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RESEARCH ARTICLE

Standardised ido-BR1 Cucumber Extract Improved Parameters Linked to Moderate Osteoarthritis in a Placebo-controlled Study

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Abstract: ***Background*:** According to the World Health Organization, osteoarthritis (OA) is one of the 10 most disabling diseases in developed countries, with worldwide estimates of 9.6% prevalence in men and 18.0% in women over 60 years old. Its management is not well established and involves the use of high doses of painkillers coupled with anti-inflammatory agents.

***Objective*:** In the search for alternatives to manage the disease, previous studies have shown superior properties of Q-Actin™ in managing OA-related pain compared with standard treatments. Q-actin is a cucumber extract with the anti-inflammatory iminosugar idoBR1 standardised to over 1%. This study investigated the effects of different doses (20 mg, 100 mg) of Q-Actin in a longitudinal placebo-controlled experiment.

***Methods*:** There were 101 patients with knee OA enrolled for the 180-day study, with 91 patients completing it. Patients were grouped into a placebo group (PLBO), as well as a 20mg dose (Q-Actin 1) and 100 mg dose (Q-Actin 2) groups. The PLBO group received cellulose in capsules identical to the Q-Actin capsules.

***Results*:** There was a significant improvement in the pain-related parameters over time that was dose-dependent.

***Conclusion*:** This study clearly demonstrated the effectiveness of Q-Actin compared to placebo in the management of pain related to moderate osteoarthritis.

Keywords: Q-Actin™, cucumber, osteoarthritis, *Cucumis sativus*, iminosugar, idoBR1.

1. INTRODUCTION

The WHO describes 150 musculoskeletal conditions that affect the locomotor system of individuals [1]. Those that affect joints include osteoarthritis (OA), rheumatoid arthritis, psoriatic arthritis, gout and ankylosing spondylitis and can affect articular cartilage and bones of joints such as the knees, hips, fingers, and lower spine [2]. OA is a leading cause of disability and its incidence is rising due to increasing obesity and an ageing population [3]. Risk factors can be divided into person-level factors, such as age, sex, obesity, genetics, race/ethnicity and diet, and joint-level factors including injury, malalignment and abnormal loading of the joints [2, 3].

Symptoms of OA include swelling, cracking, stiffness and pain [2, 3]. Pain itself varies in intensity, quality, and unpredictability and has an impact on mobility, mood, and sleep [4]. The diagnosis of OA is mainly made by imaging techniques but the progression of the disease as well as response to treatment are, however, evaluated by monitoring some OA-related parameters in patients linked to pain, stiffness, and physical function. These include the widely used and modified Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) [5] which is seen as reliable and sensitive to the changes in the health status of patients with OA as a multidimensional measure of pain, stiffness, and physical functional disability [4]. Other methods for diagnosis include the Visual Analog Scale (VAS), which is a pain rating scale from 0 (no pain) to 100 (worst pain) first used by Hayes and Patterson in 1921 [6] but still commonly used in clinical and home settings [7, 8] and the Lequesne's Algo-Functional Index (LFI) [9, 10].

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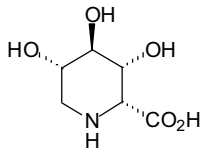
Among the management options for OA, the use of anti-depressants, physiotherapy, and various changes in the patient's life style are well known [11]. Moreover, various plant extracts have been reported as having positive effects on the management of OA [10, 12, 13]. Analgesia remains the mainstay of pharmacological treatment for symptomatic OA, including acetaminophen (Paracetamol or Tylenol), topical and oral nonsteroidal anti-inflammatory drugs (NSAIDs such as Ibuprofen or Advil), opioid medications, serotonin-norepinephrine reuptake inhibitors (SNRIs) and intra-articular injections of corticosteroids [11, 14-17]; these can be effective in pain relief but not in reversing damage and are frequently associated with adverse events. Glucosamine-chondroitin (GC), together or separately are also often used as supplements in the management of OA but there is not much strong evidence of long-term benefit of glucosamine-chondroitin on pain or function, and glucosamine or chondroitin sulfate alone on pain [18, 19].

