

COMPLEMENTARY AND ALTERNATIVE TREATMENT OF MUSCULOSKELETAL PAIN

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SUMMARY – The use of complementary and alternative medicine (CAM) is high and increasing worldwide. Patients usually use CAM in addition to conventional medicine, mainly to treat pain. In a large number of cases, people use CAM for chronic musculoskeletal pain as in osteoarthritis, back pain, neck pain, or fibromyalgia. Herewith, a review is presented of CAM efficacy in treating musculoskeletal pain for which, however, no scientific research has so far provided evidence solid enough. In some rare cases where adequate pain control cannot be achieved, CAM might be considered in rational and individual approach based on the first general rule in medicine “not to harm” and on the utility theory of each intervention, i.e. according to the presumed mechanism of painful stimulus and with close monitoring of the patient’s response. Further high quality studies are warranted to elucidate the efficacy and side effects of CAM methods. Therefore, conventional medicine remains the main mode of treatment for patients with musculoskeletal painful conditions.

Key words: *Complementary therapies; Pain – treatment; Musculoskeletal diseases*

Introduction

The definition of complementary and alternative medicine (CAM) is broad and constantly changing. In different parts of the world, the term has different meaning, knowing especially the fact that one-third of the world’s population and more than half of the poorest people in Africa and Asia have no access to conventional medicine (CM) at all. The World Health Organization (WHO), as the umbrella institution for human health, defines CAM as “all forms of health care which usually lie outside the official health sector”¹. A definition by Cochrane Collaboration is: “Complementary and alternative medicine (CAM) is a broad domain of healing resources that encompasses

all health systems, modalities and practices and their accompanying theories and beliefs, other than those intrinsic to the politically dominant health system of a particular society or culture in a given historical period. CAM includes all such practices and ideas self-defined by their users as preventing or treating illness or promoting health and well-being. Boundaries within CAM and between the CAM domain and that of the dominant system are not always sharp or fixed”².

The use of CAM is high and increasing worldwide³. According to the study by Eisenberg *et al.*, the number of CAM users in the US increased in the period from 1990 to 1997 by more than 50%⁴, while data from 2001 showed the number of CAM users in the adult US population to amount to 67%⁵. A more recent study conducted by Callahan *et al.* revealed that as many as 82% of patients with arthritis followed in primary care and 90.5% of those followed by specialist had tried at least one complementary therapy for arthritis symptoms⁶. Longitudinal studies conducted

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in Great Britain confirmed this trend⁷⁻¹². According to the 1994 research by Fisher *et al.* in Western Europe, the percentage of population reporting use of CAM was between 20% (The Netherlands) and 49% (France)¹³. WHO reports that the number of patients in developed countries (including Western Europe) using at least one form of CAM is even 70%-80%¹⁴. As for Croatia, in the study by Čizmešija *et al.*, 53.5% of patients treated by primary care used CAM in addition to conventional health care and more than half of the respondents (59.6%) informed their doctor about it¹⁵.

The most common reason for the use of CAM is pain. The large numbers of patients who are using CAM are suffering from chronic musculoskeletal pain^{16,17}. The cause of chronic pain is usually multifactorial and complex. Immediate and complete relief of chronic pain can often be an unrealistic goal, so it is necessary to establish realistic targets in the treatment of these patients. These imply a pain relief approach according to the patient's life situation ("patient specific context"), ameliorating the patient's pain and/or improving the quality of life and improving the patient's risk profile by diminishing his/her need of polypharmacy, invasive interventions and/or unproven alternative therapies^{18,19}. This approach requires a broader picture in dealing with pain through integrative medicine that combines CAM and CM. Most patients using CAM do not waive the services of CM^{6,20,21}. However, according to a study conducted in Croatia, the most frequently mentioned cause of the use of CAM (with CM) is the need of a specific therapist who will help them solve the problem which CM has not recognized or has not find a solution for²².

CAM is carried out by doctors of medicine and other CAM practitioners (acupuncturists, chiropractors, Reiki practitioners, etc.). The status of these therapists is different in different countries. In the US, there is the National Center for Complementary and Alternative Medicine as part of the National Institutes of Health. In Croatia, they are gathered in the society of alternative therapists and healers of the Croatian Association for Natural, Energy and Spiritual Medicine (*Hrvatska udruga za prirodnu, energetsku i duhovnu medicinu*, HUPED). Croatia still has no legal framework for CAM, although efforts are currently in progress to define this area. The legislation in

the European Union (EU) is different from country to country and therefore the next steps in this area will certainly be towards harmonization of the CAM legislation in all EU countries, especially having in mind the fact that the increasing use of CAM inevitably increases the number of CAM side effects¹⁴.

People with musculoskeletal pain consume a lot of different "natural health products" and other interventions, the therapeutic efficacy, side effects and mechanisms of action of which have not yet been sufficiently clarified. The aim of this review is to evaluate the efficacy and safety of CAM for the treatment of musculoskeletal pain.

