REVIEW ARTICLE

Pharmacologic Overview of Chlorogenic Acid and its Metabolites in Chronic Pain and Inflammation

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Abstract: ***Background***: Natural phenolic compounds in medicinal herbs and dietary plants are antioxidants which play therapeutic or preventive roles in different pathological situations, such as oxidative stress and inflammation. One of the most studied phenolic compounds in the last decade is chlorogenic acid (CGA), which is a potent antioxidant found in certain foods and drinks.

Objective: This review focuses on the anti-inflammatory and antinociceptive bioactivities of CGA, and the putative mechanisms of action are described. Ethnopharmacological reports related to these bioactivities are also reviewed.

Materials and Methods: An electronic literature search was conducted by authors up to October 2019. Original articles were selected.

Results: CGA has been shown to reduce inflammation and modulate inflammatory and neuropathic pain in animal models.

Conclusion: The consensus of the literature search was that systemic CGA may facilitate pain management *via* bolstering antioxidant defenses against inflammatory insults.

1. INTRODUCTION

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage [1]. Pain is a complex and subjective phenomenon, resulting from the interplay between systems signaling noxious events and pain-modulating processes [2]. More than 1.5 billion people worldwide suffer from chronic pain of varying degrees [3], with chronic pain affecting the lives of hundreds of millions [4]. Chronic pain may lead to deleterious effects on health, employment, economy, and quality of life [5]. The economic impact of chronic pain in the United States ranges from $560 billion to $635 billion a year [3], which is greater than the economic burden of heart disease, or the combined cost of cancer and diabetes.

Among all types of chronic pain, the relentless discomfort of neuropathic pain has the greatest impact on the quality of life, with approximately 3-4.5% of the global population affected [6]. Unfortunately, pain management therapies for neuropathic pain are inefficacious, problematic, or have abuse potential. Neuropathic pain is due to a dysfunction of, or damage to, a nerve or group of nerves [7]. While acute pain can be effectively managed with nonsteroidal anti-inflammatory drugs and opioids, these agents are less efficacious for chronic neuropathic pain associated with inflammation and nerve injury.

Growing evidence suggests that natural phenolic compounds play preventative and therapeutic roles in neurodegenerative diseases and inflammatory pathological states. The therapeutic potential of these bioactive compounds is due to their antioxidant and anti-inflammatory properties [8-11]. Chlorogenic acid (CGA), which is formed by the condensation of caffeic acid with quinic acid, is widely present in nature and is one of the most abundant polyphenols in the

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human diet [12]. CGA is found ubiquitously in plants, fruits, and vegetables [13]. The highest levels of CGA are found in green coffee beans [14, 15]. Coffee is widely consumed throughout the world and contains high levels of CGA. However, the roasting process reduces the CGA content. The CGA levels in a 200 ml cup of coffee have been reported to range from 70-350 mg [13]. It is unclear at this time if the levels of CGA present in brewed coffee made from roasted beans are of clinical significance.

Recently, CGA has been shown to have potent anti-inflammatory, antigenotoxic, and antioxidant activities [14-21]. Among these activities, the anti-inflammatory and antinociceptive effects are by far the least explored, but CGA-rich medicinal plants are used as traditional medicines to relieve pain in inflammatory processes in many countries [22-24]. In this review, we will summarize and interpret recent experiments in the field of phenolic compound research. This review summarizes the beneficial effects of CGA on inflammation and pain *in vitro* and *in vivo*.

2. ANTI-INFLAMMATORY PROPERTIES OF CHLOROGENIC ACID

Prolonged dysregulation of the immune system can lead to the development of non-communicable diseases, such as autoimmune disorders: 50 million Americans have autoimmune diseases [25]. The World Health Organization announced that the frequency of these diseases is accelerating across all geographic regions and socioeconomic classes. Moreover, chronic diseases are expected to account for 73% of all deaths and 60% of the global burden of disease by 2020 [26]. Immune system dysregulation has been implicated in numerous disorders. Cardiovascular diseases, cancer, chronic obstructive pulmonary disease, and type 2 diabetes are four of the most prominent chronic diseases, which may result from, or lead to, inflammation and/or oxidative stress. A considerable amount of literature suggests that oxidative stress and inflammation contribute to over 100 diseases, including arthritis, meningitis, lupus, multiple sclerosis, and Alzheimer's disease [27].

Plant-based immunomodulators can be used to prevent inflammatory disease progression or frequency. Immunomodulators can either increase or decrease the magnitude of the immune response. The immunomodulatory effects (cytokine secretion, phagocytosis promotion, macrophage activation, and immunoglobulin production) of herbal remedies have recently gained the attention of researchers [28]. CGA has strong immunomodulatory effects, which might represent a promising approach for inflammatory disease management.

The inflammatory process has three major components: hemodynamic changes, leukocytic exudation, and chemical mediators with the related hormonal responses. These components include the modulation of vascular events, chemotaxis, macrophage activation, cytokine secretion, and immunoglobulin production [29, 30]. Inflammatory stimuli induce gene expression of cytokines, initiating the inflammatory response. Tumor necrosis factor-alpha (TNF-α) is a major cytokine involved in the initiation of the inflammatory response. Its actions include induction of other cytokines, such

as interleukin (IL)-1 and IL-6, priming of polymorph nuclear leukocytes, and up-regulation of adhesion molecules. Stimulation of macrophages/monocytes, fibroblasts, and epithelial cells with IL-1β and TNF-α leads to prostaglandin (PG)-E_2 production *via* arachidonic acid metabolism, which consequently leads to edema. Therefore, impairment of TNF-α synthesis/release or impairment of other pro-inflammatory cytokines are alternative methods of PGE_2 inhibition, which can prevent edema by anti-inflammatory effects [31].

Various inflammatory stimuli and inflammatory cells such as macrophages can activate the nuclear factor kappa B (NF-κB) signaling pathway. This activation can lead to inflammation and cell proliferation [32, 33]. Following the translocation of NF-κB into the nucleus, the expression of specific genes involved in inflammation or immunomodulation is increased, leading to a cell survival response or cellular proliferation [34]. NF-κB activation also induces the transcription of inducible nitric oxide synthase, leading to nitric oxide (NO) production. NO is a pro-inflammatory mediator that contributes to the pathogenesis of inflammatory disorders [35, 36]. Overproduction of these pro-inflammatory mediators causes inflammation. Therefore, the characterization of new substances that modulate NF-κB and overproduction of pro-inflammatory mediators is a topic of considerable research interest [37]. CGA and its metabolites are being actively studied in the context of inflammation and related disorders caused by dysregulation of NF-κB.

2.1. CGA is Anti-inflammatory in Animal Models of Sepsis

During septic shock, lipopolysaccharide (LPS), the major component of external membranes in gram-negative bacteria, induces expression of TNF-α, IL-1, IL-6, NO, PGE_2, and other pro-inflammatory mediators [38, 39]. Shan *et al*. showed that CGA significantly decreased LPS-induced cyclooxygenase (COX)-2 up-regulation and inhibited PGE_2 release in RAW264.7 cells *via* attenuation of NF-κB and c-Jun N-terminal kinase (JNK)/activation protein-1 (AP-1) signaling pathway activation [40]. These results suggest that CGA may have anti-inflammatory effects by inhibiting PGE_2 production. Further, CGA, in a concentration-dependent manner, is able to strongly inhibit the production of TNF-α and IL-6 by human peripheral blood mononuclear cells stimulated by staphylococcal exotoxins [41]. Further, CGA inhibits the synthesis of other mediators, such as IL-1β, interferon-γ, monocyte chemotactic protein-1, and macrophage inflammatory protein-1α [41-43].

Additional mechanisms of CGA-mediate inhibition of inflammation include modulation of toll-like receptors (TLRs) and high mobility group box 1 in animal models of sepsis. TLRs are known to interact with pro-inflammatory mediators that are released during ischemia, and this interaction activates the innate immune system [44]. As shown in Fig. **1**, the mechanisms underlying the action of CGA include attenuation of TLR-4 expression and suppression of sepsis-induced signaling pathways, such as JNK, p38-mitogen-activated protein kinase (MAPK) and NF-κB [45-47], suggesting that CGA modulates cytokine and chemokine release, and suppresses immune cell apoptosis [48]. *In vivo* investigations corroborate these results; chronic oral admini-
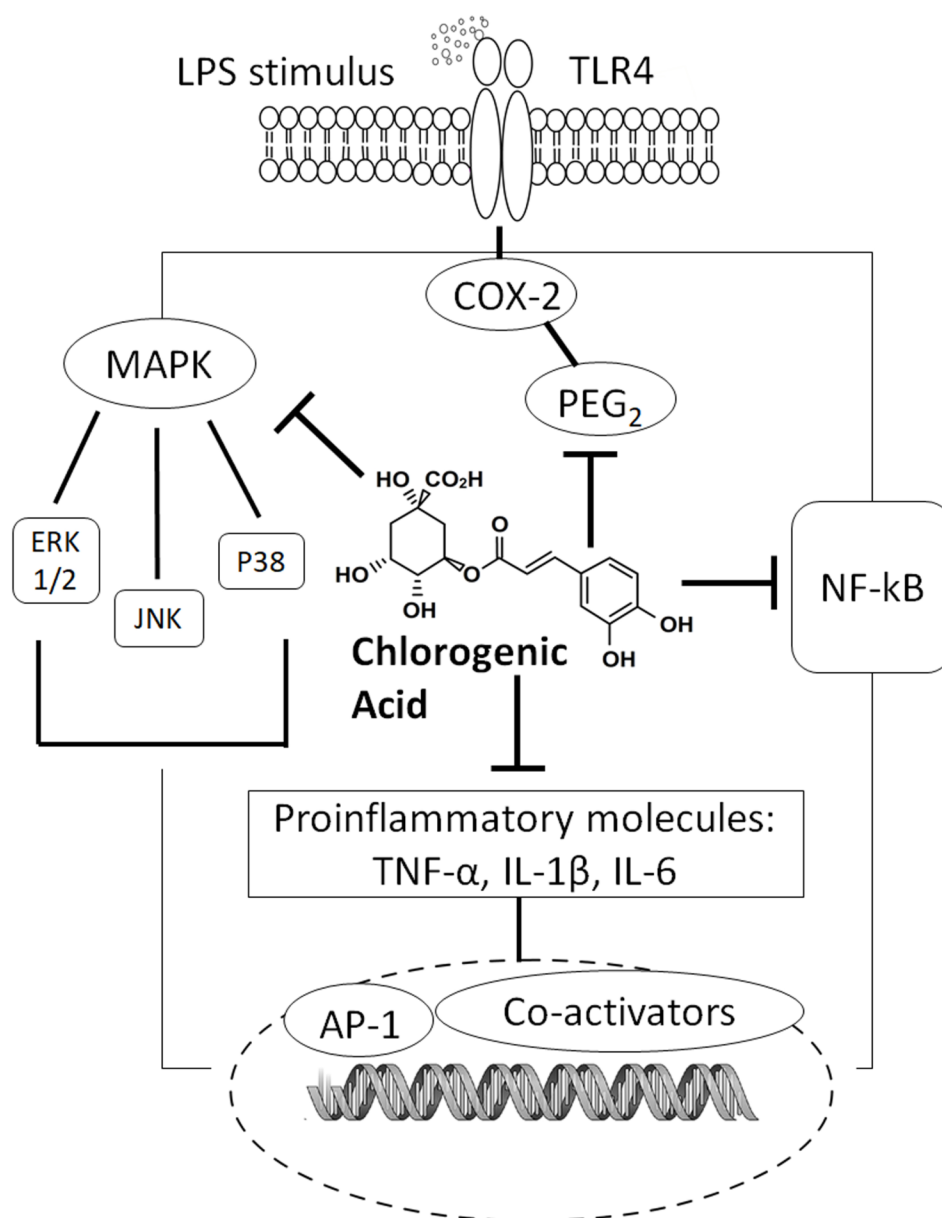
Fig. (1). Possible mechanisms of chlorogenic acid in regulating inflammation. CGA has a broad range of anti-inflammatory effects relevant to pain and other health outcomes (neuroprotective, gastroprotective, renoprotective, antirheumatic, and anti-atherothrombotic effects). CGA and its metabolites appear to contribute to its pain-alleviating mechanisms by interrelated anti-inflammatory mechanisms. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

stration of CGA prevents acetaminophen-induced hepatotoxicity: TLR-3/4 and MyD88 expression, expression of phosphorylated p65 subunit of NF-κB, and serum levels and liver mRNA expression of TNF-α, IL-1β, IL-6, and monocyte chemoattractant protein-1, are all reduced [43]. Moreover, intraperitoneal injection of CGA lowers neutrophil infiltration in the liver through the modulation of TLR-4, TNF-α, and NF-κB signaling in LPS-treated mice [46]. CGA's protective mechanisms extend to include inhibition of phosphorylation-mediated activation of JNK, p38-MAPK, extracellular signal-regulated kinase (ERK) 1/2, and upstream molecular signals [49]. High mobility group box 1, another important inflammatory factor, is released largely during immune system activation and inflammatory damage [50,

