Pain Ther (2021) 10:225–242
https://doi.org/10.1007/s40122-021-00239-y

REVIEW

Food for Special Medical Purposes and Nutraceuticals for Pain: A Narrative Review

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Received: December 7, 2020 / Accepted: January 30, 2021 / Published online: February 16, 2021

ABSTRACT

Introduction: The present paper focuses on the possible contribution of food compounds to alleviate symptomatic pains. Chronic pain can more easily be linked to anticipatory signals such as thirst and hunger than it is to sensory perceptions as its chronicity makes it fall under the behavioural category rather than it does senses. In fact, pain often negatively affects one's normal feeding behavioural patterns, both directly and indirectly, as it is associated with pain or because of its prostrating effects.

Nutritional Compounds for Pain: Several nutraceuticals and Foods for Special Medical Purposes (FSMPs) are reported to have significant pain relief efficacy with multiple antioxidant and anti-inflammatory properties. Apart from the aforementioned properties, amino acids, fatty acids, trace elements and vitamins may have a role in the modulation of pain signals to and within the nervous system.

Conclusion: In our opinion, this review could be of great interest to clinicians, as it offers a complementary perspective in the management of pain. Trials with well-defined patient and symptoms selection and a robust pharmacological design are pivotal points to let these promising compounds become better accepted by the medical community.

Keywords: Amino acids (tryptophan; phenylalanine; carnitine); Fatty acids (resolvines; PEA); Food for pain; Food for medical purposes; Magnesium; Metalloporphyrins; Selenium; Vitamins

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Key Summary Points

Nutraceuticals are products isolated or purified from foods and generally are sold in medicinal form as a supplement rather than as a food. This definition encompasses a wide range of compounds: vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandular materials, and metabolites.

Foods for Special Medical Purposes (FSMPs) are a new class of therapeutics, which can be used under medical control to cure diseases and alleviate symptoms.

Emerging literature suggests that diet constituents may play a modulatory role in chronic pain through management of inflammation/oxidative stress, resulting in attenuation of pain.

Nutraceuticals and FSMPs may have some role in the modulation of pain signals to and within the nervous system.

Very few randomised controlled trials in humans are present in the literature and, as such, the current situation does not allow us to fully support the use of nutraceuticals and FSMPs on a broader basis.

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INTRODUCTION

Chronic pain can more easily be linked to anticipatory signals such as thirst and hunger than it is to sensory perceptions as its chronicity makes it fall under the behavioural category rather than it does senses [1]. Pain and eating are two complex behaviours that are strictly correlated on a neurological level. In the occurrence of ill health, pain actively limits the normal dietary behaviour in an individual both directly and indirectly, due to physical suffering and fatigue. Moreover, in the occurrence of an eating disorder such as anorexia nervosa, pain and hunger are believed to be affected even without a neurological impairment [2]. On the other hand, obesity has also been evaluated as a possible marker for increased pain severity and it has been related to obesity in postmenopausal woman [3, 4]. When analysing chronic pain on a psychosocial level, these two opposite clinical pictures are a strong example of the correlation between pain and food. In fact, it is not the food itself but some of its natural compounds that may work as a trigger. In this field, the majority of reports claiming a beneficial use of food to control a series of signs and symptoms seem to be just anecdotical [5].

A search of the medical literature with Medical Subject Headings (MeSH) "nutraceuticals" combined with "pain relief" affords a list of about 1,900,000 websites with "nutraceuticals" for pain relief. Nutraceuticals are products isolated or purified from foods and generally sold in medicinal form as a supplement rather than as a food. This definition encompasses a wide range of compounds: vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandular materials, and metabolites. Dietary supplements can also be extracts or concentrates. This broad group of compounds was demonstrated to have a physiological benefit or provide protection against chronic diseases, such as osteoarthritis (OA), muscle pain and headaches [6, 7]. However, nutraceuticals have issues not only in Europe but also worldwide with accuracy of dose, preparation and consistent pharmacodynamics.

