Current Topics in Pharmacology
Vol. 24, 2020

Review

Use of nutraceuticals in peripheral compressive neuropathies: current clinical evidence and future perspectives

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ABSTRACT

Peripheral compressive neuropathies (PCNs) include several chronic syndromes, such as cervicobrachialgia, lumbalgia, lumbosciatalgia and carpal tunnel syndrome. All of these conditions are characterised by pain and sensorial symptoms, which include analgesia, paraesthesia and allodynia. In the absence of a surgical indication or in case of delayed intervention, the conservative treatment is based on both analgesic and anti-inflammatory drugs, with potential risks of side effects, particularly in elderly, and physical therapy. Thus, the search for effective and safe substances represents an unmet medical need. In this review, we examine the rationale for the development of a new multicomponent nutraceutical and its potential use in the treatment of PCNs. A multicomponent nutraceutical that contains acetyl-L-carnitine (ALC), palmitoylethanolamide (PEA), *Boswellia serrata* (BS), vitamin B6 and vitamin E has been recently developed (Kalanit®, Chiesi Farmaceutici S.p.A., Italy). We examine the possible mechanism of action of all components and the available clinical evidence in their clinical use in peripheral neuropathies. As a result of our search, it can be postulated that the new multicomponent nutracetical may be an effective and well tolerated supplement in the management of PCNs, either as a single agent or in combination with conventional pharmacological and/or physical therapies.

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KEYWORDS: peripheral compressive neuropathies, acetyl-L-carnitine, palmitoylethanolamide, *Boswellia serrata*, vitamin B6, vitamin E.

ABBREVIATIONS

AEA	:	Arachidonoilethanolamide
AKBA	:	Acetyl-11-keto-beta-boswellic acid
ALA	:	Alpha-lipoic acid
ALC	:	Acetyl-L-carnitine
BS	:	Boswellia serrata
BSA	:	Boswellic acids
CoA	:	Coenzyme A
CTS	:	Carpal tunnel syndrome
ERK	:	Extracellular signal regulated kinase
GABA	:	Gamma-aminobutyrric acid
GPR	:	G-protein coupled receptor
IL	:	Interleukin
NCV	:	Nerve conduction velocity
NGF	:	Nerve growth factor
NSAID	:	Non-steroidal antinflammatory drug
PCN	:	Peripheral compressive neuropathy
PEA	:	Palmitoylethanolamide
PN	:	Peripheral neuropathy
PPAR-α	:	Peroxisome proliferator-activated receptor-alfa
SFI	:	Sciatic functional index
TENS	:	Transcutaneous electrical nerve stimulation

Introduction

Peripheral neuropathy (PN) is characterised by a dysfunction of one or more peripheral nerves that leads to pain and sensorial alterations. Most PNs

may involve both motor and sensorial nerves and therefore may give origin to a variety of symptoms, which include mild-moderate pain, anaesthesia, paraesthesia and allodynia [1, 2]. If the injury does not stop rapidly, the patients may undergo worsening of both motor and sensorial symptoms. Nerve suffering may be caused by several factors and include various drugs, radiotherapy, toxic substances, certain endogenous metabolites with oxidative action (e.g. diabetic neuropathy) and several infective agents [3]. With the exception of diabetic neuropathy, which affects 25-40% of patients with diabetes mellitus, these forms are relatively rare in young adults, but their incidence greatly increases from the sixth decade of life [4, 5].

Peripheral compressive neuropathy (PCN), i.e. a neuropathy that is caused by an acute or chronic mechanic pressure of the nerve in one or more sites of its course, is a relatively common finding in clinical practice. The most common forms of PCN are: 1) the carpal tunnel syndrome (CTS), which affects one or both hands in 3-5% of adult population [6]; 2) the radicular syndromes that affect upper limbs (brachialgia and cervico-brachialgia) in about 15% of adult population [7]; and 3) the radicular syndromes of lower limbs (low back pain and lumbo-sciatica) that may affect 30-40% of elderly population [8].

The pathogenesis of peripheral compressive neuropathy: molecular and cellular mechanisms

Both CTS and radicular syndromes of upper and lower limbs are characterised by signs and symptoms caused by a nerve compression. For this reason, these syndromes are also called ‘entrapment syndromes’ [9]. In addition to the local compression, other conditions (e.g. diabetes mellitus) may increase the likelihood that a compressed nerve will undergo a pathological response. Moreover, an inflammatory reaction that may impair the normal gliding of the nerve can further contribute to the pathogenesis of PCN [10].

Irrespective of the type of nerve compression, the mechanical pressure around a nerve causes the same cellular and molecular alterations, which include: i) hypoxia/ischaemia due to the compression of vessels adjacent to the nerve for its total length [11], ii) deformation of myelin sheath due to flattening of Schwann cells [12], and iii) compression and deformation of the axon [12, 13]. These phenomena cause nerve (neuritis) or nerve root (radiculitis) inflammation, which in turn determines perineural oedema and recall of mastocytes from blood flow. Mastocytes release both vasodilating and algogenic substances, as well as cytokines, with primarily pro-apoptotic action, and secondarily pro-mitogen action on Schwann cells [14]. The inflammatory cascade is activated just few hours after the beginning of the pressory stimulation, as demonstrated in pioneering studies [15-17]. If the pressory stimulation is interrupted, a complete recovery can be achieved, but in case of persistent stimulation, the inflammatory cascade may involve the axon, with a consequent irreversible damage. Mastocytes leaked from the microcirculation release histamine and vasodilator prostaglandins, with consequent oedema around the nervous fibre and further increase of pressure that enhances the primary one. Recruiting of circulating macrophages takes place in the immediate following phase, which releases substances, particularly metalloproteinases, which damage the myelin sheath, thus giving origin to typical symptoms of PN [18, 19]. Glia cells, mastocytes and other cells contribute to neuropatic pain, both exciting nociceptive neurons and hyper-activating the pain neural loops in the spinal cord [20].

With regard to pathogenesis of CTS, hypotheses include increased pressure within the carpal tunnel due to strain, overuse, hyperfunction, and repeated or prolonged wrist extension. Chronic constriction nerve injury may be associated with infiltrating immune cells such as mast cells present in the nerve, while activated microglia are found in spinal cord [21]. Mast cells and microglia release algogenic mediators and interact with neurons to alter pain sensitivity, which contribute to the development/maintenance of symptoms characteristic of entrapment neuropathies [22].

