Journal of Innovations in Pharmaceutical and Biological Sciences (JIPBS)
ISSN: 2349-2759
Available online at www.jipbs.com

Review article

New insight on inflammation and its management: A Review

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Key words: Inflammation, COX, NSAIDs, SEGRA, Resolvins.

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Abstract

Inflammation is the defense mechanism of body in which immune system fights against something that may turn out to be harmful. It is the common link between debilitating conditions such as alzheimers, heart disease, arthritis and cancer. An effective anti-inflammatory strategy for the management of inflammation might be able to inhibit the development of inflammation without interfering in normal homeostasis. This review mainly focuses on the etiology of inflammation and newer molecules to battle the stimulus of inflammation and also accentuate on diverse studies carried out in the past. Thus, the high predominance of inflammation obliges the development of new moiety that could be safe and efficient to confer protection against inflammation is urgently needed.

Introduction

Inflammation is a protective attempt by the organism to remove the injurious stimuli and to initiate the healing process [1]. Pain, heat, redness and swelling (*i.e.* dolor, calor, rubor and tumor) are the typical characteristics of the inflammatory process. Inflammation is a dynamic process and can be classified as either *acute* or *chronic*. *Acute inflammation* is the initial response, characterized by the increased movement of plasma and innate immune system cells, such as neutrophils and macrophages, from the blood into the injured tissues. *Chronic inflammation* is a progressive change in the type of cells present at the site of the inflammatory reaction and is characterized by simultaneous destruction and healing of the injured tissue [1]. However, inflammation is the body natural defense mechanism against injury, irritant chemical or pathogens but uncontrolled inflammation has been also reported to be associated with the onset of various chronic diseases such as arthritis, autoimmune disorders, degenerative joint diseases, atherosclerosis, psoriasis, asthma, diabetes and even cancer [2].

Numerous mediators contribute to the inflammatory process; some are released without delay (*i.e.*, serotonin, histamine *etc.*), some are prepared and secreted within a short time interval (leukotrienes, prostaglandins, platelet-activating factor *etc.*), a few entail the *de novo* synthesis (interferon, interleukin, growth factors *etc.*). Both pre and pro-inflammatory cytokines like interferon (IFN), tumor necrosis factor (TNF), interleukin 1β (IL-1β), oxidative stress promote inflammation by stimulation of gene expression which depends on the availability of binding sites for the nuclear factor kappa activated B cells (NF-κB).

Inflammatory COX pathway (Figure 1)

Cyclooxygenase (COX), officially known as prostaglandin-endoperoxide synthase (PTGS), exists in two distinct isozymes, COX-1, which is constitutively expressed; and COX-2, which is inducible [3]. COX is the functional enzyme that catalyzes the first two steps namely cyclooxygenation and peroxidation, in the pathway leading to the formation of prostaglandins and thromboxane from the substrate arachidonic acid [4]. Prostaglandins can be released by any cell of the body during tissue, chemical or traumatic injury, and can induce fever, inflammation and pain. In addition, Thromboxanes, which are also hormone activators, can regulate blood vessel tone, platelet aggregation, and clot formation to increase the inflammatory response [5].

Therefore, arachidonic acid pathway becomes the major inflammatory pathway because arachidonic acid is immediately released from traumatized cellular membranes. Recently, the third isoform of COX enzyme was identified and named as COX-3 as a splice variant of COX-1, which retains intron one and have a frame shift mutation [6].

NF-κB inflammatory pathways and cytokines

The NF-κB proteins are localized in the cytoplasm of the cell and are associated with a family of inhibitory proteins known as inhibitor of κB (IκB) [7]. It controls transcription of deoxyribonucleic acid (DNA) along with production of cytokine that regulates the involvement of genes in numerous aspects of the inflammatory reaction (Figure 2). The NF-κB transcription factor induces pro-inflammatory genes encoding for the production of chemokines, cytokines, adhesion molecules like vascular cell adhesion molecules-1 (VCAM- 1) and intercellular adhesion molecules-1 (ICAM-1), inducible nitric oxide synthase (iNOS), metalloproteases

(MMP-9), including cyclo-oxygenase (both COX-1 & COX-2). The TNF-α, and especially IL-1b, can also directly stimulate enzymes known as matrix metalloproteinases, which break down extracellular collagen matrix, a hallmark of inflammatory joint disease [8].