Moreover, in recent years in Europe, the USA and Japan a new class of therapeutics has been introduced, which can be used under medical control to cure diseases and alleviate symptoms. These are labelled as Foods for Special Medical

Purposes (FSMPs) [8]. The European Commission Directive on dietary Foods for Special Medical Purposes (Directive 2006/141/EC) sets out rules for the composition and labelling of foods that are specifically formulated, processed and intended for the dietary management of diseases, disorders or medical conditions of individuals who are being treated under medical supervision [9]. These foods are intended for the exclusive or partial feeding of people with specific nutritional requirements. In other words, nutraceuticals are intended to eventually reduce the risk of diseases while FSMPs are labelled as medicines for therapeutic use under medical control.

This manuscript aims to analyse the most relevant compounds researched in peer-reviewed journals from well-known databases like PubMed, EMBASE, Medline and Google Scholar. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

NUTRITIONAL COMPOUNDS FOR PAIN

Antioxidant Properties

Excessive eating and drinking habits have been associated with increased oxidative stress and indirectly related to pain generation and maintenance. The nervous system, and particularly the brain, is vulnerable to oxidative damage [10] and it can affect the development of different neurodegenerative disorders including Alzheimer's disease [11], Parkinson's disease [12] and amyotrophic lateral sclerosis [13]. This mechanism can be of some importance in the occurrence of pervasive pain as an onset symptom in the early stage of dementia [11].

In the last decade, there have been major improvements in understanding the mechanisms underlying the transition of acute to chronic pain, the formation and exacerbation of neuropathic pain, and the development of opioid-induced tolerance and hyperalgesia especially when looking at the role of oxidative stress agents such as peroxynitrite (PN) and its reactive oxygen precursor superoxide (SO) [14]. This has led to a promising treatment strategy, namely the use of antioxidant compounds or scavengers against PN and SO to reduce oxidative stress and prevent the establishment of favourable conditions for the transition towards chronic pain states as in the management of musculoskeletal disorders in the elderly where multiple pharmacological treatments are already present [15, 16].

Anti-Inflammatory Properties

A diet rich of refined starches, sugar, saturated and trans-fats can promote inflammation [17]. In the Nurses' Health Study, women with a diet based on of red and processed meats and trans-fats, as well as refined grains, had high levels of C-reactive protein, interleukin-6 (IL-6), E-selectin, soluble intercellular adhesion molecule 1 (sICAM-1) and soluble vascular adhesion molecule 1 (sVCAM-1) [18]. A direct relationship between trans-fatty acid consumption and higher inflammatory markers such as IL-6 was also observed [19]. This has been confirmed across a number of controlled trials and observational studies [20] and recently reviewed [21].

The existing literature is very thorough on the role of nutraceuticals with a declared antioxidant anti-inflammatory activity [6, 22, 23] such as curcumin [6], resveratrol [24] and omega-3 polyunsaturated fatty acid [25]. The combination of curcumin and resveratrol can induce a significant inhibition of tumour necrosis factor-alpha (TNFα) and nitric oxide (NO) levels in painful diabetic polyneuropathy in humans [26], to attenuate thermal hyperalgesia in animals and to interfere with morphine tolerance [27]. Curcumin has been shown to provide some help in alleviating pain of different origin [6] showing effects equivalent to ibuprofen and diclofenac, without the adverse effects generally reported by patients [28].

Amino Acids

Amino acids are nitrogen-containing molecules critically necessary for the production of proteins. They can be widely found in many foods, including meat, eggs, milk, fish, plants and

nuts. They are utilised for the production and function of almost every tissue in the body, especially involving the musculoskeletal system [29]. As such they might be able to provide pain relief via accelerating tissue-healing mechanisms induced by an anabolic activity. Indeed, a mixture of essential amino acids improves pain of elderly subjects following elective surgery for hip OA within 2 weeks after operation [30]. Tryptophan, L-phenylalanine and carnitine are of particular interest (Table 1).

Tryptophan

One of the most remarkable compounds in the treatment of chronic pain is tryptophan, an amino acid precursor of 5-OH-tryptamine or serotonin, a neurotransmitter involved with noradrenaline in pain control descending systems [31]. Its use alone or in combination with a selective serotonin reuptake inhibitor (SSRI) can help in controlling the pain or in reducing the use of SSRI antidepressants on the basis of the assumption that many pain states are determined by a decreased efficiency of the serotonergic descending system and that increased supplementation along with a blockade of its elimination can lead to increased control of pain [32, 33]. Indeed, in generalized pain states in which fatigue, mood changes and diffuse pain occur, such as fibromyalgia and irritable bowel syndrome, an abnormal engagement of descending mechanisms with or without reduced inhibition has been suggested [34, 35]. However, the balance between descending controls, both excitatory and inhibitory, seems to be more important than a simple reduction of one component [33]. Unfortunately, tryptophan is available in vegetables only in small quantity and to achieve a therapeutic daily intake it is necessary to supplement dietary intake with tablets.

