

## Review Article

# NSAIDs and Natural Products Interactions: Mechanism and Clinical Implications

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## Abstract

Traditional herbal medicines is largely used in folk medicine worldwide and related to be safe by general population. The non steroidal anti-inflammatory drugs (NSAIDs) are a class of drugs, including selective or not for inhibition the isoform 2 of ciclooxigenase (COX) largely used to treat acute or chronic inflammation. Several side effects are related to long term use of NSAIDs. Despite, its widespread use as well as the natural products (NP), documented NSAIDs-NP interactions are sparse. The NP may interfere on the effect of the NSAIDs increasing the anti-inflammatory activity and also reduce tissue damages. However, NP can also produce changes leading to hepato or nephrotoxicity. This work reviews the NSAIDs-NP (green tea, resveratrol, curcumin, kava, ginkgo biloba and ephedra) interaction with an emphasis of the mechanistic and clinical considerations.

## ABBREVIATIONS

NSAIDs: Non Steroidal Anti-Inflammatory Drugs; COX<sub>1</sub>: Ciclooxigenase-1; COX<sub>2</sub>: Ciclooxigenase-2; NP: Natural Products; AA: Arachidonic Acid; PGE<sub>2</sub>: Prostaglandin E<sub>2</sub>; PGJ<sub>2</sub>: Prostaglandin J<sub>2</sub>; PGD<sub>2</sub>: Prostaglandin D<sub>2</sub>; TNF- $\alpha$ : Tumor Necrosis Factor- $\alpha$ ; IL-1 $\beta$ : Interleukin 1 Beta; GI: Gastrointestinal; NO: Nitric Oxide; FKA: Flavokawains A; FKB: Flavokawains B; FKC: Flavokawains C; FKs: Flavokawains; GABAA:  $\gamma$ -Aminobutyric Acid Type A; FDA: Food and Drug Administration; EHE: Ephedra Herb Extract; ADP: Adenosine Diphosphate; EC: Epicatechin; EGC: Epigallocatechin; ECG: EC-3-O-Gallate; ECGG: (-) Epigallocatechin-3-Gallate; IFN- $\gamma$ : Interferon Gamma; cAMP: Cyclic Adenosinemonophosphate; JAK2: Tyrosine-Protein Kinase; STAT3: *Signal Transducer and Activator of Transcription 3*; PGC-1 $\alpha$ : *Peroxisome Proliferator Activated Receptor Gamma Coactivator 1 $\alpha$* ; AMPK: 5' -Adenosine Monophosphate--Activated Protein Kinase; UCP2: Mitochondrial Uncoupling Protein 2; PI3K: Phosphatidylinositol 3-Kinase; Nrf2: Nuclear Factor Erythroid Related Factor 2; ERK: Extracellular Signal-Regulated Kinases; MAPK: Mitogen-Activated Protein Kinases; AP-1: Activator Protein 1; ICAM-1: Intercellular Adhesion Molecule 1; MCP-1: Monocyte Chemotactic Protein 1; IL-8: Interleukin 8; IL-6: Interleukin 6; IL-17: Interleukin 17; IL-10: Interleukin 10; NF- $\kappa$ B: Factor Nuclear Kappa B; ROS: Reactive Oxygen Species; SIRT: Silent Mating Type Information Regulation; PPAR: Peroxisome Proliferator Activated Receptor;

VEGF: Vascular Endothelial Growth Factor; SOD: Superóxido Dismutase; iNOS: The Inducible Nitric Oxide Synthase; PKC: Protein Kinase C; CYP2E1: Cytochrome P450 2E1; CYP3A1: Cytochrome P450 3A1; CYP1A2: Cytochrome P450 1A2; NASH: Non-Alcoholic Steatohepatitis; NAFL: Nonalcoholic Fatty Liver; LPS: Lipopolysaccharide; CD14: Cluster of Differentiation 14; GSH: Glutathione; PGC-1 $\alpha$ : Peroxisome Proliferator Activated Receptor Gamma Coactivator 1 $\alpha$

## INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most common pharmaceuticals class of drugs used in global primary health care [1-4]. The anti-inflammatory activity of NSAIDs' is attributed to the ability to inhibit of cyclooxygenase enzyme selectively or not [1,5]. The COX<sub>1</sub> is found primarily in blood vessels, kidney and stomach, responsible for the physiological stimulus (homeostatic effects - constitutive), and COX<sub>2</sub> which is responsible for induction of inflammation, pain and fever [6-8]. Stimulus that increase inflammatory mediators such as bradykinin is able to activate phospholipase A2 that hydrolyzes arachidonic acid (AA) in membrane phospholipids [9-12].

