Review

The Role and Safety of Plant-Derived Nutraceuticals as Adjuvant Treatments for Pain Management: A Narrative Review

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Abstract

Chronic pain represents a major challenge for healthcare systems worldwide. Pharmacological agents such as opioids, gabapentinoids, and non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used depending on the pain type (nociceptive, neuropathic, or nociplastic), but their use is often limited by adverse effects. Nutraceuticals and dietary supplements have emerged as potential adjuvants to conventional pain management, offering improved safety profiles. This narrative review aims to evaluate the preliminary evidence on the efficacy and safety of selected plant-derived nutraceuticals for pain management. Particular attention is given to a new fixed nutraceutical formulation containing lycopene, sulforaphane (*Brassica oleracea*), silymarin (extracted from *Silybum marianum*), reduced glutathione, escin (*Aesculus hippocastanum*), tryptophan, and green tea (*Camellia sinensis*). Although this formulation has not yet been evaluated in clinical trials, preliminary data suggest that individual components may target different pain mechanisms. None of the currently available nutraceuticals act comprehensively on all pain types. Additionally, the inclusion of hepatoprotective compounds (e.g., glutathione and silymarin) may be advantageous for patients receiving multiple medications. Current evidence on these nutraceuticals remains limited and primarily preclinical. Further randomized controlled trials are needed to confirm their efficacy and safety in human pain management.

Keywords: chronic pain; nutrients; antioxidants; safety; interactions

1. Introduction

The International Association for the Study of Pain (IASP) defines chronic pain as "*an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage*" [1]. Chronic pain affects approximately 20% of the

population in Western countries [2] and can be classified as (i) nociceptive pain, caused by actual or potential tissue damage; (ii) neuropathic pain, resulting from disease or injury affecting the nervous system; (iii) and nociplastic pain, characterized by the absence of tissue or nerve damage but with persistent activation of the nociceptive system [3,4].

Pharmacological treatment remains central to chronic pain management. Commonly used drug classes include: (i) Opioids, which act on μ, κ, and δ opioid receptors and are prescribed for both nociceptive and neuropathic pain [5–7]; (ii) Antidepressants (e.g., amitriptyline and duloxetine), which increase serotonin and norepinephrine levels, thereby alleviating neuropathic pain and comorbid mood disturbances [8,9]; (iii) Gabapentinoids (e.g., gabapentin and pregabalin), which target the $\alpha 2\delta$ subunit of voltage-gated calcium channels to reduce neuropathic pain [10,11]; and (iv) Non-steroidal anti-inflammatory drugs (NSAIDs), which inhibit cyclooxygenase (COX)-1 and COX-2 enzymes involved in the arachidonic acid cascade, thereby decreasing prostaglandin synthesis and reducing nociceptive and inflammatory pain.

Paracetamol (acetaminophen), an atypical NSAID, exerts central antinociceptive activity via COX inhibition [12,13].

However, opioids, antidepressants, antiepileptics, and NSAIDs are all associated with significant side effects and drug–drug interactions, particularly in elderly or polytreated patients [4]. Opioids, for instance, can cause tolerance, dependence, and numerous adverse effects such as constipation and confusion [7,14]. Centrally acting agents—including gabapentin, pregabalin, and serotonin–norepinephrine reuptake inhibitors (SNRIs)—may cause dizziness and somnolence [13,15,16]. Amitriptyline interacts with H1, $\alpha 1$, and M1 receptors, leading to drowsiness, weight gain, hypotension, QT prolongation, and urinary retention [17]. Gabapentin and pregabalin require renal function monitoring due to renal elimination [16], while duloxetine can increase blood pressure and is a potent cytochrome P450 2D6 (CYP2D6) inhibitor [4,8]. NSAIDs are known for gastrointestinal, renal, and cardiovascular toxicity, and paracetamol carries a risk of hepatotoxicity [18–20].

Given these limitations, nutraceuticals may enhance pharmacological efficacy while allowing for reduced drug dosages [21,22]. Nutraceuticals are bioactive compounds derived from plants or foods, generally characterized by adjuvant health-promoting activity. The term "nutraceutical" refers to *"a food or part of a food, such as a dietary supplement, that provides medical or health benefits, including the prevention and treatment of disease."*

Although several nutraceuticals—such as palmitoylethanolamide (PEA), alpha-lipoic acid, and acetyl-L-carnitine—are already used in pain management, this narrative review focuses on a new group of compounds with potential roles in chronic pain: lycopene, sulforaphane (*Brassica oleracea*), silymarin (mainly extracted from *Silybum marianum*), reduced glutathione, escin (*Aesculus hippocastanum*), tryptophan, and green tea (*Camellia sinensis*) [23]. In particular, the nutraceitical lycopene is a carotenoid pigment found abundantly in fruits and vegetables, especially tomatoes (*Solanum lycopersicum*), but also in watermelon and apricots. It exerts antioxidant, anti-inflammatory, and anticancer effects, with potential benefits in cardiovascular diseases, cancer, benign prostatic hyperplasia (BPH), diabetes, and obesity [24,25]. Silymarin, a flavonolignan complex extracted from *Silybum marianum*, exhibits hepatoprotective, hypocholesterolemic, antioxidant, anti-inflammatory, and anti-cancer activities [26]. Reduced glutathione (GSH) has antioxidant and hepatoprotective properties, acting by converting hydrogen peroxide into water [24,27]. Escin, obtained from *Aesculus hippocastanum*, is used for blunt trauma and venous insufficiency due to its anti-edematous and anti-inflammatory properties. Its pharmacological effects depend on triterpene saponins, which display glucocorticoid-like activity that reduces pain and swelling [28]. Sulforaphane, present in cabbage, broccoli, and Brussels sprouts, has anti-inflammatory, antioxidant, and anticancer actions. Its mechanisms include inhibition of

phase I metabolic enzymes and cell-cycle arrest at the G1 and G2/M phases, contributing to its protective and antiproliferative effects [24,29]. Tryptophan is an essential amino acid that must be obtained through diet. It modulates mood, sleep, pain perception, attention, and social functioning through its role as a serotonin precursor. Altered tryptophan metabolism has been associated with chronic pain and related psychological comorbidities [30]. Green tea, derived from *Camellia sinensis*, contains polyphenols such as epigallocatechin-3-gallate (EGCG), which exert antioxidant, cardioprotective, and anticancer effects. Its mechanisms of action are diverse and include inhibition of mutagenesis, angiogenesis, genotoxicity, and cell proliferation [31,32].

Despite the commercial availability of many nutraceuticals and supplements, their clinical efficacy often remains suboptimal due to low dosages of active ingredients and the absence of randomized clinical trials.