Phenylalanine

Phenylalanine, widely known for its use in the treatment of phenylketonuria, is another agent with a potential contribution in the management of chronic pain. Phenylalanine is presumed to act as an enkephalinase inhibitor and thus increases the release of enkephalins in the dorsal horns and to potentiate endogenous opioid activity [35]. According to clinical observation, co-administration of opioids and phenylalanine in cases of drug dependence required lower levels of opiates [36], supporting phenylalanine's property in increasing opioid activity. Seeds, nuts, almonds and soybeans are rich sources of phenylalanine and except for medical disorders its deficiency is less expected.

Carnitine

The amino acid carnitine is related to the proper functioning of almost all systems in the human body. Carnitine deficiency is characterized by various metabolic, cardiological and musculoskeletal problems, which vary widely in age of onset and presentation [37]. Carnitine has a potential neuroprotective role in many neurological disorders [38] enriched by the assumption that carnitine has an effect on pain reduction. According to a recent study in patients with mild to moderate carpal tunnel syndrome, the possible neuroprotective effect of carnitine relies on the improvement of mitochondrial function [39, 40]. Pain reduction is possibly achieved by the dysregulation of glutamate in the dorsal horns, via carnitine-induced activation of metabotropic glutamate receptor 2 (mGluR2) [41]. Preliminary data also suggest that metabolic pathways regarding L-carnitine synthesis may play a role in pain severity and interference in women with fibromyalgia; however, further investigation is necessary to confirm this hypothesis [42]. Carnitine can be widely found in meat and dairy products; carnitine deficiency is very rare and only due to pathological conditions.

Fatty Acids

Fatty acids of particular interest are summarised in Table 1.

Omega-3 Polyunsaturated Fatty Acids: Resolvines

Omega-3 polyunsaturated fatty acids include docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) and are present in dietary essential fat especially in fish. DHA and EPA are

Table 1 References for amino and fatty acids and trace elements cited in the text are herein reported

	Reference	First author	Year
Amino acids			
Tryptophan	[31]	Baldin	2011
	[32]	Saarto	2007
	[34]	Bannister	2009
	[35]	Russell	2000
L-Phenylalanine	[35]	Russell	2000
	[36]	Chen	2004
Carnitine	[37]	Magoulas	2012
	[38]	Maldonado	2020
	[39]	DiCesare Mannelli	2007
	[40]	Chierchio	2007
	[41]	Cruccu	2017
	[42]	Menzies	2020
Fatty acids			
Ω-3 Polyunsaturated acids: resolvines	[43]	Ji	2011
	[44]	Okubo	2010
	[45]	Seki	2009
	[46]	Serhan	2015
	[47]	Tokuyama	2011
	[48]	Prego-Dominguez	2016
	[52]	Figueroa	2013
	[130]	Russo	2018

Table 1 continued

	Reference	First author	Year
N-Palmitoylethanolamide (PEA)	[49]	Lambert	2002
	[50]	Truini	2011
	[51]	Skaper	2015
	[53]	Costa	2008
	[54]	Aldossary	2019
	[55]	Conigliaro	2011
	[56]	Scaturro	2020
	[57]	Del Giorno	2015
	[58]	Alshelh	2019
	[59]	Marini	2012
	[60]	Gugliandolo	2020
	[61]	Paladini	2016
Trace elements			
Selenium (Se)	[62]	Medina-Cruz	2018
	[63]	Kieliszek	2017
	[64]	Reinhard	1998
	[65]	Yüksel	2017
	[66]	Sousa	2018
Magnesium (Mg)	[67]	Welch	2017
	[68]	Rondón	2010
	[69]	Sun	2017
	[70]	Banerjee	2017
	[71]	Oh	2019
	[72]	Park	2020
	[73]	Tarleton	2020
Metalloporphyrins			
Iron (Fe)	[74]	Rausaria	2011
Manganese (Mn)	[75]	Li	2008

