Original Article

Natural products and anti-inflammatory activity

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The aim of this review paper was to summarise some commonly available natural products and their anti-inflammatory activity. We have collected data from MEDLINE, Current Contents and scientific journals, which included 92 publications. There are numerous natural products detailed in this literature; however we have summarized a few of the most commonly available and potent ones. In this paper, the natural products with anti-inflammatory activity including curcumin, parthenolide, cucurbitacins, 1,8-cineole, pseudopterosins, lyprinol, bromelain, flavonoids, saponins, marine sponge natural products and *Boswellia serrata* gum resin were reviewed. Natural products play a significant role in human health in relation to the prevention and treatment of inflammatory conditions. Further studies are being conducted to investigate the mechanism of action, metabolism, safety and long term side effect of these natural products, as well as interactions between these natural products with food and drug components.

Key Words: inflammation, anti-inflammatory activity, natural products, anti-inflammatory food, pain, migraine, arthritis, asthma, chronic colitis, inflammatory based diseases

Introduction

The role of natural products as remedies has been recognized since ancient times. There has been considerable public and scientific interest in the use of natural products to combat human diseases such as cardiovascular disease, cancer, and inflammatory disease (which may in any case, actually include other chronic disease, like CVD, cancer and diabetes). In spite of major scientific and technological progress in combinatorial chemistry, drugs derived from natural products still make an enormous contribution to drug discovery today.[1]

Inflammation , which is a pattern of response to injury, involves the accumulation of cells and exudates in irritated tissues, that allows protection from further damage. Inflammation has been studied for thousands of years in an attempt to combat its effects on the body. In AD 30, Celsius described the 4 classic signs of inflammation (rubor, calor, dolor, and tumor, or redness, heat, pain, and swelling), and used extracts of willow leaves to relieve them.[2] For many years, salicylate-containing plants were applied therapeutically and lead to the production of a major anti-inflammatory drug - Aspirin. Aspirin, an agent with anti-inflammatory activity, is derived from natural sources, and is used extensively in current clinical practice. Many other aspirin like drugs are now available including the non-steroid anti-inflammatory drugs (NSAIDs).

Natural products with anti-inflammatory activity have long been used as a folk remedy for inflammatory conditions such as fevers, pain, migraine and arthritis. As the inflammatory basis of disease becomes clear, anti-inflammatory food and food products become of greater interest. The British Nutrition Foundation report on phytochemicals provides a useful classification for those products, namely: terpenoids, flavonoids and allied phenolic and polyphenolic compounds and sulphur-containing compounds.[3]

Curcumin

Curcumin (Fig. 1), a low molecular weight polyphenol, is derived from the rhizomes of the plant turmeric (*Curcuma longa*), which is endemic to peninsular India. Turmeric, in the form of a paste, has been used to relieve pain and inflammation.[4] Extensive scientific research including preclinical and clinical studies revealed that curcumin has anti-inflammatory action.[5-7] Satoskar *et al*., (1986) evaluated the anti-inflammatory activity of curcumin in comparison with phenylbutazone and placebo. Both phenylbutazone and curcumin produce a better anti-inflammatory response than placebo.[5]

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Lal *et al*., (1999) studied the efficacy of curcumin in the management of chronic anterior uveitis (CAU).[6] In this study, curcumin was administered orally to 53 patients suffering from CAU at a dose of 375 mg three times a day for 12 weeks. The 32 patients who completed the 12-week study were divided into two groups: 18 patients received curcumin alone, while 14 patients, who showed a strong purified protein derivative reaction, received curcumin in addition to antitubercular treatment. The patients in both groups showed improvement after 2 weeks of treatment. All the patients who received curcumin alone improved, whereas the group receiving antitubercular therapy and curcumin had a response rate of 86%. Follow up of all the patients for the next 3 years indicated a recurrence rate of 55% in the first group and 36% in the second group. Four of the 18 patients in the first group and 3 of the 14 patients in the second group lost their vision in the follow up period due to various complications such as vitritis, macular oedema, central venous block, cataract formation and glaucomatous optic nerve damage. None of the patients reported any side effects from the drug. The efficacy of curcumin and recurrences following treatment are comparable to corticosteroid therapy, which is currently the only available standard treatment for CAU.

