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Review article

Does diet play a role in reducing nociception related to inflammation and chronic pain?

Geir Bjørklund [a,*], Jan Aaseth M.D., Ph.D. [b,c], Monica Daniela Doşa M.D., Ph.D. [d], Lyudmila Pivina M.D., Ph.D. [e,f], Maryam Dadar D.V.M., Ph.D. [g], Joeri J. Pen M.D., Ph.D. [h,i], Salvatore Chirumbolo Ph.D. [j,k]

[a] Council for Nutritional and Environmental Medicine (CONEM), Mo i Rana, Norway
[b] Research Department, Innlandet Hospital Trust, Brumunddal, Norway
[c] Faculty of Health and Social Science, Inland Norway University of Applied Sciences, Elverum, Norway
[d] Department of Pharmacology, Faculty of Medicine, Ovidius University, Constanta, Romania
[e] Semey Medical University, Semey, Kazakhstan
[f] CONEM Kazakhstan Environmental Health and Safety Research Group, Semey Medical University, Semey, Kazakhstan
[g] Razi Vaccine and Serum Research Institute, Agricultural Research, Education and Extension Organization (AREEO), Karaj, Iran
[h] Diabetes Clinic, Department of Internal Medicine, UZ Brussel, Vrije Universiteit Brussel (VUB), Brussels, Belgium
[i] Department of Nutrition, UZ Brussel, Vrije Universiteit Brussel (VUB), Brussels, Belgium
[j] Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy
[k] CONEM Scientific Secretary, Verona, Italy

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ABSTRACT

Dietary habits are fundamental issues to assess when modulating health and well-being; however, different nutritional panels may help individuals prevent acute and chronic pain. Many substances, known to be active antioxidants and anti-inflammatory compounds, should serve this fundamental task. Antinociceptive and analgesic natural compounds include flavonoids, terumbone from ginger root, curcuminoids, ω-3 polyunsaturated fatty acids, and taurine. Furthermore, correct intake of trace elements and minerals is strategic to reduce inflammation-related pain. This review addresses these items in an effort to suggest new criteria for proper dietary supplementation to prevent pain.

Introduction

The ability of the human daily diet to modulate pain onset and peripheral algesic sensitivity has recently come into the spotlight as physicians are paying increased attention to patient lifestyle, in an effort to better prevent ailments and illnesses, including the onset of chronic pain, a major cause of medical intervention, health care costs, and ambulatory counseling [1–3]. The International Association for the Study of Pain, which defined *pain* as an unpleasant feeling or an emotional experience associated with actual or potential tissue damage, is revising the traditional pain concept to better fit with the patient's own experience [4,5]. This may generate equivocal opinions about the need for a dietary advisory consensus to reduce chronic pain and to diminish recurrent medical counseling and caregiving, despite many local and global differences in nutritional habits and food supply [6]. Regardless of definitions, a growing bulk of evidence reports the fundamental role of unhealthy dietary habits and lifestyles in inducing the onset and perception of pain, thus causing an increasing number of patients returning for medical assistance [7–10].

The association between diet and the reduction of inflammation-induced nociception remains a puzzle. At least in laboratory animals, calorie restriction dampened pain caused by nerve injury from inflammation, but this effect was interestingly reversed by the inhibition of the silent information regulator 1, which is neuroprotective [11,12]. Impairments in metabolism, nutritional excess, and incorrect

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* Corresponding author: Tel.: +47 952 55 484.
E-mail address: Bjorklund@conem.org (G. Bjørklund).

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lifestyle leading to obesity may increase the nociceptive activation in the trigeminal system [13], yet obesity also may be characterized by the activation of the AMP kinase, which interestingly reduces nociception induced by inflammation [14,15]. An apparent controversial landscape characterizes the research about diet and nociception, probably because of the huge complexity of the many mechanisms and signaling pathways involved. The same promising role attributed to natural polyphenols should be reappraised in this perspective. The anti-inflammatory role of polyphenols is well recognized [16]. For example, the intake of dietary capsaicin from chili peppers has been associated with nociception reduction, probably mediated by somatostatin and opioid receptors; yet, capsaicin seems to mediate the role of the neuropeptide galanin, which is involved in the peripheral transmission of nociception [17–20]. Therefore, the feasibility of a dietary habit for reduction of pain and nociception, often caused by an inflammatory response, still represents an intriguing matter of debate because the ability to treat pain with natural products is a complex task.

Furthermore, chronic pain, such as back pain or chronic inflammatory-derived nociception, is a public health concern in most countries. According to the World Health Organization, ~5.5 billion people live in countries that lack opiate analgesics, besides lacking a healthy dietary intake [21]. Tens of millions of people in these countries suffer from pain every year without receiving proper treatment. This includes 1 million individuals with terminal HIV/AIDS; 5.5 million with terminal cancer; 0.8 million with injuries and chronic diseases, patients recovering from various surgeries, and women in labor (110 million annually) [22]. In addition to the many physical and emotional burdens, pain carries exorbitant financial costs for society. Conditions characterized by chronic pain, such as musculoskeletal diseases and headache, occupy 5 of the 10 leading causes of disability [23]. The total annual cost of chronic pain in Europe is about 1.5% to 3% of the gross domestic product [24–26], a burden that is greater than the estimated cost of cardiovascular diseases, cancer, or diabetes mellitus [27]. Common risk factors contributing to the development of chronic pain are female sex, older age, low socioeconomic or employment status, occupational factors, anamnesis of substance abuse, and violent interpersonal relations [28]. In recent years, attempts have been made to study how chronic pain is related to genetics, epigenetics, and environmental factors [29]. An unbalanced diet, plant product–enriched dietary habits, and foods containing large amounts of refined carbohydrates and ω-3 fatty acids have been considered fundamental nonpharmacologic factors that affect the development and severity of the pain syndrome [30–33].