Several reports show the side effects including peptic ulcers, mucosal lesions, intestinal perforation, bleeding, hepatotoxicity and kidney damage by the long-term and overdose of NSAIDs

[13-19]. The introduction of selective COX<sub>2</sub> NSAIDs (coxibs) into the market did not decrease the non-selective NSAIDs usage. Countries such as India [20] have no coxib available or in Brazil, even the coxibs are under controlled prescription, the non selective NSAIDs are easy to buy without any medical prescription [21-25]. In some specific people field such as in US army, the NSAIDs soldiers users of the entire active duty Army was around 69 % in 2006 and increased to 82 % (857,964 prescriptions), in 2014. The selective COX<sub>2</sub> inhibitor celecoxib, accounted for 2.4 % of these NSAIDs prescriptions in 2006 and 7.1 % in 2014 [26]. Also, according to the Agencia Española del Medicamento y Producto Sanitarios (Spain) the NSAIDs consumption increased 26.5 % throughout the 2000-2012 period. Ibuprofen was the first NSAID consumed, followed by diclofenac [27]. This is a matter of concern due the side effects that can evolve to secondary diseases.

The effect of COX<sub>2</sub> inhibition by NSAIDs promotes at the kidney, a mitochondrial oxidative phosphorylation inhibition and causes uncontrolled renal vasoconstriction in tubule renal cell decreasing the glomerular filtration and/or efflux from proximal tubule cells, leading to acute tubular necrosis. In addition, the presence of NSAIDs at the renal papillary tip also causes renal papillary necrosis [28].

The literature reports some cases of acute hepatitis and cholestatic hepatitis with celecoxib and rofecoxib. The lumiracoxib showed severe hepatic toxicity and led to withdrawal from the market [29-31].

Increase risk of hospitalization for acute hepatitis or cholestatic hepatitis were reported in Taiwan induced by celecoxib [32]. Also, it was reported the increase of liver damages with the use of others NSAIDs including nimesulide, diclofenac, ibuprofen [32,33].

The prostaglandin E2 (PGE2) act as endogenous ligands responsible for the stimulation of signal transduction pathways involved in liver regeneration, [34-36] and for up-regulation of anti-inflammatory cytokines [37-40]. The COX<sub>2</sub> is responsible for the 15-deoxy-Δ<sup>12</sup> [29,41] and 14- prostaglandin J2 (PGJ2) production, both are prostaglandin D2' (PGD2) metabolites, that inhibits the pro-inflammatory cytokines as tumor necrosis factor- α (TNF-α) and interleukin 1β (IL-1β) [37,42]. In addition, the coxib inhibition of prostaglandin synthesis decrease the liver protection against bile acid-induced apoptosis by down regulation of Bcl-2, an anti-apoptotic mitochondrial protein [43]. Bessone and co-workers (2016) proposed that the COX<sub>2</sub> inhibition by selective NSAIDs can contribute the loss of the protective mechanism of liver, leading to the progression of its damage [44].

The diclofenac is chemical related to lumiracoxib, a phenylacetic acid. Both compounds can promote the formation of a reactive iminoquinone metabolite (also present in acetaminophen structure) that can react with glutathione and cause hepatotoxicity [45,46].

The most frequent and most important adverse effect of NSAIDs, affecting approximately 20 % of patients is the gastrointestinal mucosal damage caused by inhibition COX<sub>1</sub>, decreasing prostaglandins, mucous and bicarbonate production

on the layer of stomach [47]. In addition, the use of NSAIDs can increase the chance of intestine ulceration and also death by ulcer bleeding in patients with colitis, Crohn's disease or other inflammatory intestinal diseases [48]. Until now, few drugs are used for this protection (proton pump inhibitors, such omeprazole, esomeprazole, rabeprazole and H<sub>2</sub> inhibitors, ranitidine, cimetidine). Even, there are COX<sub>2</sub> selective inhibitors the long term use are also associate to gastrointestinal (GI) damage [8,49,50].

