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Review Article

Management of inflammatory disorders: A brief review of selected ethnomedicinal plants

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Abstract

Medicinal plants have immense significance to treat various diseases and have great potential to discover and develop new therapies. This paper aims to summarize the *in vitro* and *in vivo* investigations conducted to evaluate the anti-inflammatory activities of selected medicinal plants of Bangladesh. The anti-inflammatory active molecules reported from those selected plants have also been highlighted. The species included in this review are *Abelmoschus esculentus* (L.) Moench, *Asparagus racemosus* Willd., *Blumea lacera* (Burm.f.) DC., *Butea monosperma* (Lam.) Taub., *Cheilocostus speciosus* (J.Koenig) C.D.Specht., *Mussaenda roxburghii* Hook. f., *Anthocephalus cadamba* (Roxb.) Miq., *Phyllanthus reticulatus* Poir., *Sesbania grandiflora* (L.) Pers. and *Spondias pinnata* (L. f.) Kurz. The toxic effect of these plants has also been included briefly. We hope that this overview will shed some light on the function of these plants and their molecules in the treatment of various inflammatory diseases and will attract the attention of investigators interested in designing novel therapeutic approaches.

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1. Introduction

Inflammation plays beneficial roles to maintain tissue homeostasis and protects organisms from harmful invasion of exogenous or endogenous toxins and pathogens. The primary response of inflammation is clinically characterized by local redness, swelling, heat, fever, pain, and loss of function [1-3]. However, chronic or uncontrolled inflammation leads to the development and progression of a number of diseases. The common inflammatory diseases include asthma, rheumatoid arthritis, inflammatory bowel disease, cancer, atherosclerosis, type 2 diabetes, obesity, neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, multiple sclerosis etc. which are the major threat to human health and considered to be responsible for 60% of global death [4-6]. At present, NSAIDs (non-steroidal anti-inflammatory drugs) as well as SAIDs (steroidal anti-inflammatory drugs) are commonly prescribed medications for inflammatory diseases. But the efficacy and tolerability of both can be overshadowed by their adverse effects. For instance, long term use of NSAIDs can cause ulcerations, hepatotoxicity and cardiovascular diseases etc., on the other hand, use of SAIDs are associated with hormonal disturbances, immunodeficiency, weight gain, diabetes, cataract and so on [7-10].

Numerous biochemical mediators work jointly to commence the inflammatory response, followed by recruitment and activation of other cells to resolve the response [11]. The potential inflammatory mediators include, enzymes (PLA_2, COX-1, -2); free radicals (ROS, RNS, and SOD); prostaglandins, leukotrienes,

cytokines (TNF-α, IL-1,-6) and a number of transcription factors including nuclear factor (NF-κB). Plant extracts or pure compounds have been shown to exhibit significant anti-inflammatory activity by inhibiting one or more of the aforementioned mediators and have paved the way from preclinical studies to clinical trials [9, 12]. The use of plant derived natural products in the treatment of inflammatory diseases represents a combined approach based on century old observations and experiences of traditional medicine, and modern techniques of pharmacology and phytochemistry [13]. The popularity and prescription rate of herbal medicine is increasing which indicates the shift of global trend from synthetic drugs towards medicines of natural origin which has also been considered as a promising future medicine [14] .

This review aims to summarize ten Bangladeshi plants belonging to eight different families [*Abelmoschus esculentus* (L.) Moench, *Asparagus racemosus* Willd., *Blumea lacera* (Burm.f.) DC., *Butea monosperma* (Lam.) Taub., *Cheilocostus speciosus* (J.Koenig) C.D.Specht., *Mussaenda roxburghii* Hook. f., *Anthocephalus cadamba* (Roxb.) Miq., *Phyllanthus reticulatus* Poir., *Sesbania grandiflora* (L.) Pers. and *Spondias pinnata* (L. f.) Kurz] which have been used extensively in folk medicine to heal or manage inflammation and related diseases, highlighting the anti-inflammatory molecules identified from these plants and their mode of action where reports are available. Toxicological information of these plants has also been overviewed in brief.

2. Materials and methods

A thorough literature search has been conducted using electronic databases like PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), Science Direct (https://www.sci encedirect.com/), and Google Scholar (https://scholar.google.com/) up to August 2023 for this study. The primary literature search was carried for anti-inflammatory activity and active constituents of selected plants whereas a secondary search was carried out for toxicity of the same plants namely *A. esculentus*, *A. racemosus*, *B. lacera*, *B. monosperma*, *C. speciosus*, *M. roxburghii*, *A. cadamba*, *P. reticulatus*, *S. grandiflora* and *S. pinnata.* The figure of *A. esculentus*, *A. racemosus*, *C. speciosus* and *S. pinnata*

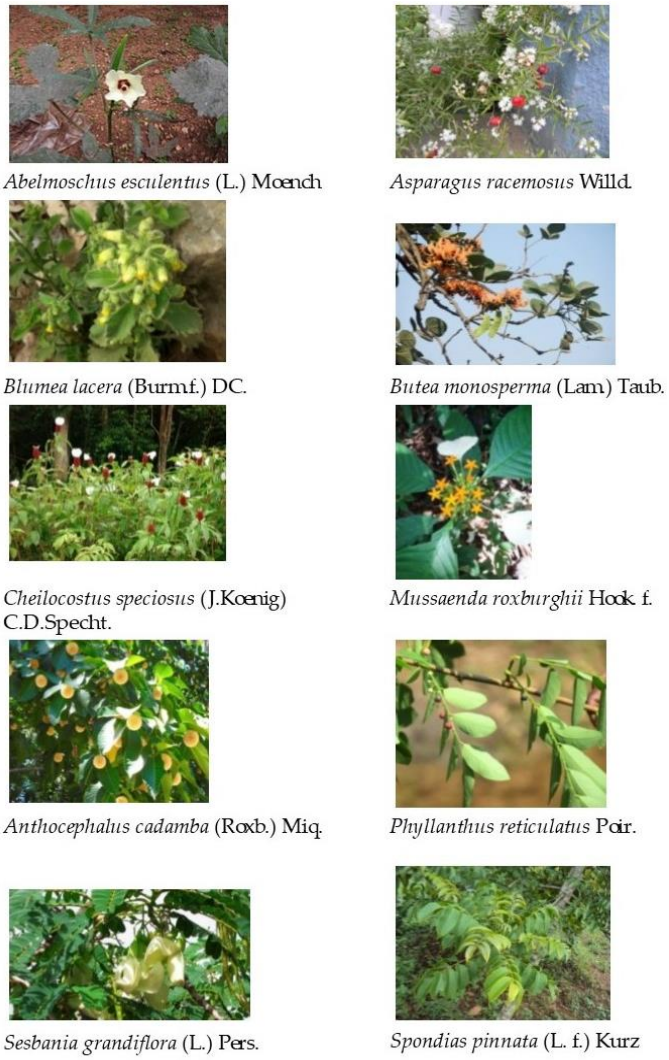


Figure 1. Anti-inflammatory plants.