The objective of this narrative review is to summarize the available evidence on the efficacy and safety of lycopene, escin, sulforaphane, green tea, glutathione, tryptophan, and silymarin in pain management as individual components. Furthermore, this review aims to contextualize the potential role of their combined use within the broader landscape of nutraceutical approaches to pain management.

2. Referent Scientific Databases

A comprehensive literature search was conducted in PubMed, Embase, and the Cochrane Library databases for articles published up to 17 March 2025. Additional studies were identified through a manual review of the reference lists of articles retrieved in the primary search. Titles and abstracts were screened for relevance prior to full-text evaluation. Subsequently, the reference lists of all eligible studies were examined to identify further relevant citations.

Studies were considered eligible if they included any of the following keywords: *pain*, *nutraceuticals*, *escin*, *sulforaphane*, *glutathione*, *tryptophan*, *green tea*, *silymarin*, or *lycopene*. All citations were imported into Mendeley, and duplicates were removed. After the initial screening, full-text articles were retrieved and assessed for eligibility by two independent reviewers to minimize selection bias.

Only studies meeting the inclusion criteria were incorporated into this narrative review. Articles were excluded if they: (i) were not available in full text; (ii) did not report any pain-related outcomes; or (iii) were not published in English.

3. Pharmacological Effects of Nutraceuticals on Pain

3.1. Lycopene

In an experimental model of streptozotocin-induced diabetic neuropathy, Kuhad et al. [33] demonstrated that lycopene reduces hyperalgesia by inhibiting Tumor Necrosis Factor (TNF)-α and nitric oxide (NO). The authors also suggested that cyclooxygenase-2 (COX-2) inhibition may contribute to lycopene's analgesic effects.

Zhang et al. [34] reported that repeated intrathecal administration of lycopene improved neuropathic pain in experimental models of peripheral nerve injury. In this model, TNF-α elevation associated with nerve damage downregulated connexin 43 (Cx43) in astrocytes—a protein involved in both gap-junction formation and pain transmission. Lycopene restored Cx43 expression, reversing this mechanism. Similarly, Lu et al. [35] showed that lycopene slows disc degeneration by activating Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) and reducing oxidative stress. Additionally, it protected the extracellular cartilage matrix of nucleus pulposus cells, suggesting potential benefits for cervical and low-back pain management.

Yin et al. [36], using an experimental burn injury model, observed increased mechanical pain thresholds in the dorsal horn following lycopene treatment. In this study, lycopene upregulated mammalian target of rapamycin (mTOR), glial fibrillary acidic protein (GFAP), p4EBP, and sirtuin 1 (SIRT1), while downregulating ionized calcium-binding adapter molecule 1 (Iba1). Shen et al. [37], reviewing neuropathic pain models, found that lycopene reduced cold and heat hyperalgesia and increased antioxidant defenses, including glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT). Similarly, Goel et al. [38] reported that lycopene reduced cold and thermal hyperalgesia, oxidative stress, and neurological damage, including demyelination and neuronal swelling. Hu et al. [39] confirmed that lycopene improves limb motility in animal models of neuropathic pain, likely through a reduction in oxidative stress and apoptosis.

Furthermore, lycopene exerts neuroprotective effects on microglia. Hsiao et al. [40] demonstrated that lycopene protects microglial cells stimulated with lipopolysaccharide in vitro, highlighting its potential as a powerful dietary antioxidant. However, to date, no clinical trials have evaluated lycopene for pain management in humans.

Regarding safety, lycopene is generally well tolerated, with no significant adverse effects reported in human studies [41]. Although a standardized dosage has not been established [41], rare gastrointestinal side effects, such as diarrhea, have been reported and were often associated with other factors, such as viral infections [42]. Excessive lycopene intake can cause lycopenemia, a reversible skin pigmentation [43]. Additionally, an antiplatelet effect has been observed in animal studies, but this has not been confirmed in humans [44]. Overall, studies examining lycopene alone in pain management are limited.

The proposed mechanisms of lycopene's action are summarized in Figure 1.
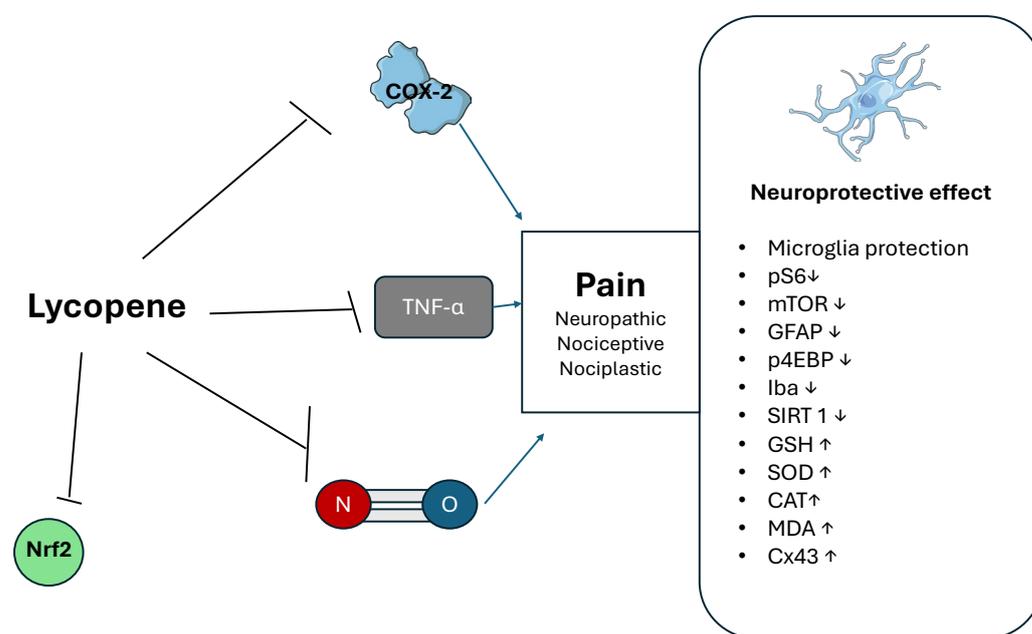
Figure 1. Mechanisms of lycopene in neuropathic pain. Although clinical evidence is lacking, lycopene has demonstrated activity in experimental models against COX-2, Nrf2, NO, and TNF-α, contributing to pain reduction. Its neuroprotective effects on microglia are mediated via multiple molecular targets. Abbreviations: CAT, catalase; Cx, connexin; COX, cyclooxygenase; GFAP, glial fibrillary acidic protein; GSH, reduced glutathione; Iba1, ionized calcium-binding adapter molecule 1; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; mTOR, mammalian target of rapamycin; NO, nitric oxide; Nrf2, nuclear factor erythroid 2–related factor 2; SIRT1, sirtuin 1; SOD, superoxide dismutase; TNF, tumor necrosis factor.
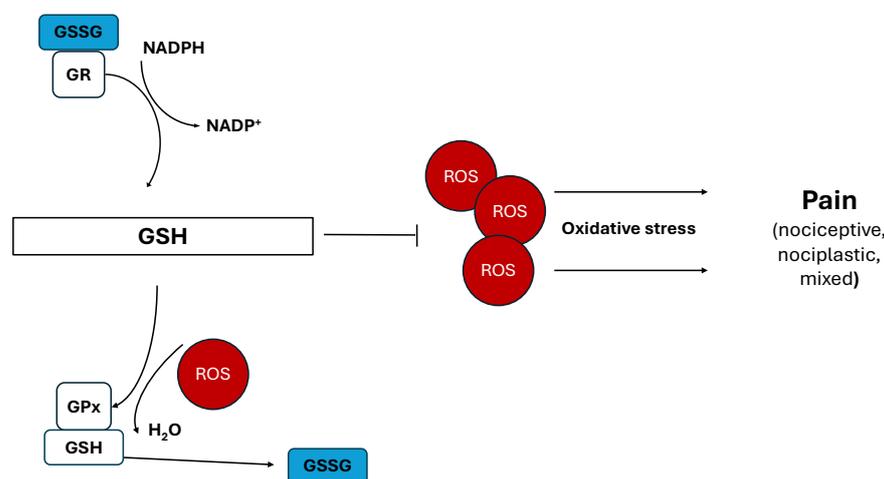
3.2. Glutathione

