

# **CHAPTER 2**

# **LITERATURE REVIEW**



## **2. Literature review**

### **2.1 Pathophysiology of hemorrhoids**

Although the exact pathophysiology of hemorrhoids remains unknown, it is considered that hemorrhoids primarily result from abnormally congested and descended anal cushions. It was assumed that hemorrhoids were a variety of anorectal varices. However, there is clear evidence that hemorrhoids and anorectal varices are distinct entities. In fact, patients with portal hypertension and varices do not have a higher incidence of hemorrhoids than normal individuals. Three theories had been proposed to understand the development of hemorrhoids [51]. The first theory proposed in early age was “The Varicose Vein Theory” which stated that piles are the result of dilation and distortion of varicose veins due to excessive straining of the anal canal. In the nineteenth century “The Vascular Hyperplasia Theory” became more popular with this belief that piles might result from hyperplasia of the ‘corpus cavernosum recti.’ Later the theory of, “Sliding Anal Canal Lining” has become most popular and widely accepted which states that hemorrhoids develop due to disintegration or deterioration of the supporting tissues of the anal cushions. There are three major anal cushions, located in the right anterior, right posterior and left lateral aspect of the anal cushions with several other minor cushions lying between them [51]. In addition to the above, a severe inflammatory reaction in hemorrhoidal specimens involving the vascular wall and surrounding connective tissue has been described, with associated mucosal ulceration, ischemia, and thrombosis [4]. The concepts of hemorrhoid formation could be categorized into four groups: sliding anal cushions (loss of fixation network), vascular abnormality, rectal redundancy, and an increased pressure on anorectal vascular plexus (Fig. 4) [1].

