Mechanism of Inflammatory Pain and Implementation of Natural Products as Rescue Route

ABSTRACT

The onset of pain is the major discomfort associated with inflammation. The inflammation is usually associated with tissue injury, irritation and infection. This leads to the release of pro-inflammatory compounds from either damaged or immune cells leading to the stimulation of nociceptors which are mainly primary afferent fibres. The stimulation of these fibres by neuropeptide, substance P, prostaglandins, leukotrienes, histamine, serotonin, protons and others leads to pain. To ease this pain, the drugs tend to either inhibit the enzymes or the nerve receptors. The major means of controlling the pain involves the inhibition of cyclooxygenase and lipoxygenase pathways. However, the effective inhibition of these enzymes tends also to impede other functional physiological activities occurring in the body, leading to health crisis. The steps in eradicating these lethal side effects have led to the various techniques including natural remedies like plants and fish oils. Therefore, this study tends to present a review on the pain sensation pathway during inflammation and how the introduction of natural products in drug therapies could prove lucrative.

KEYWORDS inflammation, irritation, infection, pain sensation

INTRODUCTION

One of the major origins of the clinical cases is usually due to the report of pain by patients. With inflammation been one of the common reasons, several methods have been developed in curbing the expression of pain, thereby controlling the inflammation. The onset of inflammation is usually initiated by various factors such as tissue injury, irritation and infection. The inflammation usually results to rubor (redness), calor (heat), tumour (swelling) and sometimes loss of function which occurs synchronously with dolor (pain). The pathway of pain sensation is usually facilitated by the action of damaged tissue on either primary afferent fibres or immune cells. The inflammation could also lead to the sensitisation of afferent nociceptor, producing secondary sensitisation of afferent fibres which possess lower threshold with hypersensitivity to stimulus, leading to chronic pain.

The earlier development of solutions to the pain in prehistoric times involved the use of herbal entities such as Ginger (Zingiber officinale), turmeric (Curcuma longa), Boswellia gum resin (Boswellia serrata) and cayenne pepper (Capsicum annuum). However, as the understanding of inflammation and pain increased over the decades, the compounds like morphine, fentanyl, resveratrol, diaryl heterocycles, aspirin, methane sulfonanilide, quercetin, curcumin and pethidine have been identified and utilised. However, the side effects elicited by these drugs tend to cause unpleasant symptoms which could be lethal in some cases. Therefore, this review tends to point out natural analgesic substitute for relieving pain with little to negligible side effects.

Neurobiology of pain sensation

The nociception is usually mediated by the fibres that are different from normal sensory stimulus as they have different receptor. The nociceptors are unmyelinated unspecialised nerve ending that transduces pain through the dorsal root ganglia and trigeminal ganglia. They transmit pain via two distinguished fibres, C fibre and Aδ fibre. The C fibre is usually characterised as being...
unmyelinated with an small diameter with impulse speed of 2 m/s responding mostly to thermal, mechanical and chemical stimuli, while the Aδ fibre been lightly myelinated with a larger diameter has a faster impulse speed of 20 m/s and responds to mechanical and mechanothermal stimuli. The difference in impulse time between C and Aδ fibres gives the reason for the initial sharp pain (epicritic) which is followed by a slow, dull long-lasting pain (protopathic) during the pain sensation which is transmitted by the spinothalamic and trigeminal pathways. Apart from these fibres, the heavily myelinated Aβ fibres function to conduct non-nociceptive input such as vibration, movement and light touch. They also inhibit nociceptive input at the spinal segment by activating the inhibitory interneurons in the substantia gelatinosa of the dorsal horn, termed as the ‘gate theory of pain control’. The visceral nociception are usually mediated by C fibres which unite with peripheral somatic nerve fibres on the substantia gelatinosa, thereby localising nociception to the somatic region. This leads to somatic muscle contraction and vasodilatation of cutaneous blood vessels.