Despite the absence of dedicated studies on reduced glutathione and pain, experimental models of neuropathic pain have highlighted the significant role of autophagy impairment/modulation and oxidative stress [45]. Accordingly, it can be hypothesized that glutathione administration may help counteract pain associated with oxidative stress (see also the Lycopene section).

The lack of clinical trials represents a major limitation. However, Setti et al. [46] suggested that the scavenging activity of glutathione and its precursor N-acetylcysteine may mitigate the effects of reactive oxygen species (ROS) in nociceptive pain. They focused on osteoarthritis, where ROS contribute to disease progression. While some experimental studies have reported efficacy with intra-articular glutathione injections, the results remain inconclusive. Furthermore, no evidence is currently available regarding the oral administration of glutathione for pain.

Oral glutathione is generally considered a very safe compound, particularly due to its hepatoprotective properties. Clinical trials have reported no significant adverse effects associated with oral administration [47–49].

The proposed mechanisms of action for pain modulation are summarized in Figure 2.

Figure 2. Proposed mechanism of glutathione (GSH) in pain modulation. The antioxidant activity of GSH may help reduce the effects of reactive oxygen species (ROS) on multiple targets, potentially alleviating nociplastic, nociceptive and mixed pain. GSH exerts its function after being regenerated from its oxidized form (GSSG). Abbreviations: GPx, glutathione peroxidase; GR, glutathione reductase; GSH, reduced glutathione; GSSG, oxidized glutathione; H_2O, water; NADP$^+$, nicotinamide adenine dinucleotide phosphate; ROS, reactive oxygen species.
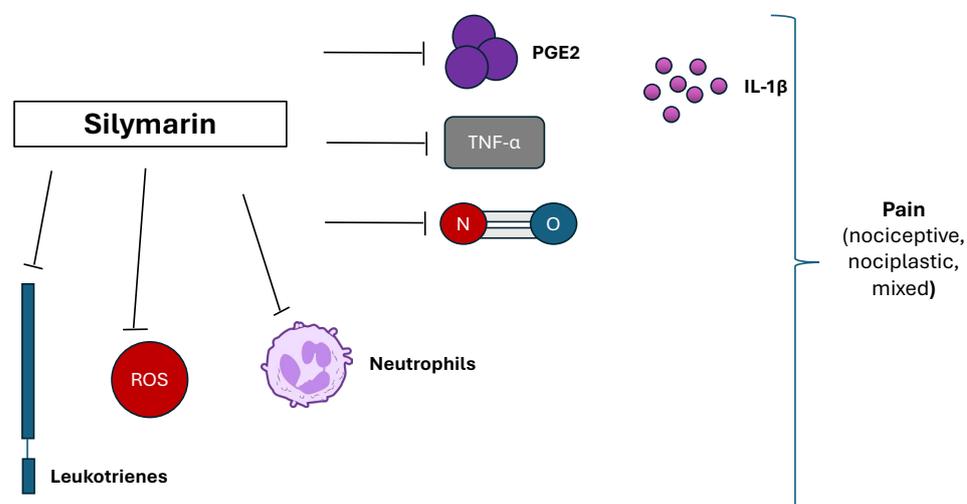
3.3. Silymarin

Only limited data are available regarding silymarin's specific effects on pain. Hassani et al. [50] demonstrated in an experimental animal model that the administration of intraperitoneal silymarin in mice prevents formalin-induced nociception through the inhibition of prostaglandin E2 (PGE2), leukotrienes, nitric oxide (NO), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α). Silymarin also acts as a scavenger, which may contribute to its beneficial properties. However, the authors reported that silymarin had no effect in experimental models of nerve injury (neuropathic pain).

In a double-arm clinical study involving 122 patients with rheumatoid arthritis, Zugravu et al. [51] evaluated silymarin as an add-on to conventional disease-modifying antirheumatic drugs. Oral administration of silymarin improved clinical outcomes, including morning stiffness, pain intensity and duration, disease activity, number of tender and sensitive joints, functional status, and mood. Notably, no significant

changes were observed in inflammatory markers, possibly due to placebo effects or a clinical–biochemical mismatch. Similarly, Elahi et al. [52] reported that a three-month treatment with silymarin (3×140 mg/day) reduced high-sensitivity C-reactive protein levels in rheumatoid arthritis patients, supporting its potential use as an adjuvant therapy.

A systematic review by Soleimani et al. [53] of 43 clinical studies concluded that silymarin is generally safe. Rare and mild side effects have been reported, including flushing, gastrointestinal disturbances, headache, irritability, hyperglycemia, muscle pain, hypercholesterolemia, heat sensation, pruritus, dysgeusia, and altered liver function tests. Most studies were conducted in patients with hepatic impairment (e.g., hepatitis, cirrhosis), and many of these symptoms are typical of such populations. In healthy volunteers, no side effects were observed. A mild inhibitory effect on cytochrome P450 enzymes (CYP2C9 and CYP3A4) has also been reported, suggesting caution when co-administered with drugs such as warfarin, a CYP2C9 substrate.