In another study**,** Lal *et al*., (2000) described the clinical efficacy of curcumin in the treatment of patients suffering from idiopathic inflammatory orbital pseudotumours.[7] Curcumin was administered orally at a dose of 375 mg three times a day for a period of 6-22 months in eight patients. They were followed up for a period of 2 years at three monthly intervals. Five patients completed the study; four recovered completely and with one patient, the swelling regressed completely with some persistent limitation of movement. No side effects were noted in any of the patients and there was no recurrence. Based on these results the author suggested that curcumin could be used as a safe and effective drug in the treatment of idiopathic inflammatory orbital pseudotumours.

The anti-inflammatory activity of curcumin is mainly due to inhibition of arachidonic acid (AA) metabolism,[8] cyclooxygenase (COX),[9,10] lipoxygenase (LOX),[11] cytokines interleukin (IL) and tumor necrosis factor (TNF)[12,13] and nuclear factor kappa B (NF-κB).[14] Curcumin is also reported to stabilize lysosomal membrane.[8]

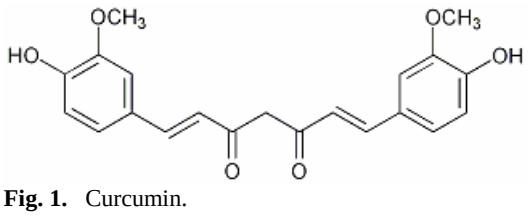


Fig. 1. Curcumin.

Parthenolide

Parthenolide (Fig. 2) is the major sesquiterpene lactone found in Mexican India medicinal plants and in feverfew (*Tanacetum parthenium*).[15] Sesquiterpene lactone-containing plants exert anti-inflammatory activity and are frequently used by Mexican Indians for the treatment of infections of the skin and other organs.[16] Parthenolide has a strong anti-inflammatory effect *in vivo*[17-19] and has long been used as a folk remedy for fevers, migraine, and arthritis**.**[20] A double-blind placebo controlled cross-over trial investigated the effect of feverfew containing parthenolide as a prophylactic treatment for migraine.[21] In this double-blind placebo-controlled cross-over study, fifty seven patients who attended an outpatient pain clinic were selected at random and divided into two groups. Both groups received a daily dose of 100 mg feverfew for 60 days in the preliminary phase (phase 1). In the second and third phases, Group A (N = 30) continued to receive feverfew for an additional 30 days and then was shifted to the placebo treatment for 30 days (100 mg daily of ground parsley). Group B (N = 27) received the first placebo treatment, for 30 days, and then was transferred to feverfew for the last 30 days. The feverfew caused a significant reduction in pain intensity compared with the placebo treatment. Moreover, a profound reduction was recorded concerning the severity of the typical symptoms that are usually linked to migraine attacks, such as vomiting, nausea, sensitivity to noise and sensitivity to light. Transferring the feverfew-treated group to the placebo treatment resulted in an augmentation of the pain intensity as well as an increase in the severity of the linked symptoms. In contrast, shifting the placebo group to feverfew therapy resulted in a reduction of the pain intensity as well as the severity of the linked symptoms. These results suggest that consuming a feverfew leaf preparation prophylactically, can ease profoundly the pain intensity and the prevalence of the typical symptoms associated with migraine attacks.

Parthenolide exerts its anti-inflammatory effect by several mechanisms. Parthenolide inhibits the expression of genes involved in inflammation such as nitric oxide (NO) synthase,[22] intracellular adhesion molecule-1,[23] and pro-inflammatory cytokines TNF-α, IL-1, IL-4, IL-8 and IL-12.[15,24-26] Parthenolide are also potent inhibitors of the pro-inflammatory transcription factor NF-κB which is a key regulator of the cellular inflammatory and immune response.[27, 28]

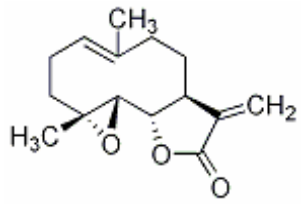


Fig. 2. Parthenolide.

