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THE DEVELOPMENT OF COX-1 AND COX-2 INHIBITORS: A REVIEW

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ABSTRACT: NSAIDs (Non-steroidal anti-inflammatory drugs) show its effect by preventing prostaglandin synthesis, which reasons ulcer complications and mucosal damage all over the gastrointestinal tract. The world's most accepted drug was aspirin for treatment of pain and inflammation without knowing that it has the ability to inhibit prostaglandin production by inhibiting the cyclooxygenase enzyme for the treatment of pain and inflammation, until the late 1970s. The discovery of cyclo-oxygenase isoenzyme (COX-1 and COX-2), and their distinct function leads to the development of COX-1 and COX-2 selective inhibitors without any gastrointestinal toxicity. Initial intimations of the second form of cyclooxygenase (COX-2), which has different sensitivity for other drugs like aspirin, finally accompanied in a stimulating period of cyclooxygenase inhibitor discovery, concluding in the overview of an absolutely new generation of anti-inflammatory drugs. The aim of this paper is to review the development of COX-1 and COX-2 inhibitors. This paper also reviews that, what are the importance and history of natural products in the treatment of inflammation as COX-1 and COX-2 inhibitor.

INTRODUCTION: Responsive phase of hyperemia and exudation of blood vessels consequences into inflammation, which leads swelling, consequent redness, heat, and pain in the tissue due to bacterial attack and many more causes like chemical hazards or physical injury [1]. Inflammation is a tissue reaction by the body against damage, which comprises a multifaceted display of enzyme initiation, arbitrator issue, cell immigration, extravasations of fluid, repair, and breakdown of tissue [2].

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There are three components of the inflammatory response, which have been identified [3, 4], and these may involve chemotactic factors [6, 7] vasoactive substances [5], degradative enzymes and superoxide [8] and the neuropeptide substance P [9]. Non-steroidal anti-inflammatory drugs (NSAIDs) works by inhibiting prostaglandin synthesis, which causes ulcer complications and mucosal damage throughout the gastrointestinal tract [10].

Earlier it is known that COX enzymes are two types, one prevailing at locations of inflammation (COX-2) and one mostly occurs in the gastrointestinal tract (COX-1). This discovery shows the imperative role of healing advancement of COX-2 inhibitors [11]. Later it is proved that COX happens in three isoforms. The first one is COX-1, which is responsible for immediate PG synthesis on basal, and upon stimulation, that also arises at high

AA concentrations. COX-2 is tempted by growth and cytokines factors and mainly engaged in the regulation of inflammatory responses. COX-3, a splice variant of COX-1, mostly occurs in heart and brain [12-15]. Inhibition of prostaglandin synthesis occurs by the central mechanism by which NSAIDs reduce inflammation and pain in arthritis and other inflammatory conditions. For many years, there is a discernment until the discovery of COX-1 and COX-2 that without gastrointestinal damage, NSAIDs could not show their therapeutic treatment [16-19]. Thus, the discovery of cyclo-oxygenase isoenzyme (COX-1 and COX-2) and their function leads the development of COX-1 and COX-2 selective inhibitors without any gastrointestinal toxicity.

The world's most accepted drug was aspirin for treatment of pain and inflammation without knowing that it has ability to inhibit prostaglandin production by inhibiting the cyclooxygenase enzyme for the treatment of pain and inflammation until the late 1970s. Initial intimations of a second form of cyclooxygenase (COX-2), which has different sensitivity for other drugs like aspirin, finally accompanied in a stimulating period of cyclooxygenase inhibitor discovery, concluding in the overview of an absolutely new generation of anti-inflammatory drugs [20]. Numerous medicinal plant classes are commonly used in traditional medicine as inflammatory therapies. There are demonstrative anti-inflammatory herbs in nearly each family in the plant kingdom. Many of these plants have proven oral and documented evidence of their use in the medication of inflammatory ailments from old times [21].

COX-1 and COX-2 Concept: The morphological structure of COX-1 and COX-2 are shown in **Fig. 1** with their catalytic active site.