The mechanisms of action of silymarin, as identified in preclinical studies, are summarized in Figure 3.

Figure 3. Mechanism of action of silymarin. Silymarin exerts anti-inflammatory and antioxidant effects on multiple targets. By reducing inflammatory cytokines, reactive oxygen species (ROS), and modulating the arachidonic acid cascade, silymarin may help alleviate inflammation and pain. Abbreviations: NO, nitric oxide; PG, prostaglandin; ROS, reactive oxygen species; TNF, tumor necrosis factor.

3.4. Escin (Aesculus hippocastanum)

Escin exerts its antinociceptive effects through multiple mechanisms: (1) it increases glucocorticoid receptor (GR) expression, exhibiting glucocorticoid-like activity; (2) it inhibits nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and hyaluronidase, which underlies its anti-inflammatory and anti-edema effects; (3) it inhibits the bradykinin pathway and protects the endothelium from hypoxic damage by reducing reactive oxygen species (ROS), modulating platelet endothelial cell adhesion molecule-1 (PECAM-1) expression, regulating phospholipase A2, decreasing leukotriene B4, and reducing neutrophil adhesiveness [28,54,55].

Several studies have examined escin in nociceptive pain, particularly in blunt trauma [54–57]. Wetzel et al. [58] analyzed the effect of a 1% or 2% escin-containing gel in 158 patients with sports-related trauma and documented that the gel produced faster tenderness and pain reduction.

Although escin primarily affects nociceptive pain, Zhang et al. [59] investigated its efficacy in an experimental model of neuropathic pain induced by chronic constriction injury

(CCI) of the sciatic nerve. In this study, 14-day escin administration improved neuropathic pain by increasing the thermal threshold and downregulating TNF, IL-1β, toll-like receptor 4 (TLR4), NF-κB, glial fibrillary acidic protein (GFAP), and nerve growth factor (NGF). However, the lack of clinical trials in neuropathic pain remains a significant limitation.

Hu et al. [60] conducted a clinical trial involving 95 patients with neck/shoulder pain. Participants were randomized into three groups: standard management (SM), SM plus a sports cream containing escin, Harpagophytum, Boswellia, and ginger, and SM plus a diclofenac patch. The group receiving the sports cream plus SM showed significantly greater improvement in pain, stiffness, mobility, work capacity, and reduced use of additional medications.

Escin is a unique molecule and the most important in its group. In certain formulations or dosages, it is considered a drug [61]. It is commonly used for blunt trauma or venous insufficiency, either topically or orally. A systematic review by Pittler et al. [62] of 14 oral formulation trials reported that adverse events were generally mild and infrequent, including dizziness, gastrointestinal symptoms, headache, and pruritus. Oral escin may also affect renal function, particularly at high doses, and is contraindicated in patients with renal impairment [61].

The mechanisms of escin's action on pain are summarized in Figure 4.
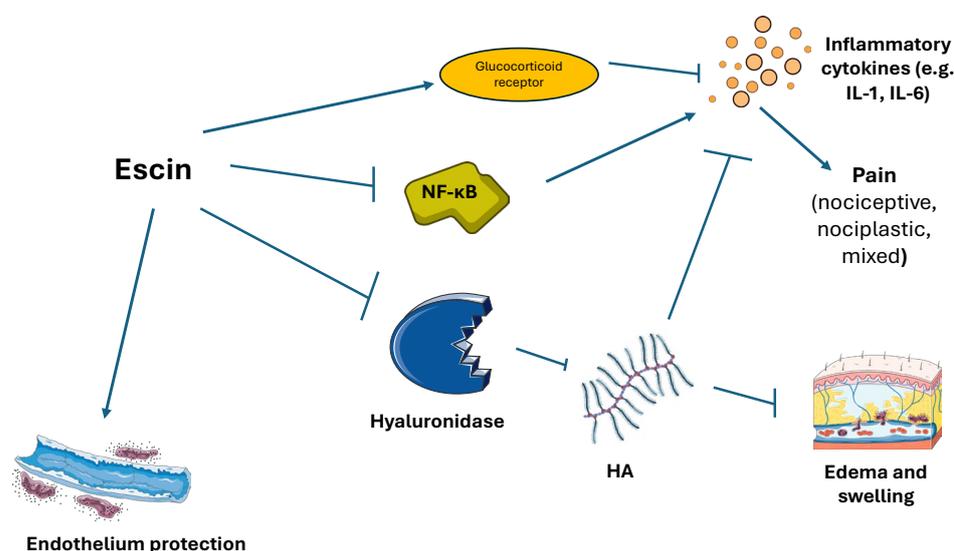
Figure 4. Mechanism of action of escin in nociceptive pain reduction. Escin exerts its effects by reducing inflammatory cytokines through glucocorticoid receptor (GR) activation or NF-κB inhibition. Additionally, it prevents edema by inhibiting hyaluronidase and the degradation of hyaluronic acid (HA). GR, glucocorticoid receptor; HA, hyaluronic acid; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells.

3.5. Tryptophan

The metabolites in the tryptophan pathway can modulate pain [63]. Damage to and dysregulation of the tryptophan–kynurenine pathway contribute to the onset and persistence of chronic pain, particularly nociplastic pain [63]. Despite this, norepinephrine, rather than serotonin (of which tryptophan is a precursor), appears to be involved in pain improvement. Accordingly, serotonin-norepinephrine reuptake inhibitors (SNRIs), rather than selective serotonin reuptake inhibitors (SSRIs), are commonly used in the treatment of neuropathic pain. However, some guidelines suggest SSRIs may be used to modulate behavioral symptoms in patients with fibromyalgia [4,64,65].

Interestingly, tryptophan metabolites, particularly 5-hydroxytryptophan (5-HTP), have been associated with erosive hand osteoarthritis and pain in the DIGICOD study of 416 patients, whereas tryptophan itself was negatively correlated with osteoarthritis [66].

Conversely, other clinical studies found no direct effect of tryptophan on pain after acute tryptophan depletion (ATD), but only on facial responses to pain [67].

King [68] reported that in five patients receiving oral tryptophan, pain symptoms and sensory deficits improved following rhizotomy and cordotomy. Schweiger et al. [69] observed that a nutraceutical containing tryptophan, vitamin D, coenzyme Q10, alpha-lipoic acid, and magnesium produced statistically significant pain improvement in patients with fibromyalgia at 1 and 3 months after starting treatment. Comparable results were reported by Rossellò-Auebach et al. [70] in 89 fibromyalgia patients receiving tryptophan, magnesium, and coenzyme Q10. Pain significantly decreased in both groups, potentially influenced by placebo effects, while sleep quality and functional impact improved only in the nutraceutical group after 3 months.