Acupuncture

Acupuncture is part of a larger system healing within the traditional Chinese medicine characterized by the insertion of fine, solid metallic needles into or through the skin at specific sites. It is more than 3000 years old. According to the traditional interpretation, bioenergy in the body flows through the meridians, which connect the surface of the body with the interior of the body, and the essence of acupuncture is that the stimulation of acupuncture points affects the "flow of energy"²³. A contemporary "Western" medical science fails to recognize the traditional interpretations of unblocking the "bioelectric magnetic force" ("QI") through the invisible energy channels (meridians) and tries to explain the possible analgesic effect of acupuncture through various neural, humoral and biomagnetic mechanisms such as changing neural innervation (local anesthesia at the insertion site completely reverses the analgesic effect of acupuncture)²⁴, by releasing endogenous opioids in the brainstem, subcortical and limbic structures²⁵, by releasing adenosine at the insertion site²⁶ and/or by changing the blood flow²⁷. In addition, when applying acupuncture, certain central nervous system (CNS) changes were observed on the functional magnetic resonance imaging (MRI)²⁸ and positron emission tomography (PET) scan²⁹. It has been shown that acupuncture as an adjuvant therapy may have beneficial effects in various diseases and musculoskeletal conditions. The two most common acupuncture therapy treatments are for neck pain and low back pain. A systematic review of the literature showed moderate evidence that chronic

mechanical neck pain was more effectively treated with acupuncture than with inactive treatment, measured immediately after treatment and during short-term monitoring (standardized mean difference -0.37 , 95% CI -0.61 to -0.12)³⁰⁻³⁴. There is limited evidence that, in the short-term period, acupuncture is more effective than massage³³. In cases of neck pain with radicular symptoms, it was found that, again in the short-term period, acupuncture was more effective than waiting list control³⁵. As for low back pain, the data do not allow firm conclusions about its effectiveness for acute pain. For chronic back pain, acupuncture was more effective in reducing pain and accelerating functional recovery immediately after treatment and during short-term monitoring, leading to the conclusion that in this indication it can be recommended as a supplement to other therapies³⁶. A meta-analysis conducted on studies with 6359 patients showed that real acupuncture was no better than "sham" acupuncture, but both were better than none, pointing out the importance of the placebo effect of acupuncture³⁷. The Cochrane Back Review Group paper, which included 20 studies, also found that the short-term effect of acupuncture was significantly better when compared to waiting list control or when acupuncture was added to another intervention³⁸. Acupuncture can reduce pain and improve joint function in patients with knee osteoarthritis (OA)³⁹. In a systematic review of literature on the effect of acupuncture in rheumatoid arthritis (RA), the authors found only two papers that met the methodological criteria and concluded that acupuncture showed no statistically significant effect on pain *versus* control group (relative improvement of 8%), although a tendency of decreasing pain was recorded (4 points on a 1-100 scale)^{40,41}. Based on the limited number of high-quality studies in fibromyalgia, the authors concluded that the treatment using real acupuncture was more effective than placebo acupuncture⁴². In order to reactivate and deactivate trigger points in the myofascial pain syndrome, "dry" injections and the injection of anesthetics had a similar effect^{43,44}. It seems that some types of acupuncture are more effective in achieving analgesia than others. This mainly refers to electroacupuncture, which strongly activates opioid and nonopioid analgesics⁴⁵. A relevant study on the effect of electroacupuncture is the one by Man *et al.*, where this method led to a

significant reduction in knee pain 24 hours after the treatment, with relative improvement of 66.6% compared to the placebo group. The relative improvement after 4 months was 5.1%, also in favor of the therapeutic group⁴⁶. It is of note that acupuncture is a safe method with few side effects. Minor and transient complications were observed in approximately 5% of cases, while serious side effects are very rare⁴⁷.

Yoga

Yoga is generally regarded as a CAM approach to health in order to improve flexibility, muscular and mental strength, emotional stability, self-confidence and peace of mind⁴⁸. A growing number of physicians and patients today recognize yoga as a complementary therapy option and try to incorporate it in the conventional methods of treating musculoskeletal diseases^{49,50}. One high quality study found that a 6-week training of Viniyoga (therapeutically oriented yoga) was slightly more effective than conventional exercise in chronic low back pain, with mean difference (MD) in Roland Morris disability questionnaire (RMDQ) of -1.8 (95% CI -3.5 to -0.1) and was moderately better than self-care educational book MD in RMDQ being -3.4 (95% CI -5.1 to -1.6)⁵¹. It has been shown that yoga has a beneficial effect in patients with knee OA as an addition to conventional treatment^{52,53}. A recent study revealed yoga (Iyengar yoga) to have a positive effect in decreasing pain, functional joint impairment and depression in patients with chronic back pain⁵⁴. Moreover, it was shown that it could reduce the symptoms of hand OA⁵⁵ and had beneficial effects in younger patients with RA⁵⁶. In a report which included 11 studies (4 randomized controlled trials (RCT) and 4 non-RCTs, heterogeneous methods of research, diagnosis and intervention), the authors' conclusion was that there was strong evidence that yoga reduced the symptoms of arthritis (swelling/tenderness of joints, pain) and disability, while reinforcing self-confidence and mental health⁵⁷. There still remains the question of the impact of other different types of yoga (Bikram, Vinyasa) on musculoskeletal symptoms.

Manual Medicine

The field of manual medicine consists of manipulation, mobilization, as well as massage and osteopathy.