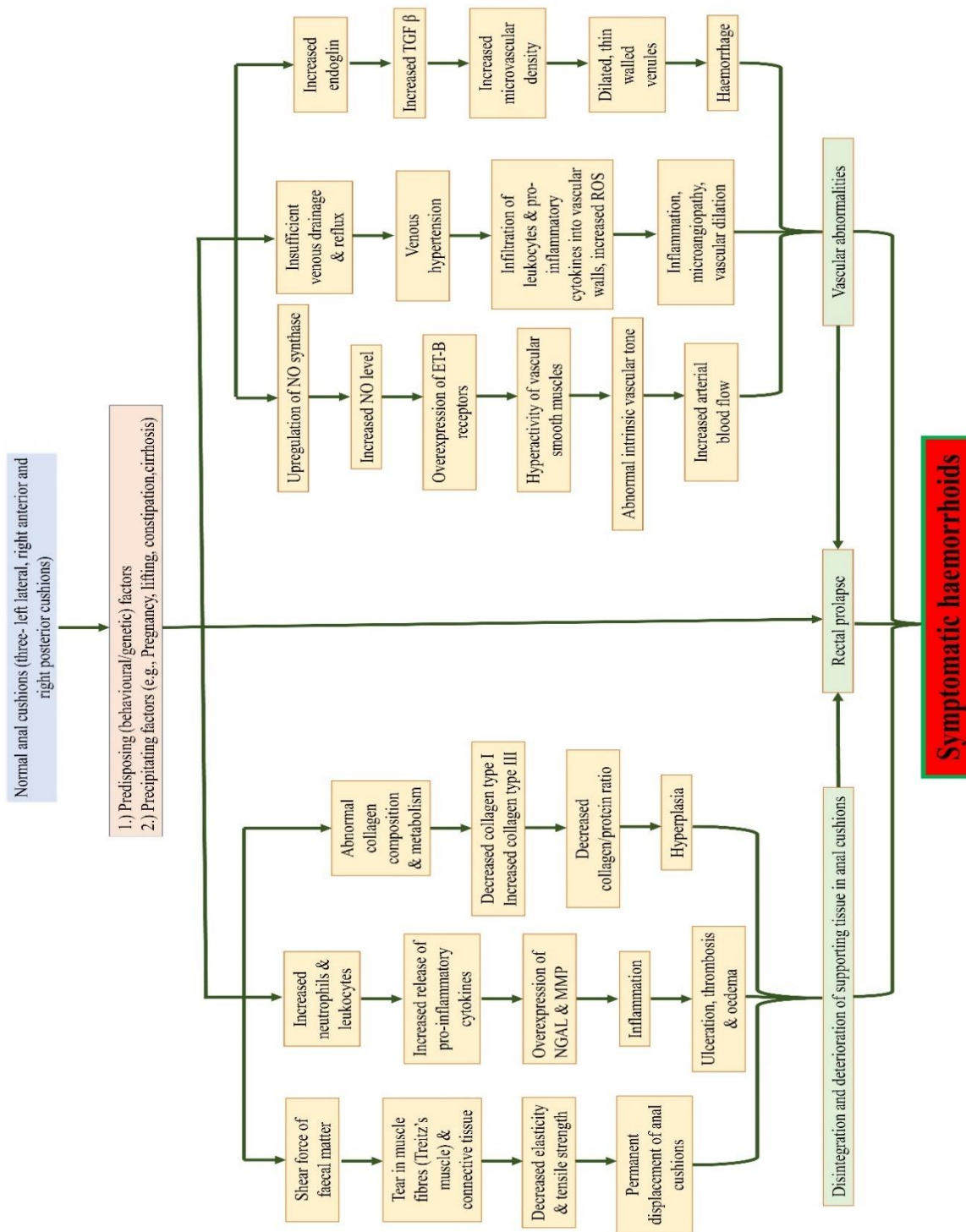


Figure 2.1: Pathophysiology of Haemorrhoids

### **2.3 Classification of hemorrhoids:**

Hemorrhoids are mainly classified based on their origin within the anal canal and their relative position to the dentate line. External hemorrhoids are dilated venules of venous plexus located below the dentate line and are covered with squamous epithelium while Internal hemorrhoids originate from the inferior hemorrhoidal venous plexus above the dentate line and are covered by mucosa. Mixed (internal-external) hemorrhoids arise both above and below the dentate line. Practically, internal hemorrhoids are graded depending upon their appearance and degree of prolapse, known as Goligher's classification:

1. First-degree hemorrhoids (grade I): Bleeding occurs through anal cushions, but they do not prolapse.
2. Second-degree hemorrhoids (grade II): The anal cushions prolapse through the anus on straining but reduce spontaneously.
3. Third-degree hemorrhoids (grade III): On straining or exertion, the anal cushions prolapse through the anus and require manual replacement into the anal canal.
4. Fourth-degree hemorrhoids (grade IV): The irreducible prolapse stays out at all times. Thrombosed hemorrhoids involving circumferential rectal mucosal prolapse are also fourth-degree hemorrhoids [52].

### **2.4 Prevalance of hemorrhoids:**

The precise prevalence of haemorrhoids is unknown because the majority of individuals are asymptomatic and do not visit a doctor for care. Of all colorectal investigations, 50% is diagnosed as haemorrhoids. As per a report, haemorrhoids were prevalent (39%) in patients with colorectal cancer undergoing routine assessment, among which 55% were

asymptomatic. The incidence of haemorrhoids are common at any age but prevalent in individuals under 45 to 65 years of age.

Hemorrhoids affect both genders equally and if remain untreated, potential medical complications are observed which may be a symptom of more serious illness. With an estimated prevalence rate of 50-85% worldwide, 75% of the Indian population are commonly affected by haemorrhoids.<sup>2</sup> Internal hemorrhoids are a common clinical condition in women, with a prevalence of 24.8%, which increases during the child-bearing years. In fact, hemorrhoids are present in 85% of woman during the second and third trimesters of pregnancy [53] with a thrombosed hemorrhoid rate of 7.9% in the last 3 months [54].

