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AN OVERVIEW: ANTI INFLAMMTORY ACTIVITY WITH MEDICINAL PLANTS

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ABSTRACT

Inflammation is a healthy process resulting from some disturbance or disease. The signs of inflammation are redness elevated heat, swelling , pain, loss of function. Inflammation process plays a protective role in our body and in some conditions produces soem negative effects such conditions include the inflammatory disorders rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, retinitis, multiple sclerosis, psoriasis and atherosclerosis. For overcoming this problem, search of newer drugs is very requisite and necessary and there are many of phytoconstituents present inplants which are playing a very important role in the treatment of inflammation. The present review shows some plant phytochemicals which having anti-inflammatory activity that have been tested in inflammatory models using modern scientific technique.

INTRODUCTION:

Inflammation is a host defence mechanism of the body and it's an essential immune response that enables the body to survival during infection or unjury and maintains tissue homeostasis in noxious conditions. According to the modern concept, inflammation is a healthy process resulting from some disturbance or disease. Inflammation is a normal response to any noxious stimulus that threatens the host and may vary from localized response to a generalized one. In other words "Inflammation is the major and complex reaction of the body against infection upon tissue injury". The role of inflammation as a healing, restorative process, as well as its aggressive role, is also more widely recoginzed today. But ine some conditions appears to be no resolution and a chronic state of inflammation develops that may last the life of the individual. Such conditions include the inflammatory disorders rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, retinitis, mulriple scelrosis, psoriasis and atherosclerosis. To overcome this problem different kind of safe and effective anti-inflammatory agents are available, including aspirin and other nonsteroidal anti-inflammatories, with many more drugs under development. So these agents which are helpful to reduce the inflammatory response are called anti-infalmmatory agent. Inflammation has a very big variety of pathological and physiological response.

Process of inflammation:

Inflammation is a localized protective reaction of cells tissues of the body to allergic or chemical irritation, injury and/or infections. The symptoms of inflammation are characterized by pain, heat, redness, swelling and loss of function that result from dilation of the blood vessels leading to an increased blood supply and from increased intracellular spaces resulting in the movement of leukocytes, protein and fluids into the inflamed regions. This is very necessary to understand the role of chemical mediators of inflammation. These mediators are the substances released as plasma proteins, or that come from cells like ms=ast cells, platelets, neutrophils and mococytes/macrophages. They are triggered by allergic or chemical irritation, injury and infections. These midiatorys, depending on the duration of injury determine the severity of inflammation and are termed pro-inflammatory fundamental factors. These substances bind to specific target receptors on the cells and may increase vascular permeability, promote neutrophil chemotaxis, stimulate smooth muscle contraction, increase direct enzymatic activity, induce pain and/or mediate oxidative damage. Examples of chemical mediators include: nitric oxide, prostaglandins, leukotrienes, vasoactive amines (histamine, serotonin), and cytokines. Although

some of the cytokines (IL-3 -4,-5,-6,-10,-13) released are beneficial by acting as anti-inlfammatory mediator within the cells.

Mechanism of inflammation:

The inflammatory process is a combination of many path was like a syntheisis of prostaglandin, interleukin or other chemo toxin, adhesive protein receptor action, platelet-activating factors. All can act as chemotactic agonists. Inflammation initiates with any stress on the membrane or by other trigger or stimuli, these activate hydrolysis for membrane phospholipid by phospholipse A into arachidonic acid, which further substrate for cyclooxygenase and lipooxygenase enzyme and byprodcut of these are prostaglandins PDE2, PGH2 and leukoteines like LTC4, LTC4 etc. several cutokines also play essential roles in orchestrating in inflammatorh process, especially interleukin-I (IL-I) and tumor necrosis factor-a (TNF-a). IL-1 and TNF are considered principal meditators of the biological responses to bacterial lipopolysaccharide (LPS, alos called endotoxin). They are secreted by mobocyted and macrophages, adipoocytes,and others cells. Working in concert with each other and various cytokines and growth factors (IncludingIL-8 and granulocyte-macrophage colony-stimulation they induce gene expression and protein synthesis ina variety of cells to mediate and promote inflammation. Prostaglandin (PGE2) or prostacyclin (PG12) release increase blood flow as well as increase blood vessel permeability by assistin in releasing of nitric oxide from endothelium derived releasing factory which cause again vasodilation adn help in sticking platelets and other chemo toxin (bradykinin, histamine) while LTs generally are pro-inlaamatory LTB4 is a potent chemaotacitc agent for polymorphonuclear leukocytes, eosinophils, and mobocytes. In higher concentarations, LTB4 stimulates the aggregation of polymorphonuclear leukocytes and promotes degranulation and the generation of superoxide. LTB4 promotes adhesion of neutrophils to vascular endothelial cells and their trans-endothelial migration and stimulates synthesis of pro-inflammatory cytokines from macrophages and lymphocytes.

TYPES OF INFLAMMATION:

Acute inflammation- Acute inflammation usually has becoming within minutes or at most hours after tissue injury, and may be characterized by the classical symptoms of redness, heat, oedema. It's a short term process. It is characterized by the exudation of fluids and plasma proteins and the migration of leukocytes, most importantly neutrophils into the injured area. This a cute inflammatory response is useful to the defense mechanism aimed at killing of bacteria, virus and parasites while still facilitating wound rapairs.

Chronic inflammation –Chronic inflammation is of a more prolonged duration and histologically by the presence of lymphocytes and macrophages, resulting in fibrosis and tissue necrosis. The chronic inflammation increases the development of the degenerative diseases such as rheumatoid arthritis, atherosclerosis, heart disease, Alzheimer, asthma, acquired immunodeficiency disorder (AIDS), cancer, congestive heart failure, multiple sclerosis, diabetes, infections, gout IBD-inflammatory bowel disease, aging and other neurodegenerative CNS depression, Chronic inflammation also has been implicated as part of the cause of the muscle loss that occurs with aging. 9 all of which are associated with immune pahtological that appears to play a key role in the onset of the condition.

MEDIATORS OF INFLAMMATION:

Inflammatory mediators are also released in allergic asthma, which is accompanied by inflammation of the airways with increased numbers of inflammatory cells accumulating in the alveolar sunmucosa. Release of mediators from these cells may be responsible for the airway hyperreactivity that is a feature of bronchial allergic asthma.

HISTAMINE:

The release of histamine from mast cells during antigenangibody reactions is well known as it its involvement in teh inflammatory response to skin injury. Also, increased numbers of mast cells are present in the rheumatoid synovium and in the asthmatiac lung, correlated with raised levels of histamine.

When the first antihistamines were discovered in teh 1940's it was hoped that they would be potent anti-inflammatory agents and, indeed, they found a role in the treatment of hay fever an dsome cutaneous inflammation. But these H_1 antihistamines are ineffective in arthritis or asthma, so that histamine did not seem to play a major part in these conditions.

The advent of nonsedation H_1 antihistamines has allowed them to be tested in much higher doses than ever before, and some evidence suggests that histamince amy, after all, play a role in allergic asthma.

BRADYKININ:

Small amounts of bradykinin cause pain, vasodilatation, and edema, all contributing to inflammation. Bradykinin-like immunoreactivity has been detected in rat pleural inflammatory exudates. Kinins are also present in nasal secretions after immunological challenge, and a kininogenase is released form human lung mast cells. Inhaled bradykinin causes bronchoconstriction in normal and asthmatic individuals, but not through release of PGs. Lack of

effective antagonists makes it difficult to assess the extent of involvement of kinins in inflammation and asthma, but there is no evidence that inhibitors of the inactivation of bradykinin, such as captopril or enalopril,exacerbate these conditions.

THE PROSTAGLANDINS:

Apart from non nucleated erythrocytes, all cells are capable of synthesizing PGs, which are released in response to many kinds of trauma or any disturbance of the cell membrane. In 1971 Vane discovered that aspirin and similar drugs inhibit the biosynthesis of PGs,and proposed that this explained their mechanism of action. In other words, the pathological release of PGs, that contributes to inflammation, fever, and pain is inhibited by aspirin and other NSAIDs.The sapirinlike drugs also share, to a grater or irritate the stomach ,nephrotoxicity in high concentrations, and interference with the birth process. It was suggested that these side effects resulted from the inhibition of the physiological release of a protective PG.

