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LIMITATIONS OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND THE UTILITY OF NATURAL PRODUCTS FOR ANTINOCICEPTIVE AND ANTIEXUDATIVE EFFECTS

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ABSTRACT

Nonsteroidal anti-inflammatory drugs (NSAIDs) express anti-inflammatory, analgesic and antipyretic effects, essentially by reversible inhibition of the rate-limiting enzyme-cyclooxygenase (COX), in the biosynthesis of prostaglandins. Among the dominant widely used medications globally are NSAIDs and are indicated for various forms of acute and chronic pain, rheumatoid arthritis, gout and pyrexia. Also some of them (aspirin for instance) are employed for prevention of secondary cardiovascular disorder due to mainly their ability to suppress platelet aggregation. Despite these applications, NSAIDs are known to present limitations in their untoward effects, hence researchers in recent times, have focused their efforts toward various chemical modifications of NSAIDs such as nitro-aspirin, des-methyl (DM)-sulindac, phosphatidylcholine (PC)-aspirin, pegylated phosphoribuprofen, dual COX/LOX inhibitors, Copper (II)/NSAIDs complexes; as well as natural product system of medicine for the discovery of agents that exert efficacy and potency with minimum adverse effects. This study reviewed the mechanisms of action, clinical applications, potential antitumor activity, interactions and limitations of NSAIDs as well as natural products with promising antinociceptive and anti-inflammatory (mainly anti-exudative) activities, utilizing the advantage of the frequent occurance of natural products as complexes of structurally related analogues to be exploited for good efficacy and safety in humans.

KEYWORDS: NSAIDs, limitations, natural products, Chikadoma, antinociceptives, antiexudatives.

1. INTRODUCTION

The first representative of a group of medications that reduce inflammation, relieve pain and fever referred to as Nonsteriodal anti-inflammatory drugs (NSAIDs) is acetyl salicylic acid commonly called by its proprietary/trade name "aspirin" courtesy of the Bayer company. This prototype drug was put into commercial form in 1897 by a German Chemist Felix Hoffmann (1868-1946) and later introduced into clinical practice in 1899. More than 1 billion prescriptions of NSAIDs is estimated throughout the world yearly, and about 30 million persons administer NSAIDs daily.[1]

With more than 40,000 tonnes of "consumption" on yearly basis.[2] However, numerous limitations are associated with NSAIDs, hence this study was aimed at reviewing the utility of natural products for antinociceptive and antiexudative effect with diminished adverse tendencies as against the limitations of NSAIDs.

2. NSAIDs

2.1 Classification

NSAIDs can be classified based on their chemical structure or according to their ability to influence activity of the COX isoenzymes.[3, 2] Based on their structure, there are the following classes of derivatives: Salicylate, propionic acid, pyrazolone, indoleacetic acid, phenylacetic acid/fenamate, oxicam/enolic acid, and niftyloacetic acid derivatives (Table 1); while based on their influence toward COX isoenzyme, NSAIDs can be classified into non-selective and selective COX-inhibitors (Table 2).

Table 1: Classification of NSAIDs based on their chemical structure.

Group (Derivatives)	Example
- Salicylate (salicylic acid) –	Acetysalicylic acid (Aspirin), sodium salicylate, methyl Salicylate.
- Propionic acid -	Ibuprofen, ketoprofen, naproxen, fenoprofen, fluribiprofen.
- Pyrazolone -	Phenylbutazone, oxyphenbutazone, sulfinpyrazone.
- Indoleacetic acid -	Indomethacin, sulindac, tolmetin
- Fenamate (phenylacetic acid) -	Diclofenac, meclofenamate, aceclofenac
- Oxicam (enolic acid) -	Piroxicam, meloxicam, tenoxicam
- Niftyloacetic acid -	Nabumetone

Table 2: Classification of NSAIDs based on influence upon cyclooxygenase isoenzymes.[3, 2]

Group (inhibitors)	Example
Non-selective COX -	Piroxicam, acetylsalicylic acid (Aspirin) Ibuprofen, neproxen
Selective COX-1 -	Flurbiprofen, ketoprofen
Sective COX-2 -	Coxibs (celecoxib, Etoricoxib, lumiracoxib) Diclofenac, mefenamic acid

Table 3: Characteristics of COX-isoenzymes.[4, 5]

