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The Effect of a Dispersible Curcumin (HydroCurc®) Compared to a Placebo for Reducing Joint Pain in an Adult Population – A Randomised, Double-Blind Study

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Keywords
Joint pain · Pain · Curcumin · Inflammation

Abstract
Introduction: This study aimed to assess the efficacy of a novel curcumin formulation, HydroCurc®, for alleviating joint pain and improving quality of life in adults. ***Method:*** A randomised, double blind, placebo-controlled study was conducted on adults aged 25–70 years reporting joint pain. Eighty participants received either curcumin or a placebo daily for 2 weeks. The primary outcome was a self-assessed reduction in pain as assessed by a visual analogue scale (VAS) for pain, completed daily in the morning and evening. Quality of life was assessed by the RAND 36-Item Health Survey (SF-36) and the Profile of Mood States (POMS). ***Results:*** VAS pain scores reduced over the 2 weeks of treatment in both groups. Morning VAS scores were significantly reduced from baseline in the curcumin and placebo groups from day 6 and 12, respectively. Morning VAS scores were significantly lower in the curcumin group compared to the placebo group for days 11, 13, and 14 ($p < 0.05$). Evening VAS scores were significantly reduced from baseline in the curcumin and placebo groups from day 5 and 6, respectively. There were no differences in the evening VAS scores, SF-36 nor POMS between groups. ***Conclusion:*** This study demonstrates that HydroCurc® is an effective option for reducing morning joint pain. Future studies would benefit from investigating whether long-term supplementation and/or a split dose can show further improvements in pain scores. © 2022 S. Karger AG, Basel

Wirkung von dispergierbarem Curcumin (HydroCurc®) zur Linderung von Gelenkschmerzen im Vergleich zu Placebo in einer Population von Erwachsenen – eine randomisierte Doppelblindstudie

Schlüsselwörter
Gelenkschmerzen · Schmerz · Curcumin · Entzündung

Zusammenfassung
Einleitung: Mit dieser Studie sollte die Wirksamkeit der neuartigen Curcumin-Formulierung HydroCurc® zur Linderung von Gelenkschmerzen und zur Erhöhung der Lebensqualität bei Erwachsenen untersucht werden. ***Methode:*** Es handelte sich um eine randomisierte, placebokontrollierte Doppelblindstudie mit Erwachsenen im Alter von 25 bis 70 Jahren, die über Gelenkschmerzen berichteten. Achtzig (80) Teilnehmer erhielten 2 Wochen lang täglich entweder Curcumin oder ein Placebo. Primäres Zielkriterium war eine Selbsteinschätzung der Schmerzlinderung anhand einer visuellen Analogskala (VAS) für Schmerzen, die täglich morgens und abends ausgefüllt wurde. Die Bewertung der Lebensqualität erfolgte mithilfe des RAND Short Form (36) Gesundheitsfragebogens (SF-36) und des Profile of Mood States (POMS). ***Ergebnisse:*** Die VAS-Schmerzscores nahmen im Verlauf der zwei Behandlungswochen in beiden Gruppen ab. Die morgendlichen VAS-Scores waren in der Curcum-

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in- und in der Placebogruppe ab Tag 6 bzw. Tag 12 im Vergleich zum Ausgangswert signifikant verringert. In der Curcumin-Gruppe fielen die morgendlichen VAS-Scores an Tag 11, 13 und 14 signifikant niedriger aus als in der Placebo-Gruppe ($p < 0,05$). Die abendlichen VAS-Scores waren in der Curcumin- und in der Placebogruppe ab Tag 5 bzw. ab Tag 6 im Vergleich zum Ausgangswert signifikant verringert. Bei den abendlichen VAS-Scores, den SF-36- und den POMS-Werten fanden sich keine Unterschiede zwischen den Gruppen. ***Schlussfolgerung:*** Diese Studie zeigt, dass HydroCurc® eine wirksame Option zur Verringerung morgendlicher Gelenkschmerzen darstellt. Ob sich durch eine Langzeit-Supplementierung und/oder eine Teilung der Dosis weitere Verbesserungen der Schmerz-Scores erreichen lassen, sollte in zukünftigen Studien untersucht werden. © 2022 S. Karger AG, Basel