Microscopic observations evidence a thinning of myelin sheath in the site of pressure, with consequent increase of electric dispersion: this phenomenon account for the reduction of the speed of conduction of the nervous impulse along

the axon, as evidenced in the electromyography and nerve conduction velocity (NCV) studies [23]. In experimental studies, it has been observed that, once the nerve pressure is ceased, the Schwann cells previously exposed to pro-apoptotic cytokines (demielinisation phase) are now stimulated by pro-mitotic cytokines, followed by a replicative phase (re-mielinisation), with potential return to a normal electric conduction [24, 25]. The role of macrophages in the secretion of pro-apoptotic and pro-mitotic cytokines in not shared by all researchers, but is the currently most reliable hypothesis [25, 26].

Treatment of peripheral compressive neuropathy: current options and future perspectives

Treatment of PCN is actually a challenge for the clinicians and an unresolved need for most patients. The low efficacy of currently available treatments is due to the physiopathological complexity of the mechanisms that cause symptoms of PCN. Apart from low back pain, in which pain is the predominant symptom, in most of the PCNs patients suffer from reduction of sensitivity, appearance of tingling at the extremities and reduction of muscular tone and strength that, in severe cases, may impair daily activities. Conservative treatments are based on both pharmacological and physical therapies. Non-steroidal anti-inflammatory drugs (NSAIDs) are poorly effective in neuropathic pain and totally ineffective in sensorial symptoms. Tricyclic antidepressants (e.g. imipramine, clomipramine) and anticonvulsants (e.g. gabapentin, carbamazepine) may improve both pain and sensorial symptoms, but should be taken lifelong and are difficult to manage, particularly in elderly or polytherapy patients [27, 28]. Benefits of physical therapy (e.g. laser therapy, ultrasounds), when applied, are generally of brief duration and there is lack of consensus on their real effectiveness [29, 30]. An ideal treatment for entrapment syndromes should be effective on both neuropathic pain and sensorial symptoms. Moreover, it should exert a neurotrophic action on both axon and glia to avoid the progressive degeneration of nervous fibres. Finally, but equally important, treatment should be safe and well tolerated for a chronic use and with few drug interactions. All these properties may be better met in a combination therapy rather than in a single drug approach. In recent years, nutraceuticals have become an interesting matter of research. A nutraceutical is defined as "*a food or part of a food that provides health benefits in addition to its nutritional content*" [31]. The term 'food' in the above definition may also include vegetables since they supply bioactive compounds effective in reducing the risk of many diseases. The interest towards the production of substances that are physiologically present in the human organism or are derived from plants used from centuries in the alternative medicine is based on several needs. The growing sensibilisation of patients towards an excessive use of traditional drugs and of chemicals in general, and the need for more natural remedies, has given a great impulse to development of nutraceuticals. Recently, the research in this field has led to a significant improvement in quality, as companies tend to apply to nutraceuticals the same principles and procedure used in the development of drugs [32]. The current evidence on characteristics and clinical experience with nutraceuticals that may have a potential benefit in the management of PN, as documented in the available literature, is reviewed in the next sections. Interest has been focused on those substances that have been reported in clinical trials to be effective, or to be potentially effective due to their mechanism of action, in the treatment of peripheral neuropathies in humans.

Acetyl-L-carnitine (ALC)

Acetyl-L-carnitine (ALC) can improve the function of different metabolic pathways in either central or peripheral neurons. ALC is the acetylated ester of carnitine, a substance naturally present in the human body, which is involved in the transport of free fatty acids from cytoplasm to the inner mitochondria, where it releases the transported fatty acid molecules and acetyl-coenzyme A (acetyl-CoA) [33]. At the mitochondria level, ALC acts on protein synthesis and transport and non-esterified fatty acid oxidation, thus contributing to the production of energy. Deficiency of ALC determines the depletion of the Krebs cycle, and thus of energy, due to the missing substrate. It is

agreed that part of the biological actions of ALC in the nerve cells is due to the competition between acetyl CoA and acetylcholine. This mechanism of action is based on the marked increase of acetylcholine in the nerve cells and of cholinergic transmission following ALC administration [34]. Moreover, several studies have documented that ALC stimulates the expression of both nerve growth factor (NGF) and its receptor, thus facilitating the processes of neuronal regeneration [35, 36].

Although several mechanisms that may determine neuropathic pain have been hypothesized, the modulation of glutammate receptor and an enhanced neuronal excitability due to excessive opening of sodium channels seem to be the basic mechanisms for all ALC forms, particularly on motor symptoms and pain [37]. The other important component, which mostly accounts for sensorial symptoms, is the reduced nerve tropism when undergoing a chronic compression. Whilst the mechanism by which ALC acts on neuropathic pain and to which extent the block of sodium channels is involved are not yet known, both the actions of ALC on the expression of the type 2 metabotropic receptor of glutammate (mGlu-2) and the neurotropic and neuroprotective mechanisms mediated by growth factors are well known [38, 39].

In animal models, ALC has been shown to be effective in lumbosacral radiculopathies [40] and in chemotherapy-induced neuropathies [41]. In trials (Table 1) conducted in patients with different types of peripheral neuropathy, in which daily doses of ALC varied between 500 mg and 3000 mg, ALC has been shown to be effective in diabetic neuropathies [42, 43] and in chemotherapy-induced neuropathies [44, 45]. In a published meta-analysis [46] based on the results of 3 studies comparing ALC and placebo (523 patients in total), ALC had a moderate effect in reducing pain in patients with peripheral neuropathic pain. Another recently published meta-analysis [47] that evaluated the effects of ALC in 6 trials conducted in patients with diabetic neuropathy has concluded that ALC appears to be effective in reducing pain due to diabetic neuropathy compared to active or placebo controls and in improving electromyographic parameters.

Overall, the results of studies conducted in humans suggest that ALC may be effective on both pain and sensorial symptoms associated to peripheral neuropathies of variable aetiology, including PCNs.