THROMBOXANE A_2 AND PROSTACYCLIN:

The antiplatelet effects of aspirin could not be explained by inhibition of the synthesis of PGE_2 or $PGE_{2\alpha}$ because these PG_s do not affect platelet aggregation to any great extent. Jowever, in 1975 samuelsson discovered that in platelets arachikonid acid (AA) is metabolized to the proaggregatory thromboxane (TX) A_2. Aspirin was shown to inhibit the formation of the exdoperoxide intermediate inthis pathway (Fig. 1). Soon after the discovery of TXA_2, another prostaglandin was discovered that showed opposite activity to that of TXA_2. Prostacyclin, as it was later termed, relaxes blood vessels and inhibits aggregation of platelets. Its synthesis in endothelia cells of blood vessel walls is of special importance.

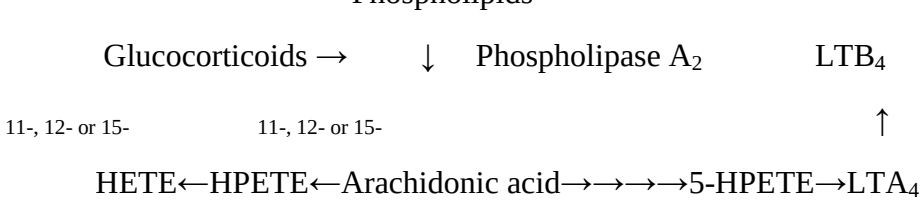
THE LEUKOTRIENES:

Slow-reacting substance of anaphylaxis (SRS-A) was identified as a product of the 5-lipoxygenase pathway of AA metabolism, and Samuelsson renamed the constituents of SRS-A as leukotrienes(LTs). In contrast to its inhibitory effects on cyclo-oxygenase, aspirin dose not in-

Figure 1. Action of aspirin on platelets.

Stimulus
↓
Phospholipase A_2
↓ Phodpholipases
Arachidonic acid
↓ Cyclo-oxgenase←Aspirin
Prostaglandin endoperoxides
↓ thrinboxane synthetase
Thromboxane A_2

Figure 2. catabolic pathway of AA.



Inhibit 5-lipoxygenase and, therefore, neither dose it in-hibit LT synthesis (Fig. 2). There is some evidence that lipoxygenase products contribute to vascular changes in inflammation. In the guinea pig skin and hamster cheek pouch, LTC_4 and LTD_4 potently increased permeability of venules to plasma macromolecules. LTB_4, LTC_4,and LTD_4 cause transient wheal and flare reactions in human skin, and LTE_4 is equipotent in the abdominal muscles of anesthetized guinea pigs. The LT antagonist FPL-55712 substanitally inhibits LTC_4 –induced bronchoconstriction and cough (14), but when administered to chronic asthmatics, FPL-55712 was only weakly active. FPL-55712 is now known to be a selective antagonist for the LTD_4 receptor, which could be related to its low activity in asthama. Anatagonists at LTC_4, LTD_4, and LTE_4 receptors such as LY 171,883 may be more effective antiasthama drugs.

PLATELET-ACTIVATING FACTOR (PAF):

The phospholipid PAF-acether is released by the action of phospholipase A_2 from most proinflammatory cells, as well as by vascular endothelial cells and platelets. It induces inflammatory reactions in various animal species and in human skin. PAF also minics teh main clinical features of asthma and is particularly effective in producing hyperreactivity and accumulation of eosinophils in lung tissue. Asthmatic patients have high levels of circulating PAF and their eosinophils make more PAF than those of normal controls. The antiasthmatic glucocorticoids, by suppressing phospholipase A_2, will thus reduce the formation of PAF. Furthermore, PAF antagonists, such as the ginkgolides, are currently being investigated for the treatment of asthma.

INTERLEUKIN-1:

IL-1 is a polypeptide produced by activated macrophages that mimics the symptoms of chronic inflammation (18). It has other names, including endogenous pyrogen. IL-1-like activity (equivalent to 1.69 U/ml) has been detected in synovial fluids from patients with rheumatoid arthritis. Its actions include activation of lymphocytes and production of fever, the latter being mediated by release of PGE_2.

Intra-articular injections of highly purified IL-1 into rabbit knee joints caused swellin, accumulation of polymorphonuclear and mononuclear leukocytes, and the loss of proteoglycan from the article cartilage. The inflammatory changes were similar to those seen in the joints if rabbits with antigen-induced arthritis 1-14 days after antigen challenge. IL-1 stimulates of collagenase that may be responsible for the cartilage breakdown.

MECHANISM OF ACTION OF NONSTEROID ANTI-INFLAMMTORY AGENTS:

The concentration of a pGE_2 –like substance is about 20 ng/ml in the synocial fluid of patients with rheumatoid arthritis. This decreases to zero in patients taking aspirin, demonstrating its effect on PG synthesis clini-cally . Carrageenan-impregnated polyester sponges implanted s.c.in rats were used to induce experimental inflammation. Periodic examination of the inflam-matory exudate contained within the sponges showed that the concentration of PGE_2 increased throughout the 24-h experiment. In addition, the output of TXA_2 and LTB_4 increased to a peak after 4-6 h and then declined over the remainder of the experiment PGE_2 causes vasodilatation and hyperalgesia,and the chemotactic property of LTB_4 probably attracts poly-morphonuclear leukocytes into the region. How –ever, the role of TXA_2 in the inflammatory response is not understood.

Evidence supporting the role of PG_S in the inflam-matory reaction was obtained by using carrageenan to induce inflammation in the raw paw. The release of endogenous PG_s was eliminated by aspirin, and then administration of low doses of exogenous PGE_2 (1.0ng) or prostacyclin (10ng) caused an increase in edema.

The possibility that aspirin like drugs influence the release of other substances, such as histamine and bradykinin, was experimentally discounted and further studies were designed to show that the antienzyme effect of aspirinlike drugs correlated with their anti-inflammatory effects. Comparing the effects of two optical isomers of naptoxen, Tomlinson *et al.* Showed that the one that possesses anti-inflammatory properties (in adjuvant arthritis and carrageenanedema) was also a potent inhibitor of PGE_2 synthesis. The other isomer was much less active in all the tests. In a survey of a whole range of NSAIDs ar therapeutic doses, the peak plasma concentrations, even allowing for protein binding, were more than sufficient to inhibit PG formation in an isolated enzyme preparation.

After demonstrating that the anti-inflammatory effects of NSAIDs are mediated cia inhibition of PG sunthesis, it was pertinent to determine whether a similar mechanism underlies the side effect profile of aspirin. This has been addressed with regard to the ulcerogenic potential of aspirin, and it is now known that prostacyclin is an important cytoprotective product of the gastric mucosa.

Administration of various PGs reverses or prevents experimental gastric ulcers, and some of the recently developed PG derivatives are now available for clinical use. On the other hand, the antienzyme activity of several NSAIDs correlates with their capacity to erode the gastric mucosa. In the clinic, NSAIDs suppress mucosal PG formation. However, salicylate decreases PG concentration in inflammatory exudates without affecting production by the gastric mucosa, and it possesses a very low erosion index. It is not known why salicylate differs from other aspirinlike drugs in this manner.

THE MECHANISM OF ACTION OF STEROIDS IN INFLAMMATION:

Corticosteroids inhibit phospholipase A_2 activity, which is necessary for the release of AA. Thus, corticosteroids ultimately inhibit the formation of PGs, TX, and the LTs. Anti-inflammatory steroids inhibit phospholipase A_2 infirectly by the release of an inhibitory protein. This has been variously termed macrocortin, lipomodulin, or renocortin, and molecular sizes of 15, 30, and 40kDa have been reported. The name lipocortin has been agreed upon and a pure, cloned form has recently become available and is claimed to be a potent anti-inflammatory agent.

