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REVIEW

A Review on Leukotriene Antagonistic Agents of Plant Origin

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ABSTRACT

Nowadays, leukotriene antagonistic agents are playing an important role in the management of asthma, rhinitis and other inflammatory diseases of the lower respiratory tract. Leukotriene antagonistic agents available in the market are montelukast, pranulukast, zafirlukast, iralukast, cinalukast, zileuton, verlukst and so on. However, due to several side effects of above allopathic medicines, the bioactive compounds of plant origin are playing a very important role as secondary metabolites. These bioactive compounds are still being used by the human beings since time immemorial in the form of herbal preparations for the treatment of various ailments as mentioned in Ayurvedic system of medicine (ASM). Many researches have been reported related to the anti-inflammatory properties of plants in the traditional medicines, which are capable of suppressing, reducing and relieving pain as well as in reducing inflammation. Therefore, there is a need to highlights some plant species and their by-products possessing anti-inflammatory and leukotriene antagonistic properties

KEYWORDS

Phytochemicals, Antagonistic agents, Anti-inflammatory, Leukotriene.

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INTRODUCTION

Leukotriene was discovered in 1938 as a smooth muscle-contracting factor in lung perfusates. It was known as slow-reacting substance (SRS) and slow-reacting substance of anaphylaxis (SRS-A) and its structure was reported in 1979, when hydrolytic enzymes released from phospholipids of the cell membrane, then arachidonic acid is oxygenated by a lipoxygenase into 5-hydroperoxy-6,8,11,14-eicosatetraenoic acid. This product is further converted to leukotrienes [1].

Leukotrienes (LTs) are the member of lipid mediators family that play an important role in the pathogenesis of inflammation, which is located in the leukocytes from arachidonic acid metabolism which is a precursor of this pathway. Leukotrienes are reported in two pathways. One is LTB4 that is the mediator of inflammation. LTB4-R1, LTB4-R2 and CysLTs (LTC4, LTD4, and LTE4) are also play important roles in LTB4 pathways in inflammation. They induce their actions with the help of G-protein-coupled receptors, CysLTR-1 and CysLR-2, which play important role in inflammatory disorders especially asthma, rheumatoid arthritis and inflammatory bowel disease (IBD) [2].

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Since immemorial time, medicinal plants are being used by the peoples for the treatment of many diseases including asthma, allergy and other respiratory disorder [3] and the medicinal plants are the unique source of natural product that can be used as alternatives of allopathic medicines for the treatments of various ailments [4]. Therefore, plants are a very important source of medicines for the longevity of human beings. In many developing countries like India also, plant based herbal medicines are being used in primary healthcare needs. According to the World Health Organization (WHO), around 80 % of the world population still depend and rely on herbal products. Ayurveda, Siddha and Unani systems of traditional medicines have documented number of medicinal plants for the treatment of various ailments [5]. Many medicinal plants and their parts used possess medicinal properties against various diseases [6]. The present mini review highlights the natural products of plants that possess pharmacological activities for the management of asthma, allergy and other respiratory disorders. In the present study, the following plants have been reported as leukotriene antagonistic agents.

***Boswellia serrata* Roxb. (Burseraceae):** It has been used traditionally in Ayurvedic system of medicine and is well known for its anti-inflammatory activities. The inhibitory activities against analgesic [7], anti-inflammatory [8,9] and anticancer properties of this plant has been reported [10,11].

***Camellia sinensis* (Theaeceae):** It is known as green tea and one of the most commonly used beverages in the world. It contains a high amount of polyphenols, catechins, mainly epigallocatechin-3-gallate (EGCG) [12,13]. It has been shown that EGCG inhibited the transcription necrosis factor-kappa-B (TNF-αB) in conjunction with pro-inflammatory cytokines IL-1β-inducible nitric oxide synthase (Inos) and COX-2.

***Curcuma longa* (Zingiberaceae):** It is a perennial herb and well known as turmeric powder, which is culinary herb and used as spices. Many studies of this plants have been reported for the inhibition of phospholipase, lipoxygenase, cyclooxygenase-2, leukotrienes, thromboxane, prostaglandins, nitric oxide, collagenase, elastase, hyaluronidase, monocyte chemo-attractant protein-1 (MCP-1), interferon-inducible protein, tumor necrosis factor (TNF) and interleukin-12 (IL-12) [14].

