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# Review Article
# Some NSAIDs Offer Antioxidant Effect in the Brain Only in Combination with Other Antioxidant Products

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## Abstract

Of the drugs consumed in the hospital wards, analgesics are the first in place with 35.43%. The purpose of the present paper was to know if analgesics attenuate multi-tissue oxidative damage via the activation of antioxidative activities, anti-inflammation and anti-apoptosis and their roles in improving functional outcomes. Assays of some biomarkers such as Malondialdehyde (MDA), Nitric Oxide (NO), Superoxide Dismutase (SOD), Glutathione (GSH) and Glutathione Peroxidase (GSH-Px) have provided inalienable evidence of these analgesic effects. The treatment with analgesics, in general, have demonstrated to attenuate oxidative stress and inflammation, with a decreased level of MDA and NO and a decreased expression of NF-κB and cyclooxygenase-2 (COX-2). The use of Nonsteroidal Anti-inflammatory Drugs (NSAIDs) also increases Nrf2 protein and Heme Oxygenase-1 (HO-1) protein expressions, antioxidant enzymes and SOD activity. Moreover, the treatment with analgesics decreased the apoptotic potentials of the biomarkers, which is in line with the tunnel assay. In this work, we analyzed the changes in the antioxidant status of analgesic drugs and the role of these in improving functional outcomes. Moreover, we investigated if analgesic use offered protection against oxidative damage present in several diseases.

Key words: Biomarkers, NSAIDs, oxidative damage, SOD activity, analgesics, glutathione peroxidase, interleukin-6

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

## INTRODUCTION

Pharmaceutical drugs constitute a primordial base in the treatment of hospitalized patients and their incorrect use could give rise to grievous consequences on the integrity and improvement of the patients[1]. Recent studies on pharmaco-epidemiology have permitted us to know the patterns of prescription and consumption of an oral unitary dose of drugs. These studies have shown that the most prescribed and consumed drugs are analgesics (35.43%) followed by anti-inflammatory drugs (6.95%) (Table 1), anti-aggregates (2.85%), antibiotics (6.20%), anticonvulsants (2.66%), antihypertensives (10.10%), anti-ulcers (5.61%) and gastrokinetics (7.38%), which represent more than 77% of total drug consumptions[2]. The most consumed Nonsteroidal Anti-inflammatory Drugs (NSAIDs) was ketorolac. The principal structures of these drugs are shown in Table 1.

It is necessary to investigate and clearly outline the mechanisms involved in a drug side effect since all drugs have a certain level of this effect even in normal and adequate doses. Proposals that have been put forward in this regard points to acute or chronic oxidative stress and the inflammatory state as the cause of most of the drug side effects. Many pro-inflammatory-associated pathologies have been linked with acute or chronic stress. The targets of drug actions in the mitigation of pathologies are directed to protein kinases and mitochondrial permeability transition regulating proteins as well as to transcription factors associated with the regulation of metabolic activities and with the balance of live cells and dead cells. They also act on the unfolded protein response that maintains the normal functioning of the Endoplasmic Reticulum (ER) and prevents ER stress. In addition, other targets of drug actions are on the nuclear receptors such as peroxisome proliferator-activated receptors and isoprenoid synthesis[3].

**Oxidative stress in pharmacology:** Cells and tissues usually suffer damages as a consequence of oxidative stress generated by drug consumption. A demonstration of this is the injury and death caused on liver tissue by Reactive Oxygen Species (ROS) generative by acetaminophen and N-acetyl-p-amino-phenol[4]. This proves that the dysfunction of mitochondria, increased levels of calcium in the cytosol and oxidative stress, including deficit in metabolic energy could be influenced by glutathionylation[5]. The death of tissues provoked by ROS and other conditions as a result of acetaminophen and other NSAIDs activate the machinery of the different forms of autophagy, especially macroautophagy, to clean the dead organelles and dysfunctional components and to restore cellular recycling in affected organ tissues[6]. The damages generated in liver tissues and other organs may be detected in serum parameters such as ROS, Aspartate Aminotransferase (AST), malondialdehyde, liver tissue markers, alanine aminotransferase as well as reduced Glutathione (GSH) levels and catalase enzyme activity[7]. In addition, hepatic tissue damage can be detected through the measurement of transaminase enzyme level in blood and by western blot[8]. Other parameters to demonstrate liver damage include the measurement of the levels and activities of important enzymes that metabolize drugs such as NADH-cytochrome b5 reductase (CYTB5, Glutathione (GSH), GSH S-transferase (GST), Glucose-6-Phosphate Dehydrogenase (G6PD) and cytochrome P4502E1 (CYP2E1)[9]. Trettin *et al.*[10], conducted a study to determine the impacts of acetaminophen on the balance of vasodilatation and vasoconstriction dependent on COX and established that this drug favours vasoconstriction. This effect of acetaminophen can be blocked by increasing the endothelial NO generation. Nonetheless, it has been shown that acetaminophen at pharmacological concentration induces zero effect on the production and bioavailability of recombinant human endothelial NOS or inducible NOS in the hepatocytes. In addition, at high doses, acetaminophen has not been associated with an increase in oxidative stress.

