

## INTEGRATIVE MEDICINE SECTION

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# Conditional Recommendations for Specific Dietary Ingredients as an Approach to Chronic Musculoskeletal Pain: Evidence-Based Decision Aid for Health Care Providers, Participants, and Policy Makers

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### Abstract

**Objective.** Approximately 55–76% of Service members use dietary supplements for various reasons; although such use has become popular for a wide range of pain conditions, decisions to use supplements are often driven by information that is not evidence-based. This work evaluates whether the current research on dietary ingredients for chronic musculoskeletal pain provides sufficient evidence to inform decisions for practice and self-care, specifically for Special Operations Forces personnel. **Methods.** A steering committee convened to develop research questions and factors required for decision-making. Key databases were searched through August 2016. Eligible systematic reviews and randomized controlled trials were assessed for methodological quality. Meta-analysis was applied where feasible. GRADE was used to determine confidence in the effect estimates. A decision table was constructed to make evidence-informed judgments across factors required for decision-making, and recommendations were made for practice and self-care use. **Results.** Nineteen dietary ingredients were included. Conditional evidence-based recommendations were made for the use of avocado soybean unsaponifiables, capsaicin, curcuma, ginger, glucosamine, melatonin, polyunsaturated fatty acids, and vitamin D. In these cases, desirable effects outweighed undesirable effects, but there was uncertainty about the trade-offs, either because the evidence was low quality or because benefits and downsides were closely balanced. **Conclusions.** The evidence showed that certain dietary ingredients, when taken as part of a balanced diet and/or as a supplement (e.g., pill, tablet, capsule, cream), may alleviate musculoskeletal pain with no to minimal risk of harm. This finding emphasizes and reinforces the critical importance of shared decision-making between Operators and their health care providers.

**Key Words:** Systematic Review; Meta-analysis; Dietary Ingredients; Dietary Supplements; Musculoskeletal Pain

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## Introduction

Musculoskeletal (MSK) injuries are a leading cause of pain, medical encounters, lost duty time, and disability within the military due to the extreme demands of physical training and combat missions [1–3]. Although MSK pain is typically treated with medications (e.g., nonsteroidal anti-inflammatories [NSAIDs], injections, physical therapy, acupuncture, and other modalities [4]), alternative approaches are needed. Dietary ingredients may be one such option. Dietary supplement use for a wide range of conditions, including pain, has become increasingly popular, with about 70–74% of the general adult population and 55–76% of Service members using dietary supplements for various reasons [5,6]. Despite their popularity, evidence for their use is unclear [7–10], and decisions to use these supplements may be driven by information that is not evidence-based (e.g., advice from peers, family members, and other sources). It is imperative that evidence-based research be used to inform decisions regarding such use to ensure safe and effective management of MSK pain.

As part of the US Special Operations Command's Preservation of the Force and Family Behavioral Health Program, this project sought to determine whether current research on dietary ingredients for chronic MSK pain could provide sufficient evidence to inform decisions for both practice and self-care use. To achieve this, state-of-the-science evidence methodologies were applied to provide clear, comprehensive, and unbiased information to the Special Operations community and enable key stakeholders and subject matter experts to make evidence-based recommendations to inform policy decisions regarding dietary ingredients for improving pain and pain-related (e.g., psychological health, quality of life) outcomes.

The aim of this article is to describe the resulting evidence-based recommendations made for the use of dietary supplements. This paper is the second in a series of articles [11–13] that detail the methodological approach and relevance of this work to Special Operators, specific evidence-based recommendations, and implications for policy decisions. It is important to note that although formal processes were followed and recommendations made, this is not intended to serve as a formal clinical practice guideline.

## Methods

The project's full methodological approach is detailed within the first of this series of three articles ([Supplementary Data: Detailed Methodology](#)) [13]. Briefly, 1) the authors followed the Institute of Medicine guidelines to ensure transparent processes were followed and mitigate any conflicts of interest to carefully select and recruit an unbiased group of key stakeholders and subject matter experts [14]. The committee, named the

Holistic Evidence Review Board (HERB), was convened to develop the criteria to inform the clinical question(s), definitions ([Table 1](#)) [4,15–19], and factors required for decision-making ([Supplementary Data: GRADE Grid](#)); 2) a review team, independent of the HERB, then conducted a series of systematic reviews to assess the current state of the evidence and to explore the safety and efficacy of various dietary ingredients for treating pain and related outcomes ([Supplementary Data: Summary Report](#)); 3) the gathered evidence was integrated with the expertise of those subject matter experts; and 4) modified Delphi methods were used to develop evidence-based recommendations for the use of dietary ingredients and priority areas in need of future research following the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework [13,20–23]. The series of systematic reviews used to inform recommendations are reported in the [Supplementary Data: Summary Report](#).

Conditional recommendations were made when the desirable anticipated effects outweighed the undesirable effects but there was uncertainty about the trade-offs, either because the key evidence was of low quality or because the benefits and downsides were closely balanced. No recommendations were made either because the quality of the evidence was too low or trade-offs were so closely balanced that any recommendation would be too speculative. Recommendations against the current use of an ingredient, based on available evidence, were made when undesirable anticipated effects outweighed the desirable effects or the downsides clearly outweighed the benefits overall.

## Results

Nineteen dietary ingredients were identified and evaluated using systematic review methods ([Supplementary Data: Detailed Methodology and Summary Report](#)) [13]. Integrating the evidence with the HERB clinical acumen across the factors required for decision-making, three types of recommendations were ultimately made for these dietary ingredients ([Figure 1](#)).

This article details dietary ingredients for which conditional, evidence-based recommendations were ultimately made; recommended ingredients include avocado soybean unsaponifiables (ASU) [24–30], capsaicin [31–41], curcuma [42–51], ginger [52–62], glucosamine [63–68], melatonin [69–71], polyunsaturated fatty acids (PUFA) [72], and vitamin D [73–85].

Although uncertainties remain, thereby precluding any strong recommendations for immediate use, these dietary ingredients, when taken as part of a balanced diet, applied as a cream, or administered as a supplement, may help alleviate pain from chronic MSK conditions and are suggested for use. In these cases, health care providers should be prepared to help individuals make decisions consistent with their own values, and Special

**Table 1.** Focused PICOS used to define the narrowed research question: Are there dietary supplements/ingredients that can safely mitigate chronic pain in adults (18+ years old) with musculoskeletal disorders?

|                    |   |
|--------------------|---|
| Population         | <ul style="list-style-type: none"> <li>Adults (18+ years) with chronic pain due to musculoskeletal disorders.</li> <li>Chronic pain was defined as ongoing or recurrent pain, lasting beyond the usual course of acute illness or injury (i.e., &gt;3 months and occurring at least half of the days over the past 6 months), and which adversely affects the individual's well-being [4, 15].</li> <li>Musculoskeletal pain was defined as pain affecting the bones, muscles, ligaments, or disorders of the muscles, nerves, tendons, joints, and cartilage, and disorders of the nerves, tendons, muscles, and supporting structures of the upper and lower limbs, neck, and lower back that are caused, precipitated, or exacerbated by sudden exertion or prolonged exposure to physical factors such as repetition, force, vibration, or awkward posture [16, 17]. Note that headaches/migraines and musculoskeletal pain conditions resulting from another disease or injury (e.g., fracture, contusion, abrasion, laceration) were excluded.</li> </ul> |
| Intervention       | Any single or multiple (e.g., combination of ingredients) dietary ingredient(s) [18, 19].   |
| Control/comparison | Sham, no treatment and/or active comparator.  |
| Outcome(s)         | Pain, physical function, sleep, mood (anxiety/depression), stress, cognitive performance, global health, health-related quality of life, behavioral, resource use, adverse events.  |
| Study design       | Peer-reviewed systematic reviews/meta-analyses and/or randomized controlled trials presented in the English language.   |