Introduction

Joint pain can be a debilitating condition and common source of chronic pain [1]. Though commonly seen in older populations [2–4], it can affect individuals of any age to varying degrees [4, 5]. Joint pain can arise for several reasons including arthritis [3–5], infection [6], autoimmune disease [7], inflammation of surrounding areas [8], and mechanical injuries [9]. It can occur in any joint, with knee pain being the most frequently cited in adults [3, 4]. While being multifactorial in nature, the underlying pathophysiological mechanism of joint pain is the sensitization of nociceptive receptors by inflammatory mediators [1, 8, 10, 11]. Continuous input from the affected joint can bring about peripheral and central sensitization where nociceptive fibres become increasingly responsive to normally innocuous stimuli, even arising from areas unrelated to the original site of pain [1, 8, 10, 11]. Central sensitization in particular brings about the development and maintenance of chronic joint pain [8, 10].

Current therapies for acute and chronic joint pain typically involve acetaminophen, nonsteroidal anti-inflammatory drugs, and opioids [8, 12, 13]. However, continuous uses of these treatments are associated with unfavourable adverse effects as well as concerns about drug toxicity and dependency potential [8, 12, 13]. The potential side effects of pharmaceuticals not only increase healthcare costs [12], they are also contraindicated in individuals whose risk of drug toxicity is greater, such as those with underlying diseases [12, 13], the elderly, or pregnant women [14]. As chronic pain can decrease quality of life [8], there is a need for therapies that effectively reduce pain with mild or no side effects.

A compound generating a lot of interest for its therapeutic properties is curcumin. The primary active compound of the turmeric plant (*Curcuma longa L.*), curcumin, has been used medicinally for nearly 4,000 years in Asian and Middle Eastern communities [15]. Several clinical and preclinical trials have shown curcumin's ability to reduce arthritic symptoms such as pain, to improve physical function, and quality of life, while reducing usage of analgesics [16–19]. The beneficial effects of curcumin are likely due to its reported anti-inflammatory and antioxidant properties [16–19]. Curcumin's ability to potentially target multiple aspects of the inflammatory pathway highlights its potential use as a therapeutic agent for joint pain [16–21].

The limitation to curcumin acting as a therapeutic compound is its traditionally poor bioavailability due to its lipophilic nature [16–19]. To overcome this, LipiSperse®, a cold water dispersible (CWD) technology, is specifically designed to increase the bioavailability of lipophilic agents, such as curcumin, in the aqueous gastrointestinal environment [22]. HydroCurc® is a novel curcumin formulation utilising LipiSperse® CWD technology previously shown to increase curcuminoid absorption by approximately 3-fold [22]. The aim of this study was to assess the efficacy of a dispersible curcumin (HydroCurc®) in alleviating joint pain and improving quality of life in otherwise healthy adults.

Materials and Methods

Clinical Trial Design, Registration, and Ethical Approval

A randomised, double-blind, placebo-controlled study was performed, investigating the efficacy of 440 mg Hydrocurc® (containing approximately 396 mg of curcuminoids) for alleviating joint pain and improving quality of life over a 2-week period.

This study was conducted between March 2020 and September 2020. Both the curcumin and placebo capsules were manufactured and tested by Pharmako Biotechnologies Pty Ltd (Sydney, Australia) under Good Manufacturing Practices (GMP).

