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RESEARCH ARTICLE

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Safety and Efficacy of Moderately-High Dose Turmacin® (Turmerosaccharide >10% w/w) Supplementation on Joint Discomfort in Healthy Adults - A Pilot Proof-of-Concept Single Arm Study

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ABSTRACT

Turmeric is well-known for its analgesic, anti-inflammatory and anti-arthritic properties but 69.4% of the turmeric rhizome contains Turmerosaccharides whose clinical benefit is still unexplored. Turmacin®/NR-INF-02 is an aqueous extract of Turmeric containing Turmerosaccharides (>10%w/w) with negligible curcuminoids. Previous study with low dose Turmacin® confirmed its safety and efficacy in alleviating induced knee pain in healthy volunteers. Hence, this study aimed to assess the safety and explore the efficacy of moderately high dose Turmacin®. It was an open-label, single-arm interventional trial conducted from August 2018 – January 2019 in a tertiary care teaching hospital. Turmacin® was administered for seven days to 15 healthy volunteers as four capsules of 500 mg each in the morning with food. The stair mill at a speed of 60 steps per minute was used to induce knee pain and Visual Analogue Scale (VAS) was used to measure the pain intensity. Assessments were performed at baseline, Days 5 and 7. One participant reported dyspepsia of mild grade that resolved on its own. When compared to baseline, time to initial discomfort significantly increased on Day-5 (Mean Difference [MD] = 30s, $p = 0.016$) and Day-7 (MD = 32s, $p = 0.007$). Whereas the maximum VAS score decreased with time and on Day-7 and it was significantly low when compared with baseline (MD = −0.93, $p = 0.008$). In summary, Turmacin® supplements given at a dose of 2 g/day was safe and tolerable. Similar to the previous study with low dose Turmacin®, there was a significant increase in pain threshold and decrease in the maximum pain score post intervention.

KEYWORDS

Curcuma longa; knee; pain; turmacin; turmeric; turmerosaccharides

Introduction

Turmeric (Curcuma longa) has been used for a very long period for its culinary, cosmetic and medicinal uses. It has been in use for nearly 4000 years in the Ayurveda stream of traditional medicine for various respiratory disorders like bronchial asthma,

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rheumatism, liver disorders, anorexia, inflammation and swelling (Prasad and Aggarwal 2011) It has been widely researched and scientifically proven for its analgesic (Agarwal et al. 2011), anti-inflammatory (Jurenka 2009), anti-oxidant (Sharma 1976), anti-arthritic (Funk et al. 2010), and anti-cancer (Aggarwal et al. 2003) properties. These studies have mostly focused and attributed the effects on the curcuminoids and the oil containing tumerones (Yue et al. 2010; Liju et al. 2011). However, the curcuminoid free portion of turmeric accounts to nearly 69.4% of the entire rhizome and largely been left unexplored for its possible medicinal effects (Amalraj et al. 2017). The powdered rhizome as a whole, has long been used in cooking and is generally considered safe.

Strenuous exercise in healthy individuals acts as a mechanical stressor on chondrocytes of knee, and it predisposes the joint to increased inflammatory responses, leading to compromised joint function and joint stiffness (Girandola et al. 2016). The literature is now replete with a lot of studies delineating the possible beneficial role of curcuminoids in knee pain caused by osteoarthritis (Perkins et al. 2017), however studies evaluating the potential use of Turmerosaccharides is limited. A recent study by Raj *et al.* comparing low dose Turmerosaccharides (Turmacin® 0.5 g and 1 g daily) in a randomized placebo-controlled trial demonstrated its safety and efficacy in alleviating induced knee pain in healthy volunteers (Raj et al. 2020). Since the efficacy was already established at low dose, the current study on high dose Turmerosaccharides (>10% w/w), an aqueous based extract of turmeric (Turmacin®) standardized to at a moderately-high dose of 2 g per day was conducted as a single arm study with the objective to assess primarily the safety and also explore the efficacy on acute knee joint pain or discomfort upon exertion.

Methods

Ethics

The study was conducted in accordance with the principles of Good Clinical Practice that is based on the Declaration of Helsinki (Fortaleza, 2013). The study also abided by the National Guidelines for Ethical Research in Human Participants (Indian Council of Medical Research Guidelines, 2017) and Schedule Y, Drugs and Cosmetics act (1940) and rules (1945) (Central Drugs Standard Control Organization). The study was approved by the institutional ethics committee vide reference number 09/2018 and it was also registered prospectively in the clinical trials registry of India vide reference number CTRI/2018/03/012367. A written informed consent was obtained from all potential participants.