were obtained from Wikimedia Commons under GNU free documentation license (https://en.wikipedia.org/wiki/GNU_Free_Documentation_License) whereas *B. lacera, B. monosperma, S. grandiflora, M. roxburghii, N. cadamba* and *P. reticulatus* were obtained from the web page 'Flora of Bangladesh', from the Survey of Vascular Flora of Chittagong and the Chittagong Hill Tracts Project, Bangladesh National Herbarium (https://bnh-flora.gov.bd), Ministry of Environment & Forest, People Republic of Bangladesh (Fig 1). These plants were selected based on their extensive therapeutic use in traditional medicine to manage and cure inflammatory disorders. The common name, local name and traditional uses of these plants included in Table 1 were extracted mainly from the books of Professor Abdul Ghani and Sarder Nasir Uddin, and few other references.

Table 1: Traditional uses of the selected plants

Plant name (Family)	Common name (Local name)	Traditional use(s)	Reference(s)
Abelmoschus esculentus (L.) Moench (Malvaceae)	Okra, (Bendi or dherosh)	**Leaf and root:** Mucilage is used in gonorrhea and other venereal diseases. **Seed:** Carminative, stomachic, antispasmodic, demulcent, stimulant and tonic. Infusion, decoction and tincture of seeds are used in atonic dyspepsia, hysteria, nervous debility and other nervous disorders. As inhalation used in hoarseness and dryness of mouth, catarrh of the bladder and air passages. Seed paste with milk is used to cure leucoderma and itch. Fresh plant juice is used as febrifuge and expectorant. The plant is also considered to have diaphoretic, diuretic, emollient and vulnerary properties, and is used in diarrhea, constipation, urinary calculi, jaundice, gastric ulcer, colitis, cystitis, hepatitis and diabetes.	[34, 35]
Asparagus racemosus Willd. (Liliaceae)	Asparagus or wild asparagus (Shatamuli or shatavari)	**Root:** Aphrodisiac, alterative, tonic, demulcent, diuretic, bilious dyspepsia, flatulence, diarrhea and dysentery. Used in acidity, as hair tonic and to promote lactation in mother, and appetite and nourishment in children. Root juice with milk is used in gonorrhea. This plant is strong diuretic and used in the treatment of various urinary disorder including cystitis, and also in diabetes and jaundice. It is used with other plants in respiratory troubles. The plant is considered to possess anti-dyspepsia and anti-tussive properties, used in dry cough, gastric ulcer, tumor, tuberculosis, infection, joint stiffness, neuronal disorders, liver diseases, and as a tonic to promote fertility and reducing menopausal symptoms.	[34, 36-38]
Blumea lacera (Burm.f.) DC. (Asteraceae)	(Kukursunga or shialmutra)	**Leaf:** Juice possesses astringent, febrifuge, stimulant, anthelmintic, diuretic, stomachic, antispasmodic properties, and is used to prepare astringent eye lotion. **Root:** Astringent, febrifuge, and is mixed with black pepper, given in cholera and piles. The plant also has deobstruent, digestive, liver tonic, anti-inflammatory and expectorant properties.	[34, 36, 39, 40]
Butea monosperma (Lam.) Taub. (Fabaceae)	Mother of Thousands (Pathorkuchi)	**Leaf:** Diuretic and is used to cure boils, pimples, worms, tumors, piles and hemorrhages. **Bark:** Astringent, alterative, aphrodisiac and is useful in tumor, ulcer and bleeding piles. Decoction is given for catarrh, cold, cough, fever, hemorrhage and menstrual disorders. **Root:** Causes temporary sterility in women and is used to treat night blindness. **Flower:** Decoction is given in diarrhea and dysentery and is used as emmenagogue and anthelmintic. Also used in liver disorder.	[34, 41-43]

Table 1: (*Continued*)

Plant name (Family)	Common name (Local name)	Traditional use(s)	Reference(s)
		Gum: Astringent, decoction or tincture is used for acid indigestion, diarrhea and dysentery. It is also useful in bruises, erysipelatous inflammation and ringworm. **Pods:** Used to treat worm infestation, cuts, wounds, urinary problem, and as tonic. **Seed:** Laxative, purgative, anthelmintic (paste is a very useful remedy for ringworm), antifungal and antibacterial. According to other literature, *B. monosperma* leaves are helpful to treat eye ailments. Roots cure night blindness. Bark is used in the treatment of bone fractures, anal infections, dysentery and piles. Gum is useful in stomatitis, cough and corneal opacities. Flower is useful in the treatment of leprosy, gout, skin diseases and burning sensation.	
Costus speciosus (J.Koenig) Sm. (Zingiberaceae) Accepted name: *Cheilocostus speciosus* (J.Koenig) C.D.Specht.	Spiral ginger (Keu, tara, kura or kemak)	**Bark:** Used in burning sensation on urination. **Rhizome and root:** Astringent, stimulant and aphrodisiac. Used in catarrhal fever, cough, dyspepsia, worms, skin disease, otitis, spermatorrhea, and snake bite. Root juice is used in paralysis, rheumatism, seminal emission, and with other plants in food poisoning and gout. Leaf extract is used in jaundice with other plants whereas leaf and root juice is used with another plant in osteoarthritis. Curry of young shoots is advised to eat in case of indigestion. Other uses include in the treatment of rabies, anemia, bronchitis, flatulence, asthma, helminthiasis, leprosy, pneumonia, dropsy, inflammation, hiccough, fever and urinary diseases.	[34, 36, 44]
Mussaenda roxburghii Hook.f. (Rubiaceae)	(Chauri-chaonri gach, sildaura or supaila)	**Leaf:** Paste is applied on the cutting wound to stop bleeding, on forehead to cure headache, in case of snake bite on the snake bite place and in skin disease. Leaf and stem extract is used for hot water bath in the treatment of edema. **Root:** Fresh juice is taken in epilepsy, food poisoning pediatric diseases and pyorrhea. **Flower:** Paste (prepared from leaves and flowers) is applied on the navel region to treat abdominal pain and also applied externally on the breast to heal breast pain.	[36, 41]
Neolamarckia cadamba (Roxb.) Bosser or *Anthocephalus cadamba* (Roxb.) Miq. (Rubiaceae)	Wild cinchona (Kadam)	**Leaf:** Decoction is used as gargle in aphthae and stomatitis. Paste is used in the treatment of dyspepsia. Bruised leaves are used on boils to remove subdermal inflammatory deposits. Dried powdered leaves are used as anthelmintic and for washing wounds in the throat. Fresh leaf juice is consumed to treat leucorrhea and increase menstrual flow.	[34, 36, 45]

