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Review Article

Genus *Blepharis* (Acanthaceae): A review of ethnomedicinally used species, and their phytochemistry and pharmacological activities

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ABSTRACT

Ethnopharmacological relevance: *Blepharis* is an Afro-Asiatic genus belonging to the family Acanthaceae. It comprises 126 species that occur in arid and semi-arid habitats. Some species of *Blepharis* are used in traditional medicines in different countries mainly for their anti-inflammatory, would healing activities along with treatment of gastrointestinal disorders and bone fractures.

Aim of the review: The present review aims to collate and analyze the available data and information on distribution, traditional uses, chemical constituents and pharmacological activities of *Blepharis.*

Methods: Scientific information of genus *Blepharis* was retrieved from the online bibliographic databases like MEDLINE/PubMed, SciFinder, Web of Science and Google Scholar and secondary resources including books and proceedings.

Results: Seven species of *Blepharis* were found to be reported frequently as useful in folklore in Asian and African countries. *B. maderaspatensis* was found to be widely used in Indian traditional medicines whereas the *B. ciliaris* and *B. edulis* were common in folklore of Egypt, Jordan, and Arabia. Active phytochemicals of *Blepharis* are flavonoids from *B. ciliaris*, alkaloids from *B. sindica*, phenolic acid derivatives, and phytosterols, and derivatives of hydroxamic acids from *B. edulis* resulted in possessing diverse biological properties such as anti-microbial, anti-inflammatory, and anti-cancer.

Conclusion: Various species of *Blepharis* were found to be used in traditional medicine systems in African and Asian countries. Few of these species were studied for their bioactive chemical constituents however the activity guided isolation studies are not performed. Similarly, detailed pharmacological studies in animal models to explore their mechanism of action are also not reported. Future studies should focus on these aspects related to the medicinally used species of *Blepharis.* The detailed and comprehensive comparative analysis presented here gives valuable information of the currently used *Blepharis* species and pave the way to investigate other useful species of *Blepharis* pertaining to ethnobotany, phytochemistry and discovery of new drugs.

Keywords: *Blepharis*; Acanthaceae; Ethnomedicine; Bioactive compounds; Pharmacology

Abbreviations

AAEC, ascorbic acid equivalence capacity; ABTS, 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid); BOA, 2-benzoxazolinone; CCl_4, carbon tetrachloride; DIBOA, 2,4-dihydroxy-1,4-benzoxazin-3-one; DPPH, 1,1-diphenyl-2-picrylhydrazyl; GAE, gallic acid equivalence; GC-MS, gas chromatography-mass spectrometry; HRBC, human red blood cell; LDL, low-density lipoproteins; LPS, lipopolysaccharide; NO, nitric oxide; NO, nitric oxide; TEAC, trolox equivalent antioxidant capacity; TFC, total flavonoid content; TPA, total phenolic content;

1. Introduction

Medicinal plants have long been using as a mainstay of primary health sources among different communities worldwide (Atanasov et al., 2015). The prolonged reliance on medicinal plants as therapeutic agents had become a normative basis in addressing the traditional knowledge of different communities especially among developing countries. The discerning properties and paramount therapeutic importance of medicinal plants have drawn the attention of industrialized communities (Hoareau and DaSilva, 1999). Recently, researchers have adopted the traditional knowledge of medicinal plants in the bioprospecting of natural products as a new source of functional food, nutraceuticals and vital source for drug discovery and development (Atanasov et al., 2015; Heinrich, 2010).

Blepharis, an Afro-Asiatic genus, is widely distributed in hot, arid and semi-arid regions of the old world tropics and subtropics with the center of diversity in eastern and southern Africa (McDade et al., 2005). It is the largest genus in the family Acanthaceae comprising 126 species (The Plant Lists, http://www.theplantlist.org/1.1/browse/A/Acanthaceae/Blepharis/, retrieved on June 13, 2020). *Blepharis* species have characteristic flowers with colourful petals and many of these plant species are of economic importance for their application as natural dye and ornamentals products (Chopra, 1973; El-Shanawany et al., 2013). Few species of *Blepharis* such as *B. ciliaris* (L.) B.L.Burtt, *B. edulis* (Forssk.) Pers., *B. linariifolia* Pers., *B. scindica* Stocks ex T.Anderson, *B. maderaspatensis* (L.) B.Heyne ex Roth are widely used in several countries in Africa and Asia, where they are used for curing many infectious and chronic diseases, inflammatory conditions, bone ailments, and parasitic complications (Khare, 2001; Mohamed et al., 2015). There are only a few studies on chemical constituents and pharmacological activities of the *Blepharis* plant extracts and isolated compounds from *Blepharis* species. It is therefore important to have a clear idea about the scientific progress on the genus related to its traditional uses, phytochemistry and pharmacological activities to design future studies on these species. The review of the current state of science related traditional uses, phytochemistry and pharmacological aspects of *Blepharis* is still lacking. Hence, the main aim of this review is to systematically review and analyze the available information of *Blepharis* reported on its traditional uses, ethnopharmacological studies, chemical constituents and pharmacological and toxicological properties of the plants of genus. Along with that we have analyzed the research gaps and proposed future recommendations.

2. Methodology

Scientific information on genus *Blepharis* was retrieved from the online bibliographic databases like MEDLINE/PubMed, SciFinder, Web of Science and Google Scholar and secondary resources including books and proceedings. Scientific names of the species and their synonyms were crosschecked with the information of The Plant List (http://www.theplantlist.org/). Only articles with rigorous quality of taxonomical information and pharmacological study design were selected for the review.

3. Description and geographical distribution

Blepharis genus has distinctive and rather diverse morphological features that had been adopted as a diagnostic tool in the taxonomy of *Blepharis* taxa. The studies have described and reported the general floral characteristics of *Blepharis* including the features of inflorescences, bracts, bracteoles, stamens, pistils of *Blepharis* flowers and the fruits (Muhaidat et al., 2018; Vollesen, 2000).

Description: Herbs, perennial [annual herbs or shrubs], without cystoliths, anisophyllous. Leaves usually in pseudo-whorls of 4 [or opposite], sessile to subsessile; leaf blade margin entire to dentate. Flowers axillary and solitary or many in terminal dense headlike spikes; bracts often clustered in up to 5 pairs, imbricate, leathery, margin often bristly dentate with bristles barbed; bracteoles absent [or 2]. Calyx included in bracts or ± exserted, 4-lobed; lobes in 2 unequal opposite pairs, thickened-horny at base, posterior and anterior lobes larger and 2–7-veined, lateral pair smaller and 1-veined. Corolla tube shorter than limb, expanded from base and constricted near apex; limb a single (lower) lip; lip elongate, 3[–5]-lobed. Stamens 4, didynamous, inserted at or near apex of corolla tube; filaments bony, with lower pair straight and upper pair curved, broad, flattened, usually bifurcate apically into a branch bearing an anther and a toothlike appendage; anthers 1-thecous; theca bearded. Ovary glabrous, with 2 ovules per locule; style linear; stigma 2-cleft. Capsule not stipitate, oblong to ellipsoid, 2(–4)-seeded; retinacula present. Seeds discoid, covered with long branched hygroscopic trichomes (Hu et al., 2011).

Blepharis is an Afro-Asiatic genus characterized by its broad ecological distribution range extended across the tropical and southern Africa, southern parts of the Middle East, Central Asia, India, southern China, with the occurrence of one species in Indonesia (Thulin and Vollesen, 2015; Vollesen, 2000). Table 1 catalogues the geographical distribution and habitat of ethnobotanically useful *Blepharis* species.

