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Osteoarthritis and Cartilage

Effect of a combination of *C. longa* and *B. serrata* extracts on hand osteoarthritis. Results of a double-blind, randomized, placebo-controlled, multicenter trial

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SUMMARY

Objective: To evaluate the efficacy and safety of a combination of patented *C. longa* and *B. serrata* extracts (CBTIL) in patients with hand osteoarthritis compared with placebo.
Design: This 3-month, multicentre, randomized, double-blind, placebo-controlled study enrolled patients with symptomatic hand osteoarthritis, with a body mass index ≤ 35 Kg/m^2, and who met the American College of Rheumatology criteria for osteoarthritis of the hand (CUBO/NCT 05570123). Participants received either two tablets of CBTIL or two placebo tablets per day. The primary endpoint was the difference in pain change on the visual analog scale between baseline and month 3. Secondary outcomes included the number of painful and swollen joints, functional score, quality of life, patient global assessment, grip strength, analgesic consumption, and treatment tolerance.
Results: 162 patients were randomly assigned to receive CBTIL (n=83) or placebo (n=79). In the Intention-to-treat analysis, the mean decrease (indicating pain relieve) from baseline to month 3 on the pain scale (primary endpoint) was −24.7 mm (95% Confidence Interval (CI) [−30.7 to −18.7]) in patient assigned to CBTIL group and −16.2 mm (95% CI [−22.5 to −9.9]) in patients assigned in placebo group (Difference between groups: −8.5 mm (95% CI [−16.4 to −0.6]; p = 0.03). At 3 months, the patient's global assessment (−9.6 mm [95% CI −16.9 to −2.2]), the percentage of patients achieving an acceptable symptom status (PASS) (Odd ratio (OR) 1.9 [95% CI 1.0 to 3.8]), Short Form-36 (SF-36) pain (7.1 units [95% CI 1.7 to 12.4]), and SF36 health change (6.7 units [95% CI 1.2 to 12.2]) were significantly improved by CBTIL compared to placebo. Other

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outcomes did not significantly differ between the two groups. No significant difference was observed regarding adverse events between the groups.

Conclusions: CBTIL relieves pain in patients with hand osteoarthritis. Together with its safety, this clinically relevant symptomatic effect suggests that CBTIL may be an alternative to oral NSAIDs and analgesics for managing symptomatic hand osteoarthritis.

Introduction

In Europe, osteoarthritis of the hands (HOA) is one of the most common forms of osteoarthritis (OA).[1] By 2050, an estimated 279 million people will suffer from HOA.[1,2] The disease is associated with hand pain, stiffness, functional limitations, decreased grip strength, and a reduced quality of life.[2] According to the latest recommendations from the European League Against Rheumatism (EULAR) for managing HOA, topical Non Steroidal Anti-inflammatory Drugs (NSAIDs) are the first-line pharmacological treatment, and oral analgesics, particularly NSAIDs, should be considered for a limited period to relieve symptoms.[3] Intra-articular glucocorticoid injections may be considered only in patients with painful interphalangeal joints. Given the limited number of available pharmacological treatments, looking for efficient, well-tolerated alternatives is essential. Plant-natural compounds could be an alternative. In 2018, Liu et al.[4] published a systematic review and meta-analysis, including 69 randomized placebo-controlled clinical trials with 11,586 participants, investigating 20 dietary supplements for managing OA. They concluded that some supplements, such as *C. longa and B. serrata* extracts, had moderate and clinically meaningful effects on pain and function in patients with OA in the short term. However, the studies included few patients and mainly investigated knee OA. No study evaluated the effect of *C. longa* or *B. serrata* alone or in combination in patients with hand OA, representing a subgroup different from knee OA patients. Furthermore, we cannot extrapolate that an active treatment for knee OA is also effective for HOA. We recently investigated the impact of *C. longa and B. serrata extracts* (CBTIL) and standard care on HOA.[5] This open-label, non-controlled, post-observational study based on 232 patients indicated that this combination of plant extracts might decrease pain intensity, painful joints, and oral and topical NSAID consumption. This preliminary observation justified the design of a randomized controlled trial to evaluate the effect of a combination of patented extracts of *Curcuma longa* (CURTIL03) and *Boswellia serrata* (BOSTIL01) on HOA. *In vitro*, we demonstrated that CURTIL03 and BOSTIL01 had different effects on the transcriptome of OA chondrocytes and acted on different but complementary pathways to induce anti-oxidant, detoxifying, anti-inflammatory, and anti-catabolic activities.[6] The genes most over-expressed by CURTIL03 were anti-oxidant, detoxifying, and cytoprotective genes involved in the Nrf2 pathway. The genes down-regulated were mainly pro-inflammatory cytokines and chemokines. Conversely, the antioxidant/detoxifying activities of BOSTIL01 were linked to activation of the Nrf1 and PPARα pathways. The anti-inflammatory effects of BOSTIL01 were associated with increases in Growth Differentiation Factor (GDF)15, decreases in cellular cholesterol uptake and genes involved in fatty acid metabolism, and down-regulation of Toll-like receptor (TLR) activation. Like CURTIL03, BOSTIL01 reduced the expression of A Disintegrin And Metalloproteinase with Thrombospondin Motifs (ADAMTS)1, 5, and Matrix Metallo-Proteases (MMP)-3 and -13 genes. The combination of CURTIL03 and BOSTIL01 was significantly more effective than CURTIL03 or BOSTIL01 alone on numerous genes, such as Interleukin (IL)-6, chemokine ligand 2 (CCL)2, ADAMTS1, and 5. This in vitro study justifies their combined use in the treatment of OA.[6]

It is unknown whether combining these plant extracts can relieve the symptoms of patients suffering from HOA. We sought to evaluate the efficacy of CBTIL, a combination of extracts CURTIL03 and BOSTIL01, in patients suffering from symptomatic HOA.