Table 1: (*Continued*)

Plant name (Family)	Common name (Local name)	Traditional use(s)	Reference(s)
		Bark: Astringent, febrifuge and tonic. Used in malarial fever and snakebite. Bark is used with other plant in the treatment of stomachache. **Root:** Root is used with other plants to treat body pain. **Flower:** Used as gurgle to remove the foul smell from mouth	
Phyllanthus reticulatus Poir. (Euphorbiaceae)	(Chitki or panjuli or panseuli, or pankushi)	**Leaf:** Astringent, diuretic and alterative. Juice is used to cure diarrhea in children and mixed with camphor and cubeb used as a remedy for spongy and bleeding gums. Paste is applied externally on boils and juice is used in dysentery. **Bark:** Astringent, diuretic and alterative. **Root:** Fresh juice is taken to cure malaria. Paste prepared from root and leaf is applied externally on boils and fresh juice from leaf and bark is used to control diabetes. Other uses in traditional medicine include in the treatment of smallpox, asthma, syphilis and inflammation.	[34, 36, 46]
Sesbania grandiflora (L.) Pers. (Fabaceae)	(Bakful or bagful)	**Leaf:** Crushed leaves are applied as a poultice in sprains and all types of bruises, swelling, rheumatism and itching. **Bark:** Decoction is taken orally to treat fever, diarrhea, dysentery and diabetes. **Root:** Paste is applied externally in the treatment of rheumatism. **Flower:** Juice is used in the eyes to relief dimness of vision. The plant is considered to have antibacterial, anthelminthic, antitumor and contraceptive properties and other uses include treatment of colic disorder, jaundice, catarrh, headache, epilepsy, stomatitis, smallpox, sore throat and headache.	[41, 47]
Spondias pinnata (L. f.) Kurz (Anacardiaceae)	Wild mango or hog-plum (Amrha or piayala)	**Leaf:** Aromatic, acidic and astringent and leaf juice is used in earache. **Bark:** Astringent and is used in the treatment of dysentery, diarrhea and vomiting. Paste is applied topically to treat sprains and rheumatism. Bark and wood are used in the treatment of gonorrhea and leucorrhoea. **Gum:** Demulcent **Fruit:** Antiscorbutic and astringent and used in bilious dyspepsia. This plant is used with other plants in the treatment of anemia, asthma, hyper acidity and scurvy. The plant is also considered to be useful in digestive issues, constipation, diabetes mellitus, dementia, gastroenteritis and other infestations.	[34, 36, 48]