Research now indicates that blocking the activation of NF-kB along with other inflammation mediators is the major mechanism for reducing inflammation. Moreover, excessive and long-lasting expression of pro-inflammatory mediators could be harmful to the host; since incorrect regulation of NF-κB has been linked to life threatening diseases such as cancer, septic shock, autoimmune diseases *etc.*

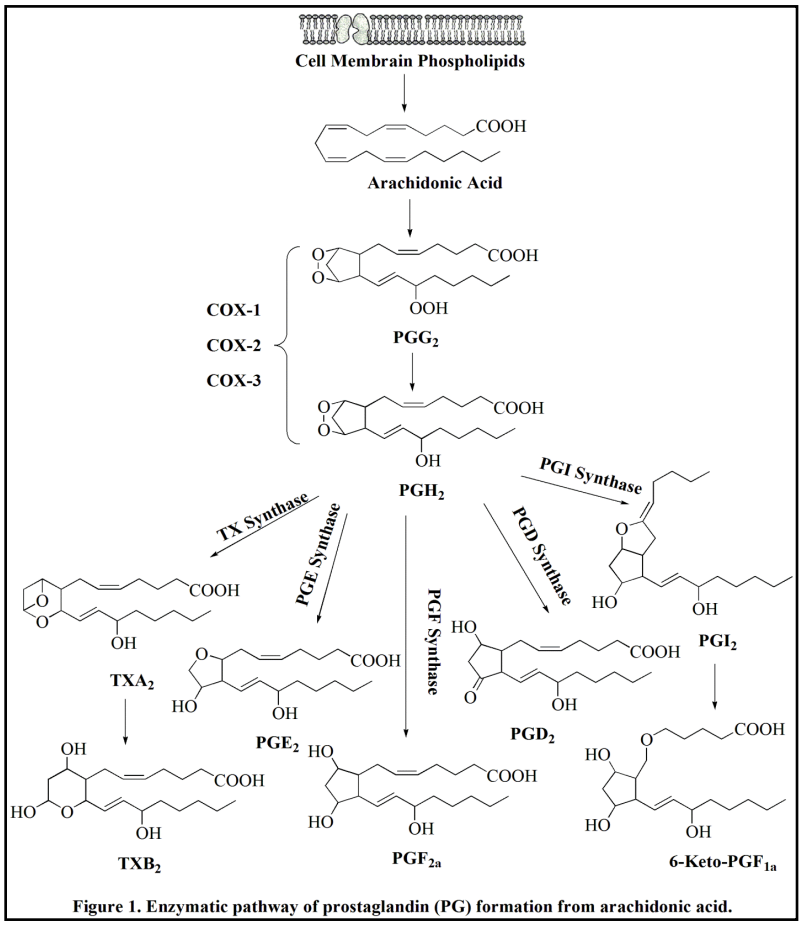

Figure 1. Enzymatic pathway of prostaglandin (PG) formation from arachidonic acid.