precursors of a new family of pro-resolving mediators of inflammation called resolvines. Resolvines can dampen pain via multiple mechanisms reducing inflammatory factors, the glia and the spinal cord synaptic plasticity [43]. It is very interesting to note that resolvines are strongly induced not only in the periphery during acute inflammation but also in the

dorsal root ganglia and spinal cord [44]. Even if resolvines can be seen as a novel and extremely interesting approach both to prevent and cure pain associated with inflammation control, they are metabolically unstable in that they are rapidly inactivated in vivo, thereby reducing their possible utilization. A novel and more stable form of resolvines has been under study [45].

High serum concentration of omega-3 polyunsaturated fatty acids is associated with anti-nociception and lower levels of inflammatory mediators [46]. Dietary supplementation has shown reduction of pain related to rheumatoid arthritis, inflammatory bowel disease, neuropathy and dysmenorrhoea [47], with the largest effect on dysmenorrhoea according to recent a systematic review and meta-analysis [48].

N-*Palmitoylethanolamide (PEA)*

N-Palmitoylethanolamide (PEA) is a shorter and fully saturated analogue of anandamide [49]. PEA is a natural compound from soybean lecithin, egg yolk and peanut meal. PEA is accumulated during inflammation and has a number of anti-inflammatory effects, including effects in clinically relevant animal models of inflammatory as well as neuropathic pain. PEA is produced during inflammation and it was proposed that PEA acts as an "ALIAmide" (autacoid local inflammation antagonist amide) via its action on mastocytes, a pivotal cell in the inflammatory process. Moderation of mast cell activity has been suggested to contribute to the reduction of endoneurial edema, relieving conduction blocks in electromyographic studies in patients with chemotherapy-induced painful neuropathy [50]. PEA modulates local cells, degranulation and the reduction in the production of many inflammatory mediators such as TNFα and neurotrophic factors like nerve growth factor (NGF) [49, 51].

Furthermore, metabolic products related to *N*-acetylethanolamine metabolic pathways of omega-3 polyunsaturated fatty acids seem to present antihyperalgesic effects, mediated by reduction of painful biomarkers in the spinal cord [52]. PEA also shows a direct action on pain mechanisms. In a model of neuropathic pain in animals (chronic constriction injury of the sciatic nerve), PEA was able to reduce both thermal hyperalgesia and mechanical allodynia [53]. Its mechanisms of action are mediated by the cannabinoid (CB1) and transient vanilloid (TRPV1) receptors, suggesting that the most likely antinociceptive mechanism might be the so-called entourage effect due to the PEA-induced inhibition of the enzyme catalysing the endocannabinoid anandamide (AEA) degradation [51, 54]. These data have been clinically confirmed in humans with neuropathic compression pain [55], in subjects with chronic low back pain [56, 57], in fibromyalgia [58], in nociceptive pain due to temporomandibular joint arthritis [59] and confirmed in pooled meta-analysis data in both chronic and neuropathic pain associated with neuroinflammation [60].

In addition PEA is thought to play a role as a glial modulator by targeting alpha peroxisome proliferator-activated receptors (PPARα), expressed on neurons and astrocytes, pain mediators which are activated as a response to nerve damage. Recent evidence suggests a reduction in oscillatory activity along the ascending pain pathway for patients with chronic neuropathic pain [61].

Trace Elements

Trace elements of particular interest are summarised in Table 1.

Selenium (Se)

Selenium (Se) can be found in Brazilian nuts, fish, meat and eggs and, in addition to its antioxidant properties, regenerates vitamins C and E and boosts the immune system's function by improving its ability to fight infections and cancer cells [62, 63]. Regarding pain syndromes, lower Se levels have been found in cases of chronic pain conditions and especially in patients with fibromyalgia [64]. In an animal experiment in which a fibromyalgia-like syndrome was provoked, low dose of supplementation with Se was associated with a decrease in the fibromyalgia-induced hyperalgesia, reactive oxygen species (ROS), apoptosis and Ca^{2+} entry.