Cucurbitacins

Cucurbitacins were originally isolated as the bitter principles of the Cucurbitaceae, and later founded in genera within other plant families.[29] Cucurbitacins are a group of highly structurally diverse triterpenes, characterized by the tetracyclic cucurbitane nucleus skeleton, namely, 19-(10→9β)-abeo-10α-lanost-5-ene (Fig. 3).[30] According to the characteristics of their structures, cucurbitacins are divided into twelve categories.[28] Cucurbitacins such as cucurbitacin B, D, E, I, dihydrocucurbitacin B, cucurbitacin R have anti-inflammatory activity.[31-33] Peters *et al*.,(1999)

reported that cucurbitacin B shows anti-inflammatory action in experimental models *in vivo*.[32] Recio *et al*., (2004) evaluated the anti-inflammatory activity of dihydrocucurbitacin B and cucurbitacin R via several experimental models of pain and inflammation. The results indicate that both compounds show inhibition activities of carrageenan-induced mouse paw oedema, phospholipase A_2 (PLA_2)-induced mouse paw oedema, and serotonin-induced mouse paw oedema.[33]

Although the cytotoxicity of cucurbitacins was known before 1800 AD, very little is known about the mechanism of the effect of cucurbitacins at the cellular and molecular level. Peter *et al*., (1999) reported that the anti-inflammatory activity of cucurbitacins from *Wilbrandia ebracteata* can be related to the inhibition of the production of prostaglandin E_2 (PGE_2).[32] Recently it was reported that 23, 24-dihydrocucurbitacin D (DHCD) may exert anti-inflammatory activity by inhibition of NO generation through blocking NF-κB activation, and DHCD could be a useful substance for developing anti-inflammatory drugs.[34]

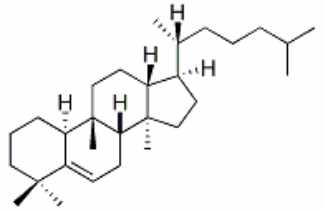


Fig. 3. Basic structure of cucurbitacin.

1,8-Cineole

1,8-Cineole (cineole, eucalyptol) (Fig. 4), a monoterpene oxide, is present in many essential oils from eucalyptus, sage, rosemary, psidium and other plants.[35] 1,8-cineole is often employed by the pharmaceutical industry in drug formulations as a percutaneous enhancer.[35] It is also considered useful for the treatment of bronchitis, sinusitis and rheumatism.[36] Santo *et al.,* (2000) used experimental inflammation in rats to verify the anti-inflammatory action of 1,8-cineole; the results showed that the 1,8-cineole has an inhibitory effect on carrageenan-induced paw oedema, cotton pellet-induced granuloma, and the acetic acid-induced increase in peritoneal capillary permeability.[36] In another study, Santo *et al*., (2004) found that 1,8-cineol can prevent colitis induced by trinitrobenzene sulfonic acid in rats.[37] Juergens *et al*., (2003) evaluated the anti-inflammatory efficacy of 1,8-cineol in treatment of asthma.[38] In this double-blind, placebo-controlled trial, thirty-two patients with steroid-dependent bronchial asthma were randomly allocated to receive either 200 mg 1,8-cineol three times a day or placebo in small gut soluble capsules for 12 weeks after determining the effective oral steroid dosage during a 2 month run-in phase. The steroid-saving effect of 1,8-cineol in severe asthma was investigated. The results showed that daily prednisolone dosage reduced by 36% in the treatment group, only 7% in the placebo group (P = 0.006), twelve of 16 patients receiving 1,8-cineol achieved a reduction of oral prednisolone, only 4 in the placebo group (P =0.012). These results suggest an anti-inflammatory activity of 1,8-cineol in asthma and a new rational for its use as mucolytic agent in upper and lower airway diseases.

Juergens *et al.,* (1998) investigated the effect of 1,8-cineole on AA metabolism in blood monocytes of patients with bronchial asthma, where 1,8-cineole was shown to inhibit leukotriene B_4 (LTB_4) and PGE_2.[39] The same group reported that 1,8-cineole inhibits the production of TNF-α, IL-1β, LTB_4 and thromboxane B_2 (TXB_2) highly in a dose-dependent manner.[40]

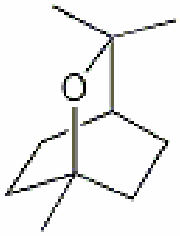


Fig. 4. 1, 8-Cineole.

