ORIGINAL RESEARCH

A Complex of Three Natural Anti-inflammatory Agents Provides Relief of Osteoarthritis Pain

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ABSTRACT

Background • Devil's claw (*Harpagophytum procumbens*), turmeric (*Curcuma longa*), and bromelain are nutraceuticals that have demonstrated anti-inflammatory and analgesic properties and may be potential solutions in the treatment of acute or chronic joint pain. Their analgesic effect, however, is generally considered mild to moderate, and the relevance of their clinical use remains subject to discussion.

Objectives • The aim of the study was to evaluate the clinical relevance of the efficacy of a marketed complex of 3 plant extracts—*H procumbens*, *C longa*, and bromelain (AINAT, 650 mg)—in the treatment of degenerative joint pain.

Methods • A multicenter, observational, prospective, open-label survey was conducted in 8 rheumatology centers. The study included 2 groups, 1 group with participants suffering from chronic osteoarthritis (OA) pain and 1 group suffering from acute OA pain.

Setting • The research team carried out the study under daily practice conditions.

Participants • A total of 42 patients (36 women; mean age = 67 y) suffering from acute or chronic, degenerative spine or joint pain participated.

Intervention • Two 650-mg capsules of AINAT were administered 3 x/d to patients with acute pain and 2 x/d to patients with chronic pain.

Outcome Measures • At baseline, and during a follow-up visit at 15 d for the acute pain group and 60 d for the chronic pain group, the research team obtained each participant's global assessment (PGA) and each rheumatologist's global assessment (RGA), as well as each participant's pain score, using for each of them a 100-mm visual analogue scale (VAS). The clinical relevance of the efficacy was evaluated by comparing the outcome measures at endpoint to the values defining the patient acceptable symptom state (PASS) and by comparing the variations (in mm and %) between baseline and endpoint to those defining the minimal clinically important improvement (MCII). Tolerance was also assessed by collecting adverse events at each visit and by using a 4-point scale (very good to bad) at the endpoint.

Results • At baseline, the VAS pain score (standard deviation) was 69.1 mm (15.4) and 68.0 mm (18.2) for patients with acute and chronic pain, respectively. At the endpoint, the scores decreased to 42.1 mm (21.1) and 37.8 mm (25.9), respectively. This reduction of pain, as a percentage as well as an absolute value, corresponds to the required definition of MCII, particularly in patients with chronic joint pain. At the endpoint, most of the patients in both groups reached the level of pain defined as the PASS. No withdrawals occurred due to treatment side effects.

Conclusion • The improvement of joint pain was clinically relevant in patients treated with AINAT for both acute and chronic OA pain. Considering its excellent tolerance profile, the tested complex of 3 plant extracts with anti-inflammatory properties may be a valuable and safe alternative to NSAIDs in patients suffering from degenerative joint diseases. (*Altern Ther Health Med.* 2014;20(suppl 1):32-37.)

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Pain is the main symptom in osteoarthritis (OA) and is responsible for impaired function and loss of quality of life. Management of OA pain, which is often the first presenting cause of a visit to the doctor for OA-related symptoms, is regularly managed by a combination of pharmaceutical and nonpharmacological strategies that are currently recommended in several recognized guidelines.[1-5] The aim of the treatment is to control pain and improve function and health-related quality of life while avoiding therapeutic toxicity. The recommendations of the Osteoarthritis Research Society International (OARSI) specify that the treatment of knee OA should be tailored to the individual patient, taking into account factors such as age, comorbidity, and the presence of inflammation.[3] Indeed OA mainly affects the elderly and frail. Lanas et al[6] showed that most patients with OA who required NSAIDs for pain control showed a high prevalence of gastrointestinal (GI) and cardiovascular (CV) risk factors and that over half of the patients had either a high GI or a high CV risk or both. The researchers concluded that the prescription for NSAIDs should be very carefully considered in patients with OA.