These findings suggest that tryptophan supplementation may modulate pain, particularly nociplastic pain. Tryptophan does not act directly on nociplastic pain but rather on concomitant symptoms that are integral to this condition, including behavioral alterations and sleep disturbances [24,69]. These symptoms are known to have a bidirectional relationship with pain, exacerbating its intensity [71,72].

The lack of clinical trials investigating tryptophan as a single intervention represents a significant gap in the literature.

Overall, tryptophan has a favorable safety profile. Reported side effects are generally mild and include gastrointestinal discomfort, dizziness, and tremors. However, as a serotonin precursor, tryptophan may increase the risk of serotonin syndrome when administered with other drugs affecting the serotonergic pathway [73,74].

The adjuvant effects of tryptophan on pain are summarized in Figure 5.
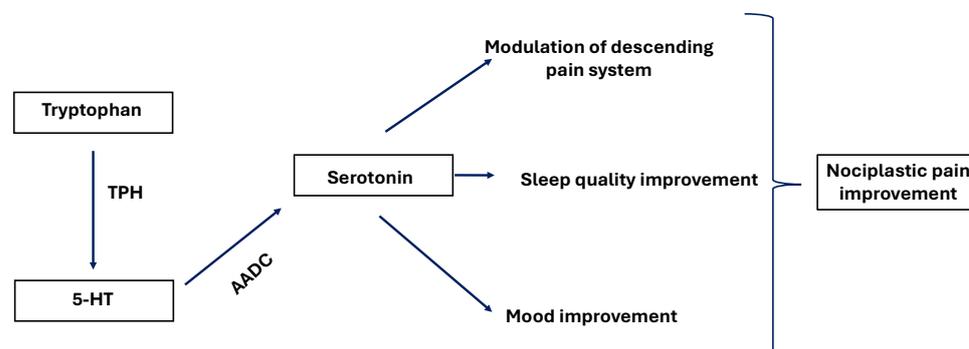
Figure 5. Adjuvant effects of tryptophan in nociplastic pain. Tryptophan does not directly act on pain, as suggested by the mixed results of clinical and preclinical studies. Instead, it appears to modulate the descending pain system. Additionally, it reduces several symptoms associated with nociplastic pain—such as insomnia and mood alterations—through its conversion to serotonin. AADC, L-amino acid decarboxylase; TPH, tryptophan hydroxylase; 5-HT, 5-hydroxytryptamine.

3.6. Green Tea (Camellia sinensis)

Green tea exhibits anti-inflammatory, antinociceptive, and antioxidant properties. Epigallocatechin-3-gallate (EGCG), the primary active component of green tea, mediates nociceptive pain relief by inhibiting the expression of genes responsible for inflammatory cytokine production. Clinical studies indicate that green tea is effective in alleviating nociceptive pain, particularly in patients with rheumatoid arthritis and osteoarthritis [75,76].

In an open-label randomized clinical trial, 50 patients with knee osteoarthritis were assigned to receive either diclofenac alone or diclofenac combined with green tea tablets [76]. Compared with diclofenac alone, the combination group showed statistically significant improvements in VAS pain scores, total WOMAC scores, and WOMAC physical function. Gastrointestinal side effects occurred in only one patient. Additionally, EGCG significantly

reduced inflammatory cytokine levels. A modest weight loss associated with green tea supplementation may provide an additional clinical benefit.

Green tea extracts have also demonstrated efficacy in topical applications for nociceptive pain, particularly when used in combination with other therapies. In our study, the combination of high-intensity pulsed electromagnetic fields (HI-PEMFs) and a topical cream containing devil's claw, green tea, and arnica significantly reduced low back pain [75]. HI-PEMFs likely enhance compound penetration, increasing therapeutic efficacy. Treatment resulted in a statistically significant reduction in NRS scores (from 7.59 ± 2.49 to 1.90 ± 2.26).

Beyond nociceptive pain, numerous experimental studies have investigated green tea in neuropathic pain models. EGCG targets several key pathways, including neuronal nitric oxide synthase (nNOS)/NO, chemokine (C-X3-C motif) ligand 1 (CX3CL1), Janus kinase (JNK), NF-κB, and TNF-α. The reduction of CX3CL1, which modulates microglia–neuron interactions, decreased thermal hyperalgesia, suggesting that EGCG acts via the nNOS/NO pathway to reduce allodynia. Moreover, hyperalgesia and pain perception are mitigated through EGCG's effects on JNK and NF-κB signaling [77].

Essmat et al. [78] evaluated 194 patients with diabetic neuropathy in a clinical trial. Pain scores, assessed using VAS and the Toronto Clinical Scoring System (TCSS), significantly improved at 8 and 16 weeks in the treatment group. Both the anti-inflammatory and hypoglycemic effects of green tea were considered important contributors to the modulation of diabetic neuropathy.

Overall, green tea extract is well tolerated. The most reported side effects in clinical trials are mild gastrointestinal symptoms, such as abdominal discomfort [79]. Very high doses may cause liver dysfunction, potentially due to pro-oxidant effects observed only at elevated intakes. The European Food Safety Authority (EFSA) recommends a daily intake limit of 800 mg/day, as higher doses can increase serum transaminases [80,81].

Green tea mechanism of action on pain modulation is summarized in Figure 6.
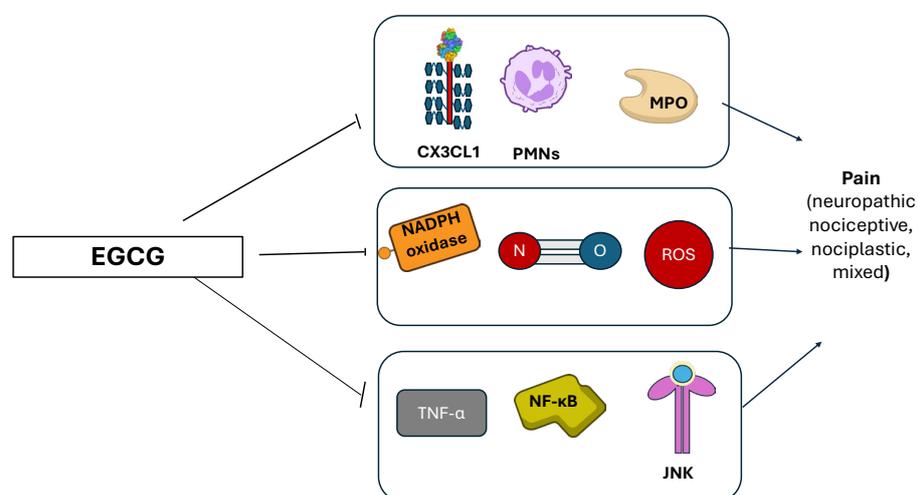
Figure 6. Mechanism of action of green tea on pain. Green tea shows stronger evidence of efficacy compared to other compounds, particularly in nociceptive pain. It inhibits or modulates multiple cytokines and proteins, reduces reactive oxygen species (ROS), and influences nitric oxide (NO) signaling. These mechanisms may contribute to nociceptive, nociplastic, neuropathic and mixed pain relief. Additionally, the modulation of adhesion molecules and polymorphonuclear leukocytes (PMNs) has been shown to reduce neuropathic pain in experimental models. CX3CL1, chemokine (C-X3-C motif) ligand 1; EGCG, epigallocatechin-3-gallate; JNK, Janus kinase; NADPH, nicotinamide adenine dinucleotide phosphate hydrogen; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; MPO, myeloperoxidase; NO, nitric oxide; PMN, polymorphonuclear leukocytes; ROS, reactive oxygen species; TNF, tumor necrosis factor.