Methods

Study design

This was a randomized, double-blind, placebo-controlled, multicenter, 3-month, parallel-group study of patients with HOA (CUBO/NCT 05570123). The study was conducted in 11 centers in Belgium from September 2022 to January 2024, using good clinical practice guidelines and the Declaration of Helsinki.

The Central Ethics Committee (EC) at Ghent University Hospital, Belgium (670_OM 017) and appropriate local ECs approved the study and any amendments. The protocol followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines and can be obtained by contacting the first author.[7,8]

Eligible subjects were centrally randomized in a 1:1 ratio to the investigational or placebo group according to a randomization scheme advised by the statistician. The randomization blocks were stratified by sites.

Study population

Patients were adults with painful HOA who met the American College of Rheumatology classification criteria for hand OA. Inclusion criteria were age ≥ 40 years, body mass index (BMI) ≤ 35 kg/M^2, pain at least half of the days in the previous month and for at least 48 h before the inclusion/baseline visit, pain ranged between 40 and 80 mm on a 100 mm visual analog scale (VAS) on at least one hand over the last 24 h at baseline. Main exclusion criteria were predominant or isolated thumb base OA, severe and uncontrolled diseases (such as peptic ulcer, renal impairment, hepatic dysfunction, hematologic disease, cancer), hand OA secondary to previous inflammatory diseases and any painful syndrome of the upper limb that may interfere with evaluation of hand pain; inflammatory rheumatic diseases, scheduled surgery for hand OA or any surgical procedure anticipated within the next 6 months, anticoagulant (coumarin compounds) and heparin treatment, intra-articular injections of corticosteroids in the past three months in any joint or hyaluronic acid intra-articular injection in any hand joint within the past 6 months before joining the study, slow-acting drugs and/or dietary supplement for OA (soybean and avocado extracts, glucosamine, chondroitin, diacerein, nutritional supplements based on curcumin and/or boswellic acids) started < 3 months before the study, physiotherapy for hand pain in the past month and other treatments for hand OA such as oral corticoids, methotrexate, hydroxychloroquine, colchicine and sulfasalazine.

Intervention

Patients were randomized 1:1 using a computer-generated randomization code to receive two tablets (one morning and one evening) of

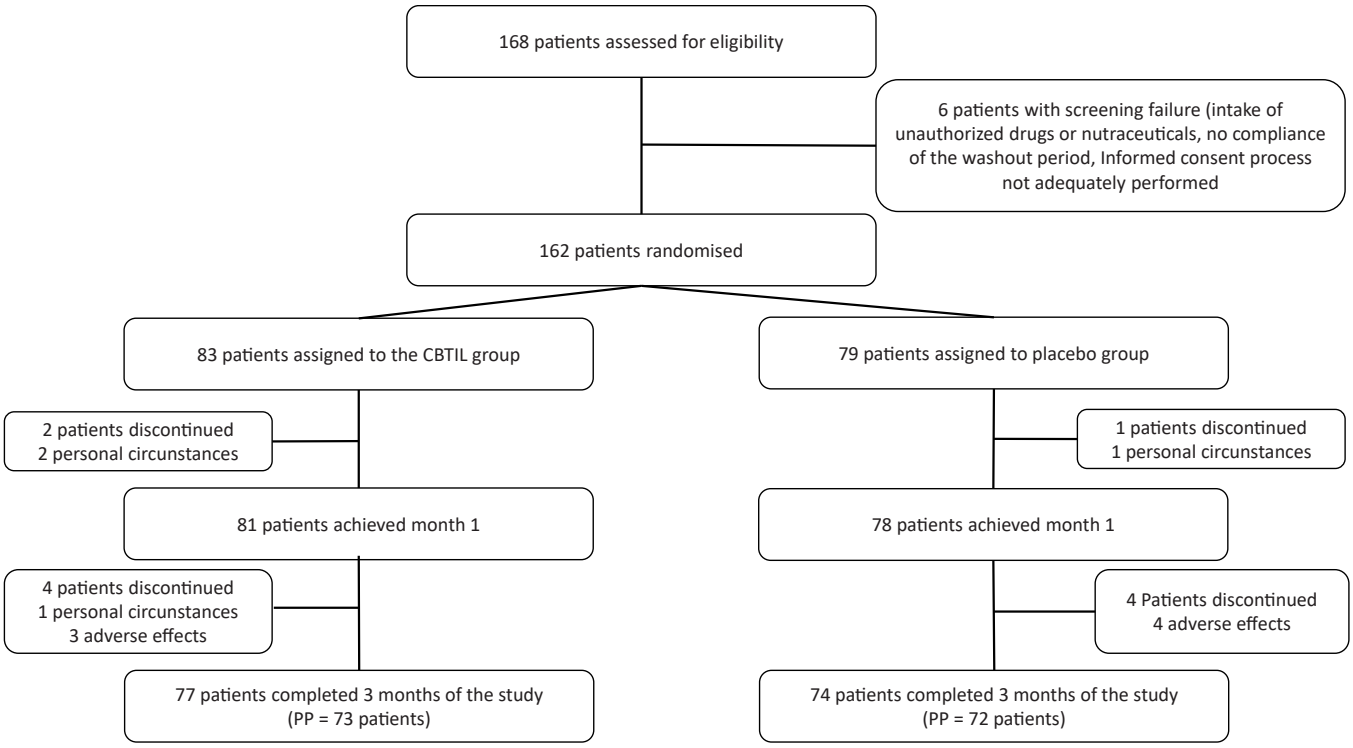

Fig. 1 Osteoarthritis and Cartilage

The flow of patients with HOA through the study.