Manipulation is by definition the application of high velocity and low amplitude manual thrusts to the joints slightly beyond the passive range of joint motion⁵⁸. Basically, in the spine it aims to change the mechanical behavior of the functional spinal unit. Mobilization is the application of manual force to the joints within the passive range of joint motion that does not include a thrust. In practice, manipulation and mobilization are mainly used in the same package of treatment. Although it is often related to chiropractic, spinal manipulation dates back to ancient times. Spinal manipulation is believed to have been practiced in China as far back as 2700 BC. Also, it is described in the Hippocrates' papers⁵⁹. In India, it was considered as an act of hygiene and it made part of surgery. The modern period of spine manipulation begins in 1975, when the first scientific conference in the USA was held⁶⁰. Manipulation and mobilization are most commonly used in treating back pain and neck pain, although there is still no consensus on the disorders which can be treated with manipulative techniques. It has been suggested that manipulation and mobilization should be used in segmental intervertebral joint dysfunction, subluxation or functional spinal lesions (FSL). The result of successful manipulation is the recovery of normal function and decreasing the symptoms caused by FSL. A systematic analysis of 42 studies by Bronfort *et al.* reviewed the efficacy of spinal manipulation and mobilization in patients with chronic low back pain. The authors' conclusion was that there was moderate evidence on spinal manipulation with strengthening exercises being as effective as the use of non-steroid anti-inflammatory drugs (NSAIDs) with therapeutic exercise (in the short-term and long-term follow-up). Furthermore, there was moderate evidence that mobilization was more efficient than therapeutic exercise, limited evidence that manipulation was better than physical therapy and home exercises, and that it was as effective as chemonucleolysis in cases of lumbar disk herniation, but less effective than therapeutic exercise after herniated disk surgery⁶¹. In their previous study, the same authors found moderate evidence that spinal manipulation had a better analgesic effect than mobilization and diathermy in patients with acute low back pain and limited evidence of faster recovery compared to conventional physical therapy⁶². Van Tulder *et al.* reviewed 25 randomized studies regarding spi-

nal manipulation in patients with acute and chronic back pain. They concluded that spinal manipulation was more effective than placebo and equally effective as other conservative treatment methods for back pain (drugs, physical therapy, medical gymnastics and low back pain school)⁶³. In another review, Assendelft *et al.* analyzed 39 RCTs and failed to find evidence that spinal manipulation was superior to other standard methods in the treatment of patients with acute or chronic back pain⁶⁴. As for chronic neck pain, in a systematic review, moderate evidence was found that spinal manipulation and mobilization reduced pain in the short-term and long-term period⁶⁵, and there was strong evidence for reducing pain and improvement of function when applying therapeutic exercise alongside with manipulation/mobilization⁶⁶. Spinal manipulation is the only CAM method for treating back pain incorporated in guidelines for the treatment of acute low back pain in some countries⁶¹.

Massage is a soft tissue manipulation technique applied for a localized pain caused by fascial muscle tension⁶⁷. It is part of standard therapy in physical and rehabilitation medicine, i.e. it is used in everyday clinical practice. A systematic review of papers on the effectiveness of massage in reducing back pain showed its impact on subacute and chronic nonspecific low back pain⁶⁸, but its effect on neck pain was not proved⁶⁹. In patients with knee OA it improved the function and decreased pain even in the long-term follow-up⁷⁰. It was shown that massage could decrease pain and improve the quality of life in patients with fibromyalgia, in the short-term⁷¹.

Osteopathy is a manipulative technique with a broader view in order to restore proper musculoskeletal function of the body. Therefore, it is defined as "the science, arts and philosophy, which is based on precise palpatory procedures and well-defined principles (functional unity, homeostasis, self-regulation, a holistic approach ...)". The founder of osteopathy was Andrew Taylor Still, an American physician and surgeon who laid its foundations back in 1874. Compared to other manipulative techniques, there are much less of clinical studies concerning osteopathy. A small study found that patients in an osteopathic treatment group required significantly less medication (pain killers, anti-inflammatory agents and muscle relaxants, for all $P < 0.001$) and used less physical therapy ($P < 0.05$)

than standard medical therapy group⁷². Arienti *et al.* from the Italian Institute of Osteopathy claimed that osteopathic treatment was effective in reducing pain in patients with spinal cord injuries⁷³. Because of the insufficiency of larger clinical studies and strong evidence for the effectiveness of osteopathic treatment, a rational approach and restraint is suggested.

Static Magnets

Static magnets are sold in different forms, e.g., incorporated into arm and leg wraps, mattress pads, bracelets, necklaces and shoe inserts⁷⁴. They are marketed with claims of effectiveness in reducing pain, although evidence of scientific principles of biological mechanisms to support such claims is very limited^{75,76}. Static magnets industry is a multi-billion dollar industry⁷⁷. Although the exact mechanism in pain reduction is not certain, the proposed one is the attenuation of neuronal depolarization by shifting the membrane resting potential of nociceptive C fibers⁷⁸ and/or promotion of an increase in blood flow through the skin and the subcutaneous and muscular tissue⁷⁹. A systematic review and a meta-analysis of 9 randomized placebo controlled trials failed to prove the efficacy of static magnets in pain reduction (weighted mean difference (WMD) on the 100-mm visual analog pain scale (VAS) was 2.1 mm, 95% CI 1.8 to 5.9 mm, $P=0.29$)⁷⁵. A study by Richmond *et al.* investigated the effect of magnetic and copper bracelets (2 groups wearing magnetic bracelets with different levels of magnetism, one group wearing copper and one group wearing demagnetized bracelets) over 16 months and concluded that there were no differences regarding pain, stiffness or physical function in patients with OA⁷⁶.

Supplements

Glucosamine, chondroitin, diacerein

Glucosamine and chondroitin are parts of proteoglycans. It has been proposed that glucosamine stimulates the production of glycosaminoglycans (the key structural components of cartilage) and normalizes the cartilage metabolism, inhibits its degradation and fibrillation, and have an anti-inflammatory effect, resulting in a decrease of pain and other symptoms, i.e. improving/maintaining function, as well as retarding the progression of OA^{80,81}.