**Compounds against oxidative stress:** Some natural products in combination with analgesic drugs provide tissue or cellular protection. For example, saponins exhibit significant liver protection against acetaminophen (APAP) overdose. Its administration alters the phosphorylation of AMPK and PI3K/Akt as well as the downstream signals including the Bcl-2 family, caspase and NF-κB signalling pathways[11]. Flavonoids attenuate inflammatory mediator production such as Nitric Oxide (NO), Tumour Necrosis Factor-α (TNF-α), Interleukin-6 (IL-6) and Interleukin-1β (IL-1β)[12], while others like berberine reduce the expression of pro-inflammatory cytokines, HMGB1, p-p65 and cleaved caspase-1 and inhibits the infiltration of macrophages and neutrophils[13]. Pro-oxidants are chemicals that induce oxidative stress either by generating reactive oxygen species or by inhibiting antioxidant systems that induce cellular damage[14].

Table 1: Chemical structures of common analgesic drugs

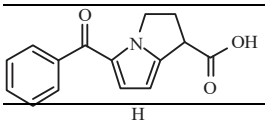
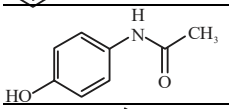
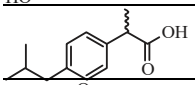
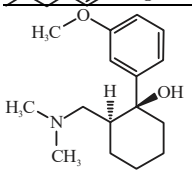
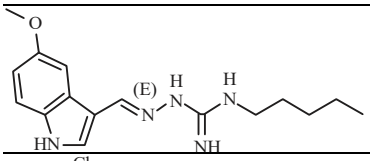
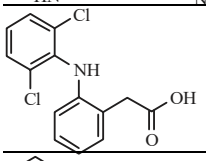
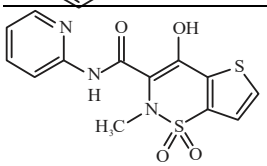
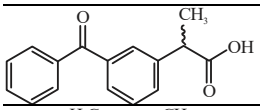
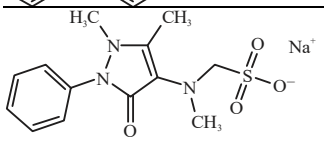
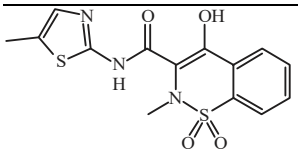
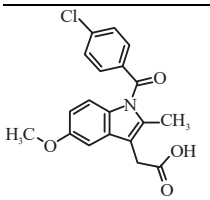
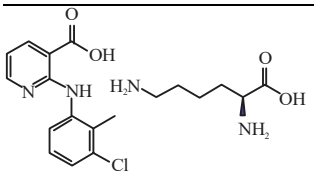
| | |
|---|---|
|  | Ketorolac<br>(±)-5-benzoyl-2,3-dihydro-1*H*-pyrrolysine-1-carboxylic acid, 2-amino-2-(hydroxymethyl)-1,3-propanediol |
|  | Paracetamol<br>*N*-(4-hydroxyphenyl) acetamide<br>*N*-4- hydroxyphenyl) ethanamide |
|  | Ibuprofen<br>(RS)-2-(4-isobutylphenyl)-2-methylpropanoic acid |
|  | Tramadol<br>(±)-*cis*-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride |
|  | Tegaserod<br>(2*E*)-2-[(5-methoxy-1*H*-indol-3-yl)methylene]--pentyl hydrazine carboxymidamide |
|  | Diclofenac<br>2-(2-[(2,6-dichlorophenyl)amino]phenyl) acetic acid |
|  | Tenoxicam<br>(3*E*)-3-[hydroxy(pyridin-2-ylamino)methylene]-2-methyl-2,3-dihydro-4H-thieno[2,3-e][1,2]thiazin-4-one 1,1-dioxyde |
|  | Ketoprofen<br>(*RS*)-2-(3-benzoylphenyl)propanoic acid |
|  | Metamizol<br>[(2-phenyl-1,5-dimethyl-3-oxo-2,3dihydro-1H-pyrazol-4-il)methylamino]methylsulphonate sodic |
|  | Meloxicam<br>4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide |
|  | Indomethacin<br>2-[1-chlorobenzoyl)- 5-methoxy-2-methylindole-3-il] acetic acid |
|  | Clonixinate lysine<br>L-Lysin mono(2-((3-chloro-2-methylphenyl)amino)-3-pyridine carboxylate) acid; 2-[3-chloro-2-methyl-phenyl)amino]pyridine |