Alternative medicines—such as nutraceuticals, phytotherapy, and acupuncture—are widely used in patients' self-medication but also are often prescribed by physicians for OA patients for whom NSAIDs are not effective, poorly tolerated, contra-indicated, or refused.[7] Preparations made from the secondary tubers of devil's claw (*Harpagophytum procumbens*) are frequently used with success in patients with OA and low back pain.[8] Other nutraceuticals such as bromelain, an enzyme extracted from pineapple, may also offer a safer alternative or adjunctive treatment for OA than current conventional treatments.[9] Among the most used dietary supplements, curcumin, which is the principal biochemical component of the spice turmeric (*Curcuma longa*), continues to demonstrate increasing evidence that it possesses potent anticatabolic, anti-inflammatory, antioxidant, and consequently antiosteoarthritic properties.[10,11]

Despite a number of randomized controlled trials, however, that show that these nutraceuticals are able to alleviate OA pain, their analgesic effect is generally considered to be mild to moderate. The clinical relevance of their use remains subject to discussion, and they are not yet recommended in the treatment of OA.[1-4] AINAT, 650 mg, is a nutraceutical dietary supplement (Laboratoire de Rhumatologie Appliquée, Labrha, Lyon, France) and is composed of an association of *H procumbens*, *C longa*, and bromelain. Its properties make it potentially useful as an alternative to pharmaceutical anti-inflammatory agents.

The aim of the current study was to demonstrate whether the relief of pain obtained with AINAT was clinically relevant and whether such a nutraceutical could be helpful in daily clinical practice for patients suffering from OA, especially for those patients for whom NSAIDs are contra-indicated or refused.

METHODS

Participants

This prospective, multicenter, open pilot study with a standardized follow-up was conducted by 8 rheumatologists on outpatients who were suffering from degenerative lower-limb (knee and hip) or spinal diseases and who were referred to the rheumatologist because of painful OA. For all of these patients, the physician had determined that they required NSAIDs; however, NSAID therapy was either contra-indicated because of comorbidities and/or concomitant therapies or refused by the patient (usually due to poor tolerability, inefficacy, or personal choice). The research team identified patients with acute pain as those individuals having a flare-up that had occurred fewer than 15 days prior to the start of the study (acute pain group) and patients with chronic OA pain as those individuals who had experienced pain for more than 3 months (chronic pain group). Patients fulfilled the following inclusion criteria to be enrolled in the study: (1) symptomatic osteoarthritic of the knee, hip, shoulder, or spine; (2) pain ≥ 40 mm on a 100-mm visual analogue scale (VAS Pain); and (3) signed informed consent. Because it was an observational trial, there were no exclusion criteria (eg, comorbidities, age, treatments) except the concomitant intake of NSAIDs during the follow-up period.

Intervention

Since the study involved an open observational survey, all participants received treatment with AINAT, a nutraceutical composed of an association of *H procumbens* (300 mg/capsule), *C longa* (200 mg/capsule), and bromelain (150 mg/capsule). For participants with acute pain, 2 capsules were administered 3 times daily for a 2-week period, and for participants with chronic OA pain, 2 capsules were administered twice daily for a period of 2 months. Participants were authorized to continue their previous OA therapies, such as physiotherapy, acetaminophen, and symptomatic slow-acting drugs for OA—such as glucosamine, chondroitin, diacerein, and avocado soybean unsaponifiables—at stable doses during the period from baseline to follow-up.

Data Sources

After their informed consent was obtained, participants were asked to fill out a standardized questionnaire at baseline, including the participant's self-assessment of pain on a 100-mm VAS Pain. The VAS Pain was a 100 mm-long horizontal line, which contained word descriptors at each end: *no pain* to *unbearable pain*. The patient represents their perception of the amount of pain they were feeling during the 48 hours before the visit by marking a vertical line between 2 ends. The VAS score was measured in millimeters from the left end of the line to the point indicated by the patient. Similarly, the patient's global assessment (PGA) of their OA was obtained. The rheumatologist's global assessment (RGA) was also obtained. At the follow-up visit for participants in each group, the same outcome measures were obtained again.

Table 1. Characteristics of Participants at Baseline (Clinical Data)

Study	Pain Baseline on VAS (SD)	Pain Endpoint on VAS (SD)	Baseline-Endpoint (SD, %)
Acute Pain n = 18	69.1 mm (15.4)	42.1 mm (21.1)	-26.4 mm (19.8, -38.9%)
Chronic Pain n = 24	68.0 mm (18.2)	37.8 mm (25.9)	-31.1 mm (20.2, -46.4%)

Tolerance was assessed by collecting the adverse events at each visit. At the end of the follow-up, patients were asked to self-assess the tolerance using a 4-point Likert scale (ie, *How did you consider the tolerance of the treatment?*—with options including *very good*, *good*, *fair*, or *bad*).