Palmitoylethanolamide (PEA)

Palmitoylethanolamide (PEA) is an endogenous fatty acid amide produced from the copulation of a saturated fat acid containing 16 atoms of carbon (palmitic acid) with etanolamine (Figure 1).

PEA was first identified in 1954 during the extraction of the lipidic fraction from the egg yolk, which is the greatest alimentary source of PEA [48]. High PEA concentrations are also present in soya lecithin, oil and peanut butter. PEA belongs to the class of etanolamides, a class of lipid mediators of the inflammation. It is synthesized in response to tissue injury/stress, as a mechanism to restore/maintain homeostasis with anti-inflammatory, pain-relieving and neuroprotective actions [49]. A number of studies on PCNs and other peripheral neuropathies have demonstrated that PEA exerts anti-inflammatory and anti-nociceptive actions: these effects seem to be mediated by both inhibition of mastocyte degranulation and modulation of macrophage response to inflammatory stimulations caused by compression of nerve sheath [50, 51]. The results of studies showing that PEA levels change in settings of tissue injury, especially in situations associated with inflammatory and neurodegenerative processes, and the large body of evidence showing that the systemic administration of PEA elicits anti-inflammatory, anti-nociceptive, and neuroprotective effects, support this hypothesis [49]. It has also been reported that PEA is subject to the mechanism of physiological mast cell regulation, in which mast cells are able to synthesize

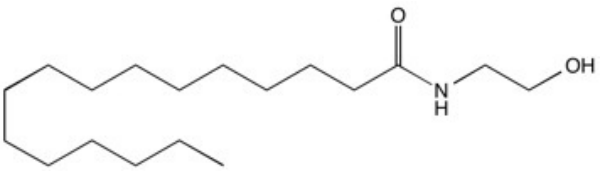

Figure 1. Chemical structure of Palmitoylethanolamide.

Table 1. Efficacy of Acetyl-L-carnitine in clinical trials including patients affected by peripheral neuropathies.

References	No. of patients	Type of neuropathy (aetiology)	ALC dose and route	Outcome variables	Results
[94]	94	Cervical and lumbosacral neuropathic pain	500 or 1.000 mg/day i.m. for 15 days	Pain VAS, neurological motility	ALC was superior to placebo in motility and pain VAS
[95]	1.097	Peripheral neuropathies of various aetiologies (including PCN)	1.000 mg/day i.m. for 10 days, then 2.000 mg/day oral for 20 days	NCV, neurological signs and symptoms	There were significant improvements in NCV in patients with impairment at baseline, and in pain intensity. Normalisation of neurological signs and symptoms was achieved in a significant proportion of patients
[96]	333	Diabetic neuropathy	1.000 mg/day i.m. for 10 days, then 2.000 mg/day oral for one year	NCV, pain VAS	ALC was superior to placebo in mean NCV (mainly in sensory sural, sensory ulnar and motor peroneal nerve) and amplitude (mainly in motor peroneal nerve) in patients with impairment at baseline. Mean VAS scores for pain were significantly reduced from baseline by 39% in LAC-treated patients compared with 8% in the placebo group
[42]	1.257	Diabetic neuropathy	500 or 1.000 mg/day oral for one year	Pain VAS, CSS, NCV	ALC was superior to placebo in pain improvement. Nerve conduction velocities and amplitudes did not improve, whereas vibration perception improved in the ALC group
[44]	25	Antineoplastic neuropathy	3.000 mg/day oral for 8 weeks	TNS, NCV	All patients except one reported symptomatic relief. Sensory neuropathy grade improved in 60% of patients, motor neuropathy in 79% of patients and TNS in 92% of patients.
[97]	90	Antiretroviral toxic neuropathy	1.000 mg/day i.m. for 42 days	Pain VAS, TSS, MPQ	ALC (1000 mg/day) was superior to placebo in reducing mean VAS. The proportion of patients with improvement in TSS was greater in the ALC group compared to placebo
[98]	64	Sciatic pain	1.180 mg/day oral for 60 days	NIS-LL, NSC-LL, TSS	ALC and tioctic acid (600 mg) were effective in clinical signs and symptoms. Mean improvements were greater with tioctic acid than with ALC

Table 1 continued..

References	No. of patients	Type of neuropathy (aetiology)	ALC dose and route	Outcome variables	Results
[45]	239	Chemotherapy-induced neuropathies	3.000 mg/day oral for 8 weeks	NCV, electrophysiology	Peripheral sensory neuropathy and electrophysiology parameters significantly improved with ALC compared to placebo.

Abbreviations: i.m. = intramuscular; VAS = Visual Analogue Scale; ALC = acetyl-L-carnitine; PCN = peripheral compressive neuropathies; NCV = Nerve Conduction Velocity; CSS = Clinical Symptoms Score; TNS = Total Neuropathy Score; MPQ = McGill Pain Questionnaire; NIS-LL = Neuropathy Impairment Score in the Lower Limbs questionnaire; NSC-LL = Neuropathy Symptoms and Change in the Lower Limbs questionnaire; TSS = Total Symptom Score.

Table 2. Efficacy of palmitoylethanolamide in clinical trials including patients affected by peripheral neuropathies.

References	No. of patients	Type of neuropathy (aetiology)	PEA dose and route	Outcome variables	Results
[99]	636	PCN	300 or 600 mg/day oral for 21 days	Pain VAS, RDQ	PEA 600 mg was superior to PEA 300 mg, and both PEA dosages were superior to placebo, on both pain and quality of life
[58]	111	PCN	300 mg/day oral for 21 days	Pain VAS, use of analgesics/ NSAIDs	PEA was superior to placebo on pain. PEA was associated with a significant reduced exposure to analgesics/NSAIDs vs. placebo
[100]	85	Lumbosciatica due to neuropathic pain	300 mg/day oral for 21 days	Pain VAS, ODI, SF-12	Treatment with PEA was more effective than standard treatment in pain VAS and physical component of the SF-12, with similar improvements in ODI
[101]	41	Neuropathic LBP	1.200 mg/day oral for 21 days, then 1.200 mg/day oral for 30 days	Pain VAS	At end of treatment, patients treated with PEA had significantly less pain compared to standard treatment
[102]	50	CTS in diabetes	1.200 mg/day oral for 2 months	Pain VAS, BCT, electrophysiology	Patients treated with PEA had improvements in pain VAS, functional status of the BCT questionnaire, SCV and SAP compared to untreated controls

Table 2 continued..

