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A Review on Medicinal Plants as a Source of Anti-inflammatory Agents

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ABSTRACT

Inflammatory diseases including different types of rheumatic diseases are a major and world wide problem. Gastrointestinal side effect is the major problem associated with the presently available non-steroidal anti-inflammatory agents. Now a days world population moves towards herbal remedies for treatment of such ailments. The numbers of plants have been screened for their anti-inflammatory and anti-arthritic activity, but only few of them reached up to the clinical level. This problem is mainly due to purely academic oriented research. Researchers have to lay emphasis on the phytoconstituents obtained from that plant for the specific treatment of such disease and not only to increase the number of plants having anti-inflammatory activity but have to work towards tapping their therapeutic utility by finding out the mechanism of action at molecular level. In this review we have described some of the families with respect to its anti-inflammatory mechanism of action.

Key words: Anti-inflammatory, herbal products, plant families

INTRODUCTION

Inflammatory diseases including different types of rheumatic diseases are a major cause of morbidity of the working force throughout world. This has been called the King of Human Miseries (Shah *et al.*, 2006). Inflammation is a dynamic process that is elicited in response to mechanical injuries, burns, microbial infections and other noxious stimuli that may threaten the well-being of the host. This process involves changes in blood flow, increased vascular permeability, destruction of tissues via the activation and migration of leucocytes with synthesis of reactive oxygen derivatives (oxidative burst) and the synthesis of local inflammatory mediators, such as prostaglandins (PGs), leukotrienes (Shah *et al.*, 2008a) and platelet-activating factors induced by phospholipase A₂, cyclooxygenases (COXs) and lipoxygenases. Arachidonic acid is a key biological intermediate that is converted into a large number of eicosanoids with potent biological activities.

The two major pathways of arachidonic acid metabolism are the COX pathway, which results in the formation of both PGs and thromboxanes and the 5-lipoxygenase pathway, which is responsible for the formation of leukotrienes and 5S-hydroxy-6E, 8Z, 11Z, 14Z-eicosatetraenoic acid (5-HETE). Classic examples of herbs traditionally used to treat inflammation in Western medicine are *Matricaria chamomilla* L. and *Arnica montana* L. (Asteraceae), *Salix alba* (Salicaceae) and *Glycyrrhiza glabra* (Fabaceae).

Other well-known plant products with anti-inflammatory activity are the distillate of *Hamamelis virginiana* (witch hazel; Hamamelidaceae), *Echinacea* species including *Echinacea angustifolia* (purple coneflower; Asteraceae), *Ananas comosus* (pineapple; Bromeliaceae), *Abelmoschus esculantus* (bhindi, Malvaceae) (Shah and Seth, 2010).

Common examples of Asian anti-inflammatory plants are *Curcuma domestica* Val. and *Curcuma longa* L. (turmeric), *Curcuma xanthorrhiza* Roxb. (temoe-lawaq), *Zingiber officinale* Rosc. (Zingiberaceae), *Colocassia esculenta* (Shah *et al.*, 2007) and *Momordica charantia* (Shah *et al.*, 2008b).

The yellow principle of *Curcuma longa* L. is a yellow pigment, curcumin. This dye inhibits the enzymatic activity of both COX and Nitric Oxide Synthetase (NOS) and showed clinical potentials for the treatment of inflammation. *Zingiber officinale* L. (ginger) is native to Gingi area near Pontichery, India and the first European to have seen the whole living plant is said to be the Venetian Marco Polo around 1285. It was used to flavor food and beverages by the Greeks and Romans, who imported it via the Red Sea. During the Middle Ages, ginger was an important economical product controlled by the Venetians. Venetians had established houses of business at Constantinople and Sudak on the shore of the Black Sea, had the monopol of ginger, which was brought by caravannes following the Silk Road. The Venetian monopol survived until the late 15th century when Portuguese navigators were able to sail via the cape to Mozambique and then direct to India to Calicut. Ginger was brought in South America for cultivation by Francisco Mendoza and was exported to Spain as early as 1547. The plant contains arylalkalones, which inhibit the enzymatic activity of COX with potentials for the treatment of inflammation.

Encompassing approx 6000 medicinal plant species, the medicinal flora of Asia and the Pacific comprise a fantastic source of pharmacologically active products and the number of plant species principally used for the treatment of inflammation can be estimated to be more that 380. This study will focus on the potentials of medicinal plants of Asia as a source of original anti-inflammatory drugs, with particular interest payed to inhibitors of phospholipase A2, COX, lipoxygenases, elastase and NOS.