**Inflammation and pain**

The inflammation belongs to the class of natural protective procedures employed by the body after an injury, necessary for initiating the healing process. The damaged cells due to the injury are programmed to release the inflammatory substance that causes the stimulation of nociceptors. These inflammatory substances (Table 1) tend to either sensitize or stimulate the nociceptors. Although not fully understood, it is reckoned that sensitation of nociceptors is associated with cytosol cAMP/Ca2+ increase. The studies revealed that the administered dibutyryl-cAMP, Ca2+ ionophore or BaCl2 caused hyperalgesia with high Ca2+ levels while the administration of prostaglandins (PGs) or sympathomimetics such as dopamine and norepinephrine lead to increase cAMP synthesis which caused hyperalgesia. The involvement of Ca2+ was confirmed when hyperalgesia was absent following Ca2+ channel blockage. Its pathway has been speculated, involving the activation of ligand-gated ion channels, voltage-dependent calcium ion channels, metabotropic N-methyl-D-aspartate receptors and neurokinin-1 receptors on the cell membrane by substance P and glutamate.

This leads to increased intracellular Ca2+ which could also activate protein kinase C, necessary for reducing pain threshold. The chemical substance (Table 1) at the region of inflammation may either stimulate the nociceptors directly or activate the immune cells.

**Direct modulators of Nociceptors**

The most inflammatory substance that acts primarily on nociceptors is produced at the site of inflammation (Fig. 1). They tend to carry their effect through various interactions with the cellular membrane. Some of these include modulators, include protons, serotonin, ATP, bradykinin and nerve growth factor (NGF).

The protons are released by damaged cells and function by increasing ion permeability of primary afferent fibres, stimulating the receptors. The protons also tend to reduce the pH level leading to the activation of acid-sensing ion channels (ASIC), thereby lowering the threshold of C fibre and Aδ fibre to pain sensation. Similar to protons, serotonin directly interacts with primary afferent fibres.

The bradykinin is formed by the action of high molecular weight kininogen on kallikrein in the vicinity of the inflamed tissue. They display synergistic activity with NGF and PGs which could stimulate proinflammatory cytokine. They associate with G protein-coupled BK B1 and BK B2 receptors, the activating protein kinase C that sensitises and stimulates the receptors.

The NGF usually illicits its effect by tyrosine kinase A (TrkA) receptor which sensitises the nociceptor, thus potentiating the activities of other agents. They also increase the sensitivity of TRPV1 receptor to heat, causing pain. NGF also degranulates mast cells by releasing more mediators including NGF, which causes hyperalgesia, leading to the neutralisation of NGF as an inhibitory response. The ATP functions by acting on non-peptidergic primary afferent nociceptors via Pα,β,δ and Pα,δ,fg receptors causing pain.

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### Table 1: Inflammatory mediators

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Origin</th>
</tr>
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<tbody>
<tr>
<td>Substance P</td>
<td>Primary nerve afferents</td>
</tr>
<tr>
<td>Leukotrienes</td>
<td>Damaged nerve fibres</td>
</tr>
<tr>
<td>Histamine</td>
<td>Mast cells</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Platelets</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>Damaged nerve fibres</td>
</tr>
<tr>
<td>Potassium</td>
<td>Damaged nerve fibres</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>Plasma</td>
</tr>
</tbody>
</table>

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**Fig. 1** Effectors of direct inflammation.
Role of immune cells

The release of chemoattractant and chemokines by the affected tissues have a tendency to attract innate immune cells like macrophages, dendritic cells, mast cells, innate lymphoid cells and neutrophils via diapedesis, chemotaxis and leukocyte binding. They oppose infection pending the arrival of adaptive immune response involving T cells.

The neutrophils and macrophages are the major innate immune cells. The response of neutrophils at the site of inflammation is usually quick and in increasing numbers during the first 24 h. They release pro-inflammatory factors such as tumour necrosis factor α (TNF-α), lipoxygenase (LOX) product, IL-6, IL-1β, cytokines and reactive oxygen species for the efficient regulation of nociceptor stimulation. They incline support to macrophage infiltration by secreting chemokines/chemotactiant MIP-1α, MIP-1β and IL-1β. The macrophages release TNF-α, IL-1β, IL-6, MIP-1α, MIP-1β and MCP-1 on arrival, these pro-inflammatory factors initiate repairing activities while stimulating nociceptors via synergistic means. The macrophages also play the role of cleaning the site of inflammation by removing the dead cells and debris.

