A REVIEW ON FEW ANTI-INFLAMMATORY AGENTS OF HERBAL ORIGIN

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RECEIVED : 4 March, 2017

There has always been a search for drugs that can be used as anti-inflammatory agent without causing many side effects. Many synthetic drugs reported to be used for the treatment of inflammatory disorders are of least interest now a days due to their potential side effects and serious adverse effects. Due to these reasons herbal drugs have started to gain popularity in several human ailments due to the absence of several problems in them, which are associated with synthetic preparations. The primary objective of this review is to provide an overview of the recently explored anti-inflammatory agents belonging to phytoconstituents like alkaloids and phenylpropanoids. A large number of compounds of alkaloid and phenylpropanoid skeleton, isolated from medicinal plants have been shown to possess anti-inflammatory activity. This paper brings in notice such agents.

KEYWORDS : Anti-inflammatory, Essential Oils, Phenylpropanoids, Alkaloids.

ABBREVIATION

AIAs : Anti-inflammatory agents

COX-1 : Cyclo-oxygenase-1

COX-2 : Cyclo-oxygenase-2

5-HT : 5-hydroxytryptamine

NSAID : Non-steroidal anti-inflammatory drugs

IL-1 : Interleukin- 1

IL-6 : Interleukin- 6

NO : Nitric oxide

PGE2 : Prostaglandin E2

TNF-α : Tumor necrosis factor-alpha

INTRODUCTION

1.1 ANTI-INFLAMMATORY AGENT

The word "inflammation", derived from the latin word "inflammare", [to set on fire], is a complex biological process including several chemical mediators which are induced by vascular tissue of the body, when it comes in contact with several harmful stimuli like pollens, irritants, pathogens, and damaged cells. It provides a protective comeback that helps in healing of tissues. Sometimes, inflammation seems to produce events that are quite serious and become chronic like occurrence of rheumatoid arthritis and hay fever which may be life threatening [1, 2]. Hence, proper representative measures are to be taken against it.

Inflammations are generally characterized by certain regular events such as redness, swelling, heat, pain, and at certain times lead to exudation and loss of function. The process of inflammation involves several events and mediators which are potent chemical substances found in the body tissues, such as prostaglnadins, leukotrienes, prostacyclins, lymphokines, and chemokines like interferon-α [IFN-α], γ, interleukin [IL]-1, IL-8, histamine, 5-hydroxytryptamine [5-HT], and tissue necrosis factor-α[TNF-α] [3]. These mediators produce several chemical pathways and events to evoke a complementary response against external stimuli.

Studies show that in a very few cases, inflammations are tolerable; but in almost 99% of cases, inflammations seem to be severe and intolerable, and if not treated properly with initial first aid along with proper diagnosis and drug therapy, they may lead to loss of life. Examples of some diseases where inflammations are quite harmful include asthma, rheumatoid arthritis, vasculitis, and glomerulonephritis [4, 5]. Hence, drug therapy used against inflammation must be satisfactory enough to decrease its severity.

Synthetic drugs had been used widely to treat inflammations and related diseases. But almost 90% of the drugs used against inflammation produce drug related toxicities, iatrogenic reactions, and adverse effects complicating the treatment process [6-8]. Hence, a shift in the area of anti-inflammatory treatment has been observed from the use of synthetics to natural therapy.

Anti-inflammatory drugs of synthetic origin are classified as steroidal and nonsteroidal anti-inflammatory agents. The origin of these chemical compounds started when salicylates were isolated from leaf extract of willow bark *Salix alba* and were potentially used by the people of North America in 200 BC and regarded as first generation anti-inflammatory agents [9].

Following this first anti-inflammatory agent, acetyl salicylic acid was synthesized and, likewise, other synthetic compounds came into existence thereof. Examples of such agents include propionic acid derivatives like ibuprofen, flurbiprofen, naproxen; anthranalic acid derivatives like mephenamic acid, oxicam derivative piroxicam, pyrrole, indole; and pyrrazolone derivatives like ketorolac, indomethacin, and phenylbutazone [10].

