aromatic stomachic and carminatives for diseases caused by vata disorders, used for incence	Powder	Segawa et al. (1999)
D. hedyotideus	Whole plant	China	Treatment of eczema, urticaria, psoriasis, bone fracture, and traumatic injuries		Medica (1999), Xiao et al. (2011)
D. gambleanus	Leaves	India	Wound healing	The paste is applied to external cracks and pimples	Karuppusamy (2007)
D. lanuginosus	Whole plant	Nepal	Treatment of diarrhea, kidney problems, and wounds	Used with other herbs	Lama et al. (2001)
D. hancei	Whole plant	China	alleviate gastric mucosal injury	Mixed with *Acanthopanax senticosus* (Rupr. & Maxim.) Harms, *Panax notoginseng* (Burkill) F.H.Chen and, *Valeriana officinalis* L.	Guo (2020)
D. reptans	Leaves and roots	Malaysia Peninsular	Alleviation of colic, constipation, and dysentery	Decoction	Uphof (1968)
Didymocarpus atrosanguineus	Whole plant	Peninsular Malaysia	Administered as a protective medicine after childbirth	Infusion	Miller (2000)
Didymocarpus crinitus	Roots	Peninsular Malaysia	Used as a protective medicine after childbirth and wound healing	Poultice	Miller (2000)
Didymocarpus platypus C.B. Clarke	Roots	Peninsular Malaysia	Treatment of cough	Decoction	Miller (2000)

resulted in an array of secondary metabolites. Structurally diverse and biologically active compounds have been identified from *Didymocarpus pedicellata, D. corchorijolia* Wall., *Didymocarpus atrosanguineus* Ridl., *Didymocarpus crinitus* Jack, *D. tomentosa*, *D. leucocalyx*, *D. hedyotideus*, *D. aurantinca*, *D. oblonga*, and *D. podocarpa* (Bose and Adityachaudhury, 1978; Gowda et al., 2012; Haldar et al., 1989; Lone et al., 2016; Lowry, 1972; Prameela et al., 2015; Prasad and Chandra, 2017; Segawa et al., 1999; Xiao et al., 2011). To date, a total of 166 chemical compounds have been reported from *Didymocarpus* species, including terpenoids, flavonoids, fatty acids, phenolic compounds, alcohols, aldehydes, esters, among others (Bhaskar and Seshadri, 1973; Bhattacharyya, 1979; Bose and Adityachaudhury, 1978; Gowda et al., 2012; Lowry, 1972; Prameela et al., 2015; Prasad and Chandra, 2017; Rao et al., 1966; Segawa et al., 1999; Seshadri, 1965). Phytochemical studies within the genus *Didymocarpus* have shown similarities with other Gesneriaceae species (Verdan and Stefanello, 2012), resulting in the isolation and characterization of terpenoid and flavonoid metabolites as the two predominant chemical classes (Fig. 2). Terpenoids and flavonoids comprise 45 and 25 compounds, respectively, of the total isolated chemical compounds from this genus (Gowda et al., 2012; Prameela et al., 2015; Segawa et al., 1999). The majority of the compounds isolated from *Didymocarpus* species are attributed with various medicinal properties such as anticancer, antimicrobial, antifungal, antiviral, anti-hyperglycemic, analgesic, anti-inflammatory, and antiparasitic activities (Ninkuu et al., 2021; Panche et al., 2016; Tsiapara et al., 2009). Knowledge of the pharmacological activity of *Didymocarpus* species is important because it provides a scientific basis for understanding their traditional medicinal use and mode of action mechanisms. The presence of various phytoconstituents in the whole plant, roots and leaves of different species of the genus *Didymocarpus* justifies the traditional

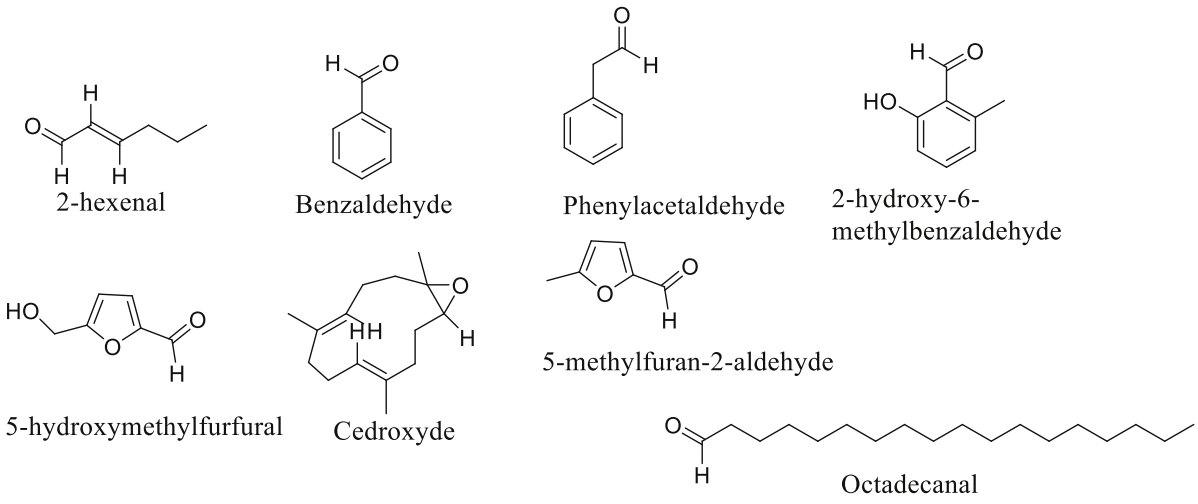
herbal uses of these plants in the treatment and management of various diseases and are also promising agents for the production of novel pharmaceuticals in the field of drug discovery.

The detailed information for these compounds is summarized in Table 2. Phytochemical studies of *Didymocarpus* species also led to the isolation of phytoconstituents, some of which have been reported isolated in trace amounts. Some examples include; 5,6-dimethyl-2,3-dihydro-1,4-dioxin, 5-hydroxy-7-methoxy-2-phenyl-4H-1-benzopyran-4-one, and 5,9,9-trimethyl-5-phosphatricyclo[6.1.1.02,6]dec-2-ene (Prameela et al., 2015; Prasad and Chandra, 2017; Segawa et al., 1999).

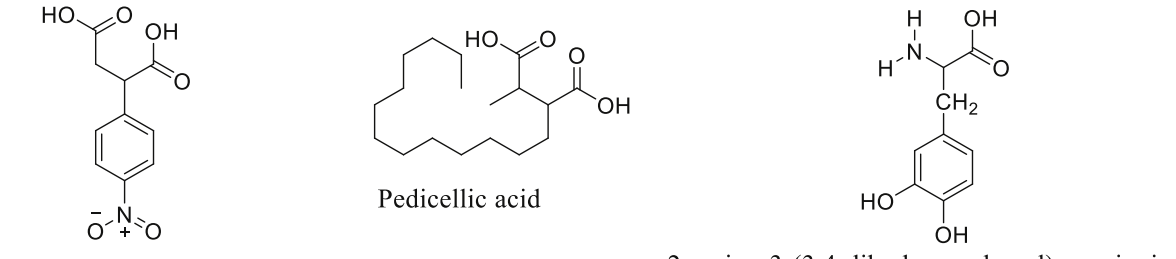
The chemical structures of some of the compounds isolated and characterized from the genus *Didymocarpus* are shown below.



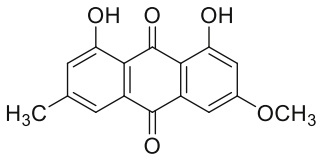
Alcohols



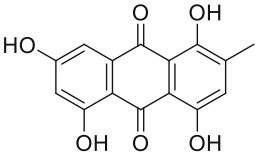
Aldehydes



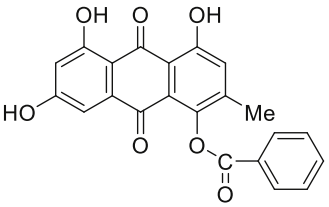
Carboxylic acids **Amine**



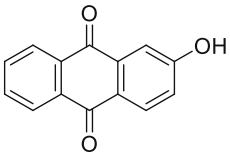
Physcion



Catenarin

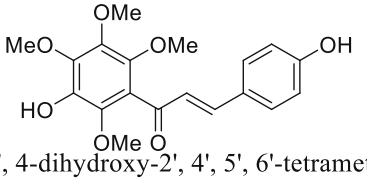


1,6,8-trihydroxy-4-benzoyloxy-3-methylanthraquinone

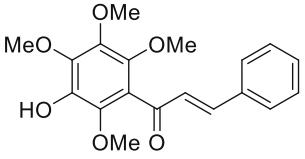


2-hydroxy-9,10- anthraquinone

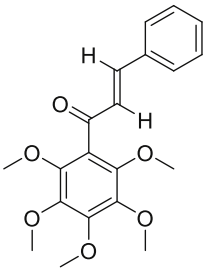
Anthraquinones



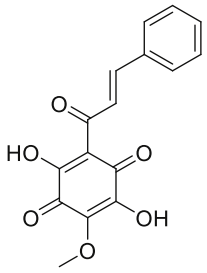
3', 4-dihydroxy-2', 4', 5', 6'-tetramethoxychalcone



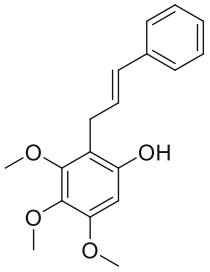
3'-hydroxy-2',4',5',6'-tetramethoxychalcone