Role of eicosanoids in immune response: The eicosanoids occurs virtually in all tissues. They possess a hormone-like feature with a brief life-span. They mediate physiological reactions during inflammation, vascular dilation, blood clotting and immune response. The eicosanoids can be subdivided into PGs, leukotrienes (LT), thromboxanes (TxA) and prostacyclins (close relatives of PGs, such as PGI2 which is a potent vasodilator and anticoagulant); the PGs and LT serves as the major regulators of inflammation.

The eicosanoids are synthesised by the action of phospholipase on phospholipids of the cell membranes. An important pathway is the action of phospholipase A2 on phospholipids yielding arachidonic acid (AA). Apart from the cell membrane phospholipids, AA can also be acquired directly through diet. They could also be synthesised from omega-6 polyunsaturated fatty acids present in the diet.

The AA is the key precursor in the synthesis of potent inflammatory mediators with support from cyclooxygenase (COX) and LOX pathways. As a result, most drugs make effort to control inflammation by targeting the reactions of AA and its derivatives.

Role of COX and LOX in inflammation

The AA is a polyunsaturated 20-carbon fatty acid embedded in cell membranes as a phospholipid ester and serves as the precursor for the PG synthesis. In response to a wide variety of stimuli, the free AA is released which is subsequently converted via COX, lipoxygenase (LOX) and cytochrome P450 enzyme catalysis to various lipid mediators known collectively as eicosanoids.

COX and their role in inflammation

The COX is an integral membrane protein found mainly in the microsomal membranes with distinct active site for cyclooxygenase and peroxidase activity. About three COX isozymes have been identified in nature; COX 1 which is mostly responsible for the housekeeping; COX 2 majorly induced during inflammation and COX 3 which is identified among canine with high sensitivity for acetaminophen and related compounds.

The COX 1 and 2 isofoms catalyse the first committed step in the biosynthesis of PG's, thromboxanes (TxA) and other eicosanoids. The production of these eicosanoids is dependent on the availability of AA. The release of AA from membrane phospholipids is mediated by either secretory (sPLA2) or cytoplasmic (cPLA2) phospholipases. Once AA is released, the COX isofoms catalyse two sequential reactions. The initial COX reaction converts AA to prostaglandin G2 (PGG2). The subsequent peroxidase (POX) reaction reduces PGG2 to prostaglandin H2 (PGH2) which is then converted by various cell-specific isomerases and synthases to produce five biologically active primary PG's that include prostaglandin D2 (PGD2), prostaglandin E2 (PGE2), prostaglandin F2α (PGF2α), prostacyclin (PGI2) and thromboxane A2 (TxA2) as shown in Fig. 3. These products act as secondary messengers by interacting with prostanoid G protein-coupled receptors as well as other receptors.

The COX 1 had been ubiquitous functions in maintaining the physiological homeostasis by facilitating the

Fig. 2 Omega-6 fatty acid metabolism.

- Omega-6 Fatty Acid
- Linoleic Acid
- delta-6-desaturase
- Gamma-Linolenic Acid (GLA)
- delta-5-desaturase
- PGE1 (anti-inflammatory)
- Arachidonic Acid
- COX
- LOX
- PGE2 (pro-inflammatory)
- LTB4 (pro-inflammatory)

J Pharm Biomed Sci | Vol. 06 No. 06 | 350–359
production of relevant prostaglandins. This categorises it as a ‘housekeeping’ enzyme. In disparity, the COX 2 is absent in most tissues, but its expression is rapidly induced by stimuli such as pro-inflammatory cytokines (IL-1β, TNFα), lipopolysaccharides, mitogens and oncogenes (phorbol esters), growth factors (fibroblast growth factor, FGF; platelet-derived growth factor, PDGF; and epidermal growth factor, EGF), hormones (luteinising hormone, LH) and disorders of water–electrolyte hemostasis, resulting in the increased synthesis of PGs in inflamed and neoplastic tissues. Thus, amongst several differences between COX 1 and COX 2, the COX 2 is peculiar to pathological processes such as inflammation and cancer. However, further findings have shown that the COX 1 plays a role in inflammation, additional verdicts also shows that COX 2 occur in several tissues similar to COX 1.