3.7. Sulforaphane (Brassica oleracea)

Sulforaphane exhibits anti-inflammatory and antioxidant effects in experimental models, targeting key pathways including Nrf2, IL-1β, TNF-α, and calcitonin gene-related peptide (CGRP) [82].

In an animal model of chronic constriction injury (CCI)-induced neuropathic pain, Wang and Wang [83] demonstrated that intraperitoneal sulforaphane reduced inflammatory cytokines and alleviated pain and allodynia in a dose-dependent manner. The administration of naloxone attenuated sulforaphane's effects on behavioral sensitivity without altering inflammatory cytokine levels, suggesting that sulforaphane enhances μ-opioid receptor expression, likely through a selective effect on neurons rather than immune cells. Similar anti-inflammatory effects were observed in other neuropathic pain models, including diabetic neuropathy [84,85].

Redondo et al. [86] reported that sulforaphane (5–10 mg/kg) reduced inflammatory pain and enhanced morphine analgesia by preventing oxidative stress and inflammation induced by peripheral injury. These findings suggest that sulforaphane, alone or in combination with morphine, may represent a novel approach for chronic inflammatory pain management.

Lucarini et al. [87] explored sulforaphane's effects in oxaliplatin-induced neuropathic pain, showing that hydrogen sulfide (H_2S) release and potassium Kv7 channel modulation contributes to its neuroprotective and analgesic effects. Thus, sulforaphane's benefits in neuropathic pain may involve reduced ROS and inflammation as well as activation of potassium channels via H_2S signaling.

Guadarrama-Enríquez et al. [88] evaluated intraperitoneal sulforaphane in models of edema and nociceptive pain. Using the plantar test, they found that sulforaphane exerted both central and peripheral antinociceptive effects, with efficacy comparable to NSAIDs and opioids such as tramadol, ketorolac, and indomethacin. The compound inhibits multiple inflammatory mediators, including COX-2, NLRP3, IL-6, IL-1β, and NF-κB. Variations in myrosinase activity, triggered by simple chopping or chewing, influence sulforaphane bioavailability across different *Brassica oleracea* varieties.

Lu et al. [89] highlighted sulforaphane's role in delaying intervertebral disc degeneration via Nrf2 activation. Sulforaphane enhances Nrf2 nuclear translocation, increasing heme oxygenase-1 (HO-1) expression and promoting ROS clearance. Mechanisms include increased Nrf2 transcription (via reduced promoter methylation) and prevention of Keap1 binding through chemical modification of cysteine residues (mainly Cys151), reducing Nrf2 ubiquitination and degradation.

A recent experimental study by Zamora-Diaz et al. [90] demonstrated promising effects of sulforaphane in fibromyalgia, both alone and in combination with gabapentin, showing synergistic effects potentially related to shared modulation of calcium channels.

However, not all studies reported positive outcomes. In an experimental model of knee osteoarthritis, Silva Rodrigues et al. [91] found that sulforaphane reduced joint inflammation but did not alleviate pain.

Sulforaphane is frequently used as an adjuvant therapy in cancer patients. A systematic review of eight studies by ElKhalifa et al. Ref. [92] found that the most common side effects were gastrointestinal symptoms, with occasional reports of taste alteration and headache.

Across eight studies, only one patient dropped out. Of the study populations, 36 patients (44.4%) reported at least one adverse event (52.5% in the sulforaphane group vs. 36.5% in the placebo group). Most adverse events were mild (89% grade 1; 11% grade 2), with no grade 3/4 events reported. Daily oral sulforaphane at 60 mg for six months was generally well tolerated, with no statistically significant difference in reported symp-