Parameter	COX-1	COX-2
Gene size	25 kb	8.6 kb
Exons	15	10
Chromosome	9q33.2	1q31.1
mRNA	2,8 kb	4.1 kb
Gene expression	Constitutive (ubiquitous)	Constitutive (brain, thymus, gut, and kidney) and inducible (sites of inflammation, infection,
Factors promoting expression	-	cytokines, lipopolysaccharide,
Amino acid composition	599	604
Molecular weight	68.5 kDa	70 kDa
Cell localization	Nuclear envelope, endoplasmic reticulum	Nuclear envelope, endoplasmic reticulum
Cofactors	1 molecule heme	1 molecule heme
Acetylated regions	Ser 530	Ser 516
Substrates	arachidonic acid, aminoacids, γ-linoleic acid	arachidonic acid, aminoacids, γ-linoleic acid, α- linoleic, eicosapentaenoic acid

The classification of NSAIDs based on cyclooxygenase isoenzymes into COX-1 and COX-2 is not absolute rather relative since in a concentration dependent manner, all NSAIDs can inhibit both COX-1 and COX-2 activity *in vitro*. It is the ratio between the 50% inhibitory concentration ($1C_{50}$) values that has been employed in the determination of the rate of COX-2 selectivity of NSAIDs. Even the most selective COX-2 inhibitors such as lumiracoxib and etoricoxib, can also inhibit COX-1 activity when administered at high doses.[6] Aspirin vice versa, is a prototype non-selective COX inhibitor but at low doses (75-300 mg) it reduces platelet aggregation by predominantly inhibiting more than 70% COX-1 and less than 5% COX-2.[7] The same aspirin at higher doses (more than 1,200 mg) manifests pronounced anti-inflammatory and analgesic effects by inhibition of both COX-1 and COX-2 isoenzymes.[5]

2.2 Mechanism of action

Reversible suppression of the function of COX is the basis of biological activity of NSAIDs COX, reputed as the rate-limiting enzyme in the biosynthesis of prostaglandin, is a homodimeric enzyme necessary for the conversion of arachidonic acid to prostaglandine H_2. This is the first step that is crucial for further biosynthesis of prostanoids and thromboxanes). Two isoforms of this protein are known to exist in human namely COX-1 and COX-2. COX-2 is found to be inducible isoform expressed only at sites of inflammation, cancer or infection; while COX-1 is constitutive and expressed in all tissues. COX-1 plays an important role in homeostasis and regulates gastric cytoprotection; thrombosis, platelet aggregation, and kidney function. The concentration of COX-2 can be raised up to 10-50 times in response to mitogenic or oncogenic stimuli. This is equally true in response to inflammatory signals such as TNF-α, 1L-1β, and lipopolysaccharide.[2] Due to untoward cardiovascular and other effects of COX-2 selective inhibitors, subsequent re-evaluation and scrutiny seems to shift from the initial absolute inducible nature and has widely been established that COX-2 is constitutively present in specific discrete sites and maintains vital non-inflammatory-related physiological roles.[4] Although

structurally heterogeneous, all members of NSAIDs possess a single common mechanism of action to block prostaglandin synthesis, yet various NSAIDs have other actions that may contribute to differences between the drugs such as neutrophil aggregation and adhesion, cytokins production and cartilage metabolism; superoxide radical production are superoxide scavenging. In addition, data suggesting the central analgesic effects of NSAIDs exist based on various mechanisms of action including glycin-dependent modulation of pain, effect on β-endorphin, modulation of inhibitory fast synaptic currents in lamina I and II of the dorsal horn.[8, 9]

2.3 Clinical application

Based on their main pharmacological and therapeutic effects, the clinical use of NSAIDs can be summarized in three main perspectives.[10, 11]

i. For Analgesia - in both acute and chronic pain situations such as toothache, headache, dysmenorrhea, and post-operative pain. Induction of peripheral analgesia by NSAIDs via inhibition of COX activity and prostaglandin biosynthesis is well documented cum central analgesic effects based on established mechanisms.[9]

ii. For fever - antipyretic effect is based on controlled thermoregulation induced by binding of prostaglandin G_2 (PGE_2) to EP_3 receptors on neurons within the preoptic anterior hypothalamic area. In the hypothalamic region, via exposure to exogenous pyrogens (pathogen-associated molecular patterns), cells of the immune system generate and release interleukins, TNFα and other endogenous pyrogens to stimulate the synthesis of PGE_2. Though the antipyretic activity of NSAIDs is linked to their ability to inhibit prostaglandin synthesis, yet in abnormal elevation of body temperature like malignant hyperthermia and heat stroke, conditions known to be independent of the COX- mediated pathway, NSAIDs have no effect.[12]

iii. For inflammation- anti-inflammatory especially and mainly anti-exudative action in both acute and chronic inflammatory conditions such as gout and rheumatoid arthritis are part of what NSAIDs are known for.