Among the species of *Blepharis*, *B. attenuata* Napper is reported to grow in the Saharo-Arabian and Sudanian regions (Townsend & Feinbrun-Dothan, 1980; Muhaidat et al., 2012). Vollesen (2000) reported that *B. attenuata* is the only *Blepharis* member that migrated north and colonized in desert areas of Egypt, West Bank and Jordan. Another species, *Blepharis ciliaris* is reported from Egypt, Iran, Jordan, Oman, Pakistan and Sudan (Table 1) (Vollesen, 2000; Akhani et al., 2008).

Blepharis edulis is widely distributed in among Asian and African countries. It is found in Egypt and some eastern African countries from central Tanzania through Kenya to Eritrea and Somalia (Malombe et al., 2002). In Asia, it is found in Pakistan, Iran, India, Afghanistan (Aynehchi et al., 1985; Kapoor, 1990). A taxonomic study in eastern Africa have confirmed the presence of two species, *B. edulis* and *B. boranensis* Vollesen, from central Tanzania through Kenya to Eritrea and Somalia, with the latter is found Borana region (Kenya, Ethiopia and Somalia) and Sodere, Ethiopia, while the former remains variable and widespread (Malombe et al., 2002). *Blepharis gypsophila* Thulin & Vollesen is an example of newly identified species endemic to the south-eastern Ethiopian region in particular Ethiopia, Somali National Regional State (Thulin and Vollesen, 2015).

Blepharis linariifolia is distributed in African countries including Burkina Faso (Sawadogo et al., 2006), Sudan (El Ghazali et al., 1987) and Somalia (Samuelsson et al., 1991). *Blepharis maderaspatensis*, as the species name maderaspatensis indicates, was first found in Madeira Islands in the Atlantic Ocean, near tropical Africa, South Africa, Madagascar, and it is also extended to Asia (Vijayalakshmi and Kripa, 2016).

188 *Blepharis saudensis* Y. Masrahi, & M. Basahi has been recently identified from a small island in
189 the Red Sea of Jazan Province, Saudi Arabia (Basahi and Masrahi, 2019). From the
190 aforementioned reports, it's clear that there was a debate over the number of the reported *Blepharis*
191 species occurring among different localities, pertaining with the identification of additional and/or
192 new species following taxonomic surveys. *Blepharis scindica* is widely found in Pakistan (Ahmad,
193 1986; Leghari et al., 2007; Perveen et al., 2009).
194
195 **Table 1:** Distribution record of the ethnomedicinally used *Blepharis* species in different countries.

***Blepharis* species**	**Country**	**References**
B. ciliaris (L.) B.L.Burtt Syn. *Acanthus edulis* Forssk., *A. pectinatus* Willd. ex Nees; *A. tetragonus* R.Br., *Ruellia ciliaris* L., *R. ersica* Burm. f.	Saudi Arabia	(Muschler, 1970; Taeckholm, 1974; Boulos, 1981; Boulos, 1995)
	Egypt	(Boulos, 1981, 1995; Muschler, 1970; Taeckholm, 1974)
	Oman	(Akhani et al., 2008; Vollesen, 2000)
	Iran	(Akhani et al., 2008; Vollesen, 2000)
	Pakistan	(Ageel et al., 1987; Akhani et al., 2008; Vollesen, 2000)
	Sudan	((Abdel-Fattah and Ali, 2005; El Ghazali et al., 1997; Ghazal, 2015; Tounekti et al., 2019))
	Jordan	(Muhaidat et al., 2018; Qasem, 2015)
B. edulis (Forssk.) Pers. Syn. *Acanthpodium delilii* H.Buek; *A. spicatum* Delile; *Acanthus delilei* Spreng.; *B. obovata* Chiov.; *B. persica* (Burm.f.) Kuntze	Saudi Arabia	(Boulos, 1995; Ghazal, 2015; Taeckholm, 1974)
	Egypt	(Ashour, 2012; Boulos, 1995; Shamso, 2010; Taeckholm, 1974)
	Iran	(Mahboubi et al., 2013)
	Pakistan	(Saqib et al., 2012)
	India	(Pande and Pathak, 2009)
B. integrifolia (L.f.) E.Mey. & Drège ex Schinz Syn. *Acanthus integrifolius* L.f.; *A. repens* Vahl; *B. molluginifolia* Pers.; *B. repens* (Vahl) Roth; *B. rupicola* Engl.; *B. saturejifolia* Pers; *B. setosa* Nees.	India	(Hebbar et al., 2004; Senthilkumar et al., 2006)
B. linariifolia Pers. Syn. *Acanthopodium hirtum* Hochst. ex Nees. *B. hirta* (Hochst.) Martelli, *B. passargei* Lindau	Mali	(Inngjerdingen et al., 2004)
	Somalia	(Samuelsson et al., 1991)
	Sudan	(El Ghazali et al., 1987; Issa et al., 2018)
B. maderaspatensis (L.) B.Heyne ex Roth	China	(Hu et al., 2011)

Syn. *Acanthus ciliaris* Burm.f.; *A. maderaspatensis* L.; *B. abyssinica* Hochst. ex A.Rich.; *B. boerhaviifolia* Pers.*; B. boerhaviifolia* Roth.*; B. breviciliata* Fiori*; B. calaminthifolia* Pers.*; B. gueinzi* T.Anderson; *B. procurrens* Nees*; B. rubiifolia* Schumach*. B. taehuei* Oberm.*; B. togodelia Solm ex* Schweinf.	India	(Ganesan et al., 2004; Ijinu et al., 2016; Kottaimuthu, 2008; Vijayalakshmi and Kripa, 2016)
B. panduriformis Lindau	Tanzania	(Maregesi et al., 2007)
B. scindica Stocks ex T.Anderson Syn. *Acanthopodium grossum* Wight; *B. sindica* Stocks ex T.Anderson	Pakistan	(Bibi et al., 2015; Perveen et al., 2009)

4. Ethnomedicinal uses

Out of 126 *Blepharis* species, seven species have been mainly used in ethnomedicines for various purposes (Table 2). A total of 117 use citations were recorded under 45 ailment categories and 16 use category following Cook (1995) and Kunwar et al., (2018). For those uses, all plant parts are being used while the use of leaves was predominant followed by seeds, whole plant, root, and young shoot and plant ash (Table 2).

Blepharis ciliaris: It is widely distributed in most North African countries (Boulos, 1981; Vollesen, 2000). Its leaves and whole plants are utilized in traditional medicine for the treatment of sores, cough, inflammations, skin wounds, cold, toothache, lung diseases, and renal disorder. It is employed as astringent, appetizer, diuretic, and anti-asthmatic (El-Shanawany et al., 2014, 2013). The roots charcoal 'Kohl-el-agouz' is applied to the eyes to improve vision (Boulos, 1981; El-Shanawany et al., 2013). In Sudan, the poultice of the whole plant of *B. ciliaris* is used among tribes of northern Kordofan state for the treatment of swelling (El Ghazali et al., 1997).

Blepharis edulis: It is known as Shikhi in Ayurvedic system. It is reported to treat asthma, cough, fever, inflammation of the throat (Kirtikar and Basu, 1994; Pande and Pathak, 2009). It is reported to be used for festering wounds, alleviating gastric ulcers, astringent to bowels and also as an appetizer in Pakistan (Usmanghani et al., 1997). The plant is reported to be useful in the treatment of wounds, ulcers, nasal hemorrhages, asthma, throat inflammation, purgative, disorders of liver and spleen (Gupta et al., 2004). The root is considered diuretic and beneficial in urinary discharges

and dysmenorrhea. The seeds are considered to be diuretic, aphrodisiac, expectorant, deobstruent and useful in strangury and conjunctivitis (Pande and Pathak, 2009). Plant leaves and seeds are reported to be eaten by both humans and ruminants. The leaves are commonly sold in the Indian markets, and it is known as "Utingana" (Deshpande, 2006). It is used as good forage for sheep, goats, and camels for increasing milk production (Birit and Laddha, 2001; Kirtikar and Basu, 1994).