References	No. of patients	Type of neuropathy (aetiology)	PEA dose and route	Outcome variables	Results
[103]	20	Sciatic pain, LBP, hernia and vertebral stenosis	1.200 mg/day oral for 30 days plus oxycodone	Pain VAS	A significant decrease of pain VAS was observed at Day 30
[104]	26	CTS	600 or 1.200 mg/day oral for 30 days	Discomfort score, electrophysiology, Tinel's sign	PEA significantly improved the reduction of median nerve latency time, with dose-dependent effect. Tinel's sign presence and symptoms of discomfort were also reduced
[105]	610	Chronic pan due to different causes (439 patients with neuropathies)	1.200 mg/day oral for 21 days, then 600 mg/day oral for 28 days	NRS for pain	PEA significantly decreased pain intensity, irrespective of the associated pathological condition, including patients without concomitant analgesic therapy
[106]	118	Lumbosciatica due to neuropathic pain	600 mg/day oral for 30 days	Pain VAS, ODI, SF-12	Significantly larger improvements were seen in the PEA group compared to standard treatment for pain VAS and the physical component of the SF-12, with no significant effects between groups in ODI and mental component of the SF-12
[107]	112	Lumbosciatica	600 mg/day oral for 30 days	Pain VAS, ODI, SF-12	A significant decrease in pain and an increased quality of life in men were observed with PEA over standard therapy. Differences between groups were significant only for pain in women
[108]	61	CTS	600 mg/day oral for 60 days	Pain VAS, BCT, electrophysiology	Treatment with PEA elicited improvements in the functional status scale of the BCT compared to placebo, but not on clinical and electrophysiological parameters
[109]	100	LBP with or without lumbosciatica	1.200 mg/day oral for 30 days, then 600 mg/day oral for 30 days	Pain VAS	A significant decrease in pain VAS was observed after the first cycle of therapy, and was followed by a further decrease in the second cycle in patients with severe baseline pain

Abbreviations: PCN = peripheral compressive neuropathies; PEA = palmitoylethanolamide; VAS = Visual Analogue Scale; RDQ = Roland-Morris Disability Questionnaire; NSAIDs = non-steroidal anti-inflammatory drugs; ODI = Oswestry Disability Index; SF-12 = 12-item Short Form, LBP = low back pain; BCT = Boston Carpal Tunnel Questionnaire; SCV = sensory conduction velocity, SAP = sensory nerve action potential amplitude; NRS = numeric rating scale.

on demand the natural mediator PEA [52]. Effects of PEA are exerted by means of a double mechanism of action. On one hand, it has been demonstrated that PEA stimulates peroxisome proliferator-activated receptor-alfa (PPAR-α), a nuclear receptor expressed by a number of immune cells that plays a key role in the activation and maintenance of the inflammatory response [22, 53]. The involvement of PPAR-α in the mechanism of action of PEA has been demonstrated in a study [22], in which mice with an induced damage of the sciatic nerve were treated with subcutaneous PEA 30 mg/kg: on day 14, PEA prevented pain threshold alterations, whereas PPAR-α null mice did not respond to treatment. This study suggests that PEA can directly intervene in the nervous tissue alterations responsible for pain *via* a PPAR-α-mediated mechanism. On the other hand, the molecule shows affinity for G-protein coupled receptor (GPR)-55 and GPR-119, which are very similar to receptors for endogenous endocannabinoids CB1r and CB2r, toward which PEA does not possess a direct ligand capacity [54, 55]. However, a PEA analogue, arachidonoilethanolamide (AEA), better known as anandamide, is a potent ligand of CB1r and CB2r, and some authors hypothesize that the administration of PEA may increase the levels of endogenous amandamide, with indirect effect on opioid-type neuropathic pain [56, 57].

The effects of PEA on humans have been investigated in several trials conducted in patients with PN, including PCN. A search for trials with PEA published in the last 10 years has identified a number of trials, which included more than one thousand of patients treated with PEA (Table 2). Overall, studies reported a significant effect of PEA in the treated disease, although the extent of benefit varied based on the used dosage (300-600 mg). PEA resulted to be effective both when compared with placebo and when used as add-on therapy to conventional treatments, and in one trial [58] allowed a marked decrease in the use of NSAIDs and/or analgesics. The optimal dosage was 600 mg/day, either when given as a single agent or as add-on therapy.

A review published in 2015 [59] that examined the results of 8 studies with PEA in patients with nerve compression syndromes concluded that PEA proved to be effective and well tolerated. A pooled meta-analysis on 12 studies [60] that evaluated the efficacy and safety of micronized and ultra-micronized PEA on pain intensity in patients suffering from chronic and/or neuropathic pain showed that PEA elicits a progressive reduction of pain intensity significantly stronger than controls, irrespective of patients' age or gender, or the type of chronic pain. Another more recent review that evaluated the effects of PEA on pain [61] based on 10 studies including data from 786 patients who received PEA and 512 controls concluded that PEA may be a useful treatment for pain and is generally well tolerated, but further, well-designed, randomized, placebo-controlled trials are needed to provide reliable estimates of its efficacy. Synergistic effects of ALC combined with PEA have been reported in a mice model of neuropatic pain [62], in which doses of ALC 100 mg/kg and PEA 5 mg/kg that did not show a significant activity when given as single agents, determined a complete remission of neuropathic pain after 8 days of concomitant administration. Conversely, a significant alleviation of neuropatic pain was observed when ALC and PEA were given as single agents, but at higher doses (100 mg/kg and 10 mg/kg, respectively).

Boswellia serrata (BS)

The extract of resin produced by the ripe berries of the *Boswellia serrata* (BS) plant is used from centuries in the Indian traditional medicine for its anti-inflammatory and immunomodulant properties [63]. In the last 10 years, at least a dozen of biologically active substances has been extracted from this resin, all being moderately acid and known as Boswellic acids (BSA) [64, 65]. The mechanism of action of BSA, particularly of the acetyl-11-keto-beta-boswellic acid (AKBA), seems to be dual: i) inhibition of release of histamine from mastocytes, and hence inhibition of vasodilation and oedema [66]; ii) inhibition of 5-lipooxygenase, i.e. the enzyme responsible for the synthesis of leukotriens, which are in turn inducers of mastocyte degranulation and exert a peripheral vasodilating action [67].