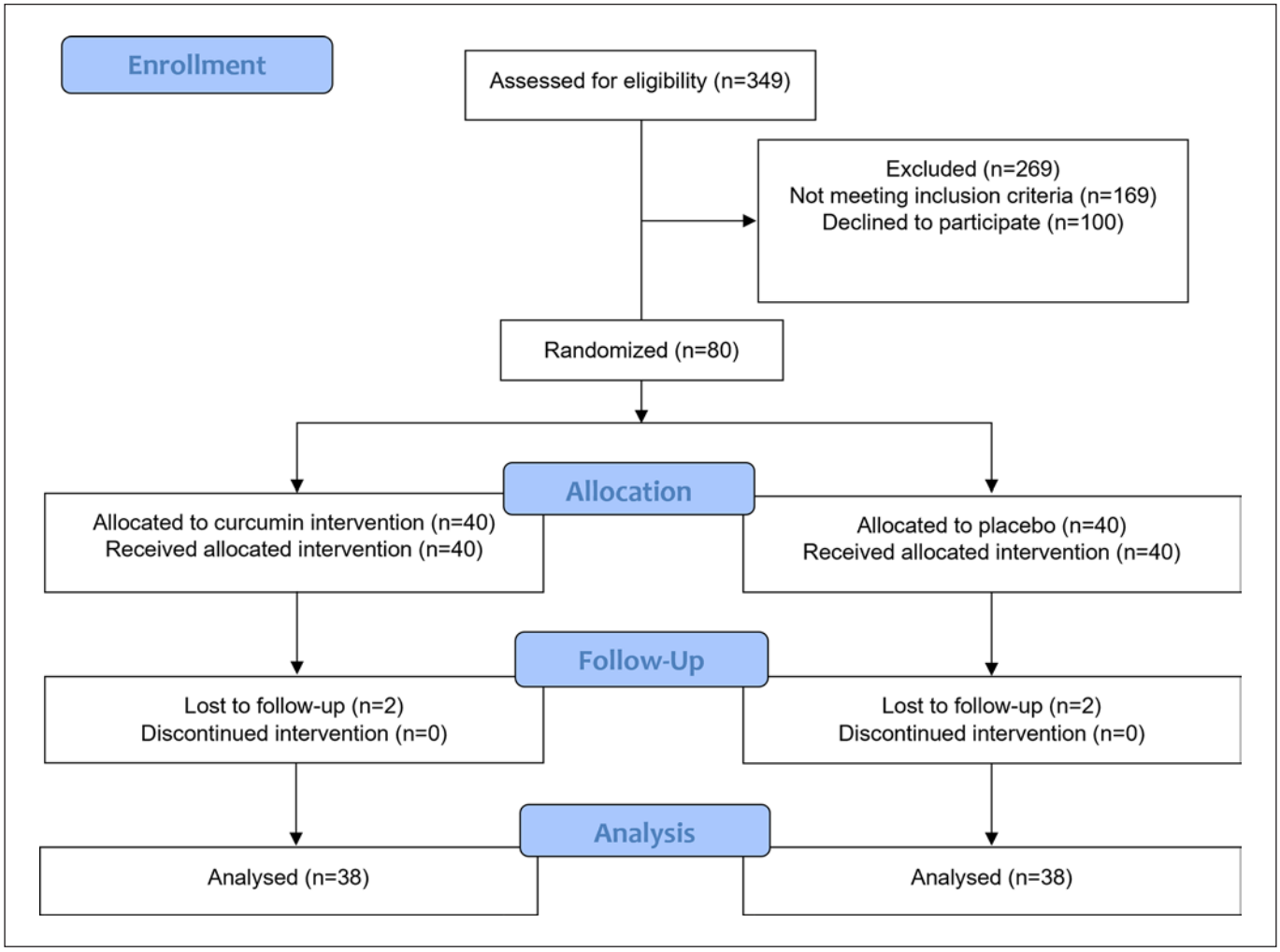
This trial was conducted in compliance with the current International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP), the Therapeutic Goods Administration (TGA) Note for Guidance on Good Clinical Practice, and ethical guidelines outlined in Additional Ethical Considerations. The study was approved by Bellberry human ethics (approval number 2019-05-397-A-3) and registered with the Australian New Zealand Clinical Trials Register (registration number ACTRN12619001467123).