INHIBITORS OF PHOSPHOLIPASE A2

Phospholipase A2 or phosphatide acylhydrolase 2, is an enzyme that catalyzes the hydrolysis of the acyl group attached to the 2-position of intracellular membrane phosphoglycerides. This hydrolysis release arachidonic acid from membrane phosphoglycerides. Arachidonic acid is the precursor of Pgs, thromboxanes and leukotrienes. In regard to the possible mechanisms observed so far, the inhibition of phospholipase A2 is mediated via lipocortine or by direct interaction with the enzyme itself. The former mechanism utilizes a protein known as lipocortine, the synthesis of which is commanded by steroidal hormones and steroid like plants known as triterpenoids. Examples of lipocortine-mediated phospholipase A2 inhibitors that are of therapeutic value and potent anti-inflammatory drugs are cortisone, prednisolone and betamethasone. The other possible mechanism involves a direct binding with the enzyme itself, a mechanism thus far unused in therapeutics, but with promise. One such compound is also a triterpene: betulinic acid (Bernard *et al.*, 2001). When looking for an inhibitor of phospholipase A2 from medicinal plants, one could look into plant species that are traditionally used as snake-bite antidotes because hemolytic and myolytic phospholipases A2 are often present in snake venom, which results in damage to cell membranes, endothelium, skeletal muscle, nerves and erythrocytes.

Other medicinal features to consider when searching for plants with potential as phospholipase A2 are abortifacient, analgesic, antipyretic and hypoglycemic uses. Such features are present in the following plant species.

Aristolochiaceae: The family Aristolochiaceae is a family of herbaceous plants often used in Asia and the Pacific to counteract snake poisoning, promote urination and menses, mitigate stomachache and treat dropsy and skin diseases. During the past 20 years, members of this family, especially from the genus *Aristolochia* have attracted much interest and has been the subject of numerous chemical and pharmacological studies. The anti-inflammatory property of *Aristolochia* species is probably the result of a direct interaction between aristolochic acid and derivatives of phospholipase A2. *Aristolochia indica* L., *Aristolochia kaempferi* and *Aristolochia recurvilabra* Hance are used for the treatment of inflammatory conditions.

***Aristolochia indica* L.:** Indian *Aristolochia*, also known as Indian birthwort, *ishvara* (Sanskrit), or *adagam* (Tamil), is a bitter climber native to India. The medicinal material consists of the rhizome, which is to resolve inflammation (India), counteract insect poison and as an antipyretic (Philippines and Vietnam). The rhizome contains aristolochic acid, which inhibits *in vitro* and dose-dependent phospholipid hydrolysis by the human synovial fluid phospholipase A2, snake venom phospholipase A2, porcine pancreatic phospholipase A2 and human platelet phospholipase A2 (Vishwanath *et al.*, 1988).

***Aristolochia kaempferi* Willd.:** The plant is herbaceous and develops small yellow flowers in the summer. The fruits are cylindrical or ovoid, 3-7×1.5-2 cm, dehiscent capsules. The drug consists of the fruit, which is shaped like human lungs and is therefore recommended in China for all forms of pulmonary infections. Other diseases for which they are prescribed are hemorrhoids, ascite and heartburn. The plant is known to contain phenanthrene alkaloid derivatives including aristoliukine-C, aristofolin A and E, aristolochic acid-1a methyl ester and aristolochic acid, as well as kaempferol-3-O-rutinoside and quercetin kaempferol-3-O-rutinoside (Wu *et al.*, 1998, 2000).

The plant is known elaborate a series of quite unusual phenanthrene alkaloid derivatives, of which aristoliukine-C, aristofolin A and E, aristolochic acid-1a methyl ester and aristolochic acid. Other chemical constituents found in this plant are flavonoid glycosides such as kaempferol-3-O-rutinoside and quercetin kaempferol-3-O-rutinoside (Wu *et al.*, 1998, 2000).

Exposure to Aristolochiaceae family is associated with the development of cancer in humans. A significant advance is the toxicological effects of aristolochic acid has been provided by Pezzuto *et al.* (1988). They showed that aristolochic acid is a mutagen.

***Aristolochia recurvilabra*:** The drug consists of the rhizome. It is highly esteemed and was, at one time, worth 300 silver taels. The rhizome can be easily mistaken for ginger. It is used to treat digestive disorders, fluxes, diarrhea, dysentery and snake bites. Levi *et al.* (1998) reported cases of hepatitis following ingestion of teas containing aristolochic acid.

Hong *et al.* (2002) showed that a methanol extract of *Aristolochia debilis* is a potent inhibitor of COX-2 activity.

Myristicaceae: The Myristicaceae family has attracted a great deal of interest on account of its ability to produce series of unusual phenylacylphenols-of possible symbiotic origin-that might have some potential for the treatment of inflammation. One such compound is YM-26567-1 from *Horsfieldia amygdalinia* (Wall.) Warb. isolated by Mikaye *et al.* (1992).