In neurodegenerative processes, neuro-inflammation is known to play an important role and there are evidences showing that NSAIDs possess the potential to diminish the risk for Alzheimer's disease (AD)[13] as well as Parkinson's disease.[14] Amyloid β –protein (Aβ) accumulates within the brain in Alzheimer's disease, and NSAIDs have been reported to inhibit the activity of gamma-secretase, the enzymes responsible for cutting the transmembrane region of the amyloid β-protein precursor to form the Aβ.[15] NSAIDs contribute to the removal of plague and debris by modulating the phagocytic activity of microglia.[16] Celecoxib and aspirin may be helpful in managing the symptoms of schizophrenia and other neuropsychiatric disorders.[17, 18] Since the 1970s, it has been known that acetylsalicylic acid can reduce the risk of pre-eclampsia[19] and Celecoxib in a meta-analysis of randomized, placebo-controlled, double blind trials, appears to be a safe and efficacious treatment in alleviating particularly first-episode schizophrenia and other psychotic symptoms.[20]

Acetylsalicylic acid is also indicated for women undergoing assisted reproductive technology for the purpose of optimizing the chance of live birth.[21] Though the role of aspirin in primary cardiovascular disease appear controversial[22], low-dose regimes are being embraced for prevention of secondary cardiovascular disease on the account of their ability to suppress platelet aggregation[23], but because the enzyme COX-2 is not expressed in these cells selective COX-2 inhibitors do not affect platelet aggregation.

2.4: Anti-Tumour Activity

For at least some categories of cancer such as colorectal, breast and breast cancers, preclinical and clinical investigations have shown a benefit of NSAIDs in reducing their risk.[24, 25] Epidemiological studies have supported that continued use of NSAIDs lead to a significant decline in adenomatous polyps, disease incidence recurrence as well as death from colorectal cancer.[26, 27, 28]

Reports have suggested that an antitumor effect of NSAIDs is pleiotropic and includes groups of mechanisms of action namely: COX-Indpendent pathways; influencing cancer stem cells; and related to suppression of COX activity.[29, 30] German pathologist Rudolf Virchow in 1863 was the first to describe the infiltration of tumours with white blood cells.[31] Since then till now, it is widely accepted that inflammation (chronic) is essential for tumorigenesis and of course, one of the cancer hallmarks.[32] In 1986 when the relationship existing between prostaglandins and cancer was initially reported[33], it was established that PGE and PGF production influenced the metastatic and invasive potential of mammalian esophageal carcinoma cells in athymic nude mice. In most tumour tissues, inflammatory mediators and cells can be detected modulating the function of both stromal cells and tumour thereby contributing to the adaptation of a tumour-promoting microenvironment.[34] It has been suggested that increased levels of prostaglandins especially PGE_2 and PGD_2, are involved in signaling pathways important for wide range of cancer induction and progression.[35, 36, 37, 38]

Accordingly, PGE_2 has been published as potent therapeutic target for the treatment of colon cancer[39] and thromboxane A_2 (TXA_2) has been found to participate in pathogenesis of colorectal cancer.[40, 41] In addition, TXA_2 is involved in modulation of multiple myeloma and lung cancer cell proliferation[42, 43]). It is

common knowledge that the best studied molecular target of NSAIDs is cyclooxygenase in which the COX-2 enzyme (inducible cyclooxygenase is of particular interest. This is not surprising because the expression of COX-2 is associated with inflammatory conditions and overexpressed in many solid tumours such as cancers of the prostate, pancreatic, colorectal, mammary gland and lung cancer.[44, 45] COX-2 promotes tumour growth as well as suppresses antitumour immunity.[46] Cancer-associated-fibroblasts, macrophage type 2 cells and cancer cells release COX-2 into the tumour microenvironment.[47]

Epidermal growth factor receptor (EGFR), mitogen-activated protein kinase (MAPK) members and nuclear factor-Kβ are principal upstream modulators for COX-2 in cancer cells.[47] The role of constitutive cyclooxygenase (COX-1) in cancer has universally received less attention and COX -2 has been at the forefront as a promising target for cancer therapy.[48] Nonetheless, COX-1 expression has occasionally been detected in several circumstances of cancer, including head and neck cancer, haematological tumours, colorectal, esophageal, breast and cervical cancers.[49] It was in 1995 that COX-1 was first identified as marker of ovarian cancer[50] and subsequently its overexpression has been proven in various mouse, avian and human models of ovarian cancer.[51, 52, 53] More evidences indicate that both COX-1 and COX-2 isoforms play an important role in cancerogenesis with data that at least in some situations such as serious ovarian carcinoma, COX-1 enzyme may play a pivotal role.[54, 55, 56, 49]