Study design and eligibility criteria

It was an open label, single arm interventional trial conducted over a six-month period from August 2018 – January 2019 in a tertiary care teaching hospital. All consenting adults aged between 18 and 65 years judged by the investigator to be in general good health on the basis of medical history, laboratory and clinical examination with no knee joint discomfort/pain at rest formed the sampling frame. All consecutive participants who achieved a knee joint discomfort/pain score of at least ≥ four out of 10 on

visual analogue scale (VAS) for pain after 10 min of brisk walk on the stair mill equipment during the screening visit were recruited in the study. This VAS cutoff for eligibility was based on similar previous studies (Lugo et al. 2013; Raj et al. 2020). Participants who had any previous history of any medical or surgical history involving the knee joints and women who were pregnant, or breast feeding were excluded from the study.

Investigational product (IP) and rescue medication

The IP (Turmacin®/NR-INF-02) was administered as four capsules of aqueous based extract of turmeric standardized to Turmerosaccharides (>10% w/w) of 500 mg each in the morning with food for a period of seven days. The IP contains negligible amounts/almost devoid of curcuminoids and being an aqueous extract, its bioavailability is better than that of the curcuminoids (Chandrasekaran et al. 2013). Thus, a bottle containing 30 capsules of 500 mg were dispensed at baseline visit and adherence was assessed using pill counts. All participants were allowed to take Acetaminophen 650 mg as a rescue medication on an as and when required basis for pain with a minimum time gap of 4 h between two doses and not exceeding a total daily dose of 4 g/day.

Study procedures

There was a total of five visits namely screening visit (SV)-1, SV-2, Baseline visit (BV) considered as day 1, Follow-up visits (FV) on day 5 (FV-1) and day 7 (FV-2). During SV-1 participants underwent blood investigations (Hemogram, liver enzymes, creatinine, fasting blood glucose and creatinine phosphokinase) and routine clinical examination. Electrocardiogram was performed in participants who were above 50 years of age. Those deemed as medically fit were given a 10-minute trial of stair mill (ASPEN 4000, Taiwan) on SV-2 and were requested to report the VAS score at the end of 10 min. They were also given an option to discontinue the stair-mill trial earlier if the pain/discomfort was intolerable. During the BV, FV-1 and FV-2 the participants performed the stair mill exercise. Repeat blood tests were done on FV-2.

Measurements using stair mill

The stair mill was set at a speed of 60 steps per minute and a maximum time limit of 10 min. The participants were asked to inform when they begin to feel the pain/discomfort (Lugo et al. 2013). Thus, time to initial pain/discomfort was noted. Once the participant achieved a VAS score of 3/10, the exercise on stair mill was continued for an additional two minutes. The VAS score at the end of this two minutes was considered as the final pain score (Lugo et al. 2013). The time to recovery was recorded as the time when the participants discomfort level reached the pre-exercise levels after being allowed to relax (Lugo et al. 2013). If there was a difference in pain between the two knees, the knee with the highest pain was taken as the index knee, else the right knee was chosen as the index knee (Lugo et al. 2013).

Outcome measures

The primary outcome measure was the proportion of adverse events (AEs) observed – both clinical and laboratory (Routine hemogram and biochemistry) events. The secondary outcome measures were (a) Time to initial discomfort/pain, (b) Time to a VAS score of three out of 10, (c) Maximum VAS noted after continued exercise on stair mill for a period of two minutes after attaining a VAS of three out of 10 and (d) Time to complete recovery.

Data management

Data entry was done using Microsoft excel (Publisher: Microsoft Corporation, Redmund, Washington, USA, 2016) and statistical analysis was performed using Statistical Package for Social Sciences (SPSS) for Windows, version 20.0 (Publisher: IBM, Armonk, New York, USA, 2011).