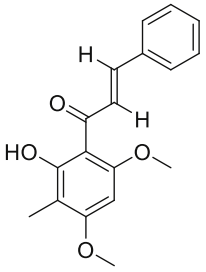
Pedicellin



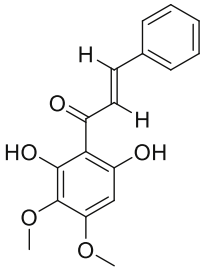
Pedicinin



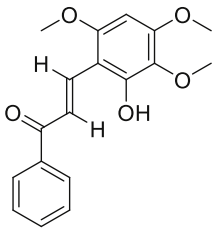
2'-hydroxy-4',5',6'-trimethoxychalcone



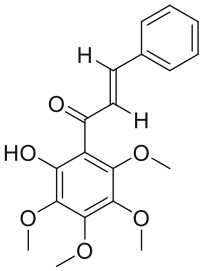
Aurentiacin



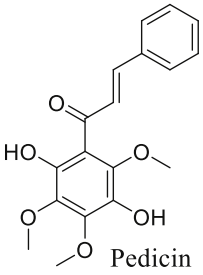
Pashanone



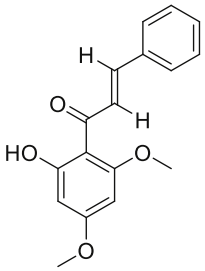
2-hydroxy-3,4,6-trimethoxychalchone



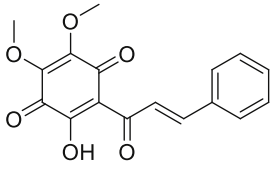
Methylpedicin



Pedicin

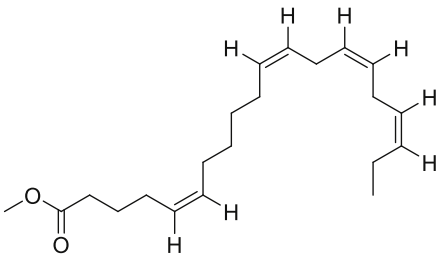


Flavokawin B

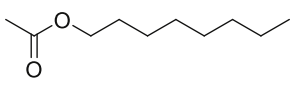


Methylpedicinin

Chalcones

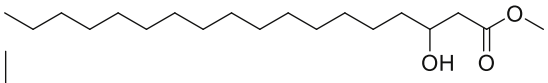


Methyl (Z)-5,11,14,17-eicosatetraenoate

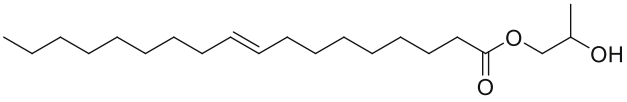


Octyl acetate

Methyl linoleate

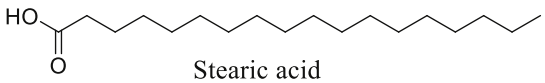


Methyl 3-hydroxyoctadecanoate

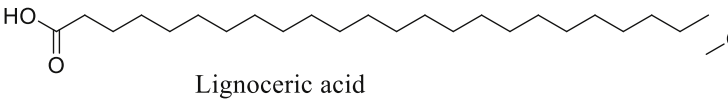


Propylene glycol monoleate

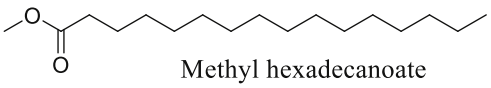
Esters



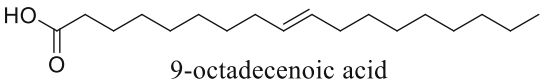
Stearic acid



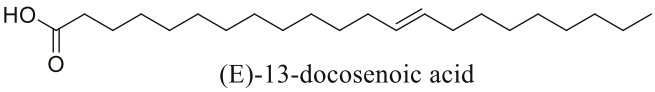
Lignoceric acid



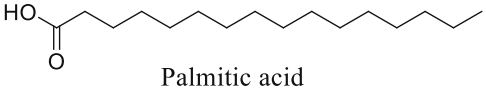
Methyl hexadecanoate



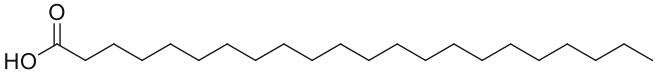
9-octadecenoic acid



(E)-13-docosenoic acid

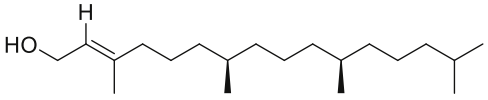


Palmitic acid



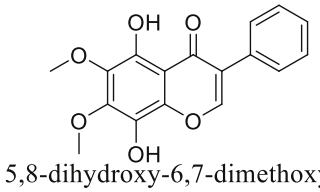
Behenic acid

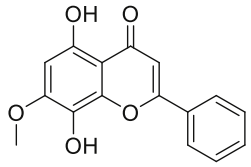
Fatty acids

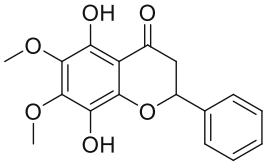


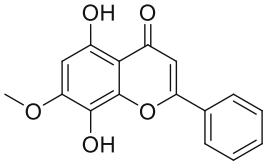
Phytol

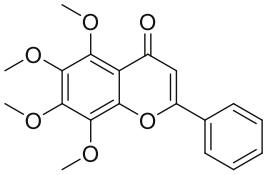
Diterpenoid

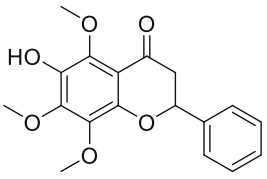

5,8-dihydroxy-6,7-dimethoxyisoflavone

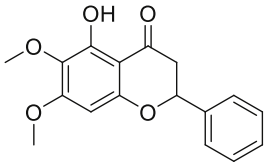

Pediflavone

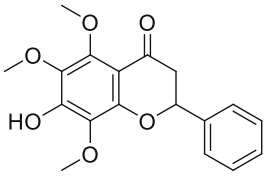

Didymocarpin A

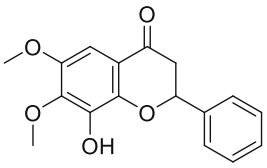

5,8-dihydroxy-7-methoxyflavone

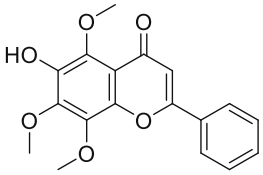

5,6,7,8-tetramethoxyflavanone

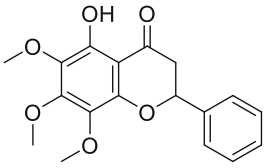

Isopedicin

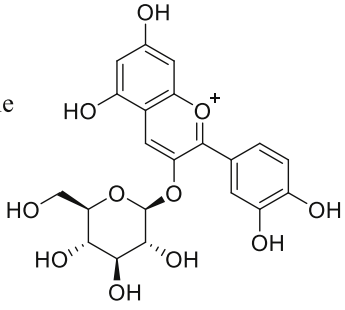

5-hydroxy-6,7-dimethoxyflavanone

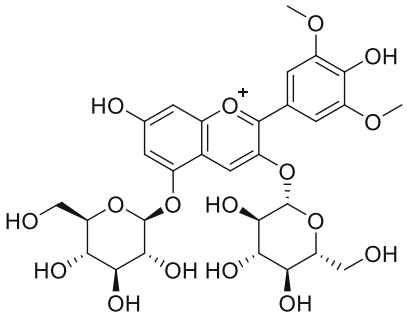

Didymocarpin

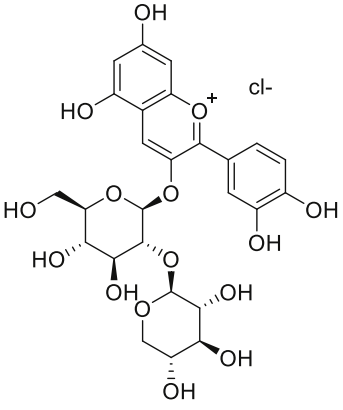

Onysilin

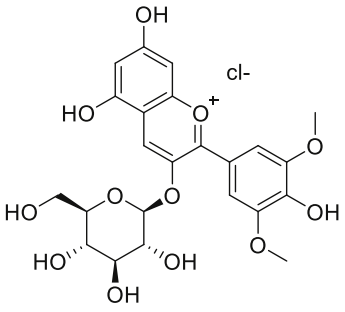

7-hydroxy-5,6,8-trimethoxyflavanone


8-hydroxy-5,6,7-trimethoxyflavanone

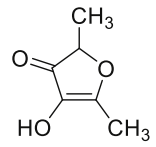

Cy-3-glycoside


Malvidin-3,5-diglucoside

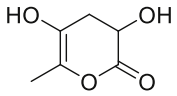

Cy-3-sambubioside


Malvidin-3-glucoside

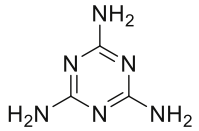
Flavonoids



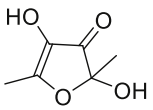
2,5-dimethyl-4-hydroxy-3 (2H)-furanone



2,3-dihydro-3,5-dihydroxy-6-methyl-4 (H)-pyran-4-one

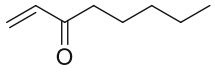


1,3,5-triazine-2,4,6-triamine

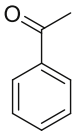


2, 4-dihydroxy-2, 5-dimethyl-3 (2H)-furan-3-one

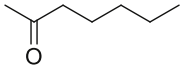
Heterocyclic compounds



1-octen-3-one

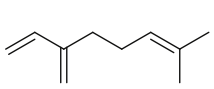


Acetophenone

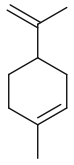


2-Heptanone

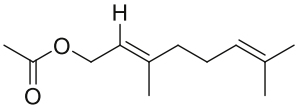
Ketones



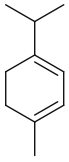
Myrcene



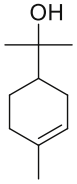
Limonene



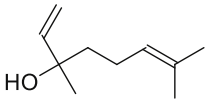
Geranyl acetate



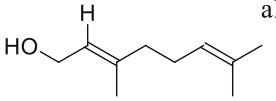
alpha-terpinene



alpha-terpineol

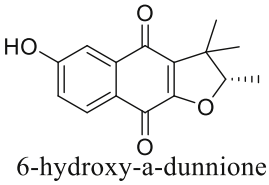


Linalool

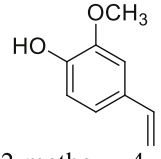


Geraniol

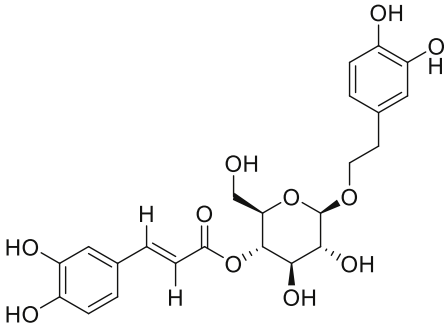
Monoterpenoids



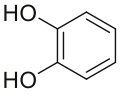
6-hydroxy-a-dunnione



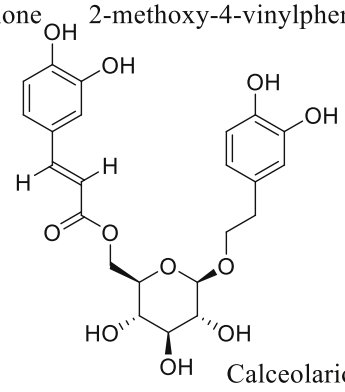
2-methoxy-4-vinylphenol



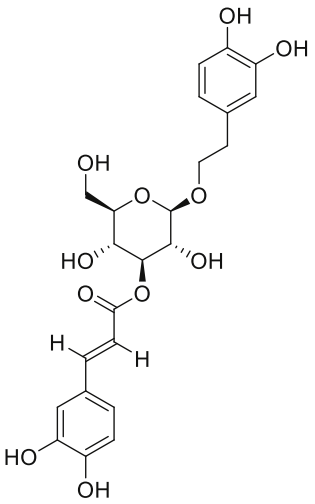
Calceolarioside A



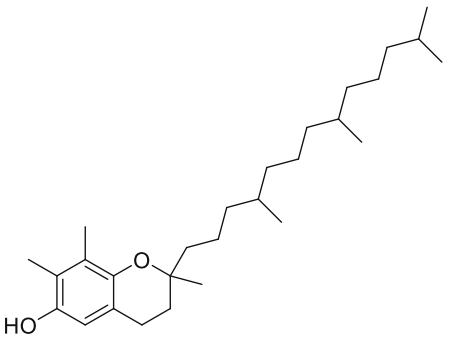
1,2-benzenediol



Calceolarioside B

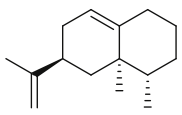


Plantainoside A

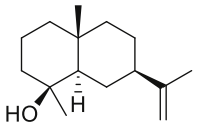


2,7,8-trimethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-6-chromanol

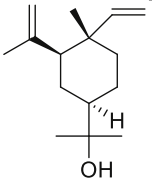
Phenolic compounds



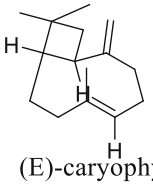
Aristolochene



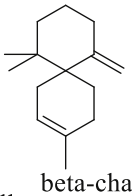
Neointermedeol



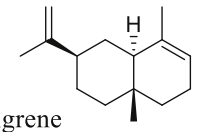
Elemol



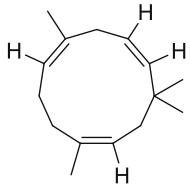
(E)-caryophyllene



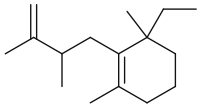
beta-chamigrene



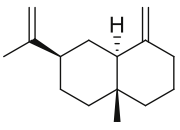
alpha-selinene



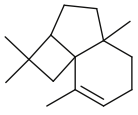
alpha-humulene



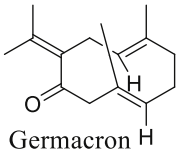
Selina-4,11-diene



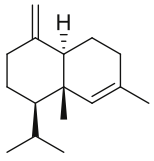
beta-selinene



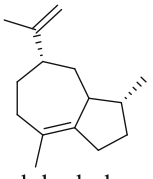
(-)-alpha-panasinsanene



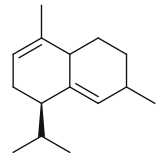
Germacron



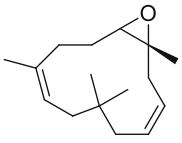
gamma-cadinene



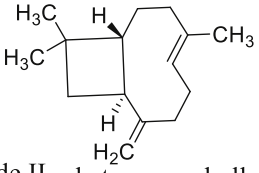
alpha-bulnesene



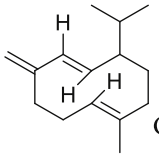
alpha-cadina-4,9-diene



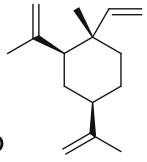
Humulene oxide II



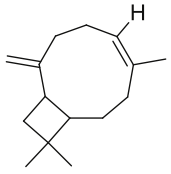
beta-caryophyllene



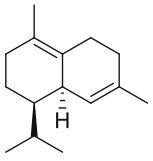
Germacrene D



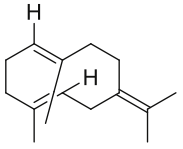
beta-elemene



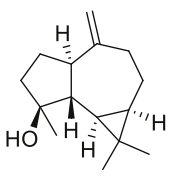
cis-caryophyllene



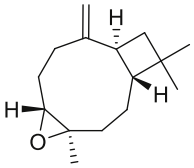
gamma-cadinene



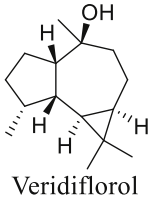
Germacrene



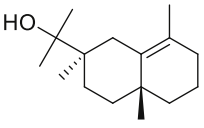
Spathulenol



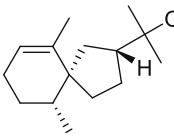
Caryophyllene oxide



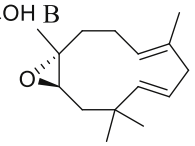
Veridiflorol



gamma-eudesmol

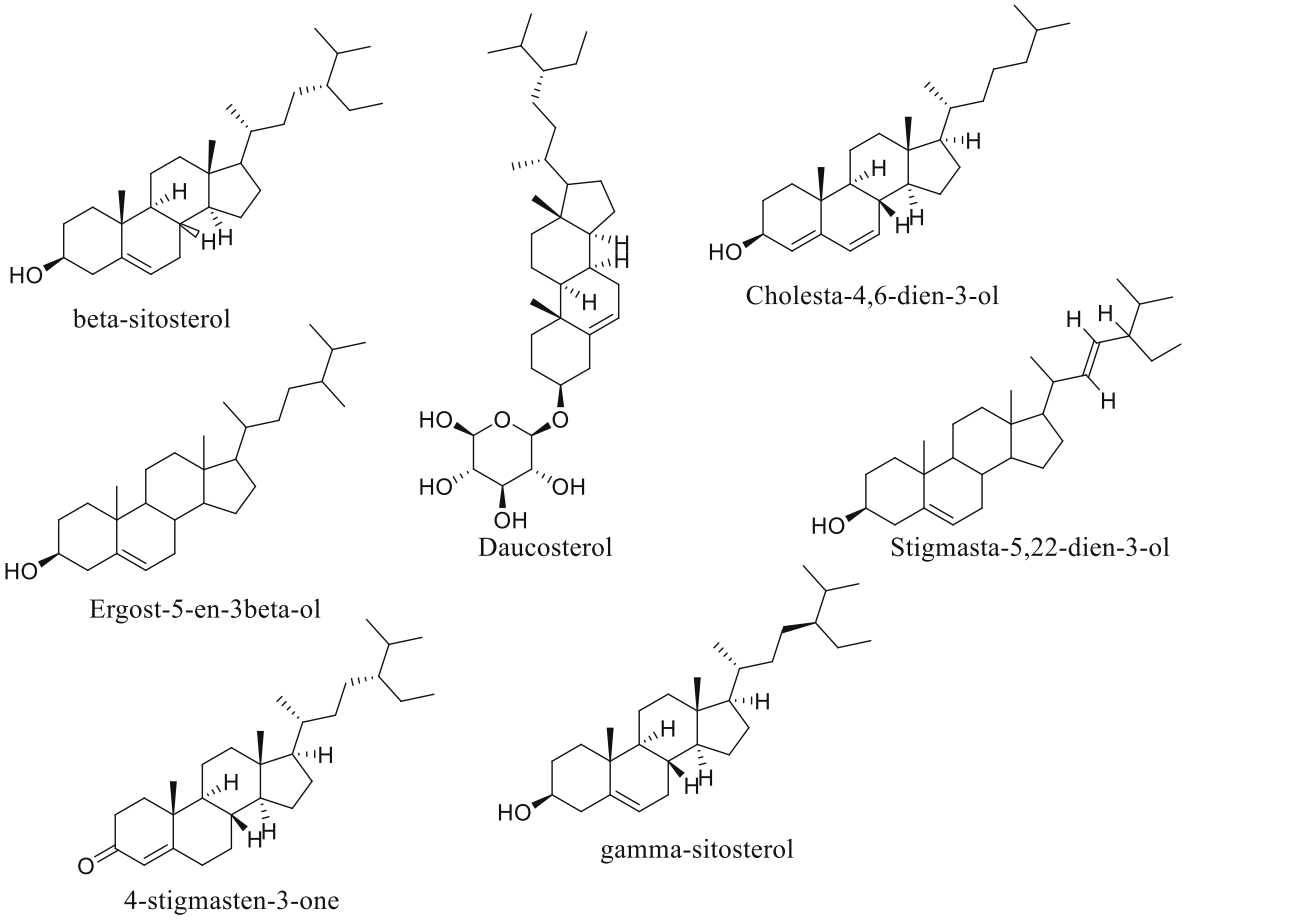


Agaruspirol



Humulene oxide

Sesquiterpenoids



6.2.1. Terpenoids

Terpenoids are among the most abundant and structurally diverse natural products with numerous pharmacological applications (Pichersky and Raguso, 2018). *Didymocarpus* species are rich in terpenoid metabolites. The different classes of terpenoids identified from this genus are discussed below.