Pseudopterosins

Pseudopterosins are a diterpene glycosides mixture from the Caribbean gorgonian *Pseudopterogorgia elisabethae*.[41,42] Pseudopterosins and *seco*-pseudopterosins are isolated as pseudopterosins A-L by Look *et al*., (1986) (Fig. 5),[41] pseudopterosins M-O and *seco*-pseudopterosins E-G by Ata *et al*., (2003),[43] pseudopterosins P-Z and *seco*-pseudopterosins H by Rodrı´guez *et al*., (2004).[42] Pseudopterosins is the first commercialized marine natural product for human use, used commercially in an Estee Lauder skin cream.[44] Look *et al*., (1986) reported that pseudopterosins A exhibits superior anti-inflammatory activity compared to some topical anti-inflammatory drugs such as indomethacin in their assay.[41] Mayer *et al*., (1998) evaluated the anti-inflammatory activitiy of pseudopterosin E and pseudopterosin A. The results showed they are both effective in reducing phorbol 12-myristate 13-acetate-induced mouse ear oedema and they exhibited *in vivo* analgesic activity in phenyl-p-benzoquinone-induced writhing.[45]

Research suggests that the pseudopterosins may mediate their anti-inflammatory effects by inhibiting eicosanoid release from inflammatory cells in a concentration and dose-dependent manner.[45] Although the pseudopterosins have not yet been developed as anti-inflammatory drugs, a partially purified extract of *Pseudopterogorgia elisabethae* is used as an additive in cosmetic products and a simpler modification of the pseudopterosins may have entered phase I clinical trials as an anti-inflammatory agent.[44]

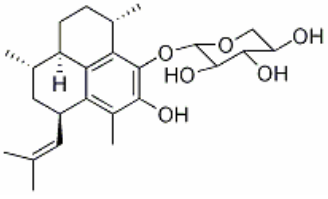


Fig. 5. Pseudopterosins A.

Lyprinol

Lyprinol, the stabilized lipid extract of the New Zealand green-lipped mussel (NZGLM) is currently used to relieve symptoms of arthritis. The oil of the NZGLM contains a complex mixture of triglycerides, sterol esters, sterols, polar lipids and free fatty acids.[46] Lyprinol has shown significant anti-inflammatory activity on adjuvant-induced polyarthritis and collagen (II)-induced autoallergic arthritis in Wistar and Dark Agouti rats.[47] Tenikoff D *et al*., (2004) compared the effect of Lyprinol and fish oil (EPA/DHA) pre-treatments on experimentally induced inflammatory bowel disease (IBD) in mice. The results showed that Lyprinol may be potentially useful in ameliorating symptoms of IBD.[48] The lack of effect of fish oil indicates that the benefit of Lyprinol is attributable to components of the stabilized lipid extract other than its omega 3 content. There are several clinical studies, either controlled or randomized, which have demonstrated significant anti-inflammatory activity in patients with osteoarthritis, rheumatoid arthritis, asthma, and other inflammatory conditions. In a multicenter trial, sixty patients with symptomatic osteoarthritis of the knee and hip were included to receive Lyprinol at a dose of 2 capsules twice a day for 4- and 8-week. After a 4- and 8-week treatment period, 53% and 80% (respectively) of patients experienced significant pain relief, and improvement of joint function. There was no reported adverse effect during this clinical trial.[49] Gruenwald *et al*., (2004) investigated the efficacy and tolerability of combination of Lyprinol and high concentrations of EPA and DHA in inflammatory rheumatoid disorders.[50] In this 12-week drug-monitoring study, fifty adult men and women with inflammatory rheumatoid arthritis received Sanhelios Mussel Lyprinol Lipid Complex. Thirty-four of 50 patients required drug therapy before and during the study. By the end of the study, twenty-one patients were able to reduce their dosage and 13 were able to terminate drug therapy. At the end of the treatment period, 38% were regarded symptom free and the number of patients with severe pain decreased significantly from 60% at baseline to 25% at the end. The special combination of Lyprinol and omega-3 fatty acids was generally very well tolerated, with only one, nonserious adverse event reported. These results showed that dietary supplement may therefore be considered an effective and well-tolerated component of treatment regimens for inflammatory rheumatoid arthritis.