A potentiation of antinociceptive effects of NSAIDs with the addition of AKBA has been demonstrated in a mice model of nociception [68].

The potential effects of AKBA on neurological pain has been studied in a murine model of lower limb radiculopathy induced by clamping of sciatic nerve, in which the administration of AKBA at three dose levels (1.5, 3 and 6 mg/kg/day) for 30 days was shown to promote the proliferation of Schwann cells and the functional recovery compared to controls [69]. The sciatic functional index (SFI), a measure of motor function obtained by evaluation of the footprint left on an absorbent paper according to a standard method [70], was evaluated at 10, 20 and 30 days. The effect of treatment on SFI was maximal for the 6 mg/kg dose, was less pronounced for the 3 mg/kg dose and was absent for the lowest dose. After 30 days from the injury, the net gain achieved with the administration of AKBA at the maximal dose (6 mg/kg/day) was equal to 18% ($p < 0.001$). Authors explained the beneficial effects of AKBA as a consequence of the activation of an extracellular kinase sensitive to specific chemicals or biological signals, probably hypoxia and the cellular apoptosis; this kinase is known as an extracellular signal regulated kinase (ERK). After 20 and 30 days from the AKBA administration at doses of 3 and 6 mg/kg, the ERK expression markedly increased, thus determining a rapid proliferation of Schwann cells and re-myelinisation of the affected nerve, as histologically documented. The re-myelinisation following ERK activation has been previously demonstrated by other researchers [71]. Authors of the article [69] concluded that the available data suggest that the increase in expression of ERK induced by AKBA 'promotes peripheral nerve regeneration with ERK protein phosphorylation playing a key role in this process'. However, authors also pointed out that the mechanism by which AKBA promotes the ERK expression remains unclear. Furthermore, it should also be clarified whether the benefit observed in the study is only due to re-myelinisation or also to a reduction of inflammatory and oedema-forming factors released after the nerve compression. The involvement of these factors cannot be ruled out, but the study did not include their assessment.

The effects of BS in humans have been investigated in a study [72] conducted in healthy volunteers in whom pain was elicited using a mechanical model. Subjects received an oral dose of BS 250 mg capsules or matched placebo. Mechanical pain was measured using an analgesymeter at baseline and at 1, 2 and 3 hours after test drug administration. The mean percentage change from baseline in pain threshold and pain tolerance force and time significantly improved in subjects treated with BS compared to placebo.

Vitamin B6 and other B vitamins

The biologically active form of vitamin B6 is the phosphorylated analogue of piridossalic acid, the piridossal-phosphate (PDF), in turn derived from the deamination of pyridoxine. Actually, both pyridine and pyridoxine may contribute to formation of PDF and, for this reason, both active substances can be administered in clinical studies with vitamin B6. Vitamin B6 is an essential coenzyme involved in a number of biological reactions, including the synthesis of some neurotransmitters, particularly the gamma-aminobutyrric acid (GABA), i.e. the target of gabapentin and pregabalin, which are the currently available most active drugs for the treatment of PN [73]. Furthermore, the serum levels of vitamin B6 in humans are inversely related with inflammatory markers and this mechanism may also be beneficial in PN [74]. A recent study demonstrated also that vitamin B6 in mesenchymal stem cells upregulated genes encoding cartilage extra cellular matrix components and SOX-9 gene, and counteracted the negative effects of interleukin (IL) β1, suggesting a role in preventing degenerative processes associated to inflammation and collagen alteration potentially involved in the pathogenesis of PCN [75].

Several trials have evaluated the effects of vitamin B6 on CTS and PN [76-78]. In one of the more recent studies [77], 40 patients with mono- or bilateral CTS were randomised to treatment with immobilisation plus pyridoxine 120 mg/day for 3 months (20 patients, 30 hands) or to conventional immobilisation only (25 patients, 30 hands). Assessments of symptoms and electromyographic characteristics (NCV and electromyography) were performed at baseline and at the end of study. At endpoint, a statistically significant ($p < 0.05$) decrease in the group treated with pyridoxine compared to control group was observed for the following symptoms; nocturnal pain, daily pain,

loss of sensitivity in fingers, muscular weakness and hand weakness. Regarding electric measures, a statistically significant improvement was observed only for the following 3 out of the 19 tested parameters: median nerve sensory latency, median nerve sensory amplitude and median nerve sensory conduction velocity.

In a study [79] conducted in 12 patients with severe CTS who were candidate to surgery, treatment with vitamin B6 150 mg/day was given for three months before surgery. Vitamin B6 blood levels were measured before and after supplementation and none of patients had levels below the normal range at baseline. At the end of treatment, 6 patients (50.0%) had a significant improvement of both symptoms and electrical parameters. To assess whether these effects were due to supplementation with pyridoxine, dosing was performed in the erythrocytes and it was observed that patients who benefited from treatment were those that had highest levels of intra-erythrocytes B6. As no other anatomical or biological parameters differed between the group of 6 patients that had an improvement in distal motor latency, i.e. a mean change from baseline of -0.63 msec, and the group of 6 patients with no change, i.e. a mean change from baseline of -0.1 msec ($p < 0.05$ between groups), authors attributed such effects to the increase of pyridoxine blood concentration. In another study in patients with CTS [76], treatment with vitamin B6 was associated with a significant improvement of pain, but without important changes in electric parameters. Although the mechanism of action of vitamin B6 on compression neuropathies is not known, an important amount of data suggests that vitamin B6 may be useful in these conditions.

Despite the encouraging results, benefits of vitamin B6 have not been reported in all studies in CTS. In a published review of studies performed in CTS, 8 out of the 14 examined studies confirmed the efficacy of vitamin B6, whereas other 6 studies did not find any difference compared to placebo or no treatment [80].