6.2.1.1. Monoterpenoids. Monoterpenoids exhibit valuable pharmacological activities, including antioxidant, anti-inflammatory, antitumor, hepatoprotective, cardioprotective, and antidiabetic, as well as neuroprotection (Jakaria et al., 2018). A total of 8 monoterpenoids, **96**–**103**, have been reported from the genus *Didymocarpus*.

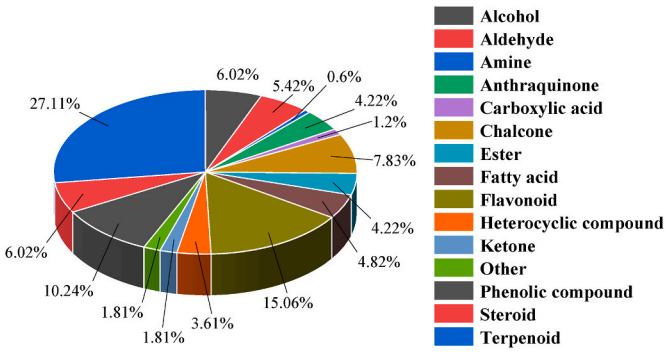


Fig. 2. Chemical classes and proportions of phytochemical compounds isolated and characterized from the genus *Didymocarpus*.

Table 2
Chemical compounds isolated from the genus *Didymocarpus*.

S/No	Chemical Class	Chemical Compounds	Species	Plant part	Reference
1	Alcohol	(E)-3-hexen-1-ol	*D. pedicellata*	Leaves	Prasad and Chandra (2017)
2	Alcohol	(Z)-hex-2-enol	*D. pedicellata*	Leaves	Prasad and Chandra (2017)
3	Alcohol	n-hexanol	*D. pedicellata*	Leaves	Prasad and Chandra (2017)
4	Alcohol	2-ethylhexanol	*D. pedicellata*	Leaves	Prasad and Chandra (2017)
5	Alcohol	Longifolol	*D. pedicellata*	Leaves	Prasad and Chandra (2017)
6	Alcohol	3,7,11,15-tetramethyl-2-hexadecen-1-ol	*D. tomentosa*	Leaves	Prameela et al. (2015)
7	Alcohol	1-methylcyclopentanol	*D. tomentosa*	Essential oil of leaves	Gowda et al. (2012)
8	Alcohol	2-pentanol	*D. tomentosa*	Essential oil of leaves	Gowda et al. (2012)
9	Alcohol	1-octene-3-ol	*D. tomentosa*	Essential oil of leaves	Gowda et al. (2012)
10	Alcohol	2, 5-monomethylene-1-rhamnitol	*D. tomentosa*	Leaves	Prameela et al. (2015)
11	Aldehyde	2-hexenal	*D. pedicellata*	Leaves	Prasad and Chandra (2017)
12	Aldehyde	Benzaldehyde	*D. pedicellata*	Leaves	Prasad and Chandra (2017)
13	Aldehyde	Phenylacetaldehyde	*D. pedicellata*	Leaves	Prasad and Chandra (2017)
14	Aldehyde	Cedroxyde	*D. pedicellata*	Leaves	Prasad and Chandra (2017)
15	Aldehyde	5-methylfuran-2-aldehyde	*D. tomentosa*	Leaves	Prameela et al. (2015)
16	Aldehyde	Hydroxymethylfurfural (syn. 5-hydroxymethylfurfural)	*D. tomentosa*	Leaves, Roots	Prameela et al. (2015)
17	Aldehyde	2-hydroxy-6-methylbenzaldehyde	*D. tomentosa*	Leaves, Roots	Prameela et al. (2015)
18	Aldehyde	Octadecanal	*D. tomentosa*	Leaves	Prameela et al. (2015)
19	Aldehyde	Cis,cis,cis-7,10,13-hexadecatrienal	*D. tomentosa*	Leaves	Prameela et al. (2015)
20	Amine	2-amino-3-(3,4-dihydroxy-phenyl)-propionic acid	*D. tomentosa*	Leaves	Prameela et al. (2015)
21	Anthraquinone	Physcion (syn.1,8-dihydroxy-6-methoxy-3-methylanthraquinone)	*D. leucocalyx*	Leaves	Segawa et al. (1999)
22	Anthraquinone	Catenarin	*D. leucocalyx*	Leaves	Segawa et al. (1999)
23	Anthraquinone	1,6,8-trihydroxy-4-benzoyloxy-3-methylanthraquinone	*D. leucocalyx*	Leaves	Segawa et al. (1999)
24	Anthraquinone	2-(methoxycarbonyl)-9,10-anthraquinone	*D. hedyotideus*	Whole plant	Xiao et al. (2011)
25	Anthraquinone	2-hydroxy-6-methyl-9,10-anthraquinone	*D. hedyotideus*	Whole plant	Xiao et al. (2011)
26	Anthraquinone	2-hydroxy-9,10-anthraquinone	*D. hedyotideus*	Whole plant	Xiao et al. (2011)
27	Anthraquinone	2,6-dihydroxy-9,10-anthraquinone 2-β-D-glucopyranoside	*D. hedyotideus*	Whole plant	Xiao et al. (2011)
28	Carboxylic acid	p-nitrophenylsuccinic acid	*D. tomentosa*	Roots	Prameela et al. (2015)
29	Carboxylic acid	Pedicellic acid	*D. pedicellata*	Leaves	(Bhaskar and Seshadri, 1973; Rao et al., 1966)
30	Chalcone	2′-hydroxy-4′,5′,6′-trimethoxychalcone	*D. pedicellata*	Leaves	Rathore et al. (1981)
31	Chalcone	Pedicin	*D. pedicellata*	Leaves	(Rao and Seshadri, 1948; Radulović et al., 2013, 2015)
32	Chalcone	Pedicellin	*D. pedicellata*	Leaves	(Grippa, 1968; Rathore et al., 1981)
33	Chalcone	2-hydroxy-3,4,6-trimethoxychalchone	*D. pedicellata*	Leaves	Rao and Seshadri (1948)
34	Chalcone	Isodidymocarpin	*D. pedicellata*	Leaves	Bose and Adityachaudhury (1978)
35	Chalcone	Methylpedicin	*D. pedicellata*	Leaves	(Bhaskar and Seshadri, 1973; Rao and Seshadri, 1948; Rathore et al., 1981)
36	Chalcone	Aurentiacin	*D. aurantinca* & *D. podocarpa*	Leaves	(Bose and Adityachaudhury, 1978; Haldar et al., 1989)
37	Chalcone	Flavokawin B	*D. corchorijolia* Wall.	Leaves	Wollenweber et al. (1981)
38	Chalcone	3′,4-dihydroxy-2′,4′,5′,6′-tetramethoxychalcone	*D. leucocalyx*	Leaves	Segawa et al. (1999)
39	Chalcone	Pashanone	*D. leucocalyx* & *D. pedicellata*	Leaves	(Segawa et al., 1999; Agarwal and Rangari, 2003; Bhaskar and Seshadri, 1973)
40	Chalcone	3′-hydroxy-2′,4′,5′,6′-tetramethoxychalcone	*D. leucocalyx*	Leaves	Segawa et al. (1999)
41	Chalcone	Pedicinin	*D. leucocalyx* & *D. pedicellata*	Leaves	(Segawa et al., 1999; Grippa, 1968; Seshadri, 1965)
42	Chalcone	Methylpedicinin	*D. pedicellata*	Leaves	(Goyal and Ikshit Sharma, 2015)
43	Diterpenoid	Phytol	*D. pedicellata*	Leaves	Prasad and Chandra (2017)
44	Diterpenoid	ent-16 a-kauranol	*Didymocarpus oblonga*	Whole plant	Mitra et al. (1987)
45	Diterpenoid	ent-16-kaurene-19-oic acid	*Didymocarpus oblonga*	Whole plant	Mitra et al. (1987)
46	Diterpenoid	Didymooblongin (syn. ent-7β hydroxy-16-kaurene-19-oic acid)	*Didymocarpus oblonga*	Whole plant	Mitra et al. (1987)
47	Ester	Methyl (Z)-5,11,14,17-eicosatetraenoate	*D. tomentosa*	Leaves	Prameela et al. (2015)
48	Ester	1,2,3-propanetriol monoacetate	*D. tomentosa*	Leaves	Prameela et al. (2015)
49	Ester	Methyl 3-hydroxyoctadecanoate	*D. tomentosa*	Leaves	Prameela et al. (2015)
50	Ester	Methyl linoleate	*D. tomentosa*	Roots	Prameela et al. (2015)
51	Ester	Octayl acetate	*D. tomentosa*	Essential oil of leaves	Gowda et al. (2012)
52	Ester	Palmitic acid 2-hydroxy-1-(hydroxymethyl) ethyl ester	*D. tomentosa*	Leaves	Prameela et al. (2015)
53	Ester	Propylene glycol monoleate	*D. tomentosa*	Leaves	Prameela et al. (2015)
54	Fatty acid	Behenic acid	*D. pedicellata*	Leaves	(Goyal and Ikshit Sharma, 2015)
55	Fatty acid	Methyl hexadecanoate	*D. tomentosa*	Roots, Leaves	Prameela et al. (2015)
56	Fatty acid	Lignoceric acid	*D. pedicellata*	Leaves	(Goyal and Ikshit Sharma, 2015)
57	Fatty acid	Palmitic acid	*D. pedicellata & D. tomentosa*	Leaves & roots	(Prasad and Chandra, 2017; Prameela et al., 2015)
58	Fatty acid	Stearic acid	*D. pedicellata*	Leaves	(Goyal and Ikshit Sharma, 2015)
59	Fatty acid	(E)-13-docosenoic acid	*D. tomentosa*	Leaves	Prameela et al. (2015)