toms compared to placebo ($p = 0.14$). Despite these findings, dosage regimens remain highly heterogeneous across studies. Sulforaphane's activity on pain is summarized in Figures 7 and 8. The mechanisms of action of all components are summarized in Table 1.
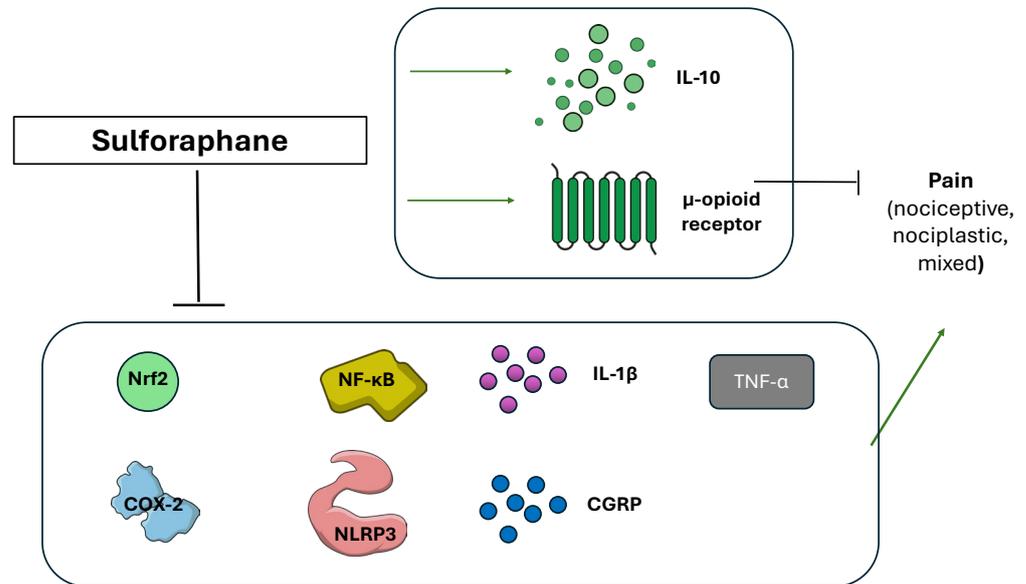
Figure 7. Sulforaphane action in nociceptive, nociplastic and mixed pain. Sulforaphane exhibits versatile effects in experimental models. It enhances IL-10 activity and opioid receptor expression, contributing to pain reduction. Additionally, it modulates or inhibits multiple inflammatory and pain mediators, resulting in overall analgesic effects. CGRP, calcitonin gene-related peptide; COX, cyclooxygenase; IL, interleukin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP, nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain-containing proteins; Nrf, nuclear factor erythroid 2–related factor protein family; TNF, tumor necrosis factor.
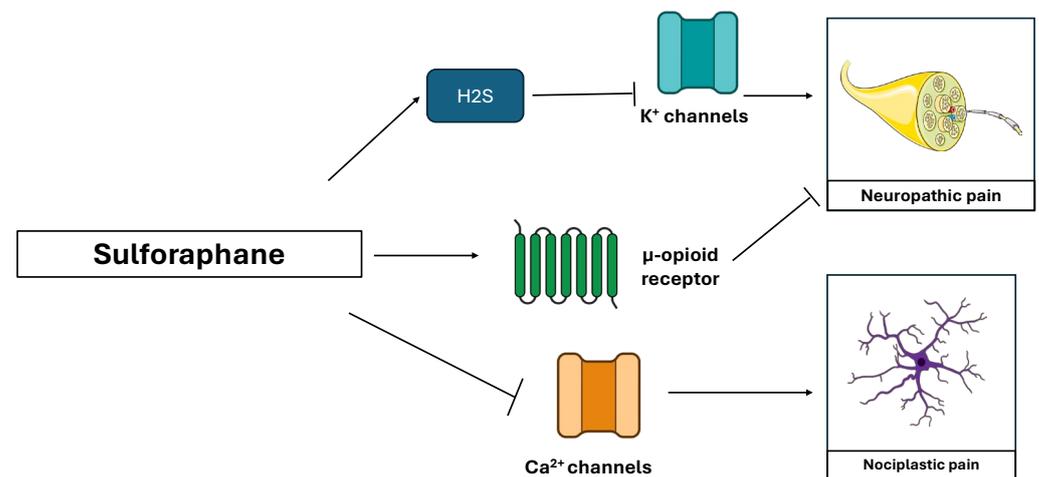
Figure 8. Sulforaphane actions in neuropathic and nociplastic pain. Evidence for sulforaphane's effects on neuropathic pain is limited. Experimental models suggest that modulation of K^+ channels and μ-opioid receptors contribute to pain relief. Ca^{2+} channels have also been proposed as a potential target, as suggested by Zamora-Diaz et al. [90]. Ca^{2+}, calcium; H_2S, hydrogen sulfide; K^+, potassium.

Table 1. Mechanism of action of each nutraceutical component.

Compound/Nutraceutical	Mechanism	References
Lycopene	TNF-α and NO inhibition.	[33]
	COX-2 inhibition	[33]
	Restoring the expression of Cx 43	[34]
	Modulation on Nrf2 and autophagy modulation	[35]
	Reduced glial activation. A decrease in the expression of markers like pS6, mTOR, GFAP, p4EBP, Iba 1 and SIRT 1.	[36]
	A reduction in thermal and cold hyperalgesia, an increase in CAT, GSH, SOD, MDA levels and signs of histopathological nerve damage, a reduction in cell apoptosis.	[37]
	Neuroprotective effect on microglia	[40]
Silymarin	Inhibition of PGE2, leukotrienes, NO, cytokines production IL 1-β and TNF-α reduction, and neutrophils infiltration. Silymarin is also a scavenger, and this may account for its beneficial properties.	[50]
Reduced glutathione	Antioxidant effects	[45]
Escin	Glucocorticoid like activity with inhibition of NF-κB and hyaluronidase	[55]
	Action on bradykinin pathway	[28]
	Antioxidant effect and endothelium protection	[54,93]
	Downregulation of TNF and IL1ß, TLR4, NF-κB, GFAP and NGF.	[59]
	Targeting of MMP9, SRC, PTGS 2, and MAPK 1, PKC, the T-cell receptors signaling pathway, TRP channels, and TNF.	[54,93]
Tryptophan	Improvement of pain related dysfunction including mood disorders and insomnia, acting on serotonin pathway.	[69]
Green tea	Inhibition of PMNs, NADPH-oxidase, myeloperoxidase, and to favor scavenging of superoxide anions.	[77]
	Inhibition of nNOS/NO; CX3CL1, JNK, and NF-κB; TNF-α.	[77]
Sulforaphane	Inhibition of Nrf 2, IL-1β, TNFα, COX-2, NLRP 3, NF-κB and CGRP	[82]
	An increase in IL-10	[88,89]
	An increase in μ opioid receptor expression	[83]
	Inhibition of the release of H2S and of potassium Kv7 channels activation	[87]

CAT, catalase; CGRP, calcitonin gene-related peptide; Cx, connexin; COX, cyclooxygenase; H2S, hydrogen sulphide; CX3CL1, chemokine (C-X3-C motif) ligand 1; GFAP, glial fibrillary acidic protein; GSH, reduced glutathione; IL, interleukin; Iba1, ionized calcium-binding adapter molecule 1; JNK, Janus Kinase; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; MMP, metalloproteinase; mTOR, mammalian target of rapamycin; NADPH, Nicotinamide Adenine Dinucleotide Phosphate Hydrogen; NGF, nerve growth factor; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP, nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing; NO, nitric oxide; NOS, nitric oxide synthase; Nrf2, Nuclear factor erythroid 2-related factor 2; PG, prostaglandin; PMN, polymorphonuclear leukocytes; PKC, protein kinase C; PTGS, prostaglandin-endoperoxide synthase; SIRT1, sirtuin 1; SOD, superoxide dismutase; SRC, Steroid Receptor Coactivator; TLR4, toll-like receptor 4; TNF, Tumor Necrosis Factor; TRP, transient receptor potential.

4. Discussion

Pain is a complex and subjective symptom, closely intertwined with lifestyle and functional impairment. Its pathogenesis is multifactorial and not yet fully understood, involving mechanisms such as inflammation, nervous system damage, and persistent sensitization [3,94,95]. Multiple treatments are available for managing this condition [96,97].

