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Review

Symptomatic efficacy of avocado–soybean unsaponifiables (ASU) in osteoarthritis (OA) patients: a meta-analysis of randomized controlled trials[1]

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Summary

Objective: To evaluate the efficacy of preparations with avocado–soybean unsaponifiables (ASUs) in osteoarthritis (OA) patients using meta-analysis on randomized controlled trials (RCTs).

Method: RCTs from systematic searches were included if they explicitly stated that hip and/or knee OA patients were randomized to either ASU or placebo. The co-primary outcome was reduction in pain and Lequesne index, leading to effect size (ES), calculated as the standardized mean difference. As secondary analysis, the number of responders to therapy was analyzed as odds ratios (ORs). Restricted maximum likelihood methods were applied for the meta-analyses, using mixed effects models.

Results: Four trials – all supported by the manufacturer – were included, with 664 OA patients with either hip (41.4%) or knee (58.6%) OA allocated to either 300 mg ASU (336) or placebo (328). Average trial duration was 6 months (range: 3–12 months). Though based on heterogeneous results, the combined pain reduction favored ASU ($I^2 = 83.5\%$, ES = 0.39 [95% confidence intervals: 0.01–0.76], $P = 0.04$). Applying the Lequesne index also favored ASU ($I^2 = 61.0\%$, ES = 0.45 [0.21–0.70], $P = 0.0003$). Secondarily, the number of responders following ASU compared to placebo (OR = 2.19, $P = 0.007$) corresponded to a number needed to treat of six (4–21) patients.

Conclusions: Based on the available evidence, patients may be recommended to give ASU a chance for e.g., 3 months. Meta-analysis data support better chances of success in patients with knee OA than in those with hip OA.

Key words: ASU, Meta-analysis, Osteoarthritis, Dietary supplements, Knee, Hip.

Introduction

Musculoskeletal diseases are prevalent and their impact is pervasive, affecting all age groups, and the associated physical disability is an enormous burden on individuals and society[1,2]. The socio-economic cost due to musculoskeletal conditions is huge, predominantly due to back pain, osteoarthritis (OA) and rheumatoid arthritis (RA)[2]. Pain is the major symptom in most arthritis patients[3], and is also the most important determinant of disability in patients with OA[4]. The prevalence of painful disabling knee OA in people over 54 years living in the United Kingdom is 10%, and 25% of these are severely disabled[5,6]. With an estimated prevalence of 3–11% in Western populations over 35 years, hip OA is the second-most frequent OA in large joints[7]. Current OA treatment aims at alleviating pain symptoms in different ways[8,9]. With rough categorization, the treatment is one of three types: non-pharmacological intervention, pharmacological treatment, or invasive/surgical intervention (including intra-articular injections, lavage, and arthroplasty)[6,7,9].

Complementary or alternative therapies (including nutraceuticals) for OA are commonly used, and it is therefore important that health care providers are aware of the evidence supporting the claims[10]. Available evidence would be easier to translate into clinical practice if the available (and published) data were analyzed and presented using an unbiased meta-analytic approach[11,12]. One proposed nutraceutical, which has shown promising results in OA patients, is avocado–soybean unsaponifiables (ASUs). Currently, the only ASU mixture investigated is made up of unsaponifiable fractions of one-third avocado oil and two-third soybean oil. Preclinical studies of ASU have shown some anti-OA properties. *In vitro*, ASU is seen to have an inhibitory effect on interleukin-1 (IL-1) and a stimulating effect on collagen synthesis in articular chondrocyte cultures[13]. Data support the notion of ASU preparations as potent inhibitors of the production of IL-8 and prostaglandin E_2 (PGE_2) by human articular chondrocytes[14]. *In vitro* data have shown ASU to stimulate aggrecan and matrix component synthesis, reduce catabolic and pro-inflammatory mediator production by human osteoarthritic chondrocytes, and partially

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counteract the inhibitory effect of IL-1 (possibly *via* the production of transforming growth factor beta (TGF-β)) and growth factors associated with cartilage homeostasis[15,16]. Accordingly, ASU seems to prevent the osteoarthritic osteoblast-induced inhibition of matrix molecule production, suggesting that this compound may promote OA cartilage repair by acting on subchondral bone osteoblasts[17]. Ernst reviewed the available data on the efficacy of ASU in OA patients and concluded that the majority of rigorous trials suggest that ASU is effective in the symptomatic treatment of OA, although the only long-term trial was largely negative, and thus more research would be justified[18]. Ernst's conclusion corresponds to a review (in Danish) by Angermann, which concludes that the available studies indicate that ASU has an effect on the symptoms of knee and hip OA, but no effect on the structural changes occurring with OA[19].

We carried out a systematic review with a meta-analysis of the available randomized controlled trials (RCTs)[20] of studies applying ASU in the symptomatic treatment of OA. Our primary aim was to obtain an up-to-date evidence based analysis which would provide a detailed view of the symptomatic activity of ASU used in the treatment of knee and hip OA[21,22]. Our secondary aim was to investigate possible causes behind the statistical heterogeneity, emphasizing clinical heterogeneity across the included studies[24]. We used meta-regression analyses[25] to implement clinical arguments, which could result in clinical inference[26].