(*continued on next page*)

Table 2 (*continued*)

S/No	Chemical Class	Chemical Compounds	Species	Plant part	Reference
60	Fatty acid	9-octadecenoic acid	*D. tomentosa*	Roots	Prameela et al. (2015)
61	Fatty acid	1-benzylidene-2-(diphenylmethylene) hydrazine	*D. tomentosa*	Roots	Prameela et al. (2015)
62	Flavonoid	5,8-dihydroxy-6,7-dimethoxyisoflavone	*D. leucocalyx*	Leaves	Segawa et al. (1999)
63	Flavonoid	Pediflavone	*D. pedicellata*	Leaves	(Goyal and Ikshit Sharma, 2015)
64	Flavonoid	Pseudoisopedicin	*D. pedicellata*	Leaves	(Goyal and Ikshit Sharma, 2015)
65	Flavonoid	Didymocarpin	*D. pedicellata*	Leaves	Bose and Adityachaudhury (1978)
66	Flavonoid	5,8-dihydroxy-7-methoxyflavone	*D. pedicellata*	Leaves	Bose and Adityachaudhury (1978)
67	Flavonoid	5,6,7,8-tetramethoxyflavanone	*D. pedicellata*	Leaves	Rathore et al. (1981)
68	Flavonoid	8-hydroxy-5,6,7-trimethoxyflavanone	*D. pedicellata*	Leaves	Rathore et al. (1981)
69	Flavonoid	7-hydroxy-5,6,8-trimethoxyflavanone	*D. pedicellata*	Leaves	Bhattacharyya (1979)
70	Flavonoid	Isopedicin	*D. pedicellata*	Leaves	(Goyal and Ikshit Sharma, 2015)
71	Flavonoid	5-hydroxy-6,7-dimethoxyflavanone	*D. leucocalyx*	Leaves	Segawa et al. (1999)
72	Flavonoid	2′,6′-dihydroxy-3′,4′-dimethoxychalcone	*D. leucocalyx*	Leaves	Segawa et al. (1999)
73	Flavonoid	3′-hydroxy-2′,4′,5′,6′-tetramethoxychalcone	*D. leucocalyx*	Leaves	Segawa et al. (1999)
74	Flavonoid	2′,5′-dihydroxy-4′-methoxy-3′,6′-dioxochalcone	*D. leucocalyx*	Leaves	Segawa et al. (1999)
75	Flavonoid	Onysilin (syn. 5-hydroxy-6,7-di-methoxyflavanone)	*D. leucocalyx*	Leaves	Segawa et al. (1999)
76	Flavonoid	Didymocarpin A (syn. 5,8-dihydroxy-6,7-di-methoxyflavanone)	*D. leucocalyx* & *D. pedicellata*	Leaves	(Segawa et al., 1999; Bhattacharyya, 1979)
77	Flavonoid	Cy-3-sambubioside	*D. atrosanguineus* Ridl.	Flower	Lowry (1972)
78	Flavonoid	Cy-3-arabinosylglucoside5-glucoside	*Didymocarpus crinitus* Jack	Leaves	Lowry (1972)
79	Flavonoid	Cy-3-glycoside	*D. crinita* & *D. atrosanguineus*	Leaves & flowers	Lowry (1972)
80	Flavonoid	Malvidin3,5-diglucoside	*D. crinita*	Leaves	Lowry (1972)
81	Flavonoid	Malvidin-3-glucoside	*D. crinita*	Leaves	Lowry (1972)
82	Flavonoid	Malvidin-5-glucoside.	*D. crinita*	Leaves	Lowry (1972)
83	Flavonoid	Malvidin-3-arabinosylglucoside-5-glucoside	*D. crinita*	Leaves	Lowry (1972)
84	Flavonoid	Cyanidin-3-arabinosylglucoside-5-glucoside	*D. crinita*	Leaves	Lowry (1972)
85	Flavonoid	Pedicidin	*D. pedicellata*	Leaves	(Goyal and Ikshit Sharma, 2015)
86	Flavonoid	(2S)-5-methoxy-6-methylflavan-7-ol	*D. tomentosa*	Roots	Prameela et al. (2015)
87	Heterocyclic compound	2,4-dihydroxy-2,5-dimethyl-3(2H)-furan-3-one	*D. tomentosa*	Leaves	Prameela et al. (2015)
88	Heterocyclic compound	2,5-dimethyl-4-hydroxy-3(2H)-furanone	*D. tomentosa*	Leaves	Prameela et al. (2015)
89	Heterocyclic compound	2-hydroxy-3-methyl-4-pyrone	*D. tomentosa*	Leaves	Prameela et al. (2015)
90	Heterocyclic compound	2,3-dihydro-3,5-dihydroxy-6-methyl-4(H)-pyran-4-one	*D. tomentosa*	Leaves & roots	Prameela et al. (2015)
91	Heterocyclic Compound	4-methyl-2-prop-1-enyl-1,3-dioxolane	*D. tomentosa*	Leaves	Prameela et al. (2015)
92	Heterocyclic Compound	1,3,5-triazine-2,4,6-triamine	*D. tomentosa*	Roots	Prameela et al. (2015)
93	Ketone	1-octen-3-one	*D. pedicellata*	Leaves	Prasad and Chandra (2017)
94	Ketone	Acetophenone	*D. pedicellata*	Leaves	Prasad and Chandra (2017)
95	Ketone	2-heptanone	*D. tomentosa*	Essential oil of leaves	Gowda et al. (2012)
96	Monoterpenoid	Myrcene	*D. pedicellata*	Leaves	Prasad and Chandra (2017)
97	Monoterpenoid	Limonene	*D. pedicellata*	Leaves	Prasad and Chandra (2017)
98	Monoterpenoid	Linalool	*D. pedicellata*	Leaves	Prasad and Chandra (2017)
99	Monoterpenoid	α-terpineol	*D. pedicellata*	Leaves	Prasad and Chandra (2017)
100	Monoterpenoid	α-cyclogeraniol	*D. pedicellata*	Leaves	Prasad and Chandra (2017)
101	Monoterpenoid	Geraniol	*D. pedicellata*	Leaves	Prasad and Chandra (2017)
102	Monoterpenoid	Geranyl acetate	*D. pedicellata*	Leaves	Prasad and Chandra (2017)
103	Monoterpenoid	α-terpinene	*D. tomentosa*	Essential oil of leaves	Gowda et al. (2012)
104	Other	5,6-dimethyl-2,3-dihydro-1,4-dioxin	*D. tomentosa*	Leaves	Prameela et al. (2015)
105	Other	5-hydroxy-7-methoxy-2-phenyl-4H-1-benzopyran-4-one	*D. tomentosa*	Roots	Prameela et al. (2015)
106	Other	5,9,9-trimethyl-5-phosphatricyclo[6.1.1.02,6]dec-2-ene	*D. tomentosa*	Roots	Prameela et al. (2015)
107	Phenolic compound	6-hydroxy-a-dunnione	*D. hedyotideus*	Whole plant	Xiao et al. (2011)
108	Phenolic compound	Methyl 1,1′,4,4′-tetrahydro-3-hydroxy-1,1′,4,4′-tetraoxo [2,2′-binaphthalene-3′-carboxylate	*D. hedyotideus*	Whole plant	Xiao et al. (2011)
109	Phenolic compound	7-hydroxy-a-dunnione	*D. hedyotideus*	Whole plant	Xiao et al. (2011)
110	Phenolic compound	(2S)-2, 3-dihydroxypropyl 1, 6, 8-trihydroxy-3-methyl-9, 10-dioxoanthracene-2-carboxylate	*D. leucocalyx*	Leaves	Segawa et al. (1999)
111	Phenolic compound	(±)-1,4-dihydroxy-2,3,6,7-tetramethoxy-10-phenyl-9,10-dihydrocyclohepta[2,1-b]4H-chromene-8,11-dione	*D. leucocalyx*	Leaves	Segawa et al. (1999)
112	Phenolic compound	3-((1E, 2E)-1-hydroxy-3-phenylprop-2-enylidene)-7-((2E)-3-phenylprop-2-enoyl)-6-hydroxy-4,5-dimethoxybenzo[b] furan-2-one	*D. leucocalyx*	Leaves	Segawa et al. (1999)
113	Phenolic compound	2((1E)-2-phenylvinyl)-5,6-dihydroxy-7,8-dimethoxy-4H-pyrano [3, 2-d]benzo[b]furan-4-one	*D. leucocalyx*	Leaves	Segawa et al. (1999)
114		1,2-benzenediol	*D. tomentosa*	Leaves	Prameela et al. (2015)

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Table 2 (*continued*)

S/No	Chemical Class	Chemical Compounds	Species	Plant part	Reference
	Phenolic compound				
115	Phenolic compound	2-methoxy-4-vinylphenol	*D. tomentosa*	Leaves, Roots	Prameela et al. (2015)
116	Phenolic compound	Plantainoside A	*D. hedyotideus*	Whole plant	Xiao et al. (2011)
117	Phenolic compound	Calceolarioside A	*D. hedyotideus*	Whole plant	Xiao et al. (2011)
118	Phenolic compound	Calceolarioside B	*D. hedyotideus*	Whole plant	Xiao et al. (2011)
119	Phenolic compound	2,7,8-trimethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-6-chromanol	*D. tomentosa*	Roots	Prameela et al. (2015)
120	Phenolic compound	Didymocarpuslignan A	*D. hedyotideus*	Roots	Tang et al. (2014)
121	Phenolic compound	Didymocarpuslignan B	*D. hedyotideus*	Roots	Tang et al. (2014)
122	Phenolic compound	Didymocarpuslignan C	*D. hedyotideus*	Roots	Tang et al. (2014)
123	Phenolic compound	7R,7′R,8S,8′S-(+) icariol A2	*D. hedyotideus*	Roots	Tang et al. (2014)
124	Polyterpenoid	Didymocarpol	*D. pedicellata*	Leaves	(Goyal and Ikshit Sharma, 2015)
125	Polyterpenoid	Didymocarpenol	*D. pedicellata*	Leaves	(Goyal and Ikshit Sharma, 2015)
126	Sesquiterpenoid	(E)-caryophyllene	*D. pedicellata*	Leaves	Prasad and Chandra (2017)
127	Sesquiterpenoid	α-humulene	*D. pedicellata, D. tomentosa*	Leaves	(Prasad and Chandra, 2017; Gowda et al., 2012)
128	Sesquiterpenoid	Selina-4,11-diene	*D. pedicellata*	Leaves	Prasad and Chandra (2017)
129	Sesquiterpenoid	Aristolochene	*D. pedicellata, D. tomentosa*	Leaves	(Prasad and Chandra, 2017; Gowda et al., 2012)
130	Sesquiterpenoid	β-selinene	*D. pedicellata*	Leaves	Prasad and Chandra (2017)
131	Sesquiterpenoid	α-selinene	*D. pedicellata*	Leaves	Prasad and Chandra (2017)
132	Sesquiterpenoid	γ-cadinene	*D. pedicellata, D. tomentosa*	Leaves	(Prasad and Chandra, 2017; Gowda et al., 2012)
133	Sesquiterpenoid	α-bulnesene	*D. pedicellata*	Leaves	Prasad and Chandra (2017)
134	Sesquiterpenoid	α-cadina-4,9-diene	*D. pedicellata*	Leaves	Prasad and Chandra (2017)
135	Sesquiterpenoid	(−)-α- panasinsanene	*D. pedicellata*	Leaves	Prasad and Chandra (2017)
136	Sesquiterpenoid	Humulene oxide II	*D. pedicellata*	Leaves	Prasad and Chandra (2017)
137	Sesquiterpenoid	Germacron	*D. pedicellata*	Leaves	Prasad and Chandra (2017)
138	Sesquiterpenoid	Neointermedeol	*D. pedicellata*	Leaves	Prasad and Chandra (2017)
139	Sesquiterpenoid	β-elemene	*D. tomentosa*	Essential oil of leaves	Gowda et al. (2012)
140	Sesquiterpenoid	cis-caryophyllene	*D. tomentosa*	Essential oil of leaves	Gowda et al. (2012)
141	Sesquiterpenoid	β-caryophyllene	*D. tomentosa*	Essential oil of leaves	Gowda et al. (2012)
142	Sesquiterpenoid	Germacrene D	*D. tomentosa*	Essential oil of leaves	Gowda et al. (2012)
143	Sesquiterpenoid	β-chamigrene	*D. tomentosa*	Essential oil of leaves	Gowda et al. (2012)
144	Sesquiterpenoid	δ-cadinene	*D. tomentosa*	Essential oil of leaves	Gowda et al. (2012)
145	Sesquiterpenoid	Elemol	*D. tomentosa*	Essential oil of leaves	Gowda et al. (2012)
146	Sesquiterpenoid	Germacrene B	*D. tomentosa*	Essential oil of leaves	Gowda et al. (2012)
147	Sesquiterpenoid	Spathulenol	*D. tomentosa*	Essential oil of leaves	Gowda et al. (2012)
148	Sesquiterpenoid	Caryophyllene oxide	*D. tomentosa*	Essential oil of leaves	Gowda et al. (2012)
149	Sesquiterpenoid	Veridiflorol	*D. tomentosa*	Essential oil of leaves	Gowda et al. (2012)
150	Sesquiterpenoid	γ-eudesmol	*D. tomentosa*	Essential oil of leaves	Gowda et al. (2012)
151	Sesquiterpenoid	Humulene oxide	*D. tomentosa*	Essential oil of leaves	Gowda et al. (2012)
152	Sesquiterpenoid	Agaruspirol	*D. tomentosa*	Essential oil of leaves	Gowda et al. (2012)
153	Sesquiterpenoid	Humulane-1,6-dien-3-ol	*D. pedicellata*	Leaves	Prasad and Chandra (2017)
154	Steroid	β-sitosterol	*D. pedicellata, D. hedyotideus*	Leaves	Xiao et al. (2011)
155	Steroid	Cholesta-4,6-dien-3-ol	*D. tomentosa*	Roots	Prameela et al. (2015)
156	Steroid	Ergost-5-en-3β-ol	*D. tomentosa*	Roots	Prameela et al. (2015)
157	Steroid	Stigmasta-5,22-dien-3-ol	*D. tomentosa*	Roots, Leaves	Prameela et al. (2015)
158	Steroid	4-Stigmasten-3-one	*D. tomentosa*	Roots	Prameela et al. (2015)
159	Steroid	21-hydroxy-β-sitosteryl linolenate	*D. pedicellata*	Aerial part	Lone et al. (2016)
160	Steroid	21-hydroxy-β-stigmasteryl linolenate	*D. pedicellata*	Aerial part	Lone et al. (2016)