OUTCOME MEASURES

The relevance of the effectiveness of the AINAT was evaluated on Day 15 for participants with acute pain and on Day 60 for those with chronic pain by comparing the endpoint values on the VAS (as changes in mm and %) to the baseline values. The research team also evaluated the nutraceutical by comparing the measures at endpoint to the values determined by the patient acceptable symptom state (PASS).[12-15] PASS is an absolute threshold to determine the point beyond which patients consider themselves well. PASS identifies the highest level of symptoms below which patients consider their status acceptable. The variations (in mm and %) between the baseline and the endpoint were also used to assess the minimal clinically important improvement (MCII).[14-16] It identifies the smallest change in measurement that the patients consider as an important improvement (ie, the minimal meaningful change at an individual level).

A descriptive analysis was performed on all the collected data. Qualitative variables were described using frequencies and percentages. Quantitative variables were described using mean, standard deviation, and some characteristics of their distribution (minimum, maximum, and median). To estimate PASS and MCII, the results of the outcome variables obtained at the last visit were used. The statistical analysis was performed using Statview 5.0 software (SAS Institute, Cary, NC, USA). All statistical tests were carried out 2-tailed at the 5% level of significance.

RESULTS

The research team enrolled 42 patients, 36 women and 6 men, with a median age of 67 years (range = 49-84) who were suffering from degenerative spine pathologies (n = 17), knee OA (n = 16), and other acute or chronic OA joint pain (n = 9) in the study.

At baseline, VAS Pain score was 69.1 mm (15.4) and 68.0 mm (18.2) for participants with acute (n = 18) and chronic pain (n = 24), respectively (Table 1). At the endpoint, the score decreased to 42.1 mm (21.1) and 37.8 mm (25.9), respectively. The decrease in the pain score was -26 mm (19.8) in participants with acute pain (-38.9%; $P < .001$) and -31.1 mm (20.2) in those participants with chronic pain (-46.4%; $P < .001$).

Table 2. Patient Acceptable Symptom State (PASS) and Minimal Clinically Important Improvement (MCII) Thresholds in OA[14]

Criterion Units	PASS mm	MCII mm (%)
Pain on VAS	35.0	-15.3 (32)

At baseline, considering the inclusion criteria (pain ≥ 40 mm), no patient reached the value defining the PASS (Table 2). The efficacy evaluation is summarized in Figure 1, Figure 2, and Figure 3. In both groups, the reduction in pain in absolute value and percentage was much higher than that defining the MCII (Figure 1 and Figure 2). The PGA and RGA decreased in similar proportions, $P < .001$ (Figure 3).

Tolerability was assessed as very good or good in 83% of the cases—87.6% for participants with chronic pain and 80% for those with acute pain. All of the participants were able to tolerate the treatment. The research team observed no serious, related, adverse events for the nutraceutical in either group, and none of the subjects dropped out of the study due to poor tolerability.

DISCUSSION

The study was not designed to compare the efficacy of AINAT to that of a placebo or another comparator. Consequently, in the absence of a control group, the real efficacy of AINAT cannot be proven conclusively, even if most of the participants improved with the treatment. Indeed, the average reduction in pain (-26.4 mm and -31.1 mm) appears much larger than the mean placebo effect commonly observed.[17,18] The present study was designed to assess whether a *clinically relevant* improvement of pain could be demonstrated following the use of AINAT.