LOX and their role in inflammation

LOX is the oxidative enzymes that catalyse the addition of oxygen into polyunsaturated fatty acids as response to inflammation, releasing pro-inflammatory and anti-inflammatory factors which include leukotrienes and lipoxins respectively. The LOX catalyse the formation of hydroperoxyeicosatetraenoic acids (HPETEs) from AA which are converted to eicosanoids. The LOX can be classified based on their ability to selectively oxygenate fatty acids in an exact position, thereby subdividing into 5-, 8-, 12- and 15-LOX. The 5-LOX tends to function mainly with inflammation. Unlike COX 1 and 2 which are widely distributed, the 5-LOX is restricted to neutrophils, eosinophils, mast cells, basophils, monocytes, macrophages and B-lymphocytes.
The 5-LOX possesses high affinity for calcium ion (Ca\(^{2+}\)), with ability to bind two Ca\(^{2+}\), thereby promoting the hydrophobicity for efficient enzymatic activity on the cell membrane. In addition to Ca\(^{2+}\), the 5-LOX depends on ATP and five-lipoxygenase-activating protein for maximal effect. Upon inflammation, the phospholipase A2-\(\alpha\) (cPLA2\(\alpha\)) present in the cytosol releases AA which activates 5-LOX for LT synthesis. The LOX catalyses the formation of AA to 5-HPETE which is converted to leukotriene A4 (LTA4). LTA4 is acted upon by LTA4 hydrolase to form dihydroxy acid leukotriene B4 (LTB4). LTA4 could also be catalysed by LTC4 synthase forming cysteinyl leukotriene 4 (LTC4) via the addition of glutathione. LTC4 is then converted to leukotriene D4 (LTD4) and glutamic acid by \(\gamma\)-glutamyltransferase (Fig. 4). LTD4 could also lose its amide bond to leukotriene E4 (LTE4) via the action of dipeptidase.

The LBT4 on formation activates phosphatidyl inositol 3-kinase pathway by binding to LTB4 receptor 1 and 2. This phosphorylates IkB\(\alpha\) thereby activating nuclear factor \(\kappa\)B (NF-\(\kappa\)B) pathway. LTC4, LTD4 and LTE4 also activate the NF-\(\kappa\)B pathway by binding to cysteinyl leukotriene receptors 1 and 2. The pathway of NF-\(\kappa\)B functions in the manifestation of pro-inflammatory genes including cytokines, chemokines and linkage molecules. LBT4 also triggers the adenylate cyclase which produces cAMP, leading to the sensitisation of nociceptors. The LOX metabolite also tends to interact with TRPV1 receptors, promoting hyperalgesia in return.

Other hyperalgesic metabolite includes histamine, serotonin and cytokines associated with mast cell degranulation. The cytokines released perform various functions among these are interleukins 1\(\beta\), noted for facilitating neutrophil chemotaxis and TNF-\(\alpha\) which possesses effective pro-inflammatory properties. The neuropeptides and neurokinin displayed by the sensory nerve endings also support analgesic and inflammatory response.

**ANTI-INFLAMMATORY MEDIATORS**

The undesirable sensation of pain following inflammation makes it a great necessity to curb its over expression. Several chemical compounds participate in controlling inflammation. These compounds could either be endogenously or exogenously produced.