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Table 2 (*continued*)

S/No	Chemical Class	Chemical Compounds	Species	Plant part	Reference
161	Steroid	stigmasterol 3-O-β-D-glucopyranoside	*D. pedicellata*	Aerial part	Lone et al. (2016)
162	Steroid	Daucosterol	*D. hedyotideus*	Whole plant	Xiao et al. (2011)
163	Steroid	γ-sitosterol	*D. tomentosa*	Leaves & roots	Prameela et al. (2015)
164	Triterpenoid	Squalene (syn. 2,6,10,15,19,23-hexamethyl-2,6,10,14,18,22-tetracosahexaene)	*D. tomentosa*	Roots	Prameela et al. (2015)
165	Triterpenoid	Lupenone	*D. tomentosa*	Roots	Prameela et al. (2015)
166	Triterpenoid	Lupeol	*D. tomentosa*	Roots	Prameela et al. (2015)

The chemical compound myrcene, isolated from the leaves of *D. pedicellata*, has been reported to facilitate transdermal absorption (Schmitt et al., 2010). Moreover, the mechanism of action of myrcene is linked to the opioid receptor due to its notable analgesic effect, which is blocked by the action of naloxone, an opioid antagonist (Rao et al., 1990). Linalool, a monoterpene alcohol, has also been identified from the leaves of *Didymocarpus pedicellata* (Prasad and Chandra, 2017). This compound possesses several biological activities such as antimicrobial, anti-inflammatory, anticancer, and antioxidant properties (Kamatou and Viljoen, 2008). In addition, linalool exhibited strong antibacterial effects against *Pseudomonas fluorescens* through membrane damage, bacterial metabolic and oxidative respiratory perturbations, interfering in cellular functions and even causing cell death (Guo et al., 2021). The compound α-terpineol has been reported to possess a wide range of biological activities, such as antihypertensive and antiproliferative effects on human erythroleukemic cells (Sabino et al., 2013), and anti-inflammatory action (Held et al., 2007), due to its inhibitory activity of superoxide production (Brand et al., 2001). Various studies have also reported the anticancer activity of α-terpineol (Trinh et al., 2011). Other monoterpenoids isolated from genus *Didymocarpus pedicellata* leaves include α-cyclogeraniol, geraniol, geranyl acetate, and α-terpinen.

6.2.1.2. Diterpenoids. Four diterpenoids **43**–**46**, including phytol and three kaurenoid diterpenes, have been identified from the leaves of *D. pedicellata* and the whole plant of *D. oblonga*. Phytol **43** has been shown to exhibit anti-inflammatory activity in acute inflammation models by inhibiting neutrophil migration partly by reducing IL-1β and TNF-α levels and oxidative stress (Silva et al., 2014). The compounds **44**–**46** have been reported to exhibit significant antifungal action against *Aspergillus niger* (Mitra et al., 1987).

6.2.1.3. Sesquiterpenoids. Some pharmacologically active sesquiterpenoids have been isolated from *Didymocapus* taxa. The compounds α-humulene, β-caryophyllene, and elemol are among the 28 sesquiterpenoids **126**–**153** identified from the genus *Didymocarpus*. A previous study reported the anti-inflammatory activity exhibited by α-humulene, given either orally or by aerosol (Rogerio et al., 2009). This study showed that α-humulene exhibited significant properties in a murine model of airway allergic inflammation, an effect presumed to be mediated by reducing inflammatory mediators, adhesion molecule expression and transcription factors activation. β-caryophyllene is an organic bicyclic sesquiterpene widely known for its numerous pharmacological activities (Francomano et al., 2019). This compound has exhibited a potent agonist activity on cannabinoid type 2 (CB2) receptors, a G-protein coupled receptor illustrating a crucial therapeutic target in various diseases (Sharma et al., 2016). In addition, this compound has been reported to be a promising lead agent in neuropathic pain neurodegenerative and metabolic diseases (Tchekalarova et al., 2018). Elemol, an active compound isolated from the leaves of *D. tomentosa*, has been reported to possess therapeutic potential in treating atopic dermatitis due to its immunosuppressive properties (Gowda et al., 2012).

6.2.1.4. Triterpenoids. Three triterpenoids (squalene 164, lupenone 165, and lupeol 166) have been isolated from the roots of *D. tomentosa*. Numerous applications of squalene have been reported, including applications as an antioxidant, moisturizer, and in treating skin disorders such as seborrheic dermatitis, acne, psoriasis, and atopic dermatitis (Huang et al., 2009). However, further studies on the mode of action of this compound are needed to explore the utilization of squalene for treating skin conditions. Lupenone has been reported to possess anti-inflammatory properties via its regulatory action on transcription factor p65, NF-kappa-B inhibitor alpha, transcription factor AP-1, NF-kappa-B essential modulator, nuclear factor NF-kappa-B p105 subunit, epidermal growth factor receptor, hypoxia-inducible factor 1-alpha, and other proteins related to the PI3K-Akt, Toll-like receptor and NF-kappa B signaling pathways (Xu et al., 2020). Xu et al. (2020) also reported that this compound reduced acute and subacute inflammation in mice and the IL-1β and IFN-γ levels in the pancreas of diabetic rats. Additionally, lupenone has been shown to inhibit protein tyrosine phosphatase 1B (PTP 1B), thus a potent alternative to type2 diabetes and obesity drug development (Na et al., 2009). A recent study also reported that lupenone could be used to treat hyperpigmentation illnesses (Villareal et al., 2013).

Over the years, extensive research has revealed lupeol possesses antimicrobial, anti-protozoal, antiproliferative, anti-invasive, and anti-angiogenic activities (Siddique and Saleem, 2011). It has also been reported to possess anticancer activity (Cmoch et al., 2008; Mallavadhani et al., 1998), anti-inflammatory activity (Huguet et al., 2000), antiarthritic potency (Agarwal and Rangari, 2003; Argay et al., 1997), and antifungal properties (Shai et al., 2008).

6.2.1.5. Polyterpenoids. Only two polyterpenoid compounds, **124**–**125**, isolated from the leaves of *Didymocarpus pedicellata* have been reported from the genus *Didymocarpus*. A previous study on the wound healing properties of *D. pedicellata* identified didymocarpol **124** and didymocarpenol **125** among the pharmacologically active compounds from this species (Mittal et al., 2020).

6.2.2. Flavonoids

Flavonoids have been reported to exhibit several biological activities, including anti-inflammatory, antihepatotoxic, antitumor, antimicrobial, antiviral, enzyme inhibition, and antioxidant activities (Iwu and Wootton, 2002). A total of 25 flavonoid compounds, **62**–**86**, have been reported from the genus *Didymocarpus*. Isopedicin has been shown to inhibit O(2)(*)(−) production in human neutrophils by elevating cellular cyclic adenosine monophosphate (cAMP) and activation of protein kinase A (PKA), resulting in inhibition of cAMP-specific PDE (phosphodiesterases), illustrating its inflammatory potential (Hwang et al., 2009). Also, malvidin-3-glucoside, isolated from the leaves of *Didymocarpus crinita*, has been shown to exhibit anti-inflammatory properties. This compound has been shown to inhibit tumor necrosis factor-alpha (TNF-α), activating the increase of monocyte chemotactic protein-1 (MCP-1), intercellular adhesion molecule-1 (ICAM-1), and the vascular cell adhesion molecule-1 (VCAM-1) production both in the protein and mRNA levels in a concentration-dependent fashion (Huang et al., 2014). Flavonoids have been shown to have a wide range of

Table 3
Summary of pharmacological activities reported from the genus *Didymocarpus*.

Pharmacological activity	Species/part	Study design/Model	Dosage	Extract/Isolated compounds	Results/outcomes	References
Antiurolithiatic	*D. pedicellata*/whole plant	*In vitro* assay: a polyherbal formulation made of plant extracts from *D. pedicellata*, *Plectranthus mollis* Spreng, *Taraxacum officinale* (L.) Weber ex F.H. Wigg, *Dendrophthoe elastic* desr and *Citrus medica* Linn was evaluated for antiurolithiatic activity against calcium oxalate urolithiasis.	200, 300, and 400 mg/kg respectively for 28 days	Triterpenoids, flavonoids, and glycosides.	Significant decrease in the quantity of calcium oxalate deposited in the kidneys, reversion of biochemical changes induced by calcium oxalate urolithiasis	Baheti and Kadam (2013)
Nephro-protective activity	Ethanolic extract of *D. pedicellata*/Aerial parts	*In vivo* assay: pretreatment of mice with D. *pedicellate* extract for one week and later injection with Ferric nitrilotriacetate (Fe-NTA) (9.0 mg Fe/kg body weight). The kidneys were then processed for post mitochondrial supernatant (PMS), cytosol, and histopathological studies. Their blood was collected for Blood Urea Nitrogen (BUN) and serum creatinine (SCr) estimation.	100 and 200 mg/kg daily for 1 week	Polyphenolics	Depletion of renal glutathione content and activities of antioxidant and phase II metabolizing enzymes, induction of oxidative damage, initiation of hyperproliferation response elevating ornithine decarboxylase activity and [^{3}H]-thymidine incorporation into DNA, elevation in serum creatinine (SCr), blood urea nitrogen (BUN)	Kaur et al. (2007)
Antioxidant activity	Ethanolic extracts of the aerial parts of *D. pedicellata*	*In vitro* assay: isolation and identification of active compounds followed by scavenging of DPPH radicals, reactive oxygen species (ROS) and NO scavenging according to established protocols	Several concentrations of 5, 10, 50, 100, 200, and 300 μg/ml	21-hydroxy- βsitosteryl n-octadec-9',12',15′-trienoate, 21-hydroxy-β-stigmasteryl n-octadec-9',12',15′-trienoate, and stigmasterol 3-O-β-D-glucopyranoside	Isolated steroidal compounds showed significant antioxidant effects by quenching 2,2-diphenyl-1-picrylhydrazy (DPPH) radicals, scavenging Reactive Oxygen Species (ROS) such as Hydrogen peroxide (H_2O_2), hydroxyl radical (• OH), and nitrogen oxide sodium nitroprusside (SNP) solution where nitric oxide (NO) donor liberated NO	Lone et al. (2016)
Antimicrobial activity	Leaves of *D. pedicellata* The powdered whole plant of *D. oblonga*	*In vitro* assay: various plant pathogenic spore-forming fungi (*Helminthosporium oryzae*, *Fusarium oxysporum*, *Rhizopus artocarpii*), 3 sclerotial pathogens (*Sclerotium rolfsii*, *Thanatephorus cucumeris*, and *Rhizoctonia oryzae*), and one plant pathogenic bacterium, *Xanthomonas campestris*, were tested for antimicrobial activity based on the agar diffusion principle Sensitivity of fungi (*Helminthosporium oryzae*, *Aspergillus niger*, *Scleroyium rolfsii*, *Rhizoctonia bataticola*), and bacteria (*Xanthomonas campestris*, *Erwinia carotovora*) to isolated compounds was assayed following the standard methods of spore germination inhibition, sclerotial germination inhibition, and agar diffusion principle	Several concentrations of 500, 250, 100 and 50 ppm Several concentrations of 500, 250, 100, 50 mg/L	Quinochalcones, chalcones and flavanones Kaurenoid diterpenes	The compounds showed significant inhibition against different types of plant pathogens even at dosages as low as 50 ppm in bacteria and in fungi Kaurenoid diterpenes showed significant inhibition to the conidia germination of *A. niger*	Biswas et al. (1981) (Mitra et al., 1987)
Cytotoxic Activity	Essential oils obtained via hydrodistillation of powdered *D. tomentosa* leaves	*In vitro* assay whereby the Brine Shrimp Lethality Test (BSLT) was done according to the standard procedure to assess the cytotoxicity of the essential oil followed by MTT	Several concentrations of 4, 8, 12, 16, 24 μg/mL	Sesquiterpenes (β-caryophyllene, α-humulene, and caryophyllene oxide)	The degree of lethality was directly proportional to the concentration of the essential oil used	Gowda et al. (2012)