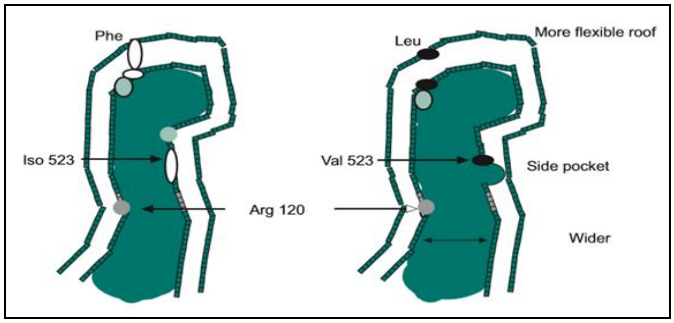


FIG. 1: MORPHOLOGY OF COX-1 (LEFT) AND COX-2 (RIGHT) ENZYME [22]

Tricyclic COX-2 selective inhibitor like Refocoxib, Celecoxib, and others act by blocking the COX-2 pocket. The selectivity is achieved due to the heavy size of the tricyclic C0X-2 inhibitor. Another important difference is the presence of leucine in COX-2 at the place of phenylalanine of COX-1, which shows greater flexibility in the upper side of the active site in COX-2. NSAIDs bind to COX-1 by reversible hydrogen-bonding and inhibition by simple steric hindrance, which leads to a great variation between COX-1 and COX-2, and in this way, selectivity can be achieved [23, 24]. Studies of fluorescence quenching suggest that the outcome of COX-2 inhibitors is time-dependent which depends upon an active process with blocking of the lower enzyme site [25]. Due to the presence of COX-2 mostly in the perinuclear envelope and COX-1 in the perinuclear membranes and endoplasmic reticulum (ER) the accessibility of the amino acid (AA) released by different PLA2 enzymes varies for each COX [26, 27]. It was showed by Kulmacz and Wang in 1995 that COX-2 could show dominant catalysis at low hydroperoxide levels whereas COX-1 proceed at high hydroperoxide levels [28, 29]. It is therefore believable that limited AAs accessibility in specific cellular conditions COX-2 activity is favored [30, 31]. As another option, it has been projected that both COX-1 and COX-2 exhibit different attachment to the specific terminal prostanoid synthases. This thought was primarily recommended for link between COX isoenzymes and PGE synthases enzymes (PGES) and then between COX isoenzymes and other terminal prostanoid synthases [32]. So far, three enzymes that catalyze the formation of PGE2 from PGH2 somewhat exactly have been recognized, namely membrane-bound PGES (mPGES) -1 [33, 34], mPGES-2 [35], and cytosolic PGES (cPGES) [32].

Prostaglandin Synthesis and Check Points for their Inhibition: Synthesis of prostaglandins shows a complex reaction mechanism which involves very specific conditions and occurs with suitable enzyme catalysis. The synthesis of prostaglandins and a possible checkpoint for NSAIDs to inhibit or regulate the synthesis is described in **Fig. 2,** as shown below.

Further, the produce PGE2 binds one or more its four specific receptor that is EP-1 to EP-4 to show its action [36].