In this context, nutraceuticals may play a valuable role in reducing reliance on pharmacological interventions. The global nutraceutical market was valued at USD 712.97 billion in 2023 [98]. Patients increasingly seek safe therapeutic options due to growing apprehension about drug use and the high number of medications consumed, particularly among the elderly [99,100].

Selecting an appropriate nutraceutical for specific clinical scenarios requires clinical research comparing the efficacy of various compounds in nociceptive, nociplastic, and neuropathic pain. Similarly, an optimal pharmacological approach depends on high-quality human pharmacokinetic studies. Since nutraceuticals are subject to less stringent regulations than pharmaceuticals, they often lack robust evidence on pharmacokinetics and real-world efficacy, despite generally acceptable safety standards. Typically, regulatory bodies such as the European Food Safety Authority (EFSA) require only safety evaluations. The bioavailability, half-life, and other pharmacokinetic properties of the same compound may vary depending on the formulation. Additionally, many nutraceuticals are plant-derived and contain multiple constituents, complicating the isolation of active ingredients [101,102]. Nevertheless, the European Union provides relatively clear regulations for herbal substances and preparations, offering companies guidance for the successful development and application of herbal medicinal products. Directive 2001/83/EC of the European Parliament and Council on the Community code relating to medicinal products for human use [103] provides comprehensive definitions, assessment procedures, marketing requirements, and analytical standards for herbal medicinal products.

The nutraceuticals most commonly used for pain management include palmitoylethanolamide (PEA), an endogenous fatty acid amide and lipid modulator [104]; acetyl-l-carnitine, a neuroprotective and neurotrophic molecule, particularly effective in neuropathic pain [105,106]; and alpha-lipoic acid, a compound with antioxidant and neuroprotective effects [107,108]. All these compounds demonstrate clinical efficacy in pain modulation [105,108,109] with excellent safety profiles. However, numerous combinations of these nutraceuticals exist on the market, and no head-to-head comparisons are available. Furthermore, to our knowledge, no nutraceutical acts simultaneously on all pain types while providing hepatoprotective effects for patients undergoing polypharmacy.

Due to its antioxidant, anti-inflammatory, neuroprotective, and hepatoprotective properties, a novel formulation containing silymarin, green tea, tryptophan, escin, lycopene, sulforaphane, and reduced glutathione may offer therapeutic benefits for patients receiving multiple treatments [26,27]. Tryptophan may additionally modulate mood and sleep, providing a broader spectrum of clinical benefits [24]. The inclusion of compounds with well-established efficacy, such as escin, green tea, and silymarin, further supports the potential reliability of this co-formulation.

Evidence summarized in this narrative review suggests that these seven substances may reduce inflammation and oxidative stress (with stronger evidence for escin and green tea for inflammation and glutathione for oxidative stress), potentially modulating both innate and adaptive immune responses and decreasing apoptosis [31,55,110]. This indicates possible synergistic or additive effects that require confirmation through preclinical and clinical studies of the combined formulation. These compounds may enhance the effects of conventional pain medications, potentially allowing dosage reductions. For example, sulforaphane may increase μ-opioid receptor expression [88], potentially mitigating drug tolerance, a major concern in opioid therapy [111]. Nevertheless, these effects require validation in well-designed clinical studies.

Currently, limited clinical evidence exists on the effects of the seven components in neuropathic pain, although preclinical data provides a rationale for their use [37]. The combination may also be beneficial in nociplastic and neuropathic pain, considering lycopene's

role in modulating microglia [40,112–114]. Evidence remains limited, with only preclinical studies for escin, lycopene, and sulforaphane, and one clinical trial for green tea. Data for nociplastic pain are even scarcer, with two clinical trials on tryptophan and a preclinical study on sulforaphane. Should these findings be confirmed in larger clinical trials, this novel nutraceutical could become a valuable adjuvant for multiple pain types.

We chose to investigate this combination because: (1) no similar formulation currently exists on the market; (2) the compounds may act additively or synergistically across all pain types; and (3) the individual components have favorable safety profiles. Despite the promising potential, further research is required to optimize the nutraceutical's efficacy in pain management. Clinical trials addressing nociceptive, neuropathic, and nociplastic pain are necessary to establish the effectiveness of the combined formulation, while safety studies must confirm the favorable profile observed for individual components. This narrative review suggests that a nutraceutical containing sulforaphane, green tea, glutathione, escin, lycopene, silymarin, and tryptophan may serve as an effective adjuvant in pain management due to the potential synergistic or additive actions of its constituents. The hepatoprotective effects of silymarin and glutathione may further reduce the risk of liver injury. However, preclinical or clinical studies evaluating the concurrent administration of these compounds as a single formulation are lacking, highlighting a critical gap for future research.

5. Conclusions

Pain is a complex, multifactorial condition that often requires a multimodal therapeutic approach. In this context, nutraceuticals represent a promising adjunct to conventional pharmacological treatments, particularly given their favorable safety profiles and potential to target various pain mechanisms, including nociceptive, neuropathic, and nociplastic pathways. The compounds discussed—silymarin, green tea extract, tryptophan, escin, lycopene, sulforaphane, and glutathione—exhibit (in preclinical or clinical studies) varying degrees of antioxidant, anti-inflammatory, neuroprotective, and hepatoprotective properties, suggesting that their combined use may enhance therapeutic efficacy while reducing dependence on conventional drugs.

Despite encouraging preclinical and limited clinical data, robust evidence from well-designed human trials is still lacking. Moreover, variability in nutraceutical formulations, bioavailability, and pharmacokinetics emphasizes the need for rigorous quality control and regulatory oversight. The regulatory framework established in the European Union, particularly under Directive 2001/83/EC, provides a comprehensive model for the safe development and evaluation of herbal medicinal products. Nonetheless, global harmonization and improved methodological standards in clinical research are essential to fully determine the efficacy, safety, and therapeutic role of these compounds in pain management. Should future clinical trials confirm the promising preclinical findings, this nutraceutical combination could become a valuable adjuvant in the comprehensive management of pain across diverse patient populations.

6. Patents

IT202300005970A1 Drolessano: Preparato energizzante, antiossidante e detossificante ad uso orale a base di licopene Broccoli, Cardo mariano, glutatione ridotto, ippocastano, teina e triptofano.

Author Contributions: Conceptualization, G.M., L.G. and S.S.; methodology, G.M. and V.R.; software, G.M. and C.V.; validation, M.C., M.E. and M.C.C.; formal analysis, D.M.A.-G.; resources, L.G.; data curation, C.P.; writing—original draft preparation, G.M.; writing—review and editing, L.G. and S.S.;

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