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Table 3 (*continued*)

Pharmacological activity	Species/part	Study design/Model	Dosage	Extract/Isolated compounds	Results/outcomes	References
		assay on Human cervical carcinoma cells (HeLa)				
Wound healing	*D. pedicellata* stem parts were crushed into powder	*In vivo* assay where the winstar rats full-thickness excision wound models were treated with a polymeric hybrid hydrogel of dimethylaminoethyl acrylate and hyaluronic acid (pDMAEMA–HA), which was impregnated with the herbal extract of *D. pedicellata*.	The swollen hydrogel of pDMAEMA-HA hydrogel (1 g each) was applied topically on the wounds on alternate days: 1, 3, and 5 days	Phenolics and flavonoids	Animals treated with the pDPi-DMAEMA-HA hybrid hydrogel group exhibited a higher level of wound closure as compared to the control and the polymeric hybrid hydrogel	Mittal et al. (2020)

anticancer properties, including the ability to modulate reactive oxygen species (ROS)-scavenging enzyme activities, participate in cell cycle arrest, induce apoptosis and autophagy, and suppress cancer cell proliferation and invasiveness (Kopustinskiene et al., 2020). Flavonoids have a dual action in terms of ROS homeostasis: they act as antioxidants under normal conditions while also being potent pro-oxidants in cancer cells, activating apoptotic pathways, and downregulating pro-inflammatory signaling pathways (Tavsan and Kayali, 2019). *Didymocarpus* species contain a variety of flavonoid compounds and may be valued for anticancer activity (Ahmad et al., 2014).

6.2.3. Chalcones

Chalcone-rich plants have a long history of application in herbal medicine, particularly in treating gastric and duodenal ulcers, bronchial asthma, food and drug poisoning, and skin diseases, including eczema and urticaria (Fenwick et al., 1990). In this regard, various pure chalcones isolated from several plants have received approval for clinical trials to treat cancer, viral, and cardiovascular disorders, while some have been included as active components in the manufacture of cosmetic products (Ni et al., 2005). Thirteen chalcones, **30**–**42**, have been identified from the genus *Didymocarpus*. A previous study reported the antifungal potential of the chalcone pashanone due to its inhibitory action against several human pathogenic fungi with minimum inhibitory concentration values as low as 4.0 μg/mL (Lee et al., 2016). Flavokawin B has also been reported to possess a significant antinociception effect against both chemical and thermal models of pain in mice, thus exhibiting peripheral and central analgesic activity (Mohamad et al., 2010). Chalcone compounds isolated from *D. pedicellata* have been shown to inhibit a-glucosidase, PTP 1B, and aldose reductase (ALR), as well as act as peroxisome proliferator-activated receptor- ∨ (PPAR- ∨) activators, illustrating their antidiabetic potency (Bhongade et al., 2021).

6.2.4. Aldehydes and ketones

A total of 9 aldehyde compounds **11**–**19** and 3 ketones **93**–**95** have been reported from the genus *Didymocarpus*. The biologically active aldehydes isolated from the genus *Didymocarpus* are hydroxymethylfurfural and benzaldehyde. Hydroxymethylfurfural, a known cytotoxic phytochemical isolated from *D. tomentosa*, has been reported to prevent cancer-related processes in breast, prostate, and endometrial cancer cells (Tsiapara et al., 2009). Previous studies on hydroxymethylfurfural revealed that this compound possesses potent nematicidal (Ntalli et al., 2010), antioxidant and anti-inflammatory (Kitts et al., 2012), and antiproliferative activities (Zhao et al., 2013). Benzaldehyde has been reported to enhance the absorption of drugs with a reduced oral bioavailability both *in vitro* and *in vivo* via the disruption of lipid bilayer integrity and enhancing membrane permeability (Wen et al., 2021). Additionally, simple alpha, beta-unsaturated ketones have been shown to inhibit the urease activity, presumably via Michael-like incorporation of a protein SH group to the double bond of the alpha, beta-unsaturated carbonyl class (Tanaka et al., 2003).

6.2.5. Anthraquinones

Seven anthraquinone compounds **21**–**27** have been isolated and characterized from the genus *Didymocarpus*. These compounds occur in their glycosidic nature, have broad applications as laxatives, and possess antifungal and antiviral properties (Yadav et al., 2019).

6.2.6. Steroids

Steroids are widely known for their potent anti-inflammatory and immune-modulating activities (Ericson-Neilsen and Kaye, 2014). A total of 10 steroids, **154**–**163**, have been isolated from the genus *Didymocarpus*. The compound γ-sitosterol is commonly known for lowering human-health-related cholesterol levels (Pollak, 1953), and has also been reported to exhibit antidiabetic activities (Balamurugan et al., 2011). A previous study on daucosterol reported that this compound showed significant immunoregulatory activity by protecting mice against disseminated candidiasis via the $CD4^+$ Th1 immune response (Lee et al., 2007).

6.2.7. Fatty acids

Eight fatty acids **54**–**61** have been reported from *Didymocarpus* species. Pharmacological studies of fatty acids have shown they exhibit significant biological activities; for instance, hexadecanoic acid, isolated from the leaves and roots of *D. tomentosa*, is known for its antibacterial activity (Manilal et al., 2009) and has also been reported to exhibit anti-inflammatory activities by inhibiting phospholipase (Aparna et al., 2012). The neuroprotective action of stearic acid has been reported whereby this compound was shown to offer protection to cortical or hippocampal slices against oxygen-glucose deprivation and N-methyl D-aspartate (NMDA) or hydrogen peroxide-induced injuries, via the phosphatidylinositol 3-kinase dependent mechanism (Wang et al., 2006).

6.2.8. Phenolic compounds

Phenolic compounds are widely known for their antioxidant properties associated with their structure-activity relationship (SAR) (Minatel et al., 2017). Seventeen phenolic compounds **107**–**123** have been identified from the genus *Didymocarpus*. Phenolic compounds isolated and characterized from *Didymocarpus* species have been shown to possess nephroprotective potency (Kaur et al., 2007).

6.2.9. Alcohols

Plant-derived alcohols are a promising source of reagents for synthetic reactions and have been shown to exhibit several biological properties (Patocka and Kuca, 2013). Alcohols display bactericidal and fungicidal activities via protein denaturation, disruption of tissue membranes, and dissolution of several lipids of the microbial agent (Ogodo et al., 2021). Ten alcohols **1**–**10** have been reported from the leaves of *D. pedicellata* and the essential oil of leaves of *D. tomentosa*.

6.2.10. Carboxylic acids

Carboxylic acids have extensive applications in pharmaceuticals

worldwide in nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, anticoagulants, and cholesterol-lowering statins (Badea and Radu, 2018; Ballatore et al., 2013). The acidity of carboxylic acids and the ability to form relatively strong electrostatic interactions and hydrogen bonds are key reasons this class of compounds is a crucial indicator in drug-target interactions (Ballatore et al., 2013). Only two carboxylic acids, p-nitrophenylsuccinic acid **28** and pedicellic acid **29**, have been isolated from the genus *Didymocarpus*.

6.2.11. Esters

Seven esters, **47**–**53**, have been identified from the genus *Didymocarpus*. A previous study reported the antispasmodic activity of ester compounds (Buckle, 2015). The spasmolytic and local anesthetic properties and the toxicity of several ester compounds have been reported (McKenzie et al., 1997). Additionally, various ester compounds have been shown to exhibit significant acetylcholinesterase inhibitory, antibacterial, and antinociceptive properties (Radulović et al., 2013, 2015).

6.2.12. Heterocyclic compounds

Although heterocyclic groups are usually incorporated in veterinary drugs, they do not exert any biological activity but rather modify the action of the target molecule (Katritzky and Rees, 2009). Six heterocyclic compounds **87**–**92** have been reported from the genus *Didymocarpus*. The bioefficacies of these compounds have not yet been reported.

6.2.13. Others

The remaining six compounds are grouped under miscellaneous because of their less popularity in the genus *Didymocarpus*. However, the pharmacological potency of these compounds is yet to be reported. These compounds include the amine 2-amino-3-(3,4-dihydroxy-phenyl)-propionic acid **20** and 3 compounds **104**–**106** isolated from this genus for the first time: 5,6-dimethyl-2,3-dihydro-1,4-dioxin, 5-hydroxy-7-methoxy-2-phenyl-4H-1-benzopyran-4-one, and 5,9,9-trimethyl-5-phosphatricyclo[6.1.1.02,6]dec-2-ene (Prameela et al., 2015; Prasad and Chandra, 2017: Segawa et al., 1999).

7. Pharmacology

Through present-day research and study of historical texts, it is evident that whole plants or their respective plant parts have been used to treat or alleviate different illnesses (Matthews et al., 1999). Currently, the use of herbal medicines is also applied in the conventional system of medicine, where plants and associated phytochemicals are being actively explored for their direct use as pharmaceutical agents (Shankar et al., 2012).

The genus *Didymocapus* has long been used therapeutically in different countries in Asia due to its wide range of biological and pharmacological activities. The broad spectrum ethnomedicinal uses of the different species of *Didymocapus* have led to the initiation of several pharmacological investigations among them antiurolithiatic, nephroprotective, antioxidant activity, antimicrobial, cytotoxic, and wound healing activities (Baheti and Kadam, 2013; Gowda et al., 2012; Kaur et al., 2007; Lone et al., 2016; Mittal et al., 2020). These biological tests were performed on extracts and constituents of *Didymocarpus* species to support the acclaimed applications of these plants in the traditional treatment of a wide range of ailments. Most of the bioassays performed for these species are *in vitro* assays, with three being *in vivo* studies. *Didymocarpus pedicellata* is the most studied pharmacologically among the *Didymocarpus* species studied for bioactivity, and the aerial parts and leaves are the most studied plant parts. Some bioactive phytocompounds have also been isolated and are associated with the biological properties reported in *Didymocarpus* species. An overview of the modern pharmacological studies on these species is detailed in Table 3 and the following sections.

7.1. Antiurolithiatic activity

Urolithiasis is a common urinary tract disorder condition that occurs due to the exit of stones from the renal pelvis to the other sections of the urinary collecting system, including the ureters, bladder, and urethra (Thakore and Liang, 2020). There is a need for effective medical care for urolithiasis because it is the 3rd most prevalent urinary system disorder (Prasad et al., 2007). Lack of treatment may lead to severe complications such as multiple infections and hemorrhage (Hajzadeh et al., 2007). Presently, known herbal drugs exert their antiurolithiatic effect via various multidisciplinary pharmacological activities, including angiotensin-converting enzyme inhibition, analgesic, diuretic, demulcent; litholytic, lithotriptic, Phospholipase A2 inhibition and by changing the concentrations of the ions in urine, for instance, increasing magnesium and citrate excretion and decreasing the calcium and oxalates (Holmes et al., 2016).

The hydro-alcoholic extract of the whole plant of *D. pedicellata* has been reported to exhibit antiurolithiatic activity against calcium oxalate stones when tested against ethylene glycol induced urolithiasis in rats (Baheti and Kadam, 2013). This study showed daily oral treatment of the test organisms with a polyherbal formulation (PHF) made of *P. mollis*, *D. pedicellata*, *T. officinale*, *D. elastic*, and *C. medica*, at 300 mg/kg significantly decreased the quantity of calcium oxalate deposited in the kidneys. The findings also revealed that treatment of the rats with these doses reverted all the biochemical changes induced by calcium oxalate urolithiasis. These findings thus support the traditional herbal usage of *D. pedicellata* in treating kidney stones (Hinsley et al., 2018; Kapoor and Kapoor, 1976).