placebo or CBTIL daily for three months. CBTIL (patent BE1027067B1) was composed of 237.35 mg *C. longa* patented extract (200.0 mg of curcumin) CURTIL03, 51.3 mg patented *B. serrata* oleoresin standardized to 65% of boswellic acids [active ingredient] (33.34 mg of boswellic acids) named BOSTIL01 and, 1.4 mg Cholecalciferol (vitamin D3). This pharmaceutical-grade CBTIL has been notified by Belgian Competent Authorities (NUT 31/167; Federal Public Service, Health, Food Chain Safety, and Environment) and commercialized under the brand name FLEXOFYTOL FORTE® (Tilman SA, Baillonville, Belgium). Randomization was stratified by center and block sizes of 4, 6, or 8. A computer generated the allocation sequence, and patients were recruited by the principal investigator of each center. The placebo and CBTIL tablets were identical in appearance. Patients, physicians, and nurses were blinded to treatments. All investigators, staff, and participants were unaware of the outcome measurements and trial results. Permitted concomitant treatments were restricted to acetaminophen (up to 3 g/day) and oral NSAIDs (maximum of seven consecutive days at the minimum effective dose), which had to be stopped within 24 h of a study visit. Topical NSAIDs were prohibited.

Outcomes

The primary outcome was the change from baseline to month 3 in mean finger pain on both hands during the last 24 h using a 0–100 mm (VAS). The question was: 'What is the global level of pain in your hands in the past 24 h?". Secondary efficacy outcomes were evaluated at 1 and 3 months: VAS pain (0–100 mm at 1 month), Patient Global Assessment (PGA, 0–100 mm VAS), number of painful joints (IP joints;(0–30) (spontaneous or under pressure, enough to blanch the tip of the examiner's fingernail(0–30)), number of swollen joints (IP joints;(0–30)), Functional Index for Hand Osteoarthritis (FIHOA, 0–30), Minimum Clinically Important Improvement (MCII) calculated on VAS finger pain (absolute change of 15 mm or relative change of 20%), Participant Acceptable important Symptom State (PASS) calculated on VAS finger pain (< 40 mm), Grip strength (using a dynamometer), the quality of life evaluated by self-reported questionnaires Short Form-36 (SF-36), consumption of paracetamol and oral NSAIDs as rescue treatments and Osteoarthritis Research Society International (OARSI) responder criteria from OMERACT-OARSI initiative.[9]

Safety and tolerance

Adverse events (AE) were assessed, and physical examinations were performed throughout the study. Safety was assessed by recording all serious adverse events (SAE), AE, and dropouts due to tolerance issues.

Statistical analysis

The sample size was adjusted to align with the study's primary objective. Indeed, the sample size was previously calculated based on absolute pain after 3 months of supplementation (https://clinicaltrials.gov/study/NCT05570123), rather than on the absolute change in pain between baseline and 3 months, as in the primary endpoint. Initially, it was estimated at 200 patients. A sample size of 160 patients (80 per group) was calculated to detect an effect size of 0.45, providing 80% power with an alpha level of 0.05 corresponding to the mean difference of −12.13 mm between active and placebo for change from baseline to 3 months in finger pain VAS. This value was calculated based on a previous study in knee OA.[10] A standard deviation of 26.96 (effect size: 0.45) was assumed for power

	Placebo (n=79)	CBTIL (n=83)
Age, years	64.0(8.1)	62.2(8.3)
Sex, female, n (%)	63(79.7)	61(73.5)
BMI (kg/m2)	26.3(4.3)	26.2(3.9)
Left dominant hand, n (%)	8(10.1)	5(6.0)
VAS finger pain (mm)	60.6(11.8)	57.8(12.1)
FIHOA(0–30)	38.3(19.8)	34.8(18.7)
Number of painful joints on the dominant hand (n,0–15)	4.5(2.9)	4.2(2.8)
Number of painful joints on the non-dominant hand (n,0–15)	4.3(2.7)	3.4(2.7)
Number of swollen joints on the dominant hand(0–15)	1.5(1.8)	1.6(1.9)
Number of swollen joints on non-dominant hand(0–15)	1.4(1.7)	1.3(1.8)
Patient global assessment (VAS; 0–100 mm)	65.7(17.9)	61.0(20.9)
Grip strength on dominant hand (Kg)	20.1(10.8)	22.2(12.6)
Grip strength on non-dominant hand (Kg)	19.7(10.1)	22.2(11.4)
SF-36 global (0–100)	59.3(17.3)	61.8(17.1)
SF-36 Physical functioning (0–100)	59.9(22.6)	66.3(19.5)
SF-36 Physical health (0–100)	46.5(40.4)	49.1(39.9)
SF-36 Energy/fatigue (0–100)	56.9(17.4)	58.4(18.9)
SF-36 Emotional problem (0–100)	72.6(40.6)	71.1(38.5)
SF-36 Well-being (0–100)	66.4(16.4)	66.6(17.7)
SF-36 Social functioning (0–100)	72.9(23.1)	71.5(22.9)
SF-36 Pain (0–100)	46.8(18.8)	50.5(19.2)
SF-36 General health (0–100)	58.5(19.4)	60.7(17.0)
SF-36 Change (0–100)	39.6(16.3)	38.2(20.0)
Participants taking Paracetamol and/or NSAIDs	25 (31.6)	23(27.7)

The data are mean (SD) or n (%). SF = Short-Form-36; BMI = body mass index; FIHOA = Functional Index for Hand Osteoarthritis; and VAS = Visual Analog Scale.