PICOS = Population, Intervention, Comparison, Outcomes and Study Designs.

|  |
|--|
| <p><b>Conditional Recommendation For</b></p> <ul style="list-style-type: none"> <li>✓ Avocado Soybean Unsaponifiables</li> <li>✓ Capsaicin</li> <li>✓ Curcuma*</li> <li>✓ Ginger*</li> <li>✓ Glucosamine, Prescription, Over-the-Counter</li> <li>✓ Melatonin</li> <li>✓ Polyunsaturated Fatty Acids</li> <li>✓ Vitamin D</li> </ul> <p><b>No Recommendation</b></p> <ul style="list-style-type: none"> <li>• Boswellia</li> <li>• Ginger*</li> <li>• Rose Hip</li> <li>• S-adenosyl-L-methionine</li> </ul> <p><b>Recommendation Against</b></p> <ul style="list-style-type: none"> <li>• Collagen</li> <li>• Creatine</li> <li>• Devil's Claw</li> <li>• L-carnitine</li> <li>• Methylsulfonylmethane</li> <li>• Pycnogenol</li> <li>• Vitamin E</li> <li>• Willow Bark Extract</li> </ul> |
|--|

\*Conditionally recommend use as a food source, not as a dietary supplement, at this time.

**Figure 1.** Recommendations.

Operators should be aware of the potential benefits and discuss the use of these ingredients with a provider. Because no strong recommendations were made to endorse an ingredient for immediate use without any caveats, there is a need to encourage discussion and debate among stakeholders before policy decisions are made.

### Conditional Evidence-Based Recommendations

Table 2 displays the ingredients where conditional recommendations were made, the graded evidence for efficacy as well as safety and other considerations examined when making recommendations. Table 3 details the summary of judgments across factors and resulting recommendations.

#### Avocado Soybean Unsaponifiables

Avocado soybean unsaponifiables are a natural vegetable extract made from one-third avocado oil and two-thirds soybean oil. ASU are commonly used for osteoarthritis symptoms, as it is believed that they slow down disease progression [86,87].

Six studies meeting the review's criteria compared ASU with placebo or chondroitin sulfate in knee and/or hip osteoarthritis populations [24–29]. Studies administered 300 or 600 mg/d of ASU for anywhere from three months to three years (Table 2; Supplementary Data: Summary Report).

Conditional recommendations were made (75% weak, in favor; 12.5% none; 12.5% weak, against) for the use of Piascledine® 300 (300–600 mg/d), a commercialized brand of ASU, as a dietary supplement for pain and related symptoms.

The low to moderate quality and certainty of the evidence suggests that Piascledine 300 or 600 mg/d is associated with a statistically significant reduction in pain (standardized mean difference [SMD] = -0.60) and improvement in function (SMD = -0.64) as compared with placebo at time points of three to six months' duration. (Supplementary Data: Summary Report). These desirable anticipated effects appeared to be moderate, whereas any undesirable effects, primarily gastrointestinal complaints noted across all treatment groups, were small to trivial. There was a high degree of statistically significant heterogeneity detected from the pooled studies, as well as risk of bias associated with some studies. Additionally, the small sample sizes reduced the certainty of the evidence evaluated.

Research trials to date appear to consistently report on the use of Piascledine 300, the majority of which are funded by the same entity that supplied the intervention. Although ASU appear to be available over the counter (OTC) and in combination with other "joint health" supplements, evidence to support their use in these formulations is unknown. Resources required for the use of ASU are highly dependent on the type of formulary. For

Table 2. Summary of findings

| Ingredient Evaluated   | Comparators                | No. Studies/Participants | Populations  | Outcomes  | Evidence  | Quality   | Adverse Events  | Considerations  |
|--|----------------------------|--------------------------|--|---|---|---|---|---|
| ASU <sup>†</sup><br>300–600 mg/d over<br>3 mo–3 y  | vs placebo <sup>‡</sup>    | 5/1,150                  | Osteoarthritis   | Pain reduction,<br>3–36 mo<br>Pain reduction,<br>3–6 mo<br>Global function, 3–36<br>mo<br>Global function, 3–6<br>mo<br>Patient's global<br>assessment for<br>improvement,<br>3–12 mo<br>No. of patients<br>requiring use of<br>medication,<br>3–36 mo  | SMD (5 trials)<br>= -0.34, 8.5 pts<br>greater reduction<br>than placebo<br>SMD (3 trials) =<br>-0.60, 15 pts<br>greater reduction<br>than placebo<br>SMD (5 trials) =<br>-0.42<br>SMD (3 trials) =<br>-0.64<br>RD (4 trials) =<br>-0.14<br>RD (3 trials) =<br>-0.13 | Moderate<br>⊕⊕⊕○<br>Low<br>⊕⊕○○<br>Moderate<br>⊕⊕⊕○<br>Moderate<br>⊕⊕⊕○<br>Moderate<br>⊕⊕⊕○<br>Moderate<br>⊕⊕⊕○ | Mainly minor gastrointes-<br>tinal complaints in both<br>groups. No noticeable<br>differences between<br>ASU dosages.<br>Risk to experience any<br>AE:<br>vs placebo: NS<br>vs drug: insufficient data  | <ul style="list-style-type: none"> <li>Moderate-quality evi-<br/>dence supports taking<br/>ASU 300–600 mg/d to<br/>reduce pain, improve<br/>function, and reduce<br/>medication use over<br/>time.</li> <li>Concern that all eval-<br/>uated research was on<br/>a single-producer<br/>commercialized prod-<br/>uct (i.e., Piasclidine)<br/>that appeared to be<br/>funded by the prod-<br/>uct's manufacturer.</li> <li>Need to investigate<br/>whether Piasclidine is<br/>available and feasible<br/>to obtain.</li> <li>Need more research<br/>on OTC version be-<br/>fore recommending an<br/>OTC version.</li> </ul> |
| Capsaicin <sup>‡</sup><br>Patches (0.1% or<br>22–37.4 ug/cm <sup>2</sup> ):<br>4–12 h over 3–4<br>wk<br>Creams (0.0125–<br>0.25%): 2–4 x/d<br>over 3–12 wk | vs placebo<br><br>vs other | 8/1,159<br><br>2/194     | Back pain, myofas-<br>cial/soft tissue pain,<br>TMJ, osteoarthri-<br>tis, rheumatoid<br>arthritis<br><br>Fibromyalgia,<br>osteoarthritis | Pain reduction, mean<br>4 wk<br>Patient's global as-<br>sessment for im-<br>provement, mean 4<br>wk<br>Only one study compared capsaicin with another comparator<br>(i.e., usual care). Both high (i.e., 0.25% capsaicin) and<br>low (i.e., 0.025% capsaicin) doses were effective. Although a<br>higher dose may produce more burning sensation, the<br>application of the product may be required less frequently,<br>and preliminary evidence suggests that pain relief<br>occurs quicker at this higher dose. | SMD (8 trials) =<br>-0.56, 14.0 pts<br>greater reduction<br>than placebo<br>RD (7 trials) =<br>-0.21  | High<br>⊕⊕⊕⊕<br>High<br>⊕⊕⊕⊕  | Primarily burning, itch-<br>ing, and irritation<br>reported in both<br>groups; more partici-<br>pants in the capsaicin<br>group seemed to report<br>adverse events com-<br>pared with the placebo<br>group.<br>Risk to experience any<br>AE:<br>vs placebo: NS; heteroge-<br>neity detected<br>vs drug: insufficient data | <ul style="list-style-type: none"> <li>High-quality evidence<br/>supports capsaicin to<br/>reduce pain and rec-<br/>ommends it as either a<br/>cream or a patch, at<br/>lower doses to begin<br/>treatment.</li> <li>Indicated for neuro-<br/>pathic pain as second-<br/>line treatment; may<br/>also be effective for<br/>musculoskeletal pain.</li> <li>Be aware of possible<br/>burning sensation<br/>upon application, es-<br/>pecially at higher<br/>doses (0.25%).</li> <li>Invest in resources in<br/>dose response study to<br/>understand dose re-<br/>sponse curve.</li> </ul>                                  |