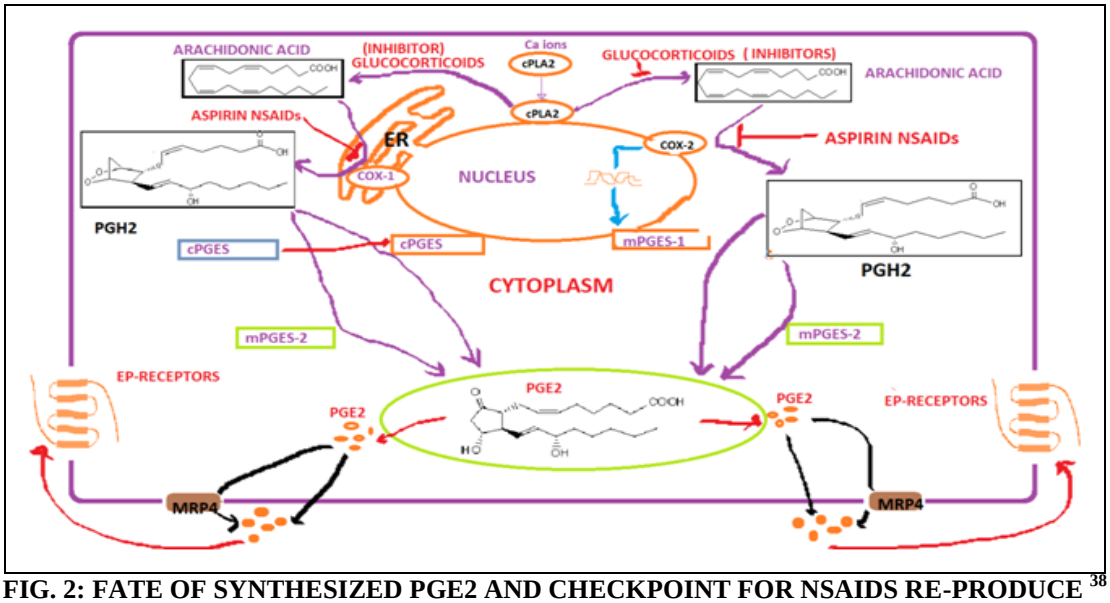


FIG. 2: FATE OF SYNTHESIZED PGE2 AND CHECKPOINT FOR NSAIDS RE-PRODUCE [38]

Next to all these, cytosolic enzymes, specifically 15-ketoprostaglandin Δ^{13}-reductase and 15-hydroxyprostaglandin dehydrogenase metabolized the excess of synthesized PGE2 because they could not be stored. In the case of cancer, 15-hydroxy-prostaglandin dehydrogenase is deregulated [37].

The Development of Field and Discovery of COX-2: The structural analysis of COX, that it has dual hydroperoxidase nature and cyclooxygenase activity [39], is suspecting and need further study for complete understanding. COX is dimeric membrane-bound protein, which has many encounters for purification and were not sequenced until 1988 [40, 41]. Additional issues obscuring the explanation of efficiency variances comprised the huge dissimilarities in assay environments which was used by various groups and variances in the kinetics of the COX inhibitors; these are still a problem today. Some of COX- inhibitors shows 'competitive reversible' inhibition, while others displayed uncommon inhibitory effects for instance the 'competitive non-reversible' inhibition that is detected specifically indomethacin group drugs [42]. Among all the groups, only aspirin shows a mechanism in which it irreversibly acetylated a seine residue (Ser530) for the cyclooxygenase inhibition. This discovery strengthened the thought expressed by many groups that the non-steroidal anti-inflammatory drugs were a structurally diverse group of drugs with extensively dissimilar pattern of inhibition activity. So, it is clear that alterations in inhibitory power could be the outcome of reasons other than the isozymes existence [43, 44].

Deep analysis of inflammation in rabbit kidney induced by ligation of the urethra shows that [45] that the contaminated organ surprisingly developed a massive ability to generate prostaglandins because of *de novo* synthesis of the fresh enzyme, but there was no proposal shown that the new enzyme was a different form [46, 47]. In the next few years, the occurrence of two discrete forms of COX in brain tissue was established, which shows different sensitivities to indomethacin [48]. Different pharmacological analysis in gastrointestinal tissue also supports the fact that NSAIDs have variable selectivity for inhibition in dissimilar tissues [49].

COX *g*m RNA and *de novo* synthesis of an enzyme are induced during the medication of vascular smooth muscle cells with epidermal growth factor [50] or fibroblast and monocytes with early inflammatory inducements like as interleukin-1 [51, 52] or lipopolysaccharide [53]. Needleman's and his coworker stated "Clearly, those putative enzyme pools may arise as different gene products, possibly through the expression of different COX genes" in his paper [54]. It is also reportable that glucocorticoids inhibit the initiation of this new COX isoenzyme while the amount of enzyme remains unchanged in the cells [55]. Although, it was also reported that one of the two isoforms of rat ovary was regulated by hormones, using immunological techniques [56].

After the development of field, the next work was the identification of different forms of COX enzyme. Simmons and his co-workers recognized

that there is a specific mRNA transcript which was coded for protein synthesis while examining the appearance of early response genes in fibroblast transformed with Rous, which had a from top to bottom sequence similarity, but dissimilar to the seminal vesicle COX enzyme [57]. In this way, a COX isozyme had been discovered. At the same time, Herschman and his colleagues revealed a specific cDNA which encoded a protein with a foretold structure similar to COX-1during the analysis of phorbol-ester-induced genes in Swiss 3T3 cells [58] and also explained that the product of this gene is a cyclooxygenase enzyme [59] which initiation was inhibited by dexamethasone [60]. Correspondingly, revealing results are also showed in cultured rat mesangial cells [61], mouse fibroblasts [62], RAW 264.7 cells [63], the ovary [64, 65], rat alveolar macrophages [66, 67] and other cell types [68].