There is now some dispute with respect to its mode ofaction, for lipocortins appear to be identical to calpactins. Calpactins bind calcium and also phospholipid, and it has been suggested that this property, rather than the direct inhibition of phospholipase A_2, is responsible for the reduction in eicosanoid formation.

DUAL INHIBITION OF CYCLO-OXGENASE AND 5-LIPOXYGENASE:

By preventing AA release, steroids neutralize the two main pathways of the AA cascade and are powerful anti-inflammatory agents. Drugs that inhibit both cyclo-oxygenase and 5-lipoxygenase would be expected to possess the same anti-inflammatory activity as steroids but with the advantage of not containing a steroid nucleus. BW755C inhibits both enzymes but is also causes hemolysis and will not be available for clinical use. In the sponge model of inflammation, equivalent anti-inflammatory doses of BW755C and dexamethasone similarly inhibited PG production and cell migration. However, indomethacin only suppressed PG production.

As a result of these encouraging pharmacological effects, there are several other dual inhibitors of cyclooxygenase and 5-lipoxygenase currently undergoing development. It is anticaipated that they may possess therapeutic effects superior to conventional aspirinlike drugs in chronic inflammation or anaphulactic broncho constriction.

Selective 5-lipoxygenase inhibitors are also undergoing clinical investigation. Piriprost, an inhibitor of LT formation, blocks LT release from lung tissue of astnatic patients challenged with

allergen. In vivo, piriprost inhibits bronchoconstriction in sensitized monkeys induced by inhalation of *Ascaris suum* antigen. However, piriprost administered to asthmatics failed to prevent the bronchoconstriction resuting from allergen challenge. It is possible that blocking of the lipoxygenase pathway may shunt AA toward increased formation of bronchoconstrictor cyclo-oxy-genase products such as PGD_2.

DIFFERENCES BETWEEN ASPIRIN AND SALICYLATE:

Aspirin and salicylate are considered to be equally potent as anti-inflammatory agents, nut salicylate is less potent than aspirin in inhibiting PG synthesis by a crude enzyme preparation from guinea pig lung (7). In contrast, an anti-inflammatory dose (3g) of aspirin or salicylate reduced the urinary output of PG metabolites in humans by 85-95%.

When prostacyclin was discovered and its antithrom-botic effect realized, clinical studies were already in progress to investigate whether aspirin possessed anti-thrombotic activity by inhibiting TXA_2 synthesis. Subsequently, the dose of administered aspirin was progressively reduced in the hope of selectively inhibiting TXA_a production while preserving prostacyclin synthesis. This was achieved by administering 40 mg aspirin daily, and it led to a re-ecaluation of the pharmacokinetics of aspirin and salicylate to explain this low-dose selectivity. In males who were given therapeutic doses of aspirin daily, the peak systemic plasma concentration of aspirin was about 2µg/ml after about 15 min. Within 1-5 h the plasma aspirin concentration has decayed to zero. However, the peak plasma salicylate concertration, formed by deacetylationof aspirin, increased to about 10 times that of aspirin and was maintained for several hours. Aspirin irreversibly inhibits platelet cyclo-oxygenase. Therefore, it was proposed that after gastrointestinal absorption, aspirin inhibits platelet cyclo-oxygenase within the presystemic circulation. About 60% of the absorbed aspirin is deacetylated to salicylate during the first pass through hte liver, and the resulting plasma aspirin concentration in the systemic circulation may well be too low to be associated with any significant cyclo-oxygenase-inhibiting activity in systemic tissues, including the vessel wall.

Another contributing factor to the selective inhibition of platelet TXA_2 production by aspirin is that platelets cannot regenerate cyclo-oxygenase. To stimulate prostacyclin production, infusions of bradykinin were given to volunteers. Two tablets of aspirin blocked TXA_2 prodcution by platelets for the duration of the experiment, but prostacyclin production revocered within 6h, which possibly regenerate cyclo-oxygenase.

Peompted by these findings, experiments were conducted to measure the concetations of aspirin and salicylate in inflammatory exudates with the carrageenan-impregnated polyester sponge

implants. The findings paralleled the previously described pharmacokinetic study in volunteers. After oral administration of aspirin (200mg/kg) to these rats, the peak concentration of aspirin (about 1.5 µg/ml) in inflammatory exudates was considerably lower than that of aspirin or salaicylate equally reduced the concentration of PGE_2 and TXB_2 in inflammatory exudates. Finally, the effects of aspirin and salicylate on the inhibition of cyclo-oxygenase in explants of inflamed tissue were examined. Comparison of the potencies with the relative concentratins of aspirin and salicylate meadured in inflammatory exudates after oral administration showed that, although aspirin did not reach high enough concentrations to inhibit cyclo-oxygenase to any great extent, there was a sufficient concentration of salicylate to considerably inhibit PG synthesis.

Thus, as Dreser suggested in 1899, aspirin may be a prodrug to deliver salicylate to its site of action.

COX-2 SELECTIVE AGENTS AND THE COXIBS:

Coxibs belong to a class of nonsteroidal anti-inflammatory drugs (NSAIDs) that are used to treat pain and inflammation in variety of acute and chronic conditions. They gave been principally employed for treating rheumatoid and osteo-arthritis, and other arthritic diseases, dental and surgical pain in post-operative settings, dysmenorrhoea, and acute injuries. The coxibs have also been explored for the prevention of colorectal and some other cancers as well as Alzheimer's disease although the outcomes of these studies have not been particularly favourable largely through lack of efficacy and/or cardiovascular complications. Indeed, the apparent high risk of myocardial infarctions and the exacerbation of symptoms of hypertension and elevation of blood pressure led to the worldwide dramatic withdrawal of one of the leading members of the coxib class, rlfecoxib, by the Merck company on September 29, 2004. This has been followed by the recommendation of the US Food and Drug Adminostration in April 2005 that Pfizer Inc, the company manufacturing other leading coxibs (celecoxib and valdecoxib) also withdraw valdecoxin from the US Market because of the same adverse events. Questions have now been posed whether a cardio-renal syndrome is associated with the entire class of coxibs – a class effect that may account for the mortality or non-fatal myocardial infarctions and elevation of blood pressure associated with these drugs, possibly in at risk subjects (as yet undetermined). The US FDA has subsequently specified a black box warning on the use of celecoxib and all other coxbis (that remain on the market or in clinical trial) and also a general warning of cardiovascular risk with all other NSAIDs. The Eropean medicines Evaluation Agency (EMEA), now the European Medicines Agency (EMA) has also re-evaluated the cardiovascular risk with the coxibs and has recommended

only restricted use of these drugs. Thus, in somewhat over half a decade since their much-heralded introduction as being safer to the gastrointestinal tract and kidneys than traditional NSAIDs and with rofecoxib and celecoxib having achieved worldwide market domination, they have now plummeted from sales to almost ocscurity in the therapeutic armamentarium. There are indications, however, that celecoxib may find its way back onto the world markets but the future of rofecoxib is less certain and maybe it will find applications (e.g. in juvenila rheumatioid arthritis in which it was especially effective) but under very strictly restricted conditions. Another Merck drug, etoricoxib, might not be associated with an excess risk of cardio-renal effects and associated myocardial infarction and exacerbation of hypertension. Likewise, although less adequate data are available with lumiracoxib, there are suggestions this drug may not have the same risks as seen with rofecoxib or other coxibs.

A key factor that has emerged from the analysis of reasons why rofecoxib, valdecoxib, and celcoxib may have led to development of the cardio-renal syndrome though to underlie muocardial infarction and hypertension appears to have been that these effects were apparent with high dose levels of these drugs. It is possible that in some of the conditions where they were being used (e.g. a colorectal preventative trial of rofecoxin and celecoxib and post-operative coronary bypass in the case of valdecoxib) may have been conditions where there were appreciable manifestations of disease stress that led to pre-disposition to the development cardio-renal syndromes and myocardial infacrction. A major factor was dosage and the data indicates that the cardio-renal syndrome and cardiovascular risks were only evident with high doses of these drugs. Another factor which has emerged is that the principal mode of action of these drugs, to specifically inhibit the enzyme, cyclooxygenase-2 (COX-2) may have been a major factor causing teh development of these site effects-this being an example of what is known as “mechanism-based” toxicology.