***Horsfieldia amygdalinia* (Wall.) Warb:** The anti-inflammatory property of *Horsfieldia amygdalinia* (Wall.) Warb is confirmed *in vitro*. Mikaye *et al.* (1992) reported that YM-26567-1 from the fruit of this plant competitively inhibits the enzymatic activity of phospholipase A2. In the course of further screening for YM-26567-1 derivatives, YM-26734 was selected and inhibited phospholipase A2 from rabbit platelets with an inhibition concentration 50% (IC₅₀) value of 0.085 mM (Mikaye *et al.*, 1992).

Medicinal caprifoliaceae: The family Caprifoliaceae comprises approx 400 species, of which *Lonicera japonica* Thunb., *Lonicera affinis* Hook and Arn, *Lonicera confusa* DC, *Sambucus javanica* Reinw. ex. Bl, *Sambucus sieboldiana* (Miq.) Graebn and *Weigela floribunda* (Sieb. and Zucc.) K. Koch. are used to treat inflammatory conditions in Asia and the Pacific. There is an expanding body of evidence to suggest that biflavonoids from this family might hold some potential as phospholipase A2 inhibitors. One such compound is ochnaflavone from *Lonicera japonica* Thunb.

***Lonicera japonica* Thunb.:** The anti-inflammatory and antipyretic properties of *Lonicera japonica* Thunb. are confirmed and involve a biflavonoid, ochnaflavone, strongly inhibited the enzymatic activity of rat platelet phospholipase A2 (IC₅₀ approx 3 µM). This activity was strong and dependent of the pH, noncompetitive and irreversible. In addition, the inhibitory activity of ochnaflavone is rather specific against group II phospholipase A2 than group I phospholipase A2 (IC₅₀ approx 20 µM). These results indicate that the inhibition of phospholipase A2 by ochnaflavone may result from direct interaction with the enzyme (Chang *et al.*, 1994).

INHIBITORS OF COX

An example of a medicinal plant used for the treatment of inflammation based on its activity on COX is *Harpagophytum procumbens* DC (Pedaliaceae), or devil's claw, which has long been used in South Africa for the management of pain and inflammation. Two isoforms of COX, designated COX-1 and COX-2, are known to catalyze the synthesis of PGs from arachidonic acid. A body of evidence suggests that PGs are involved in various physiopathological processes including carcinogenesis. COX-1 is present in most tissues, whereas COX-2 is inducible by carcinogens, cytokines and tumor promoters and therefore involved not only in inflammation, but also the growth of cells. Thus, compounds that inhibit the activity of COX-2 might also be an important target for cancer chemoprevention. Nonsteroidal anti-inflammatory drugs are widely used in the treatment of pain and inflammation associated with acute injury or chronic diseases, such as rheumatoid arthritis or osteoarthritis. Classic examples of COX inhibitors of therapeutic value are aspirin, paracetamol, ibuprofen and recently introduced and withdrawn coxibs such as celecoxib (Celebrex®) and rofecoxib (Vioxx®). Coxibs abrogate the formation of cardioprotective PGI₂, leading to a rise in blood pressure, atherogenesis and heart attack by the rupture of an atherosclerotic plaque.

There is, therefore, a need for original coxibs and one might think to look into the medicinal flora of Asia and the Pacific, as an increasing body of evidence suggests the families Apocynaceae, Clusiaceae, Asteraceae, Polygonaceae, Lamiaceae and Convolvulaceae to elaborate ast sources of biomolecules which are able to inhibit the enzymatic activity of COX.

Apocynaceae: The family Apocynaceae consists of about 250 genera and 2000 species of tropical trees, shrubs, woody climbers, or herbs classically known to elaborate monoterpenoid indole alkaloids of therapeutic usefulness, such as vinblastine and vincristine characterized from the aerial part of *Catharanthus roseus* G. When looking for such principles, one might investigate members of the subfamily Plumerioideae, which includes the Plumerieae (*Alstonia*, *Aspidosperma*, *Catharanthus*), Tabernaemontaneae (*Crioceras*, *Tabernaemontana*, *Tabernanthe*, *Voacanga*), Rauvolfieae (*Ochrosia*, *Rauvolfia*, *Kopsia*, *Vallesia*) and Carissae (*Hunteria*, *Melodinus*, *Picalima*). About 80 species of plants classified within the family Apocynaceae are medicinal and are often used to treat gastrointestinal ailments, reduce fever and pains and treat diabetes and infectious diseases. *Alstonia scholaris* (L.) R. Br, *Plumeria rubra* L. *sensu lato*, (*Plumeria acuminata* Ait, *Plumeria acutifolia* Por, *Plumeria alba* L.), *Ervatamia divaricata* (L.) Burk. (*Ervatamia coronaria* Stapf, *Tabernaemontana coronaria* Willd, *Tabernaemontana divaricata* R. Br.), *Trachelospermum jasminoides* (Lindl.) (*Rynchospermum jasminoides* Lindl.) and *Trachelospermum asiaticum* (Sieb. and Zucc.) Nak. are used in Asia to treat inflammation and have virtually been unstudied as a source of COX inhibitors.