The current situation is that the biological activity of COX-2 inhibitors has been stupendously investigated, while the number of the available COX-1 inhibitors is extremely limited and very small, pitiable part of them have been investigated for antitumour activity[57, 58, 49] (Vitale et al., 2016; Tortorella et al., 2016; pannunzio and coluccia, 2018). In a report, COX-2 has shown to play a significant role in cancer stem cell biology.[59] The antitumour action of aspirin and other NSAIDs as indicated in experimental data, may be due to the selective induction of apoptosis within human intestinal stem cells with changed Writ signaling pathway.[60] COX-independent mechanisms of anti-tumour activity of aspirin-like drugs are not unrelated with their tendency to influence Writ signaling pathway, down-regulation of proto-oncogenes such as c-myc, DNA mismatch repair systems, transcription factors and induction of oxidative stress.[61, 12, 2]

Many researchers in their endeavour to elucidate the antitumour effect of NSAIDs emphasize that the mechanism should also involve DNA to some degree and the processes of transcription and translation.[62] But because most NSAIDs at physiological pH are anions, this poses an obstacle in accessing and interacting with the polyanionic strands of DNA. This explains why interaction between NSAIDs and DNA is reported sparingly by a limited number of investigations.[63] The electrostatic repulsion between the deprotonated negatively charged form of DNA could be surmounted by combining NSAIDs with metal ions. Many studies reported that concomitant administration of copper and NSAIDs exerts a synergetic effect. Meloxicam and Piroxicam can form complexes at physiological pH with CU (II) hence a proposed hypothetical model of interaction between these compounds and DNA, which involves intercalation most likely[64] Following various complexes of NSAIDs compounded and characterized, these compounds have been found to express a more pronounced anti-inflammatory and tumour effects, possess reduced gastrointestinal toxicity compared to individual agents.[65, 66]

2.5 Interactions

The pharmacokinetic or/and pharmacodynamics interaction of drugs concomitantly administered with NSAIDs have been reported, some of which may be clinically significant. NSAIDs can inhibit drug metabolism or interfere with renal excretion of such drugs; displace other agents from their plasma protein binding sites.[67] NSAIDs used concomitantly with other antiplatelets and anticoagulant medications, results to excess risk of upper gastrointestinal bleeding.[68] NSAIDs can during the use of diuretics, ACEIs, and beta adrenergic blockers, adversely influence blood pressure control. Conversely, some treatments are known to influence the rate and extent of aspirin absorption.[69]

2.6 Limitations

Until recently 1999, gastrointestinal toxicity represented the major safety concern of NSAIDs application with symptoms ranging from milder dyspepsia to severe bleeding and ulceration.[70, 71] Apart from GIT toxicity, the major adverse limitations of NSAIDs affect kidneys, central nervous system, platelet function and cardiovascular system especially with COX-2 inhibitors.

The prevalence in the rate and severity of nephrotoxicity with NSAIDs increase in patients with certain risk factors such as heart failure, diabetes, renal dysfunction and in elderly people. It is important to recognize that in the mammalian kidney, prostaglandins regulate vascular tone as well as salt and water homeostasis playing an important role in hemodynamics[72], hence NSAIDs increase sodium reabsorption that leads to peripheral edema via the inhibition of prostaglandin (PG_2). The resultant adverse effect ranges from electrolyte retention, reduced glomerular filtration to nephritic syndrome and chronic renal failure; also observed is hyperkalemia.[73, 74]

Selective COX-2 inhibitors have been associated with adverse effects in the cardiovascular system such as elevated blood pressure and risk of atherothrombotic events, mechanism of which is not fully known but the interaction between prostanoids and T cells has been implicated.[75] However, it is not surprising, since COX-2 enzymes generates biologically active molecules that

supports regulation of blood pressure, endothelial thromboresistance, renal haemodynamics as well as in pathophysiology of pain and inflammation such as PGE_2 and PGI_2.[76] In the United States of America and Europe, rofecoxib and valdecoxib (COX-2 inhibitors) have been withdrawn from the market following their cardiovascular adverse effects, confirmed in long term placebo-controlled trials.[77] Decrease in prostaglandin production by NSAIDs can induce alternative leukotriene pathway, leading to bronchoconstriction. NSAIDs- or Aspirin-exacerbated respiratory disease (AERD) comprising asthma, Nasal polyps (referred to as Samter's triad) and aspirin sensitivity are instances of COX inhibition on the respiratory system. Some prostaglandins exhibit important regulatory tendencies on respiratory epithelial cells hence AERD affects approximately 7% of asthmatic patience and 0.3%-0.9% of general population in the USA.[78, 79, 80] Prostaglandins E_2 and D_2 are especially involved in bone remodeling. They do this by mediating the control of osteoblast and osteoclast functions having a mitogenic effect on osteoclasts and stimulations of their biological activity.[81] Prostaglandins behave as paracrine regulators of the bone remodeling cycle[82]; and NSAIDs should be avoided in high risk patients having been suggested as a risk factor for impairment of bone healing.[83]

3. Utility of chemically modified NSAIDs and natural products

Due to the challenges posed by limitations and adverse effects of conventional nonsteroidal anti-inflammatory drugs, a good number of research groups have in recent times, directed attention towards the exploration and discovery of nonconventional chemically modified drugs as well as alternative system of medicine, especially for antinociceptive and antoexudative effects.

