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Review Article

CURRENT DEVELOPMENTS ON ANTI-INFLAMMATORY NATURAL MEDICINES

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ABSTRACT

New anti-inflammatory substances are still vitally necessary due to intolerable side effects of the marketed anti-inflammatory drugs; however, the search for the novel entity against inflammation is challenging because of the complexity of the inflammatory process and its role in host defense to infections. Nature is the source of remedies for the mankind. Among the different biological activities of natural products that have been published till date, anti-inflammation is one of the most reported effects. In this review, we have discussed the current (2009–2018) information of some single natural products (quercetin, parthenolide, resveratrol, curcumin, cucurbitacin, capsicin, 1,8-cineole, bromelain, boswellic acid, lyprinol, and coumarin), plant products (garlic, ginger, papaya, blueberry, aloe, broccoli, olive, and rosemary), and non-plant products (marine sponges, mushrooms, and honey) having anti-inflammatory effects. Current information is mainly based on the molecular mechanisms of the above-mentioned products.

Keywords: Single natural products, Plant products, Non-plant products, Anti-inflammatory activity, Molecular pharmacology.

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INTRODUCTION

Inflammation is the response to body aggression by a pathogen agent, an allergen, a toxic compound, a tissue lesion, etc. It is generally a phenomenon with fever and tiredness, with local symptoms, pain, and edema. During the inflammatory process, monocytes are rapidly recruited to the damaged or infected tissue, where they can differentiate into macrophages and leads to the regulated production of various pro- and anti-inflammatory mediators including cytokines, such as tumor necrosis factor-α (TNF-α) and interleukins (IL-1β -2, -4, -6, and -12), chemokines, such as neutrophil chemotactic factor IL-8, monocyte chemotactic and activating factor, transcription factors, such as nuclear factor-κB (NF-κB) signal transducers and activators of transcription (STAT), protein kinases, such as mitogen-activated protein kinases (MAPK), methyl-accepting chemotaxis protein (MCP), macrophage migration inhibitory factor (MMF) and inducible enzymes, such as cyclooxygenase (COX-2), 5-lipoxygenase (5-LOX), inducible nitric oxide synthase (iNOS) [1-5]. Inflammation may be the cause of several chronic diseases such as arthritis, diabetes, obesity, cancer, neurodegenerative diseases, autoimmune disorders, dementia, scleroderma, allergy, asthma, bronchitis, inflammatory bowel disease, and cardiovascular diseases, which have been increased dramatically over the last three decades [6,7]. Non-elective nonsteroidal anti-inflammatory drugs (NSAID) and COX-2 selective inhibitors are associated with various adverse effects, such as gastric ulceration, acute renal failure, and increased cardiovascular risk [8-11]. Hence, it is essential to find out newer drug leads for the treatment of inflammation.

SINGLE NATURAL PRODUCTS WITH ANTI-INFLAMMATORY ACTIVITIES

Quercetin

Quercetin, a naturally occurring polyphenol, found in a wide variety of food, such as, berries, broccoli, red onions, apples, grapevines and tea and have significant anti-inflammatory effects in both acute and chronic inflammatory conditions [12]. It inhibits the production of inflammation-producing enzymes (COX and LOX) [13]. Quercetin also exhibited protective effect against inflammation induced by hydrogen peroxide in human umbilical vein endothelial cells and indicated that the effect was mediated through the downregulation of vascular cell adhesion molecule 1 and CD80 expression [14]. Quercetin reduced inflammation in sarcoidosis patients by inhibiting the synthesis of pro-inflammatory cytokines, TNF-α and IL-8 [15]. Several recent clinical and preclinical findings suggest quercetin as a promising natural treatment for inflammatory skin diseases such as atopic dermatitis [16].

Parthenolide

Parthenolide, a sesquiterpene lactone, is extracted from the shoots of *Tanacetum parthenium* has been used to treat inflammatory conditions such as arthritis. It has NF-κB inhibiting properties in macrophage cell lines [17]. Studies are done on the parthenolide-depleted (PD) feverfew, which confirmed the inhibition of release of pro-inflammatory mediators such as TNF-α, IL-2, IL-4 from human mononuclear cells, prostaglandin-E_2 (PGE_2), and NO. In addition, PD- feverfew inhibits the release of tissue plasminogen activator induced from human skin equivalents [18].