Statistical analysis plan

Since this was a pilot study and the primary outcome measure was descriptive in nature, a formal sample size estimation was not performed. It was decided to recruit $N = 15$ participants. The baseline demographic characteristics and the AEs were summarized using descriptive statistics. Shapiro-Wilk tests was used to test for normal distribution, and non-normal distribution of all parameters were confirmed. Hence, non-parametric methods were used for subsequent analysis. The change in secondary outcome measures over the study duration were initially assessed using Friedman's test. Those which showed statistical significance was subjected to multiple comparisons (BV versus FV-1; BV versus FV-2 & FV-1 versus FV-2) using Wilcoxon signed rank test. The statistical significance was set at $p < 0.05$ except when multiple comparisons were done where the p value was adjusted using simple Bonferroni's correction (Bland and Altman 1995) and the new statistical significance for those results were $p < 0.017$. An intention to treat analysis was performed.

Results

Baseline demography

A total of $n = 24$ participants were screened and $n = 15$ were recruited. The reasons for screen failure ($n = 9$) included unwillingness to consent ($n = 5/9$), VAS score < 4 out of 10 during SV-2 ($n = 3$) and pregnancy ($n = 1$). There was one female participant who withdrew consent immediately after the baseline assessment (before taking any IP) and the results of the remaining $N = 14$ participants are presented here. The minimum and maximum age of participants were 20 and 56 respectively. The mean (SD) age was 25.79 (11.21) years. Majority of them were male participants ($n = 11/14$; 79%).

Safety outcome measures

One participant suffered from dyspepsia of mild grade on day-1 but resolved spontaneously by day-3 on continuous usage. There were no other AEs that were recorded

among the study participants during the study period. All laboratory values (routine hemogram and biochemistry) continued to remain within normal limits.

Efficacy outcome measures

The baseline values of the efficacy measures are summarized in Table 1. There were no participants who stopped the stair mill exercise inbetween due to intolerable pain/discomfort at any of the visits. The change over time for the parameters time to initial discomfort ($p = 0.030$) and maximum VAS pain score ($p = 0.012$) were significant (Table 2). Post hoc analysis revealed that time to initial discomfort significantly increased on FV-1 and FV-2 when compared with baseline. Whereas, the maximum VAS pain score, although showed a trend toward lower score at FV-1, it achieved statistical significance only on FV-2 when compared with baseline. There was no difference with regards to time to VAS 3/10 and time to Complete recovery.

Discussion

This was an open label, single arm interventional pilot study with $N = 15$ healthy participants that was conducted to assess the safety and explore the efficacy of a relatively high dose (2 g/day) of aqueous based extract of turmeric, standardized to

Table 1. Baseline efficacy parameters.

Variable	Statistic	Value
Time to Initial discomfort/pain (mm:ss)	Minimum, Maximum (range)	00:50, 02:16 (01:26)
	Mean (SD)	01:21 (00:24)
Time to VAS 3/10 (mm:ss)	Minimum, Maximum (range)	02:07, 05:10 (03:23)
	Mean (SD)	03:23 (00:46)
Maximum VAS	Minimum, Maximum (range)	4, 6 (2.00)
	Mean (SD)	5.00 (0.877)
Time to Complete recovery (mm:ss)	Minimum, Maximum (range)	01:15, 02:53 (01:38)
	Mean (SD)	01:57 (00:34)

VAS – visual analogue scale, SD – standard deviation.

Table 2. Mean (SD) of efficacy parameters at baseline & follow-up.

							Mean difference (P value [*post-hoc* analysis*])		
		Day 5		Day 7			D0 *vs* D5	D0 *vs* D7	D5 *vs* D7
Parameter	Baseline	Mean (SD)	% Change from D0	Mean (SD)	% Change from D0	P value (overall model)	Mean (SD)	Mean (SD)	Mean (SD)
Time to Initial discomfort/pain (mm:ss)	01:21 (00:24)	01:51 (00:40)	37.04	01:53 (00:43)	39.51	0.030	00:30 (0.016)	00:32 (0.007)	00:02 (1.000)
Time to VAS 3/10 (mm:ss)	03:23 (00:46)	03:49 (01:12)	12.81	03:38 (01:32)	12.32	0.492	Not applicable		
Maximum VAS	5.00 (0.877)	4.43 (1.02)	−11.4	4.07 (0.730)	−18.6	0.012	−0.57 (0.159)	−0.93 (0.008)	−0.36 (0.132)
Time to Complete recovery (mm:ss)	01:57 (00:34)	01:47 (00:55)	−8.55	01:56 (00:46)	−0.85	0.789	Not applicable		

VAS – visual analogue scale, SD – standard deviation.
*The adjusted level of significance using bonferroni's correction is p value < 0.017.