51]. Administration of CGA attenuates systemic HMGB-1 accumulation *in vivo* and prevents mortality induced by endotoxemia and polymicrobial sepsis [45, 52].

The anti-inflammatory activity of CGA in animal models of sepsis may be related to its antioxidative properties [49, 53-56]. For example, as a free radical scavenger and antioxidant, CGA prevents chemically-induced damage in the liver and in primary cortical neurons by reducing oxidative damage and apoptosis [49, 55]. Integrating intracellular pathways with the inhibition of NF-kB activation and/or inhibition of pro-inflammatory cytokine release are similar components of both antioxidant and anti-inflammatory mechanisms [57-59].

2.2. CGA May Be Protective in Neurodegenerative Inflammatory Disease Models

Inflammation is a major contributor to the pathogenesis of chronic diseases such as diabetes, neurodegeneration, and cancer [60, 61]. CGA may have beneficial health outcomes (such as neuroprotective, gastroprotective, renoprotective, antirheumatic, and anti-atherothrombotic effects) against many inflammatory disorders [62-65]. The mechanism by which CGA is beneficial in inflammatory disease states may be due to its immunosuppressive effects; pro-inflammatory factors released by activated microglia may contribute to the progression of neurodegenerative diseases, whereas CGA prevented neurotoxicity caused by microglial activation and ultimately improved survival of dopaminergic neurons [66]. Notably, CGA protects dopaminergic neurons against neuro-inflammatory conditions associated with Alzheimer's disease [67]. In addition, it has been reported that CGA was able to improve some measures of cognitive function [68]. CGA may show neuroprotective effects in the case of pro-inflammatory factor-mediated neurodegenerative disorders [66]. Possible mechanisms of immunosuppression in a model of LPS-stimulated primary microglial activation include suppressing: NO production, TNF-α release, and NF-κB translocation. Oral administration of coffee extract and CGA has been reported to protect against retinal degeneration as well [64, 65]. While optimistic, the results of these clinical studies would need to be replicated by independent researchers in order to conclude that CGA is a viable treatment for Alzheimer's disease or other degenerative diseases.

Bioactive polyphenolic compounds have the potential to act as pro-oxidants under certain circumstances [69]. Notably, the concentration of the compounds determines their antioxidant or pro-oxidant activity. Pro-oxidant activity can induce damage to biomolecules such as DNA, lipids, or proteins [70]. Excess CGA intake for prolonged periods may cause pro-oxidative effects [71] on the liver, kidneys, and bone marrow [20, 56]. Intravenous CGA at high doses has been reported to cause DNA damage [72] and a range of inflammatory reactions in rats [73]. In humans, high doses of CGA can cause cardiovascular complications [74], headache, diarrhea, emesis, asthma, pruritus, anxiety, liver damage, and kidney damage [75-77]. However, CGA doses required to have pro-oxidative effects or induce an inflammatory response were in excess of the typical human diet. Therefore, dietary supplementation with CGA should be in moderation for optimal health.

2.3. CGA Metabolites Exhibit Anti-Inflammatory Properties

CGA has a broad range of anti-inflammatory effects relevant to pain. *In vitro* studies suggest that possible mechanisms of CGA's anti-inflammatory effects involve inhibition of: NF-kB [40, 41, 47, 78], TNF-α [47], IL-1β [47], IL-6 [41], PGE$_2$ [40, 41] and JNK/AP-1 signaling pathway activation [40]. Further, CGA inhibits the synthesis of other mediators, such as interferon-γ, monocyte chemotactic protein-1, and macrophage inflammatory protein-1α [41-43]. Moreover, CGA metabolites caffeic acid [37, 79, 80] and ferulic acid [81, 82] have also been reported to have anti-inflammatory effects. These findings indicate that the anti-inflammatory effects of CGA are not limited to the parent molecule. The metabolites of CGA appear to contribute to its pain-alleviating mechanisms by interrelated anti-inflammatory mechanisms.

Caffeic acid is a major metabolite of CGA with extensively-documented anti-inflammatory activity. Caffeic acid decreased NO and PGE$_2$ production and downregulated TNF-α, COX-2, and inducible nitric oxide synthase levels in LPS-stimulated RAW264.7 cells. Caffeic acid also suppressed the nuclear translocation of AP-1 family proteins and the related upstream signaling cascade composed of IL-1 receptor-associated kinase (IRAK)-1, IRAK4, transforming growth factor β-activated kinase 1, MAPK kinase 4/7, and JNK [80]. These results indicate that the antioxidative effect of caffeic acid and its restoration of redox balance are responsible for caffeic acid's anti-inflammatory action [37].

Detailed examination of the minor CGA metabolite sinapic acid also shows anti-inflammatory properties. Sinapic acid was able to inhibit LPS-induced expression of NO, PGE$_2$, TNFα, IL-1β, and NF-κB in a dose-dependent manner *in vitro* [83]. However, Jin *et al.* showed that a single dose of CGA was not sufficient to alter TNF-α levels in the supernatant of LPS-stimulated RAW cells [84]. On the other hand, the herbal formula of *Rosae Multiflorae Fructus*, which contains a remarkable amount of CGA, demonstrated anti-inflammatory properties in LPS-stimulated RAW264.7 cells due to its regulatory effects on the NF-κB and MAPK signaling pathways [78]. Ferulic acid, another metabolite of CGA, exerts anti-inflammatory effects *via* similar mechanisms as CGA [79, 82]. Such variations in findings between studies on metabolites and herbal extracts may be due to the use of different dosing regimens.

Table **1** lists a summary of CGA's anti-inflammatory effects *in vitro*. Table **2** summarizes CGA's anti-inflammatory effects *in vivo*.

3. EFFECTS OF CHLOROGENIC ACID IN INFLAMMATORY AND NEUROPATHIC PAIN MODELS

Primary afferents in the periphery transduce information about noxious stimuli by synapsing onto second-order neurons in the dorsal horn of the spinal cord. The second- order neurons decussate the spinal cord, ascend, and project to the thalamus. In the thalamus, the second-order neurons synapse onto the third-order neurons, which project to the somatosensory cortex. Modulation of any part of the spinothalamic pathway, especially the dorsal horn, can result in changes in pain transmission, and ultimately pain perception [7]. For example, peripheral nerve injuries cause neural plasticity, which leads to central sensitization of the spinal neurons and enhancement of nociceptive transmission [7, 85-87].

Both peripheral and central sensitizations are involved in neuropathic pain, and the mechanisms are very complex. Neuropathic pain results from tissue damage, inflammation, or injury of the nervous system. Neuropathic pain is characterized by three sensory abnormalities: (i) increased sensitivity to painful stimuli (hyperalgesia); (ii) perception of innocuous stimuli as painful (allodynia); and (iii) spontaneous pain [88]. Nerve injury leads to an inflammatory response,

Table 1.   Chlorogenic acid modulates pain and inflammation *in vitro*.

	Compound	Method	Model	Dose	Response	Refs.
Anti-inflammatory effects	CGA	Staphylococcal exotoxin-stimulated inflammation	Human peripheral blood mononuclear cells	0.2, 2, 20, and 200 µg/ml	Anti-inflammatory; inhibited production of TNF-α and IL-6	[41]
	CGA	LPS-induced inflammation	RAW264.7 cells	37.5 µg/ml	Anti-inflammatory; decreased LPS-induced cyclooxygenase (COX)-2 upregulation, inhibited PGE2 release, attenuated activation of NF-κB and JNK/AP-1 signaling pathways	[40]
	CGA	LPS-induced inflammation	Primary culture of microglia	1-4 mM	Improved survival of dopaminergic neurons; suppressed NO production, TNF-α release, and NF-κB translocation	[66]
	Caffeic acid	LPS-induced inflammation	RAW264.7 cells	100-400 µM	Decreased NO and PGE2 production; downregulated TNF-α, COX-2, and iNOS levels; suppressed nuclear translocation of AP-1 family proteins, IL-1 receptor, IRAK-1, IRAK4, TGF-β,TAK1, MAPKK-4/7, JNK	[80]
	Rosae Multiflorae Fructus extract	LPS-induced inflammation	RAW264.7 cells	25, 50, 100, and 200 µg/ml	Anti-inflammatory; regulatory effects on NF-κB and MAPK signaling pathways	[78]
Pain modulatory effects	CGA	Whole-cell patch-clamp recordings in an inflammatory environment	Rat trigeminal ganglion neurons	0.2 mmol	Promoted Kv channels activation and inactivation under inflammatory conditions	[122]
	CGA	Acid stretch test	Rats; rat dorsal root ganglia neurons	0.01, 0.1, 1, and 10 µM	Ameliorated the acidosis-evoked pain; inhibited acid-sensing ion channels in rat dorsal root ganglia neurons	[126]
	CGA	Extracellular single-unit recordings	Rat trigeminal spinal nucleus caudalis neurons (SpVc)	0.1-10 mM	Local CGA injection into the periphery suppressed SpVc neuron excitability	[127]
	CGA	Whole-cell patch-clamp recordings	Rat trigeminal ganglion neurons	0.2 and 1 mmol	Enhanced Kv activities	[121]

prompting the release of several ions, histamine, TNF-α, ATP, PGs, leukotrienes, cytokines, and nerve growth factor. During this inflammatory response, macrophages release a variety of inflammatory mediators, and the expression of these mediators is regulated by different intracellular signaling pathways, such as NF-κB [89]. This cocktail of mediators serves as a mechanism of enhanced inflammatory response to an injured nerve and contributes to neuropathic pain [88].