**Endogenous anti-inflammatory mediators**

This involves techniques employed by the body in controlling inflammation. An understanding of this mechanism also helps the researcher to develop effective anti-inflammatory compounds. The naturally synthesised anti-inflammatory cytokines IL-10 and IL-1ra participate by preventing the release of NGF and influx of neutrophils respectively. Apart from cytokines, the opioid synthesised by immune cells employ mu and kappa opioid receptors in peripheral tissues, controlling intolerable inflammatory pain. Also, in-house cannabinoiids such as anandamide, 2-arachidonylglycerol and palmitoylethanolamide activate cannabinoids receptors (CB1 and CB2), preventing mast cell degranulation. The metabolism of omega-3 fatty acids tends also to synthesise the anti-inflammatory eicosanoids which help to balance the role of pro-inflammatory mediators.
Implementation of natural products in inflames

Exogenous anti-inflammatory mediators

The information on inflammation and its mechanism provides an effective means of controlling analgesic conditions. Apart from other compounds used to regulate inflammatory sensations, the involvement of AA metabolism is the major means of controlling hyperalgesia during inflammation.

The connection of COX in controlling pain is the chief pathway employed by the researchers. This is due to the fact that the COX plays the major pro-inflammatory role among other activities. As a result, several non-steroidal anti-inflammatory drugs (NSAIDs) are developed as antagonist to COX. However, the non-selective COX inhibitors when administered affect the physiological role of COX, thereby affecting the housekeeping functions of COX (Table 2). This led to the development of selective COX-2 inhibitors, as they are more expressed during inflammation.

Non-selective COX inhibitors

These categories of drugs block both the COX 1 and COX 2. Most common is aspirin, which covalently modifies by acetylating the distinct serine residue within the active site of the enzyme. Since the housekeeping enzyme blocks side effects arising from gastroduodenal ulceration, the platelet malfunction to renal function impairment leading to NSAID gastrotoxicity also surfaced when such drugs are ingested. The nonselective NSAIDs exhibit three modes of binding: i) reversible binding (ibuprofen), ii) rapid, low affinity reversible binding followed by a time-dependent, higher affinity, slowly reversible binding (flurbiprofen), iii) rapid, reversible binding followed by a covalent modification of the enzyme (aspirin). Other nonselective drugs include indomethacin and meclofenamate. Due to the adverse side effects of NSAIDs administration, selective COX 2 inhibitors emerged.

Selective COX inhibitors

They lack a specific carboxylic group that enables the targeting of COX-2 only. They exhibit time-dependent inhibition of COX-2. Based on structural orientation, the selective COX-2 inhibitors can be categorised.

The majority of selective COX-2 inhibitors are diarylhetocycles. The historical origins of diarylhetocycles as pharmacophores can be traced back to the anti-inflammatory agent phenylbutazone. A common structural feature of these tricyclic molecules is the presence of

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Table 2: Physiological functions of prostaglandins.

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<th>Tissue/organ</th>
<th>Mediators</th>
<th>Function(s)</th>
</tr>
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<tbody>
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<td>Female reproductive organs</td>
<td>PGE(<em>2), PGF(</em>{2\alpha})</td>
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<td>Cardiovascular system</td>
<td>TXA(_2), PGI(_2)</td>
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</tr>
<tr>
<td></td>
<td>TXA(_2), PGE(<em>2), PGF(</em>{2\alpha})</td>
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</tr>
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<td>Arterial vasodilation</td>
</tr>
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<td>Venous vasoconstriction</td>
</tr>
<tr>
<td></td>
<td>PGE(_2), PGI(_2)</td>
<td>Patency of the fetal ductus arteriosus</td>
</tr>
<tr>
<td>Respiratory system</td>
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<td>Bronchodilation</td>
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<tr>
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<td>PGE(_2), PGI(_2)</td>
<td>Renin release</td>
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<td>Inhibition T and B lymphocyte activation and proliferation</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>PGE(_2), PGD(_2), PGI(_2)</td>
<td>Fever</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td></td>
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<td>Pain</td>
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Fig. 5 Metabolism of omega-3 fatty acids.