Despite the growing bulk of data, a close relationship between pain and diet cannot be fully assessed unless a thorough general survey on the population's lifestyle, dietary habits, and incidence of chronic pain is implemented. Actually, the majority of studies about the preventive and healing activity of some dietary nutrients against neurogenic and inflammation-related pain is anecdotal, with few evidence-based papers [34–37], including some negative results [37,38].

The outcome of numerous studies has shown that pain is related to various conditions, such as alterations in nociceptive sensitivity and inflammatory disorders. Nutritional supplements containing ω-3 polyunsaturated fatty acids (PUFAs), vitamin D, taurine, selenium, magnesium, zinc, flavonoids, zerumbone, and curcumin, in addition to balanced exercise, can significantly enhance the analgesic effect of standard therapy regimens for conditions accompanied by chronic pain.

Research on the ability of defined dietary habits to reduce pain and nociception caused by inflammation is particularly complex. With the preliminary purpose to elucidate the existence of possible associations between diet and pain, the present review evaluated different dietary and lifestyle habits to obtain insights about a promising strategy to alleviate a variety of clinical inflammatory pain syndromes.

Insights on the role of the gut microbiome–brain axis and metabolism in the relationship between pain and diet

Short-chain fatty acids

Nutrients meet the gut microbiota initially before being absorbed as bioactive products. Therefore, any issue regarding the relationship between diet and pain is closely related to the gut microbiome (GM). Simple constipation may be associated with GM dysbiosis or functional impairments in the intestinal microflora but, interestingly, this condition may exacerbate chronic pain in several body regions as an indirect effect of an enteric neurochemical disorder [38–40]. The role of the gut microbiome–brain axis (GMBA) in metabolism and inflammation is crucial [41,42]. This suggests that a defined dietary intake may elicit a complex modulation in the interplay between metabolism and the GMBA/immune system cross-talk [43]. In this sense, some bioactive lipids such as the *N*-acylethanolamine (NAE) family, of which members are palmitoylethanolamide, *N*-arachidonoylethanolamine, oleoilethanolamide, and short-chain fatty acids (SCFAs) such as butyrate, are retrieved as fundamental modulators of this interplay [44,45]. NAEs are endogenous mediators of widespread chronic pain, particularly during acute tissue traumas [46]. In high-fat fed (HFD) experimental rats, a good functional GM, containing bacteria such as *Coprococcus, Faecalibacterium, Roseburia,* and *Eubacterium* can convert excesses of acetate from the HFD into butyrate [47]. In this sense, SCFAs are important mediators of pain, fundamentally because they modulate inflammation [48]. Acetate, propionate, and butyrate are SCFAs considered to be anti-inflammatory mediators produced by dietary fibers from GM, endogenous ligands of the orphan G protein-coupled receptors GPR41 and GPR43, which can tune the inflammatory response to pain [48–50]. A diet enriched in plant-derived fibers such as *Psyllium* may alleviate pain in irritable bowel syndrome (IBS) via the GM-released SCFAs [51]. The role of SCFAs as either algesic or analgesic substances is still a current matter of debate [52]. Butyrate is produced by fermentation of dietary fibers in the colon, but there is some debate regarding its analgesic use, particularly for IBS [52].

However, SCFAs as acetate and propionate are considered anti-inflammatory mediators [53]. Furthermore, butyrate is reported to reduce the mortality rate substantially in lipopolysaccharide-induced septic shock in mice by increasing the expression and release of interleukin (IL)-10, thereby dampening inflammation [54]. The intake of dietary fibers is fundamental to reducing the risk for abdominal and musculoarticular pain [55–58], presumably owing to SCFAs acting as mediators and immunomodulators [59–62].

Polyamines

Polyamines such as spermidine, spermine, and putrescine are currently considered promising antinociceptive substances, and many of them are naturally present in legumes such as beans or soybeans, in cereals and mushrooms, and in algae [63–65]. Fundamentally, they are endogenous regulators of the ion channels vanilloid receptor 1 (TRPV1), acid-sensitive receptors and glutamatergic receptors, both AMPA/kainate and *N*-methyl-D-aspartic acid (NMDA) receptors.

For these reasons, polyamines are mediators of nociception, mainly via TRPV1 stimulation [66]. Although polyamines are potent inhibitors of neural inducible nitric oxide synthase (iNOS), the role of nitric oxide (NO) in neurogenic pain and inflammation

is quite controversial owing to its functional duality in dynorphin spinal neurotoxicity [67]. However, polyamines are considered potent antinociceptive compounds, particularly at high doses [68]. Gut microbiota produces polyamines. Therefore, GMBA can modulate nociception transmission via polyamine-production [69]. The role of GMBA and polyamines, also entering with diet, represents a major issue in preventing nociception and reduce pain, thus needing further insightful research [70,71]. Polyamines are a good example of the complexity with which such ubiquitous molecules are involved in an increase in pain phenomena despite the ability to dampen nociception in certain complex conditions. For example, polyamines target the NMDA receptor [72,73]. In this context, polyamine-deficient diets are dietary and therapeutic tools against pain [74].