Ethnopharmacological use of medicinal plants with anti-inflammatory properties may be a starting point for the discovery of new classes of analgesics for neuropathic pain. As we have explained, neuropathic pain is modulated by the immune and inflammatory systems. Therefore, there has been considerable interest in investigating the antinociceptive and anti-inflammatory effects of phenolic compound-rich plants, such as those with CGA. For example, *Cnidium officinale* is

traditionally used in Korea to attenuate pain and increase stamina [90]. Postoperative, neuropathic, and menopausal pain models confirmed that *C. officinale* extracts attenuate hypersensitivity [91]. Further, in the rat spared nerve injury model, *C. officinale* inhibited the induction of the proinflammatory cytokines and calpain-3 in dorsal root ganglion neurons, which may be due to its CGA and ferulic acid contents. Similarly, *Mansoa alliacea*, native to the Brazilian Amazon, is used in the treatment of fever, convulsions, and head and neck pain [92]. Phytochemical screening of *M. alliacea* revealed the presence of several phenolic compounds, such as ρ-coumaric acid, luteolin, apigenin, ferulic acid, and CGA. *M. alliacea* extracts exhibit antinociceptive activity in the CFA model of inflammatory pain model, which may be δ-opioid receptor-mediated, in addition to CGA's anti-inflammatory properties [93]. The consensus of the literature is that extracts derived from CGA-containing plants produce antinociception in animal models [22-24, 93]. While pure

Table 2.   Chlorogenic acid modulates pain and inflammation *in vivo* in rodent models.

	Compound	Method	Model	Dose	Response	Refs.
Anti-inflammatory effects	CGA	Piroxicam (NSAID)-induced ulcer	Rats	5, 25, and 50 mg/kg	Gastroprotective effect without altering the secretory functions; inhibited neutrophil migration; restored levels of antioxidant enzymes; blocked increase in TNF-α and leukotriene β4; did not restore prosta-glandin levels	[148]
	CGA	Acetaminophen-induced hepatotoxicity	Mice	10, 20, and 40 mg/kg	Reduced acetaminophen-induced TLR-3/4 and MyD88 expression; attenuated serum levels and liver mRNA expression of TNF-α, IL-1β, and IL-6	[43]
	CGA	LPS-induced inflamma-tion	Mice	50 mg/kg	Decreased neutrophil infiltration in the liver; modulated TLR-4, TNF-α, and NF-κB signaling	[44]
Pain modulatory effects	CGA	CCI	Rats	0.5, 1, and 2 mg in 10 µL	Reduced mechanical and cold hyperalgesia; no effect on thermal hyperalgesia	[96]
	CGA	Streptozotocin-induced diabetic neuropathy	Rats	100 mg/kg	Antihyperalgesic; chronic treatment reduced diabetes-induced hyperalgesia	[94]
	CGA	CCI	Rats	50, 100, and 200 mg/kg	Inhibited mechanical hyperalgesia; antihyperalgesic activity without impairing motor coordination	[95]
	CGA	Carrageenan-induced paw edema, formalin test	Rats	10, 50, and 100 mg/kg	Anti-inflammatory and anti-nociceptive	[17]
	Caffeic acid	Carrageenan-induced inflammation	Mice and Rats	200 mg/kg	Antihyperalgesic; reduced neutrophil-, free radical-, and nitric oxide-mediated hypernociception	[114]
	Ferulic acid	CCI	Rats	50 mg/kg	Antihyperalgesic; decreased P2X3 receptor-mediated primary afferent sensitization	[115]
	CGA isolated from aqueous fraction of *Bidens pilosa*	LPS-induced knee joint inflammation, CFA-induced arthritis	Rats	2.5, 5, 10, 20, and 40 mg/kg	Anti-inflammatory; inhibited TNF-α and IL-1β pro-duction	[97]
	Methanol frac-tion of *Cheilan-thes farinose*	Carrageenan-induced inflammation, formalin test, tail-flick test	Mice	200 and 400 mg/kg	Strong anti-inflammatory and antinociceptive	[24]
	Cnidium officinale ex-tracts	Spared nerve injury, plantar incision, and ovariectomy rat model of menopausal pain	Rats	30, 100, and 300 mg/kg	Antihyperalgesic; attenuated hypersensitivity in all pain models; decreased mechanical hyperalgesia; inhibited proinflammatory cytokines and calpain-3 in dorsal root ganglia neurons	[91]
	Mansoa alliacea extract	CFA-induced inflamma-tory pain model	Mice	10 and 100 mg/kg	Antihyperalgesic and antinociceptive; reversed ther-mal hyperalgesia, but did not reduce the CFA-induced edema nor myeloperoxidase activity	[93]
	Ethanolic fraction of *Ur-tica circularis*	Formalin test, hot plate test, acetic acid stretch test	Mice	10–300 mg/kg (intraperitoneal) 250 mg/kg and 500 mg/kg (per os)	Antinociceptive in the acid stretch test and formalin test	[20]

CGA is not effective for the treatment of acute pain [94], it may possess antinociceptive activity in tonic and inflammatory pain models, such as formalin- and carrageenan-induced pain [17] and chronic neuropathic pain models [94-96]. CGA's effectiveness in chronic neuropathic pain models may be due to CGA's anti-inflammatory properties. Dos Santos *et al*. suggested that the antinociceptive effect of CGA in inflammatory pain is associated with its inhibitory activity on peripheral TNF-α and NO [17]. Other studies using dif-ferent pain models reported that CGA-rich fractions of the medicinal plants *Urtica urens*, *Urtica circularis*, and *Cheilanthes farinosa* exhibit antinociceptive effects, which were attributed to their CGA content [22-24]. These studies posited that the effect of CGA on various animal models of pain was due to CGA's anti-inflammatory activity. Many authors noted that CGA has an inhibitory effect on peripheral synthesis or release of select inflammatory mediators, including TNF-α, NO, and several interleukins [17, 22, 97-99].

Chronic constrictive nerve injury (CCI) is a peripheral neuropathic pain model that initiates an inflammatory cascade [100, 101]. Both acute and chronic schedules of intraperitoneal CGA treatment inhibits mechanical hyperalgesia in CCI-induced neuropathic pain [95]. Moreover, CGA-mediated antinociception did not affect motor performance, suggesting that CGA is not psychoactive [95]. While intrathecal CGA had no effect on thermal hyperalgesia, CGA was able to reduce mechanical and cold hypersensitivity in the rat CCI model [96]. Histopathological analysis of the sciatic nerve confirmed that the antihyperalgesic effects of CGA in the CCI model was due to attenuation of the inflammatory cascade [95].

The results of these CCI studies suggest that the site of action of CGA's antihyperalgesic effects may be in spinal or supraspinal pathways. Supporting the hypothesis of a central site of action, intrathecal studies with a wide array of compounds determined that CGA's effects are, at least in part, mediated spinally by gamma-amino butyric acid $_A$ (GABA$_A$) receptors. GABAergic transmission in the spinal cord has been demonstrated to modulate pain processing [102, 103]. GABA$_A$ receptor agonists have been shown to attenuate hyperalgesia and allodynia induced by nerve injury [104-106]. The antihyperalgesic effects of CGA were partially reversed by GABA$_A$ receptor antagonist bicuculline [106]. This finding suggests that CGA is effective against mechanical and cold hyperalgesia due to its activation of GABAergic transmission in the spinal cord. Conversely, a variety of antagonists, such as strychnine (glycinergic), yohimbine (adrenergic), naloxone (mu opioidergic), and methysergide and ondansetron (serotonergic) failed to reverse the antihyperalgesic effects of CGA [96]. The antinociceptive effects of CGA in inflammatory and neuropathic pain are also related to its inhibitory effects on the release or synthesis of inflammatory mediators, such as TNF-α, NO, and ILs [17, 97, 107]. While the exact mechanisms underlying CGA's role against neuroinflammation are largely unknown, one possible explanation is linked to the suppressor role of CGA on the release of NO from LPS/interferon-γ-stimulated C6 astrocyte cells [17].

Oxidative stress is a key mediator in all phases of painful neuropathy, including the development, maintenance, and resolution of neuropathy [108, 109]. Peripheral nerve injury initiates an inflammatory process, which is often associated with free radical damage. *In vivo* and *in vitro* studies have shown that the antioxidant activities of CGA occur by inhibiting the formation of reactive oxygen species (ROS) or by scavenging them [18, 98]. Thus, CGA may have a beneficial and important role in the prevention of oxidative stress. Recent studies suggest that ROS may contribute to the development of neuropathic and inflammatory pain [88, 110-113]. Additionally, various phenolic antioxidants have been shown to exhibit antinociceptive activities in ROS-related pain [107, 114, 115]. Presumably, CGA exhibits this activity due to its antioxidant activities of inhibiting and/or scavenging ROS.

3.1. Effects of Chlorogenic Acid on Ion Channels Involved in Neuropathic Pain

Voltage-gated potassium channels (Kvs) are physiological regulators of membrane potential in sensory neurons. Kv 1.4 channels present on small diameter nociceptive neurons (A^δ and C fibers) in the dorsal root ganglia [111] regulate the activity of those neurons [117]. The inhibition of the Kv 1.4-type channel leads to hyper-excitability and hyperalgesia [118]. Clinically, Kv malfunctions lead to neuronal excitability in various pathologic conditions, such as chronic pain, migraine, and multiple sclerosis [119, 120]. Notably, CGA strongly enhances Kv activities in rat trigeminal ganglion neurons during treatment naïve [121] and PGE$_2$-induced inflammatory conditions [116], resulting in a gradual decrease of the excitability of neurons involved in signaling neuropathic and inflammatory pain [118, 121, 123-125]. Hyperpolarization of sensory ganglia may be an alternative explanation for CGA's antinociceptive effects in animal models. Therefore, Kvs are a putative therapeutic target for inflammation and neuropathic pain disorders [121, 125].

In addition to Kvs, peripheral acid-sensing ion channels have been suggested to be involved in various pain conditions. CGA was able to inhibit acid-sensing ion channels in rat dorsal root ganglia neurons and trigeminal ganglion neurons [126, 127], which indicates yet another novel peripheral antinociceptive mechanism of CGA. Further, peripheral application of CGA attenuated acidosis-induced pain [126] and trigeminal nociceptive pain [128].

3.2. Use of CGA and Active Metabolites as Complementary and Alternative Medicine for the Treatment of Rheumatoid Arthritis

Phenolic compounds and flavonoids are widely used in complementary and alternative medicine as treatments for arthritic diseases [128-130]. Rheumatoid arthritis (RA) is the most common inflammatory arthritis that leads to disability. Prolonged RA affects multiple joints, which are often affected in a fairly symmetrical fashion. Due to pathological progress, the inflammatory activity causes tendon tethering and erosion, and destruction of the joint surfaces, leading to an impaired range of movement and deformity [131]. Herbal remedies have been used in the treatment of the fever, pain, and inflammation related to RA in Asian and Mediterranean countries [131-134]. Herbal remedies aim to alleviate inflammatory mediators of RA, such as TNF-α, IL-1, IL-17, PGE$_2$, and NO.

As briefly mentioned above, the first stage in the metabolism of CGA is hydrolysis to caffeic and quinic acids. Caffeic acid is subsequently metabolized to ferulic and vanillic acids [98]. Caffeic acid exerts antihyperalgesic activity in carrageenan-induced inflammatory pain in mice and rats by reducing neutrophils, free radicals, and nitric oxide-mediated hypernociception [114]. In addition, sodium ferulate, the sodium salt of ferulic acid, exhibits antihyperalgesic effects on CCI-induced neuropathic pain by decreasing P2X3 receptor-mediated primary afferent sensitization [107, 115]. These findings suggest that the antinociceptive effects of CGA may be a result of action by CGA itself and/or by its metabolites. Therefore, either CGA or its metabolites may alleviate RA.