(continued)

Table 2. continued

| Ingredient Evaluated  | Comparators  | No. Studies/Participants | Populations                         | Outcomes   | Evidence  | Quality   | Adverse Events   | Considerations   |
|---|--|--------------------------|-------------------------------------|--|---|---|--|--|
| Curcuma* <sup>†</sup><br>700–2,000 mg/d<br>over 6–12 wk                                   | vs placebo   | 3/223 <sup>‡</sup>       | Osteoarthritis                      | Pain reduction, mean 2 mo<br>Global function, mean 2 mo<br>Reliance on medication, mean 2 mo   | SMD (3 trials) = -1.05, 26.25 pts greater reduction than placebo<br>SMD (3 trials) = -0.87<br>RD (3 trials) = -0.50 | Low<br>⊕⊕○○<br>Very low<br>⊕○○○<br>Very low<br>⊕○○○ | Mainly minor gastrointestinal complaints in both groups.<br>Risk to experience any AE:<br>vs placebo: insufficient data<br>vs drug: insufficient data  | <ul style="list-style-type: none"> <li>Curcuma is suggested as a useful dietary source (500 mg 2–3x/d) but is not recommended as a dietary supplement until there is more high-quality evidence available.</li> <li>Available in food and should be considered as a dietary source.</li> <li>High-priority research area due to potentially large beneficial effects.</li> <li>Need to develop a robust research protocol to enhance the quality of the evidence.</li> </ul> |
|   | vs other   | 5/72 <sup>‡</sup>        | Osteoarthritis rheumatoid arthritis | Studies (N = 2) comparing curcuma with ibuprofen seemed to indicate improvement in pain over time and, in some cases, more improvement than ibuprofen. Another study also found curcuma to be generally superior to glucosamine sulfate. |   |   |  | <ul style="list-style-type: none"> <li>Need to develop a robust research protocol to enhance the quality of the evidence.</li> </ul>   |
|   | *Studies (N = 3) combining curcuma with other ingredients showed promising results, significantly improving pain and physical function compared with placebo but not celecoxib.  |                          |                                     |  |   |   |  |  |
| Ginger* <sup>†</sup><br>Capsule: 250–1,000 mg/d over 3–12 wk<br>Ointment: 6 g/d over 6 wk | vs placebo <sup>‡</sup>  | 6/741                    | Osteoarthritis                      | Pain reduction<br>Self-reported disability   | SMD (5 trials) = -0.30, 7.5 pts greater reduction than placebo<br>SMD (4 trials) = -0.22                            | Moderate<br>⊕⊕⊕○<br>Moderate<br>⊕⊕⊕○                | Bad taste or various forms of stomach upset; none “serious” but some resulted in trial discontinuation.<br>Risk to experience any AE:<br>vs placebo: 12% greater risk for someone to experience an AE following ginger (RD = 0.12, 95% CI = 0.02, 0.23, P = 0.02, I <sup>2</sup> = 49.00%)<br>vs drug: insufficient data | <ul style="list-style-type: none"> <li>Insufficient strong research on use as a supplement.</li> <li>Already available in tea/food; no additional risk in obtaining ginger via food sources.</li> <li>Divergent opinions regarding feasibility, acceptability, and suitability.</li> <li>Invest more in research, specifically in larger trials.</li> </ul>  |
|   | vs other <sup>‡</sup>  | 2/187                    | Osteoarthritis                      | Two studies compared ginger with ibuprofen and reported mixed results. The higher the dose (e.g., 1,000 mg), the more likely a positive benefit for ginger only.   |   |   |  |  |
|   | *Studies combining ginger (N = 4) with other ingredients were heterogeneous. Overall, combination products showed positive benefit for reducing pain and possibly overall health/quality of life but not for improving function. |                          |                                     |  |   |   |  |  |

(continued)

Table 2. continued

| Ingredient Evaluated                               | Comparators | No. Studies/ Participants          | Populations                                   | Outcomes  | Evidence  | Quality   | Adverse Events  | Considerations   |
|--|-------------|------------------------------------|---|---|---|---|---|--|
| Glucosamine Rx/<br>OTC <sup>†</sup>                | vs varying  | 3 trials on<br>pCGS,<br>RottaPharm | Osteoarthritis                                | Pain reduction  | SMD (3 trials) =<br>-0.27, 6.75 pts<br>greater reduction<br>than comparator | Moderate<br>⊕⊕⊕○  | Although may cause nau-<br>sea, heartburn, diar-<br>rhea, constipation,<br>drowsiness, skin reac-<br>tion or headache, glu-<br>cosamine sulfate at<br>1,500 mg/d is tolerated<br>at least as well as 1,200<br>mg/d of ibuprofen.              | <ul style="list-style-type: none"> <li>Moderate-quality evi-<br/>dence supports the use<br/>of glucosamine in the<br/>form of pCGS at<br/>1,500 mg/d and sug-<br/>gests that it has simi-<br/>lar effects to<br/>ibuprofen but takes<br/>longer to obtain a<br/>response.</li> <li>Effects of pCGS com-<br/>bined with prescrip-<br/>tion chondroitin are<br/>still unknown.</li> <li>pCGS implementation<br/>requires obtaining a<br/>supplement with the<br/>same purity levels of<br/>the pCGS ingredients.</li> <li>OTC appears safe,<br/>but types and effects<br/>of formulations are<br/>unknown.</li> <li>Consider OTC dosage<br/>and interference with<br/>other products.</li> </ul> |
| Melatonin <sup>§</sup><br>3–10 mg/d over<br>4–8 wk | vs placebo  | 1/32                               | Myofascial temporo-<br>mandibular<br>disorder | Pain<br>Sleep   | $P < 0.05$<br>$P < 0.05$  | Insufficient data<br>to determine<br>the quality of<br>evidence | No studies reported on<br>AEs; non-RCTs report<br>that side effects (e.g.,<br>drowsiness, headache,<br>dizziness, nausea) are<br>uncommon.<br>Risk to experience any<br>AE:<br>vs placebo: insufficient<br>data<br>vs drug: insufficient data | <ul style="list-style-type: none"> <li>Melatonin is broadly<br/>used, accepted, and<br/>available in Rx and<br/>OTC versions as a<br/>sleep aid. It may also<br/>help with combating<br/>pain, although the re-<br/>search is yet of low-<br/>quality evidence.</li> <li>Although available as<br/>10 mg capsules, lower<br/>doses of 3–5 mg/d are<br/>only recommend until<br/>more and higher-qual-<br/>ity evidence is avail-<br/>able and long-term<br/>effects are known.</li> </ul>  |
|  | vs other    | 2/141                              | Fibromyalgia                                  | Two studies showed that melatonin was effective, and in some<br>cases more effective, than other comparators in improving<br>pain, sleep, health-related quality of life, mood, and<br>physical function. |   |   |   |  |

(continued)