PUFAs

Long-term dietary intake of ω-3 PUFAs is considered particularly effective in modifying the human gut microbiota, by decreasing the presence of *Faecalibacterium* and increasing *Bacteroidetes* and butyrate-producing bacteria of the *Lachnospiraceae* family [75]. Puzzling cross-talk between body fatty acids and GM seems to regulate the activity of ω-3 PUFAs in the intestinal microenvironment, allowing the induction of changes in the GM composition and a final anti-inflammatory response [76]. Diets containing linoleic and linolenic acid (LA) are strategic for modulating pain and itchy skin [77]. From diet-derived PUFAs, inflamed skin contains many immunomodulators, such as 11-hydroxy-epoxy- or 11-keto-epoxy-octadecenoate LA derivatives, in addition to four previously identified 9- or 13-hydroxy-epoxy- or 9- or 13-keto-epoxy-octadecenoate LA derivatives [77]. In patients with rotator cuff–related shoulder pain, a modest therapeutic effect was observed by administering dietary ω-3 PUFAs [78,79].

Various PUFAs will provide a wide series of different prostaglandins, which can participate in the peripheral anti-inflammatory mechanisms [80,81]. The role of PUFAs in GM homeostasis is crucial, suggesting that a proper intake of ω-3-PUFAs, with an adequate ratio of ω-6 to ω-3, may be strategic in ensuring the correct GM homeostasis and its relationship with the anti-inflammatory and antinociceptive role of PUFAs [82,83]. Intake of ω-3 PUFAs appears particularly suitable in reducing joint pain in several inflammatory conditions [84]. The ability of ω-3 PUFAs to prevent chronic pain, particularly during dysmenorrhea, has been extensively reviewed [85–89].

The majority of pain syndromes is related to inflammation [90], and interestingly, the human GM, which is directly modulated by daily diet, is considered a master tuner of the onset and development of neurogenic pain and inflammation [45,91,92]. Pain sensing in the nervous system could be induced by inflammation, initiated by tissue injury and a cascade of biochemical reactions [93]. This evidence should suggest that a fundamental dietary habit, able to prevent or reduce pain, is mostly represented by anti-inflammatory or immunomodulatory natural molecules.

Diet and inflammation pain

Anti-inflammatory and antinociceptive molecules present in the diet

Polyphenols and phenolic acids: Role of inflammation and transient receptor potential channels

Plant-derived polyphenols are widely acknowledged substances able to modulate inflammation and act as anti-inflammatory substances [94–96]. A dietary regimen containing plant-derived flavonoids may be suggested as adjuvant therapy in IBS [97,98]. At least in experimental laboratory rodents, 5 to 100 mg/kg oral caffeic acid (3,4 dihydroxycinnamic acid) exhibited an analgesic activity comparable to oral nimesulide (4 mg/kg) in reducing peripheral algesic effects in mice and rats [99]. Caffeic acid present in red wine, plums, berries, and particularly in spices, is a well-known antioxidant molecule [100] and is present in a synergistic form with further phenolic acids (*p-coumaric* acid, ferulic acid, caffeic acid phenetyl ester [CAPE]) and flavonoids. In its more active form, CAPE, the compound can alleviate neuropathic pain by inhibiting the p38/nuclear factor (NF)-κB in microglia, thereby exerting an anti-inflammatory action and dampening the production of the proinflammatory cytokines tumor necrosis factor (TNF)-α, IL-6 and IL-1β [101]. Experimental animal models of acute gouty arthritis showed that *p*-coumaric acid, acting as an anti-inflammatory molecule, reduced the inflammation caused by monosodium urate crystals in rats [102]. Dimers ferulic acid were recently synthesized and showed a powerful analgesic effect; they exhibited a powerful non-opioid antinociceptive action that was mediated predominantly through the adenosine 3 receptor [103].

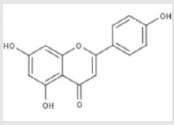
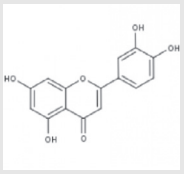
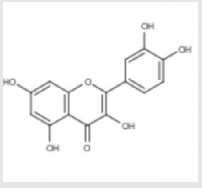
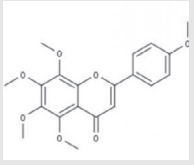
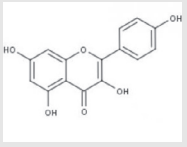
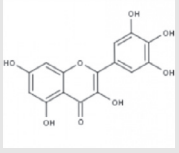
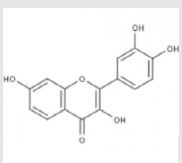
The antinociceptive effect exerted by natural phenolics may not necessarily involve an anti-inflammatory mechanism. The flavonol myricitrin acts as an antinociceptive molecule by affecting the nitric oxide/L-arginine pathway and the protein kinase C (PKC) pathway, and its effect is not inhibited by an opioid antagonist such as naloxone. Evidence suggests that this flavonoid exerts an analgesic action by targeting specific chemical or mechanical pathways of pain [104]. The flavonoid zerumbone, found in wild ginger, showed an analgesic effect by targeting the biochemical NO pathway in the same manner as myricitrin, the 3-O-α-L-rhamnopyranoside of myricetin. More precisely, these compounds are found to affect the L-arginine-NO-cGMP-PKC-K^+ATP channel pathways and the TRPV1 and kinin B2 receptors [105]. Table 1 summarizes the antinociceptive effects of the most common flavonoids found in fruits, vegetables, and plant-derived juices [106–124].

Fundamentally, at least three main ways can be outlined to describe the antinociceptive and analgesic effects of plant-derived flavonoids:

1. Inhibiting the inflammatory signal and modulating the cyclooxygenase (COX)-2 activity;
2. Targeting the L-arginine/NO signaling (chemical way);
3. Interacting with neuromodulating pathways, including the γ-aminobutyric acid (GABA) receptor signaling and the opiate receptors.