3.1 Nonconventional NSAIDs

The design and development of nonconventional NSAIDs usually by various chemical modifications is targeted at strong therapeutic effect with a better safety profile; majority of which are in preclinical and initial stage of clinical trials.[84, 2]

a. **Phosphatidylcholine (PC) aspirin**: This is also known as NSAIDs-with-phosphatidylcholine, which rely on the preponderance of PC amongst the gastric phospholipids that form extracellular lining on the mucous gel layer thereby protecting the underlying epithelium from gastric acids.
b. **Nitro-aspirin:** This is nitric oxide-releasing-NSAIDs, relying on the fact that nitric oxide (NO) plays a protective role by maintaining gastric mucosal integrity in the gastrointestinal tract through increasing the mucosa secretion as well as mucosal blood flow plus inhibiting neutrophil aggregation. NO exerts beneficial effect on the CVS by inhibiting platelet aggregation and adhesion.[85] At the preclinical level NO has been shown to repair NSAID-induced damage while epidemiologic studies have revealed that the use of NO-donating agents with aspirin or NSAIDs leads to increase risk of gastrointestinal bleeding.[86]
c. **Pegylated phosphoribuprofen:** This is a pegylatedphospho-NSAIDs noting that polyethylene glycol protects ibuprofen from the hydrolytic mechanism of esterases.
d. **Des-methyl (DM)-Sulindac**: This represents the esterified/amidated NSAIDs.
e. **Dual COX/LOX inhibitors**: Several of these mixed preparations were conceived to overcome some of the limitations presented by NSAIDs during blockade of the arachidonic acid metabolism which can result in generation of proinflammatory mediators -leukotrienes and lipoxins via the lipoxygenase pathway. It should be recognized that leukotrienes and lipoxygenases are potential targets for the management of many pathological conditions including asthma, Alzheimer's disease, cardiovascular disease and various inflammatory diseases. So dual COX/LOX inhibitors are of great importance.[87, 88]
f. **CU (II)/NSAIDs mixed preparations:** Examples include meloxicam-and piroxicam/ CU (II) complex preparations.[64]

Complexes with NSAIDs increase anti-inflammatory effect and simultaneously reduce gastrointestinal toxicity in comparison to NSAIDs used alone.[64]

3.2 Natural products with antinociceptive and antiexudative effects

Flavonoids, terpenoids, steroids, phenols, glycosides, alkaloids and tannins are among the products of secondary metabolism by plants and they are referred to as natural products.[89] Numerous scientific evidences that buttress successful management of pain and inflammation using natural products abound. In the plant kingdom, there are representative analgesic and anti-inflammatory herbs in almost each family.[90] *Lupinus arboreus* is of great medicinal value with proven antinociceptive and anti-inflammatory activities.[91] Some other medicinal plants that exert analgesic or/and anti-inflammatory activities are shown in Table 4.

Table 4: Plants with documented analgesic/anti-inflammatory activities.[92]