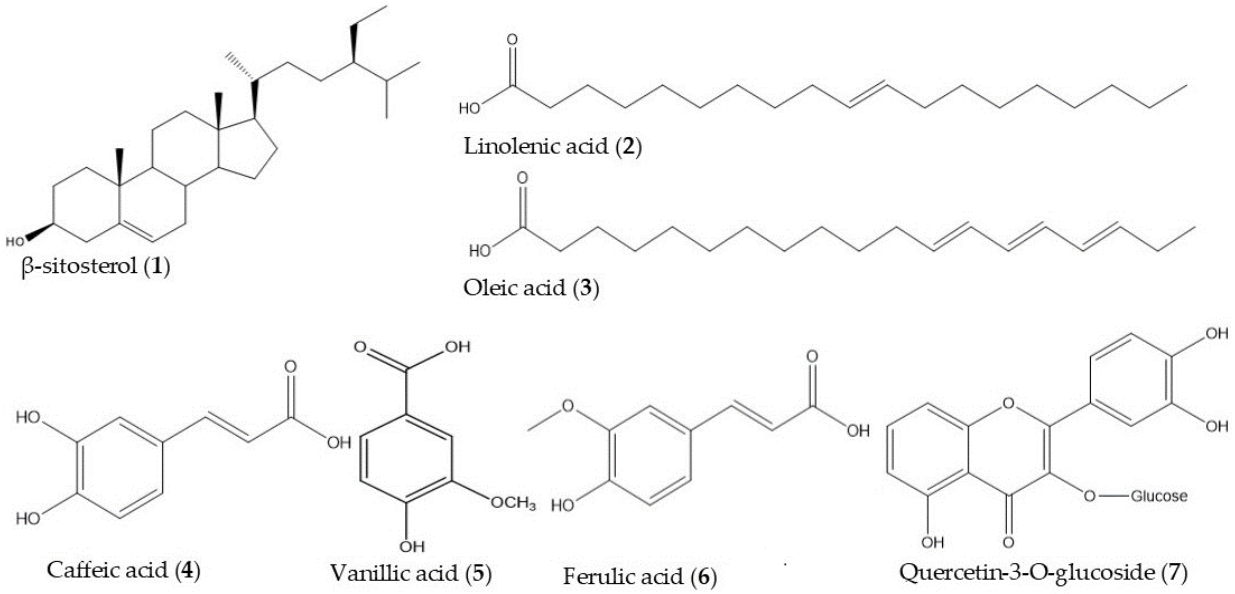


Figure 2. Anti-inflammatory compounds isolated from *A. esculentus*

3. Results and discussion

3.1 Abelmoschus esculentus (L.) Moench

A. esculantus or okra is an annual herb and important vegetable crop which is grown in tropical, subtropical and warm temperate regions of Africa, Asia, Southern Europe and America [15]. The fruit is a common vegetable in tropical countries. Nevertheless, fruit as well as other parts of this plant demonstrated significant anti-inflammatory properties in several studies. *A. esculantus* fruit extract suppressed LPS-induced NO, TNF-α, IL-1β and Akt (protein kinase B) mediated NF-κB pathway in murine microglial cells [16]. Fruit extracts as well as lectin (a protein) isolated from mature seeds of this plant inhibited carrageenan induced paw edema in both mice and rats [17-19]. Extract from whole plant has also been reported to inhibit hemolysis [20]. *A. esculentus* fruit extracts demonstrated wound healing properties in both *in vivo* and *in vitro* experimental models by down regulating inflammatory mediators [21, 22]. Raw and cooked extracts from this plant inhibited NO production, COX-2, iNOS expression, and the cytokines, TNF-α, IL-6 and IL-1β, in LPS and H_2O_2 induced RAW 264.7 cells confirming its anti-inflammatory properties [23]. The extracts were also found nontoxic in that study. However, in other studies, this plant has shown cytotoxic potential against BHK-21 cell [24]. The mRNA levels of pro-inflammatory cytokines (TNF-α, IL-6 and IL-1β) have been reduced by the leaf extract of *A. esculentus* but not by the fruit extract of this plant [25]. Polysaccharide isolated from this plant exhibited antidepressant effects by inhibiting the expression of TLR4, the nuclear translocation of NF-κB and high levels of proinflammatory cytokines (IL-6 and TNF-α), and also by enhancing the MAPKs (mitogen-activated protein kinases) signaling [26]. Different parts of okra i.e., flower, fruit, leaf and seed contain wide array of biologically active compounds among which β-sitosterol (**1**) [27], linolenic acid (**2**) and oleic acid (**3**) (Fig. 2) [15] are reported anti-inflammatory molecules [28-31]. Phenolic constituents from *A. esculentus* exhibited high binding affinity to COX-2 and NF-κB in molecular docking studies where caffeic acid (**4**), vanillic acid (**5**) and ferulic acid (**6**) (Fig. 2) were the lead molecules [32]. Anti-inflammatory molecule like quercetin-3-O- glucoside (**7**) (Fig. 2) has been detected in this plant along with series of other molecules in GC-MS study [33].

3.2 Asparagus racemosus Willd.

A. racemosus is an extensively used herb in Ayurvedic medicine system. This spinous under shrub commonly grows at low altitudes of tropical and subtropical countries [49]. In *in vivo* experimental models, this species has shown significant reduction of rat paw edema induced by carrageenan and

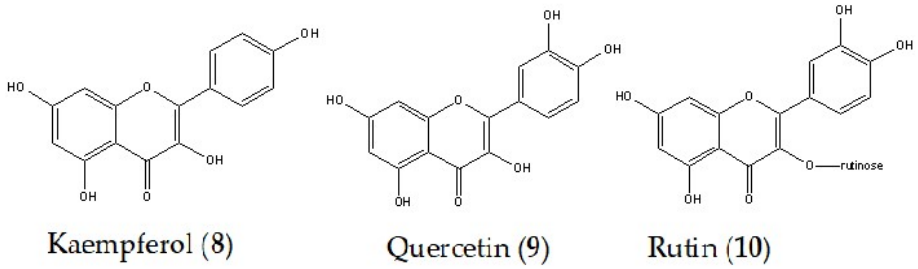


Figure 3. Anti-inflammatory compounds isolated from *A. racemosus*

serotonin [50, 51]. Whereas *in vitro* assays demonstrated that this plant has promising RBC membrane stabilization activity [49, 52, 53]. *A. racemosus* extract demonstrated anti-inflammatory activity by reducing pathology of inflammatory bowel disease (IBD) in oxazolone induced zebra fish IBD (inflammatory bowel disease) model [54]. Sarsasapogenin (a steroidal saponin) isolated from this plant exhibited neuroprotective effect by inhibiting amyloid β protein (Aβ) fibrillation as well as acetylcholinesterase (AChE), butyrylcholinesterase (BuChE), beta site cleaving enzyme 1 (BACE1) and monoaminoxidase B (MAO-B) which are the key enzymes involved in the pathogenesis of Alzheimer's disease [55]. The LD_{50} of *A. racemosus* root extract has been found to be 505 mg/kg body weight of mice [56] and showed toxicity on liver and spleen tissues of rats on long term administration [57]. A broad range of biologically active constituents has been isolated from different parts of this plant [58] among which kaempferol (**8**) [59], quercetin (**9**) and rutin (**10**) (Fig. 3) [60] are well studied anti-inflammatory bioflavonoids.

3.3 Blumea lacera (Burm.f.) DC.

B. lacera is an herbaceous weed that commonly grows in the uncultivated lands of Bangladesh, India, Australia, China, Malaya and tropical Africa. There are several reports on *in vitro* anti-inflammatory activity of *B. lacera*, studied using protein anti-denaturation and RBC membrane stabilization assays [61-63]. This species has demonstrated protective action against rat enterocolitis which is considered to be attributed mainly by the anti-inflammatory and anti-oxidant properties of the plant [64]. Aerial part extract of this plant inhibited writhing reflexes and ear edema in the experimental mice model and showed cytotoxicity (LC_{50} = 5.4 µg/mL) in brine shrimp lethality bioassay [65]. Extract and compounds from this plant showed ulcer healing property investigated using *in vivo* and *in silico* models respectively and the extract did not show any sign of toxicity as well as abnormalities up to the dose of 5000 mg/kg of body weight [65, 66]. *B. lacera* leaf extract as well as its liposomal preparation were found effective against CCl_4-induced liver injury in rats [67]. *B. lacera* leaf extract demonstrated significant anti-hemorrhoid activity in croton oil-induced hemorrhoid rat model and also inhibited protein denaturation. In the same study, the extract did not show any sign of behavioral or neurological toxicity in rats and zero mortality up to a dose of 2000 mg/kg of body weight [68]. The plant is rich in flavonoids, alkaloids, glycosides, terpenoids, and essential oil components [69, 70] including anti-inflammatory molecules like quercetin (**9**) [68], 1,8-cineole (**11**), α-pinene (**12**), caryophyllene (**13**) (Fig. 4) etc . GC-MS analysis revealed the presence of different components in this plant including neophytadiene, 1,2-epoxyundecane, hexadecanoic acid and phytol as major constituents [67, 71].