Interestingly this last effect was mediated through transient receptor potential melastatin 2 (TRPM2) and transient receptor potential vanilloid 1 (TRPV1) in the sciatic nerve and the dorsal root ganglion, suggesting the utilization of Se in clinical practice as a complement in the treatment of fibromyalgia [65]. Additionally α-(phenylselanyl)acetophenone, an organic compound of selenium, demonstrates antioxidant, antidepressant and antinociceptive activities in animal models, possibly by intervening in monoamine oxidase (MAO-A) inhibition [66].

Magnesium (Mg)

Wholegrain bread, brown rice, nuts, green leafy vegetables, fish, meat and dairy products are rich sources of Mg. A deficiency in the essential mineral Mg can result in painful muscle cramps. Thus, it is inferred that a Mg intake will reduce muscle pain and produce muscle relaxation in all conditions [67]. However recent studies suggest that Mg has a much more direct involvement in the amelioration of pain. Experiments in rats with induced diabetic neuropathy showed that per os administration of Mg abolished thermal and tactile allodynia, decreased the development of mechanical hypersensitivity, and reduced *N*-methyl-D-aspartate receptor (NMDA) sensitivity in the spinal cord [68]. This finding was reaffirmed quite recently, as intrathecal sulfate application of Mg in rats proved to attenuate remifentanil-induced postoperative hyperalgesia again by downregulating the NMDA receptor activity in the spinal cord [69]. Thus Mg-mediated blockade of NMDA receptors can be a promising new therapeutic option for the management of chronic pain conditions, even especially when central pathways are involved. Clinical application up to now regards efficacy of Mg administration in cases of migraine [70], postoperative chronic knee pain [71] and chronic pain [70, 72, 73].

Iron (Fe) and Manganese (Mn)

Metalloporphyrin complexes with Fe and Mn have been identified as possible therapeutic agents as they show potent action in a model of carrageenan-induced thermal hyperalgesia and mechano-allodynia in a model of chronic neuropathic pain in animals [74]. Manganese deficiency is very rare in humans. The very limited evidence in humans suggests that Mn deficiency might cause bone demineralization and altered mood and increased premenstrual pain in women [75]. As far as we know there are no data on their efficacy in humans even if it is common sense that vitamins and minerals are essential for a balanced diet now encompassed under the label of nutraceuticals.

Vitamins

Vitamins of particular interest are summarised in Table 2.

Vitamin B

Vitamin B complex has multiple roles in the production and function of multiple cells within the body and also displays antioxidant actions. A diet with wholegrain bread, rice, cereals, fruits, peas, broccoli, eggs, liver, kidneys, chicken, meat and dairy products provides sources of all subgroup substances of vitamin B complex [76]. The role of subgroups of vitamin B complex as an adjuvant in causing analgesia is quite controversial. It seems that vitamin B as a supplement itself is not able to produce a strong analgesic effect, but it contributes and synergistically enhances the action of anti-inflammatory agents in both humans and animals [77–80].

Investigations in chemical and thermal models of nociception in mice suggested that the antinociceptive effect of some vitamin B groups may involve inhibition of the synthesis and/or action of inflammatory mediators [81]. However, a more direct analgesic and possible neuroprotective role of vitamin B complex has been also described in recent research studies in animals, implicating either the activation of astrocytes and microglial cells and increase in synthesis of γ-aminobutyric acid (GABA) [82] or the modulation of TRPV1 [83] as possible underlying pathophysiological mechanisms. A combination containing vitamin B has been

Table 2 References for vitamins (B; C; D and K; E) cited in the text are herein reported

Vitamins	Reference	First author	Year
Vitamin B	[76]	Ang	2008
	[77]	Kuhlwein	1990
	[78]	Reyes-Garcia	1999
	[79]	Levin	2009
	[80]	Caram-Salas	2004
	[81]	França	2001
	[82]	Yu	2013
	[83]	Kopruszinski	2015
	[84]	Jhun	2020
Vitamin C	[85]	Undurti	2001
	[86]	Fain	2005
	[87]	Dionne	2016
	[88]	Ekrol	2014
	[89]	Kim	2016
	[90]	Carr	2014
	[91]	Zeraati	2014
	[92]	Mikirova	2012
	[93]	Carr	2017