Coxibs are strictly classed as *Functional analogues* since aside from the general chemical features in common with members of this class there are few common specific chemical features that uniformly describe their properties. There are, of course, some features of the biochemical interactions of these with the enzyme, COX-2, which mediates their main pharmacological actions. With the possibly unique exception of lumiracoxib, the other coxibs are tricyclic compounds with high pKa values (pKa 8-9). These contrast with the conventional NSAIDs that are weakly acidic compounds with pKa values of about 3-5, derived from either aryl-carboxylic acids or keto-enolic compounds. The coxibs are diarly-heterocycles that have a *Cis-stilbene* moiety substituted in one of the pendant phenyl rings with a 4-methylsulphone(e.g. rofecoxib) or sulphonamide (e.g.

celcoxib) substituent (Figure2). These moieties are critical together with the diaryl heterocyclic structure in determining their actions as highly specific COX-2 inhibitors.

The odd drug apparent in these chemical associations within the coxiba is lumiracoxib. This drug is an analogue of the traditional acid NSAID, diclofenac, and does not have the tricyclic character of the other coxibs but is an aniline-phenylacetic acid. The 2,6-dichloro-substituents of diclofenac are replaced by 2-chloro, 6-fluoro-moieties in lumoracoxib. There are indications that the COX-2 specificity of lumira-coxib. Perhaps this drug should not be classed as a coxib in view of the lack of associations both chemically and possibly pharmacologically with the other coxibs.

The term coxib derives logically from *cox-inhibit*or and appears to have been a marketing ploy by the two major companies that developed these drugs to discriminate them from other NSAIDs. Whether such a pharmacological description is justigiable is debatable especially since the claims for markedly improved GI safety with the conxibs are now being increasingly challenged in relation to at least the risk of serious GI adverse reactions observed with low-risk NSAIDs such as diclofenac or ibuprofen.

RATIONLAFE FOR THE DISCOVERY OF COXIBS:

The discovery in 1991 of two COX enzymes that are responsible for the synthesis of inflammatory prostaglnanding gave a new basis for understanding how these molecules regulate and mediate inflammatory reactions, pain and fever, as well as a number of diverse physiological reactions such as blood flow, thrombosis, and gastrointestinal, renal and resproductive functions. About two years previously, a unique COX enzyme was discovered that was produced in response to inflammatory stimuli. In a short while, the genes coding for two separate enzyme proteins were isolated and cloned. By convention the enzyme that is responsible for the production of physiologically important prostaglandins and thromboxane A_2 is termed COX-1. The other enzyme, which is responsible for prostaglandins involved in inflammation and pain and is induced upon stimulation with various inflammatory stimuli (lipopolysaccharide, growth factors etc.), is known as COX-2. Actually the term COX refers to the cyclooxygenase enzyme activity and since peroxidase activity is also present, both enzymatic properties exist in one protein which is termed prostaglandin G/H endoperoxide synthase or PGHS. COX-1 is present in PGHS-1 and COX-2 in PGHS-2. Because the enzymatic activity is the functional response to the gene-regulated and expressed production of prestanoids (Prostaglandis and thromboxane A_2) it is usual to term the two isoforms COX-1 and COX-2 for short.

SOME IMPORTANT MEDICINAL PLANTS ANTI-INFLAMMAATORY ACTIVITY:

The following plants were found to have anti-inflammatory activity due to the presence of their bio active compounds like flavonoids, saponins, terpenoids, alkaloids, glycosides ect. *Mikania cordata, rubia coadifolia, ambraosia artemisiaefolia, turnera ulmifolia, euphorbia royleama, culcasia scandens, aerva lanata, heterotheca inuloides, indula viscose, eupatorium bunnifolium, atractylodes lancea, dalberia sissoo, scoparia dulcis, rubia cordifolia, curcuma zedoaria, vitex peduncularis, lourteigia balloteafolia, sideritis anariensis, lavandula angustifolia, artistolochia bracteats, bauhinia variegate, hedera colchica, awolanthus suaveolens, tilia argentea, Petrocarpus marsupium and coccina indica, daucus carota, plumeria acuminate, zizphus lotus, Ficus rligiosa, Hedychium coronarium, stachys sehtschegleevii, aspilia afticana, phyllanthus reticulates, P. Amarus, symplocos cochichnensis, faidherbia albida, solanum trilobatum, barleria cristata, bauhinia purpures, sophora flavescens, pseudarthria visida, tecomella undulate, acacia catechu, russlua virescens, delonix elata, and burkea Africana, achillea millefolium, aconitum heterophyllum, adhatoda vasica nees, adansonia digitata, aegle marmelos, aloe vera, azardirachta indica, annona squamosa, baccharis incarum, bacopa monnieri, barleria prionitis, bonafousia sananho, boussingaultia gracilis,boswellia serrata, bryophullum pinnatum, bursera simaruba, Caralluma thberculata, cassia fistula, Cassia obtusifolia, Citrus auranticum, Commiphora mukul, Corida ulmifolia, curcuma longa, daphne paotica, elephantophs scaber, emblica officinalis, erythrospermum monticoloum, garcinia mangostana, hammada elegans, hedera thombea, iberis amara, kirkia acuminate, lantana camera, lippie geminate, lippie nodiflora, lycopodium clavatum, mangifera inidca, marsdenia condurango, mikania cordata,moringa olifera, paederia foetida, palisota hirsute, petiveria alliaceae, phyllanthus polyphyllus, piper longum, piper ovatum, pluchea indica, ricinus communis, rheum australe, rubrus ellipticus, saussurea costus, sesbania sesban, sida cordifolia, sidium guajava, swertia chirata, T. Buxifolium, T. Flavum, T. Micrantha, Tinospora deversifolia, Tuberaria lingosa, thespesia populnea, vinca rosea, visnea mocanera, vitex negundo, xeromphis spina, zanha Africana, zingiber officinalae,acacia modesta, adenentherapavonina, alnizialebbeck, alpiniagalangal, alstoniascholaris, andrograpispaniculata, argyreiaspeciosa, balanitesaegyptiaca, bambus vulgaris, barleriacristata, bauhinia purpurea, boswelliaserrate, bowdichiavirgilioides, calotropisprocera, camellia sinensis, carumcopticum, cassia fistula, chloranthuseretus, crotalaria juncea, dilleniaindica, dregeavolubilis, drimysangusrifolia, echoliumviride, ficusamplissima, ficusbengalensis, foeniculumvulgare, gynadropsispentaphylla, holopteleaintegrifolia, hygrophilaspinosa, gypericum, rumeliacum, lonidiumsuffruticosam, kalanchoecrenata, lamiophlomis rotate, lantana trifolia, leonotis nepetaefolia, leucasasper, Lotus pedunculat, mallotus philippinensis, malvaparviflora, mitragynaparvifolia, monochoriavaginalis, morngaoleifera, mortoniagreggii, nothospondiasstaudtti, onosmaaucheranum, onosmaisauricum, onosmasauricum, onosmasericeum, passiflorafoetida, pedilanthus tithymaloides, petroselinum trispum, pimentaracemosa, pinusdensifloara, piper sp, piperlongum, piper sarmethosum, plantogomajo, plumeria acuminate, polyalthia longifolia, punicagranatum, phyllanthusamarus, phyllanthusemblica, riveahypocrateriformis, rhododendron arboretum, rungiapectinata, rungiarepens, rubiacardifolia, sapindustrifoliatus, schimawallichiii, sclerocaryabirrea,*