Table 1: Continued

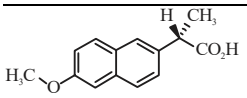
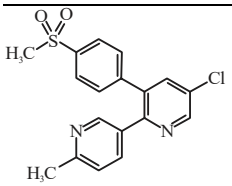
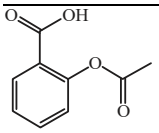
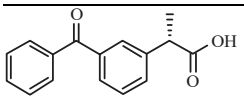
| | |
|---|---|
|  | Naproxen<br>(S)-2-(6-methoxy-2-naphtil)propanoic acid |
|  | Etoricoxib<br>5-chloro-6′methyl-3-[4-methylsulphonyl)phenyl]-2,3'-bipyridine |
|  | Acetylsalicylic acid<br>2-Acetoxybenzoic acid |
|  | Dexketoprofen<br>(2S)-2-[3-(benzoyl)phenyl]propanoic acid |

Table 2: Main reactive oxygen species

| Name | Formula | Formation |
|---|---|---|
| Superoxide | $O_2^-$ | Intermediate in $O_2$ reductions to $H_2O$ |
| Hydroxyl | HO | Powerful oxidant in biological systems |
| Peroxyl | ROO | Low oxidant ability, but high diffusibility |
| Alkoxyl | RO | Medium oxidant ability with lipids |
| Hydrogen peroxide | $H_2O_2$ | Originated from $O_2$ |
| Hypochlorous acid | $HClO^-$ | Formed through myeloperoxidase action |
| Singlet oxygen | $IO_2$ | Molecularly excited oxygen through sunlight and radiation |

*Adapted from Juárez and Calderón (17)

**Origin of free radicals:** Free Radicals (FR) are reactive species that possess unpaired electron, which principally comes from nitrogen and oxygen metabolism. They are generated from normal metabolic reactions and can be increased by exogenous factors[15]. The conformation of these FR consists of one hydroxyl radical, one superoxide anion and FR that come from organic compounds such as alcoxyl, peroxyl, hydrogen peroxide and singlet oxygen[16]. Free and hydroxyl radicals are more abundant in organic compounds and are the main source of these substances (Fig. 1). Reactive oxygen species refers to chemical species such as hypochlorous acid, hydrogen peroxide, hydroperoxides and epoxide metabolites that act like oxidants but are not FR see Table 2[17].

In tissues and cells, these species have been associated with oxidative stress. In biological systems, most of the Reactive Oxygen Species (ROS) are produced by the action of Lipoxygenases (LOX) enzymes on arachidonic acid metabolism as well as that of other polyunsaturated fatty acids. The inhibitors of LOX have been shown to possess anti-inflammatory activities and therefore, can offer protection to patients who suffer from inflammatory diseases or neurodegenerative disorders[18,19]. The increasing list of substances denominated as lipid messengers has been implicated in neuronal, oligodendrocytes, astrocytes and microglial interactions as well as in the interactions of microvasculature and other cells. Developing brains experiencing the onset of hypoxia and hence oxygen toxicity are successfully treated with a single dose of acetylcholinesterase (AChE) inhibitors.

Selective neuronal death can be caused by free radicals produced in vascular endothelial cells and inflammatory responses in perivascular microglia. In neurons that are metabolically compromised, cells such as inflammatory cells are known to release cytokines and other harmful compounds and these harmful substances usually aggravate oxidative damage in these neurons. Likewise, in the pathophysiology of neurodegenerative diseases, mechanisms involving oxidative stress, vascular factors and inflammation have been reported[20,21].