Porana sinensis, Erycibe obtusifolia, and *Erycibe schmidtii* are CGA-containing plants widely used in traditional medicine for the treatment of joint pain and RA. The efficacy of CGA extracts from these plants has recently been

validated in rodent models of tonic, visceral, and inflammatory pain [135]. The mechanism underlying these effects has been proposed to involve the inhibitory activity of CGA on PGE$_2$ synthesis [135]. Further, CGA isolated from the aqueous fraction of *Bidens pilosa* showed anti-inflammatory effects in LPS-induced knee joint inflammation and complete freund's adjuvant induced arthritis by inhibiting TNF-α and IL-1β production [97].

Hypericum perforatum (H. perforatum) is used in traditional medicine in Europe as an agent to reduce inflammation and promote healing. *H. perforatum* is commercially available for therapeutic use in Brazil and strongly modulates inflammation and oxidative stress [136]. *H. perforatum* and other *hypericum* species have a well-documented antinociceptive role in rodents in different pain models [137-142]. The Iowa Center for Research on Botanical Dietary Supplements investigated the bioactivities of the constituents extracted from *H. perforatum* (including hyperforin, hypericin, pseudohypericin, quercetin, quercitrin, isoquercitrin, rutin, amentoflavone and CGA) in regards to their role in LPS-induced PGE$_2$ production [143]. While extracts did not produce high enough concentrations of the target compounds to inhibit inflammation, amentoflavone, CGA, pseudo-
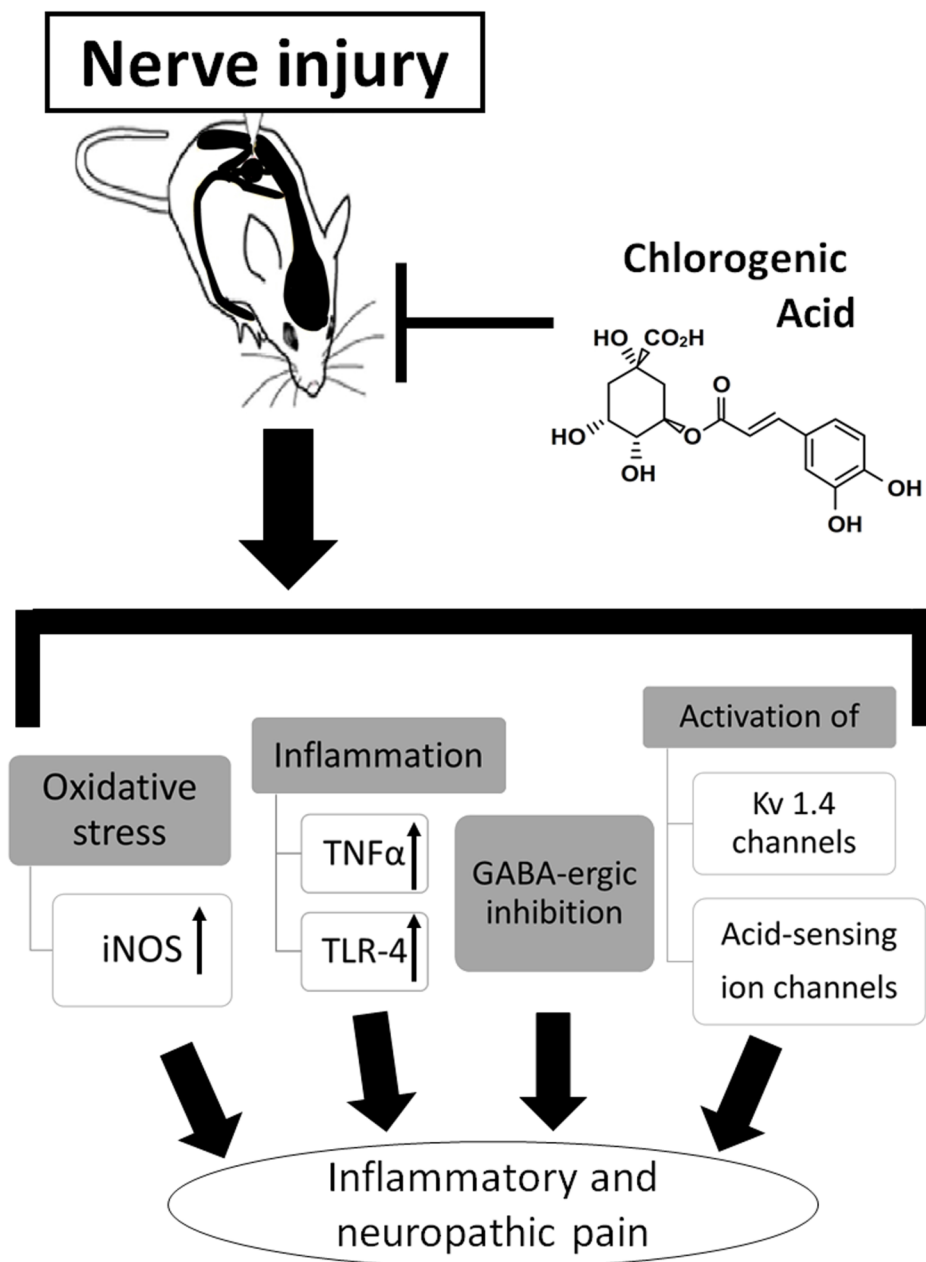

Fig. (2). Possible mechanisms of chlorogenic acid in regulating inflammatory and neuropathic pain. CGA inhibits inflammatory and neuropathic pain; however, CGA does not alleviate acute pain. The anti-inflammatory, antioxidant, neuroprotective, and neurotrophic activities of CGA most likely underlie its antinociceptive effects. Furthermore, CGA-mediated antinociception does not affect motor performance, suggesting that CGA is not psychoactive. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

hypericin, and quercetin inhibited LPS-induced PGE_2 activity in their pure forms [143, 144]. CGA was less effective than the other bioactive compounds identified in *H. perforatum* extracts [144]. However, CGA reduced the proliferation of IL-1β-induced fibroblast-like synoviocytes by regulating the activation of the NF-κB and Janus-family tyrosine kinase/signal transducer and activator of transcription-signaling pathways (JAK/STAT) [145, 148]. Together, these studies suggest that pure CGA, or in combination with other bioactive extracts, may be a treatment for arthritis.

Much like the reports of CGA's efficacy in neuroinflammatory diseases [62-65], the findings of these complementary and alternative medicine studies may be overly optimistic; double-blind, placebo-controlled clinical trials are needed in order to confirm the validity of CGA as a putative treatment for human pain conditions. One randomized placebo-controlled trial demonstrated that oral consumption of either CGA-weak (420 mg CGA) and CGA-rich (780 mg CGA) coffee was sufficient to increase plasma antioxidant capacity greater than baseline levels, which was greater than placebo [146]. Similar results were reported by Corrêa *et al*. [147], who found increased plasma antioxidant capacity after subjects drank coffee for four weeks. In a metabolic analysis, coffee consumption led to an increase in serum coffee-derived compounds, such as caffeine, chlorogenic acid, and caffeic acid metabolites. Significant changes were also observed for serum concentrations of interleukin IL-18, 8-isoprostane, and adiponectin. These observations suggest that coffee consumption may have therapeutic utility as an antioxidant, though the clinical efficacy of CGA for the treatment and management of pain in humans remains to be elucidated.

Ex vivo pain-related experiments are summarized in Table **1**. The effects of CGA on *in vivo* pain models are summarized in Table **2**.

CONCLUSION

As summarized in Fig. **2**, CGA has the therapeutic potential to act against inflammatory and neuropathic pain *via* a variety of mechanisms; however, CGA does not alleviate acute pain. The anti-inflammatory, antioxidant, neuroprotective, and neurotrophic activities of CGA most likely underlie its antinociceptive effects. Furthermore, CGA-mediated antinociception does not affect motor performance, suggesting that CGA is not psychoactive.

Non-addictive pain treatment options with fewer side effects are needed in order to curb the ever-increasing wave of pain patients who become opioid addicts. The integration of ethnopharmacology with modern technologies has the potential to lead to the discovery of new analgesic medicines. Overall, CGA is an intriguing candidate for analgesic development. Indeed, a recent patent application (Pub. No. US2019/0255007 A1) aims to capitalize on the therapeutic potential of CGA in pain. The recent surge in popularity of green coffee dietary supplements, in addition to the ubiquitous nature of CGA in the diet, warrants future studies into the extent to which CGA modulates biochemical responses in the human body.

LIST OF ABBREVIATIONS

AP-1	=	Activator protein 1 (c-jun and c-fos)
CCI	=	Chronic constrictive nerve injury
CGA	=	Chlorogenic acid
COX	=	Cyclooxygenase
ERK	=	Extracellular signal-regulated kinase
GABA	=	Gamma-Aminobutyric acid
IL	=	Interleukin
IRAK	=	Interleukin 1 receptor-associated kinase 1
JNK	=	Jun N-terminal kinase
Kv	=	Voltage-gated potassium channel
LPS	=	Lipopolysaccharide
MAPK	=	Mitogen-activated protein kinase
NF-κB	=	Nuclear factor kappa B
NO	=	Nitric oxide
PG	=	Prostaglandin
RA	=	Rheumatoid arthritis
ROS	=	Reactive oxygen species
TLR	=	Toll-like receptor
TNF-α	=	Tumor necrosis factor-alpha

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

REFERENCES

[1]   Merskey, H.; Bogduk, N. Classification of chronic pain, descriptions of chronic pain syndromes and definitions of pain terms. 2nd ed.; Iasp Press: Seattle, **1994**.

[2]   Stannard, C. F.; Booth, S. Churchill's Pocketbook of Pain, 2nd ed; Churchill; Livingstone, **1998**.

[3]   Interagency Pain Research Coordinating Committee. National pain strategy: a comprehensive population health-level strategy for pain. https://iprcc.nih.gov/sites/default/files/HHSNational_Pain_Strategy _508C.pdf201 (Accessed May 5, 2019).