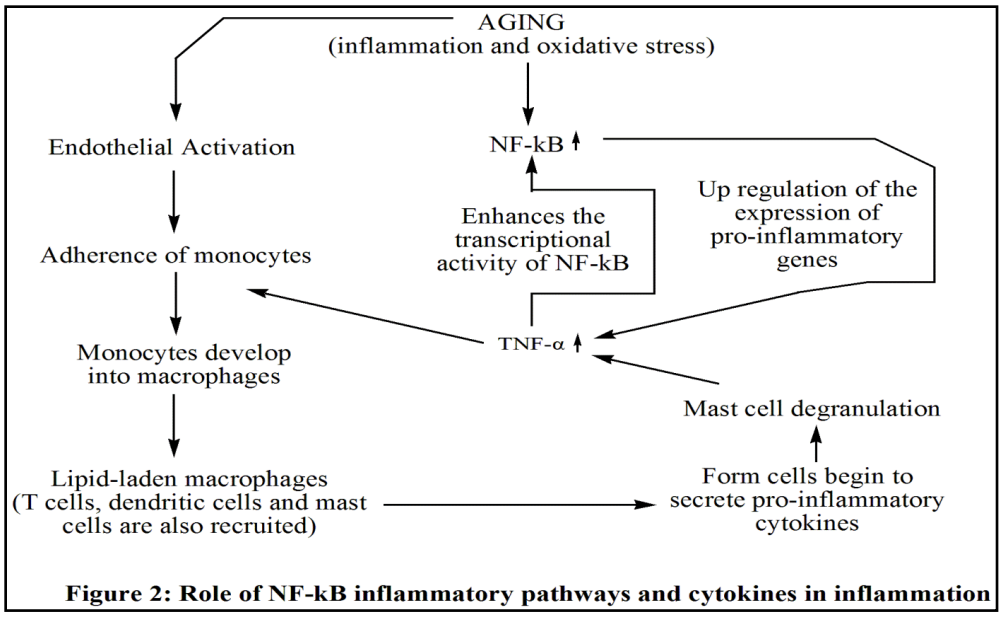

Figure 2: Role of NF-kB inflammatory pathways and cytokines in inflammation

Inflammation associated with Cancer metastasis

Cancer metastasis is a process by which tumor cells disseminate from the primary tumor through body fluids, which can settle and grow at a site other than the primary tumor site. Metastasis is facilitated by four essential steps: detachment, migration, invasion and adhesion. Metastasis is regulated by various signaling pathways and is affected by the surrounding extracellular matrix (ECM). It is now known that metastasis genes are stress-response genes that physiologically contribute to inflammation, wound healing and stress-induced angiogenesis [9]. Moreover, CD_4 are lymphocyte-homing receptors and play an important role in lymphocyte homing, inflammation, cell signaling, adhesion, migration, aggregation and hyaluronan (HA) decomposition.

In addition, chemokines are peptide signaling cytokines that act as a chemoattractants to guide the migration of cells. They are involved in a variety of physiological and pathological conditions including lymph node organogenesis, inflammation, infection, tissue repair, initiation, and progression of cancer. Additionally, to shift the microenvironment to a metastasis-promoting state, cancer cells need to either transform the resident normal stroma cells to facilitate their growth/invasion or recruit other metastasis-promoting stromal cells to remodel the microenvironment. The macrophages within tumor are referred to as tumor-associated macrophages (TAM), which upon activation by cancer cells, can release a vast diversity of growth factors, proteolytic enzymes, cytokines, and inflammatory mediators [10].

Anti-inflammatory strategies

An effective anti-inflammatory drug should be able to inhibit the development of inflammation without interfering in normal homeostasis [1]. In most of the cases, the genesis of pain is inflammatory, regardless of the etiology. Moreover, with the elucidation of the role of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α [11], interleukin (IL)-1β, and vascular endothelial growth factor (VEGF), there is now a clear understanding of the pathways by which many anti-inflammatory drugs can alleviate inflammation and relieve pain [1]. These pro-inflammatory cytokines result in chemo attractant for neutrophils and help them to stick to the endothelial cells for migration. They also stimulate white cell phagocytosis and the production of inflammatory lipid prostaglandin E2 (PGE_2).

Non-steroidal anti-inflammatory drugs (NSAIDs)

At present, NSAIDs have broad clinical importance in treating pain, fever and inflammation and hence become the most prescribed drugs as anti-inflammatory agents [12]. NSAIDs ability to interfere with the production of prostaglandin during the inflammatory cascade is the major mechanism cited for the anti-inflammatory success of these medications [Figure 3] [13]. These agents also inhibit the NF-κB pathway in endothelial cells to inhibit leukocyte recruitment [14]. NSAIDs have evolved from blocking both COX-1 and COX-2 to selectively only blocking COX-2 in order to inhibit the inflammatory response and reduce the production of inflammatory PGs and TX. The major push to develop the selective COX-2 inhibitors, without affecting the COX-1 dependent PGs has been the recognition of significant complications associated with the nonselective COX-1 and COX-2 NSAIDs.

Apart from the beneficial anti-inflammatory, antipyretic and analgesic effects of nonselective NSAIDs, the use of these agents also associated with various unwanted side effects such as physiological homeostasis [15], skin atrophy [16], impaired memory [17], steroid-induced osteoporosis [18], gastric erosions, which can become stomach ulcers and in extreme cases can cause severe haemorrhage, resulting in death [19].