Table I Osteoarthritis and Cartilage

Baseline characteristics of hand osteoarthritis (OA) participants who received CBTIL or placebo in the modified ITT population.

calculation. All outcomes were analyzed in the modified intent-to-treat (mITT) population, which included all randomized patients who received at least one product dose. The primary outcome was assessed by analysis of covariance models with baseline measurement as a covariate. The last observation carried forward, and imputation was used to find missing values for the primary outcome. The primary outcome was also analyzed in the per-protocol (PP) population, which included all randomized participants with available primary endpoints and no significant protocol deviations. Continuous outcomes were analyzed as the change from baseline using repeated measures mixed-effects linear models, with the patient identification number as a random effect and baseline score, treatment group, time (baseline, 1 month, and 3 months), and interactions between treatment groups and time as fixed-effect factors. Categorical endpoints were analyzed after 1 and 3 months by logistical regression using randomized treatment as a factor and the baseline endpoint value as a covariate. For categorical efficacy endpoints, missing data were handled by non-responder imputation. $P < 0.05$ was considered statistically significant.

Results

Participants

Between September 2022 and January 2024, 168 patients were screened, and 162 were randomly assigned to receive CBTIL (n = 83) or a placebo (n = 79), forming the mITT population (Fig. 1). Of these, 77 (92%) patients in the CBTIL group and 74 (94%) in the placebo group completed the 3-month study (PP population). The mean age of participants was 63.1 years (Standard deviation (SD) 8.3), and 124 (76.5%) were women. Baseline characteristics were similar between groups (Table I).

Primary and secondary clinical outcomes

In the modified ITT population, the mean change in VAS pain (primary outcome) between baseline and month 3 was −24.7 mm

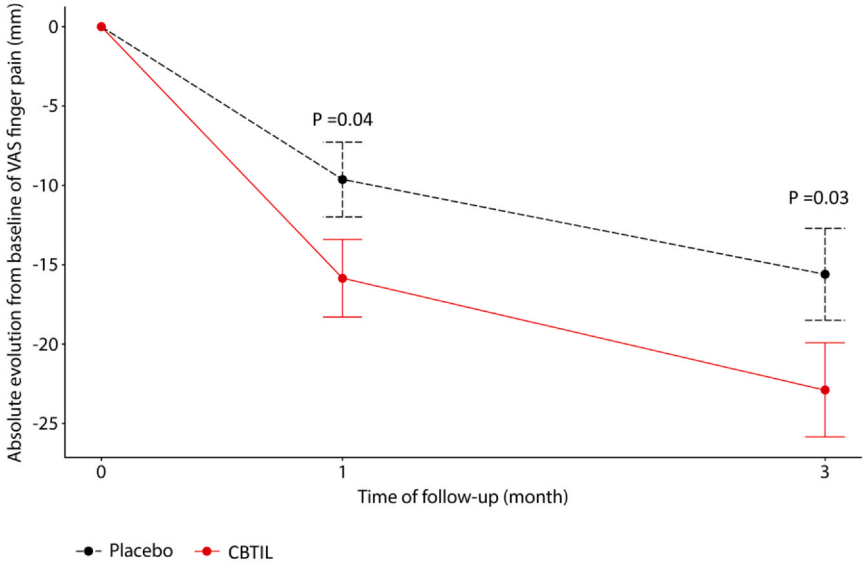

Fig. 2 Osteoarthritis and Cartilage

Mean change in VAS pain between baseline, month 1, and month 3 presented as least squares means for each group (with standard errors) in both treatment groups.