In a randomized controlled clinical trial with patients suffering from moderate osteoarthritis, a standardised cucumber product, Q-Actin™, was more efficacious than GC in the management of pain [13]. Toxicological studies of Q-Actin™ have established its no-observed-adverse-effect level (NOAEL) as ≥1000 mg/kg bw/day [20]. The active component of Q-actin™ is reported to be an iminosugar amino acid, idoBR1 (1), a novel anti-inflammatory molecule with good oral availability and stability *in vivo* [21]. Iminosugar amino acids appear to be very rare in Nature; they have no obvious functional or structural similarity to current OA medicines but are analogues of uronic acids such as glucuronic and iduronic acid (important components in glycosaminoglycans). Due to the speciality required for analytical detection, idoBR1 was only recently discovered in certain cucumbers in a study on the anecdotal anti-inflammatory claims on cucumbers and it was shown by isolation and synthesis to reduce LPS-induced pro-inflammatory cytokine tumour necrosis factor alpha (TNFα) in both *ex vivo* human serum and THP-1 cells [22]. TNFα can drive degenerative changes when chronically elevated. idoBR1 has been shown to give a dose-dependent reduction in the LPS-induced production of not only TNFα but also other inflammatory markers including IL-6, nitric oxide and the transcription factor NF-*κ*B [21, 22]. idoBR1 is standardized to > 1% in Q-actin™. This study builds on the previous report [13] and compares the use of Q-Actin™ at two doses *versus* placebo in the management of moderate osteoarthritis.



idoBR1 (1)

2. MATERIALS AND METHODS

2.1. Study Participants

The study was conducted in Delhi from March 2019 to September 2019. It included only non-hospitalized knee OA patients (males and females of Indian origin aged 40-75 years) with a BMI between 24 and 29. The 101 participants enrolled were required to restrict the use of non-steroidal anti-inflammatory drugs (NSAIDS) such as Ibuprofen, as well as other medications previously prescribed for their condition. Scheduled visits and tests according to the protocol during the study period were also stipulated. A written and signed informed consent had to be obtained from each participant. Ninety-one participants completed the study.

2.2. Participant Exclusion Criteria

OA patients with a history of recent clinical trial participation (30 days) were excluded from the study as well as patients on restricted drugs (such as ibuprofen, and aspirin) or recreational drugs and heavy drinkers. Also excluded were patients with mental disorders, pregnant and lactating women and patients with a history of hypersensitivity caused by dietary allergies (*e.g.* chicken and eggs) or from rescue medication (paracetamol) and patients with a history of GC use within the previous 3 months.

2.3. Study Design

The study was a placebo-controlled, randomized, double-blind study with three groups. There were 101 normal-weight non-hospitalized knee OA patients enrolled into either treatment or placebo groups, distributed in each group as shown in Table **1**.

2.4. Study Products and Administration

Patients in the Q-Actin group were divided into two groups, one group receiving four capsules of low-dose Q-Actin (20 mg) per day and a second group receiving four capsules of high-dose Q-Actin (100 mg) per day. The third group received four capsules of placebo (identical-looking capsules each containing 100 mg of cellulose powder). The Q-Actin and placebo capsules had similar appearance, shape, size, color, and odor. At baseline, all the participants provided personal information as well as demographic, nutritional status, and medical history information, recorded in a questionnaire completed with the assistance of trained personnel. Follow-up evaluations were done at 30-day intervals (30, 60, 90, 120, and 180 days).

The trademarked Q-Actin™ Lot B19F026 used in this study was a proprietary aqueous extract of *Cucumis sativa* standardized to 1.1% idoBR1 iminosugar and supplied by IminoTech Inc. It was manufactured under current good manufacturing practice (cGMP) conditions using a patented process that concentrates the idoBR1 iminosugar to ≥1%.