**Role of NSAIDs in oxidative stress:** The daily consumption of Nonsteroidal Anti-inflammatory Drugs (NSAIDs) worldwide has been calculated to the tune of 30 million people. NSAIDs are groups of heterogeneous drugs that have

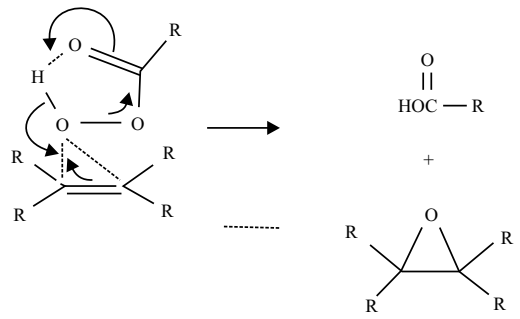


Fig. 1: Free and hydroxyl radical come from organic compounds

anti-inflammatory, analgesic and antipyretic properties. In tissues, combinations of these drugs are believed to promote the generation of cyto-genotoxicity, oxidative stress and free radicals[22]. Many researchers have worked with some analgesic drugs capable of reducing chronic oxidative stress and inflammation in different models[23]. In the brain and liver, ketorolac has been reported to promote oxidative damage by enhancing protein carbonyl contents, hydroperoxide and lipid peroxidation, by producing alterations in antioxidant status depicted by increased activities of enzymes such as glutathione peroxidase, catalase and superoxide dismutase[24]. Inhibition of Se-GPx is very notable with NSAIDs like piroxicam, tiaprofenic acid, naproxen and ketorolac. These analgesics have also been associated with reduced Glutathione S-transferase (GST). Moreover, analgesics such as dipyrone, acemetacin, tenoxicam and Na-salicylate have been reported to increase the activities of Chloramphenicol Acetyltransferase (CAT) enzyme[25]. Diclofenac, the most frequently consumed NSAIDs, is implicated in oxidative stress induction[26]. Numerous NSAIDs, due to their ability to provoke oxidative stress, can induce $Ca^{(2+)}$ dependent mitochondrial permeability transition[27].

In general, due to the existence of several anti-inflammatory drugs, the prescription and dispensation of NSAIDs have been witnessing high drug substitution. The pharmacological anti-oxidant actions of the NSAIDs are mainly associated with their structure, lipophilic properties and electron distributions (Table 1).

NSAIDs have many adverse effects on the gastrointestinal (GI) tract which could cause different health problems such as bleeding, intestinal occlusion or perforation that may have a fatal end. The mechanism through which NSAIDs provoke damage on GI lies in their inhibitory ability on the synthesis of prostanoids, COX-1 and COX-2. This can produce adverse effect on the gastrointestinal barrier, making it more permeable and consequently provoking low-grade inflammation, erosions and ulcers that give rise to bleeding, protein loss, stricture formation and perforation[28]. Efforts to find mitigation for this GI side-effect of NSAIDs have led to the discovery that indomethacin decreases oxidative stress[29].

In clinical practices, poor understanding of the nociceptive pathways makes the treatment of inflammatory diseases associated with pain difficult. This is demonstrated by the fact that acute ischemic stroke is characterized by inflammation and oxidative stress. In addition, the levels of erythrocyte sedimentation rate, high-sensitivity C-Reactive Protein [hs-CRP], white blood cell count and fibrinogen that are markers of inflammation are found to be high in these patients[30].

The persistent inflammatory state may progress to chronicity and thus, could be fatalistic to healthy tissue, which in the brain leads to irreplaceable neuronal loss[31]. Hyperglycemic state is a constant condition in inflammatory diseases including apoptotic death of macrophages, which is a common occurrence in circumstances of high glucose concentrations, hence, can bring about lipid spillage from macrophages into the vessel wall intracellular spaces[32].

**Oxidative stress in neurologic diseases:** The underlying condition in neurologic diseases is inflammation and degeneration of the Central Nervous System (CNS). It has been found that inducible nitric oxide synthase (i.NOS) exacerbates this condition by mechanisms that increase the production of NO, the precursor biomolecule of Reactive Nitrogen Species (RNSs). These biomolecules are used as a marker of neuroinflammation in Multiple Sclerosis (MS), Alzheimer's Disease (AD), ischemia, Spinal Cord Injury (SCI) and inherited peroxisomal and lysosomal disorders. iNOS converts l-arginine to nitric oxide with l-citrulline as a byproduct[33]. NO regulates indirectly the expression and the activity of certain proteins, for example, NF-kappa B. This action is carried out when NO binds to a protein thiol molecule to produce Nitric Oxide Synthase (NOS), a process called S-nitrosylation. As indicated before, the action of cyclooxygenase (COX) enzyme on arachidonic acid gives rise to the production of some prostanoids such as prostaglandins, prostacyclin and thromboxane $A^2$. However, prostaglandin can be produced through other pathways different from the COX pathway. This prostaglandin-yielding non-COX pathway is regulated by nitroxidative species formed by NO and superoxide including peroxynitrite ($ONOO^-$) which is the byproduct of the collusion of NO and superoxide[34]. Therefore, to modulate the multiple roles of NO, COX enzymes play an important role since NO is the signal-activator of COX[35]. The constitutive isoforms of NOS are NOS-1 and NOS-3 while that of COX is COX-1. These