According to statistics in the United States, more than a million people a year suffer from hemorrhoids, about 4.4 % of the American population with a peak between 45 and 65 years old and a decline after age 65. Moreover, hemorrhoids were uncommon in patients under 20 years old. Furthermore, 50 % of adults who are over the age of 50 have experienced the symptoms of hemorrhoids.

In a digestive disease supplement to the National Health Interview Survey, participants were asked if a doctor had ever diagnosed them with hemorrhoids. The survey data were extrapolated to the US population. An estimated 23 million adults (13% US population) were diagnosed with hemorrhoids in the prior year. An estimated 36 million adults (20% US population) were ever diagnosed with hemorrhoids. Women were more likely to report hemorrhoids than men (24% vs 16%). Overall, 21% (7.7 million) reported having had surgery for their hemorrhoids.

In 2004, there were 306,000 hospital discharges for hemorrhoids. Demand for hemorrhoid therapy has been predicted to increase 23% over the next twenty years. Data from the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey from 2010 show that hemorrhoids were the third most common outpatient gastrointestinal diagnosis with nearly 4 million office and emergency department visits annually. Visits for hemorrhoids were more frequent than for colon cancer, diverticular disease, irritable bowel syndrome or inflammatory bowel disease [55].

### 2.5 Management of hemorrhoids:

The main strategies for the management of hemorrhoids include several surgical and non-surgical procedures which are represented in **Table 2.1**.

**Table 2. 1-** Currently available treatment for hemorrhoids

Treatments	Grade I	Grade II	Grade III	Grade IV	Acute thrombosis or strangulation
<b>Dietary and lifestyle modification</b>	+	+	+	+	+
<b>Medical treatment</b>	+	+	+(selected)		
<b>Non-operative treatment</b>	+	+			
Sclerotherapy	+	+			
Infrared coagulation	+	+			
Radiofrequency ablation	+	+	+(selected)		
Rubber band ligation					
<b>Operative treatment</b>					
Plication		+	+		
DGHAL		+	+		
Hemorrhoidectomy		+(selected)	+	+	+(emergency)
Stapled hemorrhoidopexy			+	+	

DGHAL: Doppler-guided hemorrhoidal artery ligation; +: Applicable.

### **2.6 Medical treatment:**

Therapeutic management of hemorrhoids ranges from dietary and lifestyle modifications to radical surgery, depending on their grade. Conservative approaches are recommended initially for patients with low-grade disease. Such approaches are also preferred for most patients who are pregnant, debilitated, or immunocompromised, patients with coagulation disorders and patients with Crohn's disease or conditions that confer a predisposition to poor healing. In particular low-grade internal hemorrhoids and non-thrombosed external hemorrhoids (grade I hemorrhoids) can be effectively treated with dietary and lifestyle modifications [1]. Furthermore, there are several modern and traditional medications used which are available in a variety of formats including tablets, suppositories, creams, and wipes. The main goal of medical treatment is to control acute symptoms of hemorrhoids. Oral therapy is based on flavonoids, mesoglycan, and calcium dobesilate. Local therapy is based on corticosteroids, analgesics, vasoconstrictors, and barrier creams composed of several active ingredients such as sodium hyaluronate and *Aloe vera* [1].

**Table 2. 2-** Medical treatment available currently for treating haemorrhoids

Medication	Treatment duration	Therapeutic effect	Side effects or notes
<b>Oral pharmacological therapy</b>			
Daflon 500 (90% diosmin 10% hesperidin)	At least 12 weeks	Decrease risk of bleeding, persistent pain and itching; reduced recurrence rate	None reported
Mesoglycan	Symptomatic treatment	Manage phlebitis and deep venous thrombosis	None reported
Calcium dobesilate	3 weeks (A) Symptomatic treatment (B)	Decrease pain and itching; improve endoscopically observed inflammation	Fever, gastrointestinal disorders, skin reactions, arthralgia and agranulocytosis
<b>Oral herbal therapy</b>			
<i>Aesculus hippocastanum</i> (horse chestnut) seed extracts (HCSE)	Symptomatic treatment	Reduce capillary permeability and associated edema	None reported
<i>Ruscus aculeatus</i> (butcher's broom)		Improve venous tone and emptying	None reported
<i>Centella asiatica</i>		Improve wound healing and capillary permeability	None reported