2.5. Measurement of OA Parameters

At all visits, except on day 180, subject diaries and study products were provided to be collected at follow-up visits and OA parameters were assessed using the WOMAC, VAS, and LFI indices.

Participants were instructed to record their daily consumption of the study product and required to report adverse

Table 1. Study groups.

Group Number	Treatment	Enrolment (Completed)*
PLBO	Placebo	34 (30)
Q-Actin 1	Low-dose Q-Actin (20 mg)	35 (32)
Q-Actin 2	High-dose Q-Actin (100 mg)	32 (29)

Note: *The number of patients initially enrolled is listed, with the number that completed the study in parentheses.

Table 2. Baseline data for all patients in the study pooled from study centers.

-	Q-Actin 1 Group	Q-Actin 2 Group	Placebo Group
Participants	35	31	34
Age distribution (years)	40 - 62	42 - 70	41 - 69
Gender Distribution	-	-	-
Male, (%)	47	42	46
Female (%)	53	57	54
Anthropometry	-	-	-
Weight (kg)	82 ± 12	79 ± 18	80 ± 15
BMI (kg/m^2)	26 ± 2	26 ± 3	26 ± 2
Pain Intensity	-	-	-
WOMAC	78 ± 21	80 ± 15	80 ± 11
VAS Score (mm)	62 ± 10	59 ± 16	66 ± 11
LFI Score (points)	16 ± 4	15 ± 6	16 ± 8

events in their diaries, while questionnaires were administered by personnel at all study visits.

The primary endpoint was defined as the change in total WOMAC score from the baseline through Day 180 for both the Q-Actin groups and the placebo group. Secondary clinical endpoints for both protocols were similar and included the change from baseline through Day 180 *vs* the placebo group for all endpoints, including the following scores: 1) mean VAS, 2) mean WOMAC and 3) LFI. There were no changes in the trial protocol after initiation.

WOMAC VA3.1, VAS, and LFI questionnaires were used. The WOMAC questionnaire collects data on pain (0 - 20 points), stiffness (0-8 points), and physical function (0-68 points) grouped into three categories for a maximum score of 96. The VAS questionnaire includes a maximum of 70 points from seven pain-related questions. The LFI questionnaire records daily activities for a maximum score of 24.

2.6. Rescue Medications

About 400 mg Ibuprofen tablets were prescribed by the study physician to certain participants (maximum 400 mg thrice daily; total 1,200 mg) as rescue analgesia during the study based on the pain intensity reported. Those participants were advised not to take the rescue medicine for more than 3 days.

2.7. Compliance

Compliance was recorded in two ways. Participants were instructed to complete a diary containing daily dosing of Q-Actin or placebo and, secondly, they were asked to bring their bottles to each visit so that the remaining capsules could be recorded in the case report form.

2.8. Statistical Analysis

Results were expressed as relative scores in percentages. Statistical analysis of data was done using SAS software. The effect of Q-Actin at low (20 mg) and high (100 mg) doses was measured as the reduction in WOMAC, VAS, and LFI scores from Day 0 to Day 180 and by comparison with the placebo group at baseline and visits. Wilcoxon's signed rank test was used to examine intra-group and inter-group pairwise changes. The magnitude of pain reduction resulting from the use of Q-Actin at low and high doses was studied using one-way ANOVA followed by Tukey's multiple comparison tests. Results were significant at the 95% CI.

3. RESULTS

3.1. Study Population Baseline Data

The baseline data is given in Table **2**.

Table 3. Effects of different doses of q-actin on patients' WOMAC scores*.