The mechanism by which Lyprinol exerts its beneficial effect remains to be elucidated. Lyprinol has been shown to reduce the proinflammatory LTB_4 in human monocytes.[51] It is currently postulated that Lyprinol elicits an anti-inflammatory effect, via EPA inhibition of both 5-lipoxygenase (5-LOX) and COX arachidonate oxygenation pathways.[52] A human study has shown NZGLM lipids reduce levels of TXB_2, PGE_2, and IL-1β, with similar potency to low-dose omega-3 polyunsaturated fatty acids supplementation.[53]

Bromelain

Bromelain is a crude, aqueous extract obtained from both the stem and fruit of the pineapple plant, which contains a number of proteolytic enzymes.[54] Bromelain has been shown to have a number of beneficial effects including reversible inhibition of platelet aggregation, angina pectoris, bronchitis, sinusitis, surgical traumas, thrombophlebitis, pyelonephritis and enhanced absorption of drugs.[54] Currently, bromelain is used for acute inflammation and sports injuries. It is not a licensed medical product and is freely available to the general public in health food stores and pharmacies in the USA and Europe.[55]

A large body of scientific research shows that bromelain is a potential product for treatment of osteoarthritis.[55] Bromelain was first reported to be used as an anti-inflammatory for use in both rheumatoid arthritis and osteoarthritic patients in 1964.[55] Walker *et al*., (2002) investigated the effects of bromelain on mild acute knee pain of less than 3 months duration in otherwise healthy adults.[56] In this open, dose-ranging postal study, two validated questionnaires (WOMAC knee health Index and the Psychological Well-Being Index) were completed at baseline and after one month's intervention with bromelain, randomly allocated to volunteers as either 200mg or 400mg per day. Seventy-seven subjects completed the study. In both treatment groups, all WOMAC symptom dimension scores were significantly reduced compared with baseline, with reductions in the final battery (total symptom score) of 41 and 59% (P = 0.0001 and <0.0001) respectively. Improvements in total symptom score (P = 0.036) and the stiffness (P = 0.026) and physical function (P = 0.021) dimensions were significantly greater in the high-dose (400 mg per day) compared with the low-dose group. Compared to baseline, overall psychological well-being was significantly improved in both groups after treatment (P= 0.015 and P= 0.0003), and a significant dose-response relationship was observed. The results show that bromelain may be effective in ameliorating physical symptoms and improving general well-being in otherwise healthy adults suffering from mild knee pain in a dose-dependant manner.

The mechanism of anti-inflammatory action of bromelain is reviewed.[55] They suggest that bromelain's anti-inflammatory action is mediated by increasing serum fibrinolytic activity, reducing plasma fibrinogen levels and decreasing bradykinin levels (which results in reduced vascular permeability) and hence reducing oedema and pain; by decreasing levels of PGE_2 and thromboxane A_2 (TXA_2); and by modulation of certain immune cell surface adhesion molecules.

Flavonoids

Flavonoids are a class of group of natural substances with variable phenolic structures widely distributed in the plant kingdom, and are found in fruits, vegetables, grains, bark, roots, stems, flowers, tea, and wine. More than 4000 varieties of flavonoids have been identified.[57] The 4 main groups of flavonoids are flavones, flavanones, catechins, anthocyanins (Fig. 6).[57] A fairly large number of plants known to contain flavonoids are used in folk medicine, in some cases as anti-inflammatory agents.[57] A variety of *in vitro* and *in vivo* experiments have shown that selected flavonoids possess anti-inflammatory acti-vity. Ternatin, a tetramethoxy flavone isolated from *Egletes viscosa*, was shown to have anti-inflammatory activity in rat carrageenan-induced pleurisy test.[58] Borissova *et al*., (1994) found that the anthocyane flavonoids in the natural

juice from *Aronia melanocarpa* have anti-inflammatory effects in histamine-induced or serotonin-induced rat hind paw test.[59] Pelzer *et al*., (1998) investigated the anti-inflammatory activity of 30 flavonoids isolated from several plants of the Compositae family, and found that all the flavonoids tested have anti-inflammatory activity depending on both their structure and the method used for the assay.[60] One of the most common flavonoids in nature is quercetin, which is normally present as a glycoside, such as quercitrin (3-rutinoside) or rutin (3-rhamnoside). Quercetin is found in abundance in onions, apples, broccoli, and berries. Quercitrin and rutin display beneficial effects in experimental inflammation in the rat reduced by trinitrobenzene sulfonic acid.[61]