Blepharis integrifolia: This plant is distributed mainly in India, where it is reported to be used by Irular, the tribal people of Marudhamalai hills, Tamil Nadu for treatment of headache (Senthilkumar et al., 2006) and used in oral health care (Hebbar et al., 2004).

Blepharis linariifolia: It is reported to be used to treat malaria, measles, whitlow, sexually transmitted infections, fever, and inflammations in Burnika Faso (Sawadogo et al., 2006). In Sudan, the macerate of whole plant is used as general tonic, for stomach pain and for bilharzia among tribes of Etern Nuba Mountains (El Ghazali et al., 1987). It's cold water extract is useful for kidney disorders (Issa et al., 2018). Also, the decoction of whole plant was reported to be used for the treatment of urine retention in West Kordofan state (Doka and Yagi, 2009). The dried and powdered aerial parts of the plant are used for toothache and wounds, where the plant powder is filled into the tooth cavity and sprinkled on the wound, respectively (Issa et al., 2018). In Somalia, the plant powder is applied topically for the treatment of local infections on the genitals and of skin burns (Samuelsson et al., 1991).

Blepharis maderaspatensis: *B. maderaspatensis* is frequently used in India. It is used by Paliyar tribes (Ignacimuthu et al., 2006), Valaiyans (Kottaimuthu, 2008), Kani tribals (Subitha et al., 2011), Malayal tribals (Subramanian et al., 2011; Suresh et al., 2011), Kanikkar tribes (Rani et al., 2011), and Hooralis tribes (Arunachalam and Parimelazhagan, 2011). It is widely acknowledged among traditional healers from Theni district, Tamil Nadu, and it is locally called as "Murivu porunthi" in Tamil language, which is famed as bone healer. Based on a consensus of local knowledge on the medicinal plants from these localities, *B. maderaspatensis* is one of the highly used plants as a traditional remedy (Jain, 1991;Pandikumar et al., 2011), and the leaves are widely used for the preparation of the herbal remedy. It is also used for ethnoveterinary purposes

(Ayyanar, Sankarasivaraman, & Ignacimuthu, 2008). The leaves of *B. maderaspatensis* are reported to be useful in wounds, ulcers, asthma, throat inflammation, ascites, liver, and spleen disorders, while roots are used against dysmenorrhea. The plant seeds are useful in strangury and conjunctivitis (Devi and Meera, 2010; Yohanrashiman, 2000).

Blepharis scindica: Its plant roots are used for urinary discharge and dysmenorrhea, whereas the plant powder is applied locally on the infections of genitals and burns (Khare, 2004). Apart from ethnomedicinal usages, *B. scindica* is used as local forage and pasture species (Bhatt et al., 2017).

There are few reports on the use of other *Blepharis* species. Watt et al. (1962) reported the use of *Blepharis capensis* (L.f.) Pers. (Syn. *B. capensis* var. *latibracteata* Oberm., and *B. capensis* var. prostrata Oberm.) for the treatment of anthrax, *B. espinosa* Phillips (Syn. *B. espinosa* var. *spinosa* Oberm.) for the treatment of coryza and *B. procumbens* (L.f.) Pers. (Syn. A*canthodium procumbens* (L.f.) Nees, *Acanthus glomeratus* Lam., *Acanthus procumbens* L.f., *Blepharacanthus procumbens* Nees, *Blepharis glomerata* (Lam.) Poir.) for the treatment of toothache in Africa (Mmatli et al., 2007). Maregesi et al. (2007) has reported the traditional uses of *B. panduriformis* Lindau against infectious diseases (Maregesi et al., 2007).

Table 2. Ethnomedicinal uses of some *Blepharis* species among different countries

***Blepharis* species**	**Country (Local name)**	**Parts used**	**Ethnomedicinal uses**	**References**
B. ciliaris (L.) B.L.Burtt	Egypt (Kohl-el-agouz)	Sd	Used as disinfectant and hemostatic for wounds and cuts.	(Afifi, 2003; Batanouny et al., 1999)
		Rt	Charcoal from the roots is applied to the eyes to improve vision and treat sore eyes.	(Afifi, 2003; Batanouny et al., 1999; Boulos, 1981; El-Shanawany et al., 2013)
		Sd	Seeds (roasted or crushed) are applied on sores, wounds, and boils as an	(Deshpande, 2006; El-Shanawany et al., 2013)

			antibacterial. Used as diuretic, aphrodisiac, and expectorant.	
		Lf, Wp	Used against skin wounds, sores, cough, cold, inflammations, toothache, and renal disorder.	(El-Shanawany et al., 2014)
	Jordan	Rt	Root powder for feeble sight, against cataract, anti-inflammatory, disinfectant, diuretic, aphrodisiac and hemorrhoids.	(Qasem, 2015)
	Saudi Arabia (Al-Zaghaf)	Rt	A powdered root is applied topically as eye drops.	(Tounekti et al., 2019)
	Sudan (Begheil)	Wp	The poultice is used to treat swelling.	(El Ghazali et al., 1997)
B. edulis (Forssk.) Pers.	India (Utangan)	Rt	The root is considered diuretic and beneficial in urinary discharges and dysmenorrhea.	(Pande and Pathak, 2009)
		Sd	The seeds are considered to be diuretic, aphrodisiac, expectorant, deobstruent and useful in strangury and conjunctivitis	(Pande and Pathak, 2009).
	Pakistan	-	Used festering wounds, alleviating gastric ulcers, astringent to bowels and also as an appetizer	(Usmanghani et al., 1997)
B. integrifolia (L.f.) E.Mey. & Drège ex Schinz	India	Lf	Used for bone fractures, skin diseases, urinary discharges, and allergies.	(Khare, 2007; Pattar et al., 2011)
		Tender St	Chewing and keeping in mouth for some time will give relief from aphthae.	(Hebbar et al., 2004)
		Lf	Leaves are crushed and paste is applied on the forehead in headache.	(Senthilkumar et al., 2006)
		Lf, Sd	The decoction of leaves is used in treatment of old persistent fever. Leaf juice boiled with sesame oil and applied externally to wounds. The seeds are considered attenuant, resolvent, diuretic, aphrodisiac, expectorant and deobstruent.	(Patil, 2010)
B. linariifolia Pers.	Burkina Faso	Lf, St	Used against malaria, measles, whitlow, sexually transmitted infections, fever, and inflammations.	(Sawadogo et al., 2006)

	Mali (Yaanso)	Sd, St	A decoction of the aerial parts is used as a wash and powder of dried plant material is applied for all kinds of wounds. Powdered seeds are mixed with oil from the seeds of *Lannea acida* A.Rich or *Sesamum indicum* L. and applied for the treatment of otitis.	(Inngjerdingen et al., 2004)
	Somalia (Yamaarug)	Wp, fresh or dried	The powder of whole plant is used for the treatment of local infections on the genitals and of skin burns.	(Samuelsson et al., 1991)
	Sudan (El Bigiel)	Wp	Decoction of the whole plant is used for treatment of urine retention.	(Doka and Yagi, 2009)
		Wp	Used as general tonic, for stomach pain and for bilharzia.	(El Ghazali et al., 1987)
		St	Maceration is used for kidney disorders and as a tonic. Infusion or maceration is used for diabetes and hypertension. Plant powder is filled into tooth cavity for the treatment of toothache. For wounds, the dried powder plant is sprinkled on the wound.	(Issa et al., 2018)
B. maderaspatensis (L.) B.Heyne ex Roth	India (Thonimalai marunthu,Poppadak-kodi)	Sd	Used for dysuria, diuretic, and aphrodisiac. Also used against diseases of nervous system.	(Mohan et al., 2010; Yoga narasimhan et al., 1982)
		Lf	Leaves are ground with egg, black gram and onion and applied for bone fracture in humans and in livestock.	(Ganesan et al., 2004)
		Lf	Leaf paste is mixed with the powdered black gram, crushed onion and white yolk of one egg and the mixture is applied topically over the fractured bones. Also, the paste is mixed with lime juice and applied on cuts.	(Ignacimuthu et al., 2006)
		Lf	Leaves mixture with other plants (leaves of *Pterospermum suberifolium* (L.) Willd. stem bark of *Drypetes*	(Kottaimuthu, 2008)