Table 2. continued

| Ingredient Evaluated   | Comparators  | No. Studies/Participants | Populations  | Outcomes   | Evidence  | Quality          | Adverse Events  | Considerations   |
|--|--|--------------------------|--|--|---|------------------|---|--|
| PUFA <sup>†</sup><br>300–9,600 mg/d<br>over<br>4–48 wk;<br>1–2 g/d noted as<br>most effective        | vs any<br>comparator                                 | 46/2,873                 | Rheumatoid arthritis,<br>osteoarthritis, my-<br>algia, other MSK<br>conditions   | Pain reduction   | SMD (46 trials) =<br>-0.40, 10 pts<br>greater reduction<br>than comparator<br>Subgroup analyses:<br>Omega-3 only, SMD<br>= -0.47<br>Low (i.e., ≤1.35 g/d)<br>PUFA dose, SMD =<br>-0.55  | Moderate<br>⊕⊕⊕○ | Fishy aftertaste, halitosis,<br>heartburn dyspepsia,<br>nausea, loose stools, and<br>rash, though generally<br>well tolerated at doses<br>of 3–4 g/d; higher doses<br>associated with in-<br>creased risk of bleeding<br>and stroke.<br>Risk to experience any<br>AE:<br>vs placebo: insufficient<br>data<br>vs drug: insufficient data | <ul style="list-style-type: none"> <li>Available in food; should be considered as a dietary source.</li> <li>Nutrition education is important to ensure proper amounts of PUFA are being obtained via diet and/or supplementation to avoid possible overdose.</li> <li>Increase understanding on best formulation (e.g., Omega 3/6 ratios).</li> </ul>   |
| Vitamin D <sup>†</sup><br>400–300,000 IU/d<br>over anywhere<br>from a single dose<br>to 2 mo<br>–2 y | vs placebo <sup>‡</sup><br><br>vs other <sup>‡</sup> | 11/1,442<br><br>3/413    | Fibromyalgia, low<br>back pain, MSK<br>pain, osteoarthritis,<br>rheumatoid<br>arthritis<br><br>Fibromyalgia, MSK<br>pain | Pain reduction<br><br>There were no reported differences between vitamin D<br>and an active comparator (i.e., triglyceride solution).<br>No significant differences were reported between high<br>(i.e., 1,000 IU)/low (i.e., 400 IU) vitamin D dosages.<br>Overall, both oral and intramuscular<br>routes of vitamin D improved pain, physical function, and<br>health-related quality of life, though in some cases only the<br>intramuscular route was found to be effective. | SMD (8 trials) =<br>-0.55, 13.75 pts<br>greater reduction<br>than placebo<br><br>There were no reported differences between vitamin D<br>and an active comparator (i.e., triglyceride solution).<br>No significant differences were reported between high<br>(i.e., 1,000 IU)/low (i.e., 400 IU) vitamin D dosages. | Low<br>⊕○○○      | <ul style="list-style-type: none"> <li>Infrequent AEs; concern that higher vitamin D doses are associated with more AEs.</li> <li>Risk to experience any AE:<br/>vs placebo: NS<br/>vs drug: insufficient data</li> </ul>   | <ul style="list-style-type: none"> <li>Low-quality evidence suggests that vitamin D reduces pain.</li> <li>Recommended at doses of 2,000 IU/d, not to exceed 4,000 IU/d.</li> <li>Can be obtained via food and sun exposure, but Special Operators should not solely depend on these sources due to potential lack of exposure.</li> <li>Concern for potential overdose; recommend low doses until further research is conducted.</li> </ul> |

AE = adverse event; ASU = avocado soybean unsaponifiables; CI = confidence interval; MSK = musculoskeletal; NS = nonsignificant; OR = odds ratio; OTC = over-the-counter; pCCGS = prescription patented Crystallized Glucosamine Sulfate; PUFA = polyunsaturated fatty acids; RCT = randomized controlled trial; RD = risk difference; SMD = standardized mean difference.

<sup>†</sup>Data from existing meta-analysis used.

<sup>‡</sup>New meta-analysis conducted.

<sup>§</sup>No meta-analysis conducted.

<sup>¶</sup>Includes data from multiple arms (placebo and other comparators).

Table 3. Judgments across factors for decision-making

| Ingredient<br>Total Votes in<br>Favor/Total<br>Possible Votes* | Effect Size for Pain<br>Reduction/Quality | Certainty of the<br>Evidence Across all<br>Outcomes | Desirable Effects<br>Outweigh<br>Undesirable | Justification of<br>Resource<br>Requirements | Acceptable to<br>Stakeholders             | Feasible/Suitable<br>to Implement         | Decision  |
|--|---|---|--|--|---|---|---|
| ASU<br>18/40   | SMD = -0.60<br>Low<br>⊕⊕○○                | 0 4 0 4 0<br>VL L NS M H<br>In favor = 4            | 0 0 2 3 3<br>N PN DK PY Y<br>In favor = 6    | 0 3 1 3 0<br>N PN DK PY Y<br>In favor = 3    | 3 3 0 1 1<br>N PN DK PY Y<br>In favor = 2 | 1 2 2 3 0<br>N PN DK PY Y<br>In favor = 3 | 75% weak, in favor<br>12.5% none<br>12.5% weak, against |
| Capsaicin<br>40/40   | SMD = -0.56<br>High<br>⊕⊕⊕⊕               | 0 0 0 1 7<br>VL L NS M H<br>In favor = 8            | 0 0 0 5 3<br>N PN DK PY Y<br>In favor = 8    | 0 0 0 8 0<br>N PN DK PY Y<br>In favor = 8    | 0 0 0 5 3<br>N PN DK PY Y<br>In favor = 8 | 0 0 0 5 3<br>N PN DK PY Y<br>In favor = 8 | 62.5% strong, in favor<br>37.5% weak, in favor          |
| Curcuma <sup>†</sup><br>22/40                                  | SMD = -1.05<br>Low<br>⊕⊕○○                | 3 5 0 0 0<br>VL L NS M H<br>In favor = 0            | 0 0 2 6 0<br>N PN DK PY Y<br>In favor = 6    | 0 1 1 6 0<br>N PN DK PY Y<br>In favor = 6    | 0 2 1 5 0<br>N PN DK PY Y<br>In favor = 5 | 0 2 0 4 1<br>N PN DK PY Y<br>In favor = 5 | 75% weak in favor<br>12.5% none<br>12.5% weak, against  |
| Ginger <sup>†</sup><br>22/40                                   | SMD = -0.30<br>Moderate<br>⊕⊕⊕○○          | 0 2 0 6 0<br>VL L NS M H<br>In favor = 6            | 0 1 0 7 0<br>N PN DK PY Y<br>In favor = 7    | 0 3 0 5 0<br>N PN DK PY Y<br>In favor = 5    | 0 5 1 2 0<br>N PN DK PY Y<br>In favor = 2 | 0 6 0 2 0<br>N PN DK PY Y<br>In favor = 2 | 37.5% weak, in favor<br>37.5% none<br>25% weak, against |
| Glucosamine (Rx)<br>37/40                                      | SMD = -0.27<br>Moderate<br>⊕⊕⊕○○          | 0 0 0 8 0<br>VL L NS M H<br>In favor = 8            | 0 0 2 6 0<br>N PN DK PY Y<br>In favor = 6    | 0 0 0 5 3<br>N PN DK PY Y<br>In favor = 8    | 0 0 0 6 2<br>N PN DK PY Y<br>In favor = 8 | 0 0 1 3 4<br>N PN DK PY Y<br>In favor = 7 | 37.5% strong, in favor<br>62.5% weak, in favor          |
| PUFA<br>38/40  | SMD = -0.40<br>Moderate<br>⊕⊕⊕○○          | 0 2 0 6 0<br>VL L NS M H<br>In favor = 6            | 0 0 0 4 4<br>N PN DK PY Y<br>In favor = 8    | 0 0 0 6 2<br>N PN DK PY Y<br>In favor = 8    | 0 0 0 5 3<br>N PN DK PY Y<br>In favor = 8 | 0 0 0 5 3<br>N PN DK PY Y<br>In favor = 8 | 50% strong, in favor<br>50% weak, in favor              |
| Melatonin<br>22/40   | Insufficient data                         | 2 5 1 0 0<br>VL L NS M H<br>In favor = 0            | 0 0 3 5 0<br>N PN DK PY Y<br>In favor = 5    | 0 2 2 4 0<br>N PN DK PY Y<br>In favor = 4    | 0 1 1 6 0<br>N PN DK PY Y<br>In favor = 6 | 0 1 0 6 1<br>N PN DK PY Y<br>In favor = 7 | 75% weak, in favor<br>12.5% none<br>12.5% weak, against |
| Vitamin D<br>25/40   | SMD = -0.55<br>Low<br>⊕⊕○○                | 0 8 0 0 0<br>VL L NS M H<br>In favor = 0            | 0 3 0 5 0<br>N PN DK PY Y<br>In favor = 5    | 0 1 0 7 0<br>N PN DK PY Y<br>In favor = 7    | 1 0 1 6 0<br>N PN DK PY Y<br>In favor = 6 | 1 0 0 7 0<br>N PN DK PY Y<br>In favor = 7 | 100% weak, in favor                                     |