The mechanism by which flavonoids exert their anti-inflammatory effects involves the inhibition of COX and LOX activities, eicosanoid biosynthesis, and neutrophil degranulation. Selective flavonoids such as quercetin inhibited both COX and LOX activities.[62] Wang *et al*., (1999) found that anthocyanins and their aglycone, cyanidin, from tart cherries could inhibit the activities of COX-1 and COX-2.[63] Hou *et al*., (2005) found that anthocyanidins inhibit lipopolysaccharide-induced COX-2 expression by activating mitogen-activated protein kinase (MAPK) pathways and provide the first molecular basis for the anti-inflammatory properties of anthocyanidins.[64] Damas *et al*., (1985) suggest that catechin dimers at low doses have an anti-inflammatory effect which may depend on prostaglandin synthesis inhibition.[65]

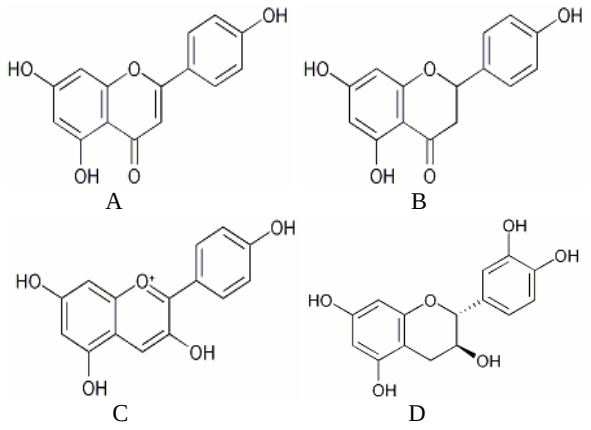


Fig. 6. The structure of each group of flavonoids (A) Flavone, (B) Flavanone, (C) Anthocyanin, (D) Catechin.

Saponins

Saponins are a group of glycosides found in many plants. Saponins can be classified into two groups based on the nature of their aglycone skeleton. One group consists of the steroidal saponins and the other group consists of the triterpenoid saponins (Fig. 7).[66] There are a number of saponins isolated from various plants which have anti-inflammatory activity.

Just *et al*., (1998) isolated three saponins (Fruticesaponin A, Fruticesaponin B, Fruticesaponin C) from *Bupleurum fruticescens*, and investigated their anti-inflammatory effects. All of them exert anti-inflammatory activity in a mouse oedema assay, however Fruticesaponin B has the highest anti-inflammatory activity.[67] Seven triterpene saponins were isolated from the methanolic extract of the aerial parts of *Bupleurum rotundifolium* by Navarro *et al*., (2001).[68] All these saponins proved to be effective against 12-*O*-Tetradecanoylphorbol-13-acetate (TPA)-induced ear oedema in mice, only two saponins were active in reducing the TPA multiple-dose model of skin chronic inflammation in mice.[68] Esculentoside A, a triterpenoid saponin, isolated from *Phytolacca esculent*, suppressed the acute and chronic inflammation strikingly in different animal models.[69]

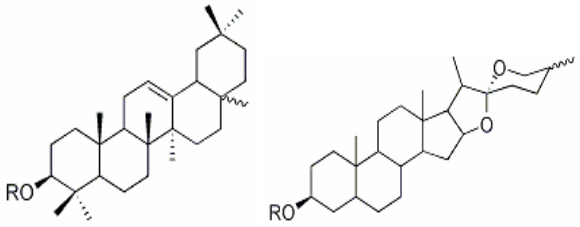
Two triterpenoid saponins, kalopanaxsaponin A and pictoside A, were isolated from the stem bark of *Kalopanax pictus* and showed significant anti-inflammatory activity at the oral dose of 50 mg/ml evaluated by vascular permeability test.[70] Choi *et al*., (2002) reported that Kalopanaxsaponin A, extracted from *Kalopanax pictus*, could reduce rheumatoidal syndromes in the rat treated with Freunds complete adjuvant reagent through anti-oxidative mechanisms.[71]