Witch hazel ( <i>Hamamelis virginiana</i> extract)		Astringent, anti-inflammatory, and hemostatic effects	Internal use of extracts is not recommended because of the tannin content
<b>Topical pharmacological therapy</b>			
Local anesthetics			
Lidocaine	Symptomatic treatment	Provides temporary relief of acute symptoms of hemorrhoids	Less of an effect on bleeding; possible local allergic reaction, irritation, and pruritus
Pramoxine			
Dibucaine			
Chetocaina			
Antispasmodic agents			
Glyceryl Trinitrate (GTN)	2 weeks	Reduce the resting anal canal pressures; decrease rectal bleeding, anal pain, throbbing, itching, and irritation	Headache, dizziness, nausea, vomiting, and pruritus
Nifedipine	Symptomatic treatment	Symptomatic relief; relaxation effect on the internal anal sphincter	Headaches, sphincter pain, hypertension, fecal incontinence, nausea and vomiting
Vasoconstrictors			
Phenylephrine	Symptomatic treatment	Provides temporary relief of acute symptoms of hemorrhoids, such as	Influences tone of the internal anal sphincter

		bleeding and pain on defecation	
<b>Anti-inflammatory agents</b>			
Hydrocortisone acetate	Symptomatic treatment	Provides temporary relief of acute symptoms of hemorrhoids	Local allergic reaction and potential chronic perianal dermatitis due to long-term use
5-aminosalicylic acid (5-ASA)		Reduces intensity of pain, bleeding, and tenesmus; decreases congestion of the hemorrhoidal venous plexus	Fewer side effect than topical corticosteroids
<b>Topical herbal therapy</b>			
Aloe vera	Symptomatic treatment	Reduces pain, swelling, and itching of burns; Reduces healing time after hemorrhoidectomy	None reported
<i>Aesculus hippocastanum</i> seed extracts (HCSE)		Lacks clinical evidence	Reduce capillary permeability and associated edema

## 2.7 Plant profile



**Figure 2. 2:** Young and mature plant of *Blumea lacera* (Burm.f.) DC showing leaf, stem and flower buds.

*Blumea lacera* (Burm.f.) DC. is an annual herb with a strong odor, distributed throughout the plains of northwest India, up to an altitude of 2,000 m. A herbaceous plant, tomentose, capitula in axillary and terminal dense to lax panicles, achene, ribbed, pappus whitish, camphor-like odor, highly variable, in grassland, field, roadside and forest edge. The stems of this hairy or glandular herb are erect, simple or branched, very leafy and 1-2 ft in height. The leaves are obovate or oblanceolate, 5-12 cm long, 2-6 cm wide, smaller toward the top, stalked, and toothed or (rarely) lobulated at the margins, leaves are eaten as a vegetable. The bright yellow flowering heads are about 8 mm across, borne on short axillary cymes, and collected in the terminal, spike-like panicles. The involucre-bracts are narrow and hairy. The achenes are not ribbed, are somewhat 4-angled, and are smooth.

### 2.7.1 Distribution

Tropical Africa, South East Asia, throughout the plains of India, ascending to 700 m, Bangladesh, Nepal, Indonesia, Malaysia, Philippines, Thailand, Vietnam.

**2.7.2 Classification\***

Kingdom: Plantae – Plants, Planta, Vegetal, plants

Subkingdom: Viridiplantae

Division: Tracheophyta – vascular plants, tracheophytes

Class: Magnoliopsida

Order: Asterales

Family: Asteraceae – sunflowers, tournedos

Genus: *Blumea* DC. – false oxtongue

Species: *lacera* (Burm. f.) DC. – blumea

[\*Retrieved [12/ 7/2018], from the Integrated Taxonomic Information System on-line database, <http://www.itis.gov>.].