NP have been used in popular medicine as remedy for the treatment or "cure" of diseases since the beginning of civilization [51,52]. Up to now, NP is still largely used as herbal preparations (tea, infusion, extract, capsule) and their active molecules have been also isolated and used in therapeutics to treat several diseases [53-57].

The interaction between NSAIDs and NP can be good or danger, leading to increase of anti-inflammatory activity or increasing several adverse effects [19]. The purpose of this review is to show the mechanism of this interactions and clinical implications for the liver and kidney. The figure 1 shows the mechanism of action of action of NSAIDs and the interference of some NP in this mechanism.

## NATURAL PRODUCTS AND NSAIDS INTERACTION

### Kava (*Piper methysticum*)

The root of a Pacific Islanders native pepper plant called kava kava (*Piper methysticum*) is used to prepare a psychoactive beverage to be drink in religious ritual [58,59]. With this knowledge, the occidental medicine, have been used kava to induce sleep and decrease anxiety disorders [60], reported in clinical trials studies [61,62]. However, it is related to rare but severe cases of hepatotoxicity [63,64]. Several explanations have been postulated for this side effect, however, but none of them were established. Narayanapillai and co-workers (2014) related that Flavokawains A and B (FKA and FKB) present in kava potentiate the induction of hepatotoxicity caused by acetaminophen [65]. Also, it was shown that kavain is the major kava's component and is responsible to potentiate γ-aminobutyric acid type A (GABAA) receptors [66].

However, kava was banned from US and Europe therapeutics but its use is already used in several countries [67,68]. Food and Drug Administration (FDA) and European regulatory agency warnings have been diffused since 2002 [69,70]. Studies showed different concentration of FKA, B and C in different kava cultivars that can vary around 20 fold that can explain difference amounts of FKA and FKB in the products of the market, and also different final results [71], due to this different concentration, the hepatotoxicity is not a linear effect.

The presence of hepatotoxicity compounds FKA and B in kava extract can potentiate the liver damage when co-administrated with NSAIDs (mainly the diclofenac chemical related, that can metabolize to iminoquinone derivatives) The level of the injury depends of FKs amount and patient liver conditions. Drug cirrhosis can be precipitated by NSADS-kava in multiple drugs users' patients, elderly and alcohol chronic individual.

## Ephedra (*Ephedra sinica*)

Ephedra herb is defined as a terrestrial stem of *Ephedra sinica*, according to 17<sup>th</sup> edition of Japanese Pharmacopoeia [72]. Ephedra was described to have an antiviral or antibacterial role, by the activation of immune system [73,74].

The anti-inflammatory effects and analgesic activity of ephedra were previously reported in literature [75-77]. Hyuga (2017) reported that ephedrine alkaloids-free may be the responsible by the anti-inflammatory and analgesic effects [78]. The same researcher reported the anti-metastatic and antitumor effect of ephedra herb extract (EHE), by the suppression of the hepatocytes growth factor-c-Met signaling pathway through the inhibition of c-Met tyrosine kinase activity. Also, they demonstrated the effect of herbacetin glycosides in EHE, which shows c-Met-inhibitory activity and analgesic action [78]. This NP contains ephedrine alkaloids such as ephedrine and pseudoephedrine as the principal active compounds [75], used mainly in pharmaceutical preparation for upper respiratory disease, in combination with other drugs.

Despite the beneficial effect of ephedra, its use has been restricted in some countries due to the sympathomimetic effect leading to several alterations of physiological responses, such as increased blood pressure, vasoconstriction, bronchodilation and increasing heart rate [79].