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Omega-3 Fatty Acid

Alpha-Linoleic Acid

delta-6-desaturase

Steridonic Acid

delta-5-desaturase

Eicosatetraenoic Acid

Eicosapentaenoic acid

Docosahexaenoic acid

PGE\(_3\)

LOX

LTB\(_5\)

(anti-inflammatory)

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Table 1: Metabolic functions of omega-3 fatty acids.

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1,2-diaryl substitution on a central 5-membered ring system. Generally, for this class of diarylheterocycles, they contain para-SO₂NH₂ moiety which increases the inhibitory COX-2 potency and improved the oral absorption. In the design of selective COX-2 inhibitors, the various types of tricyclic diarylcarbocycles have been evaluated extensively. The examples include cyclobutene or cyclobutenone, cyclopetenone and 6-membered aromatic ring such as benzene. The diphenylcyclpentenes and cyclopentenones were among the first series of compounds to be evaluated for COX-2 selectivity with no gastric complications.

The 1,5-diarylpyrazole class of compounds exhibited excellent in vitro COX-2 inhibitory potency and selectivity. Celecoxib was the first diarylhetercyclic selective COX-2 inhibitor approved for the clinical use. Further studies exploiting the structural difference in COX-1 and COX-2 showed that the replacement of para-SO₂NH₂ pharmacophore in celecoxib and the para-SO₂Me pharmacophore in rofecoxib by linear azide (N3) or a sulfonyl azido group could increase its potency since His513 in COX-1 is replaced by Arg513 in COX-2.

In addition, the diarylhetercycles possessing a central 5-membered isoxazole ring are regioisomeric diaryl isoxazoles that shows an excellent in vitro activity profile. They possess a para-SO₂NH₂ substituent (valdecoxib) as shown in Fig. 6. The additional work revealed that regioisomeric 3,4-diarylisoxazoles with para-SO₂Me substituents exhibit excellent in vitro COX-2 inhibitory activity and in vivo anti-inflammatory activities (e.g., isoxazole regioisomer).

The extensive evaluation of the 3,4-diaryl furanone class of diarylhetercycles compounds indicated their positive activity, whereas, their regioisomer was inactive. An example includes the (S)-enantiomer of 3-isopropoxy-5-ethyl-5-methyl derivative of rofecoxib with the oral absorption increased by C5 hydroxylation.

In addition, the diarylhetercycles with central 6-membered pyridine ring, central 6-membered pyrano-none ring and central 6-membered pyridazinone ring have shown similar effects. The members of the methane sulfonanilide class of COX-2 inhibitors generally exhibit preferential COX-2 selectivity. These compounds are characterised as the derivatives of alkylsulfonanilides with nimesulide been the first discovered drug.

**Side effects of COX-2 inhibitors**

Although beneficial, the inhibition of COX-2 affects the proper functions of various systems such as reproductive, cardiovascular and renal systems.

**Effects of COX-2 inhibitors in cardiovascular system:** The role of COX-1 in mediating thromboxane for thrombosis is usually opposed by prostacyclin produced by COX-2. Therefore, the inhibition of COX-2 leaves the action of COX-1 uncontrolled leading to the formation of thrombosis causing heart failure.

Also some drugs like Celecoxib shunts AA from the COX-2 pathway (Fig. 7) to the 5-LOX pathway producing leukotrienes B₄ which is a potent bronchoconstrictors and vasoconstrictors leading to cardiovascular risks of defects.

**Effects of COX-2 inhibitors in reproductive function:** The inhibition of COX-2 tends to cause defects in the rupturing of follicles during ovulation, it also affects fertilisation and implantation of the zygote in the uterine wall.
Effects of COX-2 inhibitors in brain function: The COX-2 inhibitors are very essential in the neonatal and final brain development, as they are the major sources of prostaglandin production. Their inhibition could therefore lead to some symptoms of neurological disorders.