A meta-analysis by Vlad *et al.* showed that the benefit from glucosamine and chondroitin was not proven, while glucosamine hydrochloride preparation alone was not efficacious⁸². In a recent systematic review including 25 studies with 4963 patients, the Cochrane Collaboration reported that the effectiveness of glucosamine was limited to glucosamine sulfate but was not demonstrated for glucosamine hydrochloride. Differences between the preparations of the original manufacturer (Rottapharm) compared to the others were also emphasized. Compared to placebo, the authors found a 22% decrease for pain and an 11% improvement of function (a change according to the initial value) by using Lequesne index, while, surprisingly, there was no statistically significant positive effect on the dimension of pain, function and stiffness in the WOMAC questionnaire⁸³. Similar to some international guidelines, the stand of the Croatian Society of Rheumatology is that, along with other therapeutic modalities, it might be rational to try to treat patients with knee/hip OA with glucosamine and/or chondroitin, and if the obvious response fails after 6 months, their usage should be stopped⁸⁴.

Diacerein is a derivative of anthraquinone, which has an inhibitory effect of IL-1 β *in vitro*. It also has a proven structural-modifying effect in patients with hip OA^{85,86} as well as a mild analgesic effect^{87,88}. Diarrhea and flatulence are the most common side effects. In Croatia, diacerein is not registered.

Lipids

Avocado/soybean unsaponifiables (ASU)

The most thoroughly investigated lipid mixture is Piascledine (Pharmascience, Inc., Montreal, Quebec, Canada). Piascledine consists of 1/3 avocado and 2/3 non-saponified soybean, the oil fraction, which does not create soap after saponification. Four double-blind placebo-controlled studies and one systematic review evaluated the effect of avocado/soybean unsaponifiables (ASU) on hip and knee OA⁸⁹⁻⁹³. Two three-month RCTs, one for knee OA and hip OA⁸⁹ and the other only for hip OA⁹⁰, showed that 300 mg ASU once a day reduced the NSAID intake. A six-month RCT on the effect of ASUs on hip and knee OA confirmed its significant positive effect on OA symptoms when compared to placebo⁹¹. In a 2-year study on hip

OA, 300 mg once a day did not slow down narrowing of the joint space width⁹². A systematic review of the impact of ASUs suggested further research because three RCTs confirmed its good performance, but a long-term RCT denied it⁹³. The conclusion of recent studies points to the positive effect of ASUs for knee and hip OA⁹⁴, as well as for rheumatoid arthritis (RA)⁹⁵.

Polyunsaturated fatty acids (PUFAs)

Polyunsaturated fatty acids (PUFAs) are classified as n-3, n-6 and n-9, depending on the position of the last double bond in the fatty acid chain. The main dietary PUFAs are n-3 (linolenic and eicosapentaenoic acid) and n-6 (linoleic and arachidonic acid). Omega 3 is found in soybean oil, canola oil, flaxseeds, walnuts and fish oils, whereas omega 6 can be found in safflower, corn, soybean, sunflower oils and meat. The modern western diet is relatively low in omega 3 fatty acids and relatively rich in omega 6 acids in comparison with the western preindustrial societies and eastern countries diet. Laboratory and animal studies have shown that diet rich in omega 3 fatty acids may be beneficial for patients with joint diseases⁹⁶. In a meta-analysis of placebo-controlled studies it has been concluded that omega 3 fatty acids can relieve joint in doses greater than 2.7 g for a period longer than 3 months, with a remark that studies were of variable quality⁹⁷. According to the best evidence synthesis in a meta-analysis that observed the products made from a lipid extract from New Zealand green lipped mussel (*Perna canalicus*) rich in omega 3 fatty acids, limited evidence for their efficacy in OA and other joint diseases has been shown⁹⁸.

Cetyl myristoleate

Cetyl myristoleate (CMO) is the cetyl ester of myristolic acid. It has been identified as an anti-inflammatory agent and as an immune system modulator. Two relevant trials have been performed until now. In the first RCT, oral CMO capsules were compared with placebo capsules (six capsules/day over 68 days of treatment) among 64 patients with chronic knee OA over 68 days of treatment. Patients treated with CMO capsules had a significantly increased knee flexion (10.1°) compared with the placebo group (1.1°) and function, but there was no difference in knee ex-

tension⁹⁹. In the second trial, CMO topical application was compared with placebo topical application among 40 patients with knee OA. Patients applied a standardized amount of cream over a 10- to 12-cm area two times daily for 30 days. Patients applying CMO cream demonstrated greater improvements in the range of movement and function and no major adverse effects were reported¹⁰⁰.

Phytochemicals and Plants (Extracts)

Ginger (Zingiber officinale) and turmeric (Curcuma longa)

People with musculoskeletal pain consume a lot of different 'natural health products' therapeutic efficacy, toxicity and mechanisms of action of which have not yet been sufficiently clarified. Ginger and turmeric are herbs from the same family (Zingiberaceae). Ginger is a very popular spice produced in more than 100,000 tons *per* year worldwide. In the traditional medicine of Japan, China and India, it is known and recognized for its anti-inflammatory effect on musculoskeletal diseases¹⁰¹. Studies on the effect of ginger on musculoskeletal pain are contradictory. In some studies it was shown to be moderately more efficient than placebo in reducing symptoms in treating knee OA^{102,103}; in one study, its efficacy did not differ from that of placebo in the first 3 months, however, demonstrating superiority in the next 3 months¹⁰⁴, whereas in another study there was no difference in the efficacy when compared to placebo¹⁰⁵.