3.4 Butea monosperma (Lam.) Taub.

B. monosperma is indigenous to tropical and sub-tropical parts of Asia and is found throughout Bangladesh, India, Nepal, Sri Lanka, Myanmar, Thailand, Laos, Cambodia, Vietnam, Malaysia and Western Indonesia. This plant exhibited notable anti-

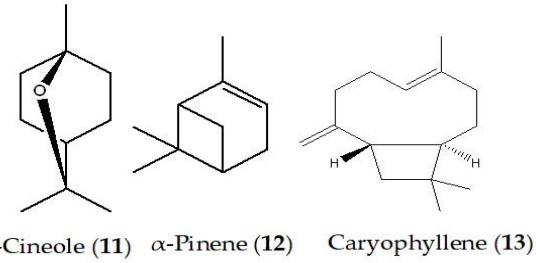


Figure 4. Anti-inflammatory compounds isolated from *B. lacera*

inflammatory activities in several *in vitro* and *in vivo* studies. For instance, fixed oil from *B. monosperma* seed attenuated carrageenan induced paw edema in rats [72], flower extracts inhibited inflammatory mediators like IL-1β, IL-6 and IL-8, prostaglandin E_2 production and MMP-1, -2, -9 and -10 secretion as well as carrageenan induced paw edema and cotton pellet implanted granuloma in rats [73-75]. Extracts from this plant have also been found to protect RBC membrane from lysis [76, 77]. In acute oral toxicity assay the leaf extract of this plant was found safe up to a dose of 4,000 mg/kg rat body weight with no mortality [78]. A wide array of bioactive secondary metabolites has been isolated from different parts of the plant including β- sitosterol (**1**) **(Fig. 2),** lupeol (**14**), lupeonone etc. [79, 80]. Butrin (**15**), isobutrin (**16**) [81] and butein (**17**) **(Fig. 5)** [82] characterized from *B. monosperma* showed potent anti-inflammatory activity by down-regulating the synthesis of TNF-α, IL-6 and IL-8 via NF-κB inhibitory pathway in human mast cells [83].

3.5 Cheilocostus speciosus (J.Koenig) C.D.Specht.

C. specious is a herbaceous ornamental plant distributed in the tropical and subtropical regions of Asia, Africa and the Americas [84]. Rhizome and aerial part extracts of this plant have been reported to possess strong activities against inflammation and arthritis [85, 86]. Extracts from different parts of this plant have shown RBC membrane stabilization and protein anti-denaturation action *in vitro* studies and inhibition of paw edema in animal models [87-90]. A large number of compounds have been characterized from this plant [84] among which 22, 23-dihydrospinasterone (**18**), dehydrocostus lactone (**19**), dehydrodihydrocostus lactone (**20**), and stigmasterol (**21**) (Fig. 6) exhibited potent anti-inflammatory activity via lowering the levels of cytokines, PGE_2, lipoxgenase-5 and COX-2 [91] whereas a diosgenin (**22**) (Fig. 6) is found to inhibit NO and TNF-α in lipopolysaccharide (LPS) stimulated RAW 264.7 macrophages [92]. In a recent study, *C. speciuosus* extract has been found to ameliorate zearalenone (a non-steroidal estrogenic mycotoxin) induced toxicity in rats by modulating iNOS, inflammatory-related genes, and the Nrf_2 pathway. In the same study, GC-MS analysis of the extract revealed several compounds which azulene being the major one [93].

3.6 Mussaenda roxburghii Hook. f.

M. roxburghii is a wild perennial herb that grows in the foothills and moist shady places of Bangladesh, India, Nepal, Bhutan and Myanmar [94, 95]. Extracts from the leaf and roots of this plant have shown RBC membrane stabilization and protein anti-denaturation action in *in vitro* studies [96-98]. GC-MS analysis of the shoot ethanol extract has allowed characterizing compounds from *M. roxburghii* [95] including anti-inflammatory moieties for example, vitamin E (**23**) [99], neophytadiene (**24**) [100] and squalene (**25**) (Fig. 7) [101, 102].

3.7 Anthocephalus cadamba (Roxb.) Miq.

A. cadamba (synonym: *Neolamarckia cadamba*) is an evergreen flowering tree distributed in different parts of Bangladesh, India, Nepal, Myanmar, Sri Lanka, Cambodia, Laos, Philippines, Malaysia, Indonesia, Papua New Guinea and Australia [103]. It is an important plant in Ayurveda due to the usefulness of its different parts for the management of a number of health hazards [45]. This plant has been investigated in several studies for its anti-inflammatory activities. Its stem bark extract exhibited potent anti-inflammatory properties *in vivo* experiments by suppressing histamine induced paw edema and cotton pellet induced granuloma whereas *in vitro* experiments, the bark fractions have shown protein anti-denaturation and human RBC membrane stabilization activities [104-107]. Again, extracts from leaf, fruit and flowering top of *A. cadamba* exhibited significant human RBC membrane stabilization action [108-111]. *A. cadamba* leaf extract exhibited accelerative wound-healing properties in diabetic rat model [112]. A wide variety of compounds has been revealed from this plant using GC-MS analysis and some of those have shown to be potential for the management of Alzheimer's disease via *in silico* molecular docking analysis [113]. In a recent study, neocadambine D (**26**), 3β-dihydrocadambine (**27**) and 3β-isodihydrocadambine (**28**) (Fig. 8) isolated from *A. cadamba* showed better anti-inflammatory effects than that of the positive control, dexamethasone [114]. In another study, GC-MS analysis of bark extract revealed the presence of a series of phytoconstituents including tetradecanoic acid, n-hexadecanoic acid, gamma-sitosterol, hexadecanoic acid, 2- hydroxy-1-(hydroxymethyl) ethyl ester, octadecanoic acid, 2,3-