WOMAC							Percentage Change from Baseline at D^{180}
Product	**D_0**	**D_{30}**	**D_{60}**	**D_{90}**	**D_{120}**	**D_{180}**	
PLBO	80 ±11	78 ± 9	76 ± 10[a]	75 ± 12[a]	74 ± 9[a]	76 ± 11[a]	5
Q-Actin 1	78 ± 21	70 ± 6[a,b]	66 ± 9[a,b]	63 ± 10[a,b]	59 ± 11[a,b]	53 ± 10[a,b]	32.1
Q-Actin 2	81 ± 16[c]	72 ± 5[b]	67 ± 7[a,b,c]	61 ± 11[a,b,c]	56 ± 10[a,b,c]	49 ± 8[a,b,c]	39.5

*Results are expressed as the mean ± SD. a-Denotes significant difference ($P < 0.05$) between baseline and the different time points within the same group. b-Denotes significant difference ($P < 0.05$) between Q-Actin (Q-Actin 1 and Q-Actin 2) and PLBO group at a specific time point. c-Denotes significant difference ($P < 0.05$) between Q-Actin 1 and Q-Actin 2 at a specific time point.
Abbreviations: WOMAC, Western Ontario McMaster Universities Arthritis Index; PLBO, placebo; Q-Actin 1, patients treated with low-dose Q-Actin (20 mg); Q-Actin 2, patients treated with high-dose Q-Actin (100 mg).

Table 4. Effects of different doses of Q-actin on patients' VAS scores*.

VAS							Percentage Change from Baseline at D^{180}
Product	**D_0**	**D_{30}**	**D_{60}**	**D_{90}**	**D_{120}**	**D_{180}**	
PLBO	66 ± 11	66 ± 9	64 ± 10	63 ± 6 [a]	64 ± 12	63 ± 8 [a]	4.5
Q-Actin 1	59 ± 16 [b]	53 ± 7 [a, b]	47 ± 7 [a, b]	43 ± 6 [a, b]	39 ± 7 [a, b]	36 ± 9 [a, b]	39.0
Q-Actin 2	62± 10 [b,c]	52 ± 8 [a, b]	46 ± 5 [a, b,c]	42 ± 8 [a, b,c]	38 ± 5 [a, b,c]	34 ± 7 [a, b,c]	45.2

Note: *Results are expressed as the mean ± SD. a-Denotes significant difference ($P < 0.05$) between baseline and the different time points within the same group. b-Denotes significant difference ($P < 0.05$) between Q-Actin (Q-Actin 1 and Q-Actin 2) and PLBO group for a specific time point. c-Denotes significant difference ($P < 0.05$) between Q-Actin 1 and Q-Actin 2 for a specific time point.
Abbreviations: VAS, visual analog scale; PLBO, placebo; Q-Actin 1, patients treated with low-dose Q-Actin (20 mg); Q-Actin 2, patients treated with high-dose Q-Actin (100 mg).

Table **2** shows the distribution of baseline information for all the participants who were involved in the study. Some participants (10 out of 101 enrolled as shown in Table **1**) dropped out from the study, and the study was completed with 91 OA patients. The age distribution of participants involved in the study ranged from 40-62, 42-70, and 41-69 for the Q-Actin 1, Q-Actin 2, and the PLBO groups, respectively. In all the groups, there were more female than male participants. The mean value for participants' BMI was 26 ± 2 kg/m^2, 26 ± 3 kg/m^2, and 26 ± 2 kg/m^2 for Q-Actin 1, Q-Actin 2, and PLBO groups, respectively. Their WOMAC mean values at the start of the experiment were 78, 81, and 80 for the Q-Actin 1, Q-Actin 2, and PLBO groups, respectively.

The mean VAS score values were 52, 59, and 66 mm Q-Actin 1, Q-Actin 2, and PLBO groups, respectively at the beginning. The mean LFI score values were 16, 15, and 16 for the Q-Actin 1, Q-Actin 2, and PLBO groups, respectively.