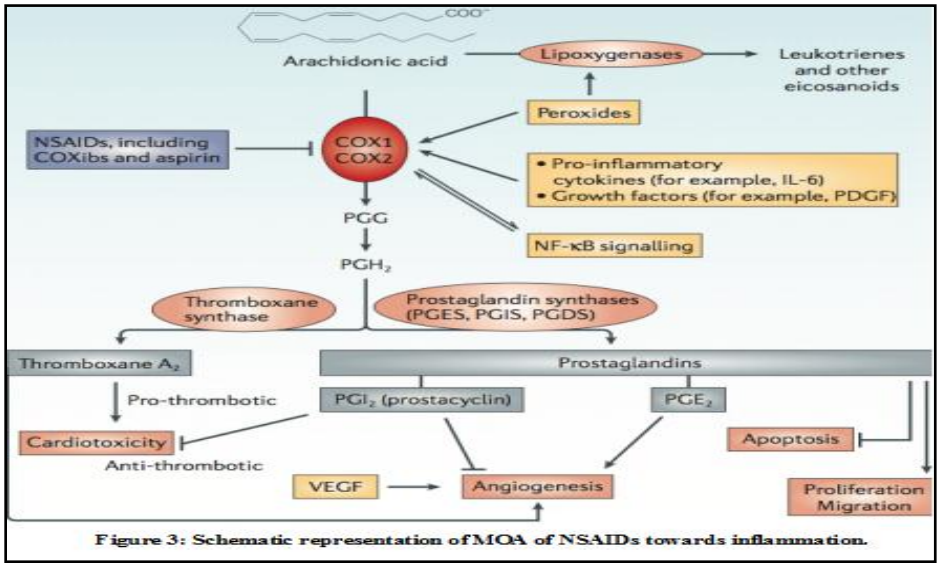

Figure 3: Schematic representation of MOA of NSAIDs towards inflammation.

Selective COX-2 inhibitors coxib's

The rationale behind the development of these inhibitors was the discovery of the COX-2 isozyme and the characterization of its role in production of anti-inflammatory and analgesic effects by selective inhibition of COX-2 isoenzyme. By blocking COX-1, which also normally acts to protect the gastrointestinal mucosa, nonselective NSAIDs and aspirin can cause significant gastric tissue damage [20]. Specifically, NSAIDs are believed to wipe out the entire inflammatory mediated proliferative phase of healing associated with WBC actions. In 1999, celecoxib (Celebrex) was the first selective COX-2 inhibitor approved by the Food and Drug Administration (FDA) for treatment of arthritis pain [21]. Rofecoxib (Vioxx) was approved several months later, followed by valdecoxib (Bextra) [22].

In addition, they also reduce the incidence of gastrointestinal ulcers and erosions which were seen with standard NSAIDs therapy [23]. Celebrex, Vioxx, and Bextra quickly became the mainstay for the treatment of chronic pain conditions related to inflammation [24]. Thus, it was concluded from numerous researches that selective COX-2 inhibitors are of great interest as they may present an alternative therapeutic option in treating inflammation in cirrhosis with ascites in which renal function is critically dependent on PGs [25]. The general acceptance of these drugs was due to the perceived lack of serious gastrointestinal side effects that had been associated with the nonselective class of NSAIDs [26]. The structure of currently used NSAIDs and coxibs is provided in Figure 4.

However, selective COX-2 inhibitors are also found to be associated with life-threatening side effects. On September 30, 2004, Merck Research Laboratories announced the global withdrawal of rofecoxib (Vioxx), its primary selective COX-2 inhibiting NSAID [27]. In addition, by inhibiting COX-2 that blocks production of prostacyclin (PGI_2) there is unopposed thromboxane which will increase the clotting risk as PGI_2 prevents formation of platelet clotting. Therefore, inhibiting PGI_2 led to the increased risk of thrombotic cardiovascular and cerebrovascular events [28-29]. Moreover, NSAIDs are also associated with undesirable effects on kidney function [30]. As a result, using NSAIDs during dehydration or preexisting chronic renal disease can stimulate the renin–angiotensin system, which may cause acute renal failure through inhibition of prostaglandin synthesis [30].