			roxburghii (Wall.) Hurus) and added to the yellow yolks of 2 eggs ground into a fine paste is applied on fractured bones.	
		Lf	Juice extracted from the leaf is heated with ginger oil and applied topically on affected places to heal wounds.	(Ayyanar and Ignacimuthu, 2009)
		Lf	During bone fracture, leaves paste with white of egg, black gram and onion are applied on the fractured area in humans and stock during night for one month.	(Samuel and Andrews, 2010)
		Lf	Hooralis tribes mix the paste of leaves with lime-juice and applied on cuts.	(Arunachalam and Parimelazhagan, 2011)
		Lf	For the treatment of jaundice and to strengthen liver. It is also used to treat cut wounds.	(Pandikumar et al., 2011)
		Lf	Kanikkar tribes uses the paste prepared from fresh leaves with water is applied externally once in a day for a period of one week to heal the wounds.	(Rani et al., 2011)
		Lf	Used for wounds healing, as a diuretic, and to treat cancer.	(Baskar et al., 2012)
		St	The aerial parts are used to cure cut wounds and muscle joining.	(Divya and Manonmani, 2013)
		Lf	Used by hyperlipidaemic subjects as an alternative therapeutic tool to treat hyperlipidemia.	(Rajasekaran, 2013)
		Lf	Leaves are ground and formed into a paste and applied or taken orally to treat bone fracture and deep cuts.	(Subitha et al., 2011)
		Lf	For the treatment of cut and wound.	(Subramanian et al., 2011)
		Lf	Leaves are ground with egg and onion and applied externally for bone fracture.	(Suresh et al., 2011)

		Lf	The juice is applied topically against cuts and wounds.	(Senthilkumar et al., 2013)
		-	Used against dropsy, swellings, and edema.	(Nandagopalan et al., 2014)
		Lf	Leaf juice with lime are mixed and applied for cure cuts.	(Gurusamy et al., 2016)
		Lf	Leaf juice is taken orally against throat troubles and asthma.	(Kumar and Alagumanian, 2016)
		Wp	The whole plant made into paste and then applied over bone fracture site.	(Shiddamallayya et al., 2016)
		Lf, Stash	Aerial parts are used for wounds and fusion of broken bones. Leaf paste ground with egg and onion applied for bone fractures, and the juice is used for throat troubles and asthma. Plant ash is used for dropsy, swellings, edema, gout, dry alcoholic extracts as potent diuretic, and crushed and mixed plant parts for venereal diseases.	(Vijayalakshmi and Kripa, 2018)
		Wp	The decoction of the whole plant is used to treat abdominal gas trouble.	(Venkatachalapathi and Paulsamy, 2018)
		Lf, Wp	Used as topical paste to heal bone fracture and for treatment of heart pain. Some ingredients are added as egg white or black gram.	(Xavier et al., 2018)
		Lf, Rt, Sd	Leaves are used to cure wounds, ulcers, asthma, throat inflammation, ascites, liver and spleen disorders. Seeds are used strangury and conjunctivitis. Roots are used against dysmenorrhea.	(Devi and Meera, 2010; Yohanrashiman, 2000)
	Nigeria	Lf	A paste of the leaves is mixed with black gram powder, crushed onion and white egg yolk and the mixture is applied topically over fractured bones.	(Burkill, 2004; Sowemimo et al., 2013)

	Tanganyika	Lf	The whole plant is burnt to ash and mixed with oil for rubbing onto swollen legs after it has been washed in warm water.	(Burkill, 1985; Sowemimo et al., 2013)
B. panduriformis Lindau	Tanzania (Mukilabaigi)	Wp	The decoction of the whole plant is used orally for the treatment of dysentery.	(Maregesi et al., 2007)
B. scindica Stocks ex T.Anderson	India (Bhangari)	Rt, Sd	Seeds are boiled in milk and taken as tonic. It is also given to cattle to increase milk production. Roots are used for urinary discharge and dysmenorrhea.	(Bhandari, 1990)
		Sd, Rt Wp	Cream coloured seeds are boiled in milk and used as an invigorating tonic. It is also given to cattle to increase milk production. Roots are used for urinary discharge and dysmenorrhea. Powdered plant is applied locally on infections of the genitals and on burns.	(Khare, 2001; Lal et al., 2012)
		Wp	Powdered plant is applied locally on the infections of genitals and on the burns.	(Khare, 2007)
		Sd	Used as aphrodisiac.	(Mathur, 2012)
	Pakistan (Bhangari)	Sd	The powder of seeds is used in the treatment of earache.	(Ahmad, 1986; Baquar and Tasnif, 1967)
			As tonic, seeds are boiled in milk. Seeds are given to cattle to increase milk production.	(Rechinger, 1991)
			Seeds are used as dried powder or as a decoction to treated earache, eye diseases, and urine discharge.	(Bibi et al., 2015)

Lf: Leaf; Rt: Root, Sd: Seed; St: Shoot; Wp: Whole plant

5. Bioactive chemical constituents

Compounds belonging to different phytochemical classes, have been isolated and identified from different parts of *Blepharis.* Total 10 flavonoids, 9 phenolic acid derivatives and 8 other

compounds were reported from the *Blepharis* species (Table 3) along with some other compounds from essential oils. Polyphenolic compounds including flavonoids (Figure 1) and phenolic acid derivatives (Figure 2) represents the major class as revealed from literature. Genistein-7-*O*-(6″-*O*-*E*-caffeoyl)-*β*-$_{D}$ glucopyranoside was isolated and identified from the aerial parts of *B. ciliaris* along with other compounds such as verbascoside, *cis*-verbascoside, protocatechuic acid and naringenin-7-*O*-(6″-*E*-*p*-coumaroyl)-*β*-$_{D}$-glucopyranoside were identified for the first time from this plant species (El-Shanawany et al., 2013). Dirar et. al. (2019a) recently isolated and identified four phenolic compounds namely; verbascoside, vanillic acid, apigenin, and 6″-*O*-*p*-coumaroylprunin from *B. linariifolia* acetone extract which had antioxidant and enzyme inhibitory activities. Afifi (2003) had identified a novel 4'-*O*-diglycoside of decarboxyrosmarinic acid from *B. ciliaris*, along with other known flavonoid glycosides; apigenin 7-*O*-glucoside and apigenin-7-*O*-(3"-acetyl-6"-*E*-*p*-coumaroyl)glucoside (Afifi, 2003). The chemical structure of the novel compound was established as 3',4'-dihydroxy-*β*-phenyl ethyl caffeate-4'-*β*-*O*-$_{D}$-galactopyranosyl-(1'"→4")-*α*-*O*-$_{L}$-rhamnopyranoside (9'-decarboxy rosmarinic acid- 4′ -*O*- *(1* →4)-galactosyl rhamnoside). The compounds 7-*O*-6"-*p*-coumaroyl glucosides of both apigenin and naringenin were reported from the seeds of *B. scindica* (Ahmad et al., 1984),while the respective 3"-acetyl congeners were reported from *B. ciliaris* (Harraz et al., 1996). Harraz et al. (1996) have identified two novel acylated flavonoids from *B. ciliaris* which are apigenin 7-(3"-acetyl-6"-*E*-*p*-coumaroyl)glucoside and naringenin 7-(3"-acetyl-6"-*E*-*p*-coumaroyl)glucoside (Harraz et al., 1996).