Trial Participants

A total of 80 otherwise healthy males and females aged between 25 and 70 years old reporting joint pain were recruited from Brisbane and surrounding areas to take part in this 2-week study (Fig. 1). All participants that met the study criteria, provided written informed consent prior to starting the trial.

Participants were recruited through mailing lists and public media outlets. Interested participants underwent a health assessment with a trial coordinator including lifestyle, current medications, and medical history to assess eligibility for the trial. Participants were required to be generally healthy, reporting joint pain

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Fig. 1. Participant flow diagram.

not associated with acute injury or long-standing disease, able to provide informed consent, and agree not to change their current diet or exercise nor take any pain medication for the study duration. Female participants were required to be either using a prescribed form of birth control, were abstinent or post-menopausal. Participants were excluded for any unstable or serious illness (e.g., kidney, liver, GIT, heart conditions, diabetes, thyroid gland function malignancy), malignancy or treatment for malignancy within the previous 2 years, diagnosed with rheumatoid arthritis, bursitis and/or gout, received/prescribed coumadin (Warfarin), heparin, daltaparin, enoxaparin or other anticoagulation therapy or had a history of infection in the month prior to the study. Participants were also excluded if they had any serious mood disorders or neurological disorders such as MS, were active smokers or took nicotine, had a history of drug abuse, had chronic past and/or present alcohol use (>14 alcoholic drinks per week), were allergic to any of the ingredients in the active or placebo formula, participated in any other clinical study in the past 1 month or had any condition which in the opinion of the investigator made the participant unsuitable for inclusion. Pregnant females, lactating women or non-menopausal, non-abstinent females that were not on any suitable form of contraception were excluded from the study.

Trial Product

The investigation product was HydroCurc®, containing 376 mg of curcuminoids and 50 mg of the delivery system, Lipisperse®. The placebo was maltodextrin housed in opaque capsules appearing identical to the curcumin product. The products were stored in the trial product container at room temperature and away from direct sunlight. Both the investigational and placebo products were enclosed in containers that were identical in function and appearance. Supplements were taken as a single capsule in the evening with water. This regime was selected based on current evidence for the investigational product as directed by the manufacturer and on previous clinical trials.

Trial Description (Intervention and Study Procedures)

Once enrolled in the study, participants were randomly allocated to either the placebo comparator group ($n = 40$) or the active intervention group, curcumin ($n = 40$). Upon enrolment, participants had their heigh and weight recorded and completed quality of life assessments as measured by the RAND 36-Item Health Survey (SF-36), Profile of Mood States (POMS) questionnaire, and gastrointestinal intolerance questionnaire. Following the completion of the questionnaires, participants first completed a 3-day baseline pain-recording period. During the baseline recording period, participants took no supplements and recorded pain values

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using a visual analogue scale (VAS) for pain twice daily (once in the morning and once at night). Upon the completion of the 3-day baseline period, participants started to take their allocated supplement daily as described. During the supplement period, participants continued recording pain values using a VAS for pain twice daily (morning and night). The pain VAS is a continuous unidimensional scale consisting of a line, 100 mm in length and with 2 descriptors for symptom extreme at each end of the scale. Descriptors included "no pain" (score of 0) or "worst imaginable pain" (score of 100) [23]. Participants were required to fill out the pain VAS score online throughout the trial. In the event participants were unable to complete the measure online, a paper version with a standardised scale on it was also provided.

Outcome Measurements

The primary outcome for this study was change in joint pain assessed via VAS scores in the morning and evening. The change in VAS score was calculated as the difference from baseline (calculated as the mean of the scores recorded over the 3-day baseline period) at each day and this change was compared between groups. Secondary outcomes included: height and weight, change in quality of life as measured by the SF-36, POMS, and gastrointestinal intolerance questionnaires. Safety was assessed throughout the study with participants regularly monitored for any gastrointestinal complaints and adverse events. All adverse events, either spontaneously reported by the participant or noticed by an investigator were reported when required. All secondary outcomes were assessed at baseline and upon study completion.