***Tripterygium wilfordii* (Hook) (Celastraceae):** The root of this plant is used for the treatment of inflammatory diseases like rheumatoid arthritis, asthma, nephritis. The root possesses anti-inflammatory properties due to the presence of triptolide [15]. It has inhibitory activities against CIA (collagen-induced-arthritis) in mice and rat [16,17], INOS (isoform of NO synthase) gene expression, JNK pathway (c-Jun N-terminal kinase) [17], lipopolysaccharide, cyclooxygenase-2 (COX-2), matrix metalloproteinase-3 (MMP-3), matrix metalloproteinase-13 (MMP-13) in articular chondrocytes [18] and IL-1, IL-17 and TNF-α in human chondrocytes.

***Aegle marmelos* (Rutaceae):** This plant is known as Bel or Bilwa locally. The aqueous extract of this plant was also reported for anti-inflammatory activities in adult albino rats using carrageenan induced paw edema model and cotton pellet induced granuloma and the standard drug indomethacin was used [19].

***Bryophyllum pinnatum* (Crassulaceae):** Aqueous leaf extract of this plant shows anti-inflammatory potential at 100 mg/kg body weight [20]. The various purified fractions of leaves of this plant were investigated on chemically-induced inflammation in rodents model. These fractions reduced significantly formaldehyde-induced paw edema in rats. These inhibitions were found to be statistically significant ($p < 0.05$-0.01, 0.001) as compared to the control. The methanolic extract of this plant was found to be highly significant for anti inflammatory activities [21].

***Albizia lebbeck* (Mimosaceae):** This plant is also known as Siris. The bark extract of this plant was obtained by cold exhaustion/percolation by using solvent system *viz*. petroleum ether, ethyl acetate and methanol which were applied on rat at 200 and 400mg/kg body weight that showed 27.51 % and 36.68 % anti-inflammatory activities, respectively [22].

***Cassia fistula* (Fabaceae):** It is commonly known as the Golden Shower in English, Indiana Laburnum in American language and Rajavriksha in Hindi. It is native to India, Amazon and Sri Lanka and diffused in various countries including Mexico, China, Mauritius, East Africa, South Africa and West Indies. The aqueous and methanolic extracts of barks of this plant were applied in wistar albino rats and observed that the phytoconstituents such as flavonoids and bioflavonoids were responsible for anti-inflammatory activities [23].

***Cassia occidentalis* (Caesalpiniaceae):** It is an important member of family Fabaceae. This plant is known as Kasamarda and it has been mentioned in several ancient Ayurvedic books *viz*. Rajnighantu, Dhanwantari, Bhavaprakasa and Rajballaba. It possess active ingredients such as anthraquinones derivatives and their glycosides. Sreejith *et al*. [24] examined anti-inflammatory activity of ethanolic extract of *Cassia occidentalis* at 250 mg/kg body weight carrageenan-induced paw edema in model of albino rat.

***Cynodon dactylon* (Poaceae):** An anti-inflammatory activity of aqueous extract of this plant was reported in carrageenan induced paw edema model of albino rats. During the experiment, three different doses of 200, 400 and 600 mg/kg were applied orally in albino rats and have observed that the aqueous extract of *Cynodon dactylon* was found to be effective in reducing inflammation ($P < 0.001$) [25].

***Emblica officinalis* (Euphorbiaceae):** It is mostly grown in India, China and Indonesia. Its leaves and fruits are very useful for anti-inflammatory and antipyretic activities. Moreover, this plant is used as a pickle in India and famous culinary herb for making pickles and murabba. It is also used in triphala churna of Ayurveda and for anti-inflammatory activity [26].

***Hibiscus rosa-sinensis* (Malvaceae):** The methanolic leaves extract of this plant was also tested in paw edema model of albino rats for anti-inflammatory activities. Indomethacin was used as a standard drug for anti-inflammatory activity. However, extract of this plant when given orally at 250 and 500 mg/kg body weight showed anti-inflammatory activities [27].