Plant	Family	Used/studied part
Agerantum conyzoides	Asteraceae	Leaf
Sambucus ebulus	Caprifoliaceae	Rhizome
Caralluna tuberculata	Asclepiadacea	Flower, leaf
Diodia scandens	Rubiaceae	Aerial part
Ficus platyphlla	Moraceae	Bark
Turner ulmifolia	Turnderaceae	Leaf
Bryophyllum pinnatum	Crassulaceae	Leaf
Icacina trichantha	Icacinaceae	Tuber
Siderites spp	Lamiaceae	Flowers
Euphorbia royleana	Euphorbiaceae	Latex
Curcuma longa	Zingiberaceae	Rhizome
Pothomorphe peltata	Piperaceae	Leaf
Mitracarpus scaber	Rubiaceae	Leaf
Taxodium distichum	Taxodiaceae	Fruit
Moringa oleifera	Moringaceae	Stem
Anthurium cerrocampuse	Araceae	Stem
Centaurea cyamus	Asteraceae	Flowers
Heterotheca inuloides	Asteraceae	Flowers
Dalbergia sissoo	Fabaceae	Leaf
Terminalia ivorensis	Compositae	Leaf
Scutelleriae biocalensis	Scutellaceae	Leaf
Calotropis spp	Asclepiadacea	Flowers
Dicliptera chinensis	Acanthaceae	Aerial part
Tithonia diversifolia	Compositae	Aerial part
Calligonum comosum	Polygonaceae	Aerial part
Agerantum conyzoides	Asteraceae	Leaf
Agerantum conyzoides	Asteraceae	Leaf
Alchornea cordifolia	Euphorbiacea	Leaf
Butea frondosa	Papilionaceae	Leaf
Chasmanthera dependens	Menispermaceae	Leaf
Emilia sonchifolia	Asteraceae	Leaf
Tanacetum parthenium	Asteraceae	Leaf
Syzygium cumini	Myrtaceae	Bark
Premna herbacea	Verbanaceae	Root
Anthurium cerrocampanese	Araceae	Leaf
Culcasia scandens	Araceae	Leaf
Aspilia africana	Compositae	Leaf
Bryophyllum pinnatum	Crassulaceae	Leaf
Entada abyssinica	Mimosaceae	Leaf
Aspilia africana	Compositae	Leaf
Holmskiodia sanguinea	Verbanaceae	Leaf
Opuntia fiscusindica	Cactaceae	Stem
Croton lecheri	Rubiaceae	Leaf
Orbignya phalerata	Aracaceae	Fruit
Rheo spathaceae	Commelinacea	Leaf
Ambrosia artemisiaefolia	Compositae	Leaf
Cissus trifoliate	Vitaceae	Root
Teucrium buxifolium	Lamiaceae	Aerial part
Ficus elastic	Moraceae	Root
Psidium guianense	Myrtaceae	Leaf
Anthurium Cerrocampanese	Araceae	Leaf
Cedrus deodora	Pinaceae	Wood
Anthurium Cerrocampanese	Araceae	Leaf
Aegle marmelos	Rutaceae	Root, bark
Moringa oleifera	Liliaceae	Fresh juice, gel

Adapted with slight modification from: Ohadoma SC. Pharmacological assessment of Lupinus arboreus Sims (Fabaceae) methanol extract and fractions for antinociceptive and anti-inflammatory effects. A Ph.D Thesis, Department of Pharmacology and Toxicology, University of Nigeria, Nsukka, 2014. Available online at UNN Visual Library 2014 p.31.

3.2.1 Flavonoids with antinociceptive and anti-inflammatory activities

Flavonoids are one of the largest classes of naturally-occurring polyphenolic compounds.[93] This group of plant pigments is largely responsible for the colors of many fruits and flowers, and over 4,000 flavonoid compounds have been characterized and classified according to chemical structure. The word "flavonoid" comes from the Latin flavus which means yellow; however some flavonoids are red, blue, purple or white.[95] Chemically, they are C6-C3-C6 compounds in which the two C6 groups are substituted benzene rings, and the C3 is an aliphatic chain which contains a pyran ring.[96] Flavonoids occur as O- or C-glycone.[95]

Numerous medicinal plants contain therapeutic amounts of flavonoids, which are used to treat disorders of the peripheral circulation[95], to lower blood pressure[97], to improve aquaresis[98], as anti-inflammatory, antispasmodic[98] and anti-allergic agents.[95] The many pharmacological effects of flavonoids are linked to their ability to act as strong antioxidants and free radical scavengers, to chelate metals, and to interact with enzymes, adenosine receptors, and biomembrane.[99, 95] Some flavonoids also possess antimicrobial activity.[100]

The flavonoid glycoside, chrysoeriol 7-0-b-D glucopyranosyl (2 1) – D-apiofuranoside isolated from *Dalbergia volubilis* exhibited anti-inflammatory activity.[101] A flavonoid from *Hedychium spicalum* showed a significant activity with less ulcerogenic index than phenylbutazone.[102] Two new flavanone glycosides, diinsininol and diinsinin from rhizomes of *Sacropthyte piriei* (Balanophoraceae), showed IC_{50} values of prostaglandin synthesis inhibition 9-20 µm and 13-14 µm respectively and in the inhibition of platelet-activating-factor-induced exocytosis, IC_{50} values of 49 and 39 µm, respectively.[103]

Three flavonoids identified as (i) 4' hydroxy3', 5' liprenylisoflavanone (ii) 4' hydroxy 6, 3', 5' triprenylisoflavano-ne (iii) 3, 9-dihydroxy-2, 0 diprenylprterocarpene (erycrystagallin)[104] were isolated from a methanol extract of bark of the Samoan medicinal plant *Erythrina variegate* (Leguminosae). The compounds were shown to possess phospholipase A_2 (PLA_2) inhibitory activity. The compounds-Dicadalenol, Caryolane-1, 9 b-diol and quercetin isolated from aerial parts were identified as the active principle of Boswellia resin, inhibiting the key enzyme in leukotrine biosynthesis, 5-lipooxygenase (5-LOX). Of the boswellic acids characterized, 3-0-acetyl-11-keto-b- boswellic acid (AKBA) proved to be the most potent inhibitor of 5-LOX.[105]