Finally, Needleman's group concluded that the inflammation is an inducible form of COX, which had been cloned by both Simmons and Herschman [55]. Therefore, on the basis of evidence, it is obvious that the stimulated form of the cyclooxygenase appeared basically in the brain named COX-2 [69]. COX-1/2mRNA differentially appears [70] in human tissues, and both the genes have a dissimilar chromosomal pattern in rodents [71] and humans[72]. And further promoter examination assured an ultimate variance between the two isoforms of COX, that is, COX-2 promoters become active on cellular stress and inactive by glucocorticoids [73]; however, COX-1 mostly appeared in the gastrointestinal tract of rat, dog and monkey [74]. So, on the basis of the above facts, COX-2 blocking should be the ideal therapeutic application of NSAIDs, whereas COX-1 blocking leads problems like gastric ulcer and decrease in platelet aggregation[75-77]. If these schemes are true, then a selective COX-2 inhibitor would be an ideal drug. But most of the NSAIDs in practice inhibited both the isoforms with a higher or lower extent, but drugs like as 6-MNA and BF389 also show some selectivity of action [78].

COX-2 as a Therapeutic Target for Inflammation, Cancer and Alzheimer's Disease: PGEs cause exudation of plasma, irritation, and pain in a synergistic manner with the involvement of enzyme and another cofactor during inflammation [79]. Arthritis is a form of inflammation in animals that causes induction of COX-2 and believed to be accountable for the rise in PG production [80]. COX-2 induction has been recognized in rheumatoid arthritis, and osteoarthritis affected cartilage in human [81]. PGEs sensitize peripheral sensory nerve endings positioned at the site of inflammation [82,] which causes pain during inflammation. It is also thought that COX products accountable for the transmission of pain responses through spinal cord [83, 84].

Though, it is not clear how COX isoforms involved in pain during inflammation [85]. COX-2 inhibitors (*e.g.,* DFU) with a high degree of selectivity inhibit hyperalgesia (pain) in rats [86]. Actually, COX-2 induction in the spinal cord may induce the process of sensing pain, which has been demonstrated to inflammatory inducements in the paw in rats [87, 88]. In humans, COX-2 selective inhibitors like as rofecoxib shows the analgesic effect when used during post-dental surgery [89].

Giovannucci and his colleagues find that a relatively low dose of NSAIDs (aspirin) for a long time decreases the risks of developing colon cancers in a patient; nevertheless, the mechanism is not well known [90, 92]. This beneficial effect of NSAIDs (COX-2) had been shown by Smalley and his colleague in case of adenocarcinomas in human [91], by DuBois groups in isolated cells in culture [92] and by Williams in animal models [93]. In all these cases, the COX-2 level increases. COX-2 has been recognized in other cancers such as oesophageal [94], gastric [95], and pancreatic cancer [96].