The phytochemical analysis of the PHF identified the presence of triterpenoids, flavonoids, and glycoside compounds that may be associated with the therapeutic properties of the formulation (Baheti and Kadam, 2013). However, the specific chemical compounds in the polyherbal decoctions are still unknown and clinical trials demonstrating their efficacy for treatment of urolithiasis are limited. Understanding the pathophysiology of stone formation, the specific phytochemicals responsible for antiurolithiatic activity, and the mode of action of these plant-based medicines are of great importance for developing safe and effective antiurolithiatic drugs. Also, multiple herbal medications are generally thought to be more effective than a single herbal agent in traditional medicine practice (Zhong et al., 2013). As a result, traditional medicine prescriptions typically combine several herbs, with only a few components contributing to the main effect of the prescription. Baheti and Kadam (2013) is the only study on the genus *Didymocarpus* which demonstrates that combining several types of herbs can enhance the biological effects or facilitate the delivery of the primary component in the treatment of urolithiasis. Moreover, this study justifies the traditional application of *D. pedicellata* in treating renal diseases such as urolithiasis, neuro-ureterolithiasis, and burning micturition.

7.2. Antioxidant activity

Reactive Oxygen Species (ROS) are associated with the occurrence of several chronic illnesses including, atherosclerosis, diabetes mellitus, parkinson' disease and arthritis in human beings (Hogg, 1998). Researchers currently focus on probing for safe and effective plant-based isolated compounds and extracts with antioxidant potency to combat these diseases by neutralizing the free radicals (Benzie, 2003).

Kaur et al. (2007) investigated the pretreatment of mice with ethanolic extracts of aerial parts of *D. pedicellata*. They revealed that this extract offers protection against Fe-NTA mediated decline in the activities of renal antioxidant enzymes in mice. This extract also significantly scavenged DPPH, O_2, and H_2O_2 free radicals at IC_{50} values of 16–17, 110, and 165 μg/mL, respectively. Additionally, due to their reducing power, these extracts quenched the nitric oxide sodium nitroprusside solution by releasing a significant amount of nitric oxide. The aforementioned activities have been attributed to the *D. pedicellata* action of

inhibiting Fe-NTA + H_2O_2 induced DNA sugar damage and peroxidation of renal microsomal lipids due to the presence of polyphenolic compounds (Pacifici and Davies, 1991).

In a similar study, the bioactive phytosterols namely, 21-hydroxy-βsitosteryl n-octadec-9',12',15′-trienoate, 21-hydroxy- β-stigmasteryl n-octadec-9',12',15′-trienoate, and stigmasterol 3-O-β-D-glucopyranoside, isolated from the aerial parts of *D. pedicellata* have been shown to effectively and dose-dependently scavenge Reactive Oxygen Species (ROS) such as hydrogen peroxide and • OH and NO (Lone et al., 2016). The compounds 21-hydroxy- βsitosteryl n-octadec-9',12',15′-trienoate and 21-hydroxy- β-stigmasteryl n-octadec-9',12',15′-trienoate were particularly shown to effectively and dose-dependently quench DPPH radicals with the highest DPPH radical scavenging activity reported at concentrations of IC_{50} of 44.1 and 38.5 μg/mL, respectively.

These phytosterols have previously been reported to possess reducing power and free radical scavenging activities, thus contributing to the plant's potent antioxidant activity, possibly due to their synergistic effects (Ruch et al., 1989). They can be regarded as significant contributors to the antioxidant activity of *D. pedicellata*. The intake of these phytosterols may also have a potential function in reducing diseases such as cancer (Lone et al., 2016), thus serving as important leads for novel drug discovery. Other reported action mechanisms of phytosterols include suppressing the oxidation and consumption of alpha-tocopherol in beta-linoleoyl-gamma-palmitoyl phosphatidylcholine (PLPC) liposomal membranes, illustrating their activity as antioxidants, modest radical scavengers, and stabilizers in the lipid membranes (Yoshida and Niki, 2003).

7.3. Nephro-protective activity

In order to support or refute the ethnomedicinal use of *D. pedicellata* in the treatment of renal diseases, researchers conducted a study on the ethanolic extracts of the aerial parts of *D. pedicellata* (Kaur et al., 2007). Kaur et al. (2007) showed that these extracts exhibited significant renal toxicity activity against ferric nitrilotriacetate (Fe-NTA) mediated renal oxidative stress and nephrotoxicity in mice. This study also revealed that pretreatment of mice with *D. pedicellata* extract led to a significant and dose-dependent recovery in activities of renal antioxidant enzymes, including catalase (CAT), glucose-6-phosphate dehydrogenase (G-6-PD), and glutathione peroxidase (GPX) in mice from 9.84 to 26.65% (for GPX and CAT, respectively) with a lower dose of extract and from 32.81 to 55.58% (for G-6-PD and CAT) respectively. *Didymocarpus pedicellata* extract was also shown to confer protection against Fe-NTA induced lipid peroxidation and modulation in activities of quinone reductase and xanthine oxidase by restoring their activities close to their respective saline-treated controls, as well as significantly protecting against Fe-NTA associated elevation in BUN (up to $p < 0.001$) and SCr (up to $p < 0.001$). A previous study on the nephroprotective effect *Eurycoma longifolia* herbal extracts on paracetamol-induced nephrotoxicity in rats also reported similar results (Chinnappan et al., 2019).

The pretreatment with the extract also dose-dependently prevented Fe-NTA induced elevation in renal ornithine decarboxylase (ODC) activity by significantly reducing elevated DNA synthesis (Kaur et al., 2007). Histopathological observations showed that pretreatment with *D. pedicellata* preserved renal architecture close to normal; superior protection was reported against necrotic changes, cast formation, and tubular modulation. Similar histopathological findings were reported in winstar albino rats when treated with the ethanolic extracts of *Azima tetracantha* roots (Konda et al., 2015).

The *Didymocarpus pedicellata* extracts have been shown to contain a high concentration of total polyphenolics, which may be linked to the potent biological activities reported (Kaur et al., 2007), possibly due to the action of polyphenolics to reduce the incidence of glomerular and renal tubular lesions (Cardoso et al., 2020). Understanding how phenolic compounds interact with cellular signaling pathways and how they affect gene expression will provide a better understanding of the treatment and potential prevention of renal toxicity.

7.4. Antimicrobial activity

Different flavonoid compounds isolated from *D. pedicellata* have been reviewed against various microorganisms affecting both humans and animals in this study. Didymocarpin, didymocarpin-A, isodidymocarpin, pedicellin, pedicinin, methylpedicinin, and their derivatives have been reported to exhibit various deleterious effects against plant pathogenic fungi and bacteria (Biswas et al., 1981). This study showed that the compounds 2′,5′-Dimethoxy-4′-hydroxy-3′,6′-quinochalcone, isodidymocarpin, didymocarpin-A, and didymocarpin inhibited spore germination of microorganisms including *R. artocarpii, H. oryzae*, *F. oxysporum*, and *R. oryzae* at concentrations of 50 ppm. Pedicellin, didymocarpin, and pedicinin exhibited significant antibacterial action against *X. campestris* plant pathogen at concentrations of 100 ppm.

Mitra et al. (1987) evaluated the antimicrobial activity of kaurenoid diterpenes isolated from the whole plant of *D. oblonga*. Findings from this study showed that didymooblongin diterpene and its derivatives showed significant inhibitory activity to the germination of conidia of *A. niger* up to 50 mg/L concentration. In a similar study, the leaf extracts of *Didymocarpus humboldtiana* have also been reported to inhibit the growth of both gram-positive and gram-negative bacteria (Kindo et al., 2007). These results illustrate that flavonoid and kaurenoid diterpenes isolated from *Didymocarpus* species appear to offer possibilities against fungal pathogens.

The presumed antimicrobial mechanisms of flavonoids, particularly quinochalcones, include the inhibition of nucleic acid formation, inhibition of the plasma membrane functions, energy metabolism inhibition, obstruction of the attachment and biofilm synthesis, inhibition of the porins located on the cell membrane, disruption of the membrane permeability, and attenuation of the pathogenicity (Xie et al., 2015). Additionally, the presence of α, β unsaturated carbonyl bridge linking ring A to ring B in these compounds has also been associated with their antimicrobial activity (Rosa et al., 2019). Although antibacterial compounds are widely distributed in the plant kingdom, these metabolites are rarely evaluated *in vivo*. Also, the action mechanisms of kaurenoid diterpenes are limited, and further studies in this area are being carried out (Ambrosio et al., 2008). *Didymocarpus* species may hold promise in discovering antibacterial and antifungal agents with a broad spectrum of activity based on the enumerated antimicrobial properties. More research, particularly *in vivo* studies of active samples and cytotoxic assays is required to substantiate this knowledge-informed hypothesis. The genus' extracts and constituents have a few promising antimicrobial properties, which support some of its traditional applications in treating diarrhea and wounds.

7.5. Cytotoxic activity

The cytotoxicity action of the essential oil extracted from *D. tomentosa* leaves has been reported, whereby the degree of lethality was directly proportional to the concentration of the essential oil used (Gowda et al., 2012). This study revealed a reduction in HeLa cells viability in a dose-dependent manner with increasing oil concentrations from 0 to 16 μg/mL, where most cells remained viable at lower doses, and the cell viability reached 50% at a concentration of 11.4 μg/mL. Various studies have reported similar findings in plant species from other families, such as *Consolida orientalis* L., *Ferula assa-foetida* L., *Coronilla varia* L. (Nemati et al., 2013). According to the National Cancer Institute Plant Screening Program, a crude extract is regarded as having significant cytotoxicity when the IC_{50} value in carcinoma cells is lower than 20 μg/mL (Mahavorasirikul et al., 2010), illustrating the potent cytotoxic activity of *D. tomentosa* leaf oil.

Sesquiterpenoid compounds, including β-caryophyllene, α-humulene, and caryophyllene oxide, previously reported to possess cytotoxic activities (Kubo and Morimitsu, 1995; Silva et al., 2008), have been

isolated in the essential oil of *D. tomentosa* leaves with β-caryophyllene as a major constituent (32.3%) (Gowda et al., 2012). The compound β-caryophyllene has also been reported to possess apoptosis-inducing potential against tumor cell lines (Amiel et al., 2012). The presence of cytotoxic activity of sesquiterpenoids is discussed in many studies in different species (Abu-Izneid et al., 2020). The cytotoxic activity of this compound on brine shrimps and HeLa cell lines has been attributed to the synergistic effect of β-caryophyllene and α-humulene, as reported by a similar study (Legault and Pichette, 2007). The presence of cytotoxicity may indicate the anticancer action of these compounds; thus, in-depth studies are needed to assess the mechanism of action responsible for cytotoxicity and *in vivo* evaluation of these molecules and extracts.

7.6. Wound healing

Chronic wounds are one of the leading illnesses linked with skin damage and usually arise from different types of topical injuries (Orsted et al., 2003). Moreover, diabetes patients are susceptible to wounds since it takes relatively long to heal (Amiel et al., 2008). Presently, traditional medicines are being actively explored for direct application as therapeutic agents for treating wounds (Fayemi et al., 2018). In this regard, the polymeric hybrid hydrogel of dimethylaminoethyl acrylate and hyaluronic acid (pDMAEMA-HA), when impregnated with herbal extract of *Didymocarpus pedicellata* (pDPi-DMAEMA-HA) hybrid hydrogel, has been reported to effectively cure wounds in rats (Mittal et al., 2020). This study reported that animals treated with pDPi-DMAEMA-HA hybrid hydrogel group exhibited a high level of wound closure by forming a new epidermis extending toward the wound centers in all the treated wound lesions, thus reducing the wound area. The histopathologic results from this study revealed that pDPi-DMAEMA-HA hybrid hydrogel and polymeric hybrid hydrogel-treated groups showed increased cutaneous wound healing activity in addition to a high level of cellular and tissue repair and healing. The activities mentioned above may be attributed to the action of hyaluronic acid in various stages of wound repair. A similar study reported the activity of hydrogels to maintain a physiologically moist microenvironment, provide an adhesion effect on the wound region, and enhance the contraction and closure rate of the wound during the early stage of the wound healing process (Singh et al., 2019). In addition, it has also been reported that during the initial stages of a wound healing process, HA enhanced fibroblast proliferation, angiogenesis, and matrix deposition and could therefore contribute to the contractile force generation at the wound region (Eming, 2014). These studies suggest that polymeric hybrid hydrogel and pDPi-DMAEMA-HA hybrid hydrogel displayed the potential to be used as a prototype to discover new effective wound healing agents. The report by Mittal et al. (2020) provides a pharmacological insight into the use of *D. pedicellata* in the ethnomedicinal management of wounds. This study also presents the plant as a possible wound healing agents using the extract in a polyherbal formulation with other herbs, since herbal medicines are commonly administered as a mixture of many extracts. These hybrid formulations have the potential to treat a wide range of wounds, including burns, skin irritation, fractures, accidental wounds, cuts, skin rupture, diabetic wounds, and foot ulcers. This study by Mittal et al. (2020) is the only wound healing assay so far done for this genus.