A new diterpenoid, tolypodial has been established from the terrestrial Cyanobacteria tolypothrix nodosa (HT-58-2).[106] Tolypodiol and its monoacetate derivative show potent anti-inflammatory activity in mouse ear oedema assay.[106] The antipyretic and anti-inflammatory activity of a new sesquiterpene, spartidienedione isolated from *Psila spartioides* (Asteraceae) were evaluated in rabbits and guinea pigs.[107] At a dose of 25 mg/kg, this substance showed anti-inflammatory activity and antipyretic activity. Two new sesquiterpene cyclopentenones, dysidenones A, B and a new sesquiterpene aminoquinone, dysidine, all containing the same rearranged drimane skeletone have been isolated along with bolinaquinone from Sponge dysidea species.[108] Bolinaquinone, dysidine and a 1:1 mixture of dysidenone A and B significantly inhibited human synovial phospholiphase A_2 (PLA_2) at µm concentration.[108]

The oleoresin fraction of *Commiphora mukul* exhibited significant anti-arthritic and anti-inflammatory activities[109, 110] (Satyavati et al., 1969; Shukla, 1986). Methanol leaf extract of Chikadoma exhibited significant anti-arthritis activity.[111] Chikadoma is the common Nigeria nomenclature for *Lupinus arboreus*, derived from a certain lead researcher Dr. Chika Ohadoma who conducted extensively pioneering novelty work on the plant.[112] A steroidal compound isolated from *C. mukul* displayed a significant activity which is dose dependent and more potent than the resin fraction present in *C. mukul*[110] (Shukla, 1986). β- sitosterol isolated from *Cyperus rotendus* possessed potent anti-inflammatory activity against carrageenan and cotton pellet-induced oedema in rats and was comparable to hydrocortisone and oxyphenbutazon[113] (Singh 1970). Quercetin, quercetin 3-0-rhamnoside (quercitrin) and quercetin 3-0-rutinoside (rutin) from 80% MeOH extract of leaves of *Morinda morindoides* (Rubiaceae) also showed similar inhibition of classical pathway complement system[114] (Climanaga, 1995).

The dichloromethane extract of the aerial parts of *Tanacetum microphyllum* (Compositae) yielded two anti-inflammatory flavanoids: 5, 7, 3' trihydroxy-3, 6, 4'-trimethoxy flavone (Centaureidin) and 5, 3'-dihydroxy-4'-methoxy-7- carbomethoxyflavonl[115] (Abad et al., 1993). Three flavonoids, 7-0 methylaromadendrin, rhamnocitrin, and 3-0 acetylpadmatin, isolated from Inula viscose (Asteraceae) dichloromethane extract were shown to have 12-0 tetradecanoylphorbol-13-acetate induced oedema inhibitory activity in mice.[116] Some other flavonoid subtypes, eg. Coumarins and xanthones, have been shown to inhibit the COX-1/COX- 2 catalyzed prostaglandin (PG) biosynthesis in vitro.[117, 118, 119] The coumarin Calophylolide from the nuts of *Calophyllum inophyllum* (Clusiaceae) effectively reduced the increased permeability induced by the chemical

mediators involved in inflammation, like histamine, serotonin and bradykinin. The ED_{50} was found to be 144.1, 250 and 135.5 mg/kg p.o., respectively against these mediators.[120] Four coumarins, 7-methoxycoumarin (herniarin), 6, 7-dihydroxycoumarin (aescuetin), 6-methoxy-7-glucosidyl coumarin (Scopolin), and 6-hydroxy-7-methoxycoumarin (Scopoletin), were isolated from the ethanol extract of the flower tops of *Santolina oblongifolia* Boiss. (Compositae).[121] The isolated compounds showed marked activity as inhibitors of eicosanoidrelease from ionophore stimulated mouse peritoneal macrophages.[121] Magniferin, a xanthon C-glucoside from *Canscora decussatta*, mangostin and related compounds from *Cerinia mangostana*[122] and xanthones from *Calophyllum scohyllum* and *Mesua ferrea* are shown to have anti-inflammatory activity.[123]

3.2.2 Terpenoids and steroids with antinociceptive and anti-inflammatory effects

Several triterpenoids and steroids have been isolated from extracts of plants with anti-inflammatory effect. In most instances, the anti-inflammatory activity of such extracts has been attributed to the isolated compounds.