***Trachelospermum asiaticum* (Sieb. and Zucc.) Nak.:** The plant is used in Korea to treat rheumatism, heal abscesses and ulcers and sooth laryngitis. To date, this anti-inflammatory property is not confirmed and it will be interesting to learn whether it is be mediated via inhibition of the enzymatic activity of COX as measured with an ethanol extract of stem of *Trachelospermum jasminoides* (Lindl.) (Li *et al.*, 2003). If confirmed, this activity might involve alkaloids or lignans, such as arctigenin and/or flavonoids or iridoids, which are known to occur in the plant (Inagaki *et al.*, 1973).

Asteraceae: An example of Asteraceae reported to inhibit COX is *Cichorium intybus* L., or chicory (17). In Asia, *Chrysanthemum sinense* Sab. (*Chrysanthemum morifolium* Ramat) and *Bidens bipinnata* L. are used as anti-inflammatory on account of their likely ability to inhibit COX.

***Bidens bipinnata* L.:** In Taiwan, a decoction of the plant is drunk to treat diarrhea. The antivenom property may involve inhibitors of phospholipase A2 and possibly COXs because extracts of *Bidens pilosa* L. inhibit the enzymatic activity of COX *in vitro* (Jager *et al.*, 1996).

Lamiaceae: The family Lamiaceae comprises 200 genera and 3200 species of aromatic herbs including *Mentha piperita*, (peppermint, British Pharmaceutical Codex, 1954), *Lavendula officinalis* (lavender oil, British Pharmaceutical Codex, 1963), *Salvia officinalis* (sage, British Pharmaceutical Codex, 1934) and *Rosmarinus officinalis* L. (rosemary oil, British Pharmaceutical Codex, 1963). About 60 species of Lamiaceae are of medicinal value in Asia and the Pacific and, in regard to the potentials of Lamiaceae against COX, one might set the hypothesis that the stockhouse of diterpenes present in this family could be an interesting source of COX inhibitors. A significant advance in that field of research has been provided by the study of Pang *et al.* (1996).

Using ionophore-stimulated rat peritoneal leukocytes, they identified from *Sideritis javalambrensis*, a labdane called labdane F2, which inhibits the generation of COX and 5-lipoxygenase products of arachidonate metabolism (Pang *et al.*, 1996). An example of anti-inflammatory Lamiaceae where COX could be involved are *Ocimum basilicum* L. and *Glechoma brevituba* Kuprian which are described next.

***Ocimum basilicum* L.:** In India, the juice expressed from the leaves is used as nasal douche and the plant is used to treat inflammation and assuage chronic pain in the joints. In Malaysia, the juice expressed from the leaves is drunk to calm cough and the plant is used to abrogate pregnancy. In Cambodia, Vietnam and Laos, the leaves are used to break fever. The anti-inflammatory property of the plant is confirmed by Singh *et al.* (1996). They showed that the fixed oil inhibits carrageenan-induced and arachidonic acid-and leukotriene-induced paw edema, possibly by blockade of the enzymatic activity of both COX and lipoxygenases demonstrated for *Ocimum sanctum* L. and Holy basil (Singh *et al.*, 1996).

Possible constituents responsible for COX inhibition might be phenolic compounds, such as phenylpropanes. Phenylpropanes are simple alkylated phenolic substances, which inhibit the PG synthesis. Such compounds are responsible for the anti-inflammatory properties of several medicinal plants in the family Convolvulaceae (Pongprayoon *et al.*, 1991; Dewhirst, 1980).

***Glechoma brevituba* Kuprian:** The plant is used in China to reduce fever, promote urination and the heart tone and to cure colds and gravel. The pharmacological potential of *Glechoma brevituba* Kuprian. remains unexplored. An interesting feature of the *Glechoma* species is their ability to elaborate long-chain unsaturated fatty acids with antiinflammatory, analgesic, antipyretic potentials. One such fatty acid is (9S, 10E, 12Z)-9-hydroxy-10,12-octadecadienoic acid, an antagonist of PGs E1 and D2 (Kuhn *et al.*, 1989; Henry *et al.*, 1987).

Glechoma species also contains a very unusual series of alkaloids (Kumarasamy *et al.*, 2003), the structural features of which have some similarity to rofecoxib. Therefore, it would be interesting to learn whether these alkaloids hold any potential as a COX inhibitor or not.