Table 2 continued

Vitamins	Reference	First author	Year
Vitamins D and K	[95]	Jansen	2013
	[96]	Bhan	2010
	[97]	McCarthy	2015
	[98]	Shinchuk	2007
	[99]	Matossian-Motley	2016
	[100]	Shipton	2015
	[101]	Waikakul	2012
	[102]	Lee	2008
	[103]	Jesus	2013
	[104]	Laslett	2014
	[105]	Haque	2010
	[106]	Huang	2013
	[107]	Wepner	2014
	[108]	Diao	2017
	[109]	McAlindon	2013
	[110]	Helde-Frankling	2017
	[111]	Kalueff	2007
	[112]	Garcion	2002
	[113]	Helde-Frankling	2017
	[114]	Cury	2011
	[115]	Ambrozewicz	2019
	[116]	Lanham-New	2008
Vitamin E	[117]	Packer	1991
	[118]	Edmondsa	1997
	[119]	Blankenhorn	1986
	[120]	Ziaei	2005
	[121]	Shobeiri	2014
	[122]	Argyriou	2006
	[123]	Wadleigh	1992
	[124]	Kim	2006

shown to ameliorate the progression of osteoarthritis in humans [84].

Vitamin C

Vitamin C is an additional nutrient ingredient, present in oranges, strawberries, broccoli, peppers and potatoes. It is considered a strong antioxidant agent with multiple physiologic and metabolic effects [85]. Vitamin C deficiency has been directly associated with general musculoskeletal pain [86], spinal neck and low back pain, arthritis and rheumatism [87]. Furthermore, according to several studies, vitamin C supplementation on a daily basis helps in preventing the development of complex regional pain syndromes (CRPS) [88], might ameliorate pain symptoms in post-herpetic and cancer-related pain [89, 90] and decreases the dose of opioid consumption in experiments with mice [91].

Despite its multiple contributions in clinical pain reduction, the exact pathophysiological mechanism of vitamin C is more speculated than known. Vitamin C has anti-inflammatory properties by means of decreasing markers of inflammation in blood circulation [92], perhaps via its antioxidant mediation. This feature might contribute to a more general analgesic effect. However, vitamin C is a crucial cofactor for the production of serotonin, noradrenaline and endorphins involved in pain neuromodulation. As such, recent evidence suggests that these mechanisms are potential additional contributors to the analgesic effect exhibited by vitamin C [93].

Vitamins D and K

Vitamin D can be found in oily fish, red meat, liver, egg yolks and cereals. Additionally, the body makes good use of vitamin D, which comes from the sun or from a supplement, to build stronger bones. Poor vitamin D status frequently occurs in the general population and even more in disease states for two main reasons: low exposure to the sun and lack of vitamin D intake [94].

Lack of vitamin D is clearly associated with pain due to pathological skeletal conditions such as osteoporosis [95] and osteomalacia [96]. Moreover, as vitamin D also contributes to correct functioning of muscle, studies also showed that low serum levels of vitamin D are linked to muscle cramping and menstrual pain [97]. Poor body vitamin D status may represent an important risk factor for development and/or maintenance of both acute and chronic pain in various nonspecific musculoskeletal pain [98]. More recent evidence suggests that deficiency of vitamin D is linked to a higher prevalence of musculoskeletal pain [99], chronic pain [100], failed back surgery syndrome (FBSS) [101], neuropathic pain [102], fibromyalgia [103], OA [104] and rheumatoid arthritis [105]. On the other hand, supplementation of vitamin D has been found to improve pain in ambulatory subjects with nonspecific musculoskeletal pain [106], fibromyalgia [107], knee OA [108, 109] and in palliative care [110].

As a neuroactive steroid, vitamin D modulates the sensitivity of both neurotransmitters and relevant receptors as well as the signal transduction of pain, in the brain and the periphery [111]. It possesses a neuroprotective role by upregulating neurotrophins [112] and perhaps contributes to pain relief via various anti-inflammatory actions such as inhibition of cycloxygenase-2 (COX-2), upregulation of prostaglandins and downregulation of inflammatory cytokines and excessive T lymphocyte infiltration [113]. An additional antinociceptive feature concerns the inhibition of NO, which moreover contributes to the development of central sensitization [114].