IMPLEMENTATION OF NATURAL PRODUCTS IN CURBING INFLAMMATORY PAIN

The side effects elicited by various anti-inflammatory drugs tend to still point out the need for a better remedy in curbing inflammation. It is generally accepted that the herbal plants tend to possess effective chemicals which may be potent against inflammation with milder side effects. Since most of the anti-inflammatory drugs are made up of synthetic component, the switch into plant use has become a major route. The major chemical groups from natural sources with potency against inflammation include polyphenils, flavonoids, terpenoids, alkaloids, anthraquinones, lignans, polysaccharides, saponins and peptides.

Among the phytochemicals, flavonoids tend to be the most effective, especially against phospholipase and TNF-α. Based on structural orientation, the flavonoids also tend to inhibit COX and 5-LOX pathways. Quercetin, a bioflavonoid also possess ability to prevent histamine release. Apart from flavonoids, alkaloids and terpenoids have been reported to be effective against rheumatism and joint edema. The curcumin have also been studied to be effective against 5-LOX and COX with no report of gastrointestinal bleeding when used alone.

The phenolic glycoside extracts from willow bark plant also tend to inhibit COX by preventing the formation of PG. It possesses a milder and long-lasting effect than the other synthetic drugs. Capsaicin from cayenne pepper also tends to have an inhibitory effect on COX. Boswellic acids from Boswellia also inhibit leukotriene production by blocking 5-LOX.

Apart from the use of herbal products in relieving inflammation, a regulation of diet so that more omega-3 fatty acids are ingested may prove quite effective. This is due to the fact that the PG or LT produced due to inflammatory response depends on the cellular membrane composition, which is determined by diet. Since most diets are rich in linoleic and AA, a shift to more consumption of omega-3 fatty acids may displace AA from cellular membrane and also compete for COX and LOX pathways, thereby increasing the production of anti-inflammatory chemicals upon inflammatory response.

CONCLUSION AND RECOMMENDATION

Among several sensations of inflammation, the stimulation of nociceptors causing pain still remains the major discomfort. With proper knowledge and insight on how pain is stimulated, the use of several drugs has been displayed in curbing inflammation and pain. Although, most of these drugs tend to illicit lethal side effects rendering the primary reason of administration, the least worries. The effort to find a better means of easing inflammatory pain has led the researchers to trace back to historical times on how the ancestors handled these cases and locating active chemicals responsible for them. Most of the remedies are usually found among the herbal products. However, a major setback in this approach shows that not enough studies are done on the pathway of already uncovered anti-inflammatory herbal products, as studies on these pathways may provide an alternative means of curbing inflammation and inflammatory pain with minimum side effects.

Prospects of herbal products as potent anti-inflammatory medication

Role of Annonamuricata

It is commonly recognised as soursop and employed mainly by the settlers of the northeast and southeast regions of Brazil. It is used traditionally as a remedy for various ailments including insomnia, hypertension, diabetes and serve as antispasmodic and anti-inflammatory agent.

The studies on the plant have shown the presence of alkaloids and essential oils as the major chemical constituents. The research showed that the oral administration of ethanolic extracts from Annonamuricata leaves had the activity of antinociceptive and anti-inflammatory properties in rats. The study suggested that one or more pathway was inhibited by the extracts as the effect was comparable to indomethacin, although, the proper explanation on the principle of action is still lacking.

Role of Anogeissus acuminata

It is locally known as Button tree, Buchakrama, Peddmanu and Pasichettu among the Indian populace. It is identified as the modest sized tree with small leaves. The phytochemical screening revealed the presence of alkaloids, flavonoids, steroids and terpenoids in it. The further studies revealed the anti-inflammatory and analgesic activity of A. acuminata leaves in Swiss albino rat.

Roles of Voacanga Africana

It is more peculiar to the African continent, it spans from Senegal to Sudan and Nigeria to Angola and Zaire and flourishes below the forest canopy. It is employed traditionally for washing wounds and easing hernia. It is also used to prevent premature parturition. The studies have also shown its anti-inflammatory and anti-analgesic activity of the plant leaves. The further studies identified the presence of saponins, tannins, flavonoids, terpenes, anthraquinone and cardiac glycosides in the leaves of the plant but with little knowledge on its active component and their mechanism of action.
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