	1 month of treatment				3 months of treatment			
	Placebo[a]	CBTIL[a]	Between-groups[b]	P value	Placebo[a]	CBTIL[a]	Between-groups[b]	P value
Primary outcome								
Change in mean finger pain (VAS mm, 0–100 scale)					−16.2(−22.5;−9.9)	−24. (−30.7;−18.7)	−8.5(−16.4;−0.6)	0.03
Secondary outcomes								
Change in mean finger pain (VAS mm, 0–100 scale)	−10.4(−15.8;−5.1)	−17.4(−22.5;−12.4)	−7.0(−13.8;−0.2)	0.04	−16.3(−22.3;−10.2)	−24.4(−30.2;−18.6)	−8.1(−16.0;−0.3)	0.04
AUC finger pain (VAS mm²)	53.6(50.9;56.4)	50.3(47.7;52.8)	−3.4(−6.8;−0.001)	0.05	99.1 (91.5;106.7)	87.9 (80.7;95.2)	−11 (−20.6;−1.7)	0.02
Change in PGA (VAS mm, 0–100 scale)	−13.4(−18.3;−8.4)	−14.8(−19.5;−10.1)	−1.4(−7.8;4.9)	0.65	−15.3(−20.9;−9.6)	−24.8(−30.2;−19.4)	−9.6(−16.9;−2.2)	0.01
Number of patients reaching PASS (n, %)	22(28.9)	38(47.5)	2.2(1.1–4.3)	0.02	31(41.9)	46(59.0)	1.9(1.0–3.8)	0.04
Number of patients reaching MCII (n, %)	28(36.8)	40(50.0)	1.6(0.83–3.1)	0.16	32(43.2)	47(60.3)	1.9(0.97–3.7)	0.05
OARSI-OMERACT responders (n, %)	27(37.5)	42(54.6)	1.9(0.99–3.8)	0.05	38(55.1)	48(64.0)	1.4(0.71–2.8)	0.32
Change in FIHOA (unit, 0–100 scale)	−3.7(−7.0;−0.4)	−5.7(−8.9;−2.5)	−2.0(−6.5;2.4)	0.37	−5.0(−8.4;−1.6)	−1.6(−4.9;1.7)	3.4(−1.2;8.0)	0.15
Change in the number of painful joints (D)	−1.2(−1.8;−0.6)	−1.7(−2.2;−1.1)	−0.5(−1.2;0.3)	0.21	−1.3(−2.0;−0.6)	−1.7(−2.4;−1.1)	−0.4(−1.4;0.5)	0.38
Change in the number of symptomatic joints (ND)	−1.1(−1.6;−0.5)	−1.4(−1.9;−0.8)	−0.3(−1.0;0.4)	0.40	−1.3(−1.9;−0.7)	−1.8(−2.4;−1.2)	−0.5(−1.3;0.3)	0.21
Change in the number of swollen joints (D)	−0.4(−0.7;−0.1)	−0.3(−0.6;−0.0)	0.1(−0.3;0.5)	0.73	−0.6(−0.9;−0.2)	−0.5(−0.8;−0.2)	0.1(−0.4;0.5)	0.76
Change in the number of swollen joints (ND)	−0.4(−0.7;−0.1)	−0.3(−0.6;−0.0)	0.1(−0.2;0.5)	0.47	−0.4(−0.7;−0.2)	−0.5(−0.8;−0.3)	−0.1(−0.5;0.3)	0.63
Change of grip strength on D hand (Kg)	2.2(0.9;3.4)	2.5(1.3;3.7)	0.4(−1.1;1.8)	0.62	2.5(1.2;3.9)	2.6(1.4;3.9)	0.1(−1.5;1.7)	0.90
Change of grip strength on ND hand (kg)	1.8(0.6;3.0)	2.3(1.2;3.5)	0.6(−0.9;2.0)	0.44	2.1(0.8;3.3)	2.5(1.3;3.7)	0.4(−1.1;1.9)	0.61
Change in SF-36 Global (unit, 0–100 scale)	3.9(1.3;6.5)	4.8(2.4;7.2)	1.0(−2.3;4.2)	0.57	6.1(3.1;9.1)	5.4(2.6;8.3)	−0.7(−4.5;3.2)	0.73
Change SF-36 Physical functioning (unit, 0–100 scale)	2.0(−1.5;5.4)	3.2(−0.1;6.4)	1.2(−3.2;5.6)	0.59	5.5(1.5;9.4)	3.4(−0.4;7.2)	−2.1(−7.2;3.1)	0.43
Change SF-36 Physical health (unit, 0–100 scale)	15.7(7.3;24.1)	13.7(5.8;21.6)	−2.0(−12.8;8.7)	0.71	22.3(13.8;30.8)	17.6(9.6;25.7)	−4.7(−15.7;6.3)	0.40
Change SF-36 Energy/fatigue (unit, 0–100 scale)	1.8(−1.2;4.8)	4.0(1.2;6.8)	2.2(−1.6;6.0)	0.26	1.7(−1.7;5.1)	4.9(1.7;8.2)	3.2(−1.2;7.6)	0.15
Change SF-36 Emotional problem (unit, 0–100 scale)	3.3(−5.3;11.8)	0.1(−8.0;8.2)	−3.2(−14.3;7.9)	0.57	8.7(0.5;16.9)	1.7(−6.1;9.4)	−7.1(−17.6;3.4)	0.19
Change SF-36 Well-being (unit, 0–100 scale)	3.1(0.2;5.9)	5.1(2.4;7.7)	2.0(−1.6;5.5)	0.27	4.2 (0.9;7.5)	3.7 (0.6;6.8)	−0.5(−4.8;3.8)	0.81
Change SF-36 Social functioning (unit, 0–100 scale)	4.4(−0.1;8.8)	4.5(0.3;8.7)	0.1(−5.6;5.9)	0.96	6.1 (1.8;10.4)	4.4 (0.3;8.4)	−1.7 (−7.2;3.8)	0.54
Change SF-36 Pain (unit, 0–100 scale)	6.4(2.7;10.0)	13.8(10.3;17.2)	7.4(2.8;12.0)	0.001	10.2 (6.0;14.3)	17.2 (13.2;21.2)	7.1 (1.7;12.4)	0.01
Change SF-36 General health (unit, 0–100 scale)	1.4(−1.2;3.9)	1.8(−0.6;4.2)	0.4(−2.8;3.6)	0.80	−0.8 (−3.6;1.9)	0.3 (−2.3;2.9)	1.1 (−2.4;4.6)	0.53
Change SF-36 Health Change (unit, 0–100 scale)	6.3(1.9;10.7)	6.5(2.3;10.7)	0.1(−5.6;5.9)	0.96	4.6 (0.4;8.8)	11.3 (7.3;15.4)	6.7 (1.2;12.2)	0.01
Compliance (% pills taken/% pills expected)	96.0(93.2;98.7)	93.5(90.9;96.1)	−2.5(−6.1;1.1)	0.18	95.4 (92.6;98.2)	97.2 (94.5;99.9)	1.7 (−1.9;5.4)	0.35
Number of patients taking NSAIDs/paracetamol (n, %)	12(15.6)	12(14.8)	1.0(0.40–2.5)	0.99	16(21.6)	11(14.3)	0.69 (0.29–1.6)	0.39