Turmerosaccharides (>10% w/w). There were no major safety concerns with just one report of mild grade dyspepsia that resolved on its own and there was a significant increase in pain threshold as assessed by the increase in time to initial discomfort and a decrease in the maximum pain score experienced during the 10-minute strenuous physical activity. These findings are in line with our previously published study performed with low dose Turmerosaccharides (Raj et al. 2020). We hypothesize that the other two measures did not reach statistical significance as they are much more subjective measures than the other two and the sample size was also small.

The under lying mechanism of action of Turmerosaccharides can be explained through *invitro* study conducted on mouse splenocytes and mouse macrophages by Chandrasekaran *et al.* that proved its immune-stimulatory and anti-inflammatory activities (Chandrasekaran et al. 2013). This study demonstrated a significant increase in Nitric oxide (NO), Interleukin (IL) −2, IL-6, IL-10, IL-12, interferon gamma (IFN γ), tumor necrosis factor alpha (TNFα) and Monocyte chemoattractant protein-1 (MCP-1) production in the mouse splenocytes and macrophages that were unstimulated to lipopolysaccharide (LPS) resulting in immune-stimulatory activity. At the same time, it also demonstrated a potent inhibitory effect toward the release of Prostaglandin E_2 (PGE_2) and IL-12 levels in LPS stimulated mouse splenocytes thereby exhibiting the anti-inflammatory activity (Chandrasekaran et al. 2013). Another study found that Turmerosaccharides significantly attenuated IL-1β-induced chondrocyte cytotoxicity and apoptosis and release of chondrocyte degradation markers such as IL-6, IL-8, Cyclooxygenase (COX) 2, PGE_2, TNF-α, Intercellular Adhesion Molecule 1 (ICAM-1) in human chondrocyte (NHAC-kn cells). It was also found that it was protective against IL-1β-induced damage to synthesis markers such as glycosaminoglycans, type II collagen and further attenuated H_2O_2-induced chondrocyte senescence (Velusami et al. 2018). Possibly through these above-mentioned mechanisms, Turmerosaccharides have shown to significantly attenuate acute and chronic inflammatory pain and to have antiarthritic effect in Rodent Models (Illuri et al. 2015; Bethapudi et al. 2017).

These findings were replicable in animal models as well. Senthilkumar *et al.* were able to demonstrate the anti-inflammatory effect of turmeric extract rich in polysaccharides but devoid of curcuminoids and turmerones in acute (carrageenan-induced paw edema and xylene-induced ear edema) and chronic (cotton pellet-induced granuloma) inflammatory animal models (Senthilkumar et al. 2014). Likewise, Bethapudi *et al.* administered Turmerosaccharides-rich (90 mg/kg) and -poor fraction (45 mg/kg) orally for 5 days on monosodium iodoacetate (MIA)-induced osteoarthritis (OA) pain Wistar rat model that mimics human OA and evaluated pain using hind limb weight-bearing ability at 1h, 3h, 6h, and 24h post last dose. Both groups showed decreased pain, but the effect of turmerosaccharides-rich fraction was superior to that of the turmerosaccharides-poor fraction (Bethapudi et al. 2017).

The human studies done till date also have proven its anti-inflammatory properties. Madhu *et al.* conducted a placebo controlled randomized controlled trial among 120 OA patients wherein Turmacin® 1 g/day was administered for 42 days. In the intervention group, post-treatment, there was a significant betterment in the VAS score, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scale and Clinician Global Impression Change (CGIC) scale (Madhu et al. 2013). A recent

systematic review of ten studies further concluded that turmeric extracts appear to have a benefit on knee OA when compared with placebo (Paultre et al. 2021). Also, a single center, double blind, triple-arm, parallel group, randomized placebo - controlled study conducted by Raj et al., similar to the current study conducted in 90 healthy volunteers [mean (SD) age = 24.84 (7.51) years, mean (SD) Body Mass Index (BMI) = 22.94 (4.78) kg/m^2, $n = 49/90$ male participants] with normal blood reports and normal BMI, randomized in a 1:1:1 ratio to placebo, Turmacin® 0.5 g and 1 g, showed a significant decrease in the mean final VAS score at 5, 7, 28, 56 and 84 days of follow up in both the Turmacin® groups as compared to placebo (Raj et al. 2020). The current study also found a significant decrease of mean VAS at Day 7 when compared to baseline. Although the other parameters showed a favorable response, they did not achieve statistical significance probably because of the small sample size. However, in order to explore a dose-response relationship we recommend a separate study with head-on comparisons as these two studies are not comparable due to the differences in study setting and the sample size.