In addition to differences in results across studies, studies with vitamin B6 conducted in CTS have also shown great heterogeneity for a number of factors, which include study design, randomisation and methods of diagnosis of CTS [81]. This evidence suggests that further randomized, controlled, double-blind studies need to be conducted in which larger CTS populations undergo pre- and post-treatment clinical evaluation, electrodiagnostic testing, and vitamin B6 level determinations.

With regard to vitamin B2 and B12, a search from available libraries on published studies on the use of these two vitamins in any form of PN did not identify any article for vitamin B12, apart from the evidence of the association between neuropathy and severe deficiency of vitamin B2 or its transporters. Conversely, some articles have been found that depict the role of vitamin B12 on neuropatic pain, and most of them have shown that vitamin B12 was administered in addition to vitamin B6. Therefore, to date vitamin B6 appears to be the only vitamin belonging to group B that has been studied with noticeable results in the treatment of PCS. Nonetheless, there is clear evidence that the neurotropic vitamins B1, B6, and B12 share a biochemical synergy across many different pathways in the nervous system [82], as summarised in Table 3, which suggests that their combined use might have a role in the treatment of peripheral neuropathy. The potential synergistic effect of vitamins B1, B6, and B12 relies on their partially overlapping biochemical pathways coupled with their peculiar mechanisms that may be important for the nervous system, especially in the view of the multifactorial pathogenesis of peripheral neuropathies. Thus, it may be postulated that vitamin B1 has mainly an antioxidant action, while vitamin B6 may be primarily neuroprotective and vitamin B12 may have a myelin regenerating role [82]. This hypothesis is supported by the evidence from a study in rats with experimentally induced diabetic neuropathy [83], in which none of the individual B vitamins (B1, B6, and B12) was as effective in alleviating neuropathic pain and restoring nerve function as the combination of the three vitamins. Notably, in this study repeated daily treatment with the cocktail of B vitamins for 7-9 days, but no any single vitamin treatment, ameliorated tactile allodynia and formalin-evoked hyperalgesia in a dose-dependent manner, whereas only vitamin B6 improved sensory nerve conduction velocity slowing when given as single agent.

Table 3. Overview on major biochemical mechanisms of action of vitamins B1, B6, and B12 for nerve function (Calderon-Ospina and Nava-Mesa 2019).

Vitamin	Processes	Coenzyme for	Implication in nervous system
B1 (thiamine)	• Glycolysis • Pentose phosphate pathway • Krebs cycle (citric acid cycle)	• Pyruvate dehydrogenase • Transketolase • Alpha-ketoglutarate dehydrogenase	Provide energy to nerve cells which are needed for synthesis of nucleic acids, neurotransmitters, and myelin
B6 (pyridoxine)	• One-carbon unit metabolism • Hcy metabolism dopamine and serotonin synthesis	• Serine-hydroxymethyltransferase • Cystathionine-beta-synthase/lyase • Aromatic L-amino acid decarboxylase	Metabolism of amino acids, neurotransmitters, and DNA/RNA
B12 (cobalamin)	• Hcy metabolism • Methymalonyl CoA pathway	• Methionine synthase • Methylmalonyl CoA mutase	Metabolism of fatty acids, amino acids, neurotransmitters, myelin, and DNA/RNA

Vitamin E

Vitamin E is a complex of 8 liposoluble molecules, 4 tocopheroles (alpha, beta, gamma and delta) and 4 tochotrienoles, also numbered with the first 4 Greek alphabet letters. Alpha-tocopherole and gamma-tocopherole are the most active forms in human organisms. Vitamin E is one of the most important antioxidant agents of the human body. It is mainly localised on the cellular membrane of erythrocytes, within the mitochondria and on the mitochondrial membrane, where it exerts a neutralising function of oxygen free radicals produced during the Krebs cycle [84]. A less known function of vitamin E is that it has an active part in the regeneration of alpha-lipoic acid (ALA) with a bidirectional mechanism: when the ALA reserves are depleted by the excessive oxidative stress, vitamin D promotes the restoring of ALA levels; conversely, when the resources of vitamin E are poor and those of ALA are elevated, ALA promotes the biosynthesis of vitamin E [85]. The mechanism of regeneration of ALA/vitamin E seems to be mediated by vitamin C and experts agree that the known effects of ALA on PN are strongly linked to the recycle mechanism described in Figure 2 [86, 87]. ALA is both lipo- and hydro-soluble, particularly in its reduced form dihydrolipoic acid. Thus, ALA is an antioxidant with a ubiquitous action in all cellular districts. In addition to these important properties, which distinguish ALA from the other natural lipophilic of hydrophilic antioxidants, its presence in all cells makes its depletion easy. For this reason, the reserves of this substance seem to be favoured by both vitamin C (hydrophilic) and vitamin E (lipophilic). This allows to maintain ALA cellular concentrations at constant adequate levels, even in case that the intake of the molecule is lower than the minimal daily requirement.

It is not easy to distinguish the effects of vitamin E from those of ALA when a subject is supplemented. However, in studies conducted in subjects with hypovitaminosis E (plasmatic concentrations < 12 μmol/L), in which signs of motor and sensorial PN were progressively developed, the integration of diet with vitamin E resulted in a slow reduction of symptoms in a few months, together with improvement of electro-physiological parameters [88, 89].

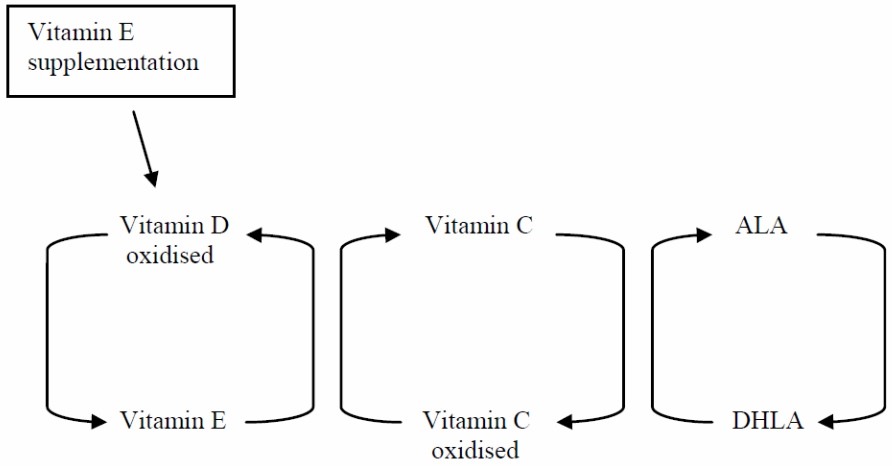

Figure 2. Mechanism of regeneration of ALA: vitamin E and vitamin C are strictly requested. Abbreviations: ALA = Alpha-lipoic acid; DHLA = Dihydro-Lipoic acid.