**2.7.3 Classical & Common names**

Ayurvedic: Kukundara, Kukkuradru, Tamrachuda, Mriducchada; Kukrondaa. Unani: Kakrondhaa. Siddha: Narakkarandai.

Hindi: Jangli Muli, Kakronda, Marathi: Bhamurda, Burando, Tamil: Kattumullangi, Narakkarandai, Telugu: Advimulangi, Karupogaku, Bengali: Kukurmuta, Kukursunga, Gujarati: Pilo Kapurio.

**2.7.4 Synonyms**

*Blumea bodinieri* Vaniot; *Blumea chevalieri* Gagnep.; *Blumea glandulosa* Benth. & DC & Thwaites; *Blumea glutinosa* DC.; *Blumea lacera* (Roxb.) DC.; *Blumea lacera* var. *cinerascens* Hook. f.; *Blumea lacera* var. *glandulosa* Hook. f.; *Blumea mollis* (D. Don) Merr.; *Blumea musra* DC.; *Blumea runcinata* DC.

**2.7.5 Traditional uses reported for *Blumea lacera* (Burm. f.) Dc**

According to Bhaavaprakaasha, the herb can cure fever, bronchial infections, vitiated blood. Traditionally, it is used internally and externally as a styptic and anti-inflammatory agent. The juice of leaves is mixed with black pepper (*Piper nigrum*) & given to cure bleeding piles. This herb is also given as anthelmintic, particularly for threadworm. Leaves and roots are used as astringent, diuretic and febrifuge. Bruises and ulcers can also be treated by applying Fresh juice or extract.

**Table 2. 3-** Reported ethnomedicinal uses of *Blumea lacera* (Burm. f.) Dc

S. No.	Ethnomedicinal uses	Parts used	Region/Trib e	Method of use	References
1.	Diuretic/edema, GI disorders, respiratory tract infection, insect repellent	-	Bagerhat & Rampal, Bangladesh	-	[37]
2.	Insecticide	Leaves	Vasubihar village, Bangladesh	Dried leaves are spread around rooms	[56]
3.	Cuts & bleeding wounds	Leaves	Thane, Maharashtra, India	Juice from squeezed leaves	[33]
4.	Bruises of toe, cuts & wounds	Leaves	Gorakhpur, U.P. India	Leaf juice (externally)	[35]

5.	<b>Piles</b>	Leaves	Bhoxas tribes, U.P. India	Fresh ground leaves with black pepper	[57]
6.	Antihelminthic, febrifuge, diuretic, antiscorbutic, antimicrobial	-	Western Ghats, India	-	[58]
7.	fever	Root	Myagdi district, Nepal	Juice of root	[34]
8.	i) <b>Piles</b> & cholera ii) Mouth diseases	Root Leaves	Trayambakeshwar hill, Nashik, Maharashtra, India	-	[59]
9.	Filariasis	Leaves	Musohor tribe, Birganj, Bangladesh	Burned ash of wasp's nest, hornet's nest & <i>bambusa glaucescens</i> with juice of leaves	[60]
10.	Indigestion	Leaves	North Bengal plain region, India	-	[61]
11.	Bleeding <b>piles</b>	-	Chandigarh region, India	-	[42]

12.	Cuts, antimicrobial	Leaves	Bihar, India	-	[62]
13.	Cuts	Leaves	Bantar tribe, Nepal	-	[63]
14.	Bronchitis, bleeding <b>piles</b> , burning sensation	Leaves	Bhilada tribe, Maharashtrast ra, India	Extract given orally	[41]
15.	Diarrhoea	Root	Tribals of Bargarh district, Orissa, India	Root paste with honey three times a day	[38]
16.	Dog bite	Root	Minority group of Christians, Dinajpur district, Bangladesh	Crushed roots	[64]
17.	i) Blood purifier ii) Urinary complication s	Roots Leaves	Tirunelveli distt. Tamilnadu, India	-	[65]
18.	Earache, fever, killing the worms	Leaves	Hosangabad distt. M.P. India	Leaf juice	[66]
19.	Cuts & Wounds	Leaves	All over India	-	[36]