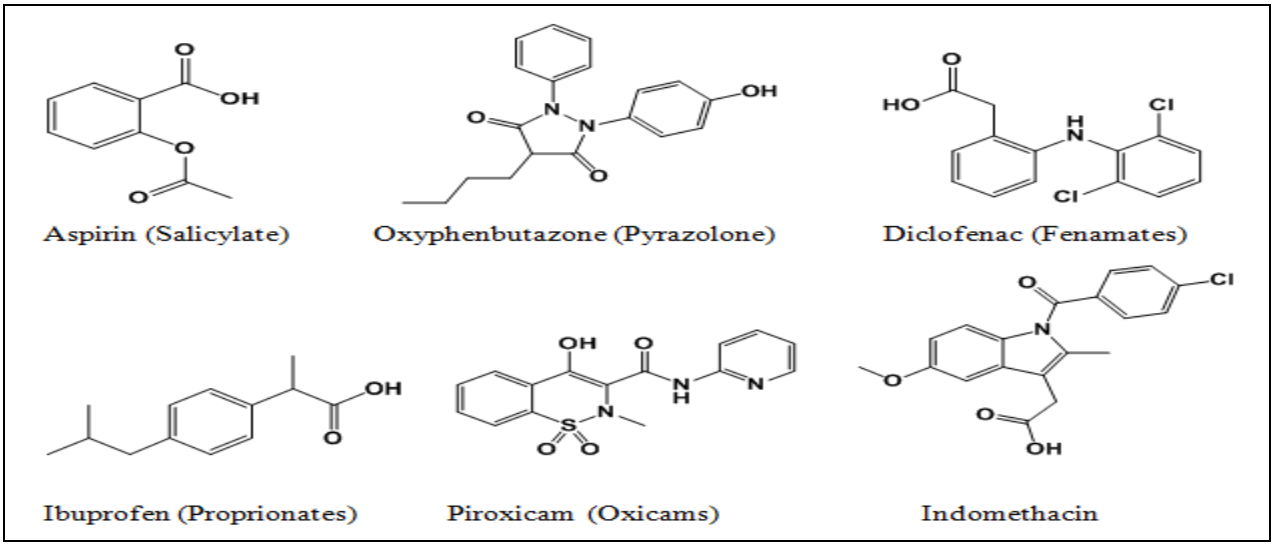
The other beneficial effect of NSAIDs related to COX suppression activity is to decreases the danger of evolving Alzheimer's disease [97] and reduce inflammation such as paracetamol without any side effect [98]. It had been shown by the Pasinetti & Aisen group that COX-2 appearance and extent is increased in the frontal cortex of brains in the case of Alzheimer's disease [99]. Additionally, PPAR-γ receptor and both isoform of COX induction is also raised in the temporal cortex of brains in theses case [100]. Therefore, NSAIDs may show effective treatment for Alzheimer's disease due to its ant-platelet properties [101]. Though studies on animals had shown that COX-2 is stimulated in neurons after kainic acid-induced seizures that are susceptible to apoptosis [102].

NSAIDs and COX-1/2 Active Compounds: The drugs celecoxib and rofecoxib were revealed on a rational basis for COX-2 selectivity [103-105]. Three-dimensional structure forecast for Cyclooxygenase-1 and Cyclooxygenase-2 demonstrate the similarity between these isoforms that how problematic to attain novel selectivity and, therefore, how predicational the rational discovery of these drugs [106-108]. Many compounds that are synthesized and screened *in-vitro* for COX inhibition [109] are described in the following **Table 1**.

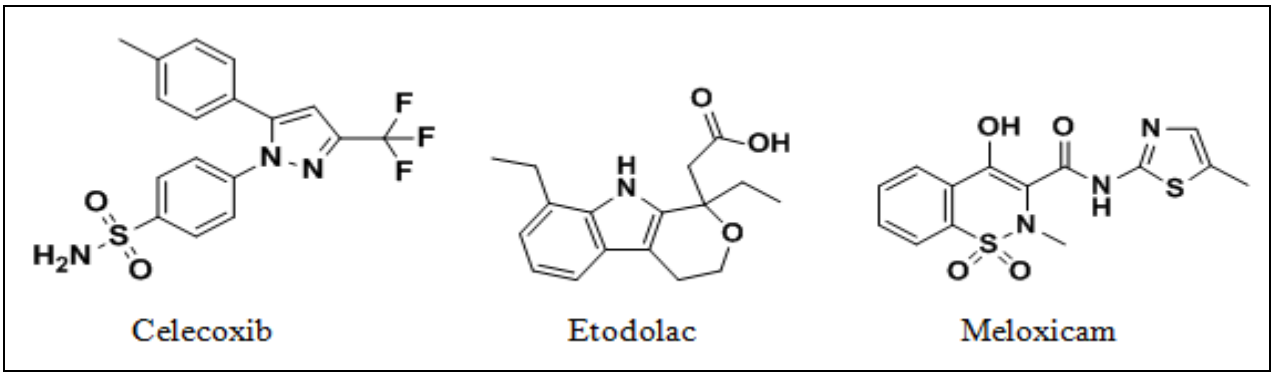
TABLE 1: SELECTIVITY OF NSAIDS AS COX INHIBITOR [109]