7.7. Spasmolytic activity

Herbal plants have a long history of treating gastrointestinal and respiratory diseases in developing nations (Maïkere-Faniyo et al., 1989). In this respect, the bioactive compound pedicellin isolated from the aqueous extract of *D. pedicellata* has been reported to exhibit papaverine-like spasmolytic activity on isolated ileum and uterus of guinea pig and ascending colon of rabbit (Saklani et al., 2015). The extract also showed significant inhibition of the carbamoylcholine produced intestinal hypermotolity in cats, and prostigmine produced intestinal hypermotolity in rats (Goyal and Ikshit Sharma, 2015). Similar findings have been reported from several species from the Asteraceae family, particularly *Baccharis glutinosa*, *B. serraefolia*, *B. trinervis*, and *B. vaccinioides* (Tortoriell et al., 1995). These findings indicate that *D. pedicellata* extracts can be used to develop effective therapies for gastrointestinal and respiratory diseases.

7.8. Antiviral activity

A study on the cytotoxicity of extracts from *Didymocarpus primulifolius* reported potential antiviral properties to the sindbis virus (Taylor et al., 1996). Previous studies on the antiviral properties of herbal extracts have reported that flavonoids, phenolics, triterpenes, and other compounds isolated from different plants interfere with host cell replication at their antivirally active concentrations as well as exhibit extracellular viricidal activities (Li and Chen, 2005). Thus, some of these viricides, particularly flavonoid-rich plants, showed significant inhibition of virus replication of picorna-, rota-, and arena viruses in the gastrointestinal tract of humans and animals (Mukherjee, 2019). *Didymocarpus* species are flavonoid-rich plants, and may possess important antiviral properties.

7.9. Antidiabetic activity

Some of the compounds identified from the genus *Didymocarpus* have previously been isolated from other medicinal plants and have shown antidiabetic properties (Bhongade et al., 2021). Chalcones isolated from the whole plant of *Didymocarpus pedicellata* have been shown to act as PTP 1B inhibitors by selectively inhibiting the protein tyrosine phosphate 1B, preventing glucose translocation from GLUT4 and decreasing glucose uptake by muscle thus raising blood glucose levels (Jiang et al., 2012). The activity of chalcones to inhibit a-glucosidase has been reported whereby these compounds reduce the absorption of dietary carbohydrates, which suppresses postprandial hyperglycemia without increasing insulin levels (Seo et al., 2005). Moreover, chalcones act as aldose reductase (ALR) inhibitors by reducing the absorption of dietary carbohydrates, resulting in the suppression of postprandial hyperglycemia without increasing insulin levels (Prasad and Chandra, 2017). Therefore, the genus *Didymocarpus* exhibits antidiabetic potential illustrating its use in traditional medicine in treating obese patients.

8. Toxicity

The pharmacological profile and safety and toxicity studies are the most crucial aspects of drug research because they reveal the adverse effects of chemicals on living organisms as well as their symptoms, mechanisms and treatments (Mensah et al., 2019). In this regard, traditional herbal medicine has numerous applications in many communities, and some are scientifically proven via phytochemical and pharmacological studies (Luitel et al., 2014). Although herbal medicines have popular indications in folk culture, the rationale behind their efficacy and safety are not well established.

A study on the quality control analysis of *D. pedicellata* using macroscopy, microscopy, physicochemical parameters, qualitative and quantitative analysis, HPTLC and HPLC fingerprint profile revealed that this species might lead to the development of quality formulations for urolithiasis with enhanced efficacy and low toxicity (Ahmad et al., 2014). Findings from this study showed that this species was free from any pesticides and aflatoxins. This study further isolated the pharmacologically active compounds from *D. pedicellata* via quantitative estimation whereby the total phenolics and flavonoid content isolated were 0.874% w/w and 1.78% w/w, respectively. These important antioxidant constituents of plants have been discussed in Table 1.

Anthraquinone compounds have been isolated from the leaves of *Didymocarpus leucocalyx* and the whole plant of *D. hedyotideus* (Segawa

et al., 1999; Xiao et al., 2011). However, the occurrence of the quinone component in the chemical structure of anthraquinones has raised safety concerns resulting in the placement of anthraquinone laxatives under critical evaluation and reassessment (Malik and Müller, 2016). Quinones are amongst a group of toxicological intermediates which causes various perilous activities *in vivo*: acute cytotoxicity, immunotoxicity, and carcinogenesis (Bolton et al., 2000). Toxicological studies on anthraquinone compounds isolated from the genus *Didymocarpus* are yet to be reported.

The bio-efficacy and toxicity of other species from this genus remain untested. In-depth toxicological studies on the genus *Didymocarpus* are necessary and may reveal novel remedies with bioprospecting potential. Also, applying hyphenated techniques and pharmacokinetic studies on *Didymocarpus* species may lead to a better understanding of their pharmacology and action mechanisms.

9. Conclusions and future perspectives

The genus *Didymocarpus* has been used in traditional medicine as single herbs or in polyherbal formulations to treat renal diseases, chronic wounds, traumatic injuries, dysentery, chronic asthma, and others. Seventeen species of the genus *Didymocarpus* have been reported to have various applications in traditional systems of medicine in several Asian countries. However, ethnobotanical data are sometimes published in hard to find and access sources, usually in languages other than English. Therefore, though the authors have made great efforts to cover the available literature as rigorously as possible, there may be possibilities that some publications, reports or books on traditional medicinal uses of the genus *Didymocarpus* escaped our exploration. Available data indicate that over 166 compounds have been identified from this genus, including terpenoids, flavonoids, phenolic compounds, and others. The genus *Didymocarpus* is associated with various pharmacological activities, including antiurolithiatic, nephro-protective, antimicrobial, anticancer, antidiabetic, cytotoxicity, wound healing, antioxidant, spasmolytic, and antiviral activities.

Firstly, phytochemical studies on the genus *Didymocarpus* illustrate that this genus mainly contains terpenoids, flavonoids, phenolic compounds, and fatty acids, while little is known about the analysis and function of organic compounds such as the amine 2-amino-3-(3,4-dihydroxy-phenyl)-propionic acid and three compounds isolated in trace amounts from this genus which include 5,6-dimethyl-2,3-dihydro-1,4-dioxin, 5-hydroxy-7-methoxy-2-phenyl-4H-1-benzopyran-4-one, and 5,9,9-trimethyl-5-phosphatricyclo[6.1.1.02,6]dec-2-ene. However, more detailed phytochemical and pharmaceutical scientific studies on these compounds are necessary to elucidate their action mechanisms and pharmacological potency.

It is worth noting that the present insight into *Didymocarpus* offers several promising prospects. *Didymocarpus* species consists of many biologically active substances, and the available reports on phytochemistry may only be the tip of the iceberg. Moreover, only *D. pedicellata*, *D. tomentosa*, *D. hedyotideus*, and *D. leucocalyx* have been studied in depth amongst the *Didymocarpus* taxa. Although some plants such as *D. villosus* and *D. aromatica* have documented ethnomedicinal uses, these species' pharmacological activity and chemical profiles are poorly investigated. Over three-fourths of plant species from the genus *Didymocarpus* have never been studied for pharmacological activities or phytochemistry. These underexplored plant species could be promising candidates for further research.

Secondly, recent studies indicate that structure-based drug design plays a crucial role in developing novel pharmaceuticals. A series of strategies can be applied to obtain effective therapeutic drugs. More research is needed to isolate and identify more compounds from *Didymocarpus* species with novel structures, particularly bioactivity-guided, structurally modified, and chemically synthesized compounds. In addition, the information on the interrelationship between isolated compounds and pharmacological activities on *Didymocarpus* species is not comprehensive and should be further studied. Although pharmacokinetics can provide scientific explanations for pharmacological and toxicological findings, these studies on the genus *Didymocarpus* are limited; thus, all-inclusive research on pharmacologically active compounds are necessary to provide comprehensive data for clinical applications.

Thirdly, *D. pedicellata*, the most studied species of the genus *Didymocarpus*, has a wide range of applications in traditional medicine in the treatment of kidney conditions, including stones, urolithiasis, neuroureterolithiasis, burning micturition, and several other renal disorders. These applications correspond to its antiurolithiatic and nephroprotective activity according to modern pharmacology. Pharmacological research on the antiurolithiatic activity of *D. pedicellata* mainly concentrates on its crude extracts. However, the optimal dose, constituents, and side effects of *D. pedicellata* are yet to be assessed. Besides, there is limited information on the action mechanism of monomeric compounds isolated from *D. pedicellata*. The specific mechanism of *D. pedicellata* in animals is also not comprehensive enough. Therefore, high-quality and well-designed *in vivo*, *in vitro*, and clinical studies are needed to explore the molecular mechanisms and relationship between pharmacologically active compounds and potential antiurolithiatic and nephro-protective activity of *D. pedicellata*.

Moreover, it has been challenging to define an exact upper cut-off dose of the various extracts of *Didymocarpus* species used. Although the test dose needs to be pharmacologically relevant, the dosage of multiple extracts obtained from *Didymocarpus* species used in previous studies was different. In many instances, a dosage of 100–200 mg/kg extracts for *in vivo* studies can be presumed as the upper limit for significant pharmacological studies. In contrast, a much lower dose range such as 30–50 μM should be considered for *in vitro* studies in the case of pure compounds (Heinrich et al., 2020). In some cases, such as in the antiurolithiatic activity of *D. pedicellata*, the pharmacological action of *Didymocarpus* species is present only with doses that might be too high for clinical use. Further toxicological studies based on animal experiments, as well as comprehensive placebo-controlled and double-blind clinical trials, are needed to ensure drug efficacy and patient safety. Additionally, it is evident that *D. pedicellata* is non-toxic and can be listed among the toxicologically safe, functional plants. However, the clinical applications of *Didmocarpus* species have been rarely described and warrant critical improvements for their industrial applications.

Finally, *Didymocarpus* species possess various biological activities, which can be applied to health care medicine with further research. Even though many pharmacological studies have not shown excellent activity, more research might confirm their bioefficacies using different extracts, fractions or isolated compounds. In addition, with the advancements observed recently in analytical techniques and quality control methods, among them the improvement and update in chromatography techniques and molecular identification methods, it is inevitable that new quality markers and quality control measures may be adopted for better quality assessment of traditional herbal medicine in the future.

In conclusion, *Didymocarpus* species have various applications in traditional systems of medicine in several Asian countries. Modern pharmacology investigations have revealed that its antiurolithiatic and nephro-protective activity supports its traditional application in treating renal diseases and kidney stones. Other pharmacological activities reported from this genus include antimicrobial, anticancer, antidiabetic, cytotoxicity, wound healing, antioxidant, spasmolytic, and antiviral activities. This paper provides a full-scale review of botanical updates, traditional herbal uses, phytochemistry, pharmacology, and toxicology of the genus *Didmocarpus*. The information in this work may provide a basis for better exploitation of the medicinal value of the genus *Didymocarpus* in the future.

Ethical statement

There are no ethical issues related to this work.

CRediT authorship contribution statement

Consolata Nanjala: Formal analysis, Investigation, Data curation, Methodology, Software, Validation, Writing – original draft, All the authors read and approved the final version of the manuscript. **Wyclif Ochieng Odago:** Formal analysis, Investigation, Software, Data curation, All the authors read and approved the final version of the manuscript. **Peninah Cheptoo Rono:** Formal analysis, Investigation, Software, Data curation, All the authors read and approved the final version of the manuscript. **Emmanuel Nyongesa Waswa:** Formal analysis, Investigation, Data curation, All the authors read and approved the final version of the manuscript. **Elizabeth Syowai Mutinda:** Formal analysis, Investigation, Data curation, All the authors read and approved the final version of the manuscript. **Millicent Akinyi Oulo:** Methodology, Software, Validation, revised the manuscript, All the authors read and approved the final version of the manuscript. **Felix Wambua Muema:** Methodology, Software, Validation, revised the manuscript, All the authors read and approved the final version of the manuscript. **Vincent Okelo Wanga:** Methodology, Software, Validation, All the authors read and approved the final version of the manuscript. **Elijah Mbandi Mkala:** Methodology, Software, Validation, All the authors read and approved the final version of the manuscript. **Josiah Kuja:** Methodology, Software, Validation, revised the manuscript, All the authors read and approved the final version of the manuscript. **Moses Mucugi Njire:**Methodology, Software, Validation, revised the manuscript, All the authors read and approved the final version of the manuscript. **Guang-Wan Hu:** Conceptualization, Funding acquisition, Project administration, Supervision, Resources.

Declaration of competing interest

The authors declare no conflicts of interest.

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