20.	Body ache, intestinal worms, malarial fever, haemostatic, <b>piles</b> (topically), antifungal	Leaves	Chitrakoot, Satna, M.P. India	Decoction crushed leaves	[67]
21.	Body ache, intestinal worms, malarial fever, haemostatic, <b>piles</b> (topically), antifungal	Leaves	Eastern U.P. India	Decoction crushed leaves	[68]
22.	Cutaneous infection	Root	Meche people, Jhapa district, Eastern Nepal	Root paste	[69]
23.	Muscular pain	Whole plant	Jalpaiguri district, W.B. India	-	[70]
24.	Anthelmintic , febrifuge, astringent, diuretic,	Leaf, Root	Naogaon district, Bangladesh	Leaf juice mixed with black pepper & root juice	[40]

	bleeding <b>piles</b> , cholera			with black pepper	
25.	Anthelmintic , febrifuge, astringent, diuretic, bleeding <b>piles</b> , cholera	Leaf, Root	Rajshahi division, Bangladesh	Leaf juice mixed with black pepper & root juice with black pepper	[71]
26.	i) Dog bite ii) Leucorrhoea	Leaves Seed	Sahjahanpur district, U.P. India	Leaf juice with black pepper & seed powder	[72]
27.	<b>Piles</b>	-	Tribal areas of M.P. India	Dried powdered material is taken as smoke	[73]
28.	Blood dysentery in children	Root	Candaka tribals of Orissa, India	Fresh root juice with honey	[39]
29.	Fever, conjunctivitis , <b>piles</b>	Leaves	Kalinjar hillock, Banda, U.P. India	-	[74, 75]
30.	i) Cuts & Wounds ii) Febrifuge, diuretic, antiscorbutic	Leaf Whole plant	Southern district of West Bengal, India	-	[76]

**2.7.6 Chemical constituents reported in *Blumea lacera* (Burm. f.) Dc**

*Blumea lacera* (Burm. F.) Dc contains many chemical constituents such as phenolics, terpenoids, flavonoids and phytosterols. The major constituents present in this plant are represented in **Table 2.4**.