Resveratrol

Resveratrol, a stilbene derivative, can be found in peanuts, grapes, berries, and red wine [19]. It was found to have anti-inflammatory activity by activating peroxisome proliferator-activated receptor, endothelial NOS, and sirtuin-1 [20-22]. Resveratrol also inhibits the COX, NF-κB, and phosphatidylinositol 3-kinase/Akt pathwas, which are involved in inflammation and many other diseases, such as various metabolic, neurodegenerative, and cardiovascular disorders. A lot of clinical trials have been reported on resveratrol, which are focused on inflammation associated disorders, many of them dealing with diabetes, obesity, cardiovascular diseases, topical diseases, cancer, and neurodegenerative diseases [23,24].

Curcumin

Curcumin is a polyphenol isolated from the rhizome of the plant Curcuma longa. It is the main ingredient of turmeric, the Indian spice, has been used for centuries in Ayurvedic medicine against inflammatory disorders. Curcumin exhibited anti-inflammatory property by the regulation of various molecular targets, including transcription factors (such as NK-κB), inflammatory cytokines (such as TNF-α, IL-1 -2, -6, and -12), protein kinases (such as MAPK, and Akt, MCP, MMF) and other enzymes (such as COX-2 and 5-LOX, iNOS). Curcumin has been shown to be effective as anti-inflammatory/anti-rheumatic agent in some clinical trials [2,3].

Cucurbitacin

Cucurbitacin E (CE) was isolated fron *Citrullus lanatus* and the compound was examined for its anti-inflammatory action. Intraperitoneal injection of CE significantly suppressed carrageenan induced rat's paw edema. The result showed that CE is potentially useful in treating inflammation through the inhibition of COX and reactive nitrogen species. The compound showed more selectivity toward COX-2 [25]. Cucurbitacin IIb (CuIIb) is one of the major active compounds in hemsleyadine tablets which have been used for clinical treatment of enteritis and acute tonsillitis. CuIIb downregulated concanavalin A-induced STAT3 and NF-κB, phosphorylation in lymphocytes [26].

Capsicin

Capsaicin is a very hydrophobic alkaloid obtained from chili peppers (*Capsicum* species). A research on capsaicin reported that it acts against neuropathic pain by activating transient receptor potential channel vanilloid subfamily member 1 (TRPV1), a nonselective cation channel, mainly located in nociceptive neurons [27]. Prolonged activation of TRPV1 by capsaicin is discussed to cause desensitization and, thus, reduced pain sensation [28]. Capsaicin is effective in the management of osteoarthritis [29].

1,8-Cineole

1,8-cineole (eucalyptol) is a cyclic ether and a natural monoterpene, a major compound of many plant essential oils, mainly extracted from *Eucalyptus globulus* oil. 1,8-cineole has anti-inflammatory properties and based on this properties, recent clinical trials have shown the beneficial use of 1,8-cineole as long-term therapy in the prevention of chronic obstructive pulmonary diseases (COPD)-exacerbations and to improve asthma control [30,31]. As non-steroidal anti-inflammatory agent, 1,8-cineole can improve steroid effects when combined with budesonide and formoterol for asthma and COPD [32]. 1,8-cineole reduced lipopolysaccharide (LPS)-induced inflammation by inhibiting NF-κB in human cell lines U373 and HeLa [33].

Bromelain

Bromelain, an enzyme, was found in pineapple used as one of the most effective anti-inflammatory agents with adequate toxicology and safety testing data. The combination of bromelain and amenthoflavone exhibited a potential anti-inflammatory action by antagonising the Phoapholipase A2 [34]. Habashi *et al.* in 2016 studied the anti-inflammatory properties of bromelain. The results showed that bromelain normalized the upregulated iNOS mRNA and inhibited NF-κB in microglial cells of rat [35].