Randomisation and Blinding

Randomisation for this study was conducted independently of the investigators. The randomisation code for the products was generated by Random Allocation Software, sealed Envelope, London, UK (www.sealedenvelope.com), with participants allocated to one of the two trial arms at time of enrolment. Arm 1 – *Active treatment - Curcumin*. Arm 2 – *Placebo.* All trial participants, investigators conducting the trial, and the biochemist analysing the samples were blind to which product participants were taking. Participants were randomised into the 2 groups through the allocation of numbered treatment bottles which were labelled identically except for the allocation number. Participants were allocated containers in numerical sequential order. The randomisation code was broken upon completion of all sample analyses.

Statistical Analysis

It was calculated that a sample size of 28 participants were required per group for power to detect a reduction from baseline of 25 mm in VAS score between the treatment group and placebo group (e.g., treatment group 55 mm reduced to 10 mm vs. placebo group reduced from 55 mm to 35 mm; SD ± 30 mm) at the completion of the study. Effect size: 0.8333, Alpha error probability: 0.05, Power 0.95. To allow for a 30% drop out, 40 participants per group were recruited.

Analysis was conducted with R, using a range of native statistical functions and functions from the packages tidyverse, rcompanion, dplyr, and ggplot as well as GraphPad Prism 8.0. Regressions, standard deviations, and R2 for slope analysis were conducted in Excel. Missing data were managed using R – prediction model. Change from baseline (Δ) was calculated for each group at each time-point, and statistical tests were conducted to compare changes from baseline within group and between groups using Mann-Whitney U tests. Results were considered statistically significant at $p < 0.05$.

Table 1. Baseline demographics of study participants

	Curcumin	Placebo
Participants, *n*	38	38
Females	29	30
Males	9	8
Mean age (SD), years	54.6 (8.4)	54.3 (10.1)
Mean weight (SD), kg	77.1 (16.7)	78.1 (14.3)
BMI	27.4 (4.3)	27.2 (3.7)

Results

Eighty participants were initially enrolled in the study with 76 participants completing the study – 38 in each group. There was a higher proportion of females to males in both groups (Table 1). Four participants withdrew from the study after completing only the baseline data collection. One person withdrew due to not wanting to possibly be in the placebo group, one developed Ross River fever during baseline collection, one had a pain flare-up due to work, and felt they would not get through with limited pain relief, and one fell sick during baseline collection and went on antibiotics. There were no significant differences in the gender proportion, age, weight, and BMI of participants between groups.

Baseline VAS scores were similar, slightly non-normal, and responded inconsistently to logarithmic transformation. Mann-Whitney U tests were used to ascertain that the means were not significantly different between treatment arms at baseline (Table 2).

Morning VAS scores were significantly reduced from baseline in both the curcumin and placebo groups from day 6 and day 12, respectively. The morning VAS score was significantly lower in the curcumin group compared to the placebo group on days 11, 13, and 14 of treatment ($p < 0.05$) (Fig. 2; Table 2).

The curcumin mean 14-day reduction in morning-recorded VAS from the baseline was approximately 37%; in the placebo group, the reduction over the same period was approximately 16%. The slope of a linear regression showed that both the active curcumin and the placebo resulted in negative slopes (–1.32 [0.11] and –0.62 [0.08], respectively). This change was predicted to be statistically significant ($p < 0.05$) using *t* test.