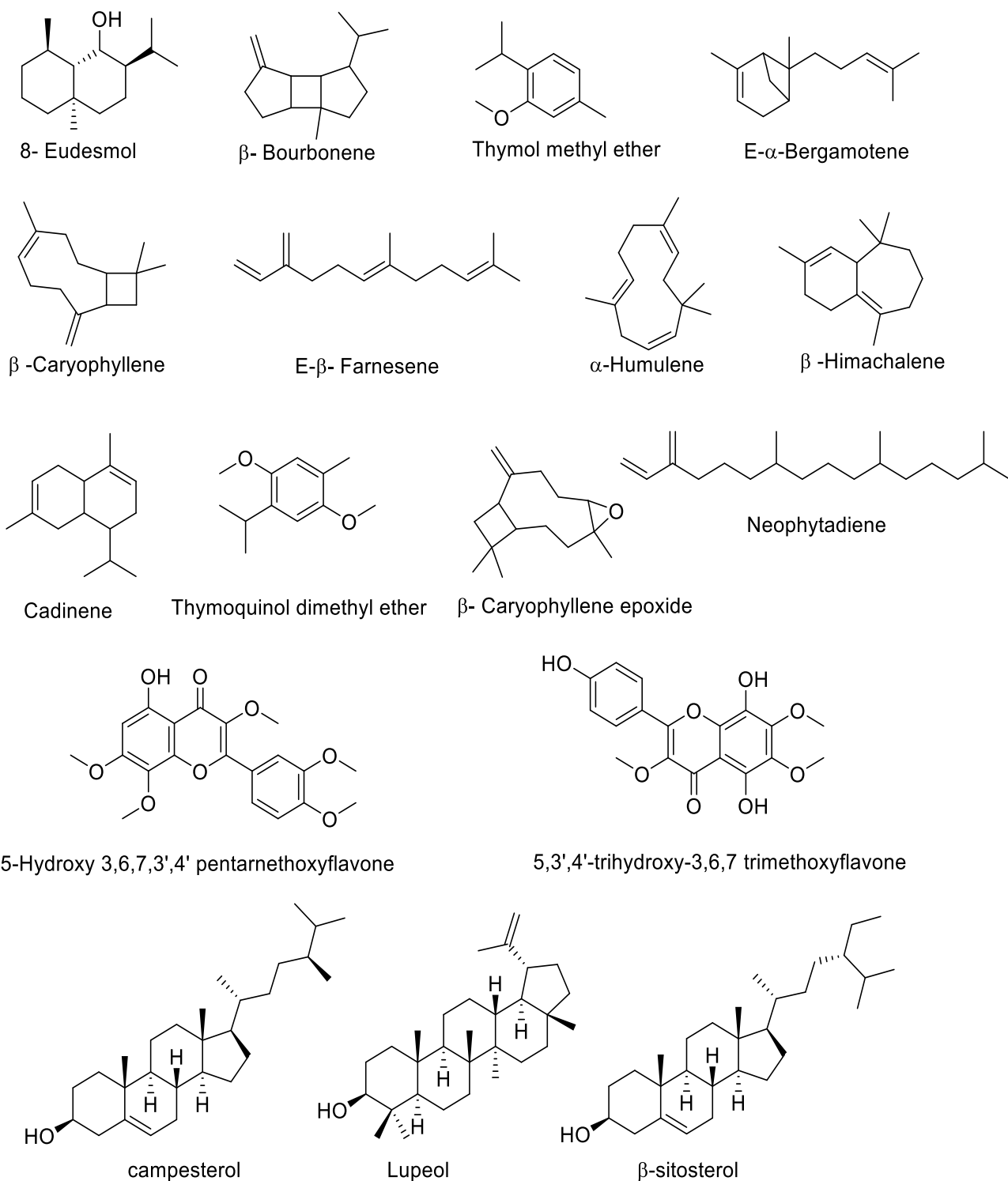
**Table 2. 4-** Reported chemical constituents from *Blumea lacera* (burm. f) DC

s. no.	Part of the plant	Chemical constituents	Reference
1.	Aerial parts	(Z)-lachnophyllum ester (25.5%), (Z)-lachnophyllic acid (17.0%), Germacrene D (11.0%), (E)-β-farnesene (10.1%), Bicyclgermacrene (5.2%), (E) -caryophyllene (4.8%), (E)-nerolidol (4.2%) (E)-lachnophyllic acid (3.3%) (E) - lachnophyllum ester (1.7%).	[77]
2.	-	4',5-Dihydroxy-3',6,7-trimethoxyflavone	[78]

		<p>3,4',5-Trihydroxy-3',6,7-trimethoxyflavone          (+)-Fenchone  <math>\alpha</math>-Pinene 7b-O-b-d-2',6'-diacetylglucopyranoside          2-Isoprenyl-5-isopropylphenol 4-O-b-d-xylopyranoside          1-(4-Angeloyloxy-3-methoxyphenyl)-3-(angeloyloxy)prop-1-ene          19a-Hydroxyurs-12-ene-24,28-dioate 3-O-b-d-xylopyranoside</p>	
3.	<p>Leaves          (GLC, GC-MS)</p>	<p>C<sub>15</sub>H<sub>24</sub>  <math>\beta</math>- Bourbonene          Thymol methyl ether          E-<math>\alpha</math>-Bergamotene  <math>\beta</math> -Caryophyllene          E-<math>\beta</math>- Farnesene <math>\alpha</math>-Humulene  <math>\beta</math> -Himachalene          Cadinene</p>	[79]