ASU = avocado soybean unsaponifiables; DK = do not know; H = high; L = low; M = moderate; N = no; NS = no included studies; PN = probably no; PUFA = polyunsaturated fatty acids; PY = probably yes; RX = prescription; VL = very low; Y = yes.

\*Eight voting members judged factors to consider together to develop recommendations. A summary weight is provided for each ingredient ranking the desirable consequences to the unknown or undesirable consequences across factors, which was done anonymously. The quality was not assigned a weight, as this was used to determine the weight of the certainty of the evidence across all outcomes assessed, and as supplied by the evidence review independently (Supplementary Data: Summary Report). Although the accumulated judgments of all factors were used to inform the recommendations ultimately made and displayed using the GRADE Grid (Supplementary Data: GRADE Grid) visually, they were not assigned a weighted summary score.

<sup>†</sup>Conditionally recommend use as a food source, not as a dietary supplement, at this time.



example, Piascledine 300 is made in France, and therefore the required resources are perhaps higher than other dietary ingredients. Because it is unknown what formulations might be beneficial beyond Piascledine 300, members had divergent opinions regarding ASU's required resources, acceptability to stakeholders, and feasibility of implementation.

Given that the desirable effects outweigh the undesirable, research should focus on understanding OTC formulations and conducting third-party evaluations before strong recommendations can be made. The purity of ASU ingredients should also be confirmed via United States Pharmacopeia (USP)-verified or NSF-certified products.

### Capsaicin

Capsaicin, one of the primary constituents of the *Capsicum* species, is an active component of chili peppers. *Capsicum* is grown worldwide and adds color, pungency (i.e., heat), and aroma to food. Capsaicin is used orally, topically, and intranasally for a variety of conditions. It is most commonly used topically for MSK conditions such as osteoarthritis, rheumatoid arthritis, neuralgias/neuropathies, back pain, fibromyalgia, and muscle spasms [88]. In fact, both low-concentration OTC and Food and Drug Administration (FDA)-approved, high-concentration (i.e., Qutenza<sup>TM</sup>) topical formulations are available.

Ten randomized controlled trials (RCTs) [31–40] compared the effect of capsaicin with placebo, usual treatment, or other capsaicin products within a variety of populations, including those with osteoarthritis, rheumatoid arthritis, and other MSK conditions. Capsaicin was delivered topically either as a patch or gel/cream; capsaicin gels/creams were labeled as Capsika gel®, Zostrix®, Dolarac<sup>TM</sup>, Finalgon®, or Sensedol®. Daily dosages of patches containing either 0.1% or 22–37.4 ug/cm<sup>2</sup> of capsaicin were applied at times ranging from four to 12 hours over three to four weeks, whereas dosages of creams containing 0.0125–0.25% capsaicin were applied at times ranging from twice to four times daily for three to 12 weeks (Table 2; Supplementary Data: Summary Report).

Conditional recommendations were made (37.5% weak, in favor; 62.5% strong, in favor) for the use of capsaicin as a cream or patch for pain and related symptoms.

Current research shows high-quality evidence and certainty that capsaicin will produce a statistically significant reduction in pain (SMD = -0.56) and the patient's global assessment of improvement (risk difference [RD] = -0.21) compared with placebo at time points closest to four weeks (Supplementary Data: Summary Report). These desirable anticipated effects were judged to be moderate overall, and the undesirable anticipated effects, primarily associated with burning, itching, and irritation, were judged to be small to trivial. Most OTC creams

contain 0.025–0.075% capsaicin and can be applied three to four times a day to the affected area. The application of higher OTC doses (i.e., 0.25%) is only recommended if the patient can tolerate the increased undesirable effects, an approach that can potentially provide quicker pain relief with less frequent applications.

Because the cost of capsaicin is highly dependent upon its dose and delivery system, it was challenging for members to judge the required resources based on the current evidence. Given the desirable vs undesirable anticipated effects, however, its use likely justifies the resource requirements and out-of-pocket expenses. Members agreed that capsaicin would likely be acceptable to stakeholders and feasible/suitable to implement for use as a cream or patch.

### Curcuma

Turmeric, commonly referred to by its Latin name, curcuma, is a plant related to ginger and is grown throughout India, parts of Asia, and Central America [89]. Curcuma is formulated into capsules, tablets, teas, extracts, and/or pastes and is used for inflammation, arthritis, stomach, skin, liver and gallbladder problems, cancer, and other conditions [90]. Turmeric root and powder are available as grocery items for cooking.

The authors identified 10 RCTs [42–51] meeting the review's inclusion criteria. Studies compared curcuma, either alone (N = 7) or combined with other ingredients (N = 3), with other dietary ingredients, NSAIDs, or placebo in samples with osteoarthritis and/or rheumatoid arthritis. Doses ranged from 700 to 2,000 mg/d over 42 days to 12 weeks (Table 2; Supplementary Data: Summary Report).

Conditional recommendations were made (75% weak in favor; 12.5% none; 12.5% weak, against) for the use of curcuma as a food source in daily diets at dose equivalents of 500 mg two to three times per day for pain and related symptoms. The HERB did not recommend curcuma as a dietary supplement at this time.

A large (SMD = -1.05) and statistically significant desirable anticipated effect was noted for pain reduction, enhanced global function (SMD = -0.87), and reduced medication use (RD = -0.50), as compared with placebo at the time point closest to two months. The quality and certainty of the evidence are very low to low. Potential risk of bias across the pooled studies, small sample size, and statistically significant heterogeneity were reasons for downgrading (Supplementary Data: Summary Report).

Curcuma was rated as a high priority research area given that its potential desirable effects outweigh the minimal undesirable effects (e.g., minor gastrointestinal complaints). Until further research is conducted, curcuma is suggested as a useful dietary source but should not be used as a dietary supplement. Costs were rated as negligible to even moderate savings. There was some disagreement as to whether curcuma would be acceptable to

stakeholders or feasible to implement. Once further research emerges, additional stakeholder debate would be required [13].