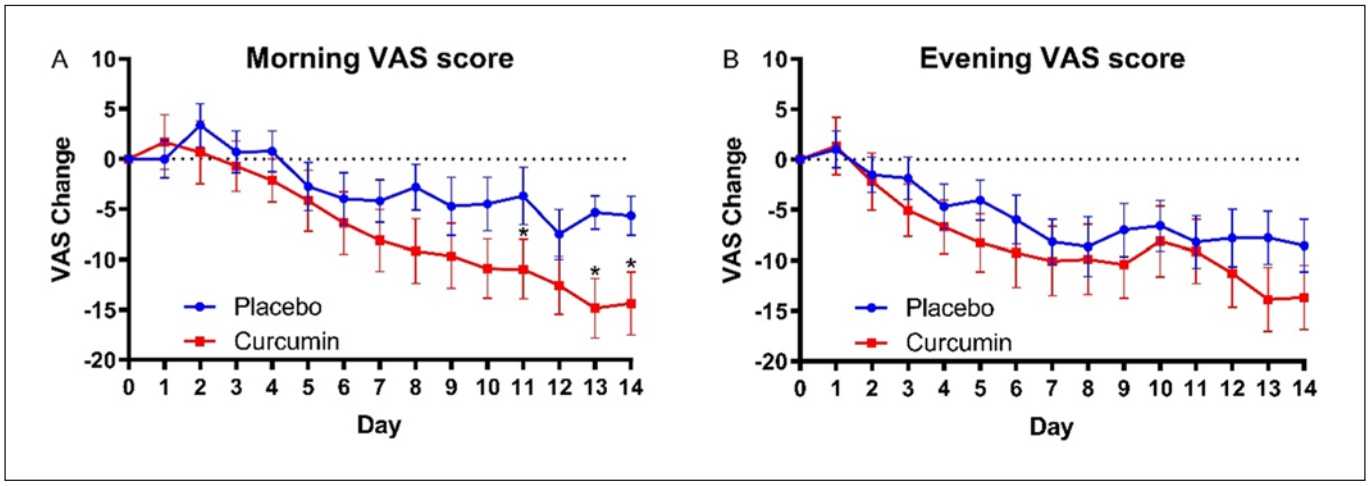
Evening VAS scores were significantly reduced from baseline in both the curcumin and placebo groups from day 5 and day 6, respectively. The change in evening VAS score was not significantly different between groups for any day (day 14, $p = 0.18$). However, the reduction followed a similar trend as the morning VAS scores, with the curcumin group continuing to decrease and the placebo group having no change from day 8 to 14 (Fig. 2; Table 2). One-sided inferential tests showed that the mean differ-

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Table 2. Daily VAS scores for pain

	Morning		Evening	
Day	Curcumin	Placebo	Curcumin	Placebo
Baseline	38.7 (21.6)	36.2 (20.6)	41.4 (19.0)	40.8 (18.2)
1	40.4 (21.6)	37.2 (20.6)	42.8 (21.4)	42.9 (22.6)
2	41.6 (21.4)	39.6 (22.4)	39.2 (18.6)	39.2 (20.6)
3	39.0 (19.9)	36.9 (23.4)	36.4 (16.0)	38.9 (20.5)
4	36.6 18.3)	37.0 (21.6)	34.7 (19.5)^	37.1 (19.5)
5	34.5 (20.1)	33.5 (22.2)	33.1 (19.8)	36.7 (22.5)^
6	32.3 (20.5)^	32.3 (21.0)	33.6 (22.7)^	34.8 (20.9)^
7	30.6 (22.4)^	32.1 (22.2)	31.3 (21.3)^	32.6 (19.4)^
8	30.3 (23.2)^	33.4 (20.8)	31.5 (21.4)^	32.1 (20.8)^
9	29.1 (19.4)^	31.5 (20.9)	31.0 (22.5)	33.8 (20.7)^
10	27.8 (20.9)^	31.8 (22.8)	33.3 (22.7)^	34.2 (22.8)^
11	28.5 (21.0)*^	32.6 (22.6)	32.3 (20.2)^	32.6 (20.9)^
12	26.8 (21.4)^	28.7 (22.6)^	30.1 (21.8)^	33.0 (23.6)^
13	23.9 (19.9)*^	30.9 (21.3)^	27.6 (20.2)^	33.0 (22.8)^
14	24.3 (19.4)*^	30.6 (20.2)^	27.8 (20.8)^	32.2 (20.9)^

Values are presented as mean (SD). ^ significant difference from baseline, $p < 0.05$; * significant difference between groups, $p < 0.05$.