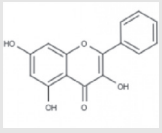
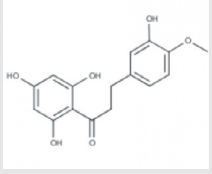
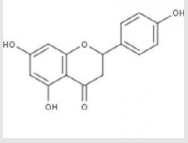
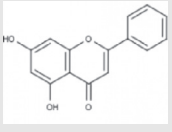
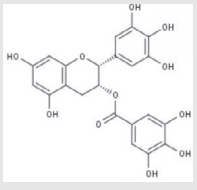
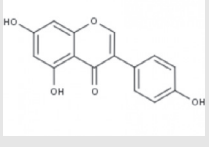
The most common way by which polyphenols inhibit pain is through their anti-inflammatory potential. Dietary flavonoids, usually contained in red wine, berries, green tea, soy, and *Zingiberaceae* family (zerumbone and curcumin), are potent anti-inflammatory and antinociceptive molecules [125,126]. In a randomized, double-blind crossover trial, daily intake of 50 g of strawberries, which are known to contain catechin, epicatechin, quercetin, kaempferol, and ellagic acid, ameliorated osteoarthritis-related knee pain by fundamentally reducing the release of proinflammatory cytokines IL-6, TNF-α, and IL-1β [127]. Similar evidence was also reported for blueberries [128]. Furthermore, many other flavonoids exert an analgesic potential by also targeting the vanilloid receptor. For example, the flavonoid hesperidin methyl chalcone reduced pain in a male Swiss mice model having induced writhing with acetic acid and phenyl-*p*-benzoquinone and paw flinching and licking by capsaicin and formalin. The analgesic effect involved both an anti-inflammatory action toward some cytokines (IL-6, TNF-α, IL-1β) with the NF-κB activation and targeting TRPV1 [129]. The activation of TRPV1 in nociceptive neurons is fundamental to “feel” pain

Table 1
Some antinociceptive and analgesic effects of the most representatives natural flavonoids contained in the human daily diet

Flavonoid	Effect		Type of study	References
		mechanism of action		
Apigenin 	↓	Pain in the hot plate test and writhing test in mice and tail-immersion tests and carrageenan-induced paw edema and cotton pellet-induced granuloma formation in rats Inhibition of PDGE2 via COX-2	Laboratory animals	[106]
Luteolin 	↓ ↑	Chronic and acute induced neuropathic pain In association with 1 mg/kg body weight morphine increases its antinociceptive effect (synergism with morphine) Anti-inflammatory effect. Blockage of norepinephrine and serotonin reuptake. Modulation of opioid receptors	Laboratory animals	[107]
Quercetin 	↓	Pain in a dose-related antinociceptive activity in chemical pain, via the L-arginine-nitric oxide, serotonin, and GABAergic systems Rheumatoid arthritis in women, reduction of pain Inhibition of the NO pathway-Modulation of GABA receptors	Laboratory animals Double-blind, randomized controlled trial	[108,109]
Tangeritin 	↑	Binding to μ- and δ-opioid receptors, via the xanthomicrol precursor Antinociceptive activity by modulation of opioid receptors	In silico and in vivo studies	[110]
Kaempferol 	↓	Pain from ethanol/HCl and aspirin pain-induced gastritis in mice Anti-inflammatory activity targeting NF-κB and AP-1	Laboratory animals	[111]
Myricetin 	↓	Pain in carrageenan-induced paw edema via the L-arginine/NO system (as myricitrin) Neuropathic pain in rats Inhibition of the iNOS/NO pathway	Laboratory animals	[112,113]
Fisetin 	↓	Diabetic neuropathic pain, targeting oxidative stress and $GABA_A$ receptors, causing regulation in allodynia and hyperalgesia Anti-inflammatory and antioxidant activity on a mitochondria-ER relationship. Modulation of GABA receptors	Laboratory animals	[114,115]

(*continued*)

Table 1 (*Continued*)

Flavonoid	Effect	mechanism of action	Type of study	References
Galangin 	↑	Protection of synoviocytes via the suppression of the NF-κB/NLRP3 pathway Anti-inflammatory activity targeting the inflammasome	In vitro studies	[116]
Hesperetin 	↓	Neuropathic pain-sciatic nerve Reduction of mechanical and thermal hyperalgesia, inhibition of the NF-κB signaling and cytokine expression	Rat model of PSNL	[117]
Naringenin 	↓	Inflammatory pain Osteoarthritis-derived pain Inhibition of the p38 MAPK/ERK signaling and consequent reduction of NF-κB activity	Laboratory animal models	[118,119]
Chrysin 	↓	Inflammation-derived pain Inhibition of the NF-κB–induced inflammation	Laboratory animal models	[120]
Epigallocatechin-3-gallate 	↓	Neuropathic pain Bone cancer pain Modulation of opioid receptor Activity on the estrogen receptors β	Clinics-Nutritional Mice models	[121 to 123]
Genistein 	↓	Neuropathic pain-sciatic nerve Modulation of the serotoninergic and GABAergic signaling	Rat model of PSNL	[124]

↓, inhibition; ↑, promotion or activation; COX, cyclooxygenase; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; GABA, γ-aminobutyric acid; iNOS, inducible nitric oxide synthase; MAPK, mitogen-activated protein kinase; NF, nuclear factor; NO, nitric oxide; PDG, prostaglandin; PSNL, partial sciatic nerve ligation.

because TRPV1, expressed in these neurons, activates the release of neuropeptides and neuromodulators, which are perceived, via the action potentials, as pain by higher central nervous system areas [130]. Because TRPV1 antagonists are fundamental to dampen hyperalgesia [131], the TRPV1-related mechanism of modulating pain by flavonoids is a further functional pathway of the antinociceptive action of phenolic substances from the diet. For example, quercetin improves paclitaxel-induced neuropathic pain in experimental rats by dose-dependently inhibiting the expression of PKC-ε and TRPV1 in spinal cords and dorsal root ganglions [132].