### Ginger

Ginger is a tropical plant widely used as a flavoring or fragrance in foods, beverages, soaps, and cosmetics. Common forms include the fresh or dried root, tablets, capsules, liquid extracts, and teas. Ginger is currently used as a dietary ingredient for nausea, rheumatoid arthritis, and osteoarthritis [91].

Ten RCTs [52–61] met the review's eligibility criteria, five of which were also included in Bartels et al.'s 2015 systematic review and meta-analysis [62] on ginger for osteoarthritis. Studies compared ginger, either alone or combined with other ingredients, with herbal, pharmacologic, and placebo comparators in osteoarthritis, rheumatoid arthritis, and chronic joint pain populations. Dosages ranged from 250 to 1,000 mg/d (delivered as a capsule) and 6 g/d (delivered as an ointment) over anywhere from three to 12 weeks (Table 2; Supplementary Data: Summary Report).

Whereas no recommendation was provided (37.5% weak, in favor; 37.5% none; 25% weak, against) for the use of ginger as a dietary supplement, members agreed that minimal adverse events have been noted and that the certainty and quality of the evidence for a small yet statistically significant reduction in pain (SMD = -0.30) and disability (SMD = -0.22) were moderate (Supplementary Data: Summary Report) [12,62]. The desirable anticipated effect was not as substantial as the other ingredients reported here; however, members agreed that it is already available in tea and food and, if readily available, could be suggested for use.

Although the critical threshold for a clinically relevant effect is debatable, the effect size of ginger does fall within the range of some other nutraceuticals/herbal medicines, and NSAIDs and may be beneficial to some individuals [62]. The exact dose is not well established, but plausible dose responses associated with ginger in higher doses (i.e., 1,000 mg) appear to produce a larger effect than lower doses (i.e., 250 mg) [62]. Risk of bias was detected across some studies evaluated. The cost appears negligible or even a moderate savings compared with other active pain medications, but members did not agree as to whether this would justify its use or out-of-pocket costs. Members mostly agreed that there are concerns over feasibility and suitability with ginger in mission planning and that it would likely not be acceptable to stakeholders for use.

### Glucosamine, Prescription/Over-the-Counter

Glucosamine is an amino sugar naturally produced in the human body. It is required for the synthesis of glucoproteins, glycolipids, and glucosaminoglycans found in the tendons, ligaments, cartilage, synovial fluid, mucous

membranes, eye structures, blood vessels, and heart valves [86]. It can also be derived from marine exoskeletons or produced synthetically [92,93]. Glucosamine sulfate and glucosamine hydrochloride are delivered orally for many MSK conditions such as temporomandibular disorder, joint pain, osteoarthritis, knee pain, and back pain. Both are also commonly combined with each other or other products (e.g., chondroitin sulfate, N-acetyl glucosamine).

Controversy surrounds the reported effectiveness of glucosamine [94]; however, a Cochrane review recently confirmed that a particular glucosamine sulfate product (Dona, Rotta Pharmaceuticals), as opposed to other formulations, was effective in reducing osteoarthritic pain [95].

Conditional recommendations were made (62.5% weak; 37.5% strong, in favor) for the use of prescription patented Crystallized Glucosamine Sulfate (pCGS) at daily doses of 1,500 mg for pain and related symptoms. It is important to note that the controversy concerning the use of glucosamine sulfate and combination products containing glucosamine largely reflects the differing regulatory status, labeling, and availability of medications in separate countries and regions of the world. Hence, to date it appears that pCGS, as supplied by RottaPharm, is the only product with a well-documented pharmacological effect [64,95].

There is moderate overall quality and certainty that this product will produce a statistically significant effect in reducing pain (SMD = -0.27) compared with placebo [64,68]. pCGS appears to be well-tolerated, as associated undesirable effects (e.g., mild gastrointestinal complaints) are small to trivial. Although pCGS shows similar effects to ibuprofen, it does take longer to obtain a response. Members mostly agreed that the cost would be negligible to even a moderate savings compared with other active ingredients for pain relief. Moreover, they concurred that it would likely justify out-of-pocket expenses and be both acceptable to stakeholders and feasible/suitable to implement, provided that any implemented supplement had the same purity levels as the pCGS ingredients, as in the RottaPharm product.

Effects of pCGS combined with chondroitin remain unknown. OTC glucosamine is available, and although the certainty of the evidence was very low to low and the desirable effects likely small, the members believed that the undesirable effects would be small to trivial. Conditional recommendations were provided for OTC glucosamine (62.5% weak, in favor; 37.5% none), should pCGS not be available to a Special Operator.

### Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is a neurohormone naturally produced by the pineal gland in the brain [96]. This hormone plays a role in sleep, with production and release related to time of day (i.e., rising in

the evening, falling in the morning) [97]. Melatonin is commonly administered orally via capsule for sleep disorders but may be also used to manage neuropathies, headaches, cancers, or osteoporosis [98].

Three RCTs meeting the review's inclusion criteria compared the effect of melatonin with either a placebo [71] or a pharmacological drug (i.e., fluoxetine [70] or amitriptyline [69]) in fibromyalgia [69,70] and myofascial temporomandibular disorder (TMJ) populations [71]. Melatonin doses ranged from 3 to 10 mg/d across four to eight weeks [71]. Baseline levels of melatonin were not reported by any study (Table 2; Supplementary Data: Summary Report).

Conditional recommendations were made (75% weak, in favor; 12.5% none; 12.5% weak, against) for short-term use of low-dose (i.e., 3–5 mg/d) USP-verified or NSF-certified melatonin products as a dietary supplement for pain and related symptoms.

Preliminary evidence demonstrates that melatonin is superior to placebo [71], and perhaps to amitriptyline [69], in reducing pain and reliance on other medications while improving sleep patterns. Little is known about how large these desirable anticipated effects may be or the potential adverse events that might be associated with long-term use. Nonrandomized trials have reported that drowsiness, headache, dizziness, and nausea are uncommon [96]. The HERB agreed that higher doses of melatonin should be avoided until further long-term studies are conducted. Melatonin is a dietary ingredient already broadly used, acceptable to many stakeholders, and available as a sleep aid, so it is likely feasible to implement for pain and sleep improvement. Associated costs are viewed as negligible or even a moderate savings compared with other pain-relieving medications. The quality and certainty of the evidence were judged to be very low to low, with insufficient studies to conduct a meta-analysis.

### Polyunsaturated Fatty Acids

Fish oil comes from various species, including mackerel, herring, tuna, halibut, salmon, cod liver, and whale and seal blubber [99]. Thus, these types of fish are dietary sources of omega-3 fatty acids, also known as n-3 fatty acids [100]. Omega-3 fatty acids are essential dietary ingredients and include alpha-linolenic acid (ALA), long-chain omega-3 fatty acids, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Fish oil supplements contain varying amounts of EPA and DHA (18–51% and 12–32%, respectively) [101]. Although ALA is mainly found in green vegetables, canola oil, and soybeans, EPA and DHA almost exclusively come from fish oil and other seafood. ALA, EPA, and DHA are types of omega-3 fatty acids but may serve different functional roles and should subsequently not be considered interchangeable. Although proprietary prescription fish oil is FDA-approved to lower levels of triglycerides, nonprescription

formulations of fish oil are also used for other conditions including chronic fatigue syndrome, cognitive function/impairment, and MSK (e.g., rheumatoid arthritis, muscle strength, muscle soreness, osteoporosis, osteoarthritis, migraines) issues [102].