The most comprehensive reporting of adverse events found these in 59% of patients receiving ginger extract compared with 37% of those receiving placebo, with gastrointestinal events particularly relating to eructation, dyspepsia and nausea as most pronounced (45% of patients taking Ginger *vs.* 16% of those taking placebo), although 70% of them were evaluated as mild. None of other trials has reported any overall excess in adverse events, although bad taste was reported in those taking ginger extract¹⁰².

Some preliminary studies showed that turmeric could somewhat improve symptoms in rheumatoid arthritis, but at concentrations no greater than those to be taken with food¹⁰⁶. So, ginger and turmeric are safe for consumption, but in small quantities have no proven effect on chronic painful rheumatic conditions.

White willow bark (*Salix alba*)

White willow bark contains salicin. Salicin is rapidly metabolized into salicylic acid, which is known to have analgesic, anti-inflammatory and antipyretic effects. The acetylated derivative of salicylic acid is Aspirin.

In the first trial, willow bark extract (dose equivalent to 240 mg salicin/day) was compared with placebo over a 2-week treatment period in 78 patients with hip or knee OA. There was a statistically significant difference in change in pain using the Western Ontario MacMaster Questionnaire (WOMAC) (willow bark 14% reduction *vs.* placebo 2% increase; $P < 0.05$)¹⁰⁷. In the second trial in 127 patients with knee or hip OA, willow bark at the same daily dose as the first trial was compared with both placebo and diclofenac sodium 100 mg/day over a 6-week period. Assessing pain by the WOMAC, willow bark was more efficacious in reducing pain than placebo (47 *vs.* 17%) and no different from diclofenac sodium (10%)¹⁰⁸. Adverse effects such as increased blood pressure, stomach upset and allergic reactions were reported.

Devil's claw (*Harpagophytum procumbens*)

Devil's claw (*Harpagophytum procumbens*) is a South African plant that grows in the regions bordering the Kalahari. Secondary tuberous roots are used to prepare powders of extracts based on the content of harpagoside, which is thought to have anti-inflammatory and anti-degradation effects. This herbal medicine, at a dose of six capsules/day (each containing 435 mg cryoground powder), was compared with diacerein 100 mg/day for a period of 4 months in 122 patients with hip and knee OA. Over the course of the study, there was improvement in pain and disability, but with no difference between treatments. Subjects taking devil's claw reported lower use of analgesics and NSAIDs. There were significantly fewer adverse event reports in the devil's claw group (16 *vs.* 34%) than in diacerein group¹⁰⁹.

Chili pepper (*Capsicum frutescens*)

Chili (spicy, cayenne) pepper contains capsaicin, which has analgesic effects. In Europe and America, topical preparations containing cayenne pepper are mainly used for the relief of pain associated with os-

teoarthritis, rheumatoid arthritis, sore muscles and joints, and for improving the circulation¹¹⁰.

According to the Cochrane Back Group study, white willow bark, devil's claw and chili pepper have significant effects in reducing pain in patients suffering from low back pain compared with placebo¹¹¹. Recent studies showed moderate evidence of effectiveness of white willow bark in reducing pain in patients with low back pain who took salicin in a dose of 240 mg for 6 weeks¹¹², as well as reduction of pain after using capsaicin for OA pain¹¹³.

Pine bark

This herbal extract has been tested in the treatment of knee OA. In the first trial including 100 patients, after 3 months of treatment with Pycnogenol 150 mg daily, the patients reported reduced pain ($P < 0.04$) and improvement in function ($P < 0.05$), whereas those on placebo demonstrated no change¹¹⁴. In the second trial that included 156 patients who were taking Pycnogenol 50 mg twice daily also reported significant improvements in function, whereas there were no changes in the placebo group. They also demonstrated a decreased use of NSAIDs (58% *vs.* 1% reduction) and consequently of gastrointestinal complications (63% *vs.* 3% reduction)¹¹⁵. No serious adverse effects were noted on Pycnogenol in either trial.

Rose hip

The efficiency of this herbal medicine has been tested against placebo in three studies in patients with OA, with sample sizes ranging between 94 and 112¹¹⁶⁻¹¹⁸. The tested doses were 1 g for 4 months, 5 g of Hyben Vital (a standardized powder) for 3 months and the same preparation for 4 months. In all three trials, there were at least some positive results regarding the use of rose hip. In a cross-over trial that included patients with OA of several sites, there was a highly statistically significant difference just for the first treatment period, an effect that the authors viewed as signaling a strong carry-over effect¹¹⁶. In the second trial in patients with hip or knee OA, at the end of the 3-month follow-up there was a significant improvement in those taking rose hip regarding performing activities of daily life, stiffness, patient global assessment, although there was no significant difference

in pain¹¹⁷. In the last trial that also included patients with knee or hip OA, both pain and hip range of motion (although not the knee range of motion) had improved more in the rose hip group¹¹⁸. None of the trials reported any difference in adverse events between the groups.