***Moringa oliefera* (Moringaceae):** This plant is commonly known as Shahjan. The aqueous and ethanolic extract of this plant, when applied in rats orally at 300 mg/kg body weight in carrageenan induced paw edema model of albino rats showed significant reduction in the percentage of paw edema [28].

***Sida cordifolia* (Malvaceae):** It is used for the treatment of inflammation in the oral mucosa, asthmatic bronchitis and nasal congestion [29]. It has been investigated as an anti-inflammatory agent for preventing cell proliferation and for enhancing liver growth [30].

***Zingiber officinale* (Zingiberaceae):** Shimoda *et al*. [31] have reported anti-inflammatory efficacy of this plant after preparing 40 % ethanolic extract of rhizome, which was given in acute and chronic inflammatory models of albino rats. Extract of *Zingiber officinale* was used orally at doses of 200 and 500 mg/kg, respectively that reduced leucocyte adherence in a carrageenan-induced model of endothelial interaction and chemotaxis [32,33].

***Abrus precatorius* (Fabaceae):** An extract of *Abrus precatorius* with croton oil was used in the rat ear and reduction in the inflammatory response was observed after 6 h compared with croton oil alone [34]. Its seeds contain number of bioactivie compounds including abrine, abraline, abrasine, abrusgenic-acid, abrusgenic-acid-methyl-ester, calcium, campesterol, choline, cycloartenol, delphinidin, gallic acid, glycyrrhizin, hypaphorine, *N*,*N*-dimethyltryptophan, *N*,*N*-dimethyltrypto-phanmetho-cation-methyl-ester, P-coumaroylgalloyl-lucodel-phinidin, pectin, pentosans, phosphorus, polygalacturonic acids, picatorine, precasine and protein trigonelline. It is also rich in various chemical constituents such as isoflavonoids and quinones *viz*. abruquinones A, B, C, O, E, F and G which are present in the root and abrusalactone A, abrusgenic acid and methyl abrusgenate ′2 reported in the aerial parts. Triterpenoids, saponins, glycyrrhizin and oleanolic acid are found in the root B and abrusosides A, B, C, O and E in the aerial parts. Abrus saponins I and II, abrisapogenol, β-amyrin, squalene, abricin, abridin, cycloartenol, campesterol, cholesterol and α-sitosterol [35].

***Ajuga bracteosa* Benth. (Lamiaceae):** Ethanolic extract of *Ajuga bracteosa* exhibited significant anti-inflammatory activity at a dose of 0.5 and 1 mg/ear in TPA-induced mouse ear edema and also exhibited a strong *in vitro* COX-1 and COX-2 inhibitory activities at 25 and 50 µg/mL concentration. 6-Deoxyharpagide exhibited highest COX-2 inhibition while the rest of the compounds exhibited weak to moderate COX-1 and COX-2 inhibition at 30 µM concentration [36]. *Ajuga bracteosa* extracted with methanol (*Ab*MA) performed much better activity in edema inhibition after treatment at 200 mg/kg dose (67.9 ± 2.6, 70.3 ± 0.9 and 74.3 ± 4.3 %). Edema inhibition at 3 h of treatment is comparable to *Ajuga bracteosa* extracted with chloroform (*Ab*CR) (74.4 ± 1.8 %). The phyto-ecdysteroids are responsible for this activity [37].

***Bauhinia variegata* (Fabaceae):** Rao *et al*. [38] reported that *Bauhinia variegata* inhibited the function of inflammation-related macrophages, reducing the levels of IL-6, tumour necrosis factor NO and interferon. It possess number of compound including 5,7,30,40-tetrahydroxy-3-methoxy-7-O-α-L-rhamno-pyranosyl (1→3)-O-β-galactopyranoside that exhibit anti-inflammatory activity [39]. The ethanolic bark extract of this plant was responsible for inhibiting the accumulation of poly-morphonuclear leukocytes *via* preventing the release of cyto-kines like tumour necrosis factor (TNF)-α and interleukin (IL)-12 in carrageenan-induced rat paw edema [40,41]. Also ethanolic extract of leaves of this plant and petroleum ether fraction of this extract in carrageenan-induced rat paw edema and cotton pellet induced granuloma in rats reduced the inflammation by inhibiting proliferation of inflammatory cells like macrophages, fibroblasts and neutrophils [42].