INHIBITORS OF LIPOXYGENASES

Lipoxygenases are present in leukocytes, tracheal cells, keratinocytes and airway and stomach epithelium and they catalyze the introduction of a molecule of oxygen to the 5-position of arachidonic acid to give the intermediate (5S)-hydroxy-(6E, 8Z, 11Z, 14Z)-eicosatetraenoic acid or 5-HETE, which is immediately followed by the rearrangement of 5-HETE to leukotrienes. Another potential site of action for anti-inflammatory drugs is, therefore, at the level of lipoxygenases, thus inhibiting the biogenesis of leukotriene and 5-HETE. The search for specific inhibitors of lipoxygenase activity from medicinal plants results in the characterization of anti-inflammatory agents. Lipoxygenase inhibitors might hold some potential for the treatment of asthma, psoriasis, arthritis, allergic rhinitis, cancer, osteoporosis and atherosclerosis. The evidence currently available suggests the families Myrsinaceae, Clusiaceae and Asteraceae have potential as sources of lipoxygenase inhibitors.

Myrsinaceae: The family Myrsinaceae consists of 30 genera and about a 1000 species of tropical plants that have attracted a great deal of interest for their quinones and saponins, which have exhibited a large spectrum of pharmacological activities. About 40 species of plants

classified within the family Myrsinaceae are medicinal in the Asia-Pacific region, particularly for the treatment of inflammatory conditions. One of these medicinal herbs is *Ardisia villosa* Roxb.

***Ardisia villosa* Roxb.:** The plant is used in China to treat contusions and rheumatic and neuralgic pains. In Malaysia, a decoction of leaves is used as bath to treat dropsy; the roots are used to reduce fever and treat cough. An interesting feature of *Ardisia* species and the Myrsinaceae family in general, is the production of a very unusual series of dimeric benzoquinones known as ardisiaquinones, which are known to inhibit the enzymatic activity of 5-lipoxygenases, a feature that could explain the frequent use of *Ardisia* species to treat inflammatory conditions. One such compound is ardisiaquinone G isolated from *Ardisia teysmanniana*, which is known to inhibit the enzymatic activity of lipoxygenase (Yang *et al.*, 2001; Fukuishi *et al.*, 2001).

Asteraceae: One of the richest sources of lipoxygenase inhibitors is perhaps the family Asteraceae, where three different types of principles have been characterized. The sesquiterpene lactone helenalin, which can be isolated from several plant species of the Asteraceae family, is a potent anti-inflammatory and antineoplastic agent. In human granulocyte, helenalin inhibited 5-lipoxygenase (IC₅₀ 9 mM after 60 min preincubation) in a concentration- and time-dependent fashion (Tornhamre *et al.*, 2001). Polyacetylenes from *Artemisia monosperma* showed some levels of activity against lipoxygenase (Stavri *et al.*, 2005). The third groups of lipoxygenase inhibitors in this family are bornyl cinnamoyl derivatives from *Verbenisa* species, such as bornyl caffeate from the South American herb *Verbenisa turbacensis* Kunth.

Apiaceae: The family Apiaceae is a large group of flowering plants which comprises some 250 genera of herbs, mostly growing in temperate regions, the principal botanical hallmark of which is the presence of umbels, dissected leaves, pungent or aromatic smell and hollowed and articulate stems. A large number of Apiaceae is of value in Western medicine, notably *Anethum graveolens* L. (dill, British Pharmaceutical Codex, 1954), *Foeniculum vulgare* (fennel, British Pharmaceutical Codex, 1963), *Apium graveolens* L. (celery, British Pharmaceutical Codex, 1949), *Carum carvi* L. (caraway, British Pharmacopoeia, 1963), *Coriandrum sativum* L. (coriander, British Pharmacopoeia, 1963) and *Pimpinella anisum* (anise, British Pharmaceutical Codex, 1954). A number of plants classified in this family are drastically toxic on account of coniine, such as *Conium maculatum* L. (hemlock leaf, British Pharmaceutical Codex, 1949).

The traditional system of medicine of the Pacific Rim uses approx 80 species of Apiaceae, for instance, *Centella asiatica* (L.) Urban (*Hydrocotyle asiatica* L.; centella, Indian Pharmaceutical Codex, 1955). The plant has been used in India since early times for skin diseases and as a diuretic. It has long been a popular remedy in India for leprosy and syphilis. However, large doses are said to have narcotic action. The plant was used also by the surgeons of Napoleon's army.

***Bupleurum chinense* DC:** A significant advance in the understanding of the anti-inflammatory properties of *Bupleurum fruticosum* has been provided by Prieto *et al.* (2004). The showed that a methanol extract from the aerial parts had a significant effect on 5-lipoxygenase activity, inhibiting both LTB₄ and 5(S)-HETE production, with IC₅₀ values of 112 and 95 µg mL⁻¹, respectively. At concentrations of 200 µg mL⁻¹, the extract inhibited COX-1 (90%) and elastase activities (54%).