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Fig. 2. Change in VAS score in the morning (**A**) and evening (**B**) over 2 weeks. *, significant difference between groups; $p < 0.05$.

ence between VAS scores after 14 days was less distinct than for the morning scores. Curcumin mean 14-day reduction in evening-recorded VAS from the baseline was approximately 33%; in the placebo the reduction over the same period was approximately 21%.

When the mean daily change (an average of morning and evening changes from baseline for each day) was considered, placebos resulted in reductions of around 7 points on the VAS scale, while the actives resulted in reductions of 14–16 points over the 14 days. These differences were found to be statistically significant ($p \approx 0.02$) between treatment groups.

Scores recorded from each aspect of both the POMS and SF-36 were within normative values at both baseline and day 14 as the data were normally distributed; differences between groups were analysed using *t* tests. The values for the total mood disturbance score of the POMS were not significantly different at baseline, 104.8 (15.3) in the curcumin group and 99.7 (18.1) placebo ($p = 0.18$). Although the POMS score for both the active and placebo group reduced at day 14 (88.6 [12.2] and 85.6 [19.6], respectively), there was no significant difference between groups ($p = 0.54$). The baseline SF-36 scores were also not significantly different at baseline, 62.6 (19.0) active and 71.3 (21.6) placebo, $p = 0.07$, or at day 14, 63.6 (18.2) and 69.7 (22.1), $p = 0.24$. Both products were well tolerated with no adverse gastrointestinal events reported.

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Discussion

This study demonstrates the effectiveness of curcumin to reduce morning joint pain in healthy adult participants over a 2-week period. These results are supported by previous studies showing curcumin's ability to reduce arthritis symptoms, improve quality of life, and reduce analgesic usage [16–19, 24–28]. Additionally, the dosage of curcuminoids used in this study is equivalent to the dose used in previous studies [16–19, 25–28].

As is common in pain studies, a strong improvement was observed in the placebo group [29]. Despite this, there was still a significant difference between groups on day 11, 13, and 14 for the morning VAS score shown in Figure 2. However, no statistical differences were seen in the evening VAS scores. The lack of difference in evening VAS scores may be due to the products being consumed in the evening before bed and after the evening VAS score was provided. Therefore, the evening VAS scores were recorded almost 24 h after supplementation. Previous pharmacokinetic studies have shown that most of the absorption of curcumin occurs in the first 8 h [22], which is likely why there was a change in the overall morning VAS score and not the evening score. This indicates that a dual dose may be a more effective dosing regimen to ensure longer lasting effects over a 24-h period.

Despite there being no statistical difference in the evening VAS, both the morning and evening VAS scores of the curcumin group were shown to steadily decrease over the 2 weeks. Whereas the placebo group scores tended to start to plateau from approximately 1 week, as shown in Figure 2. This observation indicates that a longer intervention period may be required to see if the difference between the 2 groups' VAS scores continues to increase.

The relevance these results may have on an individual experiencing joint pain is difficult to assess from these results. While reductions of pain were reported, these reductions did not translate to an improvement in quality of life (SF-36 and POMS). This is likely due to the short study duration and single dose use. However, there may have been other aspects or very specific aspects of the participants life that did improve that were unable to be detected by a general quality of life questionnaire. Despite this, a longer intervention period and/or a dual dose design may produce a greater effect on perceived pain, especially evening pain scores, which may reflect on participants' quality of life questionnaire results. Therefore, recommendation for any future study or patient use of curcumin for joint pain would be that a longer duration (>2 weeks) and/or split dose (evening and morning) would be required to see a possible impact on quality of life.

Two proposed mechanisms of action of curcumin's ability to alleviate joint pain are through its potential anti-inflammatory and antioxidant properties [16–19, 27]. Curcumin can act on multiple pro-inflammatory targets, including the major inflammatory transcription factor, NF-κB and cyclooxygenase-2 (COX-2), key components involved in the pathogenesis of pain and inflammation [16–19, 27]. Curcumin's ability to target multiple pathways provides it with greater efficacy in combating a range of inflammatory disorders, especially ones with a multifactorial origin [16–21]. Traditional analgesics, however, often only target pain perception and symptoms rather than the origin of pain or symptoms [8, 12, 13, 18, 19].