With regards to safety and tolerability, we report that a relatively higher dose of 2 g/day has shown good tolerability. Only one out of 15 participants reported mild dyspepsia which was resolved on its own by day 3. No other adverse events were reported. These were similar to those reported by Madhu et al. and Raj et al. Madhu et al. have reported two participants in the Turmacin® alone group with dyspepsia (Madhu et al. 2013) whereas Raj et al. have reported one participant with heart burn in the intervention arm (Raj et al. 2020). Even a meta-analysis of eight randomized controlled studies has concluded that turmeric preparations are generally safe (Daily et al. 2016).

This study gains its importance as Turmacin® being a plant product and having been found reasonably safe and tolerable at a moderately higher dose, it could now be further explored for its efficacy as a nutritional supplement in sports medicine as well as for its therapeutic benefit in clinical conditions such as the OA at this higher dose level. Herbal medicines being a part of complementary and alternative medicine has gained importance among the general public in the recent times because of its natural plant-based origin. The armamentarium of clinical trials evaluating the potential benefits of herbal medicines for various clinical conditions has been ever expanding such as the pomegranate seed powder in patients with type-2 diabetes mellitus (Seyed Hashemi et al. 2021), Alcea angulata Freyn & Sint. Suppository in vaginal atrophy (Kianitalaei et al. 2022), oral supplementation of whey protein in contact dermatitis (Alyasin et al. 2020) and the likewise and the authors believe that Turmacin® also stands merit to be added to this list.

The current study has a few limitations. It is a pilot study with a small sample size which is not adequately powered to pick-up less common adverse effects. Further, it was a single arm study with no comparator. Therefore, clinical efficacy and dose-response relationship could not be ascertained with certainty. However, similar to the previous study with low dose Turmacin® (Raj et al. 2020) there was a significant increase in pain threshold as observed by the increase in time to initial discomfort and a significant decrease in the maximum pain score post intervention on Day 7. The strength of the study is that it is the first study to evaluate the safety of moderately high-dose Turmacin® in humans.

Conclusion

Turmacin® (NR-INF-02) supplements given at a dose of 2 g/day to healthy volunteers is safe and has good tolerability. Similar to the study with low dose Turmacin®, there was a significant increase in pain threshold and a significant decrease in the maximum pain score post intervention. However, further larger, randomized controlled studies are required to confirm the findings of the current study, explore its dose-response relationship, and its utility in clinical conditions such as OA.

Declarations

Authors contributions

Authors testify that all persons designated as authors qualify for authorship and have checked the article for plagiarism. If plagiarism is detected, all authors understand that they will be held equally responsible and will bear the resulting sanctions imposed by the journal thereafter. The CRediT author statement is as follows:

Activity	Authors responsible
Conceptualization	JPR
Methodology	JPR, SV, RSA
Software	JPR
Validation	JPR
Formal analysis	JPR
Investigation	JPR, SV, RSA
Resources	JPR, RSA
Data Curation	JPR
Writing - Original Draft	JPR
Writing - Review & Editing	SV, RSA
Visualization	JPR
Supervision	RSA
Project administration	RSA
Funding acquisition	JPR

Disclosure statement

No potential conflict of interest was reported by the authors.

Ethics approval

The study was approved by the Institutional Ethics Committee of St. Johns Medical College Hospital, Bengaluru vide study reference number 09/2018.

About the authors

Jeffrey Pradeep Raj, Assistant Professor, Department of Clinical Pharmacology, Seth GS Medical College and King Edward Memorial Hospital, Mumbai, does research in the disciplines of Clinical Pharmacology, Non-communicable diseases, Medical education & Bioethics. He has an experience of approximately 10 years in conducting randomized controlled trials.

Shreeraam Venkatachalam, after completing his post-graduation from St. Johns Medical College is currently practicing as a consultant Consultant Arthroscopy and Trauma Surgeon, in Kurinji Hospital, Salem, Tamil Nadu, India. He is an aspiring clinical researcher in the field of orthopaedics for the last 5 years.

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