INHIBITORS OF ELASTASE

The seeds and vegetative part of plants contain several sorts of inhibitors of insect, fungal, mammalian and endogenous proteinases. These inhibitors may be involved in plant defense mechanisms against predators and participate in the development of the plant itself. Peptidic proteinase inhibitors are well studied in the families Fabaceae, Poaceae, Asteraceae and Solanaceae (Konarev *et al.*, 2002). Non-proteinaceous inhibitors of serine protease are, in comparison, less known. Among serine proteinases are human neutrophils and macrophages, which digest and degrade elastin, cartilage proteoglycans, fibronectin and foreign materials ingested during phagocytosis.

In normal physiological conditions, it is inhibited by α -1-protease inhibitor of plasma. Damage to connective tissue caused by leakage of elastases leads to damage associated with inflammatory diseases, such as pulmonary emphysema, adult respiratory distress syndrome, septic shock, cystic fibrosis, carcinogenesis, chronic bronchitis and rheumatoid arthritis. Compounds that directly inhibit elastase or its release from human neutrophils are of enormous pharmaceutical and cosmetological interest in the development of new anti-inflammatory drugs. A possible source for elastase inhibitors are the medicinal Asteraceae and Droseraceae, particularly those used as traditional medicine in Asia.

Asteraceae: The family Asteraceae is a prolific source of sesquiterpene lactones, among which, melampolides have been shown to inhibit the enzymatic activity of elastases. Melampolides are a common member of the *Melampodiinae* subtribe. Examples of medicinal Asteraceae known to elaborate melampolides are *Sigesbeckia orientalis* L. and *Mikania cordata* (Burm.f.) B.L. Robinson.

***Sigesbeckia glabrescens* Mak.:** The anti-inflammatory property of *Sigesbeckia glabrescens* Mak. is confirmed experimentally, as an intraperitoneal injection of an aqueous extract of the plant inhibited compound 48/80 induced systemic anaphylaxis in mice. The extract dose-dependently inhibited the release of histamine from peritoneal mast cells by compound 48/80. The plant has a strong antianaphylactic activity by inhibition of histamine release from mast cells (Kang *et al.*, 1997). The extract dose-dependently inhibited the active systemic anaphylaxis and serum IgE production induced by immunization with ovalbumin and interleukin (IL)-4-dependent IgE production by lipopolysaccharide (LPS)-stimulated murine whole spleen cells (Kim *et al.*, 2001).

***Mikania cordata* (Burm.f.) B.L. Robinson:** *Mikania cordata* is known to elaborate a series of sesquiterpene lactones, among which deoxymikanolide significantly inhibits acetic acid-induced writhing in mice (Ahmed *et al.*, 2001; Herz *et al.*, 1970). The plant also contains a series of melampolides that inhibit the enzymatic activity of elastase (Gutiérrez *et al.*, 1987).

Droseraceae: The family Droseraceae consists of four genera and about 100 species of perennial herbs, of which *Drosera burmannii* Vahl., *Drosera rotundifolia* L., *Drosera indica* L. and *Drosera peltata* Sm. are used in Asia for the treatment of cough. Naphthoquinones and flavonoids, which occur in this family, have not been fully studied for pharmacology and it appears that flavonoids inhibit human neutrophil elastase, hence the potential for the treatment of inflammation.

***Drosera rotundifolia* L.:** In Japan, a decoction of the plant is used to treat cough. This effect is probably mediated by flavonoids such as hyperoside, quercetin and isoquercitrin, which are known to abound in the plant (Krenn *et al.*, 2004). Quercetin from *Drosera madagascariensis* inhibits human neutrophil elastase with an IC₅₀ value of 0.8 µg mL⁻¹, as well as hyperoside (IC₅₀ 0.15 µg mL⁻¹) and isoquercitrin (IC₅₀ 0.7 µg mL⁻¹) (Melzig *et al.*, 2001).

INHIBITORS OF NITRIC OXIDE SYNTHETASE (NOS)

The NOS is an important enzyme involved in the regulation of inflammation, vascular tone, neurotransmission and cancer. The NO is generated via oxidation of the terminal guanidine nitrogen atom from L-arginine by NOS. NO is a very toxic free radical that can cause substantial tissue damage in high concentrations, especially in the brain. In stroke, for example, large amounts of NO are released from nerve cells to cause damage to surrounding tissues including neurones and myocytes. NO is also released during inflammation and is involved in the growth of tumors; it is understood that endogenously formed NO induces the malignant transformation of mouse fibroblasts.

Among NOSs, inducible NOS is involved in the overproduction of NO and is expressed in response to IL-β, tumor necrosis factor-α and LPS, the genetic expression of which is notably commanded by the NF-κB macrophages. Molecules capable of inhibiting inducible NOS and/or induction of NF-κB activation may be of therapeutic benefit in various types of inflammation. Such molecules could be of sesquiterpenic nature as discussed.