		Thymoquinol dimethyl ether (33.9%) β- Caryophyllene epoxide β- recocene I 8-Eudesmol	
4.	Aerial parts (GC, GC-MS)	β- caryophyllene (8.3%-12.0%), thymolhydroquinon- dimethylether (6.6%- 11.9%) caryophyllene oxide (11.9%-21.7%)	[80]
5.	Leaves	5-Hydroxy 3,6,7,3',4' pentamethoxyflavon e 5,3',4'-trihydroxy- 3,6,7 trimethoxyflavone	[81]
6.	Whole plant	Phytosterols, primary and secondary amides, flavonoids	[82]
7.	Leaves, inflorescence	Gneol, fenchone, coniferyl alcohol derivatives, campesterol, flavonoids lupeol, hentriacontane, hentriacontanol, alpha-amyrin, beta-	[83]

		sitosterol. Triterpenes.	
8.	Leaves	$\alpha$ -pinene-7 $\beta$ -O- $\beta$ -D- 2,6- diacetylglucopyrano side 5,4'-dihydroxy- 6,7,3'- trimethoxyflavone 3,5,4'-trihydroxy- 6,7,3'- trimethoxyflavone	[46]
9.	Whole plant (GC- MS)	Neophytadiene & Cetane	[84]
10.	Whole plant	19 $\alpha$ - hydroxyurs-12- ene-24,28-dioate 3- O- $\beta$ -D- xylopyranoside 2-isoprenyl-5- isopropylphenol 4- O-fl-D- xylopyranoside	[85]



**Figure 2. 3:** Chemical constituents reported/isolated from *Blumea lacera* Burm. F. DC.

**2.7.7 Reported pharmacological uses of *Blumea lacera* (Burm. f.) Dc**

Major pharmacological uses reported till date for *Blumea lacera* (Burm. f.) Dc have been represented in **Table 2.5**.

**Table 2. 5-** Reported pharmacological activities of *Blumea lacera* (Burm. f.) Dc

S. no.	Part of the plant	Extract	Pharmacologic al activity	Reference
1.	Whole plant	Methanol	Antidiarrheal, antimicrobial, antiatherothrom bosis, anxiolytic, membrane stabilising and $\alpha$ - amylase inhibitory activity	[86]
2.	Leaves	Methanol, ethanol, chloroform	<i>In-vivo</i> antipyretic activity, neuropharmaco logical activity, GI motility activity and acute toxicity study	[87]
3.	Leaves	Methanol	Cytotoxic activy	[88]
4.	Whole plant	n-hexane, chloroform, methanol	Antibacterial assay	[89]

5.	Whole plant	Methanol	Antidiabetic activity (alloxon induced rat model)	[90]
6.	Leaves	Distilled water	Antifungal assay	[91]
7.	Whole plant	Methanol	Antipyretic activity	[92]
8.	Leaves	Methanol	Antipyretic activity	[93]
9.	Leaves	Steam distillation	CNS activity	[93]
10.	Aerial parts	Ethanol	Enterocolitis (protective effect)	[94]
11.	Roots	Ethanol	Antidiarrheal activity	[95]
12.	-	Methanol, aqueous	Cytotoxic activity	[96]
13.	Whole aerial portion	Water & methanol	Antimicrobial study	[97]
14.	Leaves	Methanol	Hypoglycemic activity (oral glucose tolerance test)	[98]
15.	Leaves	Methanol	Antioxidant & antimicrobial activity	[99]

16.	Aerial parts	Pet. Ether	Mosquito repellent activity	[100]
17.	Whole plant	Aqueous, alcohol	Anthelmintic activity	[101]
18.	Roots	Dichloromethane	Antifungal activity	[102]