Tea-leaf saponin, a mixture of saponin separated from leaves of *Camellia sinensis* var. sinensis, inhibited rat paw oedema induced by carrageenin in a dose dependent manner.[70] Two groups of saponins, TS-1 and TS-2, isolated from root extract of *Camellia sinensis* also inhibited carrageenan-induced paw oedema in rats.[73]

Aescin, the main active constituent of *Aesculus hippocastanum*, is a complex mixture of triterpenoid saponin glycosides. It has been shown to have anti-oedematous, anti-inflammatory and venotonic properties in different animal models.[74] Wei *et al*., (2004) isolated six saponins, escin Ia, escin Ib, isoescin Ia, isoescin Ib, desacylescin I, aesculiside A, from the seed of *Aesculus chinensis*, a medicinal plant widely distributed in mid-western China. They compared the anti-inflammatory activity of four main saponins, escin Ia, escin Ib, isoescin Ia, isoescin Ib, with the total saponin extracts. Single saponins show more potent activity than total saponin extracts in mice.[75]

da Silva *et al*., (2002) isolated a new steroidal saponin from the leaves of *Agave attenuata*, and investigated it's anti-inflammatory activity using the capillary permeability assay. It inhibits the increase in vascular permeability caused by acetic acid.[76] Loni-ceroside A, isolated from the aerial parts of *Lonicera japonica*, shows anti-inflammatory activity comparable to aspirin.[77] In 2003, a new triterpenoid saponin, loni-ceroside C was isolated from the aerial parts of *Lonicera japonica* by Kwak *et al*., (2003). They found that Loni-ceroside C possesses *in vivo* antiinflammatory activity against mouse ear oedema provoked by croton oil.[78]

Buddlejasaponin IV, isolated by Jung *et al*., (2005) from the aerial portion of *Pleurospermum kamtschaticum*, significantly inhibits NO production, and it also significantly decreases PGE_2 and TNF-α release in the lipopolysaccharide-activated macrophage Raw 264.7 cells. Buddlejasaponin IV is a major bioactive saponin in *Pleurospermum kamtschaticum* and thus its inhibitory effect on NO, PGE_2 and TNF-α formation might be associated with its putative anti-inflammatory effect.[79]



A B

Fig. 7. Aglycone skeletons of (A) Triterpenoid saponins. (B) Steroidal saponins. R = sugar moiety.

Marine sponge natural products

There are many anti-inflammatory natural products from marine sponge. Eighty four anti-inflammatory compounds dominated by isoprenoid derived metabolites, especially sesterterpenes (means 2.5 terpenes) have been isolated from marine sponges.[80] The most commonly used assay to assess anti-inflammatory activity of natural products from marine sponge is the inactivation of PLA_2. PLA_2 enzymes hydrolyze phospholipids at the sn-2 position of the glycerol backbone, generating AA. AA is then metabolized via several different pathways to form the inflammatory compounds prostaglandins, thromboxanes and leukotrienes.[80]

Manoalide (Fig. 8) is probably the most well known of all anti-inflammatory products from sponge and was originally isolated by de Silva and Scheuer in 1980 from the sponge *Luffariella variabilis*.[81] Manoalide's anti-inflammatory properties have been studied extensively. The anti-inflammatory effects of Manoalide is based on the irreversibly inhibition of PLA_2 with the corresponding modification of a specific number of its lysine residues.[82] The original compound was licensed to Allergan and placed into clinical trials as a topical antipsoriatic with a company code name of AGN-190093.[44] Four anti-inflammatory pyridinium alkaloids, named spongidines A-D, were isolated from a Vanuatu sponge of the genus *Spongia*. Spongidines A-D inhibited five secretory PLA_2 enzymes and none of the compounds exhibited cytotoxic effects on human neutrophils at the concentrations tested.[83]

As well as variation in the classes of sponge natural products that possess anti-inflammatory activity, these compounds exert anti-inflammatory activity through different mechanisms. Some compounds such as Manoalide[82], spongidines A-D[83], petrosaspongiolides M-R[84] and dysidenones A, B and dysidine[85] are potent inhibitors of the enzyme PLA_2, which is intimately involved in the initial step of the inflammatory response. Cycloamphilectene 2, a novel marine diterpene isolated from the Vanuatu sponge *Axinella* sp. is an inhibitor of the NF-κB pathway, exhibits topical anti-inflammatory activity.[86]