Furthermore, mitochondrial function impairments, with subsequent oxidative stress and exacerbated reactive oxygen species (ROS) production, led to the inflammasome activation and to an inflammatory response. Moreover, because mitochondria are

particularly abundant at the peripheral terminals of sensory nerves, their role is closely related to the sensitivity of transient receptor potential (TRP) channels ankyrin 1 (A1) and TRPV1 to ROS and lipid peroxidation byproducts [133]. Noteworthy, the role of TRP channels in C-fiber activity has been particularly investigated in recent years [133,134]. A possible "vicious cycle," involving prooxidant factors in the diet, impairments in the mitochondrial bioactivity, and TRP channels, is achieved by taking into account disorders in the muscular activity and calcium signaling. In addition to the direct prooxidant activity exerted by acid molecules in the bloodstream such as lactic acid, TRPs, and the acid-sensing ion channels may play a major role in mechanical hyperalgesia in inflamed muscles [135]. This might also be associated with the fundamental relationship existing between TRPs and calcium signals [136,137]. Therefore, the pain-causing route may be associated with mitochondrial dysfunction, adenosine triphosphate-to-adenosine diphosphate (ATP-to-ADP) ratio impairment, ROS increase, and TRP/calcium-mediated inflammatory signals. The painful neuropathy induced by paclitaxel in rat peripheral nerves involved a chronic deficiency in ATP and increased ADP-to-ATP ratio [138]. Most likely, a much healthier dietary intake and oxygenated muscular activity are key factors to reduce pain exacerbation in these proinflammatory mechanisms.

The COX and the L-arginine/NO pathways in pain onset and the role of natural flavonoids

Flavonoids exert their activity on the COX pathway, particularly on COX-2 [139,140]. COX-2 inhibitors and non-selective COX inhibitors (traditional non-steroidal anti-inflammatory drugs), whose primary mechanism of action is to inhibit the synthesis of prostaglandins and other arachidonic acid derivatives and induce reduced transmission of pain signals to the central nervous system via the thin C-fiber responses to painful stimuli [141]. Thereby, both pain sensibility and secretion of proinflammatory peptides, such as substance P from C-fibers, are reduced. This results in less neurogenic inflammation and reduced stimulation of various leukocytes, including macrophages and mast cells [142,143]. There seems to be limited awareness from both physicians and health authorities that prostaglandin synthesis or some neuromodulators can also be tuned via dietary modifications [144,145]. Various PUFAs provide a series of different prostaglandins [91]. Whereas arachidonic acid (AA; 20:4 ω-6) is a precursor of the two series of prostaglandins and thromboxanes, eicosapentaenoic acid (EPA; 20:5 ω-3) is a precursor of the three series of prostaglandins and thromboxanes. However, the EPA may reduce prostaglandin function because it reacts relatively slowly. The long-chain ω-3 fatty acid docosahexaenoic acid (22:6) appears to act as a competitive inhibitor for the conversion of AA and EPA. If 5-lipoxygenase oxidizes AA and EPA, various leukotrienes are formed (four series from AA and five series from EPA). These metabolites act as immune stimulators and play a critical role in inflammation disorders, so contributing in the exacerbation of the perceptions of pain; keeping in mind that leukotrienes exhibit different degrees of action in an inflammatory milieu [146]. Diets deeply affect the synthesis and biochemical regulation of eicosanoids, thromboxanes, and prostaglandins. In particular, some flavonoids, such as the soybean isoflavonoid genistein, targets the thromboxane A_2 pathway inhibiting chronic inflammation [147], naringin reduces osteoarthritis-related pain by lowering the production of prostaglandin E2 (PGE2) and NO [148], epicatechin gallate inhibits pain associated with carrageenan rat paw edema by reducing the release of PGE2 [149]. In a few words, the inhibition by flavonoids of the prostaglandin involvement in pain is particularly focused on the inhibition of PGE2 because this prostaglandin has a great impact on pain signals [150]. A close relationship exists between COX-2 (prostaglandin [PG]E2) and NO (iNOS) [125,126]. Therefore, the activity of flavonoids on the L-arginine/iNOS/NO pathway is closely associated with PGE2 inhibition and reduced pain [104,108,112,151–154]. For example, the antinociceptive action of flavonoids such as rutin (contained in buckwheat and asparagus), robinin, and gossypetin 3-glucuronide 8-glucoside (found in green vegetables), is exerted by targeting the L-arginine/iNOS/NO pathway [155]. This kind of pain inhibition is often related to an anti-inflammatory action exerted by flavonoids, which can concurrently target a glutamate neurogenic algesic pathway, as neuropathic pain sprouts from a much more complex mechanism than a simple inflammation [156].