The second- and third-generation compounds work by inhibition of the enzyme cyclo-oxygenase [COX], which we now know to have at least two distinct isoforms: the constitutive isoform, COX-1, and the inducible isoform, COX-2. COX-1 has clear physiological functions. Its activation leads, for instance, to the production of prostacyclin, which when released by the endothelium is antithrombogenic and when released by the gastric mucosa is cytoprotective. COX-2, is induced by inflammatory stimuli and cytokines in migratory and other cells. It is therefore attractive to suggest that the anti-inflammatory actions of NSAIDs are due to

inhibition of COX-2, whereas the unwanted side-effects, such as irritation of the stomach lining, are due to inhibition of COX-1.

Drugs that have the highest COX-2 activity and a more favorable COX-2 : COX-1 activity ratio will have a potent anti-inflammatory activity with fewer side-effects than drugs with a less favourable COX-2 : COX-1 activity ratio. The identification of selective inhibitors of COX-2 will therefore lead to advances in therapy

In a study conducted by World Health Organization [WHO], none of these compounds were found to be safer, as they are associated with a series of unacceptable findings like drug-related or drug-induced toxic effects, and cause harmful adverse effects and secondary effects on long-term use [11-12].

Some common side effects of these synthetic drugs include gastric irritation, ulceration, bleeding, renal failure, interstitial nephritis, hepatic failure, headache, thrombocytopenia, hemolytic anaemia, asthma exacerbation, skin rashes, angioedema, and pruritis. Hence, this approach for treatment of inflammatory diseases by herbal drugs has keen interest to the researchers. From the study made globally, it has been known that the market for use of herbal drugs in the treatment of inflammatory diseases constitutes 83% worldwide and is expected to reach a value of around more than 95% in the forthcoming years due to increased acceptability of these preparations [13-16].

The field in which plant-based anti-inflamatory agents are being explored as a potential alternative tool in this era of 21st century has given rise to several varieties of beneficial compounds isolated from plants. These include the substances belonging to various classes of phytopharmaceuticals like alkaloids, glycosides, terpenoids, polysaccharides, flavonoids, phenolic compounds, cannabinoids, steroids, fatty acids, plant extracts and agents derived from marine organisms, and terrestrial plants.

PHYTOCONSTITUENTS (ALKALOIDS AND PHENYLPROPANOIDS) RESPONSIBLE FOR ANTI-INFLAMMATORY ACTIVITY

2.1 ALKALOIDS

Alkaloids are basic substances containing one or more nitrogen atoms, usually in combination as part of a cyclic system [17]. They are often toxic to man and many have dramatic physiological activities. Different approaches used to analyze the anti-inflammatory potential of plant and plant-derived compounds have been developed in the past years [18-22].

The important plant families containg alkaloids responsible for anti-inflammatory activities [AIAs] include Solanaceae, Compositae, Hernandiaceae, Papaveraceae, and Ranunculaceae.

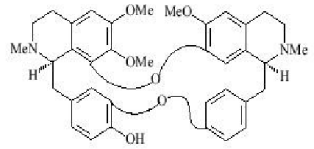
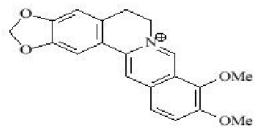
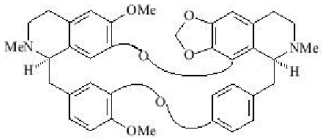
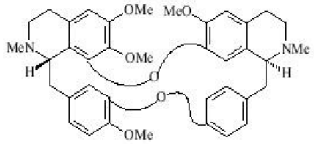
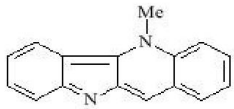
Colchicine is an established clinical agent for arthritic disease [23]. The alkaloid is present in corns and seeds of crocus like plants. Colchicine is best known for its preventive action against gout, but it also reduces pain and swelling in degenerative and immunological inflammatory disease [24]. Isoquinoline, indole and diterpene alkaloids were the most studied about their activities on inflammation. Aconitine and others alkaloids from *Aconitum* genus were screened for anti-inflammatory activity. They were effective on different assays including carrageenin-induced paw edema, adjuvant-induced arthritis and acetic acid induced vascular permeability tests [25-28].