[4]   Woolf, A.D.; Pfleger, B. Burden of major musculoskeletal conditions. *Bull. World Health Organ*, **2003**, *81*, 646-656. doi:S0042-96862003000900007 [pii]

[5]   Smith, B.H.; Elliott, M.; Chambers, W.; Smith, W.C.; Hannaford, P.C.; Penny, K. The impact of chronic pain in the community. *Fam. Pract.*, **2001**, *18*, 292-299. doi:10.1093/fampra/18.3.292

[6]   Bouhassira, D.; Lantéri-Minet, M.; Attal, N.; Laurent, B.; Touboul, C. Prevalence of chronic pain with neuropathic characteristics in the general population. *Pain*, **2008**, *136*(3), 380-387. doi:10.1016/j.pain.2007.08.013f

[7]   Millan, M.J. The induction of pain: An integrative review. *Prog. Neurobiol.*, **1999**, *57*, 1-164. doi:10.1016/S0301-0082(98)00048-3

[8]   Huang, W.Y.; Cai, Y.Z.; Zhang, Y. Natural phenolic compounds from medicinal herbs and dietary plants: Potential Use for cancer Prevention. *Nutr. Cancer,* **2009**, *62*, 1-20. doi:10.1080/01635580903191585

[9]   Kim, Y.C. Neuroprotective phenolics in medicinal plants. *Arch. Pharm. Res.*, **2010**, *33*, 1611-1632. doi:10.1007/s12272-010-1011-x

[10] Manach, C.; Scalbert, A.; Morand, C.; Rémésy, C.; Jiménez, L. Polyphenols: Food sources and bioavailability. *Am. J. Clin. Nutr.*, **2004**, *79*, 727-747. doi.org/10.1093/ajcn/79.5.727

[11] Scalbert, A.; Manach, C.; Morand, C.; Rémésy, C.; Jiménez, L. Dietary polyphenols and the prevention of diseases. *Crit. Rev. Food Sci. Nutr.*, **2005**, *45*, 287-306. doi:10.1080/1040869059096

[12] El-Seedi, H.R.; El-Said, A.M.; Khalifa, S.; Göransson, U.; Bohlin, L.; Borg-Karlson, A.K.; Verpoorte, R. Biosynthesis, natural sources, dietary intake, pharmacokinetic properties, and biological activities of hydroxycinnamic acids. *J. Agric. Food Chem.,* **2012**, *60*, 10877-10895. doi:10.1021/jf301807g

[13] Clifford, M.N. Review Chlorogenic acids and other cinnamates - nature, occurrence, dietary burden, absorption and metabolism. *J. Sci. Food Agric.*, **1999**, *79*, 362-372. doi:10.1002/(SICI)1097-0010(20000515)80:7<1033::AID-JSFA595>3.0.CO;2-T

[14] Del Rio, D.; Stalmach, A.; Calani, L.; Crozier, A. Bioavailability of coffee chlorogenic acids and green tea flavan-3-ols. *Nutrients*, **2010**, *2*, 820-833. doi:10.3390/nu2080820

[15] Ludwig, I.; Clifford, M.N.; Lean, M.E.J.; Ashihara, H.; Crozier, A. Coffee: biochemistry and potential impact on health. *Food Funct.,* **2014**, *5*, 1695-717. doi:10.1039/c4fo00042k

[16] Abraham, S.K.; Schupp, N.; Schmid, U.; Stopper, H. Antigenotoxic effects of the phytoestrogen pelargonidin chloride and the polyphenol chlorogenic acid. *Mol. Nutr. Food Res.*, **2007**, *51*, 880-887. doi:10.1002/mnfr.200600214

[17] dos Santos, M.D.; Almeida, M.C.; Lopes, N.P.; de Souza, G.E.P. Evaluation of the anti-inflammatory, analgesic and antipyretic activities of the natural polyphenol chlorogenic acid. *Biol. Pharm. Bull.,* **2006**, *29*, 2236-2240. doi:10.1248/bpb.29.2236

[18] Sato, Y.; Itagaki, S.; Kurokawa, T.; Ogura, J.; Kobayashi, M.; Hirano, T.; Sugawara, M.; Iseki, K. *In vitro* and *in vivo* antioxidant properties of chlorogenic acid and caffeic acid. *Int. J. Pharm.*, **2011**, *403*, 136-138. doi:10.1016/j.ijpharm.2010.09.035

[19] Gul, Z.; Demircan, D.; Bagdas, D.; Buyukuysal, R.L. Protective effects of chlorogenic acid and its metabolites on hydrogen peroxide-induced alterations in rat brain slices: a comparative study with resveratrol. *Neurochem. Res.*, **2016**, *41*, 2075-2085. Doi: 10.1007/s11064-016-1919-8

[20] Bagdas, D.; Cam, Etoz B.; Gul, Z.; Ziyanok, S.; Inan, S.; Gul, NY.; Topal, A.; Cinkilic, N.; Tas, S.; Ozyigit, MO.; Turacozen, O.; Gurun, MS. *In vivo* systemic chlorogenic acid therapy under diabetic conditions: Wound healing effects and cytotoxicity/genotoxicity profile. *Food Chem. Toxicol.*, **2015**, *81*, 54-61. doi: 10.1016/j.fct.2015.04.001

[21] Bagdas, D.; Cam, Etoz B.; Inan, Ozturkoglu S.; Cinkilic, N.; Ozyigit, MO.; Gul, Z.; Isbil Buyukcoskun, N.; Ozluk, K.; Gurun, MS. Effects of systemic chlorogenic acid on random-pattern dorsal skin flap survival in diabetic rats. *Biol. Pharm. Bull.,* **2014**, *37*, 361-370. doi: 10.1097/SAP.0000000000000313

[22] European Medicines Agency (EMEA). Evaluation of Medicines for Humen Use Community herbal monograph on *Urtica dioca* L. and *Urtica urens* L. *Herba*. Doc. **2008**. Ref. EMEA/HMPC/170261/2006.

[23] Domínguez, J.A.. Contribuciones a la Materia Médica Argentina. Peuser, **1982**, Buenos Aires, Argentina.

[24] Yonathan, M.; Asres, K.; Assefa, A.; Bucar, F. *In vivo* anti-inflammatory and anti-nociceptive activities of *Cheilanthes farinosa*. *J. Ethnopharmacol.*, **2006**, *108*, 462-70. doi:10.1016/j.jep.2006.06.006

[25] American Autoimmune related diseases association. https://www.aarda.org/ (Accessed May 5, 2019).

[26] Integrated chronic disease prevention and control. https://www.who.int/chp/about/integrated_cd/en/ (Accessed May 5, 2019).

[27] Lenart, N.; Brough, D.; Denes, A. Inflammasomes link vascular disease with neuroinflammation and brain disorders. *J. Cereb. Blood Flow Metab.*, **2016**, *36*, 1668-1685. doi: 10.1177/0271678X16662043

[28] Jantan, I.; Ahmad, W.; Bukhari, S.N.A. Plant-derived immunomodulators: an insight on their preclinical evaluation and clinical trials. *Front. Plant Sci.,* **2015**, *6*, 1-18. doi:10.3389/fpls.2015.00655

[29] Clark, R.A. Cutaneous tissue repair: basic biologic considerations. *I. J. Am. Acad. Dermatol.,* 1985, 13, 701-25.

[30] Stadelmann, W.K.; Digenis, A.G.; Tobin, G.R. Physiology and healing dynamics of chronic cutaneous wounds. *Am. J. Surg.*, **1998**, 176, 26S-38S.

[31] Nantel, F.; Denis, D.; Gordon, R.; Northey, A.; Cirino, M.; Metters, K.M.; Chan, C.C. Distribution and regulation of cyclooxygenase-2 in carrageenan-induced inflammation. *Br. J. Pharmacol.*, **1999**, 128, 853-859. doi:10.1038/sj.bjp.0702866

[32] DiDonato, J.A.; Mercurio, F.; Karin, M. NF-κB and the link between inflammation and cancer. *Immunol. Rev.,* **2012**, *246*, 379-400. doi:10.1111/j.1600-065X.2012.01099.x

[33] Vitiello, M.; Galdiero, M.; Finamore, E.; Galdiero, S.; Galdiero, M. NF-κB as a potential therapeutic target in microbial diseases. *Mol. Biosyst.,* **2012**, *8*, 1108-20. doi:10.1039/c2mb05335g

[34] Kopf, M.; Bachmann, M.F.; Marsland, B.J. Averting inflammation by targeting the cytokine environment. *Nat. Rev. Drug Discov.*, **2010**, *9,* 703-18. doi:10.1038/nrd2805

[35] Guzik, T.J.; Korbut, R.; Adamek-Guzik, T. Nitric oxide and superoxide in inflammation and immune regulation. *J. Physiol. Pharmacol.*, **2003**, *54*, 469-87.

[36] Zamora, R.; Vodovotz, Y.; Billiar, T.R. Inducible nitric oxide synthase and inflammatory diseases. *Mol. Med.,* **2000**, *6*, 347-73.

[37] Kim, S.R.; Jung, Y.R.; Kim, D.H.; An, H.J.; Kim, M.K.; Kim, N.D.; Chung, H.Y. Caffeic acid regulates LPS-induced NF-κB activation through NIK/IKK and c-Src/ERK signaling pathways in endothelial cells. *Arch. Pharm. Res.*, **2014**, *37*, 539-47. doi:10.1007/s12272-013-0211-6

[38] Remick, D.G.; Strieter, R.M.; Eskandari, M.K.; Nguyen, D.T.; Genord, M.A.; Raiford, C.L.; Kunkel, S.L. Role of tumor necrosis factor-alpha in lipopolysaccharide-induced pathologic alterations. *Am. J. Pathol.*, **1990**, *136*, 49-60.

[39] Hsu, H.Y.; Wen, M.H. Lipopolysaccharide-mediated reactive oxygen species and signal transduction in the regulation of interleukin-1 gene expression. *J. Biol. Chem.,* **2002**, *277*, 22131-9. doi:10.1074/jbc.M111883200

[40] Shan, J.; Fu, J.; Zhao, Z.; Kong, X.; Huang, H.; Luo, L.; Yin, Z. Chlorogenic acid inhibits lipopolysaccharide-induced cyclooxygenase-2 expression in RAW264.7 cells through suppressing NF-κB and JNK/AP-1 activation. *Int. Immunopharmacol.,* **2009,** *9*, 1042-1048. doi:10.1016/j.intimp.2009.04.011

[41] Krakauer, T. The polyphenol chlorogenic acid inhibits staphylococcal exotoxin-induced inflammatory cytokines and chemokines. *Immunopharmacol. Immunotoxicol.*, **2002**, *24*, 113-9. doi:10.1081/IPH-120003407

[42] Kang, T.Y.; Yang, H.R.; Zhang, J.; Li, D.; Lin, J.; Wang, L.; Xu, X. The studies of chlorogenic Acid antitumor mechanism by gene chip detection: the immune pathway gene expression. *J. Anal. Methods Chem.*, **2013**, 617243. doi:10.1155/2013/617243

[43] Zheng, Z.; Sheng, Y.; Lu, B.; Ji, L. The therapeutic detoxification of chlorogenic acid against acetaminophen-induced liver injury by ameliorating hepatic inflammation. *Chem. Biol. Interact.*, **2015**, *238*, 93-101. doi:10.1016/j.cbi.2015.05.023

[44] Bianchi, M.E.; Manfredi, A.A. High-mobility group box 1 (HMGB1) protein at the crossroads between innate and adaptive immunity. *Immunol. Rev.* **2007**, *220,* 35-46. doi:10.1111/j.1600-065X.2007.00574.x

[45] Lee, C.H.; Yoon, S.J.; Lee, S.M. Chlorogenic acid attenuates high mobility group box 1 (HMGB1) and enhances host defense mechanisms in murine sepsis. *Mol. Med.,* **2012**, *18*, 1437-48. doi:10.2119/molmed.2012.00279

[46] Xu, Y.; Chen, J.; Yu, X.; Tao, W.; Jiang, F.; Yin, Z.; Liu, C. Protective effects of chlorogenic acid on acute hepatotoxicity induced by lipopolysaccharide in mice. *Inflamm. Res.*, **2010,** *59*, 871-7. doi:10.1007/s00011-010-0199-z

[47] Yun, N.; Kang, J.W.; Lee, S.M. Protective effects of chlorogenic acid against ischemia/reperfusion injury in rat liver: molecular evi-

dence of its antioxidant and anti-inflammatory properties. *J. Nutr. Biochem.*, **2012**, *23*, 1249-1255. doi:10.1016/j.jnutbio.2011.06.018

[48] Chen, J.; Xie, H.; Chen, D.; Yu, B.; Mao, X.; Zheng, P.; Yu, P.; Luo, Y.; Luo, J.; He, J. Chlorogenic acid improves intestinal development *via* suppressing Mucosa inflammation and cell apoptosis in Weaned Pigs. *ACS Omega*, **2018**, *3*, 2211-2219.