While commonly used pharmaceuticals can provide symptomatic pain relief through COX production [30] or by acting on opioid receptors [31], they do not target the underlying pathology of pain. The continuous use of pharmaceuticals such as opioids is also associated with a high risk of dependency and organ toxicity. Pharmaceuticals are also commonly reported to have side effects including nausea, constipation, and sedation [8, 13, 31]. While nonsteroidal anti-inflammatory drugs, another common joint pain medication, also suppress inflammation by inhibiting COX activity, their long-term usage is associated with gastrointestinal, cardiovascular, renal, and immune-related adverse effects, impacting its adherence rate [12, 14, 18, 19]. Concomitant usage of pharmaceuticals can also potentially result in severe adverse drug-drug interactions [14]. This makes such joint pain medications contraindicated in individuals susceptible to their adverse effects [12–14]. Therefore, as joint pain is often a chronic disorder, there is a need for efficacious treatments with a good long-term safety profile that can be used by the wider population.

Curcumin has a well-established safety profile [32–36], having been used medicinally in traditional Indian, Chinese, and Middle-Eastern societies for thousands of years [15]. Research spanning several decades has reported its safety and efficacy for multiple therapeutic uses [35]. Being a naturally occurring compound, it has been found to have good tolerability and negligible side effects [32–36], making it approved by the US Food and Drug Administration (FDA) as Generally Recognized as Safe (GRAS) [37]. Up to 12g/day intake of curcumin has been shown to have no harmful effects, which is well above the dosage used in this study [37]. This study supports these findings demonstrating a good tolerability to curcumin with no adverse effects reported from a daily supplementation for 2 weeks.

Traditionally, the primary hindrance to curcumin's efficacy as a therapeutic agent is its reported low bioavailability, due to its lipophilic nature resulting in poor absorption in aqueous environments [32]. The novel bioavailable curcuminoid formulation used in this study, utilized the CWD, LipiSperse®. LipiSperse® increases the bioavailability and uptake of lipophilic agents such as cur-

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cumin in the body [22] by coating each molecule in a powder that acts to repel other molecules in an aqueous environment preventing agglomeration [22]. Previously HydroCurc® was shown to have an approximately 3-fold greater absorption compared to a standard curcumin powder [22]. The increased absorption potentially amplifies its beneficial effects allowing us to explore new therapeutic uses for curcumin.

A major limitation in this study is that it commenced at the beginning of the COVID-19 pandemic. This resulted in a change to the original study design to make it possible to complete this study with no face-to-face clinic visits. As such, there was an inability to collect any physiological data or mechanism of action to support the observed VAS pain scores. Data intended to be collected included biochemistry markers for inflammation (cytokines). Had biochemistry data been collected, there may have been systemic inflammation changes that supported the observed VAS scores. In the absence of face-to-face clinic visit, participants were instead regularly contacted via phone consultations and guided through the study with all data entered into secure websites by the participant.

Conclusion

Overall, this randomized, double-blind, placebo-controlled study showed the safety and efficacy of daily curcumin supplementation in alleviating joint pain in the morning in healthy adults. These findings suggest that water-dispersible curcumin could be a safe and viable treatment option for joint pain pathologies. Future studies would benefit from investigating whether curcumin is effective for joint pain management over a longer duration and possibly with a second daily dose.

Acknowledgments

The authors would like to acknowledge Pharmako Biotechnologies for supplying all the supplements for this study.

Statement of Ethics

This study was approved by the Bellberry Limited human ethics committee, approval number (2019-05-397). All participants provided written informed consent before inclusion into the study.

Conflict of Interest Statement

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

Funding Sources

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Author Contributions

Both David Briskey and Amanda Rao contributed equally to all aspects of the study including study design, data collection, data analysis, and manuscript revision. Georgia Roche conducted the study and prepared the manuscript.

Data Availability Statement

Data for this trial is available upon request.

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