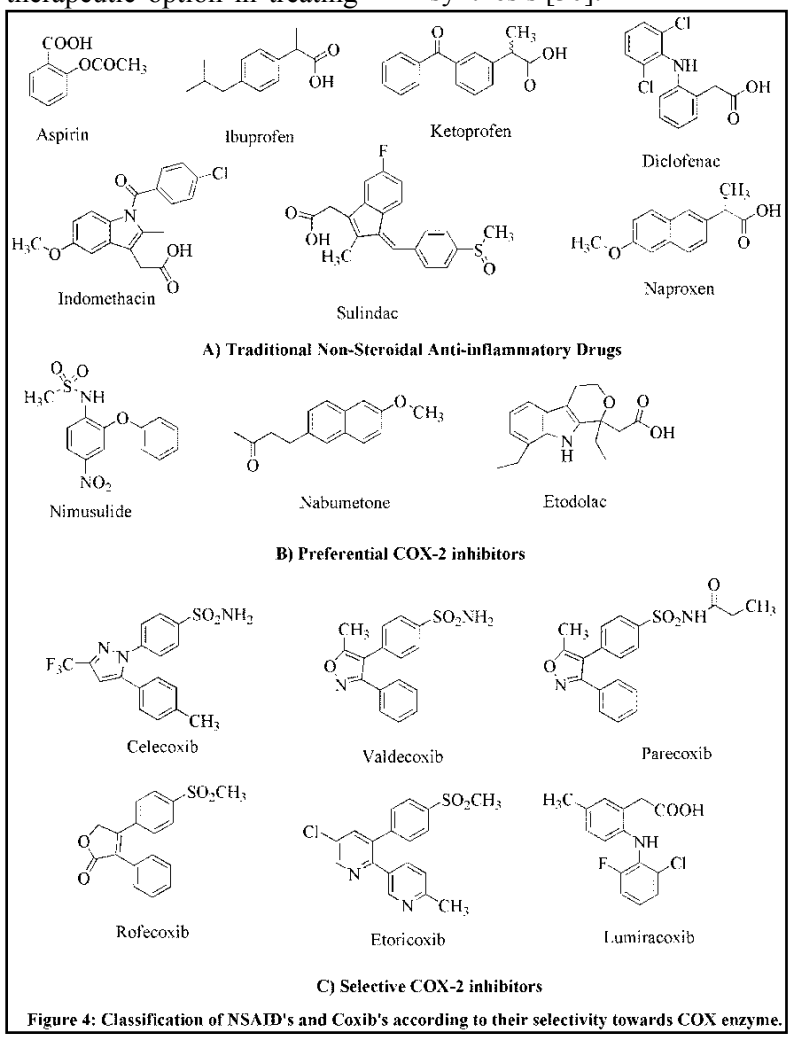

Figure 4: Classification of NSAID's and Coxib's according to their selectivity towards COX enzyme.

Glucocorticoids (GCs)

Glucocorticoids (GCs) potentiate as well as regulate the renal response of diuretics especially in patients with heart failure having refractory diuretics resistance with large doses of loop diuretics [31-32]. The primary anti-inflammatory mechanism of these potent agents is the synthesis of lipocortin- 1, which suppresses phospholipase A_2, thereby blocking eicosanoid production and resulting into the inhibition of various leukocyte inflammatory events like epithelial adhesion, emigration, chemotaxis, phagocytosis, respiratory burst due to inhibition of COX/PGE isomerase (*i.e.* COX-1 and COX-2) [33].

In addition, GCs bind with the glucocorticoid receptor (GR) and the activated GR regulates gene expression and produce anti-inflammatory effects as a result of both transactivation and transrepression process [34]. In transactivation process, the activated GR complex dimerizes, translocates into the nucleus and binds to specific sequence of DNA. This GR/DNA complex recruits the other proteins which transcribe downstream DNA into mRNA and finally to protein. Whereas in transrepression process, the activated monomeric GR attached to other transcription factors such as nuclear factor kappa B (NF-κB) and activator protein-1 (AP-1), [35] thus repressing the expression of pro-inflammatory proteins in the cortisol and preventing these from up regulating the expression of the target genes. These target genes encode proteins such as COX, Nitric oxide (NO) synthetase, phospholipase A_2, TNF β, intercellular adhesion molecule-1 (ICAM-1), and other pro-inflammatory proteins [36].

Literature survey on animal studies reveals that the side effect of GCs includes diabetogenic activity, osteoporosis, skin atrophy [36-37], impaired memory and attention deficits [38]. Moreover, they also cause immune-suppression, decreasing the function and/or numbers of neutrophils, lymphocytes (including both B cells and T cells), monocytes, macrophages, and the anatomical barrier function of the skin [39].

However Selective glucocorticoid receptor agonists (SEGRA), a newer class of anti-inflammatory drugs were introduced in 2000s and evaluated for anti-inflammatory activity. Research concludes that a SEGRA is able to transrepress without transactivation and therefore shows many of the desirable therapeutic anti-inflammatory effects with minimum undesired side effects [40]. Animal studies show that the topical administration of SEGRA inhibits peroxidase activity, skin atrophy and oedema [37]. Since November 2010, many SEGRA like BOL-303242-X and ZK 245186 [41] are under clinical studies. Apart from this, several inflammatory diseases of the eye are also treated with SEGRA because corticoids can promote glaucoma, cataract and eye infections [42]. Hence, SEGRA today proves to be a newer approach for researchers/scientists. Figure 5a and 5b represents the structure of currently used GCs and SEGRA respectively.