Boswellic acid (BA)

BAs, pentacyclic triterpenic acids, were obtained from the resin of *Boswellia serata*. Among the various BAs 11 β- BA, acetyl-β-BA, 11-keto-β-BA (KBA), and acetyl- KBA have been observed to be active as anti-inflammatory agents and the most potent one was the acetyl- KBA. From the various studies, it was observed that BAs cause downregulation of TNF-α and decrease of IL-1, IL-2, IL-4, IL-6, interferon gamma, and inhibit 5-LOX [36,37]. Some derivatives of BA and KBA with well-known anti-inflammatory drugs (i.e., aspirin, naproxen, ibuprofen and cinnamic acid) have been synthesized and evaluated for their anti-inflammatory and anti-arthritic activities. Among synthesized compounds, two compounds bearing naproxen and BA/KBA unit have displayed potent anti-inflammatory and anti-arthritic activities [38].

Lyprinol

Lyprinol is a lipid extract of the *Perna canaliculus*, which has been shown to be effective as anti-inflammatory agent in rats with carrageenan-induced pleurisy. The compound acted as dual inhibitors of COX and 5- LOX *in vitro* [39]. It has found to exhibit anti-arthritic activity [40].

Coumarin

Daphnetin, a coumarin derivative with analgesic and anti-inflammatory effects, was extracted from *Daphne odora* and exhibited anti-arthritis effect in collagen-induced arthritis rat model through modulating the balance of T-regulatory and T-helper 17 [41]. Daphnetin also showed anti-inflammatory response in BV2 microglia by depressing the pro-inflammatory mediators (IL-1β, TNF-α induced by LPS) and by inhibiting the LPS-induced iNOS and COX-2, NO formation by microglia [42]. Aurapten, another coumarin derivative isolated from Ferula szowitsiana and exhibited cancer chemopreventive properties suggested by anti-inflammatory activity of the compound [43]. Two coumarin derivatives, namely, 6-isopentenyloxy-7-methoxy-coumarin and 8-isopentenyloxy-7-methoxy-coumarin, were isolated from *Gerbera serrata* and *Haplophyllum pedicellatum,* respectively, and investigated for anti-inflammatory activity on U937-3xκB-LUC cell line. The compounds showed promising activity by inhibiting the LPS-induced NF-κB signalling pathway [44].

NATURAL PLANT PRODUCTS WITH ANTI-INFLAMMATORY ACTIVITIES

Garlic (*Allium sativum*)

The benefits of garlic to the human health have been promulgated for centuries. *A. sativum* is a plant from the genus allium is important for its production of organosulfur compounds having promising anti-inflammatory activity [45]. Organosulfur compounds (Ajoene, diallyl sulfide, diallyl disulfide, allylmethyl sulfide, S-allyl cysteine, alliin, and allicin) were evaluated in various *in vitro* and *in vivo* animal models and also experimented in human volunteers for pre-clinical studies. These compounds inhibited LPS-induced inflammation by reduction in PGs, NO, IL-1β, IL6 and TNF-α levels; increase in IL-10 levels; inhibition of COX-2, iNOS, and NF-κB activity [46].

Ginger (*Zingiber officinale*)

Ginger contains many active components of which gingerol, shogaol, and other structurally-related substances inhibit PG and leukotriene synthesis by suppressing the 5-LOX or PG synthetase. In addition, the fore-mentioned components also inhibit the synthesis of pro-inflammatory cytokines such as IL-8, IL-1, and TNF-α. Gingerol and shogaol can also inhibit LPS-induced COX-2 [47]. Shimoda *et al.* studied red ginger extract (RGE) and found that the ethanolic extract had potential to inhibit PGE_2 and NO in case of edema in rat models. RGE contains 6-shogaol, gingerdiols, and proanthocyanidins, are responsible for suppressing NO production [48].