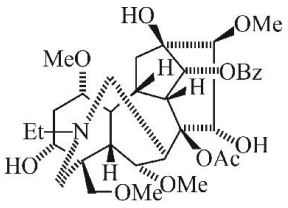
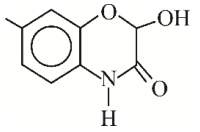
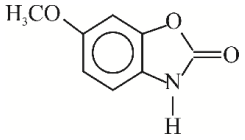
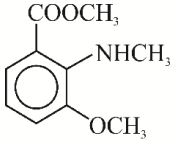
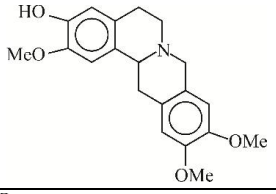
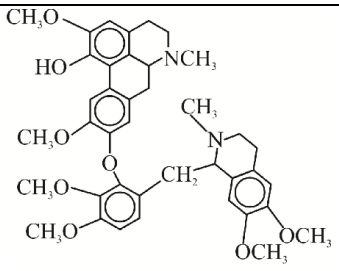
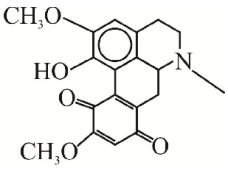
There are about 500 species of Aconitum and the species has been intensively investigated for the pharmacological activity of their alkaloids. Since anti-rheumatic properties

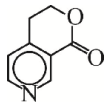
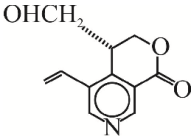
have been associated with this plant, some attention has been made to the anti-inflammatory activity of alkaloids in Aconitum [29]. Several isoquinoline alkaloids (berbamine, berberine, cepharanthine and tetrandine) were examined for anti-inflammatory activity. They showed to be active in different assays as reported by different authors [30-33]. Among these tetrandine is most promising. It is used for the treatment of rheumatic diseases. Tetrandrine is found as a prototypic tool compound for the development of new class of anti-inflammatory agents [34-35].

The alkaloids tend to be rather toxic, although the toxicity appears to be well below the therapeutic levels. The alkaloids appear to offer the considerable promise for further investigation as anti-inflammatory compounds, and some appears to be remarkably active. The Carrageen induced pedal edema was the most used model for evaluating the anti-inflammatory activity.

Table 1. Alakaloids with antiinflammatory activity

Compound Name	Structure	AntiInflammatory Activity	Ref.
Berbamine		Carragenin, IL-1, TNF induced Inflammation	36
Berberine		Carrageenin-induced inflammation;	37
Cepharanthine		Carrageenin-induced pedal edema.	38
Tetrandine		Carrageenin-induced pedal edema	39
Cryptolepine		Carrageenin-induced pedal edema	40

Aconitine		UV Light Induced Erythema Carrage enin-induced pedal edema	41, 42
Benzoxazinoid		Inhibitory activity of histamine release	43
Betonicine		Carrageenan-induced hindpaw edema	44
Damascenine		Inhibits induced edema formation in the paw	43
Discretine		Shows anti-inflammatory activity	45
Fetidine		Anti-inflammatory, hypotensive, and depresses nervous activity	46
Demethylsonodione		Moderate antiplatelet aggregation activity in vitro	47

Gentianadine		Moderate antiplatelet aggregation activity in vitro	48
Gentianamine		Carrageenin-induced pedal edema	48

2.2. PHENYLPROPANOIDS

Phenylpropanoids are a large group of organic compounds produced by plants for protection against infections, ultraviolet irradiation, wounding and herbivores. They are synthesized from the amino acid phenylalanine, that is converted into cinnamic acid. Reduction of the carboxylic acid group present in the cinnamic acid yields an aldehyde and further reduction produces monolignols such as phenylpropenes [*e.g.*, eugenol and safrole]. Natural and synthetic phenylpropanoids are under current medicinal use for their pharmacological properties [49, 50].

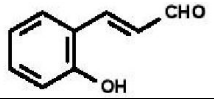
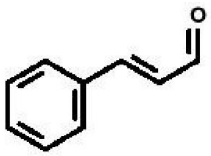
Cinnamaldehyde is a constituent of essential oils. It is known to exert anti-cancer, antifungal and anti-inflammatory effects. An increasing number of studies have described the anti-inflammatory activity of cinnamaldehyde elicited by different signaling pathways that regulate the anti-inflammatory responses.