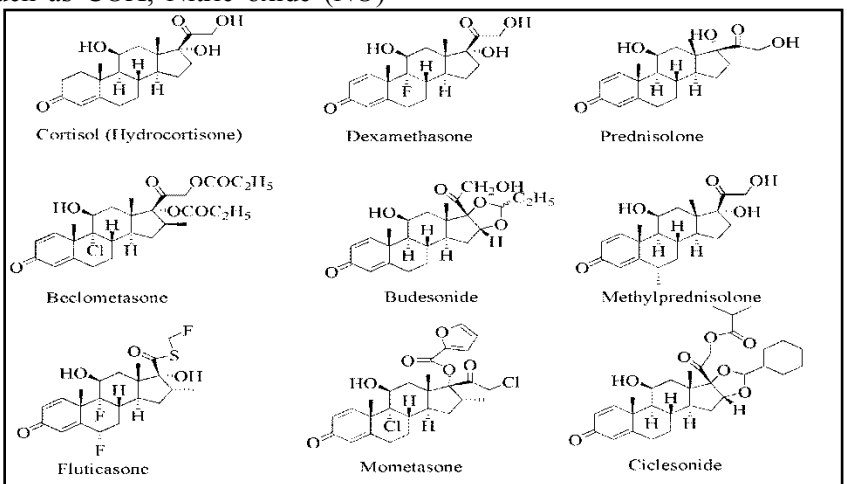

Figure 5a: Structure of some important Glucocorticoids

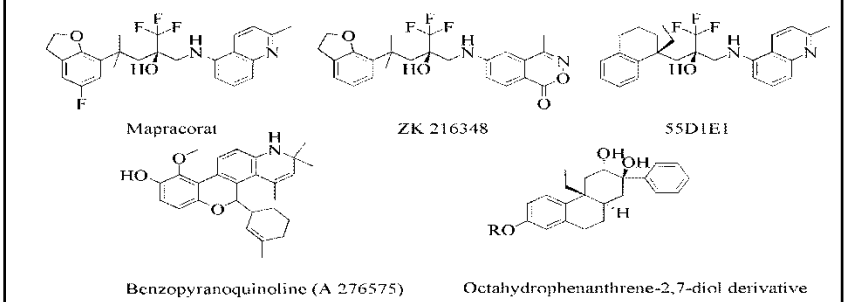

Figure 5b: Structure of some important Selective glucocorticoid receptor agonist (SEGRA)

Immune selective anti-inflammatory derivatives (ImSAIDs)

The IMULAN BioTherapeutics, LLC present the new class peptides having anti-inflammatory activity that are not related to GCs or NSAIDs known as immune selective anti-inflammatory derivatives (ImSAIDs). These agents alter the activation as well as migration of inflammatory cells responsible for inflammatory response [43]. Literature survey reveals that cervical sympathetic trunk-submandibular gland (CST-SMG) axis lead to the discovery of a seven amino acid peptide, known as submandibular gland peptide-T (SGP-T) [44]. However, SGP-T is an isolate submandibular gland, plays a key role in modulating the CSTSMG axis, and subsequently controlling the inflammation process [45]. In addition, one SGP-T tripeptide *i.e.* phe-glu-gly (FEG) and its D-isomeric form (feG) [46] are known to alter leukocyte adhesion involving actions on αMβ2 integrin, and inhibit the binding of CD16b (FCyRIII) antibody to human neutrophils [47]. In addition, several ImSAIDs also reduce nuclear expression of NF-κB [48].

Natural anti-inflammatory agents

The history of the analgesic and anti-inflammatory substances started with the use of decocted salicylate containing plants by ancient Greek and Roman physicians. Later, it was identified that salicin can be the active component of willow bark which on metabolism converts into salicylates, as a substance for reducing pain, inflammation and fever. One hundred and fifty years ago, Felix Hoffman from the Bayer Company acetylated salicylic acid and created aspirin, being the world's most used therapeutic agent [49] that inhibits the cyclooxygenase (COX) enzymes COX-1 and COX-2. Because of significant side effect profiles of steroidal and NSAIDs medications, there is a greater interest in natural compounds, such as dietary supplement and herbal remedies, which have been used for centuries to reduce pain and inflammation [50]. In contrast, numerous plant herbs and particularly plant food supplements receive great potential by European consumers as they can deliver significant health benefits at relatively lower cost. Many of these natural compounds produce significant anti-inflammatory activity by inhibiting COX or nuclear factor-kB (NF-kB) inflammatory pathways.

Anti-inflammatory Biologics: TNF inhibitors

Today biologics serve as new class of anti-inflammatory drugs, which are genetically engineered proteins derived from human genes [51]. They are designed to inhibit the pro-inflammatory cytokines like TNF and interleukin. Several inflammatory diseases, including rheumatoid arthritis, asthma, atherosclerosis, crohn's disease and psoriasis are either being treated with these agents or are under clinical investigation with these drugs [52]. These drugs not only provide relief from pain, but also helpful in blocking the important endogenous inflammatory mediators and hence possess good analgesic and anti-inflammatory potential. Earlier disease modifying anti-rheumatic drugs (DMARDs) like methotrexate, penicillamine and azathioprine have been commonly used in the treatment of rheumatoid arthritis [52].