The Ephedra alkaloids inhibit reuptake of catecholamines and act as antagonists of  $\alpha$ -2 adrenergic receptors, the functional adrenergic receptors on platelets [80,81]. According to Watson and co-workers, the increase of intracerebral hemorrhage incidence using ephedra may be related to elevations in blood pressure and also by reductions in epinephrine-mediated platelet aggregation leading to cerebral bleeding [82]. They showed that ephedrine similarly inhibits Adenosine diphosphate (ADP)-induced platelet aggregation. The use of NSAIDs that can increase blood pressure and decrease platelet aggregation, the co-administration of NSAIDs and ephedra may potentiate the risk of cerebral hemorrhage and GI ulcer bleeding.

In addition, it has been reported that ephedra's alkaloids may contribute to acute liver injury induced by TNF- $\alpha$  leading to fulminant hepatic failure and necrosis [82-85].

## Green Tea (*Camellia sinensis*)

*Camellia sinensis* is a species of shrub or small tree native from Asia and India. The leaves and leaf buds are used to produce worldwide used tea, popularly named as Green Tea. The most important polyphenolic compounds isolated from this NP include epicatechin (EC), epigallocatechin (EGC), EC-3-O-gallate (ECG), and EGC-3-O-gallate (EGCG), the major one [86].

Several *in vitro* and *in vivo* experiments have been reported showing the strong antioxidant potential of catechins [87-90]. EGCG has been reported to present anti-inflammatory [91], anti-mutagenic [92], anti-cancer [93], anti-obesity [94], anti-diabetic [95], anti-viral [96], anti-bacterial [97], neuroprotector [98] and immunomodulatory effect [86,99-102]. Also, green tea catechin is able to ameliorate periodontitis inflammation caused by *Porphyromonas gingivalis* in mice [103].

Was demonstrated the decreasing of inflammatory mediators in arthritis murine model [99,104,105]. According to Kim and co-workers (2008), the polyphenolic compounds are able to reduce the severity of arthritis inflammation in Lewis rats. Was observed the decrease of proinflammatory cytokine interleukin (IL)-17 and the increase of immunoregulatory cytokine IL-10 compared to control [106]. The EGCG regulates inflammation and joint degeneration by modulating MAPKs, Activator protein 1 (AP-1), NF- $\kappa$ B pathway and STAT signaling activated by TNF- $\alpha$ , IL-1 $\beta$  and IFN- $\gamma$  in various cell types [87,91,92].

The enzyme COX<sub>2</sub> is overexpressed in several inflammatory diseases and also is implicated in prostate and gastric cancer conditions [107, 108]. However, the use of NSAIDs is limited by the side effects such as gastric ulceration (by the inhibition of COX<sub>1</sub> isoform) and cardiovascular damage (by inhibition of COX<sub>2</sub> cardiac constitutive isoform).

The catechins demonstrated the decrease of the overexpression of COX<sub>2</sub> without interference in COX<sub>1</sub>, showing no gastric injury by decreasing PGE<sub>2</sub> [109]. In therapeutic clinic, the catechins could be beneficial in cancer conditions, with the possibility to be used in association with chemotherapeutics and low doses of selective COX<sub>2</sub> NSAIDs.

The EGCG is able to interrupt lipid peroxidation chain reaction decreasing liver damage [110,111] and it was reported that it is about 25 and 100 times more potent than vitamins E and C, respectively [112].

The daily consumption of green tea extract is associated with a lower risk of liver injury, hyperlipidemia, and inflammation [113]. The EGCG ameliorates experimental immune-mediated glomerulonephritis and its beneficial roles in chronic kidney disease [102,114]. However, some authors reported hepatotoxicity with long term use of green tea extract in oral supplementation [115,116]. These findings suggest that other components in the plant may be considered in therapeutics/hepatotoxicity. So, in this condition, the long term use or high doses of the extract/supplement can increase the potentiality of hepatotoxicity and need to be considered when combined with NSAIDs.

## *Ginkgo biloba*

The *Ginkgo biloba* extracts (ginkgo) have been used for alleviating symptoms associated with cognitive impairment, dementia, Alzheimer's disease [117], hypertension [118], asthma [119] and tinnitus [120], including the anticancer activity [121].

The active constituents related to ginkgo are the biflavones, terpenoid trilactones (ginkgolides A, B, C, J, P and Q, and bilobalides), flavonol glycosides (quercetin, catechin) and proanthocyanidins [83,122].