Figure 1. Acute Pain: VAS Score Variation From Day 1 to Day 15

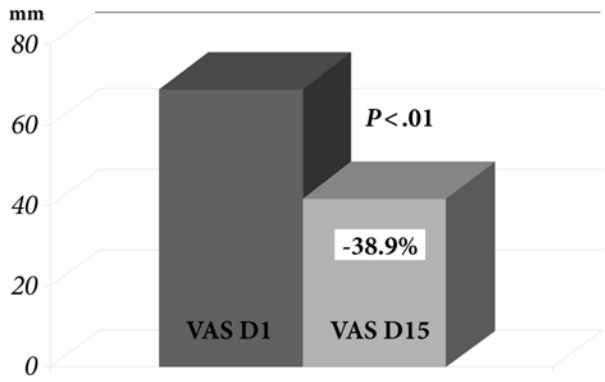


Figure 2. Chronic Pain: VAS Score Variation From Day 1 to Day 60

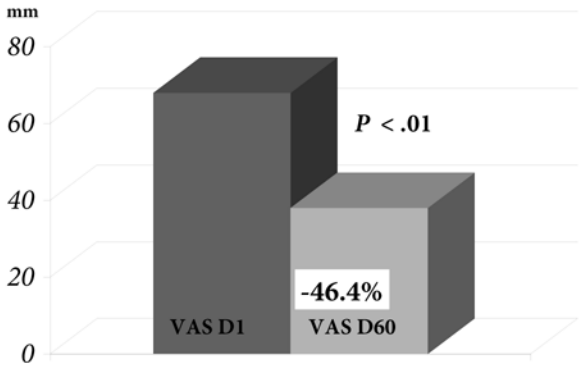
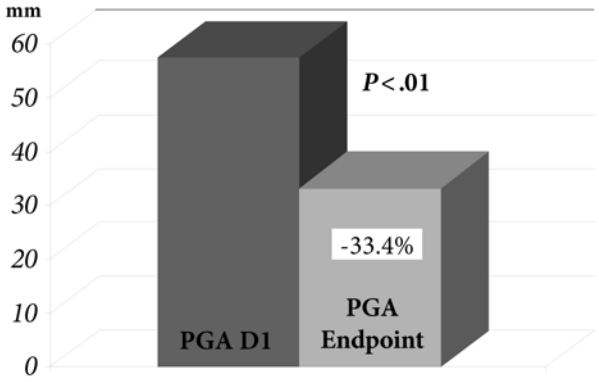


Figure 3. Participant Global Assessment Score Variation From Day 1 to Endpoint



In OA, the assessment of a treatment's clinical efficacy is usually achieved using measurement of pain and disability.[19] A number of evaluation tools have been validated for clinical trials, such as the (1) patient's pain self-assessment, (2) PGA, (3) RGA, (4) Lequesne index,[20] and (5) Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[21] indices. From these outcome measures, more complex variables have been proposed, taking into account at the same time the 3 dimensions determining OA clinical severity (pain, function, and global assessment of the condition). The response criteria in OARSI's outcome measures in rheumatoid arthritis clinical trials (OMERACT) permits presentation of results on individual patient's responses (responses = yes/no),[22-24] but these criteria are complicated to calculate and do not discriminate well between effective treatment and placebo.

In the current study, the research team chose the PASS and the MCII as tools to demonstrate the relevance of participants' clinical improvement. These 2 criteria are easy to obtain and are very useful in both clinical trials and daily practice, because they relate to what the patient is really feeling.

Regarding the results of the present study, AINAT appears to be a natural treatment that can support the alleviation of both acute and chronic, degenerative joint pain since the treatment effect is clinically relevant and higher than the MCII threshold. Furthermore, at the end of the follow-up, the mean level of pain was close to that defining the PASS.

Possible Mechanisms of Action

AINAT is a nutraceutical made of the combination of 3 plant extracts whose anti-inflammatory effectiveness has been demonstrated through clinical trials and in vitro studies. *H procumbens* is a widely used, natural, anti-inflammatory agent, traditionally used to relieve joint pain.[25] Two of the active principles of *H procumbens* are harpagoside and β-sitosterol (22,23-dihydrostigmasterol). Experimentally, extracts of *H procumbens* decrease significantly the IL-1β-induced production of metalloproteases (MMP-1, MMP-3, and MMP-9) in chondrocytes.[26,27] Stigmasterol inhibits IL-1-related effects on human's chondrocytes (ie, decreases MMP-3 and IL-13 mRNA, ADAMTS-4 mRNA, and PGE_2).[28] Numerous randomized clinical trials (RCTs) have shown that *H procumbens*, at a dosing regimen > 60 mg of harpagoside/day, was more effective than placebo in chronic low back pain and was not inferior to rofecoxib, 12.5 mg, and diacerein in OA of the knee.[29-31] In the current study, participants received a daily dose of 72 mg (chronic pain) and 108 mg (acute pain) of harpagoside, doses that previously published RCTs have demonstrated as effective.[30]