Furthermore, the combined use of vitamins D and K2 may protect redox balance and support the growth of osteoblasts [115] and thus further contribute to pain control in osteoporotic bone [116].

Vitamin E

Vitamin E is an additional important antioxidant agent and is found in plant oils like soya, corn and olive oil, in cereal products and in nuts and seeds. It helps to avoid the damage caused to the body by free radicals, protecting cell membranes from peroxidative stress [117]. Vitamin E exerts an analgesic effect in several pathologies such as rheumatoid arthritis [118], OA [119], dysmenorrhoea [120], premenstrual

syndrome [121] and chemotherapy-induced conditions [122, 123]. Interesting laboratory findings suggested that the analgesic actions of injected vitamin E were mediated through depressing the NMDA receptor activity in dorsal horns [124]. However, as vitamin E is very far from a first-line pain-relieving option, there is a lack of recent evidence for its role in pain modulation.

A summary of all compounds reviewed is reported in Tables 1 and 2.

Psychophysical Influence on Food Choice and Related Consequences

To underline the importance of the biopsychosocial model to understand the development of chronic pain syndromes and the possible role of food, it is worth noting that stress and depression can influence food choices, enhancing maladaptive metabolic responses to unhealthy meals [125]. Combination of stressor events and incongruous diet can affect mood as well as further pro-inflammatory responses to stressors with the production of cytokines also in the absence of infection or injury [126].

Indeed depression and stressful events motivate less healthy food choices with greater risk related to being female and already overweight [3, 4]. Female college students in East European countries reporting a perceived stress ate more sweets and fast foods than those less stressed. Also men modify their dietary habits in relation to psychological distress, decreasing their vegetable intake following divorce or bereavement, but then increasing vegetable consumption after remarrying. Thus, in general, depression, stress and stressful pain conditions promote less healthy food choices that can boost increased oxidative stress and inflammatory responses that can open the gate to chronic painful states.

CONCLUSION

Emerging literature suggests that diet constituents may play a modulatory role in chronic pain through management of inflammation/oxidative stress, resulting in attenuation of pain. However the diet in general is only one part of the complex rehabilitation approach of patients with chronic pain and that they should not be considered a quick-fix pill.

Two aspects come out from the critical review on nutraceuticals and FSMPs; a considerable bulk of evidence came from the basic science strongly suggesting that almost all the cited food compounds may have some role in the modulation of pain signals to and within the nervous system. Moreover, recent advances in research have described the importance of the microbiota–gut–brain axis in influencing normal physiology and contributing to disease [127]. Indeed there is evidence that microbiota which is highly influenced by food intake may have an important role also in the perception of pain [128–130]. However, on the other hand very few randomised controlled trials sufficiently well designed to reach evidence-based medicine grade A and grade B are present in the literature on humans. As such, the current situation does not allow us to fully support the use of nutraceuticals and FSMPs on a broader basis. Thus, a warning should be made about the efficacy of nutraceuticals to control pain because of the ubiquitous presence of placebo effects. Indeed, placebo effects still retain an ambiguous and unsettling presence in biomedicine [131], especially regarding pain and in areas where placebo-controlled studies are lacking. Further, a number of these agents thought to perform amazing and revitalizing effects are much more ambiguous in their analgesic efficacy. Several reasons can be claimed for this apparent scotoma of all this possible contribution to pain control. Indeed, the most important of these is the already cited lack of clinical data. Trials with well-defined patient and symptoms selection and a robust pharmacological design are pivotal to letting these promising compounds become accepted by the medical community. It goes without saying that as “pain” is much more related to thirst and hunger than other sensations, eating habits and the presence of special food compounds must be considered with more attention by all the medical stakeholders involved in pain medicine.

ACKNOWLEDGEMENTS

The authors wish to thank Prof Roberto Aquilani (MD) for his supervision of the vitamin D section.

Funding. No funding or sponsorship was received for this study or publication and the Rapid Service Fee of this article.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authorship Contribution. Authors made substantial and equal contributions to the conception and design of the article, and in drafting and revising it critically.

Disclosures. The authors Roberto Casale, Zaira Symeonidou, Sofia Ferfeli, Fabrizio Micheli, Paolo Scarsella, Antonella Paladini declare they have nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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