[49] Ji, L.; Jiang, P.; Lu, B.; Sheng, Y.; Wang, X.; Wang, Z. Chlorogenic acid, a dietary polyphenol, protects acetaminophen-induced liver injury and its mechanism. *J. Nutr. Biochem.*, **2013**, 24, 1911-9. doi:10.1016/j.jnutbio.2013.05.007

[50] Gong, Y.; Jin, X.; Wang, Q.S.; Wei, S.H.; Hou, B.K.; Li, H.Y.; Zhang, M.N.; Li, Z.H. The involvement of high mobility group 1 cytokine and phospholipases A2 in diabetic retinopathy. *Lipids Health Dis.*, **2014**, *13*, 156. doi:10.1186/1476-511X-13-156

[51] Nogueira-Machado, J.A.; de Oliveira Volpe, C.M. HMGB-1 as a target for inflammation controlling. *Recent Pat. Endocr. Metab. Immune Drug Discov.*, **2012**, *6*, 201-9.

[52] Park, S.H.; Baek, S.I.; Yun, J.; Lee, S.; Yoon, D.Y.; Jung, J.K.; Jung, S.H.; Hwang, B.Y.; Hong, J.T.; Han, S.B.; Kim, Y. IRAK4 as a molecular target in the amelioration of innate immunity-related endotoxic shock and acute liver injury by chlorogenic acid. *J. Immunol.*, **2015**, *194*, 1122-30. doi:10.4049/jimmunol.1402101

[53] Lou, Z.; Wang, H.; Zhu, S.; Ma, C.; Wang, Z. Antibacterial activity and mechanism of action of chlorogenic acid. *J. Food Sci.*, **2011**, *76*, 398-403. doi:10.1111/j.1750-3841.2011.02213.x

[54] Shibata, H.; Sakamoto, Y.; Oka, M.; Kono, Y. Natural antioxidant, chlorogenic acid, protects against DNA breakage caused by monochloramine. *Biosci. Biotechnol. Biochem.*, **1999**, *63*, 1295-1297. doi:10.1271/bbb.63.1295

[55] Kim, J.; Lee, S.; Shim, J.; Kim, H.W.; Kim, J.; Jang, Y.J.; Yang, H.; Park, J.; Choi, S.H.; Yoon, J.H.; Lee, K.W.; Lee, H.J. Caffeinated coffee, decaffeinated coffee, and the phenolic phytochemical chlorogenic acid up-regulate NQO1 expression and prevent H_2O_2-induced apoptosis in primary cortical neurons. *Neurochem. Int.*, **2012**, *60*, 466-74. doi:10.1016/j.neuint.2012.02.004

[56] Bagdas, D.; Gul, N.Y.; Topal, A.; Tas, S.; Ozyigit, M.O.; Cinkilic, N.; Gul, Z.; Etoz, B.C.; Ziyanok, S.; Inan, S.; Turacozen, O.; Gurun, M.S. Pharmacologic overview of systemic chlorogenic acid therapy on experimental wound healing. *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **2014**, *387*, 1101-1116. DOI 10.1007/s00210-014-1034-9

[57] Domitrović, R.; Jakovac, H.; Romić, Z.; Rahelić, D.; Tadić, Z. Antifibrotic activity of *Taraxacum officinale* root in carbon tetrachloride-induced liver damage in mice. *J. Ethnopharmacol.*, **2010**, *130*, 569-77. doi:10.1016/j.jep.2010.05.046

[58] Hwang, S.J.; Kim, Y.W.; Park, Y.; Lee, H.J.; Kim, K.W. Anti-inflammatory effects of chlorogenic acid in lipopolysaccharide-stimulated RAW 264.7 cells. *Inflamm. Res.*, **2014**, *63*, 81-90. doi:10.1007/s00011-013-0674-4

[59] Shi, H.; Dong, L.; Jiang, J.; Zhao, J.; Zhao, G.; Dang, X.; Lu, X.; Jia, M. Chlorogenic acid reduces liver inflammation and fibrosis through inhibition of toll-like receptor 4 signaling pathway. *Toxicology*, **2013**, *303*, 107-14. doi:10.1016/j.tox.2012.10.025

[60] Liu, Y.; Zeng, G. Cancer and innate immune system interactions: translational potentials for cancer immunotherapy. *J. Immunother.*, **2012**, *35*, 299-308. doi:10.1097/CJI.0b013e3182518e83

[61] Osborn, O.; Olefsky, J.M. The cellular and signaling networks linking the immune system and metabolism in disease. *Nat. Med.*, **2012**, *18*, 363-74. doi:10.1038/nm.2627

[62] Chen, W.P.; Wu, L.D. Chlorogenic acid suppresses interleukin-1β-induced inflammatory mediators in human chondrocytes. *Int. J. Clin. Exp. Pathol.*, **2014**, *7*, 8797-801.

[63] Bagdas, D.; Cam, E.B.; Gul, Z.; Ozyigit, MO.; Cinkilic, N.; Inan, O. S.; Isbil B. N.; Ozluk, K.; Gurun, MS. Chlorogenic Acid enhances abdominal skin flap survival based on superficial inferior epigastric artery in nondiabetic and diabetic rats. *Ann. Plastic Surgery*, **2016**, *77*, 21-25. DOI: 10.1097/SAP.0000000000000313

[64] Jang, H.; Ahn, H.R.; Jo, H.; Kim, K.A.; Lee, E.H.; Lee, K.W.; Jung, S.H.; Lee, C.Y. Chlorogenic acid and coffee prevent hypoxia-induced retinal degeneration. *J. Agric. Food Chem.*, **2014**, *62*, 182-91. doi:10.1021/jf404285v

[65] Jang, H.; Choi, Y.; Ahn, H.R.; Jung, S.H.; Lee, C.Y. Effects of phenolic acid metabolites formed after chlorogenic acid consumption on retinal degeneration *in vivo*. *Mol. Nutr. Food Res.*, **2015**, *59*, 1918-29. doi:10.1002/mnfr.201400897

[66] Shen, W.; Qi, R.; Zhang, J.; Wang, Z.; Wang, H.; Hu, C.; Zhao, Y.; Bie, M.; Wang, Y.; Fu, Y.; Chen, M.; Lu, D. Chlorogenic acid inhibits LPS-induced microglial activation and improves survival of dopaminergic neurons. *Brain Res. Bull.*, **2012**, *8*, 487-494. doi:10.1016/j.brainresbull.2012.04.010

[67] Oboh, G.; Agunloye, O.M.; Akinyemi, A.J.; Ademiluyi, A.O.; Adefegha, S.A. Comparative study on the inhibitory effect of caffeic and chlorogenic acids on key enzymes linked to Alzheimer's disease and some pro-oxidant induced oxidative stress in rats' brain-*in vitro*. *Neurochem. Res.*, **2013**, *38*, 413-419. doi:10.1007/s11064-012-0935-6

[68] Saitou, K.; Ochiai, R.; Kozuma, K.; Sato, H.; Koikeda, T.; Osaki, N.; Katsuragi, Y. Effect of chlorogenic acids on cognitive function: A randomized, double-blind, placebo-controlled trial. *Nutrients*, **2018**, *10*, 1337.

[69] Poljsak, B.; Milisav, I. The neglected significance of "antioxidative stress". Oxidative medicine and cellular longevity, **2012**, *2012*, 1-12. https://doi.org/10.1155/2012/480895.

[70] Yordi, E.G.; Pérez, E.M.; Matos, M.J.; Villares, E.U. Antioxidant and pro-oxidant effects of polyphenolic compounds and structure-activity relationship evidence. Jaouad Bouayed and Torsten Bohn, IntechOpen, **2012**. DOI: 10.5772/29471.

[71] Sakihama, Y.; Cohen, M.F.; Grace, S.C.; Yamasaki, H. Plant phenolic antioxidant and prooxidant activities: Phenolics-induced oxidative damage mediated by metals in plants. *Toxicology*, **2002**, *177*, 67-80. doi: 10.1016/S0300-483X(02)00196-8

[72] Burgos-Morón, E.; Calderón-Montaño, J.M.; Orta, M.L.; Pastor, N.; Pérez-Guerrero, C.; Austin, C.; López-Lázaro, M. The coffee constituent chlorogenic acid induces cellular DNA damage and formation of topoisomerase I-and II-DNA complexes in cells. *J. Agric. Food Chem.*, **2012**, *60*, 7384-7391.

[73] Du, W.Y.; Chang, C.; Zhang, Y.; Liu, Y.Y.; Sun, K.; Wang, C.S.; Wang, M.X.; Liu, Y.; Wang, F.; Fan, J.Y. High-dose chlorogenic acid induces inflammation reactions and oxidative stress injury in rats without implication of mast cell degranulation. *J. Ethnopharmacol.*, **2013**, *147*, 74-83.

[74] Olthof, M.R.; Hollman, P.C.; Zock, P.L.; Katan, M.B. Consumption of high doses of chlorogenic acid, present in coffee, or of black tea increases plasma total homocysteine concentrations in humans. *Am. J. Clin. Nutr.*, **2001**, *73*, 532-538.

[75] Onakpoya, I.; Terry, R.; Ernst, E. The use of green coffee extract as a weight loss supplement: a systematic review and meta-analysis of randomised clinical trials. *Gastroenterol Res. Pract.*, **2011**, *2011*, 382852, 1-6. doi:10.1155/2011/382852

[76] Rajan, R.K.; Hussein, M.Z.; Fakurazi, S.; Yusoff, K.; Masarudin, M.J. Increased ROS scavenging and antioxidant efficiency of chlorogenic acid compound delivered *via* a chitosan nanoparticulate system for efficient *In Vitro* visualization and accumulation in human renal adenocarcinoma cells. *Int. J. Mol. Sci.*, **2019**, *20*, 4667. doi:10.3390/ijms20194667

[77] Barahuie, F.; Hussein, M.Z.; Arulselvan, P.; Fakurazi, S.; Zainal, Z. Controlled *in vitro* release of the anticancer drug chlorogenic acid using magnesium/aluminium-layered double hydroxide as a nanomatrix. *Sci. Adv. Mater.*, **2016**, *8*, 501-513.