Compounds	COX-1 (IC_{50} in uM)	WBA-COX-2 (IC_{50} in uM)	WHMA-COX-2 (IC_{50} in uM)
Group (A)			
6MNA	42	146	n.d.
Aspirin	1.7	>100	>7.5
Carprofen	0.087	4.3	n.d.
Diclofenac	0.075	0.038	0.020
Fenoprofen	3.4	41	5.9
Flufenamate	3.0	9.3	n.d.
Flubiprofen	0.075	5.5	0.77
Ibuprofen	7.6	7.2	20
Indomethacin	0.013	1.0	0.13
Ketoprofen	0.047	2.9	0.24
Ketorolac	0.00019	0.086	0.075
Meclofenamate	0.22	0.7	0.2
Mefenamic acid	25	2.9	1.3
Naproxen	9.3	28	35
Niflumic acid	25	5.4	11
Piroxicam	2.4	7.9	0.17
Sulindac sulphide	1.9	55	1.21
Suprofen	1.1	8.7	8.3
Tenidap	0.081	2.9	n.d.
Tolmetin	0.35	0.82	1.3
Tomoxiprol	7.6	20	0.32
Zomepirac	0.43	0.81	0.096
Group (B)			
Celecoxib	1.2	0.83	0.34
Etodolac	12	2.2	0.94
Meloxicam	5.7	2.1	0.23
Nimesulide	10	1.9	0.39
Group (C)			
Diisopropyl fluorophosphate	>100	0.76	0.17
L745,337	>100	8.6	1.3
NS398	6.9	0.35	0.042
Rofecoxib	63	0.84	0.31
SC58125	>100	2.0	n.d.
Group (D)			
5-Aminosalicylic acid	410	61	n.d.
Ampyrone	55	203	85
Diflunisal	113	8.2	134
Nabumetone	460	1000	290
Paracetamol	100	49	64
Resveratrol	30	39	n.d.
Salicin	>100	>100	n.d.
Salicylaldehyde	>100	>100	n.d.
Sodium salicylate	4956	34440	482
Sulfasalazine	3242	2507	n.d.
Sulindac	>100	>100	58
Tamoxifen	15	95	n.d.
Ticlopidine	52	47	n.d.
Valeryl salicylate	42	2.3	n.d.

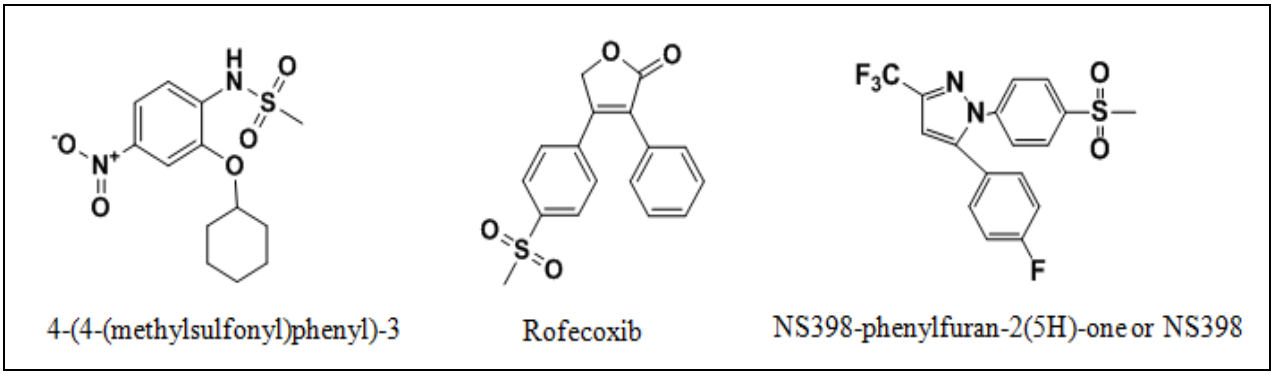
Note -: Group (A) compounds show high blocking activity for COX-1as well as for COX-2 but a low degree COX-2 selectivity. Group (B) compounds show high blocking activity for COX-1 and COX-2 with greater than 5 fold selectivity for COX-2 (WHMA/COX-1<0.2). Group (C) compounds show a low degree of blocking activity for COX-1as as well as for COX-2. Group (D) shows a low degree of blocking activity for COX-1as well as COX-2 which further study is required for confirmation [109]