semecarpusanacardium, silybummarianum simmondsiachinensis, smilax china, solanumnigrum, solanumtrilobatum, sonchusoleraceus, spilanthesacmella, tabernaemontana catharinensis, terminaliaarjuna, thespesiapopulnea, tephrosiapurpurea, trachelospermum jasminoides, trichodesma indicum, ventilagoharmandiana, vitex negundo, zingiberofficinale,Acacia catechu, allium sativum, abutilon indicum, andrographispaniculaata, anacardium occidentale, azadirachta indica, alternantherasessilis, berbeis asiatica, boswellia serrata, beta vulgaris, bacopamonnieri, bryocopsislaciniosa, bauhiniaracemosa, syzygium aromaticym, chrysanthemum indicum, curcuma domestica, curcuma longa, cyperus rotundus, cassia fistula, euphorbia heterophylla, emblica officinalis, glycyrrhiza glabra, gumnema sylvestre, hibiscus vitifolius, murraya koenigii,mangifera indica, noringa oleifera, monordica charantia, nyctanthes arbour-tristis, ocimum sanctum,piper longum, parthenium hysterophorus, phyllanthus polyphyllus, psoralea corylifolia, ricinus communis, rubia cordifolia, sida acuta, solanum nigrum, sterculia acsphigera hance, adhatoda vasica, tinospora crispa, zingiber officinale, trigonella foenum graecum, metha sorcata, cleome gunandra,portulaca pilosa, vitex leucoxylon, myrtus communis, amaranthus viridis, elephantopus scaber.

PLANTS WITH REPORTED ANTI-INFLAMMATORY ACTIVITY:

1. ***AEGLE MARMELOS (Rutaceae):***

It has been reported that aqueous root and bark extracts significantly decreased the rat paw edema induced by carrageenan. The activity was comparable to that of inuprofen. The extracts also significantly decreased granuloma weight and were thus found effective in both acute and chronic inflammation.

2. ***AGERATUM CONYZOIDES (ASTERACEAE):***

Experimentally, the leaf extract has been shown to be effective in the treatment of chronic pain in osteoarthritis and in causing a fall in rectaltemperture. Reports showed that the essential oil exhibited significant anti-inflammatory effect while the water-soluble fraction of the 70% ethanol leaf extract exhibited anti-inflammatory and analgesic properties.

3. ***ALEO VERA (LILIACEAE):***

The anti-inflammatory activity of the fresh juice has been reported. The fresh juice obtained from leaves of the plant inhibited carrageenan induced rat paw edema to a degree comparable to that of ibuprofen however, in chronic inflammation model, the extract did not significantly reduce granuloma weight in treated animals. The fresh juice was effective in acute inflammation but exhibited no effect in chronic inflammation.

4. ***AMBROSIA ARREMISIAEFOLIA:***

The ethanolic leaf extract was reported to inhibit the development of granulomatous tissue produced by croton oil-induce dinflammation in rats. The extract also significantly reduced

carrageenan-induced inflammation in rats, and inhibited early stages of formaldehyde induced arthritis in rats. The extract was more active topically than orally and believed to be more suited for use in arthritis.

5. ***ANTHURIUM CERROCAMPANENSE (ARACEAE):***

Further investigation of the dichloromethane extract revealed that it inhibited dextran, carrageenan and zymosan-induced rat paw edema which is associated with histamine and serotonin release. The extract was however not active in arachiidonic acid-induced inflammation of the rat paw suggesting the absence of involvement of the lipoxygenase pathway.

6. ***ASPILIA AFRICANA (COMPOSITAE):***

The anti-inflammatory activity of isosaline and ethanolic leaf extracts based on their effects on heat and hypotonicity-induced lysis of bovine red blood cells has beeb reported.

7. ***BRYOPHYLLUM PINNATUM (CRASSULACEAE):***

In experimental animal models, the anti-inflammatory activity of the methanolic leaf extract in acute and chronic inflammation has been demonstrated. The extract significantly inhibited carrgeenan-induced rat paw edema and inhibited the weight of granuloma tissue in cotton lellet test. The observed activity in cotton pellet granuloma test was attributed to the ability of the extract to decrease fibroblasts number and synthesis of collagen and mucopolysaccharides, which are natural proliferative agaent of granulation tissue formation.

8. ***BUTEA FRONDOSA (POPILIONACEAE):***

B. frondosa leaves are used in inflammarory conditions, skin disease, worm infestations, and haemorrhoids. The aqueous leaf extract was shown to exhibit dose dependent anti-inflammatory acitivity in carrageenan-induced rat paw edema. Teh observed activity was significant and comparable to that of ibuprofen.

9. ***CALLIGOUNM COMOSUM (POLYGONACEAE):***

C. *Comsum* is a shrun distributed throughout Arabia and growing in sandy deserts, and used by the local healers to treat stomach ailments. The stems and leaves are chewed as an ailment in toothache. Experimental evidence suggests that 10% ehtnolic extract of the aerial parts of *C. comosum* significantly reduced increase in hind paw edema induced by carrageenan.

10. ***CALOTROPIS PROCERA (ASVLEPIADACEAE):***

C. Procera is a wild growing tropical plant. It possesses multifarious medicinal properties including anti-inflammatory effects. Extracts from different parts of the plant have been reported to possess anti-inflammatory effects.

11. ***CARALLUMA TUBERCULATA (ASCLEPIADACEAE):***

C. tuberculata is a plant largely grown in Pakistan and Indian. It is consumed as food and used in ethnomedicine in the treatment of rheumatism, leprosy, blood disorders and as an anthelmintic.

12. ***CASSIA SPP (CAESALPINACEAE):***

It has been reported that the ethanolic leaf extract of some of the *Cassia* spp *(C. sieheriana, C. spectanbilis, C. siamea, C. alata and C. nodasa)* inhibited increase in paw volume induced by carrageenan.

13. ***CEDRUS DEODARA (PINACEAE):***

The effect of the essential oil *C. deodara* wood on 48/80 and nustatin- induced paw edema in rats and membrane sabilizatio has been reported. The oil also significantly inhibited nystatin-induced edema dose dependently. Further findings indicate that the wood oil exhibited membrane stabilization by inhibiting erythrocyte hemolusis induced by heat nad hhpotonicity.

14. ***CENTAUREA CYANUS (ASTERACEAE):***

C. cyuanus flower-heads are used in Eurpoean traditional medicine in the treatment of minor oculr inflammation.

15. ***CHAMANTHERA DEPENDENS (MENISPERNACEAE):***

The leaves of *C. dependens* are used as a dressing for fractures and as an embrocation for sprains and muscular pains. The methanolic leaf extract was reported to singnificantly and dose-dependentlu inhibit paw edema induced by carrageenan in rats. Teh extract inhibite cotton pellet granuloma in rats producing effect comparable to that of Indomethacin.

16. ***COSSUS TRIFOLIATA (VITACEAE):***

The extract was found more potent than phenulbutazone in acute inflammation and has similar potency of phenylbutazone in chronic inflammation. The extract inihibited heat-induced erythrocyte lysis, which is a biochemical index of anti-inflammatory activity.

17. ***CULCASIA SCANDENS (ARACEAE):***

The anti-inflammatory activity of the methanolic leaf extract and TLC fractions in egg albumin-induced acute inflammation in rats has been reported. In addition, the crude extract effectively suppressed increase in paw edema.

18. ***CURCUMA LONGA (ZINGIBERACEAE):***

Also, the anti-inflammatory activity of the volatile oil on Freund's agjuvant- induced arthritis in rats and talc-induced trno-synvitis in pigeons are documented. The results indicate that the colatile oil exhibited a highly significant early anti-inflammatory effect, probably related to its

antihistaminic and histamine depletin effect. The effect was more marked than that obtained with cortisone acetate. The antiarthritic effect of teh volatile oil of *C. longa* was attributed to a possible mediation through the hypophyseal adrenal axis.