[78] Cheng, B.C.Y.; Ma, X.Q.; Kwan, H.Y.; Tse, K.W.; Cao, H.H.; Su, T.; Shu, X.; Wu, Z.; Yu, Z. A herbal formula consisting of *Rosae Multiflorae Fructus* and *Lonicerae Japonicae Flos* inhibits inflammatory mediators in LPS-stimulated RAW 264.7 macrophages. *J. Ethnopharmacol.*, **2014**, *153*, 922-7. doi:10.1016/j.jep.2014.02.029

[79] Búfalo, M.C.; Ferreira, I.; Costa, G.; Francisco, V.; Liberal, J.; Cruz, M.T.; Lopes, M.C.; Batista, M.T.; Sforcin, J.M. Propolis and its constituent caffeic acid suppress LPS-stimulated pro-inflammatory response by blocking NF-κB and MAPK activation in macrophages. *J. Ethnopharmacol.*, **2013**, *149*, 84-92. doi:10.1016/j.jep.2013.06.004

[80] Yang, W.S.; Jeong, D.; Yi, Y.S.; Park, J.G.; Seo, H.; Moh, S.H.; Hong, S.; Cho, J.Y. IRAK1/4-targeted anti-inflammatory action of caffeic acid. *Mediators Inflamm.* **2013**, 518183. doi:10.1155/2013/518183

[81] Das, U.; Manna, K.; Sinha, M.; Datta, S.; Das, D.K.; Chakraborty, A.; Ghosh, M.; Saha, K.D.; Dey, S. Role of ferulic acid in the amelioration of ionizing radiation induced inflammation: a murine model. *PLoS One*, **2014**, *9*, e97599. doi:10.1371/journal.pone.0097599

[82] Navarrete, S.; Alarcón, M.; Palomo, I. Aqueous extract of tomato (*Solanum lycopersicum L.*) and ferulic acid reduce the expression of TNF-α and IL-1β in LPS-activated macrophages. *Molecules,* **2015**, *20*, 15319-29. doi:10.3390/molecules200815319

[83] Yun, K.J.; Koh, D.J.; Kim, S.H.; Park, S.J.; Ryu, J.H.; Kim, D.G.; Lee, J.Y.; Lee, K.T. Anti-inflammatory effects of sinapic acid through the suppression of inducible nitric oxide synthase, cyclooxygase-2, and proinflammatory cytokines expressions *via* nuclear factor-kappaB inactivation. J. *Agric. Food Chem.,* **2008**, *56*, 10265-72. doi:10.1021/jf802095g

[84] Jin, XH.; Ohgami, K.; Shiratori, K.; Suzuki, Y.; Koyama, Y.; Yoshida, K.; Ilieva, I.; Tanaka, T.; Onoe, K.; Ohno, S. Effects of blue honeysuckle (*Lonicera caerulea L.*) extract on lipopolysaccharide-induced inflammation *in vitro* and *in vivo*. *Exper. Eye Res.,* **2006**, *82*, 860-867. doi.org/10.1016/j.exer.2005.10.024

[85] Costigan, M.; Scholz, J.; Woolf, C.J. Neuropathic pain: A maladaptive response of the nervous system to damage. *Annu. Rev. Neurosci.,* **2009**, *32*, 1-32. doi:10.1146/annurev.neuro.051508.135531

[86] Price, T.J.; Cervero, F.; Gold, M.S.; Hammond, D.L.; Prescott, S.A. Chloride regulation in the pain pathway. *Brain Res. Rev.,* **2009,** *60,* 149-70. doi:10.1016/j.brainresrev.2008.12.015

[87] Woolf, C.J. Overcoming obstacles to developing new analgesics. *Nat. Med.,* **2010**, *16*, 1241-7. doi:10.1038/nm.2230

[88] Moalem, G.; Tracey, D.J. Immune and inflammatory mechanisms in neuropathic pain. *Brain Res. Rev.,* **2006**, *51*, 240-264. doi:10.1016/j.brainresrev.2005.11.004

[89] O'Neill, L.A.J. Targeting signal transduction as a strategy to treat inflammatory diseases. *Nat. Rev. Drug Discov.,* **2006,** *5*, 549-63. doi:10.1038/nrd2070

[90] Kim, H.; Song, M.J. Oral traditional plant-based therapeutic applications for pain relief recorded in North Jeolla province, Korea. *Indian J. Traditional Knowledge,* **2013**, *12, 4,* 573-584.

[91] Lim, E.Y.; Kim, J.G.; Lee, J.; Lee, C.; Shim, J.; Kim, Y.T. Analgesic effects of *Cnidium officinale* extracts on postoperative, neuropathic, and menopausal pain in rat models. *Evid. Based Complement. Alternat. Med.,* **2019**, *9698727*, 1-8. https://doi.org/10.1155/2019/9698727

[92] Pagani, E.; Santos, J.F.L.; Rodrigues, E. Culture-Bound syndromes of a Brazilian Amazon riverine population : tentative correspondence between traditional and conventional medicine terms and possible ethnopharmacological implications. *J. Ethnopharmacol.,* **2017**, *203*, 80-89. 10.1016/j.jep.2017.03.024

[93] Hamanna, F.R.; Bruscoa, I.; Severo, G.C.; Carvalho, L.M.; Faccin, H.; Gobo, L.; Oliveira, S.M.; Rubin, M.A. *Mansoa alliacea* extract presents antinociceptive effect in a chronic inflammatory pain model in mice through opioid mechanisms. *Neurochem. Intl.,* **2019**, *122,* 157-169. doi: 10.1016/j.neuint.2018.11.017

[94] Bagdas, D.; Ozboluk, H.Y.; Cinkilic, N.; Gurun, M.S. Antinociceptive effect of chlorogenic acid in rats with painful diabetic neuropathy. *J. Med. Food,* **2014**, *17*, 730-732. doi:10.1089/jmf.2013.2966

[95] Bagdas, D.; Cinkilic, N.; Ozboluk, H.Y.; Ozyigit, M.O.; Gurun, M.S. Antihyperalgesic activity of chlorogenic acid in experimental neuropathic pain. *J. Nat. Med.,* **2013**, *67*, 698-704. doi:10.1007/s11418-012-0726-z

[96] Hara, Y.; Haranishi, Y.; Kataoka, K.; Takahashi, Y.; Terada, T.; Nakamura, M.; Sata, T. Chlorogenic acid administered intrathecally alleviates mechanical and cold hyperalgesia in a rat neuropathic pain model. *Eur. J. Pharmacol.,* **2014**, *723,* 459-64. doi:10.1016/j.ejphar.2013.10.046

[97] Chauhan, P.S.; Satti, N.K.; Sharma, P.; Sharma, V.K.; Suri, K.A.; Bani, S. Differential effects of chlorogenic acid on various immunological parameters relevant to rheumatoid arthritis. *Phytother. Res.,* **2012**, *26*, 1156-65. doi:10.1002/ptr.3684

[98] Morishita, H.; Ohnishi, M. Bioactive natural products (Part F). *Stud. Nat. Prod. Chem.,* **2001**, *25*, 919-953. doi:10.1016/S1572-5995(01)80024-7

[99] Zhang, X.; Huang, H.; Yang, T.; Ye, Y.; Shan, J.; Yin, Z.; Luo, L. Chlorogenic acid protects mice against lipopolysaccharide-induced acute lung injury. *Injury,* **2010**, *41*, 746-752. doi:10.1016/j.injury.2010.02.029

[100] Bennett, G.J.; Xie, Y.K. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. *Pain,* **1988**, *33*, 87-107.

[101] Muthuraman, A.; Singh, N. Attenuating effect of Acorus calamus extract in chronic constriction injury induced neuropathic pain in rats: an evidence of anti-oxidative, anti-inflammatory, neuroprotective and calcium inhibitory effects. *BMC Complement. Altern. Med.,* **2011**, *11*, 14. doi:10.1186/1472-6882-11-24

[102] Enna, S.J.; McCarson, K.E. The role of GABA in the mediation and perception of pain. *Adv. Pharmacol.,* **2006**, *54*, 1-27. doi:10.1016/S1054-3589(06)54001-3

[103] Zeilhofer, H.U.; Benke, D.; Yevenes, G.E. Chronic pain states: pharmacological strategies to restore diminished inhibitory spinal pain control. *Annu. Rev. Pharmacol. Toxicol.,* **2012,** *52*, 111-33. doi:10.1146/annurev-pharmtox-010611-134636

[104] Hwang, J.H.; Hwang, K.S.; Kim, J.U.; Choi, I.C.; Park, P.H.; Han, S.M. The interaction between intrathecal neostigmine and GABA receptor agonists in rats with nerve ligation Injury. *Anesth. Analg.,* **2001**, *93*, 1297-303. DOI: 10.1097/00000539-200111000-00054

[105] Hwang, J.H.; Yaksh, T.L. The effect of spinal GABA receptor agonists on tactile allodynia in a surgically-induced neuropathic pain model in the rat. *Pain,* **1997**, *70*, 15-22. DOI: 10.1016/S0304-3959(96)03249-6

[106] Malan, T.P.; Mata, H.P.; Porreca, F. Spinal GABA(A) and GABA(B) receptor pharmacology in a rat model of neuropathic pain. *Anesthesiology,* **2002**, *96*, 1161-7.

[107] Zhang, A.; Gao, Y.; Zhong, X.; Xu, C.; Li, G.; Liu, S.; Lin, J.; Li, X.; Zhang, Y.; Liu, H.; Linag, S. Effect of sodium ferulate on the hyperalgesia mediated by P2X3 receptor in the neuropathic pain rats. *Brain Res.,* **2010**, *1313*, 215-221. doi:10.1016/j.brainres.2009.11.067

[108] Carrasco, C.; Naziroğlu, M.; Rodríguez, A.B.; Pariente, J.A. Neuropathic pain: Delving into the oxidative origin and the possible Implication of transient receptor potential channels. *Front. Physiol.,* **2018**, *14*, 9-95. doi: 10.3389/fphys.2018.00095. eCollection 2018.

[109] Duggett, N.A.; Griffiths, L.A.; McKenna, O.E.; de Santis, V.; Yongsanguanchai, N.; Mokori, E.B.; Flatters, S.J. Oxidative stress in the development, maintenance and resolution of paclitaxel-induced painful neuropathy. *Neuroscience,* **2016**, *333*, 13-26. doi: 10.1016/j.neuroscience.2016.06.050

[110] Gao, X.; Kim, H.K.; Chung, J.M.; Chung, K. Reactive oxygen species (ROS) are involved in enhancement of NMDA-receptor phosphorylation in animal models of pain. *Pain,* **2007**, 131, 262-271. doi:10.1016/j.pain.2007.01.011

[111] Kim, H.K.; Park, S.K.; Zhou, J.L.; Taglialatela, G.; Chung, K.; Coggeshall, R.E.; Chung, J.M. Reactive oxygen species (ROS) play an important role in a rat model of neuropathic pain. *Pain,* **2004,** 111, 116-124. doi:10.1016/j.pain.2004.06.008

[112] Park, E.S.; Gao, X.; Chung, J.M.; Chung, K. Levels of mitochondrial reactive oxygen species increase in rat neuropathic spinal dorsal horn neurons. *Neurosci. Lett.,* **2006**, *391*, 108-111. doi:10.1016/j.neulet.2005.08.055

[113] Yowtak, J.; Lee, K.Y.; Kim, H.Y.; Wang, J.; Kim, H.K.; Chung, K.; Chung, J.M. Reactive oxygen species contribute to neuropathic pain by reducing spinal GABA release. *Pain,* **2011**, *152*, 844-852. doi:10.1016/j.pain.2010.12.034

[114] Mehrotra, A.; Shanbhag, R.; Chamallamudi, M.R.; Singh, V.P.; Mudgal, J. Ameliorative effect of caffeic acid against inflammatory pain in rodents. *Eur. J. Pharmacol.,* **2011**, *666*, 80-86. doi:10.1016/j.ejphar.2011.05.039

[115] Zhang, A.; Xu, C.; Liang, S.; Gao, Y.; Li, G.; Wei, J.; Wan, F.; Liu, S.; Lin, J. Role of sodium ferulate in the nociceptive sensory facilitation of neuropathic pain injury mediated by P2X3 receptor. *Neurochem. Int.,* **2008**, *53*, 278-282. doi:10.1016/j.neuint.2008.08.008

[116] Rasband, M.N.; Park, E.W.; Vanderah, T.W.; Lai, J.; Porreca F.; Trimmer, J.S. Distinct potassium channels on pain-sensing neurons. *Proc. Natl. Acad. Sci. U. S. A.,* **2001**, *98*, 13373-8. doi:10.1073/pnas.231376298

[117] Takeda, M.; Tanimoto, T.; Ikeda, M.; Kadoi, J.; Nasu, M.; Matsumoto, S. Opioidergic modulation of excitability of rat trigeminal root ganglion neuron projections to the superficial layer of cervical dorsal horn. *Neuroscience,* **2004**, *125*, 995-1008. doi:10.1016/j.neuroscience.2004.02.029

[118] Pearce, R.J.; Duchen, M.R. Differential expression of membrane currents in dissociated mouse primary sensory neurons. *Neuroscience,* **1994**, *63*, 1041-56. doi.org/10.1016/0306-4522(94)90571-1

[119] Judge, S.; Lee, J.M.; Bever, C.T.; Hoffman, P.M. Voltage-gated potassium channels in multiple sclerosis: Overview and new implications for treatment of central nervous system inflammation and

degeneration. *J. Rehabil. Res. Dev.*, **2006**, *43*, 111-22. DOI: 10.1682/JRRD.2004.09.0116

[120] Du, X.; Gamper, N. Potassium channels in peripheral pain pathways: Expression, function and therapeutic potential. *Curr. Neuropharmacol.*, **2013**, *11*, 621-640 621.