The ginkgo reduces the nitric oxide (NO)-induced oxidative stress, acting as NO scavenger and also decreasing its production in diabetic animal models [123,124], thus protecting the animal from retinopathy and probably from nephropathy too, by the same mechanism [125].

Several reports show that ginkgo is able to inhibit the

platelet aggregation via ADP and collagen-induced through cyclic adenosinemonophosphate (cAMP) and also by increasing and the inhibition of thromboxane A2 synthesis [126-128]. The Ginkgo extract, in association with anti-platelet drugs (warfarin) [129,130] and acetylsalicylic acid [131] increase the risk of bleeding (cerebral or/and GI ulcer). The co-administration of Ginkgo and NSAIDs is not recommended [132,133].

### Curcumin

Curcumin is a polyphenolic bioactive yellow pigment present in the roots of *Curcuma longa L.* (turmeric). Its therapeutic activities have been extensively reported, mainly for cancer and inflammatory diseases' treatment [134]. Also, it present anti-platelet and potent antioxidant effect interacting with several targets, such as tyrosine-protein kinase (JAK2) / *Signal transducer and activator of transcription 3* (STAT3), 5'-adenosine monophosphate--activated protein kinase (AMPK) / mitochondrial uncoupling protein 2 (UCP2), phosphatidylinositol 3-kinase (PI3K)/Akt / nuclear factor erythroid related factor 2 (Nrf2), extracellular signal-regulated kinases (ERK), mitogen-activated protein kinases (MAPK p38), intercellular adhesion molecule 1 (ICAM-1) and monocyte chemotactic protein 1 (MCP-1) [135-141], reducing inflammatory cytokines such as NF- $\kappa$ B, IL-1 $\beta$ , IL-8, IL-6 and TNF- $\alpha$  [142]. It also reduces levels of xanthine oxidase, superoxide anion and myeloperoxidase lipid peroxidation and elevate enzymatic antioxidant activities of glutathione peroxidase, superoxide dismutase (SOD) and catalase [142,143].

Liver is the main detoxification organ of xenobiotics and drugs. However, some compounds can induce to hepatocytes damage such as the NSAIDs by the production of iminoquinones metabolites and reactive oxygen species (ROS). Reports showed that curcumin is able to decreases liver damage induced by acetaminophen [144-146]. By the beneficial effect of curcumin, it's suggested that curcumin can potentiate the activity NSAIDs and also protect the liver.

Curcumin present nephroprotective activity and have been associated with the prevention of kidney injury. It is able to increase the level of AMPK, SIRT-1/3 (silent mating type information regulation-1), PPAR  $\alpha/\gamma$  (peroxisome proliferatoractivated receptor) as well as reduce glomerular filtration rate in cardiovascular disease [143].

In addition, curcumin is mediated by the MKP-1-dependent inactivation of p38 and inhibition of NF- $\kappa$ B-mediated transcription, gastric inflammation and gastric cancer via reduced NF- $\kappa$ B p65 expression, decreased vascular endothelial growth factor (VEGF) level, and macromolecular leakage in the gastric mucosa, protecting the gastric mucosal injury induced by NSAIDs [143].

### Resveratrol

Resveratrol (3,5,40 -trans-trihydroxystibene) is an antioxidant and anti-inflammatory polyphenol present in red wine, grapes and has been extensively investigated as potential compound for the treatment of several diseases, including the cardiovascular diseases, cancer prevention, modulation of lipid metabolism, and regulation of immune system, cerebrovascular

and age-related diseases [147-151]. This phytochemical acts mainly under via AMPK/SIRT-1 subsequent peroxisome proliferator activated receptor gamma coactivator 1 $\alpha$  (PGC-1 $\alpha$ ) activating phosphorylation, increasing mitochondrial biogenesis as well as oxidative capacity [143], however, it is not totally understood.