Diet and neurogenic pain

Flavonoids and neurogenic pain

It is well known that the flavonoid quercetin, particularly abundant in red onions, berries, broccoli, and apples, exerts its antinociceptive action by involving the L-arginine/NO pathway, serotonin, and GABAergic systems [108]. Flavonoids can target $GABA_A$ receptors as analogs in the benzodiazepine binding site [157]. The flavonoid fisetin, present in strawberries, apples, persimmons, onions, and cucumbers, can reduce neuropathic hyperalgesia and allodynia in mice with type 1 diabetes mellitus via a spinal $GABA_A$ receptor signaling [114]. The antioxidant, ROS-scavenging action of flavonoids is fundamental because ROS reduce spinal GABA release and induce neuropathic pain [158].

Furthermore, at the peripheral level, flavonoids such as genistein, present in soybeans, can reduce hypersensitivity caused by ROS on C-fibers, via the transient receptor potential ankyrin 1 (TRPA1) and P2 X receptors [159]. This also could be obtained by activating the cannabinoid CB1 receptors [160], which are targeted by certain flavonoids [161,162]. At least in rats, the mitochondria are particularly implicated in the severity of paclitaxel-caused and oxaliplatin-induced mechano-allodynia and mechano-hyperalgesia, as mitochondrial dysfunction and oxidative stress are concurrently exacerbating factors in the origin of the neuropathic pain [163]. In this perspective, the potential of natural polyphenolic antioxidants contained in plant-derived foods is fundamental. Flavonoids contained in the Chinese herbal therapy "Dragon's blood" (i.e., some flavones and methylcaclchones) [164] exert an analgesic effect by dampening the production and release of substance P via the inhibition of the COX-2 signaling and intracellular calcium [165]. Elevated C-fiber activity will not only increase pain sensitivity but also may contribute to worsening the disease condition because of the subsequent increased neurogenic inflammation. For instance, substance P from C-fibers activates macrophages [140], which, in turn, produce more TNF-α [166], which can accentuate the sensitization of the C-fibers [167]. The practical conclusion of this is that the same dietary advice that can be given to obtaining a reduction in blood sugar levels in people with diabetes also can be useful for those hindered by pain, viz. limiting the intake of easily digestible carbohydrates like sweet drinks, white bread, cakes, and polished rice. Physical activity also can help to reduce blood sugar levels [168].

The ability of flavonoids to reduce hyperalgesia can also involve μ- and δ-opioid receptors [169,170], in addition to the effects on the endocannabinoid system. For example, the flavonoid morin, present in *Moraceae* fruits, such as fig, breadfruit, mulberry, banyan, and Osage-orange, reduces bone cancer pain by acting on the CB2 cannabinoid receptor system [171]. Previous reports showed that quercitrin (a glycosidic form of the flavonoid quercetin containing deoxy-mannose), quercetin, and kaempferol in *Hypericum*

perforatum extracts, can bind the μ-opioid receptors, exerting an analgesic action [172]. Luteolin and baicalin targeted the δ-opioid receptor to reduce the neurogenic pain in a rat model of carrageenan-induced paw edema [173]. More recently, a fundamental role to idiopathic pain has been attributed to sigma-1 receptors because they also regulate the endoplasmic reticulum (ER) stress and ROS signaling [174]. Interestingly, flavonoids can both target opioid and sigma-1 receptors [175–178]. The antinociceptive activity exerted by flavonoids is therefore particularly complex and exists on a wide spectra of pathways and mechanisms encompassing the chemical-driven hyperalgesia (L-arginine/iNOS/NO) pathway, TRPc and PKC-mediated pain, mitochondria impairment and oxidative stress causing inflammation) and the neurogenic hyperalgesia ($GABA_A$ receptors, opioid receptor, sigma-1 receptor, substance P), thus suggesting that daily intake of flavonoids may elicit a perception quite close to the antinociception, as a global sensation of well-being.

Further dietary compounds

Curcumin and zerumbone

Curcumin is a bioactive compound of turmeric, the root of the Curcuma plant. Clinical studies have shown that curcumin can be used to improve wound healing and to treat severe pain of patients with burn wounds, making use of its anti-inflammatory mechanisms [179,180]. Biologically, curcumin consists of a class of polyphenols termed *curcuminoids*, which are known to have antioxidant effects and are thought to dampen various types of chronic pain [181,182]. Curcumin recently has been evaluated for its use in chronic musculoskeletal pain, finding positive effects, especially in osteoarthritis and other musculoskeletal chronic pain [183]. A recent meta-analysis indicated that turmeric flavonoids resulted in pain relief in arthritis, based on internationally accepted pain scales, although more high-quality randomized controlled trials (RCTs) are needed [184]. Finally, a very recent RCT showed significant pain reduction, again in patients with osteoarthritis, and even more pronounced when combining curcumin with boswellic acid [185,186].

A common compound from *Zingiberaceae*, which includes ginger, is zerumbone, a sesquiterpenoid with antinociceptive action. The intake of antioxidant molecules able to induce an antinociceptive action, is typically different in Western and Eastern countries, despite the availability of these plant source thanks to economic globalization. Usually, anti-inflammatory flavonoids are very common in the Western diet, and the antinociceptive effect is mainly due to the ability of such molecules to counteract pain associated with inflammation, L-arginine/NO or oxidative stress, and less frequently via a neurogenic signaling pathway. Curcuminoids and zerumbones, together with isoflavonoids and catechins, are much more present in Eastern diets, where plants contain many opioid antagonists and sedative, antinociceptive alkaloids. Although many of these substances can alleviate pain via the mechanisms described here, Western and Eastern countries are characterized by these marked differences in daily diets (Fig. 1).