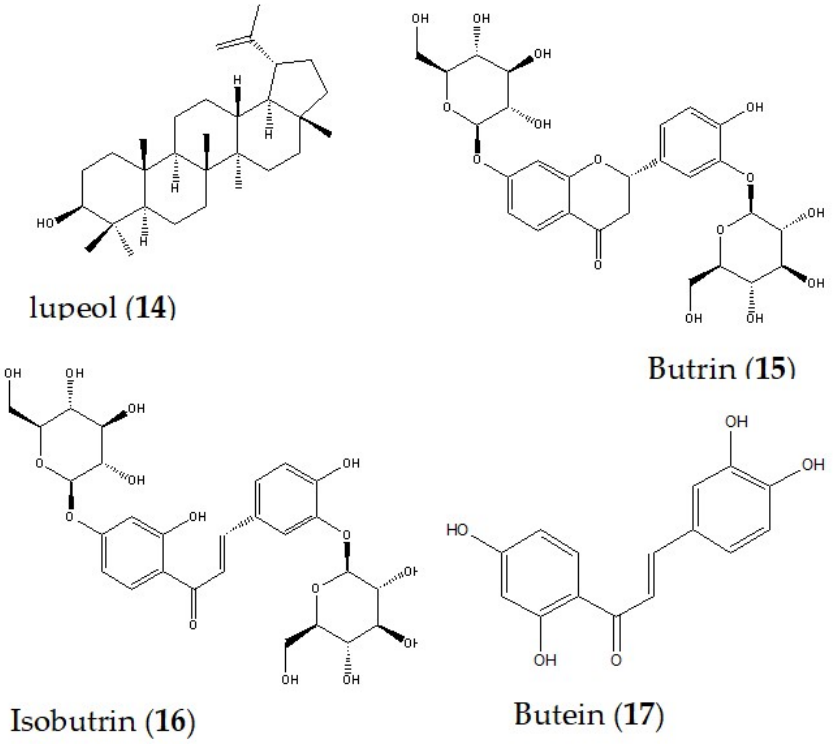


Figure 5. Anti-inflammatory compounds isolated from *B. monosperma*

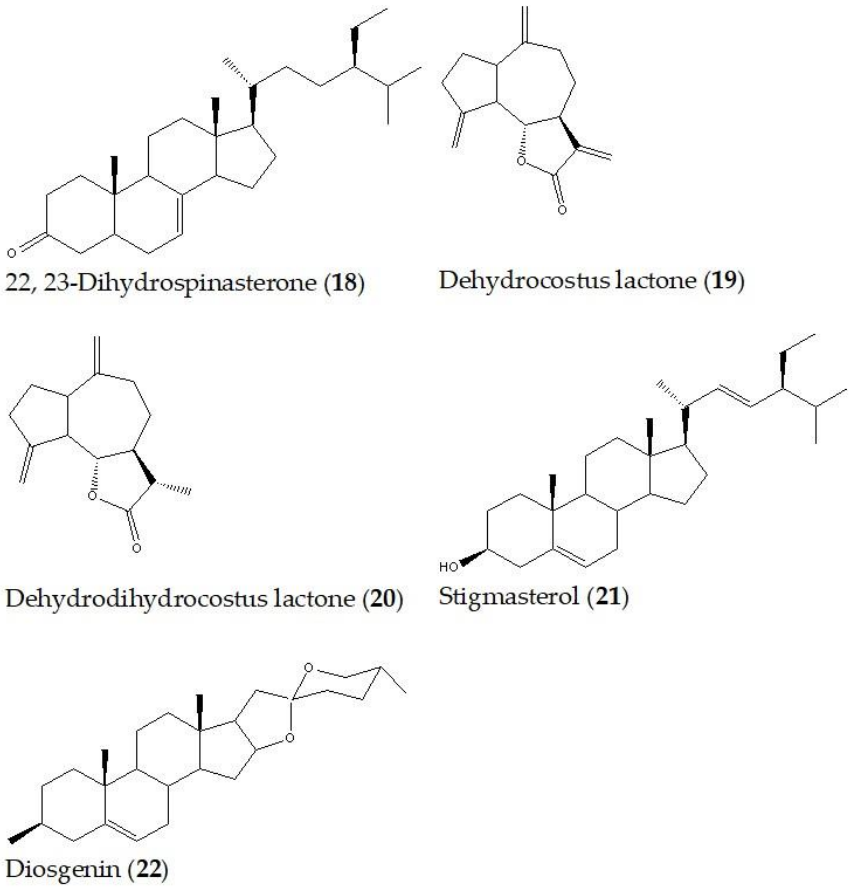


Figure 6. Anti-inflammatory compounds isolated from *C. specious*

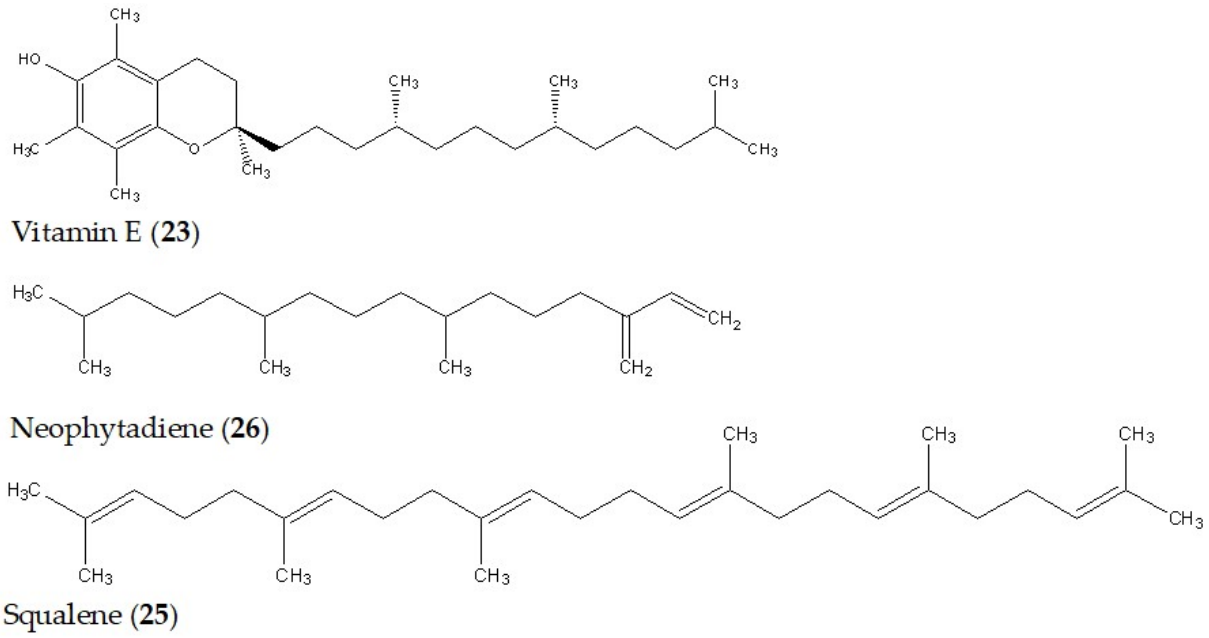


Figure 7. Anti-inflammatory compounds isolated from *M. roxburghii*

dihydroxypropyl ester, oleic acid, 9,12-octadecadienoic acid (Z,Z)- and 5-hydroxymethylfurfural as the major constituents [48]. Anti-inflammatory molecules like β–sitosterol (**1**), vanillic acid (**5**) (Fig. 2), ursolic acid (**29**), quinovic acid (**30**) (Fig. 8) etc. have been reported from this plant, where quinovic acid demonstrated potential anticancer property [115]. In another study, several other compounds have been reported from this plant including vincosamide-N-oxide and isodihydro-amino cadambine, vincosamide, vallesiachotamine, iso-vallesiachotamine, and oleanolic acid etc., among which vallesiachotamine, iso-vallesiachotamine have shown potent anticancer activity against cancer cell line whilst all of the identified compounds did not show any toxic effect on normal cells [116].