Curcumin (diferuloylmethane) is the major component of turmeric, a yellow spice derived from the plant *C longa* and a potent antioxidant with antitumor, analgesic, and anti-inflammatory properties. The anti-inflammatory and powerful antirheumatic effects of curcumin have been demonstrated in 12 studies in vitro.[32] Curcumin demonstrated potent anti-inflammatory properties by inhibiting key inflammatory mediators—IL-6, IL-8, PGE_2, and NO—and enzymes—COX-2 and iNOs.[11] Curcumin has also demonstrated antiapoptotic activities on chondrocytes[33] and proapototic effects on synovial adherent cells that are the main sources of inflammatory and degradation mediators. It has also been shown that curcumin down-regulates degradative effects observed after stimulation with IL-1β and

TNF-α of both chondrocytes and cartilage explants. In vitro, curcumin inhibits the production of metalloproteases MMP-3, MMP-9, and MMP-13 and restores type 2 collagen and glycoaminoglycan synthesis.[33-36] In a 1-week, prospective, double-blind, randomized trial including 107 participants with knee OA, Kuptniratsaikul et al[37] showed similar improvement in pain and function in participants treated with high doses of curcuma (curcuminoids: 2 g/d; eg, 1640 mg of diferuloylmethane) as compared to those receiving ibuprofen at 800 mg/day.[37] The major problem associated with the use of curcuma as a drug is the amount of curcumin in *C longa* extracts, and its relatively low bioavailability.[38] AINAT turmeric extracts contain 95% of curcumin, giving daily doses of 182.4 mg (chronic pain) to 273.6 mg (acute pain) of curcumin.

Bromelain is an extract of pineapple obtained from its stems and immature fruits and comprised of a complex mixture of proteolytic enzymes with anti-inflammatory, antioedematous, analgesic, and fibrinolytic properties. It is also believed to enhance flavonoids and glucosamine absorption and has been demonstrated to be safe when used for prolonged periods of time.[39-41] In 9 published clinical trials on knee OA, bromelain has shown therapeutic benefits at doses ranging from 160 to 1000 mg/day. In 7 clinical trials comparing bromelain to diclofenac, bromelain was not shown to be less effective than diclofenac.[42-47]

Due to past trials done individually on the 3 components included in the AINAT formula, minimal concern exists in terms of safety at the current study's established dosing regimen (3 to 6 capsules/d) and duration of treatment (15 d and 60 d). No treatment discontinuation occurred due to poor tolerability.

Combining 3 natural, anti-inflammatory compounds that offer excellent tolerability, AINAT may be a reasonable alternative to NSAIDs and COX-2 inhibitors, particularly in participants with GI, renal, or cardiovascular risk factors. Indeed, most of the conventional systemic treatments for OA—particularly NSAIDs and COX-2 inhibitors—are often responsible of severe adverse effects (SAEs): (1) cardiovascular SAEs, such as arterial hypertension, myocardial infarction, and stroke; (2) acute or chronic renal failure; (3) neurological adverse effects, such as drowsiness and dizziness; (4) gastrointestinal side effects, such as ulcers, bleeding, and perforation; and (5) hepatic side effects.[48-49]

Because of a number of limitations in the current study, including the small sample of patients and the lack of a control group, additional research is necessary to confirm the benefit to risk ratio of AINAT. It also would be prudent to determine the extent of the possibility of nutraceutical drug interactions if patients continue to take pharmaceutical therapies along with AINAT. A prospective study is still in progress to evaluate the nutraceutical's potential interaction with blood thinners in cardiac patients taking warfarin. Another example would be to determine the potential of AINAT to regulate blood sugar since the individual components have demonstrated this effect. A diabetic patient may need to adjust the dose of his or her pharmaceutical medication if using AINAT concomitantly.

The present study, however, allows the conclusion that the improvement of spine and joint pain was clinically relevant for participants treated with AINAT for both acute and chronic OA pain. Considering its tolerance profile, the tested complex of three plant extracts with anti-inflammatory properties may be a valuable and safe alternative to NSAIDs in participants suffering from degenerative joint diseases.

AUTHOR DISCLOSURE STATEMENT

Thierry Conrozier, MD, and Jean-François Marc, MD, received honorarium fees from Labrha. Jean-Luc Renevier, MD; Monique Bonjean, MD; Pierre Mathieu, MD; and Jean-Charles Balblanc, MD, have declared that they have no conflicts of interest.

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