***Boswellia serrata* (Indian roots)**

Its efficacy in knee OA was tested in three RCTs¹¹⁹⁻¹²¹. The first trial was a placebo controlled trial with a cross-over design, involving 30 patients. When receiving *Boswellia (B.) serrata*, the patients demonstrated significantly greater reduction in pain, swelling and improvement in function over 8-week treatment with 333 mg of the product three times daily. The second trial tested 5-Loxin, which is an extract of *B. serrata* enriched with 30% 3-*O*-acetyl-11-keto-beta-boswellic acid. Seventy-five subjects received 100 or 250 mg 5-Loxin, or placebo, for 90 days. Both doses of 5-Loxin conferred significant pain and function improvement compared with placebo ($P < 0.0001$ for both doses). In the last trial, *B. serrata* 333 mg three times daily was tested against valdecoxib 10 mg once daily for 6 months. At the end of the study, both *B. serrata* and valdecoxib demonstrated significant reduction in pain from baseline and the latter also in function ($P < 0.001$ all). One month after stopping treatment, the group taking *B. serrata* demonstrated maintained improvement regarding pain and function ($P < 0.001$). There were no serious adverse events reported in any study nor were adverse events of any sort significantly more common in the groups taking *B. serrata*.

Flavonoids, Uncaria, bromelainin

For some other plants or their ingredients, such as flavonoids (polyphenolic compounds in plants: tea-containing cathesins, soy isoflavonoids), *Uncaria tomentosa* and *Uncaria guianensis* (cat's claw, extract from root and inner bark of a South American vine), no evidence was found or there was the lack of evidence for their efficiency¹²².

Regarding bromelainin, which is an extract from both the stems and immature fruits of the pineapple plant, which contains a number of proteolytic enzymes with anti-inflammatory, analgesic, antiedematous, antithrombotic and fibrinolytic effects, limited

evidence was found for its effectiveness in OA, while it may have negative effect on cardiac rhythm⁹⁶.

Cannabis

There are many differences of opinion regarding the use of cannabis for medical purposes. A study conducted in The Netherlands was in favor of smoking cannabis for medical purposes¹²³. Result was good to excellent reduction in symptoms in most patients (64%) with neurological and musculoskeletal diseases and cancer anorexia/cachexia, with mostly mild side effects. A recent study by Ware *et al.* showed that smoking marijuana can reduce neuropathic pain and posttraumatic postoperative pain measured on an 11-point scale (5.4:6.1 MD, 95% CI 0.02 to 1.4; $P = 0.023$) and improve sleep ($P < 0.05$), at least for 3 months¹²⁴. The prevalent attitude is that in spite of moderate effectiveness of treating chronic pain with cannabis, it is still considered inferior to its potential harm¹²⁵. A study by Xu *et al.*, published this year, stated the ability to treat neuropathic pain with new drugs which target the CB2 receptors mostly located in the peripheral immune system (as opposed to CB1 receptors, which are mostly in the brain)¹²⁶. It opens new opportunities to create drugs with fewer side effects in treating this kind of pain.

Pomegranate, green tea, grapes

Pomegranate, green tea and resveratrol from grapes are examples of compounds whose possible analgesic and anti-inflammatory mechanisms have been recently elucidated in the article by Khalife *et al.*¹²⁷. Standardized Pomegranate Extract (PE) specifically reduces certain biochemical factors whose cascade regulates the anti-inflammatory genes and can potentially reduce cartilage destruction in OA¹²⁸. The anti-arthritis effect of green tea may be attributed to the epigallocatechin-3-gallate (EGCG) and can result in reduced synovial hyperplasia, cartilage degradation and bone resorption by protecting human chondrocytes from IL-1 β induced inflammatory responses^{129,130}. Resveratrol from grapes shows anti-inflammatory and chondroprotective activity by increasing proteoglycan synthesis and proliferation of chondrocytes and therefore may act as prevention in intervertebral disk degeneration, inflammatory changes in OA, apoptosis of chondrocytes and pannus formation¹³¹.

Articulim F

This ayurvedic herbal preparation was tested in a cross-over study in 42 patients with symptomatic OA who also had radiological changes on the affected joints. After 3-month treatment with Articulim F or placebo two capsules daily allocated in random order, patients who received Articulim F had significantly better improvement in pain and function. However, there was no difference in joint structural changes according to radiological evaluation. No adverse effects necessitating discontinuation of Articulim F have been reported¹³².

Eazmov capsules

This ayurvedic herbal preparation (*Cyperus rotundus*, *Tiospora cordifolia*, *Saussurea lappa*, *Picorrhiza kurroa* and *Zingiber officinale*) was compared with diclofenac sodium, each 50 mg three times daily, in 31 patients with OA. After 6 months of treatment, the patients who received Eazmov had less improvement in pain ($P < 0.001$) and disability ($P < 0.05$) comparing to diclofenac. However, significantly fewer adverse effects were reported by the patients allocated to Eazmov¹³³.

Vitamins

Generally, vitamins are used as supplements in case of their deficiency. Some vitamins might have an impact on musculoskeletal diseases, mainly as antioxidants. They are able to neutralize most kinds of reactive oxygen species (ROS) with a degradation effect by enzymes such as superoxide dismutase, catalase and peroxidase, or by small antioxidant molecules. When ROS are produced in increased amounts as in OA, the antioxidant capacity of cells and tissues can become insufficient to detoxify the ROS, which then contribute to cartilage degradation by inhibiting matrix synthesis, directly degrading matrix molecules or activating matrix metalloproteinases¹³⁴.