***Geranium nepalense* (Geraniaceae):** An anti-inflam-matory effects of this plant was studied on tetradecanoyl phorbol acetate (TPA) induced mouse ear edema and showed the possessed significant activity of ethyl acetate fraction of water extract at 2.5 µg/kg ($p < 0.01$) and six polyphenolic com-pounds including three flavonoids *i.e.* kaempferol, kaempferol 7-O-β-D-glucopyranoside and quercetin-7-O-α-rhamnopy-ranoside and two tannins *i.e*. pyrogallol and gallic acid and one lignin *i.e*. epipinoresinol were isolated and responsible for anti-inflammatory [43].

***Leonotis leonurus* (Lamiaceae):** Aqueous extract of this plant exhibited significant anti-inflammatory activity at a dose of 50-800 mg/kg i.p. in albumin-induced paw edema in rats [44]. Ethanol and chloroform extracts of flowering plant parts showed strong hepatoprotective and antiinflammatory activities in rats [45]. The leaf and stems extracts (methanol and water) and essential oils also showed antiinflammatory activity using 5-lipoxygenase assay [46].

***Schima wallichii* (Theaceae):** It is found in Indonesia, South China, Myanmar and North East India. The leaves contain saponins, tannins, and kaempferol [47] and used in hysteria, uterine disorders and inflammation [48]. It was also reported for anti-inflammatory and anti-plasmodial activity [49]. *Schima wallichii* reduced carrageenan-induced rat paw edema as well as tumor necrosis factor and IL-6 at doses of 150 and 300 mg/kg p.o. [48].

***Taraxacum officinale* (Asteraceae):** It contains coumarin, cinnamic acid and flavonoids [50] and used in eczema, dropsy, diabetes, anemia, hepatitis and jaundice [51]. It is reported for anti-inflammatory and diuretic properties [52]. The diuretic effects of chloroform fractions of extract of *Taraxacum officinale* in human inhibited the production of prostaglandins, INOS (isoform of NO synthase) and cytokines. The cyclooxygenase pathway was inhibited by ethyl acetate and chloroform fractions in lipopolysaccharide (LPS) stimulated macrophages [53].

The following structure of leukotrienes (Fig. 1) were reported by Henderson [54] in 1994. Commercially, details of the avail-able leukotriene antagonistic agents are presented in Table-1.

Conclusion

Here we reported the leukotriene antagonistic agents of plant origin are very safe medicines due to their no side effects and can be an alternative source of allopathic medicines. Most of them have several side effects, if patients continue for a longer duration and it may cause chronic side effects. Therefore, the present study concludes that leukotriene anatgonistic agents based on bio-active compounds of plant origin could be an excellent source of anti-inflammatory medicines.