VAS = Visual analog scale; AUC = Area Under the Curve; Functional Index for Hand Osteoarthritis (FIHOA, 0–30), Minimum Clinically Important Improvement (MCII), Participant Acceptable Important Symptom State (PASS), Dominant hand (D), non-dominant hand (ND).

a: results were expressed as least square means and 95% confidence intervals for quantitative outcomes and as numbers and percentages for qualitative outcomes

b: results were expressed as between-groups least square means difference and 95% confidence intervals, and as odds ratio and 95% confidence intervals for qualitative outcomes

[a] Results were expressed as least square means and 95% confidence intervals for quantitative outcomes and as numbers and percentages for qualitative outcomes.

[b] Results were expressed as between-groups least square means difference and 95% confidence intervals, and as odds ratio and 95% confidence intervals for qualitative outcomes.

Table II

Changes in endpoints after one month and three months of treatments with placebo or CBTIL in the modified ITT population.

Osteoarthritis and Cartilage

	Placebo (n, %) n=79	CBTIL (n, %) n=81
Total	47(59.5)	49(60.5)
Related	2(2.5)	0(0.0)
Probably related	6(7.6)	6(7.4)
Unlikely related	13(16.5)	12(14.8)
Unrelated	36(45.6)	40(49.4)
Definitive discontinuation due to AE	7(8.9)	12(14.8)
Reported SAE	0(0.0)	2(2.5)
Death	0(0.0)	0(0.0)

ITT = Intention-To-Treat, SAE = Severe Adverse Effect.

Table III Osteoarthritis and Cartilage

Number of participants who reported at least one AE according to study product in the modified ITT population.

(95% CI [−30.7 to −18.7]) in CBTIL and −16.2 mm (95% CI [−22.5 to −9.9]) in the placebo group. The difference between groups was −8.5 mm (95% CI [−16.4 to −0.6]; p=0.03) (Fig. 2). The effect size was −0.3 (95% CI [- 0.5 to −0.1]) compared to placebo.

The difference between groups was also significant in the PP population. At 3 months, the difference between groups was −6.85 mm (95% CI [−14.9 to 1.2]; p = 0.04).

In the modified ITT population, change in VAS pain from baseline at one month was higher in CBTIL than in placebo (between-groups difference: −7.0 mm (95% CI [−13.8 to −0.2], p=0.04) (Table II). PGA decrease was significantly higher in CBTIL than in placebo at month 3 (between-groups difference: −9.6 mm (95% CI [−16.9 to −2.2], p=0.01). The percentage of participants meeting the PASS and SF-36 pain improvement criteria was significantly higher in the CBTIL than in the placebo group at month 1 (between-groups difference: OR 2.2 (95% CI [1.1 to 4.3], p=0.02) and month 3 (between-groups difference: OR 1.9 (95% CI [1.0 to 3.8], p=0.04). The SF-36 pain was also significantly increased at 1 month (between-groups difference: 7.4 units (95% CI [2.8 to 12], p=0.001) and 3 months (between-groups difference: 7.1 units (95% CI [1.7 to 12.4], p=0.01) and the SF-36 health change was increased at 3 months (between-groups difference: 6.7 units (95% CI [1.2 to 12.2], p=0.01) (Table II).

Drug consumption and compliance

The global compliance mean was higher than 90% at both time points and not different in both groups at 1 month (between-group difference: - 2.5 pills (95% CI [−6.1 to 1.1]; p = 0.45) or at 3 months (between-groups difference: 1.7 pills (95% CI [−1.9 to 5.4], p=0.35) (Table II). At baseline, 31.6% of patients in the placebo group and 27.7% of patients in the CBTIL group took paracetamol and/or NSAIDs. This proportion decreased in both groups after 1 month of treatment, with no significant difference between the groups (15.6% in the placebo group; 14.8% in the CBTIL group, p = 0.45). Between the 1st and 3rd months of treatment, the number of patients taking paracetamol and/or NSAIDs tended to increase in the placebo group while remaining stable in the CBTIL group. No significant difference was observed between the groups at 3 months (21.6% in the placebo group; 14.3% in the CBTIL group, p = 0.39).

Safety

Overall, the number of adverse effects was comparable between the two groups. Sixty percent of the patients presented at least one AE (Table III). The percentage of participants with at least one AE was similar between the two groups (CBTIL: 60.0% vs Placebo: 61.4%, p=0.8). Most AEs were unlikely or unrelated to the study product (89.6%). Only 1.3% of reported AEs were evaluated as related to the study product, all were in the placebo group. Among those assessed as probably associated with the product, 8 AEs occurred in the placebo group and 14 AEs in the CBTIL group. One of the probably related AE of the CBTIL group was a severe adverse (acute hepatitis). The most frequent non-SAE were mild gastrointestinal disorders such as constipation, abdominal cramps, and nausea.