Resveratrol upregulates the SOD and decrease ROS production, inhibits phospholipase A2 and COX<sub>2</sub> activity, decreasing de PGE2 synthesis. It possess the ability to antagonizes the inflammatory cytokines NF- $\kappa$ B, TNF- $\alpha$ , IL-6 and the Inducible nitric oxide synthase (iNOS) activity, and MCP-1, promoting a very potent anti-inflammatory effect [152-154]. In addition, resveratrol is able to modulate the platelet adhesion, secretion and activation signaling preventing platelet activation [155-157]. Furthermore, several studies demonstrated that resveratrol inhibits protein kinase C (PKC) activation and intracellular calcium release, thus blocking phosphoinositide metabolism upstream platelet activation signaling [158].

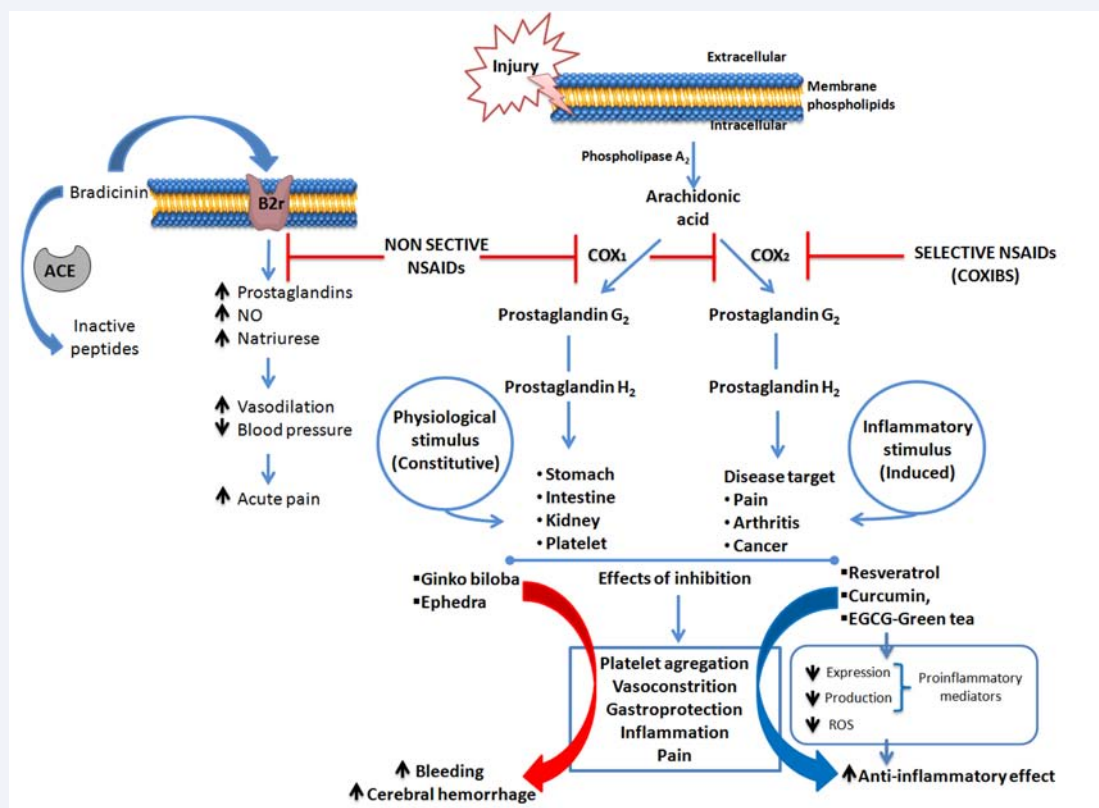
Resveratrol is able to prevent kidney damage. The nephroprotective effect has been related with the prevention of ROS generation as well as increasing of antioxidant enzymes and decreasing inflammatory cytokines. Besides, it is able to level increase AMPK, SIRT-1, PPAR [143]. In septic animals, Wu and co-workers showed the protection of kidney damage by the RES activation of SIRT1/3 in the hyper-inflammatory phase.

It's known that resveratrol improve glucose uptake and metabolism in animals and is beneficial in individuals with diabetes type 2, in clinical trials [159,160]. The use of NSAIDs in diabetics' patients is not recommended because the side effects mainly vasoconstriction and kidney damages. With this knowledge we can deduce that the use of resveratrol in Type 2 diabetic patients may be interesting by itself. In addition, this patients could use NSAIDs, once resveratrol can protect the kidney and by its anti-inflammatory effect, reducing the NSAIDs doses [161].