Table 3: Bioactive chemical constituents reported from genus *Blepharis*

Chemical compounds	***Blepharis* species (Part used)**	**Reference**
Flavonoids and flavonoids glycosides		
Apigenin	*B. scindica* (seeds)	(Ahmad et al., 1984)
	B. ciliaris (aerial parts)	(El-Shanawany et al., 2014)
	B. linariifolia (aerial parts)	(Dirar et al., 2019a)
Apigenin 7-*O*-glucoside	*B. ciliaris* (aerial parts)	(Afifi, 2003)
Apigenin-7-*O*-(6″-*E*-*p*-coumaroyl)-*β*-$_{D}$-glucopyranoside	*B. ciliaris* (aerial parts)	(El-Shanawany et al., 2013)

	B. scindica (seeds)	(Ahmad et al., 1984)
Apigenin 7-(3"-acetyl-6"-*E*-p-coumaroyl)- glucopyranoside	*B. ciliaris* (aerial parts)	(Harraz et al., 1996)
	B. ciliaris (aerial parts)	(Afifi, 2003)
Naringenin-7-*O*-(6″-*E*-p-coumaroyl)-β-D-glucopyranoside	*B. ciliaris* (aerial parts)	(El-Shanawany et al., 2013)
	B. scindica (seeds)	(Ahmad et al., 1984)
	B. linariifolia (aerial parts)	(Dirar et al., 2019a)
Naringenin-7-*O*-(3″-acetyl-6″-*E*-*p*-coumaroyl)-β-D-glucopyranoside	*B. ciliaris* (aerial parts)	(El-Shanawany et al., 2013; Harraz et al., 1996)
Rutin	*B. maderaspatensis* (leaves)	(Mohamed et al., 2015;
Blephariside A	*B. ciliaris* (aerial parts)	(Mohamed et al., 2015)
Blephariside B	*B. ciliaris* (aerial parts)	(Mohamed et al., 2015)
Genistein-7-*O*-(6″- *O*-E-caffeoyl)-β-D glucopyranoside	*B. ciliaris* (aerial parts)	(El-Shanawany et al., 2013)
Phenolic acid derivatives		
Protocatechuic acid	*B. ciliaris* (aerial parts)	(El-Shanawany et al., 2013)
Vanillic acid	*B. linariifolia* (aerial parts)	(Dirar et al., 2019a)
Methyl vanillate	*B. ciliaris* (aerial parts)	(El-Shanawany et al., 2013)
Methyl veratrate	*B. ciliaris* (aerial parts)	(El-Shanawany et al., 2013)
Verbascoside (Acteoside)	*B. edulis* (aerial parts)	(Ashour, 2012)
	B. ciliaris (aerial parts)	(El-Shanawany et al., 2013)
	B. linariifolia (aerial parts)	(Dirar et al., 2019a)
Cis-verbascoside	*B. edulis* (aerial parts)	(Ashour, 2012)
Isoverbascoside	*B. edulis* (aerial parts)	(Ashour, 2012)
Leucosceptoside A	*B. edulis* (aerial parts)	(Ashour, 2012)
9'-Decarboxyrosmarinic acid-4'-*O*-(1-4)-galactosylrhamnoside	*B. ciliaris* (aerial parts)	(Afifi, 2003)
Alkaloids		

Blepharin	*B. scindica* (seeds)	(Ahmad et al., 1984)
	B. edulis (whole plant)	(Chatterjee et al., 1990)
	B. edulis (seeds)	(Lal, 1936)
Blepharigenin	*B. edulis* (whole plant)	(Chatterjee et al., 1990)
2-Benzoxazolone	*B.edulis* (roots)	(Chatterjee et al., 1990)
Allantoin	*B. scindica* (seeds)	(Ahmad et al., 1984)
Betaine hydrochoride	*B. scindica* (seeds)	(Ahmad et al., 1984)
Steroids, triterpenoids and fatty acid derivatives		
Oleanolic acid	*B. scindica* (seeds)	(Ahmad et al., 1984)
(2*S*,3*S*,4*R*)-2[(2′*R*)- 2′-(Hydroxyeicosanoyl amino) octadecane-1,3,4-triol	*B. ciliaris* (aerial parts)	(El-Shanawany et al., 2014)
β-Sitosterol	*B. scindica* (seeds)	(Ahmad et al., 1984)
β-Sitosterol -3-*O*-*β*-D-glucopyranose	*B. ciliaris* (aerial parts)	(El-Shanawany et al., 2014)
Stigmasterol	*B. ciliaris* (aerial parts)	(El-Shanawany et al., 2014)
Stigmasterol-3-*O*-*β*-D-glucopyranose	*B. ciliaris* (aerial parts)	(El-Shanawany et al., 2014)
Stigmasterol tetracosanoate	*B. ciliaris* (aerial parts)	(El-Shanawany et al., 2014)
9-Hydroxydodecanoic acid	*B. scindica* (seeds)	(Ahmad et al., 1983)

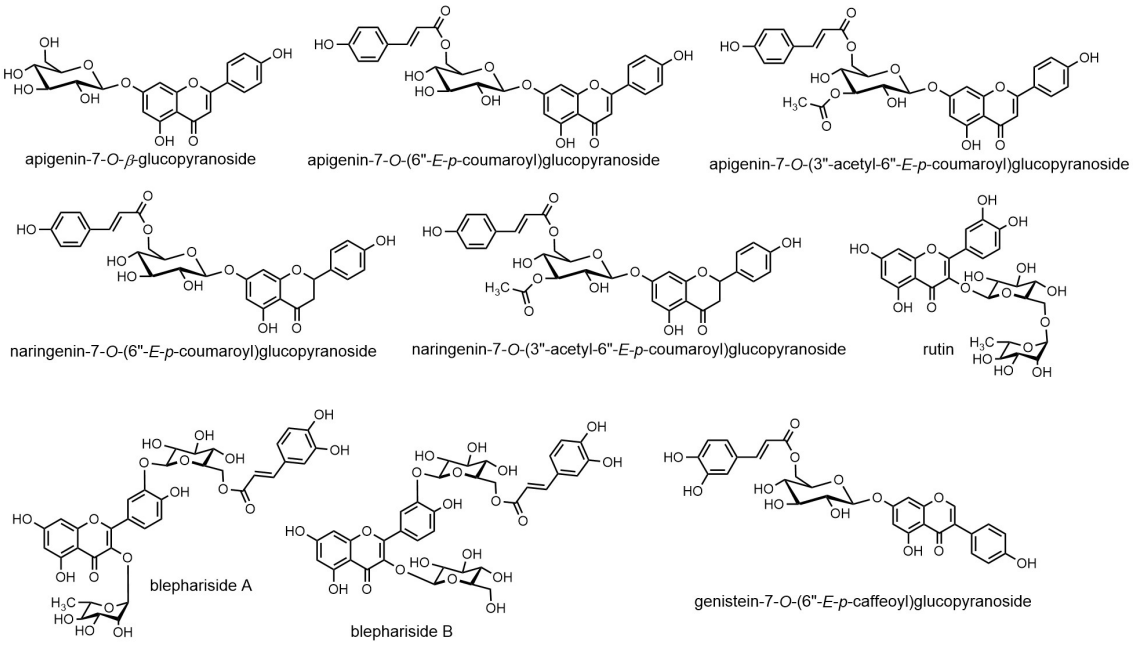

Figure 1. Structures of flavonoid derivatives from *Blepharis* species.