19. ***DALBERGIA SISSOO(FAVACEAE):***

Plants of the genus *dalbergia* have been reported to be useful in the reatment of arthritis, gonorrhoea and theumatic pains. Teh scientific evidence for the anti-inflammtory activity of *D. Sissoo* leaves has been recently provided. The ethanolic leaf extract inhibited teh edema induced by carrageenan kaolin and bhstatin in the rat paw. The extract was reported to reduce the weight of grnauloma, implying an effect on the proliferative phase of inflammation. It also reduced the intensity of the peritonela inflammation produced bu acetic acid in mice, indicating its ability to inhibit the permeability of small blood vessels.

20. ***DICLIPTERA CHINENSIS:***

The anti-inflammatory activity of *D. Chinesis* has been reported. Aqueous extract of the aerial part inhibited increae in paw edema induced by carrageenan. The extract was found effective in inhibiting the two phases of inflammatory response induced by carrageenan.

21. ***DIODIA SCANDENS:***

The leaves of this plant are used in the folkloric treatment of snake bites, theumatic inflammatory disorders, earache and veneral deseases. The antivenom propert of teh plant had been reported.

22. ***EMILIA SONCHIFOLIA:***

The pharmacological evidence for thr anti-inflammatory effects of *E. Sonchiflolia* has been further provided. Methanol and aqueous leaf extracts of the plant was shown to reduce paw edema induced by egg albumin. Teh aqueous extract was found more potent than the methanolic extract.

23. ***ENTADA ABUSSINICA STEUD (MIMOSACEAE):***

Teh result indicate that the methanolic extract significantly inhibited the development of paw edema induced by carrageenam. The etract also exhibited a dose dependent and significant inhibition of dry weight of the cotton pellet granuloma tissue formation in rats. The inhinition produced by the extract was greater that that produce by hydrocortisone.

24. ***EUPHORBIA ROYLEANA(EHPHORBIACEAE):***

The extract produced significant antiarthritic activity in subacute and chronic models of cormaldehyde and adjuvant-induced arthritis. It also inhibited teh exudates volume, leucocute migration in rats and cascular permeability in mice. However, the extract exhibited poor inhinitory effect on the granuloma formation by cotton pellet and croton oil.

25. ***FICUS PLATYPHYLLA (MORACEAE):***

Experimental evidence suggests that the methnol bark extract of *F. Platyphylla* markedly inihibted egg albumin-induced rat paw edema in a dose-relaed manner. There was significant difference between the activity of the extract and acetylsalicylic acid. The activity of the extract was attributed to its flavonoid content.

26. ***GENITANELLA ACHALENSIS (GENTIANACEAE):***

The anti-inflammatory activities of the petroleum ether, dichloromethane and methnol extracts and a fraction F_2 (obtained from chromatographic separation of the dichloromethane extract) of *G. Achlensis* have been reported [123]. In the mice ear edema induced by 12-0-tetradecanoylphorbol-13-acetate(TPA), only teh dichloromehhane extract produced significant inhibition. Of the seven frction sobrained form its chromatographic sapration, one fraction exhinited activity comparable to that of indomethacin and the fraction was shown to contain two triterpenoids oleanolic and ursolic acids as major constituents.

27. ***HETEROTHECA INULOIDES (ASTERACEAE):***

It has been reported that an active fraction obtained from the purification of aqueous extract of *H. Inuloides* exhibited potent anti-inlammatory effect. The fraction inhibited inflammation induced by carrageenan and dextran and weakly reduced arachidonic acid induced edema, and also produced gastric erythma on gastric lucosa of rats. It was concluded that inhibition of prostaglandin bisosynthesis might be involved in the anti-inflammatory activity of *H. Inuloides* though other mechanism may also be involved.

28. ***HOLMSKIOLDIA SANGUINEA (VERBENACEA):***

The aqueous extract and chloroform fractions of the leaves were reported to hae inhibited acrrageenan-induced paw edema inrats.

29. ***ICACINA TRICHANTHA (ICACINACEAE):***

The liver and kidney protective activities of methanol teh tuber extract in carnon terrahloride-poisoned rats have been reported . this effect of the extract was reportedly scavenging activity acharaveristic of many anti-iflammatory agents.

30. ***MITRACARPUS SCABER (RUBIACEAE):***

In experimental animal models, the anti-inflammatory and antimicrobial activities of the petroleum ether and methanol extracts of the leaves of *M. Scaber* have been repored. Both extracts progressively exhibited sustained inhibition of increase i paw edema induced by fresh egg albumin. The methanolic extract exhibited a higher antimicrobial activity than teh petroleum ether extract. This was suggested probably to imply that the extract might be more effective in inflammation caused by infectious microorganisms. The petroleum ether extract was however more potent than the methanolic extract.

31. ***MORINGA OLEFER (MORINGACEAE):***

The methanol root extract inhibited carrageenan-induced paw edema in rats. The extract dose-dependently inhibited increased paw weight comparable to indomethacin. Teh extract also produced inhibitory effects against Freund's adjuvant – induced chronic inflammation. These findings suffest that teh root extract is effectige in both acute and chronic inflammation and inhibits both the cell and flud accumulation to the same extent inboth acute and chronic forms of puch inflammation.

32. ***MYACRODROUN URNNDEUVA (ANACARIDACEAE):***

Experimental studies have demonstrated significant anti-inflammatory activity of the aqueous and hydroalcohol extracts of the bark in teh several animal modes. Teh ethylacetate extract has been reportd to have demonstrated highest anti-inflammatory activity when compared to the activitities of hexane, chloroform, ethulalcohol, methylalcohol and water extracts.

It has been reported that the ethulacetate extract has two main fractions- a predoninat group of substances of a chalcone nature and antoher group of mainly catechin tannins.

The catechin tannin fraction obtained by column chromatrography of teh ethuylacetate bark extract of *M. Urundeura* was reported effective in inhibiting carrageenan and dextrainindced paw edema. The tannin fraction also inhibited by carrageenan and N-formyl-methionl-L-leucyl-L-phenualanine.

33. ***NEWBOULDIA LAEVIS (BIGNONIACEAE):***

Experimental evidence suggest that a 95% ethanol leaf extract reduced the paw edema induced by fresh egg albumin and was siginificantly more potent that indomethacin. The effectiveness of the extract as an anti-inflammatory agent was attributed to possible suppression of the release of inflammatory mediators.

34. ***OPUNTIA FISCUS-INDICA (CACRACEAE):***

In a recent report, it has been shown that adjuvant- induced pouch granuloma aguided fractionation of teh methanolic extract has led to the isolation and identification of β-sitosterol as the active principle. The anti-inflammatory activity was however reported to be weak compare to hydrocortisone.

35. ***ORBIGNYA PHALERATA (ARECACEAE):***

The mesocarp fruits of *O.phalerata* is a food rich in carbohydrates and mineral salts with acclaimed anti-inflammatory and analgesic properties. In traditinla medicine, it has beenused for the treatment of menstrual pains, arthirits, leudkemia, theumatism, ulcerations, tumors, and inflammation of uterus and ovarium

36. ***POTHOMORPHE PELTATA (PIPERACEAE):***

P.peltata leaves are extensively used as an anti-inflammatory agent throughout tropical South and Central America. The *In vitro* antioxidant and free radical sacenging activities of different leaf extracts of the plant have been demonstarated.

37. ***PREMA HERBACEA (VERBENACEAE):***

P. hercacea is claimed to be useful in the treatment of fevers, inflammation, rheumatisum respiratory disorders and as a sedative. Experimental evidence suggests that the ethanolic root extract did not reduc paw edea induced by carrageenan.

38. ***PSIDIUM GUIANENSE (MURTACEAE):***

In experimental animlas, the essential oil of P. Guianense obtained by steam distillation of fresh leaves was reported to have exhibited dose dependent inhibition of edema in the rats hind paw. The anti-inflammatory activity was found to be comparable to that of indomethacin.

39. ***RHEO SPATHACEA (COMMELINACEAE)"***

The ethanolic leaf extract inhibited the development of croton oil induce dgranulomatous tissue and the early stages of formaldehyde-indcued arthritis in rats. The extract also significantly inhibited carrageenan induced inflammation in the rat paw and was found to be more active topically than orally.