Discussion

This study demonstrated that CBTIL, a combination of exclusive *C. longa* and *B. serrata* extracts, significantly alleviated pain in patients with hand OA. The ability of *B. serrata* and *C. longa* extracts (alone or in combination) to relieve patients with knee OA has been primarily described in the literature.[10,11] However, to our knowledge, this is the first and only study reporting the results of a clinical trial that respects International Council for Harmonization (ICH) recommendations and involves patients with HOA. Although the effect of CBTIL on pain is significant, it remains moderate, with an effect size of −0.3 at month 3 compared to the placebo.[12] However, this effect is higher than that of oral NSAIDs and glucocorticoids, two drugs that induce severe adverse effects in the long term. A recent network meta-analysis highlighted that the effect size of oral NSAIDs on HOA pain was −0.1 compared to placebo.[13] CBTIL effect size was even higher than intra-articular hyaluronate, intra-articular glucocorticoids, hydroxychloroquine, and topical NSAIDs' effect sizes, which were not superior to placebo[13]The CBTIL effect size was lower in HOA than in knee OA.[10] Indeed, in a previous RCT, we found an effect size of 0.4 after 3 months of treatment with CBTIL compared to placebo. This can be explained by differences in the pathophysiological and clinical characteristics of both localizations. It is also noted that a higher number of patients reached the MCI and PASS cut-off in the CBTIL group than in the placebo group, indicating that the CBTIL effect is clinically relevant for a majority (60%) of patients.

Remarkably, the effect was already significant after one month, suggesting a fast action of CBTIL. The mechanism of action of these extracts can explain these effects. Curcumin inhibits cyclooxygenase-2 and prostaglandin E2 in a concentration and time-dependent manner.[14] *In vivo* studies have shown that curcumin produces an analgesic effect by antagonizing transient receptor potential vanilloid 1, a receptor that plays a crucial role in nociception.[15] Analgesic activity has also been previously reported for Boswellia and boswellic acids, including inhibition of lipoxygenases.[16] On the other hand, CBTIL failed to improve joint function. Indeed, no significant effect of CBTIL on FIHOA or grip strength was observed compared to placebo, even a trend of strength increase was observed in the CBTIL group, but the difference did not reach significance. The significant heterogeneity of the values collected can explain the absence of the effect of joint function.

Another critical finding is CBTIL's excellent tolerance. No more adverse effects have been observed in CBTIL than in the placebo, which can be advantageous for the long-term management of patients with chronic conditions like OA.

Our study, the first to assess CBTIL in HOA, had strengths, particularly its design and rigorous patient selection and assessment, but also limitations. One limitation is that we have not included a shorter-term evaluation of pain to confirm the fast action of CBTIL. We miss the absence of imaging outcomes, such as ultrasound or X-ray, that would allow us to evaluate the influence of CBTIL on bone erosion or inflammation, and to analyze HOA subgroups, including erosive and non-erosive phenotypes. Based on the anti-inflammatory effect of CBTIL, it would be interesting to test CBTIL on a more homogeneous and well-characterized population of

inflammatory erosive HOA. Finally, the multiplicity of secondary endpoints may affect the proper statistical interpretation of the results, increasing the likelihood of obtaining a statistically significant result.

In conclusion, the investigational product used in the study is an option for healthcare providers and researchers working on novel pain relief products. We demonstrated a significant and, for many patients, clinically relevant effect of CBTIL on pain in hand OA. CBTIL can be suggested as an effective and safe natural alternative for the management of pain in HOA.

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Role of the funding source

The study was funded by Tilman SA. Tilman SA paid a CRO to monitor and manage the study's data. Tilman SA was not directly in contact with the investigators and patients. Tilman SA was not involved in analyzing and interpreting data or writing the manuscript.

Author contributions

YH and RW conceptualized and designed the study. YH, RW, and KDV drafted the original protocol. RW was the principal investigator. The data was acquired by YH, RW, FS, MD, RJ, HL, QR, MVDB, TV, JV, LVP, and KDV. YH and RW designed the statistical analysis plan. Artialis SA verified the data. Artialis SA accessed the raw data. YH and RW analyzed and interpreted the data. YH drafted the original manuscript. YH, RW, FS, MD, RJ, HL, QR, MVDB, TV, LVP, and KDV reviewed and commented on the manuscript. All authors approved the final version. YH and RW take responsibility for the integrity of the work as a whole, from inception to the finished Article. YH and RW had full access to all the data in the study and were responsible for the decision to submit it for publication.

Declaration of competing interest

YH and RW received speaker fees from Tilman SA.

Declaration of Generative AI and AI-assisted technologies in the writing process

The authors did not use generative AI and AI-assisted technologies in the writing.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.joca.2025.06.005.