3.2. Effects of Different Doses of Q-Actin on Patients' WOMAC Scores

The effects of different doses of Q-Actin on the WOMAC scores of patients included in this study are summarized in Table **3**. The results show that there is a significant difference within each group (PLBO, Q-Actin 1, and Q-Actin 2) between the WOMAC score values for days D_{60}, D_{90}, D_{120}, and D_{180} and that of the baseline (D_0). All the WOMAC score values for the patients who have received the Q-Actin treatment (Q-Actin 1 and Q-Actin 2 groups) were significantly different from those of patients in the PLBO group for the whole study period except for the baseline (D_0). Looking at the differences between the Q-Actin 1 and Q-Actin 2 groups, the table shows that the score values for patients in the Q-Actin 1 group were significantly higher than that of those in the Q-Actin 2 group for each day of the study period except for D_{30}.

3.3. Effects of Different Doses of Q-Actin on Patients' VAS Scores

The effects of different doses of Q-Actin on the VAS Scores of patients included in this study are summarized in Table **4**. The results show that there is a significant difference within each group (Q-Actin 1 and Q-Actin 2) between the VAS score values for days D_{60}, D_{90}, D_{120}, and D_{180} and that of the baseline (D_0) except for the PLBO group where the difference was shown only on D_{90} and D_{180}. All the VAS score values for the patients who received the Q-Actin treatment (Q-Actin 1 and Q-Actin 2) were significantly different from those of patients in the PLBO group for the whole study period. Looking at the differences between Q-Actin 1 and Q-Actin 2, Table **4** shows that the score values for patients in the Q-Actin 1 group were significantly higher than that of those in Q-Actin 2 group for each of the time points except D_{30}.

3.4. Effects of Different Doses of Q-Actin on Patients' LFI Scores

The effects of different doses of Q-Actin on the LFI scores of patients included in this study are summarized in Table **5**. The results show that there is a significant difference

Table 5. Effects of different doses of Q-actin on patients' LFI scores*.

LFI Scores							Percentage Change from Baseline at D^{180}
Product	D_0	D_{30}	D_{60}	D_{90}	D_{120}	D_{180}	
PLBO	16 ± 8	17 ± 4	17 ± 3	16 ± 5	15 ± 4	14 ± 8	12.5
Q-Actin 1	15 ± 6	13 ± 4 [b]	12 ± 6 [a,b]	12 ± 4 [a,b]	10 ± 3 [a,b]	9 ± 4 [a,b]	40.0
Q-Actin 2	16 ± 4	14 ± 3 [a, b,c]	13 ± 2 [a, b,c]	11 ± 3 [a, b,c]	9 ± 2 [a, b,c]	8 ± 3 [a, b,c]	50.0

Note: *Results are expressed as the mean ± SD. a-Denotes significant difference ($P < 0.05$) between baseline and the different time points within the same group. b-Denotes significant difference ($P < 0.05$) between Q-Actin (Q-Actin 1 and Q-Actin 2) and PLBO group at a specific time point. c-Denotes significant difference ($P < 0.05$) between Q-Actin 1 and Q-Actin 2 at a specific time point.

Abbreviations: LFI, Lequesne's Functional Index; PLBO, placebo; Q-Actin 1, patients treated with low-dose Q-Actin (20 mg); Q-Actin 2, patients treated with high-dose Q-Actin (100 mg).

within each group (Q-Actin 1 and Q-Actin 2) between the LFI score values for days D_{60}, D_{90}, $D_{120,}$ and D_{180} and that of the baseline (D_0). All the LFI score values for the patients who received the Q-Actin treatment (Q-Actin 1 and Q-Actin 2) were significantly different from those of patients in the PLBO group for the whole study period except for the baseline (D_0). Looking at the differences between Q-Actin 1 and Q-Actin 2, Table **5** shows that the score values for patients in the Q-Actin 1 group were significantly higher than that of those in the Q-Actin 2 group for each time point of the study period.

4. DISCUSSION

In this study, the effect of Q-Actin extract at two different concentrations (20 mg and 100 mg) was evaluated and monitored at different time intervals ($D_{0,}$ $D_{30,}$ D_{60}, D_{90}, $D_{120,}$ and D_{180}) in a placebo-controlled study. The hypothesis studied was that this idoBR1 standardized cucumber extract might have a pain suppressive or curative effect and so the effects on the OA parameters were compared to the baseline information (D_0) first and then the analysis of the effects vis-à-vis the placebo group and the extract concentration added more value to the study.