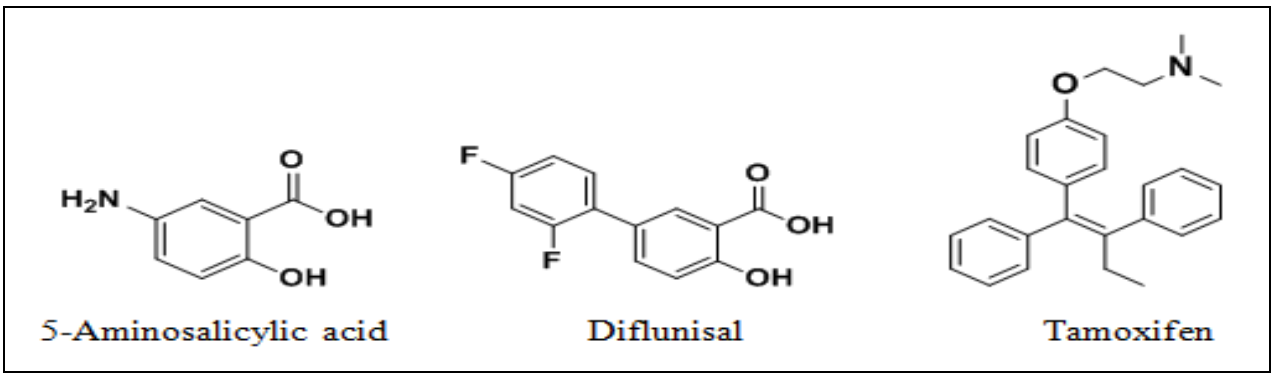
GROUP A COMPOUND



GROUP B COMPOUND



GROUP C COMPOUND



GROUP D COMPOUND

FIG. 3: STRUCTURE OF NSAIDS AND SOME COX-2 SELECTIVE COMPOUNDS

Note: Group (A) compounds, Group (B) compounds, Group (C) compounds and Group (D) compounds are described in Table 1

There are many phytochemicals that had been isolated structurally and pharmacologically characterized as an anti-inflammatory remedy in **Table 2**. Some of them show remarkable activity while others show mild, with a gastrointestinal ulcer side effect.