3.8 Phyllanthus reticulatus Poir.

P. reticulatus is a shrub and grows throughout tropical areas of Bangladesh, India, China and the Malay Islands. This plant has been reported to attenuate carrageenan induced paw edema in both mice and rats treated with bark and leaf extracts [117-120]. In *in vitro* investigations this plant inhibited lysis of RBC membrane [121]. *P. reticulatus* extract and fractions have been investigated for gastroprotective effects in several studies. The plant down regulated mRNA levels of IL-8 and TNF-α in ulcer rat models and thus claimed to possess anti-inflammatory and immunomodulatory activities [122]. Again this plant has decreased ulcer index in pylorus ligation-induced, ethanol-induced and swim stress-induced ulcer rat models [123]. Ethyl 9,12,15-octadecatrienoic acid, ethyl 9,12,15-octadecatrienoate, n-hexadecanoic acid and tocopherol have been detected as major constituents in this plant by GC-MS analysis [124]. In a different investigation, a wide range of compounds have been identified from *P. reticulatus* extract using UPLC-ESI-QTOF/MS analysis including well documented anti-inflammatory molecules like gallic acid (**31**), catechin (**32**) (Fig. 9), quercetin (**9**) (Fig. 3) etc. [125]. Other anti-inflammatory moieties isolated from *P. reticulatus* are rutin (**10**) (Fig. 3), lupeol (**14**) (Fig. 5), ellagic acid (**33**), betulinic acid (**34**) (Fig. 9), vanillic acid (**5**) (Fig. 2) etc. [126, 127].

3.9 Sesbania grandiflora (L.) Pers.

S. grandiflora is a soft wooded flowering tree that grows in Asian countries including Bangladesh, India, Malaysia and Indonesia [128, 129]. In the *in vitro* RBC membrane stabilization assay, this plant protected the cell membrane from lysis [129-131]. In different *in vivo* study models like carrageenan induced paw edema, cotton pellet induced granuloma and adjuvant-induced arthritis model, the flower [132], bark [128, 133] and root extract [134] of *S. grandiflora* successfully attenuated inflammation. In acetic acid induced ulcerative colitis this plant has been found to suppress

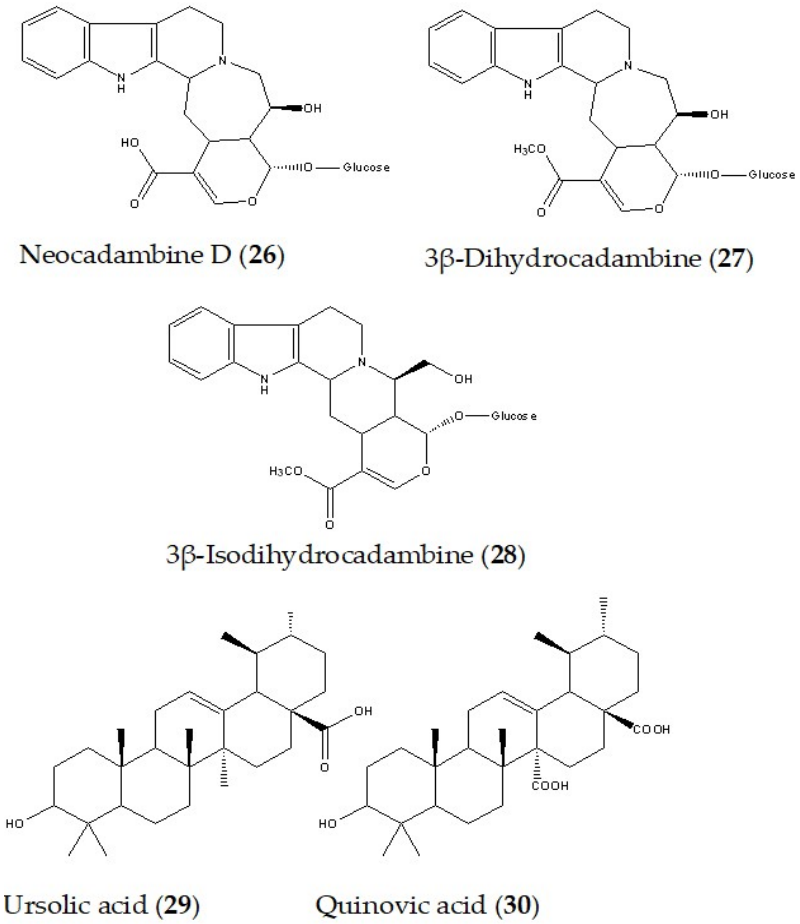


Figure 8. Anti-inflammatory compounds isolated from *A. cadamba*

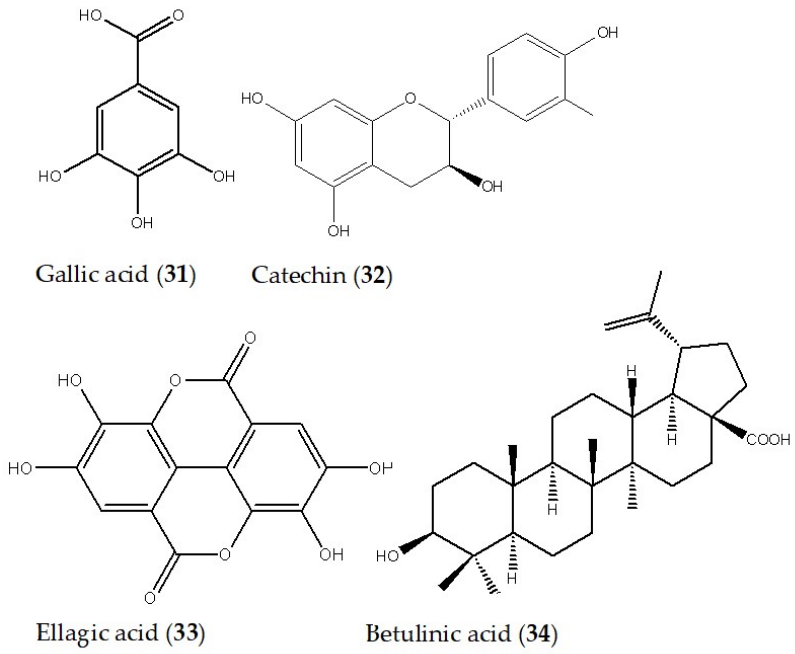


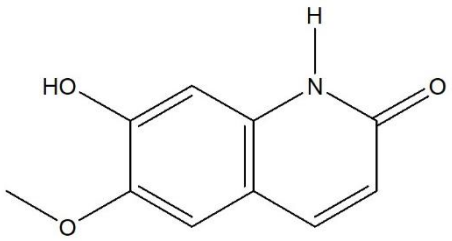
Figure 9. Anti-inflammatory compounds isolated from *P. reticulatus*

inflammatory cytokines like TNF-α and IL-6 [135]. In acute oral toxicity assay the root extract of this plant was found safe up to a dose of 2,000 mg/kg rat body weight with no mortality [136]. Molecular docking study revealed that phytoconstituents (β-amyrin, linolenic acid and L-α-terpineol) present in the leaves of this plant have a high binding affinity to prostaglandin 3 receptor E_2, which may be useful to develop peptic ulcers therapy [137]. Along with different bioactive constituents, betulinic acid (**34**) (Fig. 9) and tocopherols have been reported from this plant [138, 139].