isoforms are responsible for housekeeping tasks. The other isoforms of these enzymes are the inducible forms comprising of NOS2 and COX-2, which shape the cellular response to stress and a variety of bioactive agents. As stated earlier, the underlying mechanisms for the modulation of prostaglandin synthesis lie in the action of NO on COX, i.e. S-nitrosylation of COX, as well as on the reaction between NO and superoxide to produce peroxynitrite, a biomolecule that can inactivate prostaglandin I synthase. On the other hand, the NOS1-dynein light chain (DLC) association is enhanced by prostaglandin, thus reducing its activity[36].

The inhibitory effect of NSAIDs on the inflammatory cyclooxygenases COX-1 and COX-2 has been associated with decreased development of Alzheimer Disease (AD) in the healthy elderly population. COX-PGE(2) –EP3 signalling plays a crucial role in AD development. This was shown in the work of Shi *et al.*[37], who identified the PGE(2)-EP3 receptor as a novel proinflammatory, pro-amyloidogenic and synaptotoxic signalling pathway. In line with this finding is the decreased expression of the pro-inflammatory gene, the production of cytokine and oxidative stress by PGE(2)-EP3 receptors in the Aβ(42) peptide-induced neuroinflammation model. In addition, in the work of Liang *et al.*[38], EP2 receptor signalling was identified as a novel proinflammatory and pro-amyloidogenic pathways. These authors suggest that neuroinflammatory diseases, for instance, AD, could be mitigated through EP2 receptor-targeting therapies. In nutshell, analgesic or anti-inflammatory drugs' antioxidant activities enhance physiological functionality; however, in several diseases, they may not offer significant protection against antioxidant damage.

## DISCUSSION

Pain-relieving drugs, especially neuropathic pain, have limited efficacy and dose-limiting adverse effects. Thus, there is a convincing and urgent need to search for novel medications for the treatment of this kind of pain and others. Preclinical studies and clinical trials with experimental drugs directed to new targets have shown that these experimental drugs could be effective in the treatment of pain[39]. Several types of antioxidants also possess analgesic and anti-inflammatory properties, thus, indicating a strong relationship between inflammation and oxidative stress. Therefore, understanding the underlying mechanisms of action of anti-inflammatory and analgesic drugs, as well as essential targets in disease physiopathology, is essential to the development of novel therapeutic strategies[40].

The complex biology of the mechanisms underlying the processing of nociceptive information provides an important pathway towards the development of novel and robust therapeutics[41]. Electrical excitation of peripheral somatosensory nerves is a first step in the generation of most pain signals in the mammalian nervous system. Such excitation is controlled by an intricate set of ion channels that are coordinated to produce a degree of excitation that is proportional to the strength of the external stimulation. The disruption of this coordination results in deregulated peripheral excitability, which may underpin pathological pain states[42]. These authors consider a hypothesis suggesting that reduced functional activity of $K^+$ channels within peripheral nociceptive pathways is a general feature of many types of pain.

Indeed, analgesic-antioxidant therapy could be an effective novel treatment option, which should be tailor-made for each individual based on pain features, previous therapies, associated clinical conditions, recurrence of pain and adverse effects.

## CONCLUSION

Oxidative stress is a process that can affect the health status of living organisms. The central nervous system is more susceptible to suffer the effects of oxidative stress resulting from the appearance of chronic degenerative diseases. However, the knowledge of the study of substances such as NSAIDs well as some nutrients offers characteristics of these drugs either as a pro-oxidant or as an antioxidant by determining their neuroprotective capability.

## SIGNIFICANCE STATEMENT

This study discovered that analgesics attenuate multi-tissue oxidative damage via the activation of antioxidative activities that can be beneficial when prescribing those medications. This study can help researchers to uncover the critical areas of protection against oxidative damage present in several diseases that many researchers were not able to explore. Thus, a new theory on oxidative stress and inflammation may be arrived at.

## ACKNOWLEDGMENT

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