Zerumbone is a very common substance, which is frequently found in the diets of Eastern and North African countries. A flavonoid used in Western countries, zerumbone, also has antinociceptive and antiallodynic potentials, which is probably exerted via an anti-inflammatory pathway in nociceptive neurons [187]. Zerumbone can exert an analgesic action in a neuropathic pain by targeting the L-arginine/NO pathway and the cGMP-PKG-K^+ATP signaling as shown in mouse experiments [188], although in the same pain model, the ginger sesquiterpenoid showed an antiallodynic (mechanical) and antinociceptive (thermal) effect via the 5-HT receptor signaling [189]. The ability of ginger extracts to alleviate pain is widely known and greatly appreciated in folk medicine [190]. Ginger can counteract pain related to primary dysmenorrhea, as can mefenamic acid [191], and has shown to be effective in patients with poor response to non-steroidal anti-inflammatory drugs and those with from knee arthritis–derived pain [192]. The role of this root is therefore particularly interesting as an antinociceptive dietary panel, particularly because it has been found that its analgesic property is quite comparable to ibuprofen [193].

Minerals, essential factors, and trace elements

For reducing C-fibers hyperactivity, leading to local tissue hyperoxygenation in patients suffering from chronic skeletal muscle pains or cardiac failure, it is important to restore the intracellular antioxidant defense system in C-fibers by correcting glutathione or selenium (Se) deficiencies to counteract oxidative activation of PKC in the C-fibers, inhibiting hypersensitization of the C-fibers themselves [194]. Se deficiency is associated with pain exacerbation, particularly in cases with muscle damages and osteoarthritis [195,196]. Furthermore, it is important to correct dietary-induced overproduction of prostaglandins, which can be caused by a relatively high dietary ω-6-to-ω-3 PUFA ratio, low Se intake, or nutritional deficiency conditions leading to tissue glutathione depletion, as prostaglandins also sensitize the C-fibers to hyperalgesia [197,198] and hence will enhance the release of vasodilatory peptides from them at a given rate of lactic acid production by the muscle. In patients with chronic myofascial pain, a significant decrease in the content of Se in erythrocytes and inadequate food intake of this nutrient has been observed [199]. Supplementation of organic Se in the treatment of patients with chronic pancreatitis accompanied by severe pain led to significant pain relief in >50% of patients and a substantial reduction in the pain score [200,201]. Association between Se status and pain relief was also observed in patients with fibromyalgia [202,203] and skeletal muscle disorders manifested by muscle pain [196]. Magnesium (Mg) has attracted much attention recently for its role in alleviating pain [204–206], suggesting that Mg in the diet should play a major role in reducing pain. In an orofacial type of pain (i.e., temporomandibular joint arthritis), Mg prevented hypernociception and attenuated pain via the NMDA receptors in the subnucleus caudalis, reducing pain from the trigeminal pathway [207]. Dietary-induced Mg deficiency can, therefore, exacerbate pain sensitivity via the nociceptive pathways [208]. This may also occur for zinc (Zn) deficiency, which was observed to promote pain coming from bladder cystitis in mice via the increase of the $Ca_v3.2$ T-type Ca^{2+} channel activity in nociceptors [209]. As previously reported, Zn combined with Se is fundamental in chronic myofascial pain [199]. Moreover, Zn can inhibit TRPV1 and reduce neuropathic pain resulting from chemotherapy [210].

Recent reports have outlined that a lack of vitamin D in the body is associated with increased pain, which in observed cases required an elevation of opiate doses [211]. When deficient, vitamin D supplementation has a positive effect on muscle pain, an effect that is associated with anti-inflammation owing to a decrease in the release of cytokines and prostaglandins. Also, vitamin D has an indirect inhibitory effect on PGE2 [212]. The role of vitamin D in pain relief can not solely be explained by its role in the mineral metabolism in the bone tissue but also appears to involve regulatory effects on nociceptors and sleep, as it has been established that sleep dysregulation is associated with hyperalgesia [213]. Thus, adequate vitamin D supplementation can play a therapeutic role not only in sleep disorders but also in the prevention and treatment of chronic pain [214].

