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Insaponificabile di Soia ed Avocado (ASI)
Avocado/soybean unsaponifiables *(ASU)*

is composed of one third avocado and two thirds soybean unsaponifiables (ASUs), the oily fractions that, after hydrolysis, do not produce soap [23].

Four double-blind placebo-controlled RCTs (Table 4) and one systematic review evaluated ASUs on knee and hip OA [24-28].

- In two 3-month RCTs, one on knee and hip OA [24] and one solely on knee OA [25], 300 mg once a day decreased NSAID intake. No statistical difference in any primary or secondary endpoints was detected between 300 and 600 mg once a day [25].

- In a 6-month RCT on knee and hip OA, 300 mg once a day resulted in an improved LFI compared with placebo [26]. ASUs had a 2-month delayed onset of action as well as residual symptomatic effects 2 months after the end of treatment.
- In a 2-year RCT on hip OA, 300 mg once a day did not slow down narrowing of joint space width [27]. In addition, none of the secondary endpoints (LFI, VAS of pain, NSAID intake, and patients' and investigators' global assessments) was statistically different from placebo after 1 year.
  However, a post hoc analysis suggested that **ASUs might decrease narrowing of joint space width in patients with the most severe hip OA**. In summary, although ASUs might display medium-term (several months') symptom-modifying effects on knee and hip OA, their symptom-modifying effects in the long term (>1 year) have not been confirmed. ASUs might slow down narrowing of joint space width in patients with severe hip OA, but this requires confirmation. Based on our best-evidence synthesis, good evidence is provided by ASUs for symptom-modifying effects in knee and hip OA but at the same time, there is some evidence of absence of structure-modifying effects (Table 3). A recent systematic review on ASUs recommended further investigation because three of the four rigorous RCTs suggest that ASUs is an effective symptomatic treatment, but the longterm study is largely negative [28]. However, the fact that this long-term study was primarily aiming at demonstrating structure-modifying and not symptom-modifying effects might explain why no symptomatic effects from ASUs were detected in the long-term study. Indeed, symptoms and structural damage are known to mildly correlate in OA, and the most appropriate patients to demonstrate a structure-modifying effect might not be the most appropriate to demonstrate a symptommodifying effect. As for safety, none of the four RCTs reported significant differences in adverse effects between ASUs and placebo.
- In sheep with lateral meniscectomy, 900 mg once a day for 6 months reduced the loss of toluidine blue stain in cartilage and prevented subchondral sclerosis in the inner zone of the lateral tibial plateau but not focal cartilage lesions [29].
- **In vitro**, ASUs display anabolic, anticatabolic, and anti-inflammatory effects on chondrocytes. ASUs increased collagen synthesis [30] and inhibited the spontaneous and interleukin (IL)-1β-induced collagenase activity [23,31]. They increased the basal synthesis of aggrecan and reversed the IL1β- induced reduction in aggrecan synthesis [32]. ASUs were also shown to reduce the spontaneous and IL1β-induced production of matrix metalloproteinase (MMP)-3, IL-6, IL-8, and prostaglandin E2 (PGE2) while weakly reversing the IL1β- induced decrease in TIMP (tissue inhibiting metalloproteinase)- 1 production [23,30,32]. One study showed that ASUs decreased

the spontaneous production of nitric oxide (NO) and macrophage inflammatory protein-1β [32] while stimulating the expression of transforming growth factor-β and plasminogen activator inhibitor-1 [33]. This stimulated production of plasminogen activator inhibitor-1 could decrease MMP activation.

- The **effects of avocado unsaponifiables alone, of soybean unsaponifiables alone, and of three mixtures of ASUs, were compared** [23,32]. The mixtures were A1S2 (Piascledine), A2S1, and A1S1, with respective ratios of ASUs of 1:2, 2:1, and 1:1. All mixtures significantly reduced the spontaneous production of IL-6, IL-8, and PGE2 and the IL1β-induced production of PGE2. A1S2 and A1S1, but not A2S1, significantly reduced the spontaneous and IL1β-induced production of MMP-3 and the IL1β-induced increase in collagenase activity, but only A1S2 inhibited the spontaneous collagenase activity.For some parameters, avocado unsaponifiables or soybean unsaponifiables alone were as potent as mixtures. In some cases, a single source of unsaponifiables seemed to be active.In other cases, both sources of unsaponifiables were active with synergistic or counteracting effects. The superiority of Piascledine over different ASU mixtures or over avocado or soybean unsaponifiables alone thus remains to be demonstrated.

Table 4

Summary of trials on ingredients having at least a limited evidence of efficacy

Lead author and date [Reference]	Inclusion criteria	Duration of intervention, study design, sample size and treatment (dosage)	Sample size and dropout rate (percentage) at the end of treatment	ITT results at the end of treatment (baseline and final values or percentage change, intergroup *p* value)
ASUs				
Blotman 1997 [24]	Knee and hip OA Mean age = 64.1 years Mean wt = 70.2 kg Mean ht = 166 cm F/M: 108/55	3 months Parallel study ($n = 164$) 1. Placebo ($n = 83$) 2. ASU ($n = 81$) (300 mg × 1/day)	Placebo ($n = 76$) ASU ($n = 77$) Dropout = 6.7%	Number of patients who resumed NSAID intake Placebo ($n = 53$) (69.7%) ASU ($n = 33$) (43.4%) $p < 0.001$
Maheu 1998 [26]	Knee and hip OA Mean age = 64.1 years Mean BMI = 26.8 F/M: 118/46	6 months Parallel study ($n = 164$) 1. Placebo ($n = 79$) 2. ASU ($n = 84$) (300 mg × 1/day)	Placebo ($n = 69$) ASU ($n = 75$) Dropout = 12%	LFI score: Placebo (9.3 to 9.9, +6%) ASU (9.7 to 6.8, -30%) $p < 0.001$
Appelboom 2001 [25]	Knee OA Mean age = 65 years Mean wt = 76.5 kg Mean ht = 164 cm F/M: 205/55	3 months Parallel study ($n = 260$) 1. diclofenac ($n = 88$) 2. ASU ($n = 86$) (300 mg × 1/day) 3. ASU ($n = 86$) (600 mg × 1/day)	Placebo ($n = 76$) ASU 300 mg ($n = 74$) ASU 600 mg ($n = 75$) Dropout = 13.5%	Intake of NSAID and analgesics intake (mg/diclofenac per day) Placebo (130 to 81, -38%) ASU 300 mg (133.8 to 45.2, -66%) ASU 600 mg (123.7 to 52.5, -58%) $p < 0.01$ for each ASU group vs. placebo ASU 300 vs. ASU 600: NS
Lequesne 2002 [27]	Hip OA Mean age = 63.2 years Mean wt = 70.5 kg Mean ht = 165 cm F/M: 61/102	2 years Parallel study ($n = 163$) 1. Placebo ($n = 78$) 2. ASU (300 mg × 1/day) ($n = 85$)	Placebo ($n = 45$) ASU ($n = 51$) Dropout = 41.1%	Joint space width mm: Placebo: 2.50 to 1.90, -24% ASU: 2.35 to 1.87, -20% NS between groups