The antioxidant properties of vitamin E have been evaluated in studies conducted in patients with diabetic neuropathy. In a study [90] conducted in 21 patients with diabetic peripheral sensorimotor polyneuropathy, who were randomly assigned to receive either 900 mg vitamin E or placebo for 6 months, glycemic indexes did not show any significant changes during the study, whereas NCV in the median motor nerve fibers and tibial motor nerve distal latency improved significantly after 6 months of vitamin E supplementation. This study showed that defective nerve conduction in diabetic subjects with mild-to-moderate peripheral neuropathy may be improved by pharmacological doses of vitamin E supplementation. In another study [91], in which 92 patients with diabetic neuropathy were treated with pregabalin plus oral hypoglycemic agents or vitamin-E along with standard treatments, a significant decrease in blood glucose levels were observed in the group of patients treated with vitamin D, together with a significant reduction in total pain score and a significant improvement in physical health after 12 week of treatment. Authors concluded that vitamin-E is a natural antioxidant and it was found to be effective in reducing pain score in diabetic neuropathy patients. As further support of the maximised effects of ALC and PEA when given in combination with an antioxidant, the above described study in a mice model of neuropatic pain [62] showed that the co-administration of PEA 5 mg/kg micronised with polydatin (a substance with antioxidant activity) and LAC 10 mg/kg induced an almost complete remission of neuropatic pain after 8 days of treatment.

A multicomponent nutraceutical potentially effective in entrapment syndromes

A multicomponent nutraceutical developed by Chiesi Italy (Kalanit®, Chiesi Farmaceutici S.p.A., Parma, Italy) has been recently introduced in the Italian market. It contains five different substances: acetyl-L-carnitine (ALC), palmitoylethanolamide (PEA), *Boswellia serrata* (BS), vitamin B6 and vitamin E. This product has been developed taking into consideration the different molecular mechanisms responsible for the symptoms of PCN and the current evidence on the effects of each of the five components in clinical use. Due to its mixed composition, this multicomponent nutraceutical may be useful in the management of different conditions, which include: i) cervico-brachial radiculopathies, ii) low back pain; iii) lubosacral radiculopathies, and iv) tunnel carpal syndrome. The main properties and the current evidence of clinical characteristics of each component of the multicomponent nutraceutical are described in the previous sections.

To our knowledge, this is the only nutraceutical available on the Italian market that contains both PEA and BS, i.e. two anti-inflammatory agents

with a complementary mechanism of action, as well as it is the only patented nutraceutical that contains both PEA and ALC. Taking into consideration that the inflammation caused by vascular ischemia plays a key role in pain in PCNs, it has been considered that the BS extract may act by blocking one of the main pathways of painful symptoms. In the multicomponent nutracetical composition, vitamin E acts as an antioxidant and regenerating agent of alfa-lipic acid. ALC is known from some decades for its neuroprotectant and neuro-regenerating properties. Notably, although in the European Union ALC contained in nutraceuticals may be given up to the maximum dose of 1000 mg, the results of trials conducted in patients with different types of peripheral neuropathy, in which daily doses of ALC ranged between 500 mg and 3000 mg (Table 1), showed that ALC proved to be effective irrespective of the dose and route of administration.

It is essential that all substances of a multicomponent nutraceutical are well tolerated even for long-term treatment, to avoid that potential benefits due to the synergistic mode of action are outweighed by overexposure to risks of adverse effects. On the other hand, it would be advisable that the effects of the multicomponent nutraceutical would extend well beyond the period of observation that has been reported in the clinical experience with each of the five components.

From a safety perspective, the clinical experience has proved reassurance that all components of a multicomponent nutracetical are well tolerated in humans. It is well established that harmful side effects with the use of ALC are generally no more frequent than those reported with placebo. With regard to PEA, a number of studies have been conducted with varying numbers of subjects and varying durations of exposure (although rarely exceeding one month of treatment). When PEA has been given at the most common regimen of 300 mg twice a day, and up to the dose of 1200 mg/day, adverse effects have been reported to be absent. The safety of BS has been mainly investigated in toxicological studies [92], but the clinical experience has confirmed its safe use at doses tested in humans [72]. Vitamin B and vitamin E therapy given at doses tested in peripheral neuropathies is known to be generally safe and is associated with no or minimal adverse effects. However, it should be taken into consideration that studies on single ingredients of the multicomponent nutraceutical have been conducted on relatively short periods of treatment and that the risk/benefit profile of each single component following long-term exposure is not yet determined. Finally, any potential risk of interaction across individual components and with other drugs should be excluded.

Discussion

PCNs are a relatively common chronic condition in the general population. They are the most prevalent type of peripheral neuropathy and often represent a challenge to diagnose and treat. As a consequence, the scientific interest for neural pathology has increased exponentially over the past decade, and future research is needed to further contribute to the understanding of entrapment neuropathies. To meet this goal, a comprehensive scientific approach, including both molecular mechanisms and clinical studies, is required to better elucidate the pathogenetic mechanisms, assessment tools and their interpretation, as well as optimal management options for patients with entrapment neuropathies. Several therapies and procedures have been proposed in the management of PCNs, such as transcutaneous electrical nerve stimulation (TENS), plasma exchange, intravenous immune globulin, physical therapy or surgery, but none of these demonstrated an optimal long-term efficacy.

On the other hand, to date there are no effective and safe pharmacological therapies to treat these conditions, particularly in elderly patients, considering the potential side effect of different drugs.