40. ***SAMNUCUS EHULUS(CAPRIFOLIACEAE):***

Pharmacological evidence indicates that the methanolic thizome extrat produced anti-inflammatory activity in both acute and chronic inflammatory tests. *S. ebulus* extract inhibited teh formalin induced edema to an extent not significantly different from the effect of sodium salicylate. Teh exract also chronically inhinited teh development of formalin-indcued edema. The observed activities were arrtibuted to the plant constituents such as flavonoids, steroids, glycosides and tannins but most probably flavonoids and steroids.

41. ***SIDERITIS SPP (LAMIAEAE):***

The anti-inflammatory and anti-ulcerogenic activities of 20% decoctions of the flowering apices of these *Sideritis spp* have been demonstrated. The extracts clearly reduced planter edema induced by carrageenan with *S. incana virgata* being the most active. This was followed by *S. hirsute.* Only *S. hirsute and S, incana* were orally active.

42. ***SYZYGIUM CUMINI(MYRTACEAE):***

In the ulcerogenic screening, the extract did not show any ulcerogenic effect in both acute and chronic tests. This suggests that prostaglandin inhibition or cyclo-oxygenase-1 may not be involved in the anti-inflammatory activity of *Syzygium cumini* bark. However, the observed anti-inflammatory activity was arrtibuted to a possible inhibition of inflammatory mediators.

43. ***TANACETUM PARTHENIUM (ASTERACEAE):***

In native medicine, the leaves of *T. Parthenium* are eaten or the infusion drunk in teh treatement of arthritis, migraine and asthma. It is also clained useful for tinnitus, viertigo, fever, menstrual disorders, difficulty of labour, stomachache, toothache and insect bites.

In carrageenan-induced rat paw edema, it has been reported that ethanolic leaf extract exhibited dose dependent anti-inflammatory activity comparable to that of nmedulide.

44. ***TAXODIUM DISTICHUM (TAXODIACEAE):***

The anti-inflammtroy activity of essential oil of the fruit has been reported. The essential oil obtained bu hyudrodistillation of the fresh crushed fruits exhibited a stron anti-inflammatory activity in the rat paw edema test. The oil was as effective as diclofenac. The anti-inflammatory activity of the oil was arrtibuted to the proesenc eof α-pinene found to be the principal component of the oil.

45. ***TEUCRIUM BUDIFOLIUM (LAMIACEAE):***

Further experimental evidence has been provided for the anti-inflammatrory actitivity of *T. Buxifolium.*the hexane and methanol extracts inhibited both the acute nad chronic phases of

arthritis. The methacnolic extracat was more active against eh chronic than teh acue phase. The aqueous extract was, however, effective against both phases with activity comparable to phenylbutazone.

46. ***TITHONIA DIVERSIFOLIA (COMPOSITAE):***

The anti-inflammatory activity o fqaueoud extract of the aerial part has been reported. The results show tha t the aqueous extract inhibited paw edema induced by carrageenan. The extract was found effective in the two phases of the carrageenan induced inflammatory response.

47. ***TREMA SPP (ULMACEAE):***

The petroleum ether, ethanolic and aqueous leaf extracts were found active in carrageenan-induced edema and produced significant antiarthritic activity . in acute inflammation , *T, micrantha* ether extract caused the highest percent inhibition comparable to that of indomethacin. The obserced anti-iflammtory and antiarthritic activities were attributed inpart to the β-sitosterol in these species and perhaps to contributions from other constituents e.g. flavonoids triterpenes etc.

48. ***TRIPTERYGIUM (CELASTRACEAE):***

An ethnolic roots wood extracat has been used in the treatment of various kinds of rheumatism an autoimmune diseases including rheumatoid arthritis. The extract was reported to hae significantly improved joint symptoms relief ranging from 3 days to 2-3 weeks.

There are evidence that the ethanolic root wood extract significantly inhibited carrageenan-indcued paw edema in rats. And inhibited adjuvant-induced modularory effect on mediators of inflammation, inhibited lysozyme release, decreased superoxide production and significantly reduced prostaglandin levels.

49. ***TURNER ULMIFOLIA (TURNDERACEAE):***

The ethanolic fraction was reported to inhinit leucocyte migration,and markedly reuced the vascular permeability induced by $PGE_{2,}$ histamine and 5-HT but not bradykinin. The anti-inflammatory activity of the extract and fraction swas attributed to inhibition of mediators of early or immediate inflammatory reponse. This suggestion is consistent with the activity observed in teh cotton pellet granuloma test. Also consistent with the suggested mechniam of action is the effect of the hydroalcoholic extract on gastric lesions.

The extact inhibited gastric lesion induced by pyloric ligature, indomethacin and ethanol but was not effective in that induced by stress. Teh antiulcerogenic effect of the extract was postulatd to be due to inhibition of histamine (pyrolic-ligature ulcers) and enhancement of mucosal defensive factors such as gastric mucus (ethanol and indomethacin induce ulcers). The extact was also found effective in inhibiting arachidonic acid induced platelet aggregation thougn to be due to a selective cyclooxygenase II inhibition and consistent with the anti-ulcerogenic effect.

ISOLATED ANTI-INFLAMMATORY PLANT CONSTITUTENTS

FAGARAMIDE AND DBA:

Fagaramide (piperonyl-4-acryliciso-butylamide) and DBA (3,4-dihydro-2-dimethyl-2H-1-benzopyran-6-butyric acid), a benzopyran butyric acid derivative of xanthoixylol, are extractives

from fagara, plant ,*zanthoxylum zanthozyloides* (Rutaceae). Root extracts of fagara plant are widely used locally in the treatment of fevers of various aetiologies and sickle cell.

DBA is a bezpyran acid derivative of xanthoxylol from the fagara plant. Fagaramide, an unmodified extractive from fagara plant was found effective agains tcarrageenan-indcued paw edema in rats at a potency apporoximately twenty times less than that of indomethacin.

Faragamide was also effective against the prodtaglandin phase of acute inflammatory response where it dose-dependently inhibited *In vitro* prostaglandin dynthesis. However, it showed no effect on PGE_1 – induced potentiation of carrageenan edema in indomethacin treated rats.

Lepeol and lupeol lineolate:

The isolation of an anti-inflammatory triterpenoid, lupeol, from the n-haxane stem bark extract of *crataeva religiosa* FOrst. F. (Caparidaceae) has been reported. It has also been documented that lupeol is a major triterpene constituent of the stem bark of *Crataeva nurva* Buch-Ham (Caparidaceae) *C. nurvala* had been shown to possess anti-inflammatory and antiarthritic activities.

In an extensive and detailed anti-inflammaory activity studies, it was reported that lupeol exhibited anti-inflammatory effect in a variety of acute and chronic anti-inflammatery test models in rats and mice. The highest oral activity was btained in the carrafeenan- induced edema. Lupeol exhibited significant anti-infammatory effect in developing adjuvant arthritis in rats to a degree better than that of acetylsalicylic acid. The same activity was obtained in mice arthritis model.

In formaldehyde arthritis, lupeol was effective in the development and pattern of inflammation compared to a similar dose of acetylsalicylic acid. Lupeol also reduced exudates volume, inhibited vascular permeability induced by acetic acid in mice and also reduced total leucocyte count.

However, lupeol was not effective in inhibiting cotton pellet granuloma in rats. In exhinited no ulcerogenic, analgesic and antipyretic effects, it was thus suggested that the anti-inflammatory activity of lupeol might be due to immunosuppression and inhibition of cell migration into sites of inflammation. The latter, in turn, reduces proinflammatory chemotactic factor release.

Further experimental evidence has been provided for the anti-inlammatory activity of lupeol and also lupeol linelate which is an ester of lupeol. Lupeol lineolate was obtained form esterification of lupeol with linoleoyl chloride.