Asteraceae: There is an expanding body of evidence to suggest that sesquiterpene lactones inhibit the synthesis NO synthetase. One such compound is an ambrosanolides-type sesquiterpene known as cumanin characterized from *Ambrosia psilostachya*. This sesquiterpene inhibit the enzymatic activity of NO synthetase with an IC₅₀ value of 9.38 µM (Lastra *et al.*, 2004).

Another example is the well-known artemisinin, a sesquiterpene used as an alternative drug in the treatment of severe and multidrug-resistant malaria, which inhibits NO synthesis in cytokine-stimulated human astrocytoma T67 cells (Aldieri *et al.*, 2003).

Other sorts of NO inhibitors are triterpenes, such as ursolic acid and 2-α-hydroxy from *Prunella vulgaris* L., inhibit the production of NO by murine leukaemic monocyte macrophage cells, RAW 264.7, cultured *in vitro*. The IC₅₀ values were 17 µM for ursolic acid and 27 µM for 2-α-hydroxy ursolic (Ryu *et al.*, 2000).

***Inula chinensis* Rupr. ex Maxim.:** Hernandez *et al.* (2001) characterized from *Inula viscosa* a sesquiterpene lactone, inuviscolide, which reduces the phospholipase A2-induced edema with an inhibitory dose at which half of the phospholipase A2-induced edema was reduced, ID50, value of 98 mmol kg⁻¹ (Hernandez *et al.*, 2001).

Han *et al.* (2004) studied the mechanism of action of 1-O-acetyl-4R,6S-britannilactone, a sesquiterpene isolated from the flowers of *Inula britannica* and showed that this substance suppressed NO and PGE2 synthesis in RAW 264.7 macrophages through the inhibition of iNOS and COX-2 gene expression via a blocking the binding of NF-εB to the promoter in the target genes (Je *et al.*, 2004; Han *et al.*, 2004). Other sesquiterpenes able to inhibit the enzymatic activity of inducible nitric oxide synthase from the genus *Inula* are bigelovin, 2,3-dihydroaromaticin and ergolide, which potently inhibits the activity on LPS-induced NOS in murine macrophage RAW 264.7 cells with an IC₅₀ value of 0.46 mM, 1.05 and 0.69 mM, respectively (Lee *et al.*, 2002).

Lauraceae: The family Lauraceae consists of 50 genera and 2000 species of trees, shrubs and herbs, of which 70 are of medicinal value in the Asia-Pacific region. Lauraceae are well-known for elaborating isoquinoline alkaloids and sesquiterpenes, the latter most likely representing a vast source of material for the search for NOS. Examples of such compounds are costunolide and dehydrocostunolide found in the leaves of *Laurus nobilis* (bay leaf, laurel), the leaves of which are widely used as a spice, antiseptic, stomachic and to treat rheumatism in traditional European medicine (Matsuda *et al.*, 2000). The potential of *Neolitsea zeylanica* Nees (Merr.) as a potential source of NOS inhibitor is discussed here.

CONCLUSIONS AND RECOMMENDATIONS

In summary, most of the evidence that has emerged from the investigation of medicinal plants of Asia and the Pacific for anti-inflammatory principles shows a clear predominance of sesquiterpene lactones from Asteraceae, which are able to inhibit the enzymatic activity of lipo-oxygenase, COX, NOS and elastase and we can reasonably expect the isolation of original anti-inflammatory drugs from this large family.

Some evidence has already been presented that indicates that a large number of flowering plants owe their anti-inflammatory properties to flavonoids which inhibit a broad spectrum of enzymes and scavenge free radicals.

Such plants might be found in the Asteridae, particularly in the order Lamiales (Boraginaceae, Verbenaceae), Solanales (Convolvulaceae), Scrophulariales (Acanthaceae), Dipsacales (Caprifoliaceae) and Rubiales (Rubiaceae). *Cordia verbenacea* DC, *Cordia francisci*, *Cordia myxa* and *Cordia serratifolia* in the Boraginaceae exhibit significant analgesic, anti-inflammatory and antiarthritic properties *in vivo* (Ficarra *et al.*, 1995).

Another example of Boraginaceae is *Carmona microphylla* (Lamk.) Don, which is known to produce quinones, ehretianone and microphyllone and which has exhibited anti-inflammatory potencies *in vivo* and *in vitro* (Selvanayagam *et al.*, 1996).