Now-a-days, there are a number of biologics approved to treat rheumatoid arthritis, which includes abatarcept [53], actemra, adalimumab [54], anakinra [54], cimzia, etanercept [55], infliximab [56], orencia, rituximab [57] and simponi. In addition, biologics are the monoclonal antibodies (MAbs) employed against the pro-inflammatory mediators of inflammation, notably TNF-α, interleukins IL-1 and IL-6 [58]. Biologics may be used alone or given in conjunction with other DMARDs *e.g.* methotrexate, leflunomide, hydroxychloroquine and sulfasalazine to potentiate the beneficial anti-inflammatory action without any side effects [59].

Moreover, biologics are also found to be useful over corticosteroids in the treatment of sight-threatening disease endogenous uveitis [60]. Therefore biological DMARDs bring more beneficial for patients in various respects but due to inhibition of the immune system these agents are also associated with serious adverse effects. FDA has warned about the risk of infection from two bacterial pathogens namely, *Legionella* and *Listeria* species. The people who consume TNF inhibitors are at the high risk for developing serious infections which may lead to hospitalization due to bacterial, mycobacterial, fungal, viral, parasitic, and other opportunistic pathogenic infection [61]. However, long term use of TNF inhibitors leads to serious adverse effect like lymphoma, congestive heart failure, demyelinating disease, a lupuslike syndrome, and induction of auto-antibodies, injection site reactions, and systemic side effects [62].

Resolvins and Protectins

Natural products such as omega-3 essential fatty acids (EFAs) do have strong scientific support to be considered as an alternative and/or complementary agent to NSAIDs. The derivatives of omega-3 fatty acids; eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are collectively known as resolvins and protectins [63]. Curtis *et al.*, explain the therapeutic use of fish oil (in the form of cod liver oil), an omega-3 EFA, for the treatment of muscular, skeletal, and discogenic diseases [64]. In addition, literature review has shown that the omega-3 polyunsaturated fatty acids are some of the most effective natural anti-inflammatory agents available [65].

Table 1. Herbs with active constituents having anti-inflammatory activity.

Plant	Family	Active Ingredient	Mechanism of action	References
Curcuma longa	Zingiberaceae	Curcumin	Inhibit NF-kB pathway	[67]
Camellia sinensis	Theaceae	Catechins and epigallocatechin-3 galate	Inhibit IL-1 induced proteoglycan release	[68]
Cinnamomum camphora	Lauraceae	Capsaicin	Defunctionalization of nociceptor fibres	[69]
Pinus maritime	Pinaceae	Pycnogenol, catechin and taxifolin	Inhibits TNF-α–induced NF-kB activation	[70]
Boswellia serrata	Burseraceae	Frankincense	Inhibit the leukotriene biosynthesis by inhibiting 5-LOX.	[71]
Polygonum cuspidatum	Polygonaceae	Resveratrol	Specific inhibitor of TNF-α- and IL-1b-induced NF-kB activation.	[72]
Uncaria tomentosa	Rubiaceae	Polyphenols flavonoids, proanthocyanidins, and tannins.	Prevent the activation of the transcriptional factor NF-kB and it directly inhibits TNF-α production	[73]
Capsicum annum	Solanaceae	Capsaicin	Inhibits NF-kB pathway	[74]
Aiphanes aculeate Willd.	Arecaceae	Aiphanol and Isorhapontigenin	COX inhibitor	[75]
Dracaena loureiri	Asparagaceae	Stilbene analogs	COX inhibitor	[76]
Piper methysticum Forst	Piperaceae	Dihydrokawain, yangonin and flavokawain B	COX inhibitor	[77]
Ceiba pentandra	Malvaceae	Flavonoids	COX inhibitor	[78]
Grifola frondosa	Meripilaceae	Ergosterol and fatty acids	COX inhibitor	[79]
Agrocybe aegerita	Strophariaceae	Ergosterol and fatty acids	COX inhibitor	[80]
Ocimum sanctum Linn.	Lamiaceae	Eugenol, cirsilineol, cirsimaritin, isothymonin, apigenin and rosmarinic acid	COX inhibitor	[81]
Hypericum perforatum	Hypericaceae	Hyperforin	COX inhibitor	[82]
Cornus kousa	Cornaceae	Kaempferol, myricetin, cornin and stenophyllin	COX inhibitor	[83]
Stereocaulon alpinum Laur.	Stereocaulonaceae	9-cis-octa-decenamide	COX inhibitor	[84]
Houttuynia cordata	Saururaceae	Fatty acids	COX inhibitor	[85]
Aralia continentalis	Araliaceae	Kaurenoic acid	COX inhibitor	[86]
Dystaenia takeshimana	Umbelliferae	Coumarins, β-sitosterol and dacusterol	COX inhibitor	[87]
Cannabis sativa	Cannabaceae	Canniprene, olivetolic acid	COX inhibitor	[88]
Evodia rutaecarpa	Rutaceae	Evodiamine, rutaecarpine and goshuyuamide II	COX inhibitor	[89]
Nigella sativa	Ranunculaceae	Thymoquinone and thymohydroquinone	COX inhibitor	[90]
Zingiber cassumunar	Zingiberaceae	Phenylbutenoids	COX inhibitor	[91]
Cymbidium goeringii	Orchidaceae	Gigantol	COX inhibitor	[92]
Perilla nankinensis	Lamiaceae	Luteolin diglucuronide, apigenin diglucuronide, and semi-pure luteolin diglucuronide	COX inhibitor	[93]