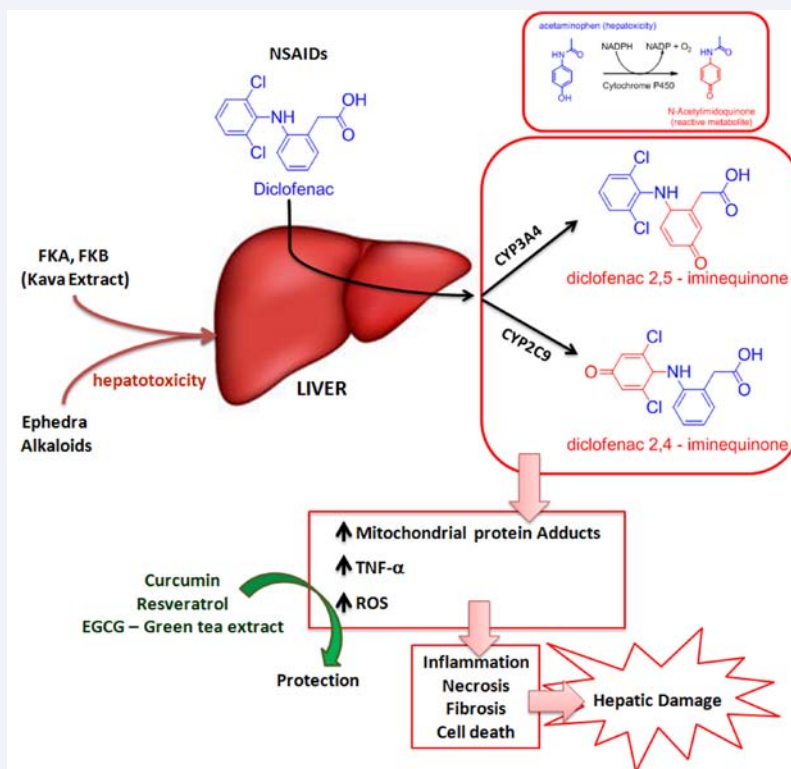
Treatment in mice with resveratrol during acetaminophen induced liver damage showed significant inhibition of cytochrome P450 2E1 (CYP2E1), cytochrome P450 3A1 (CYP3A1), and cytochrome P450 1A2 (CYP1A2) activities, as well as the pre-treatment with resveratrol able to protect against mitochondrial injury [162,163].

In other hand, Elgebaly et al. (2017), in a systematic review and meta-analysis showed that there are no evidence of resveratrol improvement in non alcoholic fat liver disease and does not alters liver fibrosis [164]. In other hand, Kessoku and co-workers (2016) reported a study performed with non alcoholic steatohepatitis (NASH)/ nonalcoholic fatty liver (NAFL) mice model, that resveratrol can improve liver inflammation and fibrosis but not steatosis, *via* inhibition of lipopolysaccharide (LPS) reactivity that is due to cluster of differentiation 14 (CD14) expression in Kupffer cells [165].