The results from this study showed that the administration of Q-Actin at a constant concentration resulted in improvements in OA parameters (WOMAC, VAS, and LFI) over time. The results reported here support the findings of the recent study which showed that the cucumber extract Q-actin standardised to >1% idoBR1 was as effective as glucosamine-chondroitin (an established treatment used in the management of OA) in mitigating OA-related parameters and at considerably lower doses [13]. With the reported anti-inflammatory activity of idoBR1 [21, 22] and the activity shown for Q-actin containing it [21], it seems likely idoBR1 is at least a key active component in the standardized cucumber extract. idoBR1 is reported to reduce the binding of hyaluronic acid (HA) to CD44 in LPS-stimulated THP-1 cells and may function as an anti-inflammatory agent by inhibiting induced sialidase involved in the production of functionally active HA adhesive CD44 in OA [21]. It has been shown that chondrocytes have more CD44 in arthritic than healthy people [23]. Because CD44 is responsible for the internalization of HA into lysosomes vesicles for degradation, if idoBR1 blocks CD44-HA adhesion, it may help to preserve the HA in the extracellular matrix. The inhibition of NF-κB by idoBR1 is also of interest since NF-κB triggers the expression of various genes which are implicated in cartilage destruction, synovial membrane inflammation and increased subchondral bone resorption [24]. There is evidence that TNFα is implicated in OA pathogenesis but antibody treatments such as Adalimumab and Etanercept have not proven to be very effective compared with placebo in reducing symptoms in studies in hand OA [25]; it may be that the broader activity of idoBR1 (and standardised cucumber extract) could make it a putative disease-modifying osteoarthritis drug (DMOAD) which acts on the key tissues involved in OA to prevent structural progression and therefore improve symptoms.

It has been shown in this study that patients who had taken Q-Actin (Q-Actin 1 and Q-Actin 2) had lower values of OA parameters as compared with patients who received the placebo capsules, further confirming the OA pain suppressive effects of Q-Actin.

The higher Q-Actin concentration (100 mg) reduced the OA-related parameters more than the low concentration (20 mg) as shown in Tables **2-4**. This supports the presence of an active ingredient(s) in the Q-Actin capsules and therefore suggests that there could be a specific dosage for an optimum activity for a given age. Similar suggestions have been made in studies on glucosamine sulfate [15].

CONCLUSION

OA has been declared by the WHO as one of the 10 most disabling diseases in developed countries, with worldwide estimates of 9.6% prevalence in men and 18.0% in women over 60 years old. This study revealed that there was a progression in pain reduction over time for both the high and low doses of Q-Actin. For each of the experimental time points, the higher dose of Q-Actin™ was more effective in reducing pain-related parameters.

AUTHORS' CONTRIBUTIONS

RJN provided the concept and initiation, HS, MSN, TK and JA were involved in the planning, execution, data analysis, and writing, AM executed and analysed the data and YBP wrote and analysed the study.

LIST OF ABBREVIATIONS

DMOAD	=	Disease-Modifying Osteoarthritis Drug
HA	=	Hyaluronic Acid
NSAIDS	=	Non-steroidal Anti-inflammatory Drugs
OA	=	Osteoarthritis
VAS	=	Visual Analog Scale
WOMAC	=	Western Ontario McMaster Universities Osteoarthritis Index

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

TreatAid's Ethics Committee approved the study with reference number TA 5112.

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committee and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

Participants were recruited after they reviewed and understood the study details and signed the IEC-approved consent form.

STANDARDS OF REPORTING

STROBE guidelines were followed in this study.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

PhytoQuest Ltd. funded the project as part of its core R&D budget to investigate potential uses of iminosugars.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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