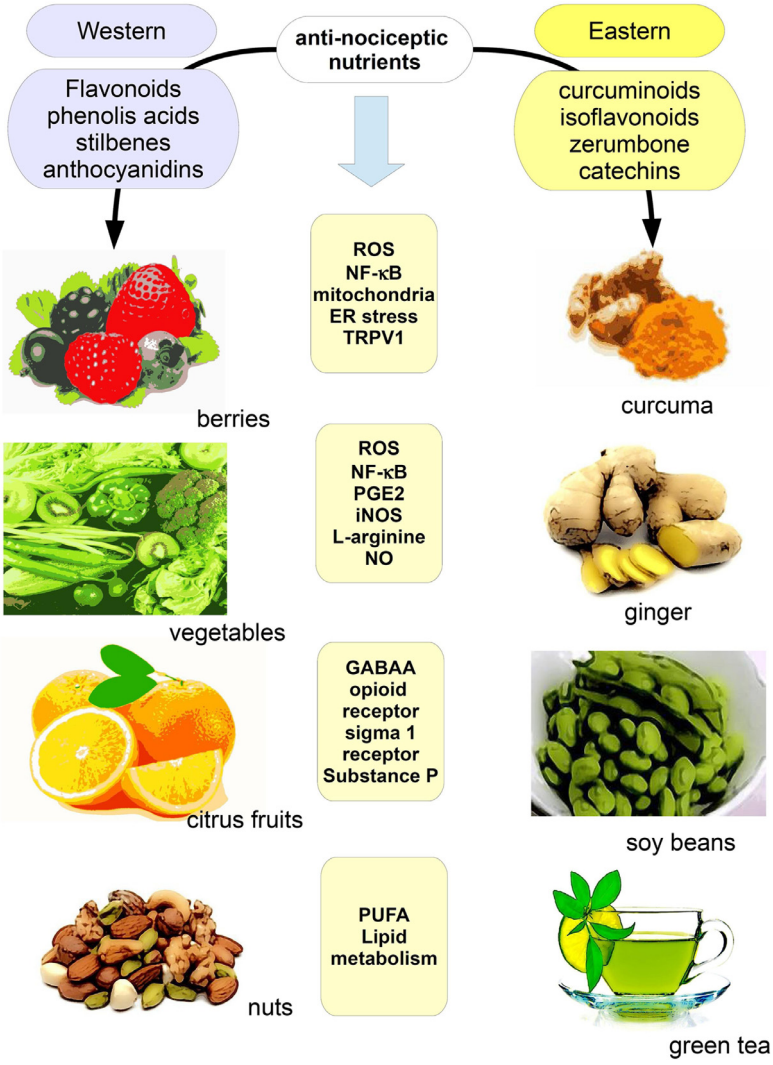


Fig. 1. Antinociceptive nutrients in common diets in Western and Eastern countries. ROS, reactive oxygen species; ER, endoplasmic reticulum; TRPV1, vanilloid receptor 1; PGE2, prostaglandin E2; iNOS, nitric oxide synthase; NO, nitric oxide; PUFA, polyunsaturated fatty acid.

A systematic review that included four RCTs with patients with chronic non-specific widespread pain showed a significant pain reduction according to a visual analog scale in patients taking vitamin D (mean difference [MD], 0.46; 95% confidence interval [CI], 0.09–0.89) [215]. These data were confirmed by the results of another meta-analysis, which included eight RCTs. A statistically significant decrease in pain intensity was shown when taking vitamin D (MD, −0.57; 95% CI, −1.00 to −0.15; $P = 0.007$) [216]. Regarding patients with headache, another study suggested some benefit of nutritional intervention [217], although a sound qualitative interpretation is still missing in this field. It should be noted that studies concerning vitamin D are known to be rather heterogeneous, yielding contradictory results, often owing to differences in pretreatment evaluation and different dosage and frequency of administration. In women, a study suggested beneficial effects of multiple nutrients on dysmenorrhea. However, no nutritional benefit has been sufficiently statistically evaluated in this disorder [218]. And in another study, vitamin D had no benefit in adults with chronic pain [219]. On the contrary, ω-3 PUFAs with vitamin D could alleviate joint pain in several inflammatory conditions [84,220].

Finally, taurine, a derivative of cysteine, is a major supplementation nutrient against pain [221,222]. It was recently reported that taurine, as a glycine A receptor agonist, enhances the analgesic effect of the selective COX-2 inhibitor celecoxib when used simultaneously to relieve central pain, thus decreasing the nociceptive response at thermo- and mechanonociception [223]. Intrathecal administration of hypotaurine in chronic damage to the sciatic nerve in rats suppressed acute, inflammatory, neuropathic pain without affecting locomotor activity [224]. A clinical study of the effectiveness of an analgesic containing tramadol, paracetamol, caffeine, and taurine in acute back pain showed a good response to treatment in 81% of the patients compared with 45% in the group that only received tramadol or paracetamol ($P < 0.001$) [225].

Concluding remarks

The present review underscores the need to establish an expert panel to evaluate data for the best dietary advisory program to reduce pain in various medical conditions. It is apparent that a recommended dietary program must face numerous cultural differences and nutritional habits worldwide, including socioeconomic burden and food availability. Nevertheless, in this review, we attempted to provide an overview of the most common food-derived molecules exhibiting an antinociceptive action in the

current scientific reports. The main themes and concerns are the availability of fruits and green vegetables, deficiency of vitamin D, and above all, the ratio of ω-3 to ω-6 in the daily diet. In many Western industrial countries, the diet is currently characterized by a much higher ratio of ω-6 fatty acids compared with other fatty acids than the ratio that humans have adapted to throughout their biological evolution. In Western societies, people are used to consuming a lot of margarine and unhealthy oils. Most margarine and even vegetable oils, with the exception of linseed, canola, and olive oils, possess a high ratio of ω-6 to ω-3.

Moreover, there have been changes in the fatty acid composition of some animal products [226]. Although green leaves and grass species in animal food have an excess of ω-3 fatty acids compared with ω-6 fatty acids, the modern concentrated corn-based feed has a very high ratio of ω-6 to ω-3. These changes have effects on the composition of the human diet. When the ratio of ω-6 to ω-3 is high, the result is a metabolic imbalance. In a patient with arthritis, it is expected that this will lead to increased prostaglandin synthesis, resulting in increased sensitization of C-fibers, and hence increased neurogenic inflammation and more pain. It can be of practical value for patients with pain to have the ratio of ω-6 to ω-3 fatty acids not higher than ~2 to 1. This would require a change of diet, with increased intake of ω-3 fatty acids, for example, rapeseed oil, fish oil, ω-3 supplementation, and so on. Nutrition guidelines should promote the reduction of the relationship between ω-6 and ω-3-fatty acids in all food. Although this may involve significant practical challenges for the food industry and agriculture, it will have a protective effect on human health, particularly in cardiovascular diseases [227].

Despite the many controversial reports about the suitability of dietary panels in preventing and reducing nociception and inflammation or neurogenic pain, diet remains, together with physical exercise and a proper lifestyle, remains a promising strategy for reducing pain burden.

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