3.10 Spondias pinnata (L. f.) Kurz

S. pinnata is a deciduous tree distributed in different parts of Bangladesh, India, Sri Lanka, China, and other Southeast Asian countries [140, 141]. Both bark and stem heart wood extracts of *S. pannata* have reduced carrageenan induced rat paw edema in a dose dependent manner [142, 143]. Whereas leaf extracts of this species demonstrated strong anti-hemolytic activity in RBC membrane stabilization assay [140, 144-146]. *S. pinnata* bark extract exhibited protective effects against the oxidative and inflammatory changes that occur during the development of mucositis [147]. The seed extract of this plant did not show any signs of toxicity in mice at a dose of 2,000 mg/kg body weight [148]. In recent years, the GC-MS technique has enabled to identify of a wide range of components from the essential oil of this plant including caryophyllene (**13**) (Fig. 4) and α-pinene (**12**) (Fig. 4) and the essential oil itself demonstrated strong anti-inflammatory activity [144]. A quinolone (7-hydroxy-6-methoxyquinolin-2(1H)-one) (**35**) (Fig. 10) isolated from *S. pinnata* has been reported to down regulate several inflammatory mediators like NO, TNF-α, IL-6, IL-1β, ROS, iNOS and COX-2, and also found to retain cytoplasmic concentration of NF-κB by inhibiting its activation in LPS stimulated RAW 264.7 cells [141]. A series of glycosides, caffeoylquinic acid and coumarin derivatives have also been reported from the fruits of this plant [149].

In the present paper, we have reviewed a total of 10 plants that possess pharmacological potential to combat inflammatory disorders. These plants are used extensively in various systems of traditional medicines in the management of inflammation and



7-Hydroxy-6-methoxyquinolin-2(1H)-one (**35**)

Figure 10. Anti-inflammatory compounds isolated from *S. pinnata*

inflammatory diseases like bronchitis, asthma, rheumatism, tumor etc. Different parts of the selected plants have been evaluated for their anti-inflammatory activities using *in vitro* and *in vivo* experimental models. The commonly used *in vitro* experiments were found to be RBC membrane stabilization and protein anti-denaturation assays and assays to examine inhibition of activated inflammatory mediators, for example, prostaglandin, enzymes (COX-2 and LOX), nitric oxide (NO), cytokines (TNF-α and ILs), NF-κB etc. Whereas the commonly used *in vivo* assays include carrageenan induced rodent paw edema, cotton pellet implemented granuloma, adjuvant-induced arthritis and acetic acid induced ulcerative colitis along with other inflammatory disease models in animals. Each of the selected plants demonstrated significant anti-inflammatory action in at least two or more of the above preclinical investigations. A number of anti-inflammatory compounds have been reported from these plants and several of them were found to suppress numerous inflammatory mediators. Among these β-sitosterol (**1**), linolenic acid (**2**), oleic acid (**3**), caffeic acid (**4**), kaemferol (**8**) quercetin (**9**), gallic acid (**31**), catechin (**32**), ellagic acid (**33**), betulinic acid (**34**) etc. are well documented anti-inflammatory molecules. Evaluation of toxicity is also crucial for the safe use of medicinal plants. Extracts from different parts of these plants demonstrated varying levels of toxicity. For example, *A. racemosus* root extract showed toxicity on liver and spleen tissues of rats on long term administration and aerial part of *B. lacera* showed toxicity to brine shrimp [57, 65]. Whereas leaf extract of *B. monosperma*, root extract of *S. grandiflora* and seed extract of *S. pinnata* were found safe in acute oral toxicity assay [78, 116, 136].

4. Conclusions

Plants have proved their remarkable therapeutic potential with time and through rigorous pharmacological and phytochemical investigations which led to the discovery of a variety of drug candidates with promising anti-inflammatory activities. The selected Bangladeshi plants reviewed in this paper possess a rich history of being used by traditional healers of the country to combat various inflammatory disorders. However, intensive research focus has yet been required for these plants for their detailed chemical investigations followed by a precise understanding of molecular mechanisms as well as toxicological evaluation.

Abbreviations

Aβ: amyloid beta; AChE, acetylcholinesterase; BACE, beta site cleaving enzyme; BuChE, butyrylcholinesterase; CCl_4, carbon tetrachloride; COX, cyclooxygenase; GC-MS, gas chromatography – mass spectroscopy; H_2O_2, hydrogen peroxide; IBD, inflammatory bowel disease; iNOS, inducible nitric oxide synthase; IL, interleukin; INF-γ, interferon-γ; LC_{50}, lethal concentration 50; LD_{50}, lethal dose 50; LPS, lipopolysaccharide; MAO-B, monoaminoxidase B; MAPKs, mitogen-activated protein kinases; MMP, matrix metalloproteinase; NF-κB, nuclear factor- κB; ng, nano gram; NO, nitric oxide; Nrf-2, nuclear factor erythroid 2-related factor-2; NSAIDs, non-steroidal anti-inflammatory drugs; PLA_2, phospholipase A_2; PGE_2, prostaglandin E_2; RBC, red blood cell; RNS, reactive nitrogen species; ROS, reactive oxygen species; SAIDs, steroidal anti-inflammatory drugs; SOD, superoxide dismutase; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-α, UPLC-ESI-QTOF/MS, Ultra-performance liquid chromatography with electrospray ionization quadruple time-of-flight mass spectrometry.

Authors' contributions

Conceptualization, investigation, data curating, writing original draft & visualization, M.A.A.; Formal analysis, review and editing, M.A. and R.Z.

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Availability of data and materials

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Conflicts of interest

All authors declare that they have no financial or commercial conflicts of interest.

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