Pain relievers or opioids, such as tramadol and oxycodone can lead to dependence and addiction, and hence these drugs generally are prescribed only when other treatments fail. Anti-seizure medications such as gabapentin may relieve nerve pain. Side effects can include drowsiness and dizziness. Also topical treatments such as capsaicin cream or lidocaine patches demonstrated modest improvements in peripheral neuropathy symptoms, but they can lead to local side effects. In addition,

certain tricyclic antidepressants, such as amitriptyline, or serotonin and norepinephrine reuptake inhibitors have been found to help relieve pain by interfering with chemical processes in brain and spinal cord that cause pain. Side effects of antidepressants may include dry mouth, nausea, drowsiness, dizziness, decreased appetite and constipation.

Due to the incidence of side effects with the use of conventional analgesics, there is a growing need, for both patients and health professionals, for products with low risk of adverse effects and no or minimal potential for drug interactions in the long-term use.

Neuroprotective therapeutic strategies through natural substances that reduce the risk of neurodegeneration are emerging. In recent years, complementary and alternative treatment modalities have been increasingly utilized by patients for neuropathy and neuropathic pain due to perceived lack of benefit from conventional medical treatment. In the management of the most common form of PCN, i.e. the CTS, the relatively high recurrence rate, potential complications of surgical intervention and patient preference make integrative therapies important options to consider when developing treatment plans for CTS. Furthermore, these therapies can be used in an integrative approach in conjunction with traditional approaches.

Among products alternative or complementary to standard pharmacological therapies that have been tested in patients with peripheral neuropathies, PEA has emerged as a potential nutraceutical, as this compound is naturally produced in many plant and animal food sources, as well as in cells and tissues of mammals (including the nervous system), and endowed with important neuroprotective, anti-inflammatory and analgesic actions [49]. PEA can be synthesized in case of demand. It is also well established that dietary supplementation of ALC may exert neuroprotective, neurotrophic, antidepressive and analgesic effects in painful neuropathies, has antioxidant and anti-apoptotic activity, and exerts neuromodulatory effects on both synaptic morphology and synaptic transmission [93]. Several published reports have highlighted the potential biological actions and molecular targets of BS plants, especially anti-inflammatory and chemopreventive activities at cellular level [92]. With regard to vitamin B family, there is ample evidence for a role of B vitamins (particularly vitamin B6) in the nervous system, where they are active in metabolic and physiologic processes needed for maintenance and nerve repair regeneration. Vitamin B6 is involved in a variety of biochemical reactions, including the amino acids and glycogen metabolism, the synthesis of nucleic acids, haemoglobin and several neurotransmitters, and contributes to normal functioning of nervous system. In addition, it seems to have a role in preventing degenerative processes associated to inflammation and collagen alteration potentially involved in the pathogenesis of PCN. Among the other natural vitamins, vitamin E contributes to cell protection from oxidative stress and circulating levels of vitamin E have been found to be significantly reduced in patients with peripheral neuropathy symptoms.

A multicomponent nutraceutical that may be useful in PNs in general, and particularly in PCNs, has been recently developed. It contains the five nutraceuticals that have been mostly used in the treatment of peripheral neuropathies and have proved to be promising, due to assumed neurotrophic action, low toxicity and favourable metabolic profile. The chemical composition of the multicomponent nutraceutical has been developed by analysing the experimental and clinical data available in literature for each of the components. As nutraceuticals are generally considered as less effective compared to drugs, the objective in the development of this multicomponent nutraceutical was to generate a mix of synergically acting substances, in order to act on painful and sensitive symptoms with one unique product.

Despite several studies have provided evidence on potential benefits of each of the five components of the multicomponent nutraceutical, these studies have strong limitations, including the following: i) the size of studies was generally small and very few studies included samples of patients adequate for a reliable assessment of efficacy and safety; ii) part of the studies lack a control group and are conducted on an open-label basis, and thus the reliability of subjective parameters measured by paints (e.g. pain via a VAS) may be questionable;

iii) there was a large variability in types of studied neuropatients, which include compression or entrapment syndromes, radiculopathies, neuropathic pain, diabetic or chemotherapy-induced neuropathies, which often coexist in the same trial. For these reasons, comparative, double blind studies vs. placebo or drugs commonly used in these conditions are needed to better understand if the recently developed multicomponent nutraceutical may be beneficial in the management of PCNs and in which type of PCNs benefits night be maximised; iv) the available trials have been conducted in relatively short period of observation, which generally lasted 1-2 months. The short period of treatment and observation did not allow to produce data on persistency of effects over time, which are of relevance in the context of conditions that may have a chronic outcome. Moreover, a long-term follow-up would also help to assess whether and to which extent potential benefits of treatment may be extended beyond the end of therapy. Finally, although all components of the multicomponent nutraceutical mix have a known safe profile, long-term risks of adverse effects and of interactions between components or with other drugs (the probability of comorbidities and of concomitant therapies is quite high in this setting of patients) should be excluded with suitable and well-designed clinical trials.

Conclusion

In conclusion, the large evidence on the pathogenesis, diagnosis and treatment of PCNs suggest that the use of specific nutraceuticals may be considered as replacement or as complement to the standard pharmacological treatments. In our review, our attention was focused on those nutraceuticals that, based on their pharmacological properties and available reports on their use in humans, may be considered as alternative treatment options in the management of peripheral neuropathies. As a result of our search, we have considered that a multicomponent nutraceutical containing five different substances with proven efficacy and safety (ALC, PEA, BS, vitamin B6 and vitamin E) may be an effective and well tolerated supplement for use in the management of PCNs, either as a single agent or in combination with conventional pharmacological and physical therapies.

The potential place in therapy of the multicomponent nutraceutical in patients with peripheral neuropathies should be investigated in double blind, placebo- or active-controlled randomised clinical trials with adequate sample sizes and duration of treatment. Findings from such studies may confirm whether the use of the multicomponent nutraceutical may be recommended in this indication, while gaining at the same time increasing awareness of the use of these substances, and information on potential drug interactions to minimize unwanted effects and adverse disease outcomes.

ACKNOWLEDGMENTS

We thank Dr. Luca Cantini (Medical Writer) for the contribution in medical writing activities for the preparation of the manuscript.

CONFLICT OF INTEREST STATEMENT

E. Baraldi is an employee of Chiesi Farmaceutici S.p.A., Parma, Italy, the company that markets Kalanit®.

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