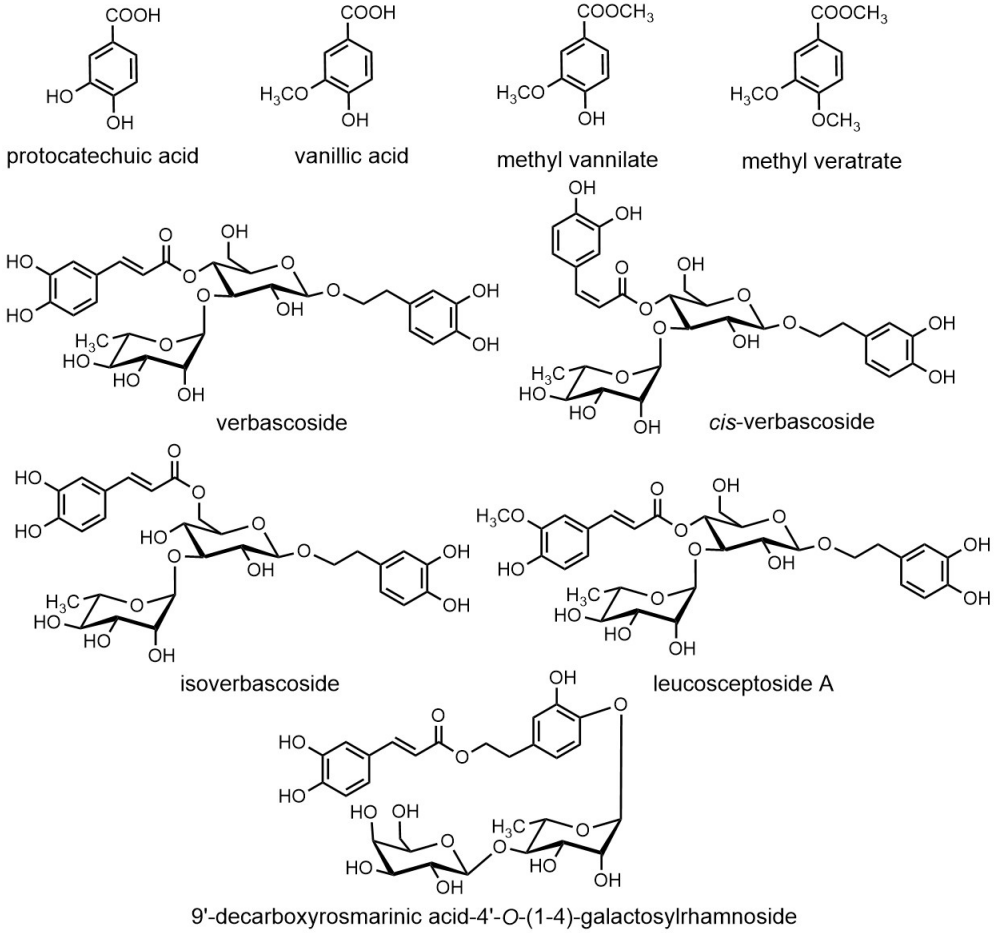

Figure 2. Structures of phenolic acid derivatives from *Blepharis* species.

Few alkaloids including derivatives of hydroxamic acids have been also identified in some *Blepharis* species (Figure 3). The bitter glucoside blepharin was first isolated from the *B. edulis* (Lal, 1936) and its structure was later confirmed as blepharin i.e. *N*-deoxy-2,4-dihydroxy-1,4-benzoxazin-3-one glucoside (N-deoxyDIBOA) (Chatterjee et al., 1990; Pratt et al., 1995). Blepharigenin (N-deoxy-DIBOA) and blepharin were reported from *B. scindica* (Ahmad et al., 1984) and 2-benzoxazolinone (BOA) has been isolated from the roots of *B. edulis* (Chatterjee et al., 1990). Allantoin and betaine hydrochloride were isolated from *B. scindica* (Ahmad et al., 1984).

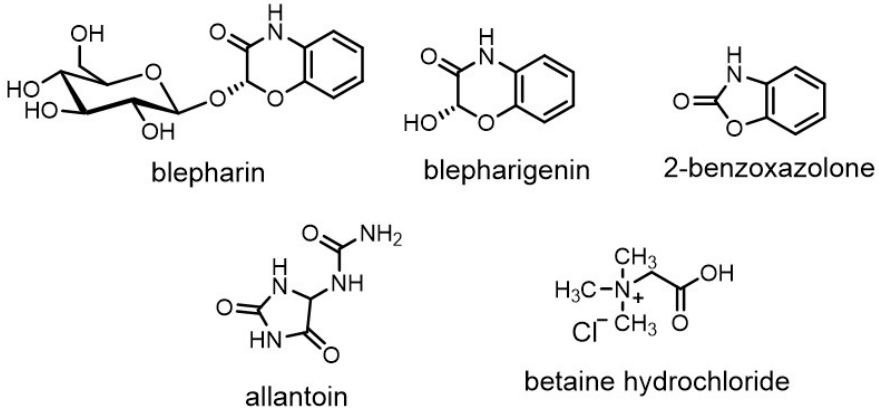

Figure 3. Structures of alkaloids isolated from *Blepharis* species.

There are also reports on isolation and identification of steroids, fatty acids and volatile compounds. El-Shanawany et al. (2014) identified a new stigmasterol tetracosanoate from the aerial parts of *B. ciliaris*. The study also reported stigmasterol and stigmasterol-3-*O*-β-$_{D}$-glucopyranose for the first time in *B. ciliaris*. The GC-MS analysis revealed the presence of 45 fatty acids, 53 hydrocarbons, and 24 sterols. The major fatty acids identified were methyl hexadecanoate (29.8%), methyl octadecanoate (14.6 %), docosanoic acid methyl ester (3.9%), methyl 8 octadecenoate (3.6%), and methyl eicosanoate (3.5%). A novel acid, 9-hydroxydodecanoic acid was reported from *B. scindica* seed oil (Ahmad et al., 1983).

Apart from detailed chemical analysis to isolate and identify compounds from the extracts of *Blepharis* species, my studies have also reported the preliminary phytochemical screening and determination of total phenolic conetents (TPC) and total flavonoid contents (TFC) of *Blepharis*

species such as *B. edulis* (Mahboubi et al., 2013; Osama et al., 2017; Saqib et al., 2012; Surveswaran et al., 2007), *B. linariifolia* (Dirar et al., 2019b; Sawadogo et al., 2006), *B. maderaspatensis* (Devarajan et al., 2015; Ijinu et al., 2016; Mohan et al., 2010; Mohankumar et al., 2017; Rajasekaran et al., 2012a; Sowemimo et al., 2013), *B. molluginifolia* (Pattar et al., 2011; Shankar and Thiripura Salini, 2014) and *B. scindica* (Mathur, 2012).

6. Pharmacological activities

Species of the genus *Blepharis* have perceived the attention of researchers for their various uses in different traditional medicine systems. Therefore, several studied have been conducted to investigate its pharmacological activities based different biological models. Most of these studies performed mainly for *B. maderaspatensis* and *B. ciliaris* along with few studies for *B. linariifolia* and *B. scindica.* Most of these pharmacological studies were performed using *in vitro* systems with very few on *in vivo* models. Most of these pharmacological activity evaluations were random screening rather than based on ethnopharmacological uses, thus they did not provide any correlation between the traditional uses and pharmacological activities. Some of these studies are discussed in detail in sections below.