Vitamin C is mostly (80%-90%) found in food (rose hips, blackcurrant, citrus fruits), but can also be synthesized from glucose. The Framingham epidemiological study showed a threefold reduction in the risk of OA progression for the middle and highest tertiles of vitamin C intake, as well as a reduced loss of cartilage¹³⁵. In a high-quality RCT, taking large amounts of vitamin C (2x1 g) led to a decrease of pain

on the VAS scale by 4-6 mm (the baseline value was 50 mm)¹³⁶. However, regarding the recommendation of taking high doses of vitamin C, especially for older people who suffer from OA, there is the need of further research which will look into the long-term effect, as well as in the safety of vitamin C.

Vitamin E was tested (in its natural form in 8 shapes or as α -tocopherol) in five RCTs. The results were divergent. Two studies showed that vitamin E was superior to placebo (vitamin E intake of 600 mg *per day*¹³⁷ and 400 IU of α -tocopherylacetate once a day¹³⁸), one showed that the effect of vitamin E (544 mg α -tocopherylacetate) was equal to the effect of diclofenac (150 mg/day) on the VAS scale of pain¹³⁹, while in two recent studies the efficacy of vitamin E was not better than placebo^{140,141}. One of the richest food sources of vitamin E is edible plant oil.

The B-complex group includes choline and inositol as well as para-aminobenzoic acid that is naturally paired with B group vitamins¹⁴². The term B-complex was created because in the past it was believed that it was just one kind of vitamin found in the extract of rice, liver or yeast. Later, the vitamins were isolated and given numbers: B1 (thiamin), B2 (riboflavin), B3 (nicotinic acid), B5 (pantothenic acid), B6 (pyridoxine), B9 (folic acid) and B12 (cyanocobalamin). Two older RCTs showed that high doses of B vitamins had no effect on pain^{143,144}. In one trial, B complex was tested among 26 patients with hand OA who had been prescribed NSAIDs. The subjects were randomly allocated to 6400 μ g folate daily with or without 20 μ g cobalamin or lactose placebo for a 2-month period. There were less tender hand joints and grip strength was greater in those receiving the folate-cobalamin combination¹⁴³. In the other trial of niacinamide, 72 patients took one tablet six times daily (total 3000 mg) or placebo for 12 weeks. Pain level did not change on placebo but was significantly reduced in those taking niacinamide, whereas the measurement of global arthritis impact improved in those on niacinamide [-29% (95% CI -6, -46)] and significantly worsened in those on placebo¹⁴⁵. In the latter trial, significantly more subjects on niacinamide reported side effects (40 *vs.* 27%; $P = 0.03$), mostly due to heartburn and nausea.

In addition, there was no evidence that a cocktail of vitamins (A, C, D) and selenium reduced the symptoms of osteoarthritis¹⁴².

Vitamin D is for historical reasons included in vitamins, although the majority of its characteristics indicate it is a hormone (steroid structure, mechanism of action)¹⁴⁶. Vitamin D is considered a prohormone with different active metabolites that play an important role in many physiological processes including the metabolism of bone and cartilage¹⁴⁷, the muscles¹⁴⁸, and lately an inverse correlation of its serum levels with disease activity in early polyarthritis¹⁴⁹ has also been emphasized. A Framingham study found a three times greater increase in the risk of hip OA progression in the middle and lowest tertile of serum vitamin D¹⁵⁰. A study on osteoporotic fractures in women noticed an increased risk of incident hip OA (joint space narrowing), which might be associated with pain at medium and lowest tertile of serum vitamin D¹⁵¹. A research by the European Male Aging Study Group revealed that patients with musculoskeletal pain had lower levels of serum vitamin D¹⁵². Indirect effects of vitamin D on pain have been reported by Bishoff *et al.*, as in their study the consumption of vitamin D (and calcium supplements) reduced the risk of fall by even 49%¹⁵³.

Glucosides

Natural remedies that contain glucosides derived from white peony root extract are believed to have anti-inflammatory, antioxidant and immunoregulatory effects. In the changed inflamed joints, a several-fold concentration of nitric oxide (NO) has been recorded, as well as increased activity of the enzyme that regulates its formation^{154,155}. Glucosides inhibit the increased levels of NO in painful and inflamed joints and change its concentration back to normal levels, thus having the potential of reducing pain and stiffness of the joints. Their effect is achieved at the molecular level, which has so far been proven in preclinical studies¹⁵⁶⁻¹⁵⁸, although there are some encouraging studies with the observation of the favorable effect of total glucosides alongside with disease-modifying antirheumatic drugs (DMARDs)¹⁵⁹⁻¹⁶¹.

Methylsulfonylmethane (MSM)

Methylsulfonylmethane (MSM) is an organic sulfur compound, which is a precursor of dimethyl sulfoxide (DMSO). It is found in very low amounts in fruits, corn, tomatoes, tea, coffee and milk. The effica-

cy of MSM in the treatment of knee OA was tested in three trials with sample sizes ranging between 50 and 118 subjects¹⁶²⁻¹⁶⁴. In all trials, MSM (at doses of 1.5, 3.375 and 6 g/day for 12 weeks) was found to be significantly more effective in improving pain compared to placebo. It was also more effective in improving function in two trials^{162,163}, and in the third one when combined with glucosamine¹⁶⁴. Adverse events were either similar between MSM and placebo groups^{162,163} or no adverse events were reported¹⁶⁶. However, a meta-analysis of 3 high-quality studies by Brien *et al.* showed that current data could not support recommendation for the use of MSM/DMSO in the treatment of OA¹⁶⁵.