[121] Zhang, Y.J.; Lu, X.W.; Song, N.; Kou, L.; Wu, M.K.; Liu, F.; Wang, H.; Shen, J.F. Chlorogenic acid alters the voltage-gated potassium channel currents of trigeminal ganglion neurons. *Int. J. Oral Sci.*, **2014**, *6*, 233-240. doi:10.1038/ijos.2014.58

[122] Liu, F.; Lub, X.W.; Zhang, Y.J.; Koub, L.; Songa, N.; Wua, M.K.; Wanga, M.; Wanga, H.; Shen, J.F. Effects of chlorogenic acid on voltage-gated potassium channels of trigeminal ganglion neurons in an inflammatory environment. *Brain Res. Bulletin*, **2016**, *127*, 119-125. doi: 10.1016/j.brainresbull.2016.09.005

[123] Birinyi-Strachan, L.C.; Gunning, S.J.; Lewis, R.J.; Nicholson, G.M. Block of voltage-gated potassium channels by Pacific ciguatoxin-1 contributes to increased neuronal excitability in rat sensory neurons. *Toxicol. Appl. Pharmacol.*, **2005**, *204*, 175-86. doi:10.1016/j.taap.2004.08.020

[124] Everill, B.; Kocsis, J.D. Reduction in potassium currents in identified cutaneous afferent dorsal root ganglion neurons after axotomy. *J. Neurophysiol.*, **1999**, *82*, 700-8. doi.org/10.1152/jn.1999.82.2.700

[125] Harriott, A.M.; Gold, M.S. Contribution of primary afferent channels to neuropathic pain. *Curr. Pain Headache Rep.*, **2009**, *13*, 197-207. doi: 10.1007/s11916-009-0034-9

[126] Qu, Z.W.; Liu, T.T.; Qiu, C.Y.; Li, J.D.; Hu, W.P. Inhibition of acid-sensing ion channels by chlorogenic acid in rat dorsal root ganglion neurons. *Neurosci. Lett.,* **2014**, *567*, 35-39. doi: 10.1021/acsomega.7b01971

[127] Kakita, K.; Tsubouchi, H.; Adachi, M.; Takehana, S.; Shimazu, Y.; Takeda, M. Local subcutaneous injection of chlorogenic acid inhibits the nociceptive trigeminal spinal nucleus caudalis neurons in rats. *Neurosci. Res.*, **2018,** *134,* 49-55. doi: 10.1016/j.neures.2017.11.009.

[128] Mahomoodally, M.F. Traditional medicines in Africa: an appraisal of ten potent African medicinal plants. *Evid. Based Complement. Alternat. Med.,* **2013**, Article ID, 617459, 14. doi:10.1155/2013/617459

[129] Akhtar, N.; Haqqi, T.M. Current nutraceuticals in the management of osteoarthritis: a review. *Ther. Adv. Musculoskelet. Dis.*, **2012**, *4*, 181-207. doi:10.1177/1759720X11436238

[130] Wang, M.; Li, K.; Nie, Y.; Wei, Y.; Li, X. Antirheumatoid arthritis Activities and chemical compositions of phenolic compounds-rich fraction from *Urtica atrichocaulis,* an endemic plant to China. *Evid. Based Complement. Alternat. Med.,* **2012**, 818230. doi:10.1155/2012/818230

[131] Yang, C.L.H.; Or, T.C.T.; Ho, M.H.K.; Lau, A.S.Y. Scientific basis of botanical medicine as alternative remedies for rheumatoid Arthritis. *Clin. Rev. Allergy Immunol.*, **2013**, *44*, 284-300. doi:10.1007/s12016-012-8329-8

[132] Dion, C.; Haug, C.; Guan, H.; Ripoll, C.; Spiteller, P.; Coussaert, A.; Boulet, E.; Schmidt, D.; Wei, J.; Zhou, Y.; Lamottke, K. Evaluation of the anti-inflammatory and antioxidative potential of four fern species from China intended for use as food supplements. *Nat. Prod. Commun.*, **2015**, *10*, 597-603.

[133] Sales, C.; Oliviero, F.; Spinella, P. The mediterranean diet model in inflammatory rheumatic diseases. *Reumatismo,* **2009**, *61*, 10-14. doi:10.4081/reumatismo.2009.10

[134] Setty, A.R.; Sigal, L.H. Herbal medications commonly used in the practice of rheumatology: Mechanisms of action, efficacy, and side effects. *Semin. Arthritis Rheum.*, **2005**, *34*, 773-784. doi:10.1016/j.semarthrit.2005.01.011

[135] Chen, Z.; Liao, L.; Zhang, Z.; Wu, L.; Wang, Z. Comparison of active constituents, acute toxicity, anti-nociceptive and anti-inflammatory activities of *Porana sinensis Hemsl.*, *Erycibe obtusi-*

folia Benth. and *Erycibe schmidtii Craib. J. Ethnopharmacol.*, **2013**, *150*, 501-506. doi:10.1016/j.jep.2013.08.059

[136] Hohmann, M.S.N.; Cardoso, R.D.R.; Fattori, V.; Arakawa, N.S.; Tomaz, J.C.; Lopes, N.P.; Casagrande, R.; Verri, W.A. *Hypericum perforatum* reduces paracetamol-induced hepatotoxicity and lethality in mice by modulating inflammation and oxidative stress. *Phyther. Res.,* **2015***, 29,* 1097-1101. doi:10.1002/ptr.5350

[137] Abdel-Salam, O.M.E. Anti-inflammatory, antinociceptive, and gastric effects of *Hypericum perforatum* in rats. *Sci. World J.* **2005**, *5*, 586-95. doi:10.1100/tsw.2005.78

[138] Apaydin, S.; Zeybek, U.; Ince, I.; Elgin, G.; Karamenderes, C.; Ozturk, B.; Tuglular, I. *Hypericum triquetrifolium Turra.* extract exhibits antinociceptive activity in the mouse. *J. Ethnopharmacol.*, **1999**, *67*, 307-12. doi.org/10.1016/S0378-8741(99)00071-9

[139] Bukhari, I.A.; Dar, A.; Khan, R.A. Antinociceptive activity of methanolic extracts of St. John's Wort (*Hypericum perforatum*) preparation. *Pak. J. Pharm. Sci.*, **2004,** *17,* 13-9.

[140] Subhan, F.; Khan, M.; Ibrar, M.; Nazar-ul-Islam, Khan, A.; Gilani, A.H. Antagonism of antinociceptive effect of hydro-ethanolic extract of *Hypericum perforatum Linn.* by a non selective opioid receptor antagonist, naloxone. *Pakistan J. Biol. Sci.,* **2007**, *10*, 792-6.

[141] Uchida, S.; Hirai, K.; Hatanaka, J.; Hanato, J.; Umegaki, K.; Yamada, S. Antinociceptive effects of St. John's wort, *Harpagophytum procumbens* extract and Grape seed proanthocyanidins extract in mice. *Biol. Pharm. Bull.,* **2008,** *31*, 240-5. doi.org/10.1248/bpb.31.240

[142] Viana, A.F.; Heckler, A.P.; Fenner, R.; Rates, S.M.K. Antinociceptive activity of *Hypericum caprifoliatum* and *Hypericum polyanthemum (Guttiferae). Braz. J. Med. Biol. Res.,* **2003**, *36*, 631-4.

[143] Hammer, K.D.P.; Hillwig, M.L.; Neighbors, J.D.; Sim, Y.J.; Kohut, M.L.; Wiemer, D.F.; Wurtele, E.S.; Birt, D.F. Pseudohypericin is necessary for the light-activated inhibition of prostaglandin E2 pathways by a 4 component system mimicking an Hypericum perforatum fraction. *Phytochemistry*, **2008,** *69,* 2354-2362. doi:10.1016/j.phytochem.2008.06.010

[144] Birt, D.F.; Widrlechner, M.P.; Hammer, K.D.P.; Hillwig, M.L.; Wei, J.; Kraus, G.; Murphy, P.; Mccoy, J.; Eve, S.; Neighbors, J.D.; Wiemer, D.F.; Maury, W.J.; Jason, P. Hypericum in infection: Identification of anti-viral and anti- inflammatory constituents. *Pharm. Biol.*, **2009**, *47*, 774-782. doi:10.1080/13880200902988645. Hypericum

[145] Lou, L.; Liu, Y.; Zhou, J.; Wei, Y.; Deng, J.; Dong, B.; Chai, L., Chlorogenic acid and luteolin synergistically inhibit the proliferation of interleukin-1 β -induced fibroblast-like synoviocytes through regulating the activation of NF-κB and JAK/STAT-signaling pathways. *Immunopharmacol. Immunotoxicol.*, **2015**, *3973*, 1-9. doi:10.3109/08923973.2015.1095763

[146] Agudelo-Ochoa, G.M.; Pulgarín-Zapata, I.C.; Velásquez-Rodriguez, C.M.; Duque-Ramírez, M.; Naranjo-Cano, M.; Quintero-Ortiz, M.M.; Lara-Guzmán, O.J.; Muñoz-Durango, K. Coffee consumption increases the antioxidant capacity of plasma and has no effect on the lipid profile or vascular function in healthy adults in a randomized controlled trial. *J. Nutrition*, **2016**, *146*, 524-531. https://doi.org/10.3945/jn.115.224774

[147] Corrêa, T.A.; Monteiro, M.P.; Mendes, T.M.; de Oliveira, D.M.; Rogero, M.M.; Benites, C.I.; Vinagre, C.G.; Mioto, B.M.; Tarasoutchi, D.; Tuda, V.L. Medium light and medium roast paper-filtered coffee increased antioxidant capacity in healthy volunteers: results of a randomized trial. *Plant. Foods Hum. Nutr.*, **2012**, *67*,277-82. DOI: 10.1007/s11130-012-0297-x

[148] Shimoyama, A.T.; Santin, J.R.; Machado, I.D.; de Oliveira e Silva, A.M.; de Melo, I.L.P.; Mancini-Filho, J.; Farsky, S.H.P. Antiulcerogenic activity of chlorogenic acid in different models of gastric ulcer. *Naunyn Schmiedebergs Arch. Pharmacol.,* **2013**, *386*, 5-14. doi:10.1007/s00210-012-0807-2