Papaya (*Carica papaya*)

Papaya belonging to the family, Caricaceae, is grown in various parts of the world, including India, tropical America and Europe [49]. It contains papain, which is responsible anti-inflammatory action [50]. A report demonstrated the significant anti-inflammatory activity of papaya leaf juice (at 0.72 ml/100 g body weight) against carrageenan-induced rat paw edema [51]. Bertrand *et al.* in 2014 experimented on papaya extract to find out the anti-inflammatory activity and the extract showed reduction in TNF-α production in dependent manner [52].

Blueberry *(Vaccinium corymbosum)*

Blueberry contains a significant amount of flavonoids, specially anthocyanins, which are the active components possessing anti-inflammatory action. Studies revealed that blueberry-enriched diet normalized the enhanced levels free radicals, gene and protein expression of inflammatory cytokines in post-traumatic stress disorder in rats [53]. Johnson *et al.* evaluated anti-inflammatory effect of anthocyanins and proanthocyanidins from fermented blueberry-blackberry beverages and observed that the compounds reduced LPS-induced inflammation through NF-κB-mediated pathway in macrophages of mouse [54]. Huang *et al.* in 2014, had done a study to investigate the inhibitory effect of blueberry's two main anthocyanins known as malvidin-3-glucoside and malvidin-3-galactoside on inflammatory response in endothelial cells. They found thatmalvidin-3-glucoside had better anti-inflammatory effect than malvidin-3-galactoside and their anti-inflammation mechanism was mediated by the NF-κB pathway [55].

Aloe *(Aloe vera)*

Aloe has been used for millennium which is more like a cactus plant, growing in hot and dry climates, containing compounds such as aloe emodin, aloin, aloesin, saponins, and terpenoids that possess anti-inflammatory actions [56]. The anti-inflammatory effects of aloe is due to the Salicylic acid which is the reason for the inhibition of formation of bradykinin and histamine and oxidation of arachidonic acid, which further is the reason for inhibition of PG synthesis [57].

Broccoli *(Brassica oleracea)*

The young broccoli sprouts contain bioactive compounds specifically sulforaphane, which has anti-inflammatory effect. Study showed that, sulforaphane, an isothiocyanate, decreased the concentration of m-RNA of the pro-inflammatory cytokines TNF-α and IL-1β in murine RAW267.4 macrophages due to pro-inflammatory stimulus with bacterial LPS [58,59].

Olive *(Olea europaea)*

The phenolic extracts from virgin olive oil (VOO) are the focus of inflammation research as major product to fight against inflammatory diseases. Studies found out the VOO intake have markers on inflammation. Recent evidence has demonstrated that the VOO- phenolic extract potentially inhibits p-38 phosphorylation which results in reduction of COX-2 expression. The inflammatory pathways relevant to VOO, namely are the arachidonic pathway and the NF-κB [60]. Oleocanthal, a polyphenolic natural compound from VOO, reported as a potential therapeutic agent for the treatment of inflammatory degenerative diseases. The anti-inflammatory activity of oleocanthal was associated with the inhibition of LPS-induced NO production in J774 macrophages [61].

Rosemary *(Rosmarinus officinalis)*

Rosemary was found to have topical anti-inflammatory effect in mice [62]. Rosemary extract has shown gastroprotective effect against gastric ulcer due to its inhibition in neutrophils infiltration and reduction in proinflammatory mediators such as TNF-α and IL-1 [63]. The anti-inflammatory potential of rosemary is due to rosmarinic acid, which reduced rat paw edema over 60% at 6 h at the dose of 25 mg/kg [64]. In another study, rosmarinic acid was evaluated for its preventive activity in a murine model of asthma. Based on the results, it was concluded that the possible molecular mechanisms of rosmarinic acid might be mediated by the suppression of ERK, JNK, and p38 phosphorylation [65].

NATURAL NON-PLANT PRODUCTS WITH ANTI-INFLAMMATORY ACTIVITIES

Marine sponges

Very recently, Ahmad *et al.* isolated 6-bromoisatin from the Muricidae mollusk *Dicathais orbita* as potent anti-inflammatory agent. The compound reduced LPS-induced acute lung inflammation in a mouse model by inhibiting the production of TNF-α and IL-1β [66]. In 2015, some diterpenoids were isolated from marine source and their anti-inflammatory activity has been shown to inhibit of NF-κB activation and to modulate of arachidonic acid metabolism [67].