The family Convolvulaceae consists of 50 genera and 1500 species of vines is of substantial interest in the search for COX inhibitors because it is known that the phenolic compounds it elaborates, such as eugenol and *N-trans*- and *N-cis*-feruloyltyramines, inhibit the synthesis of PG. Note that the closely related Solanaceae are known to elaborate feruloyltyramines and could be also considered as a source of COX inhibitors. One of these, *Argyrea speciosa*, at the doses of 50, 100 and 200 mg kg⁻¹ dose-dependently potentiates the delayed-type hypersensitivity reaction induced both by sheep red blood cells and oxazolone in rodents (Gokhale *et al.*, 2003). *Vitex negundo* L. (Verbenaceae) abrogates carrageenan- and formaldehyde-induced paw edema, inhibits antihistamine and PG synthesis and stabilizes membrane and fight oxidation (Dharmasiri *et al.*, 2003; Alam and Gomes, 2003). An ethanolic extract of the leaves of *Graptophyllum pictum* (L.) Griffith (Acanthaceae) given orally to rodents is anti-inflammatory (Ozaki *et al.*, 1989). *Acanthus ebracteatus* reduces the production of eicosanoid (Laupattarakasem *et al.*, 2003) and abrogates the edema induced by carrageenan in rats. In the Rubiaceae, extracts of *Paederia foetida* L. inhibit significantly the formation of granulation in cotton-pellet-implanted rats (De *et al.*, 1994). Note that anthocyanins and hydrolysable tannins (Rosidae, Hamamelidae) are anti-inflammatory because of their ability to scavenge free radicals, as in the case of aqueous extract of *Bridelia ferruginea*, which inhibits paw edema induced by carrageenan, with an ID50 value of 36 mg kg⁻¹ (Olajide *et al.*, 1999). Triterpene as anti-inflammatory principles are to be found particularly in the

subclass Dilleniidae and especially in the Ebenaceae (*Diospyros* species) and Capparaceae (*Crateva* species) and are known to elaborate a series of pentacyclic triterpenes including betulin, betulinic acid and ursolic acid.

Lupeol, isolated from the stem bark of *Crataeva magna* (Lour.) DC. (Capparaceae), reduces the foot-pad thickness and complement activity in arthritic rats (Geetha and Varalakshmi, 1999). Oleanolic acid saponins isolated from the roots of *Momordica cochinchinensis* (Lour.) Spreng. is anti-pruritic in rodent (Matsuda *et al.*, 1998).

In comparison to the Asteraceae, Dilleniidae and Rosidae, evidence available regarding the anti-inflammatory effects of Caryophyllaceae seems vestigial, hence the urgent need to assess this subclass for its anti-inflammatory potentials.

Caryophyllidae are an interesting source of oligosaccharides and peptides with potential anti-inflammatory and/or immunomodulating effect. These polar compounds might for instance explain the fact that the fresh juice expressed from *Aerva lanata* (L.) Juss. (Amaranthaceae) inhibits carrageenan-induced edema in rodent. Note that the seeds of *Gomphrena* species inhibit the formation of IL-6 by osteoblastic cells (MC3T3-E10) without cytotoxicity *in vitro*. Such property could be useful for the treatment of chronic rheumatoid arthritis, infection and cancer. In the Lauraceae, *trans*-cinnamaldehyde from *Cinnamomum cassia* (Lauraceae, order Laurales) inhibits *in vitro* the activity of NOS.

African medicinal plants *Cinnamomum latifolia* Sonder, *Cinnamomum myrtifolia* Stapf., *Cinnamomum transvaalensis* Burt. Davy, *Cinnamomum woodii* Engl. and *Cinnamomum wyliei* Stapf., exhibited *in vitro* potent inhibition of COX-2 (Zschocke and Van-Staden, 2000). Hong *et al.* (2002) evaluated approx 170 methanol extracts of natural products, including Korean herbal medicines, for the inhibition of PGE2 production (for COX-2 inhibitors) and NO formation (for iNOS inhibitors) in LPS-induced mouse macrophage RAW 264.7 cells. As a result, several extracts, such as *Aristolochia debilis* (Aristolochiaceae), *Cinnamomum cassia* and *Cinnamomum loureiroi* (Lauraceae), *Curcuma zedoaria* (Zingiberaceae), *Eugenia caryophyllata* (Myrtaceae), *Pterocarpus santalius* (Fabaceae), *Rehmania glutinosa* (Scrophulariaceae) and *Tribulus terrestris* (Zygophyllaceae), showed potent inhibition of COX-2 activity (>80% inhibition at the test concentration of 10 µg mL⁻¹). In addition, the extracts of *Aristolochiaceae debilis*, *Caesalpinia sappan*, *Curcuma longa*, *Curcuma zedoaria*, *Daphne genkwa* (Thymeleaceae) and *Morus alba* (Moraceae) were also considered as potential inhibitors of iNOS activity (>70% inhibition at the test concentration of 10 mg mL⁻¹).

Investigation of these active extracts mediating COX-2 and NOS inhibitory activities are warranted for further elucidation of active principles for development of new cancer chemopreventive and/or anti-inflammatory agents.

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