The authors relied upon evidence on PUFA for chronic pain presented in Prego-Dominguez et al.'s 2016 systematic review and meta-analysis [72]. The majority of examined studies compared various combinations of PUFA with placebo or other comparators for pain reduction in rheumatoid arthritis patients, with doses ranging from 300 to 9,600 mg for anywhere from four to 48 weeks (Table 2; Supplementary Data: Summary Report).

Conditional recommendations were made (50% weak; 50% strong, in favor) for the use of PUFA supplementation for pain and related symptoms, incorporated into the daily diet at 1,200 mg/d, and not to exceed 2 g/d. Whereas the undesirable effects appear to be small to trivial at low doses, >3 g/d is likely to increase the potential for adverse events (e.g., inhibition of platelet aggregation, risk of bleeding, and potentially hemorrhagic stroke at very high doses) (Supplementary Data: Summary Report).

Moderate-quality evidence suggests that the desirable anticipated effects for pain reduction (SMD = -0.40 range) are statistically significant as compared with placebo [72]. Heterogeneity is noted across the assessed studies and is likely due to varying blends of omega-3/6 used. Although research points to the association between omega-3, rather than omega-6, and pain reduction, the exact ratio, dose, and duration of PUFA use are yet to be determined; most studies, however, report benefit between 1 and 2 g/d.

PUFA do have preventive benefits, are available in food, and should be considered as a dietary source. Nutrition education is critical, moreover, to ensure that the proper amounts are being obtained via food or supplementation to avoid excessive intake. Members mostly agreed that the certainty of the evidence is moderate and that cost is negligible, with even moderate savings compared with currently used pain medications. Subsequently, PUFA are likely acceptable, feasible, and suitable to implement as a dietary food source or supplement, preferably from a USP-verified or NSF-certified product.

### Vitamin D

Vitamin D is a fat-soluble vitamin obtained from sun exposure, food, and/or dietary supplements. Vitamin D promotes calcium absorption, is necessary for bone growth, and appears to also affect skeletal muscle, immune regulation, cardiovascular health, and metabolic activities [103]. Vitamin D deficiencies can result in thin, brittle, or misshapen bones, bone pain, muscle weakness, rickets, and osteomalacia [104–106]. Vitamin D is most commonly used for osteoporosis, osteomalacia, and falls

and fractures in individuals at risk for osteoporosis [107].

The authors relied on the systematic review published by Wu et al. [85] and individual RCTs examining populations with rheumatoid arthritis, chronic low back, fibromyalgia, chronic nonspecific MSK pain, and knee osteoarthritis [73–84] to evaluate and present the evidence on vitamin D for chronic MSK pain. Ingredients were labeled calcifediol [73,75], vitamin D<sub>2</sub> [74,77], vitamin D<sub>3</sub> [76,78,79,81–83], and vitamin D [84]. Baseline vitamin D levels ranged from  $12.8 \pm 8.7$  to  $42.9 \pm 11.3$  ng/mL in the vitamin D group and  $15.0 \pm 3.0$  to  $37.3 \pm 13.2$  ng/mL in the comparator arm. Dosages ranged from 400 IU to 300,000 IU/d for anywhere from a single dose to a course of two years. All studies except one [76] that included a triglyceride solution compared vitamin D with placebo (Table 2; Supplementary Data: Summary Report).

Following a strict methodological approach and using evidence to guide judgments [13], conditional recommendations (100% weak, in favor) were made for the use of vitamin D supplementation for pain and related symptoms at doses of 2,000 IU/d, not to exceed 4000 IU/d. Higher doses should only be used for short-term treatment of vitamin D deficiency and when instructed by a health care provider. Recent evidence suggests that individuals who consume high doses of vitamin D could be at risk of vitamin D intoxication, dysregulation of calcium and phosphorous metabolism, hypercalcemia, hypercalciuria, and hyperphosphatemia. Current approaches to assessing serum levels of 25 hydroxyvitamin D do not necessarily reflect current intake or stores of vitamin D [103,108].

Based on the evidence, the HERB judged the desirable anticipated effects for pain reduction to be moderate in size (SMD = -0.55) at final follow-up, and results were statistically significant compared with placebo when used at low doses [85]. Undesirable effects were judged to be small to trivial. This research is of low quality, primarily due to concerns over heterogeneity, varying populations with potentially different baseline vitamin D levels, and varying doses and durations of intake, which make interpretation challenging (Supplementary Data: Summary Report). Members judged the certainty of the evidence to be low and agreed that cost was negligible compared with ibuprofen 2400 mg/d.

Because the desirable effects likely outweigh the undesirable, resource requirements may justify vitamin D use. Members agreed that vitamin D up to 2,000 IU per day would probably be feasible and acceptable to stakeholders when the product was produced by reputable manufacturers and sold by trusted vendors. Only some vitamin D products sold are on the United States Pharmacopeia National Formulary (USP-NF) verified product list [109]. Although vitamin D can be obtained via food and sun exposure, the HERB members agreed that Special Operators may not receive adequate exposure to sunlight due to

wearing long-sleeved clothing/tactical gear and being outside during nighttime operations.

## Discussion

Evidence-based conditional recommendations have been made for various dietary ingredients, which suggests that they could be used in support of managing chronic MSK pain, specifically for Special Operations Forces (SOF). Nineteen dietary ingredients (Figure 1) had sufficient scientific evidence available to evaluate the state-of-the-science and evidence for any desirable and undesirable anticipated effects on chronic MSK pain, function, and related outcomes through systematic review and meta-analysis techniques. The GRADE approach was used to determine the quality of that evidence by examining the risk of bias, inconsistency, imprecision, and indirectness from the pooled studies. Subject matter experts and key stakeholders evaluated the certainty of the overall evidence, weighed the desirable to undesirable anticipated effects, and considered resource requirements, acceptability, and feasibility/suitability to determine the strength and direction of evidence-based recommendations that could be practical/useful to SOF (Table 3).

ASU, capsaicin, curcuma, ginger, glucosamine, melatonin, PUFA, and vitamin D are recommended and may help alleviate chronic MSK pain. They are suggested for use when taken either as part of a balanced diet and/or as a supplement or applied as a cream. Individuals should discuss options with a health care provider before initiating use of any dietary ingredient. Individuals should also select USP-verified products when possible as they 1) contain the ingredients listed on the label in the declared potency and amounts, 2) contain no harmful levels of specified contaminants, 3) break down and release into the body within a specified amount of time, and 4) have been made according to FDA current Good Manufacturing Practices by using sanitary and well-controlled procedures [110]. Operators can also consider NSF Certified for Sport [111] products and refer to Operation Supplement Safety, a Department of Defense dietary supplement resource [112,113], to verify safety.

Because recommendations were only conditional and did not strongly endorse an ingredient for immediate use, discussion and debate among stakeholders before policy decisions are made surrounding these dietary ingredients and future efforts worthy of further investigation are encouraged.

### Weighing the Desirable and Undesirable Effects

The HERB members weighed desirable and undesirable anticipated effects based on the evidence supplied through systematic review and meta-analysis. Each conditionally recommended ingredient showed an improvement in pain over time compared with placebo or other active comparators. The quality of that evidence varied

among the dietary ingredients evaluated. For example, evidence for pain reduction via capsaicin and PUFA is high and moderate, respectively; conversely, the evidence that vitamin D will produce a statistically significant reduction in pain associated with chronic MSK pain is of low quality. Further, although curcuma shows the largest estimated effect for decreasing pain and improving global function, and perhaps decreasing medication use, the quality of the evidence is very low to low. Some ingredients showed improvement in other pain-related outcomes, but how these ingredients affect such outcomes overall and whether they influence outcomes beyond those in [Table 2](#) are unknown.