6.1. Antimicrobial activity

The antimicrobial activity, comprising antibacterial, antifungal and antiviral potentials had been reported for *Blepharis* in several studies. Mothana et al. (2009) investigated the antibacterial activity of *Blepharis spiculifolia* collected from Yemen against three Gram-positive strains namely, *Staphylococcus aureus* (ATCC 6538), *Bacillus subtilis* (ATCC 6059), *Mariniluteicoccus flavus* (SBUG 16), and two Gram-negative strains namely, *Escherichia coli* (ATCC 11229), *Pseudomonas aeruginosa* (ATCC 27853) and one fungal strain *C. maltosa* (SBUG 700). In addition to the aforementioned bacterial strains, the plants extracts had been investigated against additional three multi-resistant *Staphylococcus* strains namely, *S. epidermidis* 847, *S. haemolyticus* 535, and *S. aureus* North German Epidemic Strain. Both positive and negative controls were used (Ampicillin, Gentamicin and Amphotericin B were used as the positive control, negative controls were performed with paper discs loaded with 20 μl of methanol and 5% ethanol solvents). The study reported that only the methanolic extract had shown promising antimicrobial activity

(inhibition zones of *B. spiculifolia* MeOH extract were 12 mm for *S. aureus*, 10 mm for S. *epidermidis* and 16 mm for the resistance *S. aureus* strain).

Mahboubi et al. (2013) evaluated the antibacterial and antifungal activities of the different extracts of *B. edulis* aerial parts. The bacterial species were *S. aureus* (ATCC 25923), *Enterococcus faecalis* (ATCC 29212), *Staphylococcus epidermidis* (ATCC 14490), *Enterococcus faecium* (ATCC 25778), *Streptococcus agalactiae*, *Bacillus cereus* (ATCC 1247), *B. subtilis* (ATCC6051), *Streptococcus pyogenes* (ATCC 8668), *Staphylococcus saprophyticus* (ATCC 15305), *Klebsiella pneumoniae* (ATCC 1053), *E. coli* (ATCC 8739), *Salmonella typhimurium* (ATCC 14028), *Shigella dysenteraie* (PTCC1188), *Proteus vulgaris* (ATCC1079), *Streptococcus sanguinis* (ATCC 10556), *S. salivarius* (ATCC 9222), *Enterobacter aerogenes* (NCTC 10009) and *Pseudomonas aeruginosa* ATCC 9027. The fungal strains were *Candida albicans* (ATCC 10231), *Aspergillus flavus*, *A. niger* (ATCC 16404) and *A. parasiticus* (ATCC 15517). The study reported that the most sensitive microorganisms were *Candida albicans*, *B. cereus*, *B. subtilis*, *S. pyogenes* and *S. dysenteriae* to the aqueous alcoholic extracts with the means of 10.3-13.3 mg/ml

Devarajan et al. (2015) reported the antibacterial activity for the different extracts of leaves of *B. maderaspatensis* The inhibitory of different extracts have been investigated against four fungal pathogens (*C. albicans, C. neoformans, Mucor racemosus,* and *A. niger*) and many bacterial pathogen strains including; *B. subtilis* (MTCC 441), *Streptococcus pneumoniae* (MTCC 655), *Staphylococcus epidermidis* (MTCC 435), *K. pneumoniae* (MTCC 109), *S. typhimurium* (MTCC 98), *E. coli* (MTCC 739), *Shigella flexneri* (MTCC 1457), *P. aeruginosa* (MTCC 741), and *P. vulgaris* (MTCC 426). The study reported that the ethyl acetate extract showed highest inhibitory activity (20 mm) against *E. coli* followed by *S. pneumoniae* (14 mm). The acetone extract exhibited promising inhibitory activity against *E. coli* (18 mm) followed by *Vibrio vulnificus* (14 mm). The methanol extract showed moderate activity against most of the tested pathogens with maximum growth inhibition on *E. coli* (17 mm) followed by *V. vulnificus* (14 mm).

6.2. Activities related to gastrointestinal disorders

Many studies reported the gastric antisecretory, gastroprotective activities and spasmolytic effect of *Blepharis*. In this context, a previous study reported the anti-secretary and gastro-protective

effects of *B. maderaspatensis* on healthy Wistar albino male rats weighing about 150–250 g (Rajasekaran et al., 2012b). The study reported that the ethanol extract increased the mucus secretion and adherent mucus in the tissues with a 71.43% reduction of ulcer in HCl-ethanol induced ulcer models, at a dose of 200 mg/kg.

As for the gastro-protective effect, the study revealed that rats treated with ethanol extract showed a dose related protection. The chloroform extract was less active with only 13.39% protection in the dose level of 100 mg/kg (Rajasekaran et al., 2012b). Another study reported the spasmolytic effect of the 80% ethanol extract of *B. edulis* on isolated rabbit jejunum and the study also uncovered the mechanism of this effect. The extract showed a dose-dependent reversible antispasmodic effect at the dose range of 0.01to 3.0 mg/ml with EC_{50} of 0.61mg/ml like that of the standard drug Verapamil which showed EC_{50} of 0.35 μM (at a dose range of 0.03-1.0 μM). The study also reported that the spasmolytic effect was mediated through Ca^{2+}channel blockade (Saqib et al., 2012).

6.3. Anticancer activity

Baskar et al. (2012) investigated the anticancer activity of hexane, ethyl acetate and methanol extracts of leaves of *B. maderaspatensis* in human breast cancer cell line (MCF-7 cells), human stomach cancer cells (AGS), human lung cancer cells (A549). Extracts showed antiproliferative activities in a concentration- and time-dependent manner. Ethyl acetate and methanol extracts showed cytotoxic effects on all tested cancer cell lines at 24, 48, 72 hr. time intervals. Hexane extract was not cytotoxic towards the tested cell lines up to to the maximum tested concentration of 200 μg/ml.

6.4. Anti-inflammatory activity

Many studies reported the anti-inflammatory properties of *Blepharis* using different models. Sowemimo et al. (2013) assessed the *in vivo* anti-inflammatory activity of *B. maderaspatensis* using Wistar male rats and Swiss albino mice. The study reported that the ethanolic extract of the leaves showed promising inhibition of paw edema by 84.5% at a dose of 75 mg/kg using the carrageenan-induced paw edema model. For the histamine-induced test, the ethanol extract showed

an inhibition of 90.9%. Moderate anti-inflammatory activities were reported using the xylene-induced assay (62.65%) and the Serotonin-induced test (54.10%) (Sowemimo et al., 2013).

Similarly, the *in vivo* anti-inflammatory activity of different extracts and fractions of *B. ciliaris* has been reported by El-Shanawany et al. (2014). The study revealed that the chloroform fraction showed potential anti-inflammatory activity. Another study reported the *in vitro* anti-inflammatory activity for *B. maderaspatensis* water extract. The assay was conducted using human red blood cell (HRBC) membrane stabilization method. Water extract and the extracts containing silver nano-particles revealed a potential membrane stabilization effects (Parveen and Prabakar, 2016). Similarly, Mohamed et al. (2015) reported the anti-inflammatory activities for the compounds bephariside A and blephariside B isolated from *B. ciliaris*. The study reported that both compounds showed good anti-inflammatory activity at a dose of 10 mg/kg using the carrageenan induced paw edema.

6.5. Wound healing activity

Rajasekaran et al. (2012) had investigated the *in vivo* wound healing property for *B. maderaspatensis* on healthy Wistar albino rats of either sex and of approximately the same age, weighing about 150-250 g by excision and incision wound healing models. The ethanol extract and fractions were found to improve the different phases of wound repair, including collagen synthesis and maturation, wound contraction and epithelialization, in which promising wound healing activity was observed for the creams prepared with 5% ethanol fraction of *B. maderaspatensis*.

6.6. Anti-platelet activity

The anti-platelet activity of *B. edulis* aqueous ethanolic extract was reported on human platelet-rich plasma against epinephrine and ADP induced aggregation. The inhibitory effect of 80% EtOH extract on epinephrine-induced aggregation was 0.49 mg/ml (at doses of 0.125-1.0 mg/ml) and 0.74 mg/ml for ADP-induced aggregation (at a dose range 0.5-1.5 mg/ml). The anti-platelet activity may be attributed to the calcium channel blocking effect (Saqib et al., 2012).