Mushrooms

Elsayed *et al.* reported anti-inflammatory activities of mushrooms. Terpenoids, such as cyathins and related compounds, contained in these mushrooms are responsible for anti-inflammatory activity. They also suggested the mechanisms of action of the biologically active compounds. The compounds exhibited their anti-inflammatory effects due to reduction of IL-1β, IL-6, LTs, PGs and TNF-α levels, and, inhibition of COX-2, iNOS and NFκB activity [68]. The ethanolic extract of mushroom was assessed on stimulation of RAW264.7 macrophages for the production of the inflammatory mediator NO with liposaccharide for the anti-inflammatory action. The anti-inflammatory function of mushroom extracts is related to the potential of inhibition of specific steps leading to the NF-κB release [69]. Jedinak *et al.* in in 2011 did research on oyster mushroom concentrate (OMC), which on treatment suppressed the LPS-dependent production of TNF-α, IL-6 and IL-12 in a dose-response manner. The effect was not caused by the cytotoxicity of OMC as OMC did not affect viability of RAW264.7 cells. Only slight inhibition of cell viability was seen. Therefore, the anti-inflammatory action of OMC is by the inhibition of production of TNF-α, IL-6 and IL-12 [70].

Honey

Honey reduced inflammatory response not only in animal models and cell cultures but also in clinical trials [71]. Phenols and flavonoids present in honey are responsible for anti-inflammatory activity. These compounds were involved in regulation of proteins including of iNOS, ornithine decarboxylase, tyrosine kinase, and COX-2. Honey also inhibited the production of NF-κB, IL-1β, and IL-6 [72,73]. In an inflammatory model of colitis, honey was as effective as prednisolone treatment, without the major side effects associated with NSAIDs and corticosteroids [74].

CONCLUSION

Nature is a rich source for the development of novel lead as anti-inflammatory agent. Current interest will lead the researchers to search for new natural products with anti-inflammatory activity. It is very probable that in the coming years, more novel products will get entry into the commercial market. Based on the literature survey, we are concluding that, there are very less or no side effects of the above mentioned anti-inflammatory natural drugs. Furthermore, these are not only the ones having anti-inflammatory effects; however, there are a number of known natural products having anti-inflammatory effect and few are under research. To date, clinical trials conducted with anti-inflammatory natural products are very limited. A few of the above mentioned single natural compounds, such as quercetin, curcumin, resveratrol, CuIIb, and non-plant products, such as honey have been reached in clinical trials against inflammation. Hence, more clinical trials are necessary for the safety and efficacy of natural products, to bring them in the market as anti-inflammatory drug, either alone or in combination with other anti-inflammatory agents.

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

AD: Atopic dermatitis
COPD: Chronic obstructive pulmonary disease
COX: Cyclooxygenase
eNOS: Endothelial nitric oxide synthase
H_2O_2: Hydrogen peroxide
iNOS: Inducible nitric oxide synthase
IL: Interleukin
IFNγ: Interferon gamma
LOX: Lipoxygenase
MAPK: Mitogen-activated protein kinase
MCP: Methyl-accepting chemotaxis protein
MMF: Macrophage migration inhibitory factor
NFκB: Nuclear factor κB
NO: Nitric oxide
PI3K: Phosphatidylinositol 3-kinase
PTSD: Post-Traumatic Stress Disorder
PPAR: Peroxisome proliferator-activated receptor
PGE_2: Prostaglandin-E_2
RNS: Reactive nitrogen species
SIRT: Sirtuin
STAT: Signal transducer and activator of transcription
VCAM: Vascular cell adhesion molecule
TNF: Tumor necrosis factor

Tregs: T-regulatory
Th17: T-helper 17
TPA: Ttissue plasminogen activator
TRPV1: Transient receptor potential channel vanilloid subfamily member 1

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