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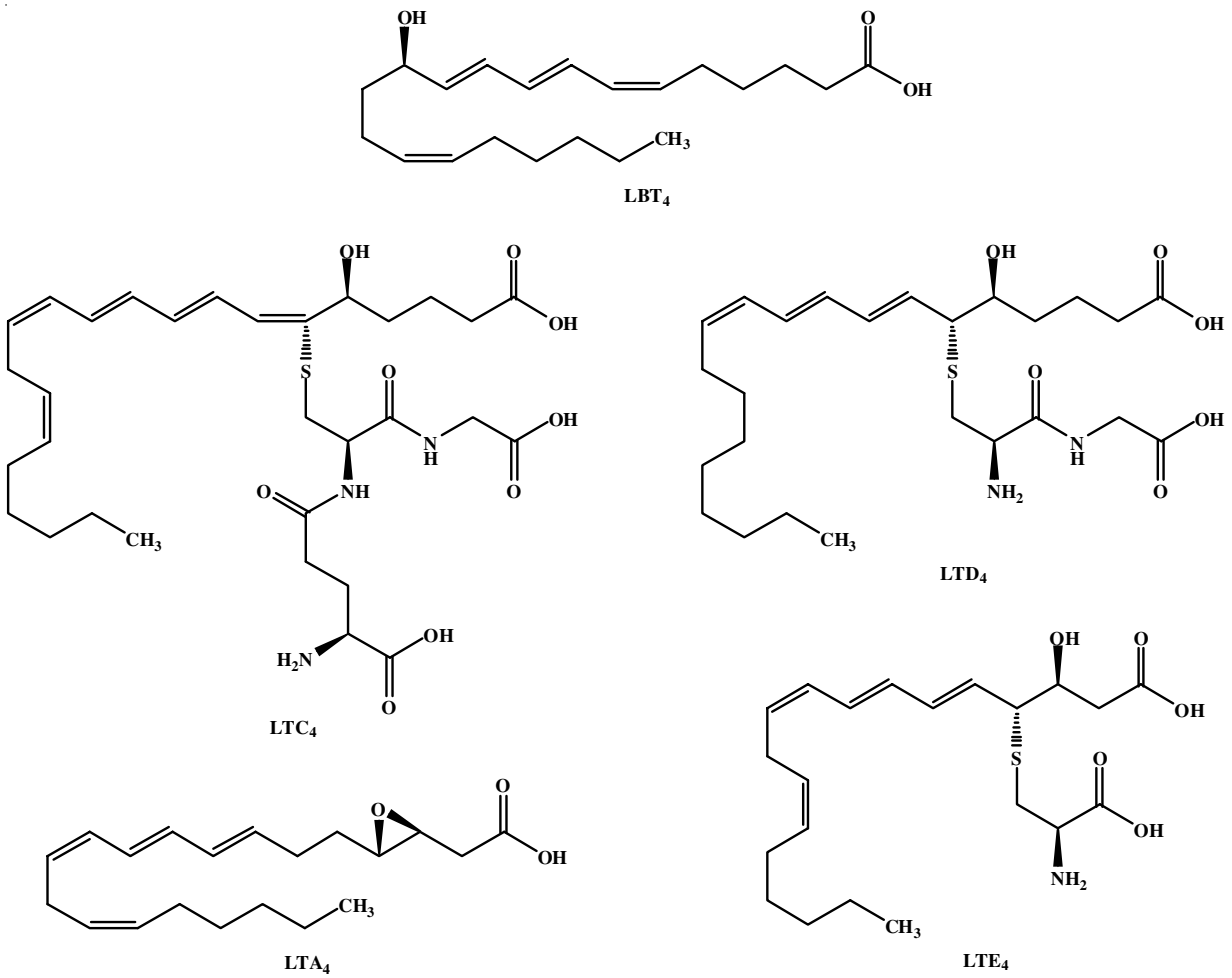

Fig. 1. Structures of leukotriene

TABLE-1
PRESENTLY AVAILABLE LEUKOTRIENE ANTAGONISTIC AGENTS

Currently available drugs	Mechanism of action	Applications/ Activity	Ref.
Zafirlukast (Accolate)	$CysLT_1$ receptor antagonist	Antiasthmatic, prophylaxis, antibacterial and anti-inflammatory	[55-57]
Zileuton (Zyllo)	5-Lipoxygenase inhibitors	Antiacne and antiasthmatic	[58,59]
Montelukast (Singular)	$CysLT_1$ receptor antagonist	Antiviral and anti-inflammatory, exercise induced asthma	[60]
Pranlukast (OnonUltair)	$CysLT_1$ receptor antagonist	Antiasthmatic and antituberculosis, reduced broncho-constriction induced by leukotriene D4 (LTD4) and antigen	[61,62]
Iralukast	Leukotriene D_4- and leukotriene E_4receptor antagonist.	Antiasthmatic, anti-inflamatory, antagonizing the bronchoconstrictive, mucus secretory effect	[63,64]
Cinalukast	Leukotriene D_4-receptor antagonist	Antiasthmatic, anti-inflamatory, bronchodilator	[65]
Verlukast	LTD_4-receptor antagonist.	Antiasthmatic, effect on airway smooth muscles, inflammation, bronchodilator	[66]
MK886 and MK-591	FLAP inhibitors	Asthma and related diseases, inflammation Mucodilator	[67]
BAYx1005	Leukotrienesynththesis inhibitors	Promissing antiasthmatic, inhibit IgE, more effective then leukotriene receptor antagonist	[68,69]

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