In addition, how substantial these reported desirable effects might be for any one individual may vary significantly. What is considered a clinically meaningful improvement in pain, as well as other outcomes, is under considerable debate and is a point of discussion by the HERB members. Bartels et al., in 2010 [[114](#)], compared the SMD from their meta-analysis with other SMDs noted from other interventions, stating,

The SMD of 0.30 for ginger compared with placebo corresponds to an effect size for pain which is only slightly above the critical threshold limit for a relevant SMD in osteoarthritis [[115](#)], and it is comparable, although a little higher, to the SMD of 0.21 seen with intake of acetaminophen [[116](#)]. The observed pain reducing effect for ginger is in the same range as SMD previously reported for other nutraceuticals/herbal medicines like diacerein with an SMD of 0.24 [[114](#)], ASU with an SMD of 0.39 [[114](#)], and rose hip powder of 0.37 [[117](#)], all in comparison with placebo. Compared to the effect of NSAIDs, the SMD for ginger has an effect size in the middle of the NSAID range of 0.17 to 0.66, all when compared to placebo [[118–120](#)].

The HERB used the effect of high-dose ibuprofen, 2,400 mg/d, reported as SMD = -0.41 compared with placebo [[118](#)], as a reference point. To date, comparative effectiveness trials across dietary ingredients are heterogeneous and challenging to pool in meta-analysis in any meaningful way. Further research is needed for comparing ingredients with placebo and other standards of care.

Undesirable anticipated effects, as reported in the evaluated studies, primarily consisted of minor gastrointestinal complaints. Given their nonserious and infrequent nature, members judged that the desirable effects outweighed the undesired across all dietary ingredients. Currently data from published studies showing how these ingredients directly compare with other active comparators in terms of varying adverse events are insufficient. There is concern that when used at higher doses, more and additional adverse events, beyond gastrointestinal issues, may occur. For example, extremely high doses of PUFA may increase the risk of both ischemic and hemorrhagic stroke [[121](#)], and extremely high doses of vitamin D could lead to intoxication [[122](#)]. Other adverse events,

though relatively mild (e.g., “bad taste” associated with ginger and PUFA) can cause some individuals to discontinue use [[62,123,124](#)].

### Certainty of the Evidence

Although the quality of the evidence was determined using the GRADE approach and was specific to each outcome evaluated, the certainty of the evidence was judged based on reviewing the evidence of effects across all outcomes where it was feasible to pool results into a meta-analysis ([Table 2](#); [Supplementary Data](#): Summary Report.) Members judged the certainty of the overall evidence for PUFA and ginger as moderate and for curcuma and vitamin D as very low to low. Further research is needed to address gaps of ingredients with low-quality studies and uncertain evidence. In some circumstances, the use of ingredients with some evidence suggesting desirable effect can be suggested when the risk of using the ingredient is minimal. In all cases, discussions with a health care provider are recommended to consider ingredient use and an approach to shared decision-making.

### Justification of Resource Requirements/Cost

Cost is an essential factor required for decision-making that affects all individuals at some level. On average, given the doses reported in the studies, the cost associated with any of these ingredients was considered negligible to moderate savings compared with commonly used pain relievers (e.g., ibuprofen 2,400 mg, estimated at approximately \$1/d to serve as a reference point for comparison). As such, most members agreed that resource requirements and out-of-pocket costs were justified.

### Other Considerations: Feasibility, Acceptability, Suitability

The HERB members agreed that capsaicin, pCGS, melatonin, PUFA, and vitamin D would probably be acceptable to stakeholders and feasible/suitable to implement as a policy of practice, whereas there was more debate concerning ginger, curcuma, and ASU. Although ginger and curcuma should both be considered a dietary food (e.g., teas, cooking ingredient) and may have the potential to pre-emptively mitigate pain, there was insufficient strong research for recommending their use as a supplement. The overall effect of ginger was relatively small, and although curcuma produced a large effect, the authors were less confident in that effect estimate. It is possible that these ingredients could be inserted into a mission planning process and added to a nutrition checklist by mission dietitians. Whether it would be feasible for Special Operators to obtain ginger and curcuma during specific operational missions is unknown.

Research on ASU evaluated by the authors was confined to the commercialized French product Piascledine. The quality of the evidence for its effects on pain reduction is moderate, diminished by potential bias of being

funded by the manufacturer. Third-party evaluations of Piascledine are needed. In addition, Piascledine 300 costs more than the other dietary ingredients and other products that claim to be made with ASU. HERB member opinions regarding Piascledine or other ASU products' (that lack rigorous clinical evidence) acceptability and feasibility were diverse.

### Remarks on the Methodological Approach

Systematic reviews provide essential information to lay the foundation for evidence-based practice but are often insufficient for making well-informed decisions. Stakeholders can easily judge the appropriateness of an intervention or treatment when high-quality evidence supports substantial desirable anticipated effects and there are minimal to no undesirable anticipated effects. In these cases, treatments are recommended with little need for further debate. Little debate is needed when treatments are judged to be inappropriate and risks clearly outweigh benefits. In between these two judgments is a massive gray area where the evidence is of low, indeterminate, or equivocal quality. Importantly, dietary ingredients are not intended to treat any particular health condition. If a particular ingredient or combination of ingredients were identified as potentially useful for mitigating or treating MSK pain, then the ingredient would be classified as a drug and required to go through the FDA Investigational New Drug Applications process [125]. Despite this, many dietary supplements are marketed for pain relief. A casual search of the National Institutes of Health's Office of Dietary Supplement's Dietary Supplement Label Database (<https://www.dslid.nlm.nih.gov/dslid/index.jsp>) yielded a total of 272 products when the terms "pain" and "muscle" were used to search for label statements or health claims. Thus, caution is urged, and obtaining ingredients through food is always preferred, unless the evidence of safety and efficacy is clear and manufacturers' production processes are verified or certified by trusted third parties.

A framework for decision-making is essential. The authors involved diverse subject matter experts and key stakeholders proactively to develop key questions and to drive the direction of evidence evaluation that illuminated critical outcomes and factors important to them. This evaluation, conducted by a third party, used processes and procedures designed to minimize bias. Factors required for decision-making for this project were adapted from the GRADE framework and specific to the Special Operations environment. The integration of systematic review results into the GRADE Evidence to Decision Framework and the use of a modified Delphi voting process seeking points of convergence and divergence enable all voices to be heard. Subsequently, recommendations about practice, policy, and next steps for research that are useful to the diversity of end users can be developed. A limitation in all research is wide

generalizability, and the framework used here can be adapted to different contexts, settings, and stakeholders to consider other essential factors important for decision-making.

### Conclusions

Conditional, evidence-based recommendations were made for the use of vitamin D (2,000 mg/d), PUFA (1,200 mg/d), curcuma and ginger (as food sources), melatonin (3–5 mg/d), a proprietary brand of ASU (300–600 mg/d), capsaicin (as a cream, 0.025–0.075% applied 3–4/d), and prescription glucosamine (pCGS, 1,500 mg/d) as alternative or supplemental approaches for mitigating pain and related symptoms associated with chronic MSK pain. These recommendations were based upon rigorous evidence evaluation and integrated with expert clinical acumen by using strict methodological criteria and processes designed and practiced to minimize bias. The process allowed for all voices to be heard with regard to reaching the greatest spread of end user impact. Caveats exist, and in some cases the quality and/or certainty of the evidence remains low; however, the resulting recommendations can serve as a decision aid for practitioners and participants to make shared decisions.

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## Supplementary Data

Supplementary data are available at *Pain Medicine* online.

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