6.7. Antihyperlipidemic activity

Rajasekaran et al. (2013) evaluated the antihyperlipidemic activities of whole plant of *B. maderaspatensis* in healthy Wistar albino male rats. Among the tested extracts, ethanol extract potentially reduced the serum total cholesterol, triglycerides, low-density lipoproteins (LDL), VLDL, AI and CRI as comparable with the standard Simvastatin. Recently, Dirar et al. (2019b) had reported the effect of different extraction solvents of *B. linariifolia* on lipase inhibitory activity. The study reported that the dichloromethane extract showed inhibitory effect (IC_{50}= 1.20 ± 0.08 μg/ml). Four phenolic compounds were isolated from *B. linariifolia* acetone extract and among them, 6″-*O*-*p*-coumaroylprunin (IC_{50}= 2.25 μM) was the most active followed by apigenin (IC_{50}= 12.46 μM) (Dirar et al., 2019a).

6.8. Antidiabetic activity

El-Shanawany et al. (2014) reported the *in vivo* glucose lowering effect of the aerial parts of *B. ciliaris* in adult albino rats. The 70% methanol extracts and fractions showed mild anti-hyperglycemic activity. Dirar et al. (2019b) reported the *in vitro* α-glucosidase inhibitory activity of different extracts of *B. linariifolia*. Among the tested extracts, polar extracts such as 50% ethanol (EtOH), 70% EtOH, and 95% EtOH showed potent α-glucosidase inhibitory activity. Evaluation of similar activity of isolated compounds from the extract revealed that apigenin was the most potent (IC_{50}= 34.73 μM) α-glucosidase inhibitor followed by 6″-*O*-*p*-coumaroylprunin (IC_{50}= 46.30 μM) (Dirar et al., 2019a).

6.9. Other activities

Mohamed et al. (2015) reported the *in vivo* hepatoprotective effect of methanolic extract of *B. ciliaris* against carbon tetrachloride (CCl_4)-induced hepatotoxicity in rats. Methanol extract and the fractions restored the hepatic marker enzymes and total bilirubin to near normal values compared to the standard drug silymarin. A recent study evaluated the effect of different extraction solvents of *B. linariifolia* on the mushroom tyrosinase inhibitory activity, where polar extracts showed potent activity (Dirar et al. 2019b)**.** Further isolation of phenolic compounds and activity analysis revealted that apigenin was the most potent inhibitor (IC_{50}= 23.14 ± 1.83 μM) (Dirar et al., 2019a). Sowemimo et al. (2013) evaluated the antinoceiceptive activity of the ethanol extracts of leaves of *B. maderaspatensis* on male Wistar rats (100-200 g) and Swiss albino mice (20-30 g). In the mouse writhing and tail clip tests, the extract produced a potent inhibition of 66.21% and

15.81% at 75 mg/kg, respectively. El-Shanawany et al. (2014) reported the antimalarial activity of the 70% MeOH of aerial parts of *B. ciliaris* and four fractions against the chloroquine sensitive *Plasmodium falciparum* using parasite lactate dehydrogenase assay. Saqib et al. (2012) evaluated the *in vitro* bronchodilatory activity of 80% ethanol extract of whole plants of *B. edulis* on rabbit tracheal preparations. Plant extract exerted inhibitory effect on high K^+ (80 mM) -induced contractions at 0.03-1.0 mg/ml with EC_{50} value of 0.33mg/ml. Inhibition of carbachol (1μM)-induced contraction at higher dose range 0.01-3 mg/ml with EC_{50} value of 0.47 mg/ml. Bronchodilator effect mediated possibly through calcium channel blocking.

7. Studies related to toxicity evaluations

The concern about the safety of medicinal plants has become a global approach pertained to the notable increased consumption of medicinal plants (Zhang et al., 2015). In this context, Rajasekaran et al. (2012b) performed an acute toxicity study for *B. maderaspatensis* ethanolic and chloroform extracts to ascertain the safe dose by an acute oral toxic class method. The study reported that no death up to 14 days of study period upon the administration of single doses (250, 500, and 2000 mg/kg) of extracts. Even at the highest dose (2000 mg/kg), there were no physical signs of toxicity as evidenced by normal breathing and the absence of tremors, convulsions, diarrhea, salivation, and paralysis in the treated animals. These observations reveal that the oral LD_{50} values are greater than 2000 mg/kg in rats. Sowemimo et al. (2013) evaluated the oral toxicity of ethanol extract of leaves of *B. maderaspatensis* on a group of six healthy male mice. The control group only received the vehicle (10 ml/kg, p.o.). With a single oral dose of the extract (5 g/kg), no signs of toxicity or changes in behavior and mortality were observed during the time of observation (24 hr. and up to seven days). No mortality was recorded.

8. Pharmaceutical formulations

Some species of the genus *Blepharis* had shown promising pharmacological properties and developed or under the development into pharmaceutical products in India. Recently, an invention aimed to develop a pharmaceutical formulation from the seeds of *B. persica* as a hepato-protective agent is underway (Gagandeep et al., 2018). Similarly, a capsule formulation of various herbs including *B. edulis* was evaluated to assess the synergistic adaptogenic activity (Rathva et al., 2017). In India, a topical formulation in the form of cream was developed for wound healing

activity using the extract of leaves of *B. maderaspatensis* (Rajasekaran et al., 2012a)**.** New and improved excipients continue to be developed to meet the needs of conventional drug delivery system and to meet the needs of advanced tablet manufacturing. Herein, a previous study was undertaken to extract mucilage from the seeds of *B. edulis* and explored its use as a tablet disintegrate. The study revealed that the dried mucilage can be used as a disintegrate in conventional tablets and could be alternate to starch (Shah and Jani, 2012).

9. Conclusions and future prospects

Among total 126 species of *Blepharis*, 7 species were found to be used ethnomedicinally in African and Asian countries and *B. maderaspatensis* was found to be the most reported species for traditional medicinal uses. Few species such as *B. ciliaris*, *B. edulis*, *B. maderaspatensis* and *B. scindica* were investigated for their chemical constituents and several compounds including flavonoids, phenolic acid derivatives, steroids and alkaloids were isolated and identified. However, none of these studies focused on the detailed bioactivity guided isolation. Similarly, various pharmacological studies were performed mainly for *B. maderaspatensis* and *B. ciliaris* along with few studies for *B. linariifolia* and *B. scindica.* Most of these pharmacological studies were performed using *in vitro* systems with very few on *in vivo* models. Most of these pharmacological activity evaluations were random screening rather than based on ethnopharmacological uses, thus they did not provide any correlation between the traditional uses and pharmacological activities. Similarly, studies focused on the exploration of the mechanism of action were rare. Many studies were also focused on simple in vitro antioxidant assays such as 1,1-diphenyl-2-picrylhydrazyl (DPPH) assays, which are of no therapeutic relevance in animals or humans (Heinrich et al., 2020). Such studies are not covered in this review. Future studies should focus on these aspects related to the medicinally used species of *Blepharis.* The detailed and comprehensive comparative analysis presented here would give valuable information of the currently used *Blepharis* species and pave the way to investigate other useful species of *Blepharis* pertaining to ethnobotany, phytochemistry and discovery of new drugs.

Conflict of Interest

The authors declare no conflict of interest.

Author contribution

A.I.D., A.A.-D., R.M.K., K.R.P. and H.P.D. wrote the initial versions of the manuscript. R.M.K., T.B., G.G., D.K.C., P.M.H., K.D. and H.P.D. revised the manuscript. All authors read and approved the final version of manuscript.

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