References

1. Cross M, Ong KL, Culbreth GT, Steinmetz JD, Cousin E, Lenox H, *et al*. Global, regional, and national burden of gout, 1990-2020, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. Lancet Rheumatol 2024 Aug 1;6(8):e507–17. [cited 2024 Oct 28]. ⟨https://pubmed.ncbi.nlm.nih.gov/38996590/⟩.
2. Richette P, Latourte A. Hand osteoarthritis: a fresh look. Joint Bone Spine 2024 Jul 1;91(4):1–7. [cited 2024 Oct 28]. ⟨https://pubmed.ncbi.nlm.nih.gov/37797830/⟩.
3. Kloppenburg M, Kroon FPB, Blanco FJ, Doherty M, Dziedzic KS, Greibrokk E, *et al*. 2018 update of the EULAR recommendations for the management of hand osteoarthritis. Ann Rheum Dis 2019 Jan 1;78(1):16–24. [cited 2024 Oct 28]. ⟨https://pubmed.ncbi.nlm.nih.gov/30154087/⟩.
4. Liu X, Machado GC, Eyles JP, Ravi V, Hunter DJ. Dietary supplements for treating osteoarthritis: a systematic review and meta-analysis. Br J Sports Med 2018 Feb 1;52(3):167–75. [cited 2024 Oct 28]. ⟨https://pubmed.ncbi.nlm.nih.gov/29018060/⟩.
5. Henrotin Y, Dierckxsens Y, Delisse G, Maes N, Albert A. Curcuma longa and Boswellia serrata extract combination for hand osteoarthritis: an open-label pre-post trial. Pharm Biol 2022;60(1):2295–9. [cited 2024 Oct 28]. ⟨https://pubmed.ncbi.nlm.nih.gov/36416059/⟩.
6. Sanchez C, Zappia J, Lambert C, Foguenne J, Dierckxsens Y, Dubuc JE, *et al*. Curcuma longa and Boswellia serrata extracts modulate different and complementary pathways on human chondrocytes in vitro: deciphering of a transcriptomic study. Front Pharmacol 2022 Aug 11;13:1–14. [cited 2024 Oct 29]. ⟨https://pubmed.ncbi.nlm.nih.gov/36034822/⟩.
7. Lepage L, Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, *et al*. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. Ann Intern Med 2001 Apr 17;134(8):663–94. [cited 2024 Oct 29]. ⟨https://pubmed.ncbi.nlm.nih.gov/11304107/⟩.
8. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. J Am Podiatr Med Assoc 2001;91(8):437–42.
9. Pham T, van der Heijde D, Altman RD, Anderson JJ, Bellamy N, Hochberg M, *et al*. OMERACT-OARSI initiative: osteoarthritis research society international set of responder criteria for osteoarthritis clinical trials revisited. Osteoarthritis Cartilage 2004;12(5):389–99. [cited 2024 Nov 18]. ⟨https://pubmed.ncbi.nlm.nih.gov/15094138/⟩.
10. Henrotin Y, Malaise M, Wittoek R, De Vlam K, Brasseur JP, Luyten FP, *et al*. Bio-optimized Curcuma longa extract is efficient on knee osteoarthritis pain: a double-blind multicenter randomized placebo controlled three-arm study. Arthritis Res Ther 2019 Jul 27;21(1). [cited 2024 Oct 28]. ⟨https://pubmed.ncbi.nlm.nih.gov/31351488/⟩.
11. Kizhakkedath R. Clinical evaluation of a formulation containing Curcuma longa and Boswellia serrata extracts in the management of knee osteoarthritis. Mol Med Rep 2013 Nov;8(5):1542–8. [cited 2024 Oct 28]. ⟨https://pubmed.ncbi.nlm.nih.gov/24002213/⟩.
12. Wang Z, Singh A, Jones G, Winzenberg T, Ding C, Chopra A, *et al*. Efficacy and safety of turmeric extracts for the treatment of knee osteoarthritis: a systematic review and meta-analysis of randomised controlled trials. Curr Rheumatol Rep 2021 Feb 1;23(2). [cited 2025 Apr 5]. ⟨https://pubmed.ncbi.nlm.nih.gov/33511486/⟩.
13. Døssing A, Nielsen SM, Kroon FPB, Balsby IM, Tarp S, Kloppenburg M, *et al*. Comparative effectiveness of pharmacological interventions for hand osteoarthritis: a systematic review and network meta-analysis of randomised trials. RMD Open 2023 Sep 21;9(3). [cited 2024 Oct 28]. ⟨https://pubmed.ncbi.nlm.nih.gov/37734873/⟩.

14. Mathy-Hartert M, Jacquemond-Collet I, Priem F, Sanchez C, Lambert C, Henrotin Y. Curcumin inhibits pro-inflammatory mediators and metalloproteinase-3 production by chondrocytes. Inflamm Res 2009 Dec;58(12):899–908. [cited 2024 Oct 28]. ⟨https://pubmed.ncbi.nlm.nih.gov/19579007/⟩.
15. Zhi L, Dong L, Kong D, Sun B, Sun Q, Grundy D, *et al*. Curcumin acts via transient receptor potential vanilloid-1 receptors to inhibit gut nociception and reverses visceral hyperalgesia. Neurogastroenterol Motil 2013 Jun;25(6):e429–40. [cited 2024 Oct 28]. ⟨https://pubmed.ncbi.nlm.nih.gov/23638900/⟩.
16. Shin MR, Kim HY, Choi HY, Park KS, Choi HJ, Roh SS. Boswellia serrata Extract, 5-Loxin®, prevents joint pain and cartilage degeneration in a rat model of osteoarthritis through inhibition of inflammatory responses and restoration of matrix homeostasis. Evid Based Complement Alternat Med 2022;2022, 3067526. [cited 2024 Oct 28]. ⟨https://pubmed.ncbi.nlm.nih.gov/36310623/⟩.