However, with the discovery that vascular inflammation is the underlying cause of coronary artery disease, fish and fish oil supplements are now recommended by the American Heart Association (AHA) for the prevention of this disease [64-65]. The active ingredients in fish oil, EPA and DHA, enhance the conversion of COX to prostaglandin E_3, which competitively inhibits the effects of the arachidonic acid conversion to prostaglandin E_2. In

addition, prostaglandin E_3 also inhibits the synthesis of pro-inflammatory cytokines (TNF-α and IL-1b). Clinical trial studies on 250 patients suffering from cervical and lumbar disc disease, revealed that 59% could substitute fish oil supplements as a natural anti-inflammatory agent as substitute of NSAIDs. Therefore, Now-a-days, it has been established that administration of lipoxins, resolvins and protectins in animal models can be helpful in the recovery process of inflammation without compromising host defenses by causing immune suppression. From a nutritional point of view, dietary supplement of the precursor omega-3 fatty acids when taken together with aspirin, may ameliorate the numerous clinical symptoms of inflammatory disorders and regulate the time course of resolution via production of resolvins and protectins [66]. Some of the official used natural compounds to treat inflammation are given in Table 1.

However, herbal medications are becoming increasingly popular because of their relatively few side effects. Nevertheless, there are also certain problems associated with these dietary supplements, and their use requires knowledge of their biological action, and potential interactions with other nutraceuticals or prescribed medications. It is important for healthcare practitioners to learn about these scientific studies to counsel patients who are taking various dietary supplements, herbs minerals and vitamins for both disease treatment and prevention.

Newer anti-inflammatory Drugs

Today a number of compounds have been synthesized and being tested clinically such as SC58125, 1.475.337 and flusolide (CGP28258). These new generation COX-2 inhibitors were found to possess more than 1,000 times selectivity for COX-2. It is, however, evident that such high degree of selectivity will not offer any advantage over the conventional NSAIDs, unless full information about their side effects is known. Early results show that these compounds do not have significant gastro or nephrotoxicity even in the larger doses. Presently, adverse reactions because of selective COX-2 inhibition are being studied, and whether these agents are real advancement or not, only time will tell; but early results show promise. Proper clarification of these issues is important because these drugs are now being used increasingly instead of the conventional NSAIDs in spite of being many times expensive.

Conclusion

The human body's natural response to injury results in inflammation characterized by pain, swelling and erythema. In order to reduce pain and swelling, a variety of anti-inflammatory agents can be effectively employed, which mainly includes non steroidal anti-inflammatory drugs (NSAIDs), steroidal anti-inflammatory agents (glucocorticoids), pharmaceutical biologics and many more. Although the use of synthetic anti-inflammatory agents often very effective, but long term use of these agents leads to various undesirable side effects like gastric ulceration, infrequently, myocardial infarction and stroke.

Nowadays, interest with plant based anti-inflammatory medicine is revived due to the increasing awareness of the health risks linked with the reckless use of current allopathic medicines. Unfortunately, India is still behind to mark its footprints in international business of herbal industry because lack of scientific approach in herbal drugs. Therefore, exploration of the more effective, potent, less toxic therapeutic agents to treat as well as reduce the signs and symptoms of acute and chronic inflammatory diseases is still a challenge for the pharmaceutical chemists. However, ongoing experiments and clinical trials should be continued to guide and provide their scientifically based effectiveness to reduce inflammation and promote wellness. It is hoped that this review article can serve as a lead for readers who are interested to work on inflammation and its treatment.

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