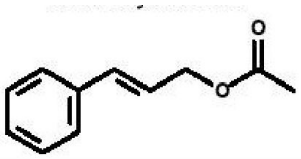
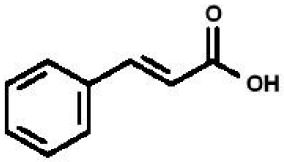
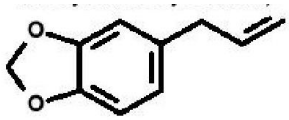
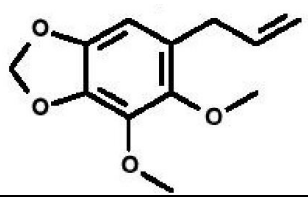
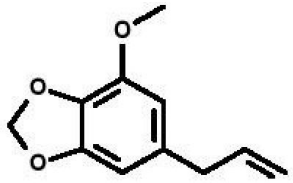
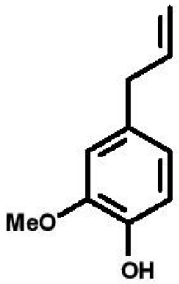
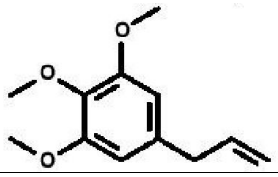
Chao and collaborators [51] also showed the anti-inflammatory activity of cinnamaldehyde obtained from the essential oil of C. osmophloeum leaves. The effect of cinamaldehye obtained from C. cassia popularly known as Cinamon on atherogenesis has been assessed, providing further evidence of the anti-inflammatory action of this species [52].

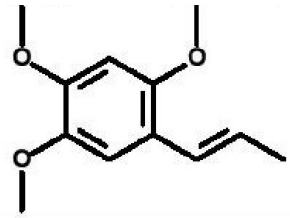
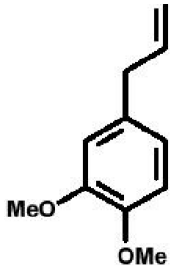
In a study by Ho and collaborators [53], the anti-neuroinflammatory activity of cinnamon and cinnamaldehyde were investigated with respect to their ability to suppress NO, TNF-α, IL-1β, and IL-6 production. The trans Cinnamaldehyde obtained from O-quixos essential oil exerts anti inflammatory effect endowed with gastroprotective property.

In another study, dillapiole and its analog dihydrodillapiole were reported to significantly suppress paw edema [54]. Eugenol,a compound was known to display pharmacological properties like hypothermic, antioxidant, anti-inflammatory and local anesthetic actions. In traditional medicinal, it is used against gastrointestinal disorders [55]. Eugenol suppressed COX expression,hence can be used as an anti-inflammatory agent [56].

Table 2. Phenylpropanoids with antiinflammatory activity

Compound Name	Structure	AntiInflammatory Activity	Ref.
2′-hydroxycinnamaldehyde		Inhibits production of nitrate, COX-2	57
Cinnamaldehyde		inhibits production of NO, inhibition of IL-1β and TNF-α,suppression of pro-IL_1 β production	58,59

Cinnamyl acetate		inhibits the production of NO and PGE_2	58
Cinnamic acid		inhibits the production of NO.	60
Saffrole		LPS inhibition	61
Dillapiole		inhibition of paw edema	62
Myristicin		suppresses production of NO, IL-6, IL-10,	63
Eugenol		It inhibits edema	64,65
Elmicin		Inhibition of COX 2	66

Asarone		Inhibition of COX-1 and COX 2 enzymes	67
Methyleugenol		Inhibits NO production.	68

Conclusion

Considerable attention is being given to the discovery of novel drugs capable of fighting inflammation, particularly those of plant origin. .Above study reveals that the category of compounds studied above *i.e*. alkaloids and Phenylpropanoids, are of anti-inflammatory values. It is expected that further studies involving clinical trials will be carried out in order to ensure a safe use of these substances as a therapeutic agent against inflammatory diseases.

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