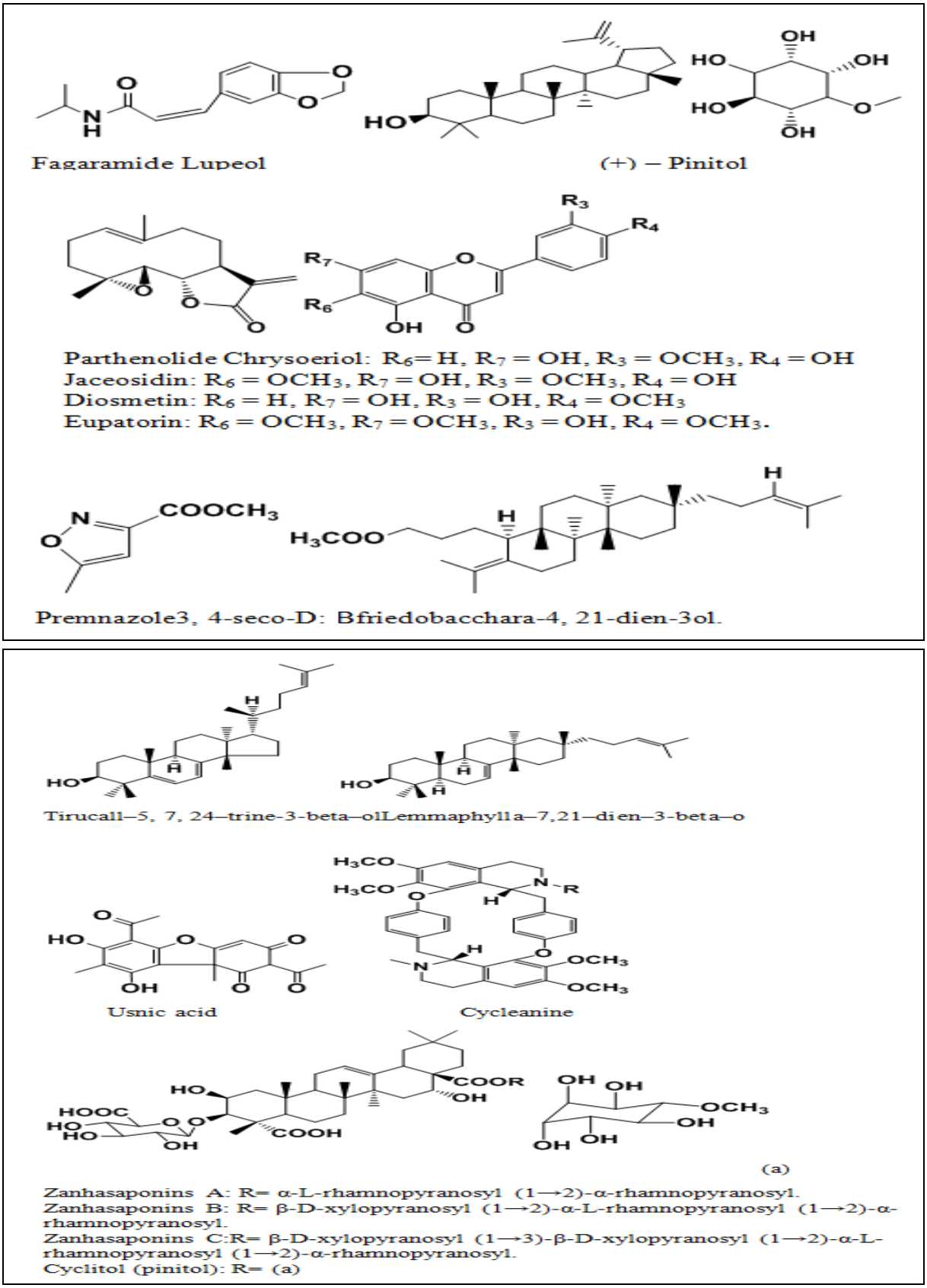


FIG. 4: STRUCTURE OF NSAIDS AND SOME COX-2 SELECTIVE COMPOUNDS ISOLATED FROM PLANT

TABLE 2: ISOLATED ANTI-INFLAMMATORY PLANT CONSTITUENTS

Compound	Plant (part)	Anti-inflammatory activity	COX Inhibition (IC_{50} in uM)
Fagaramide (piperonyl-4-acrylicisobutylamide) [110]	*Zanthoxylum zanthoxyloides* (Root)	(+)	2.06
Lupeol lupeol lineolate [111, 112]	*Crataeva religiosa* (Stem bark)	(+)	n.d.
Parthenolide	*Tanacetum vulgare*	(+)	n.d.
Methoxyflavones (jaceosidin, eupatorin, chrysoeriol, and diosmetin) [113]	(Arial part)		
(+) – Pinitol [114]	*Abies pindrow* Spach (Leaves)	(+)	n.d.
Premnazole [115]	*Gmelina arborea* (Leaves), *Premna integrifolia* (Leaves)	(+)	n.d.
3, 4-seco-D:Bfriedobacchara-4, 21-dien-3ol [116]	*Camellia sasanqua* (Seed oil)	(+)	n.d.
Tirucall–5, 7, 24–trine-3-beta–ol, Lemmaphylla–7,21–dien–3-beta–ol, Isoeuphol, Isotirucallol, (24R)–24, 25–epoxybutyrospermol, (24S)– 24, 25–epoxybutyrospermol, Isoaglaiol [117]	*Camellia japonica* (Seed oil)	(+)	n.d.
(+)-Usnic acid [118]	*Roccella montagnei* (Whole plant)	(+)	n.d.
Zanhasaponins A, B and C	*Zanha Africana* (Root bark)	(+)	n.d.
Cyclitol (pinitol) [119]			
Cycleanine [120]	*Stephania glabra* (Tuber)	(+)	n.d.

CONCLUSION: COX-1 and COX-2 involve in chronic pain associated with rheumatoid or osteo-arthritis, in protection in some form of cancer and Alzheimer's diseases. Though, link between anti-inflammatory properties of COX isoforms and these diseases is not totally understood which may be good research field for interested researcher.

NSAIDs such as Celocoxib (Pyrazolones derivative) and Rofecoxib shows a great selectivity for COX-2 isoform, therefore synthesis of analogues of these category drugs may have a good selectivity for COX-2 isoform, that could be hit and try in future.

There are many plants for which intrinsic anti-inflammatory activity is anecdote from other known pharmacological activities related to variation of the complex inflammatory response. At present, there is escalating scientific evidence for the anti-inflammatory activity of many plants. There are many plants for which the anti-inflammatory activity has been widely studied while primary sign has been recognized for others. There are many phytochemicals which had been isolated structurally and pharmacologically characterized as an anti-inflammatory remedy. But there are many plants which shows anti-inflammatory activity while their COX inhibition property is not well recognized. So, further analysis for COX inhibition for these plants may be the interesting zone for natural product researchers.

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