In adjuvant –indcued arthritis, lupeol and lupeol lineolate caused inhibition in paw diameter by 39 and 58% respectively. The synovial cavity of lupeol treated arthritic joint was found more or less oblitereated with granulome-like lesion consisting of fibrin, and inflammatory cellular infiltration.

Arthritica rats treated with lupeol lineolate showed synovial cavity with less cellula infiltration. These findings suggest that the antiarthritic acvitity of lupeol lineolate is greater that that of lupeol. The reason for lupeol's lack of activity in cotton pellet granuloma test and the activity observed in adjuvant-induced arthritis is not know. However, it may be due to differences in pharmacological characteristics of the two models of chronic inflammation. *Parthrnolide and the methoxyflavoes* .

Parthenolide and the methoxyflavones (jaceosidin, eupatorin, chysoerial and diosmetin) hae been isolated and identified from dichloromethane and methane extracts of aerial parts of *Tanacetum vulgare* (astercace).

These constituents have been reported to be responsible for the anti-inflammatory activity of the plant agains t12-10 tetrdecanoylphorbol-13-acetate (TPA) induced mouse ear edema. Parthenolide caused inhibition of modue ear edema. (ID_{50}=0.18µm/ear). The methoxy-flavone jaceosidin caused inhibition with ID_{50} of 0.5 µm/ear). Parthenolide was reportedly found to be nearly three times (in molar terms) more potent than of the most active of the flavones).

(+) – PINITOL:

Abies pindrow spach (Pinaceae) known as the "Talisapatr" tree in Sanskrit and " motinda" in Hindi is found in abundance in the deciduous forests of HImalays. The leaves have been use din Ayurvedic medicine for fever, respiratory and inflammatory disorder the leaf extracts and fractions of have been resported to possess nati-inflmmatory, analgesis, huypnoitc and antiulcerogenic activites in rats, hypotnesive effect in dogs and endurance enhancing in swim stress in mice.

(+)- pinitol inhibited edema induced by carrageenana in the rat paw in a dose-related manner. The activity of the highest dose was comparable to that of phenulbutazone.

Premabazole:

Premnzole is an isoxazole alkaloid derivative isolated from the leaves of *Gmelina arborea* ROxb and *Premna integrifolia* Linn (Verbenaceae). *G. Arbeorea* was introduced into West Africa from torpical Asia as a shade and fuel tee and is important in afforestaion programme in the savannah zones of Nigeria. The drupes, leaves, flowers, roots and bark are used in medicine. A leaf paste is applied on the head to relieve headache in fever.

P. interiglia tender plant is used for rheumatism and neuralgia. The leaves also possess carminative and galactagogoue properties. The leaf decoction is used for colic and flatulence.

Premnazole,an alkaloid was earlier prepared by total synthesis. The isolated premabazole was shown to singinficanlth reduce cotton pellet granuloma weight in treated animals. It also reduce

the weight of adrenal gland and spleen and also reduced ascorbic acid cintent in adrenal glands. The action of premnazole was arrtibuted to a probable control of the activity of adrenocortiacorropic hormone and inhibition of bradykinin synthesis through reduction in the activities of glutamate pyruvate transaminase and glutamate oxaloacetate transaminase.

SARSANAQUOL:

The isolation of an anti-inflammatory 3, 4-secotritrpene alcohol, sasanquol, from, the non-saponifiable lipids of seed oil of *Camellia sasanqua* THUNB has been reported. The structure was established by spectroscopy as3,4-seco-D:B-friendcacchara-4. 21-dien-3-ol. In anti-inflammatory test, sasanwuol inhibited ear edema induced by TPA with ID_{50} of 0.4 mg/ear.

TRITERPEE ALDOHOLS:

The isolation of seven novel naturally occurring triterpene alcohols from non-saponificbalbe lipids of seeds of *Camellia japonica* L. and sasanqua oil from seeds of *C. sasanqua* has equally been documented. The compounds include tirucall-5. 7, 24-trine-3-beta-ol, lemmaphulla-7,21-dien -3-beta-ol, isoeuphol, isotirucallol, (24R)-24, 25-epoxybutrospermol and its 24S-epimer and isoaglaiol. The anti-inflammatory effect of these compounds in the mouse ear has been reported.

Isoeuphol, isotirucallol, amixture of (24R)-24, 25- epoxybutyrospermol and its 24S epimer and a mixture of isolaglaiol and its 24S epimer (aglaiol) inhibited mouse ear edema induced by 12-0 tetradecanoylphorbol-13-acetate (TPA) with an ID_{50} of 0.2 -0.9 mg/ear.

(+)- USNIC ACID:

(+)- Usnic acid has been isolated from the whole plant of the lichen Roccella montagnei Bel. (FAm. Roccellaceae). Activites fo (+)-usnic acid earlier reportee include antibacterial, antitubercular, analgesic and antipyretic and other pharmacological activities. The anti-inflammatory activity of (+)-usnic acid has been studied.

ZANHASAPONINS A AND B, AND CYCLICTOL PINITOL:

The methanolic extract of *Zanha Africana* was found active against arahidonic acid acute edema, 12-0 teraceecanoylphornol-13-acetate (TPA) induce dchronic inflammation and oxazolone delayed type hypersenstitivity inmice. The extract also exhibited significant inhibitory acivity against *Naja naja* phospholipase A_2 using ploarogrpahic method. Oleanance –type tritrpene sapnins zanhasaponis A,B and C and the cylitol pinitol were isolated from the methanolic extract of *Zanha Africana*.

Out of the four isolated constituents, zanhasaponins A and B and the cyclitol pinitol were reported to inhibt phospolipase A_2 enzyme necessary for the release of arachidonic acid. Phospholipase A_2

inhibition prevent the formation of prostaglandins, thromboxanes and leukoteriens and is the main basis for the anti-inflammatory effect of steroids.

CONCLUSION:

It is evident from the documentation that a number of medicinal plants are medicinal plants are employed in the treatment of inflammatory disease conditions. These anti-inflammatory disease conditions. These anti-inflammatory plants have demonstrated effect in acute and chronic inflammation in experimental animal models. The effects of these various family of herbs may be due to the different structurally complex active principles or constituents present in these plants and the possible multiple targets of drug action in the complex inflammatory response.

The anti-inflammatory activity of plants is attributed mainly to the constituent such as alkaloids, falnvonids, tannins, sterols, triterpens, sesquiterpenes lactones, volatile olis resins, carbohydrates or polysaccharides flavones glycosides, polyimsatiraed fatty acids e.g palmitic, oleic and linoleic acids. These structural forms have variously been shown to exhibit pharmacological activity in the inflammatory response process naturally by interfering with the response pathway.

Consequently, falvonoids have been reported to inhibit arachidonic acid metabolism and prostaglandin synthetase. Tannins inhibit prostaglandin synthetase. While plant catechols e.g 4-nerolidyl-catechol (4-NC) have been shown to exhibit peroxuyl radical scavenging and lipid peroxidation. Glucan type polysaccharides have been reported to inhibit increase in vascular permeability while polysaccharides exhibited anti-complementary activity of all the mechanisms for the anti-inflammatory effects of these plants their actions on endogenous pro-inflammatory mediators are remarkable. The inflammatory reactions induced by the phlogistic agents used in the screening of these herbs are mediated by different endogenous mediators.

Besides their inherent anti-infmmatory and other pharmacological activities, these active principles could serve as “leads”for the development of drugs with enhanced activity profile. Already, lupeol lineolate, an ester of lupeol, obtained by esterification of lupeol with linoleoyl chloride, has been reported to exhibit greater antiarhtritic activity than lupeol.

The existence of multiple targets for drug action in th inflammatory response pathway offers numerous sites of action to the multitude of active constituents of these medicinal plants. Due to their efficacy in the herbal treatment of inflammatory disease conditions, these plants have continued to serve as alternative and complementary therapies. Mounting experimental evidence has continued to lend credence to this fact and to establish rationale for the ethnomedicinal use.

In addition, these medicinal plants will continue to serve as reservoir for development of potent drugs with less serious and life-threatening adverse effects.

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