The isolation of seven novels naturally occurring triterpene alchohols from non-saponifiable lipids of the seeds of Camellia japonica and Camellia sasanqua has been reported.[124] The anti-inflammatory activity of these compounds, tirucall-5, 7, 24-triene-3b-ol, lemmaphylla-7, 21-diene-3b-ol, isoeuphol, isotirucallol, (24R)-24, 25-epoxybutrospermol and its 24S-epimer, and isoaglaoil, was studied in mouse ear edema model. Lupeol was isolated from the hexane stem bark extract of *Crataeva religiosa* Forst. (Caparidaceae) as the anti-inflammatory component. In an extensive anti-inflammatory studies, lupeol exhibited anti-inflammatory effect in a variety of acute and chronic anti-inflammatory test models in rat and mice.[125] Lupeol ester, lupeol, lineolate, obtained by esterification of lupeol with linleoyl chloride was shown to exhibit antiarthritic activity greater than that of lupeol.

The triterpenoids of the oleanene and ursine series were found to be active against carrageenan induced oedema, formaldehyde-induced arthritis in rats. It has been suggested that the anti-inflammatory activity of the triterpenoids of the oedema series vary with the polarity of compounds which is enhanced by the number of hydroxyl groups in the molecule.[126] Oleanolic acid 3-β-glucoside isolated from the seeds of *Randia dumertorum* (25-500mg kg, p.o) showed a significant anti-inflammatory activity in the exudative and proliferative phases of inflammation in rats.[127] *Salai guggal*, the oleogum of *Boswellia serrata*, has been shown to possess anti-inflammatory and anti-arthritic activities. It was shown to be effective in controlled clinical trials in arthritic patients. Its activity may be due to the boswellic acids present in the olegum.[128]

Two new triterpene saponins having phospholipase inhibitory activity were isolated from methanol extract of the leaves of *Myrsine australis*.[104] These are 3- 0{-β-D-xylopyranosy-(1®2)-0-β-D-glucopyranosyl-(1®4) {0-β-D-glucopyrnosyl- (1®2) {-α-L-arabinosyl} 16 α-hydroxy-13β, 28-epoxyoleanane and 3 β-0-{-β-Drhamnopyranosyl}- 16-α-hydroxy-13,28-epoxyoleanane. Both compounds showed IC_{50} values of high significant, versus phorbol 42-myristate 13-acetate stimulated phospholipase in human promylocytic lukemic (HI-60)[104] cells Two oleane type triterpene saponin, zanhasaponins A and B and the cyclitol pinitol isolated from the methanol extract of root bark of *Zanha africana* (Sapindaceae) were active as inhibitors of phospholipase A_2.[116] Pentacyclic triterpenes from the 11-keto-boswellic acid series has stabilizing effect, inhibition of leucocytes migration and antipyretic activity.[129] The steroid, - spinasterol, obtained from the stem-bark of *Symplocos spicata* showed a significant activity against acute inflammation induced by carrageenan in rats and was more potent than phenylbutazone but less potent than betamethasone.[130] Six steroidal saponins were isolated from *Anemarrhena asphodeloides* Bunge (Liliaceae), a traditional Chinese medicine, and named anemarrhenasaponin I (An-I), anemarrhenasaponin Ia (An-Ia), timosaponin B-I (TB-I), timosaponin B-II (TB-II), timosaponin B-III (TB-III), and timosaponin A-III (TA-III). All these compounds provoked remarkable inhibiting effect on platelet aggregation.[131] Steroids consist of an essentially lipophilic (or hydrophobic, non-polar) cyclopentanoperhydrophenanthrene nucleus modified on the periphery of the nucleus or on the side chain by the addition of hydrophilic (or lipophobic, polar) groups.

CONCLUSION

For lead optimization through derivatization/semi synthesis, the challenge of any drug discovery effect is to identify and develop compounds with properties that are predictive of good efficacy and safety in humans. In this regard, organic synthesis plays a pivotal role. Once lead services with some desirable profiles are identified, the compounds can progress to lead optimization, entailing structural modifications with the goal of achieving optimal efficacy and pharmacokinetic/ pharmacodynamics properties.

The frequent occurrence of natural products as complexes of structurally related analogues can be exploited by the natural-product investigator as a guide for initial Structure-activity Relationship (SAR) experiments. In this regard, even simple synthetic modifications, as those obtained through “shotgun” transformations (key functional groups required for biological activity can be identified by allowing the parent compound to react with derivatizing reagents, such as alkyl halides, anhydrides, acyl halides) can be instrumental in leading to an optimized semisynthetic analogue. The knowledge gained through understanding the natural SAR and the shotgun approach can provide

an early foundation on which an overall synthetic strategy could be developed.

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Authors Contributions
OSC conceived and designed the study.
OSC, APA, OCE, OEP and MHU gathered materials and data.
OSC wrote the paper.
OSC, APA, OCE, OEP and MHU (All the authors) read and approved the paper.

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