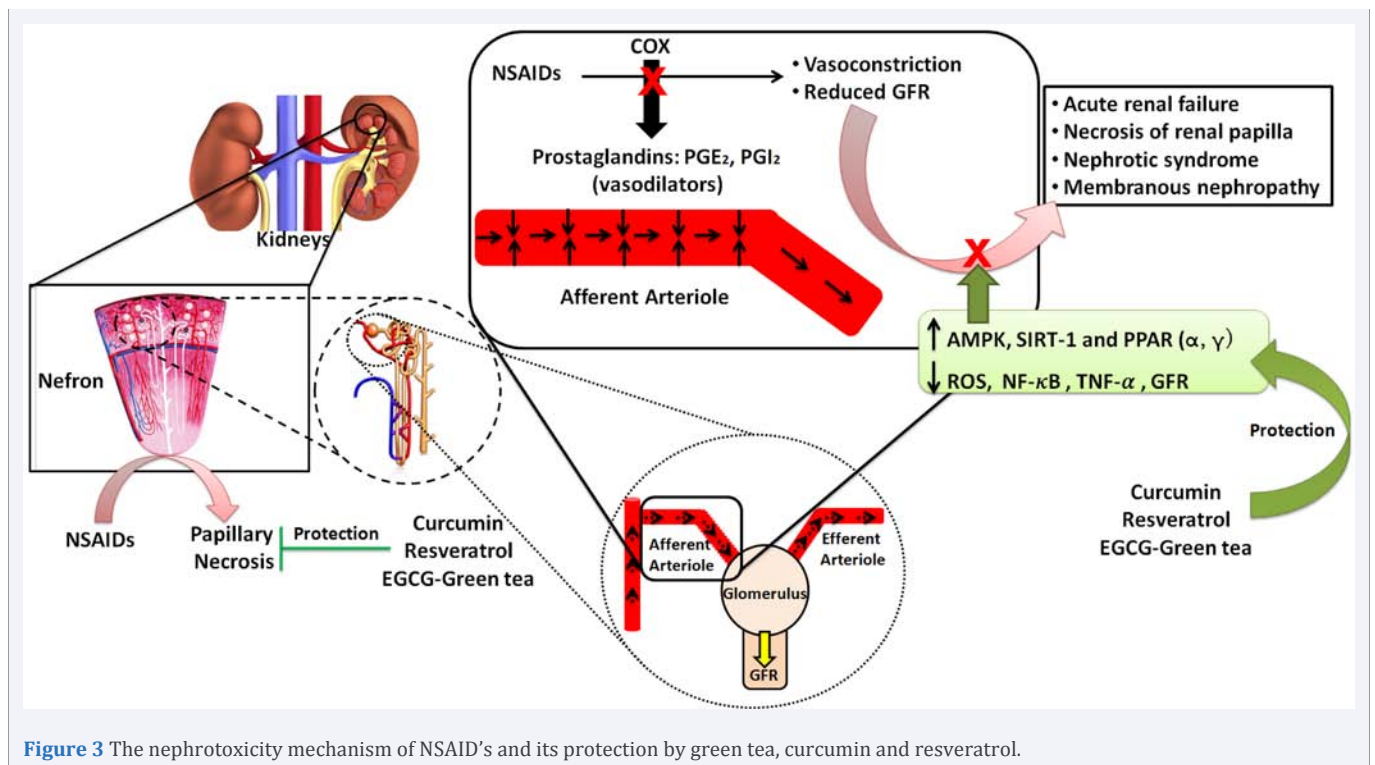
Resveratrol preserve antioxidant defenses resulting in reduction of acetaminophen-induced liver injury [166], reduce stress-induced gastric damage [167], and an increase in activity of antioxidizing enzymes SOD and glutathione (GSH) [143].



**Figure 1** NSAIDs mechanism of action and natural products (*Ginkgo biloba*, Ephedra, Resveratrol, Curcumin, Green Tea). Red line: inhibition; blue line: activation.



**Figure 2** Hepatic damage caused by diclofenac compared to acetaminophen and the protective action of green tea, ginkgo, ephedra, kava, curcumin, and resveratrol.



**Figure 3** The nephrotoxicity mechanism of NSAID's and its protection by green tea, curcumin and resveratrol.

Figure 2 and 3 shows the effect of NP interacting with the effect of NSAIDs in liver and kidney.

## CONCLUSION

NP are widely used since ancient. Acute inflammation and pain is the most motivation for the high use of NSAIDs worldwide. The concomitant use of NP and NSAIDs can be good or not, depending of the active compound. Ephedra and *Ginkgo biloba* can increase risk of cerebral hemorrhage and GI ulcer bleeding promoted by the NSAIDs and Green tea, curcumin and resveratrol possess improvement of anti-inflammatory activity and protect kidney and liver from NSAIDs damage. The liver deleterious effect of kava depends of the concentration of FKA and B form kava cultivars. High concentrations of these flavokawains and concomitant use of NSAIDs structurally similar to diclofenac can precipitate or lead to liver failure.

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