Methods

RETRIEVAL OF PUBLISHED STUDIES

RCTs of ASU treatment vs placebo were identified by means of a systematic literature search in the following bibliographic databases: Medline *via* PubMed (mid 1950s to Feb. 19, 2007), EMBASE *via* WebSpirs (1980 to Feb. 19, 2007), CINAHL *via* WebSpirs (1982 to Feb. 19, 2007), BiosisPreviews *via* WebSpirs (1980 to Feb. 19, 2007), Web of Science (1945–54 to Feb. 19, 2007), Scifinder (1907 to Feb. 19, 2007), Scopus (1966 to Feb. 19, 2007), and the Cochrane Library (1966 to Jan. 31, 2007). This was followed by searches of reference lists of original reports and review articles, retrieved through the described searches. Finally, we searched conference abstracts over the past 2 years *via* the established international societies of rheumatology, i.e., the OsteoArthritis Research Society International (OARSI), EUropean League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR).

The search strategy consisted of the relevant keywords/MESH words for OA combined with any combination of ASU, soy or avocado for wide coverage and to limit the search to controlled studies to take into account that randomization is not always clearly defined *via* keywords, and that some controlled studies may be of interest despite lack of proper randomization. With the awareness of a higher proportion of noise in the searches, titles and abstracts were reviewed for possible RCTs, and full text references were obtained for further scrutiny where relevant.

INCLUSION AND EXCLUSION CRITERIA

We included RCTs comparing a preparation of both avocado and soybean extracts with a (double masked) placebo intervention. Studies were selected if the included patients were described as having clinical or radiographic evidence of OA. Two reviewers (RC and HB) crosschecked and agreed on diagnostic criteria in each trial. We excluded studies in conditions such as non-OA joint pain, RA, pain due to surgery or injury, and studies with mixed patient groups such as those with both OA and RA, unless the subgroup data for OA were available. No language restrictions applied.

QUALITY ASSESSMENT

The quality of studies was assessed based on randomization, masking and withdrawal. The complete reports of the RCTs that were selected for inclusion in the meta-analysis were scored by two reviewers for quality (RC and EMB), using a validated instrument[27]. The score was given as follows: if the study was described as randomized (+1); if the study was described as double masked (+1); and if there was a (detailed) description of withdrawals and drop-outs (+1). In addition, if the random allocation and the double blinding were properly described and appropriately put into practice, each item received one point extra. Conversely, if the methods (randomization and masking) were not considered appropriate, one point was subtracted from each item.

DATA EXTRACTION

Two reviewers (RC and EMB) undertook data extraction independently. Disagreements were resolved by discussion. A customized form was used to record authors of the study, year of publication, trial design, study length,

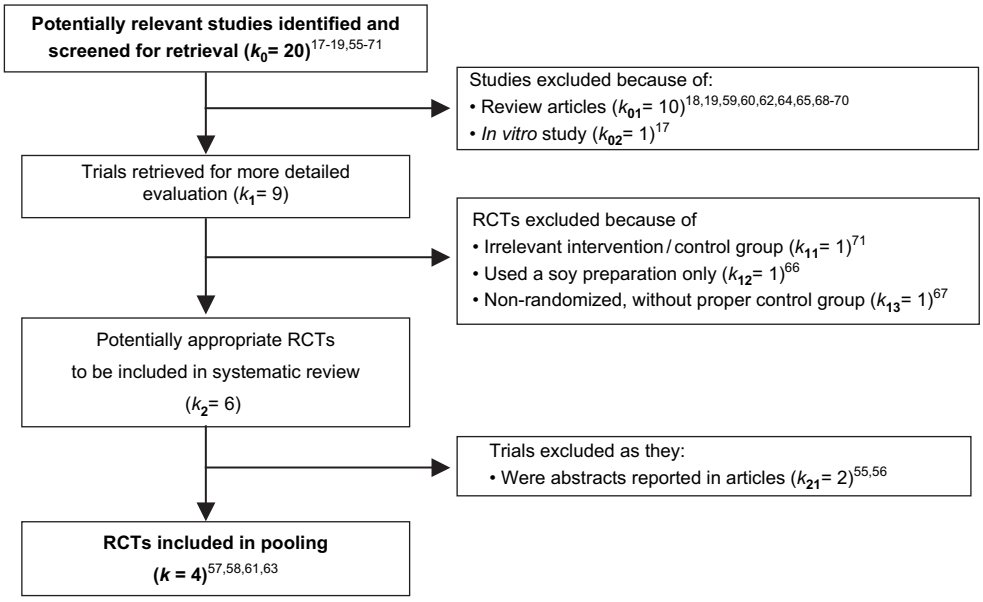

Fig. 1. Flow of RCTs included in the systematic review.