S-adenosyl methionine

The efficacy of S-adenosyl methionine (SAME) in treating OA of the knee, hip or spine has been tested in six trials with sample sizes ranging between 36 and 493¹⁶⁶⁻¹⁷¹. In all trials, the dose tested was 1200 mg *per day* and the comparators were celecoxib 200 mg/day (16 weeks of treatment), piroxicam 20 mg/day (12 weeks), indomethacin 150 mg/day (28 days), ibuprofen 1200 mg/day (two trials, 30 days both), naproxen 750 mg/day and placebo (30 days). In all trials, SAME was found to be equivalent in efficacy as NSAID and more effective than placebo for pain and function where this was measured separately for a global score of which pain and function were a major part^{170,171}. In a meta-analysis of the efficacy and safety, which included trials of i.v. administration, there was no significant difference between the likelihood of patients taking SAME and placebo to report adverse effect but patients taking SAME were less likely to report an adverse event than those taking an NSAID (odds ratio (OR) 0.42; 95% CI 0.29 to 0.61). The drop-out rate in the trials was highest for those receiving an NSAID (6.9%), followed by placebo (5%) and lowest for SAME (2.6%)¹⁷².

Topical rubefacients

Rubefacients (which contain salicylates and nicotinamides) cause skin irritation and are believed to reduce various musculoskeletal pain. A systematic review by Matthews *et al.* showed that according to the results of 7 RCTs (6 placebo and 1 active controlled study) there was no evidence to sup-

port the notion that topical rubefacients may suppress acute painful conditions. Regarding their effect on chronic pain, an analysis of 9 RCTs (7 placebo and 2 active controlled studies) showed that they were not as effective as topical NSAIDs¹⁷³.

Hyperimmune milk

In two RCTs, the effect of hyperimmune milk in OA was tested. This milk is produced by cows that are immunized with intestinal bacterial antigens in order to get milk with an increased concentration of high molecular weight immunoglobulins (IgG) and supposed to contain anti-inflammatory low weight components. The efficiency of hyperimmune milk has not been scientifically verified^{174,175}.

Collagen hydrolysate

Collagen hydrolysate is generated by enzymatic degradation of gelatin, which itself is produced by hydrolysis of collagen extracted from animal bones and skin. *In vitro*, type I or type II collagen hydrolysate dose dependently increased type II synthesis by chondrocytes¹⁷⁶. In mice, it accumulates in the articular cartilage¹⁷⁷. Its effect on musculoskeletal symptoms has not been proven^{178,179}.

Mind-Body Therapy

Mind-body therapies include cognitive behavioral therapy, hypnosis, biofeedback and mindfulness meditation. For many patients, the addition of a mind-body approach to treating chronic pain has a beneficial effect on their quality of life. From the above stated therapies, cognitive behavioral therapy is often included in the conventional treatment of chronic pain and relies on scientifically based knowledge and theories of cognition, emotions and behavior, their interaction and possibilities to change¹⁸⁰. The report of the Cochrane group (40 studies) showed that cognitive behavioral therapy had a favorable effect on pain, disability and mood¹⁸¹.

Conclusion

There is an extremely large number of products and CAM interventions on the market today, which are mainly presented through the media as effective

in treating musculoskeletal pain. The majority of data presented in this paper are of insufficient methodological quality, there is a striking paucity of RCTs, evidence is based on a small number of trials which generally included a small number of patients. One must take in consideration the publication bias favoring papers with positive results.

So, generally, with some exceptions, there is no solid enough scientific evidence to support the use of CAM in musculoskeletal painful conditions. To be able to clearly define the mechanism of action of most of the CAM interventions, additional high-quality studies that deal with their molecular basis and mechanism of action are required, while clinical data are missing too. On the other hand, most of CAM medications/interventions are free from major adverse effects and usually are associated with minor adverse effects. A rational attitude using them only in some situations when conventional medicine is not effective in controlling pain might be considered, but always keeping in mind the first rule of medicine "not to harm".

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Sažetak

KOMPLEMENTARNO I ALTERNATIVNO LIJEČENJE MIŠIĆINOKOŠTANE BOLI

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Diljem svijeta zabilježen je porast učestalosti uporabe proizvoda i usluga komplementarne i alternativne medicine (KAM). Bolesnici primjenjuju KAM zajedno s metodama konvencionalne medicine i to prvenstveno za liječenje boli. U velikom broju slučajeva radi se o kroničnoj mišićnokoštanoj boli, primjerice kod osteoartitisa, križobolje, vratobolje ili fibromijalgije. U ovom se preglednom radu prikazuje učinkovitost KAM u liječenju mišićnokoštane boli, za koju zasada ne postoje čvrsti znanstveni dokazi. U nekih, i to rijetkih bolesnika u kojih se nikako ne može postići zadovoljavajuća kontrola boli eventualno bi se mogla razmotriti mogućnost primjene KAM u sklopu racionalnog i individualnog pristupa temeljenog na općem pravilu „ne štetiti bolesniku” i na korisnosti primjene tih metoda u pojedinog bolesnika, odnosno u skladu s pretpostavljenim mehanizmom bolnog podražaja, a uza strogo praćenje terapijskog odgovora. Postoji potreba za studijama visoke kvalitete kojima bi se razjasnilo pitanje učinkovitosti i nuspojava KAM. Stoga konvencionalna medicina ostaje glavni način liječenja bolesnika s bolnim mišićnokoštanim stanjima.

Ključne riječi: Komplementarno liječenje; Bol – liječenje; Mišićnokoštane bolesti