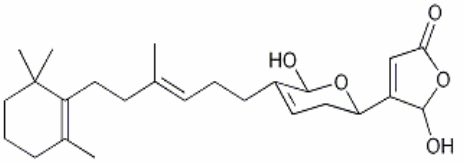


Fig.8. Manoalide

Boswellia serrata gum resin

Boswellia serrata is native to India and has been used in traditional Ajurvedic medicine for the treatment of inflammatory diseases in India.[87] The gum resin of *Boswellia serrata* called 'salai guggul' or 'Indian olibanum' is obtained from the bark of *Boswellia serrata* after injury. It is fragrant and burns with a pleasant odour and is used as incense in religious ceremonies and worship. In recent years the gum resin has been used extensively in pharmaceutical formulations for relieving pains and aches, particularly associated with arthritis. Many commercial formulations of salai guggul in the form of ointments, creams and capsules are available on the market.[88] *Boswellia serrata* gum resin contains a monoterpene essential oil (3-10%), resin acids (60-70%), and water soluble gum (about 20%). *Boswellia serrata* gum resin has been reported to have anti-inflammatory activity. There are several clinical trials which shown to improve symptoms of ulcerative colitis and Crohn's disease. As a result of its alleged safety, boswellia was considered superior over mesalazine in terms of a benefit-risk evaluation.[89] Gupta *et al*., (2001) studied the gum resin of *Boswellia serrata* for the treatment of chronic colitis.[90] In this study, thirty patients with chronic colitis were included. Twenty were given a preparation of the gum resin of *Boswellia serrata* at a dose of 300mg three times a day for 6 weeks, and 10 patients were given sulfasalazine at a dose of 1g three times a day for 6 weeks and served as controls. Out of 20 patients treated with *Boswellia serrata* gum resin, 18 patients showed an improvement. In the control group 6 out of 10 patients showed similar results with the same parameters. Out of 20 patients treated with *Boswellia serrata* gum resin 14 went into remission while in the case of sulfasalazine remission rate was 4 out of 10. This shows that a gum resin preparation from *Boswellia serrata* could be effective in the treatment of chronic colitis with minimal side effects. Research has shown that it is perhaps the triterpenoid boswellic acids in the *Boswellia serrata* gum resin which exert the anti-inflammatory acition.[91] Boswellic acids inhibit the enzyme 5-LOX, thereby reducing the production of the potent inflammatory mediators, the leukotrienes.[92]

Conclusions

Current interest leads to the search for new natural products with anti-inflammatory activity. Extensive scientific research deals with the finding, extracting, pharmacological effects and mechanism by which natural products exert their activity. As demonstrated in this review, the potential for natural products as sources of drugs to cover a very wide range of pharmacological effects is now being realized. It is probable that within a few years novel agents from natural products will enter the commercial industry as anti-inflammatory drugs. At the same time, the place of anti-inflammatory foods in the human diet will be better defined and developed; and may constitute a safer and more comprehensive approach to human health than isolated food components or extracts.

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Original Article

Natural products and anti-inflammatory activity

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天然产物及其抗炎活性

本文的目的是总结目前常见的天然产物及其抗炎活性。我们从 MEDLINE，Current Contents 和学术期刊上收集相关信息，共涉及到 92 篇文章。文献报道有大量的天然产物，我们仅仅对其中几种最常见效果较明显的几种天然产物进行了总结，本文综述了姜黄素、小白菊内酯、葫芦素、1,8-桉叶素、伪厥素、Lyprinol、菠萝蛋白酶、类黄酮，皂甘、海洋海绵动物天然产物和印度乳香树脂等天然产物。天然产物在人类健康中对预防和治疗炎症疾病起重要的作用，但天然产物的作用机制、代谢和安全性，天然产物长期的副作用效果以及这些天然产物与食品药物成分的相互作用等方面还需要进一步研究。

关键词： 炎症、抗炎活性、天然产物、抗炎食品、疼痛、偏头痛、关节炎、哮喘、慢性大肠炎、炎症疾病。