



Original Research Article (Clinical)

A randomized, double blind placebo controlled study of efficacy and tolerability of *Withania somnifera* extracts in knee joint pain

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ABSTRACT

Background: Root extracts of *Withania somnifera* (Ashwagandha) are known to possess analgesic, anti-inflammatory and chondroprotective effects. An aqueous extract of roots plus leaves of this plant has shown to yield higher percentages of withanolide glycosides and, accordingly, may possess better analgesic, anti-inflammatory and chondroprotective effects than root alone extracts.

Objectives: To evaluate efficacy and tolerability of a standardized aqueous extract of roots plus leaves of *W. somnifera* in patients with knee joint pain and discomfort.

Material and methods: Sixty patients with knee joint pain and discomfort were randomized in a double-blind manner to *W. somnifera* 250 mg, *W. somnifera* 125 mg and placebo, all given twice daily. Assessment was done by Modified WOMAC, Knee Swelling Index (KSI), Visual Analogue Scale (VAS) at baseline and at the end of 4, 8, 12 weeks. Tolerability was assessed by incidence of adverse effects in treatment groups. Student's 't' test and ANOVA were used to compare mean change from baseline within and between the study groups. A $p < 0.05$ was considered significant.

Results: At the end of 12 weeks, compared to baseline and placebo, significant reductions were observed in mean mWOMAC and KSI in *W. somnifera* 250 mg ($p < 0.001$), *W. somnifera* 125 mg ($p < 0.05$) groups. VAS scores for pain, stiffness and disability were significantly reduced in *W. somnifera* 250 mg ($p < 0.001$), *W. somnifera* 125 mg ($p < 0.01$) groups. *W. somnifera* 250 mg group showed earliest efficacy (at 4 weeks). All treatments were well tolerated.

Conclusions: Both the doses of an aqueous extract of *W. somnifera* produced significant reduction in outcome variables, with the 250 mg group showing significantly better response. In addition, the therapeutic response appears to be dose-dependent and free of any significant GI disturbances.

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1. Introduction

1.1. Background

Knee joint pain and discomfort are the most prevalent of the chronic rheumatic symptoms and is a leading cause of disability in most countries worldwide [1]. The prevalence of joint pain and discomfort due to osteoarthritis (OA) increases with age and

more so with female gender, though males are also affected. OA contributes to a higher disease burden in men below the age of 50 and in women over the age of 50 [2]. Most of the disability arising due to OA is due to involvement of hip and knee joints [3]. Knee OA is likely to become the fourth most important global cause of disability in women and eighth most important in men [4].

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used drugs for the symptomatic treatment of pain in OA. However, NSAIDs are associated with serious gastrointestinal adverse effects which limit their use in many patients [5,6]. Other drugs like opioids and non-opioid analgesics and intra-articular steroids may not be effective in all patients [5,6].

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Hence, there is a specific need for effective and safe drugs in the treatment of OA.

Herbal medicines have been explored for their usefulness in OA for a long time. *Withania somnifera* (Ashwagandha), a plant belonging to the family Solanaceae, is widely used in Ayurvedic medicine for this purpose. It is an ingredient in many formulations prescribed for a variety of musculoskeletal conditions (e.g., arthritis, rheumatism), and as a general tonic to improve overall health [7]. Roots of the plant reportedly exhibit anti-inflammatory, anti-tumour, anti-stress, antioxidant, immunomodulatory, haematopoietic and rejuvenating properties [8]. There is evidence of effectiveness of *W. somnifera* in various rheumatologic conditions due to its anti-inflammatory properties [9]. In a randomized, double-blind, placebo-controlled, cross-over study in patients with OA, treatment with roots of *W. somnifera* produced a significant drop in severity of pain and disability score. It also acts as an analgesic that soothes nervous system from pain response [10]. Chemical composition of *W. somnifera* extracts vary widely depending on which part of the plant is used as well as the extraction solvent and procedure, and thus different extracts are expected to elicit different clinical response. Sensoril[®] is an aqueous extract of *W. somnifera* roots plus leaves and contains withanolide glycosides, Withaferin-A and oligosaccharides as the major components. There are very few human studies evaluating the effects of *W. somnifera* root extracts, in combination with other herbal products, in patients with symptoms of knee joint pain and disability and there are no human studies reported with an aqueous extract of roots plus leaves of *W. somnifera*.

2. Objectives

To evaluate the efficacy and tolerability of a standardized aqueous extract of roots plus leaves of *W. somnifera* using Modified WOMAC index score, pain relief as assessed by Visual Analogue Scale (VAS) and changes in Knee Swelling Index (KSI) in patients with pain and discomfort of knee joint.

3. Methods

3.1. Study design

The study was a prospective, randomized, double-blind, placebo-controlled trial with 1:1:1 allocation ratio of the participants in to the 3 study groups. The study was approved by the local Institutional Ethics Committee.

3.2. Study participants

3.2.1. Eligibility criteria

The patients were screened for their eligibility to participate in the study during the screening visit (Visit 1).

a. Inclusion Criteria

Patients with knee joint pain and discomfort of either gender aged between 40 and 70 years, for at least 6 months duration and meeting the American Rheumatology Association (ARA) functional class I to III and who recorded baseline pain scores of at least 40 mm on the VAS monitored at baseline visit were enrolled. Patients who discontinued all current analgesic therapy, including NSAIDs, over the counter pain medications and topical analgesics for 7–10 days prior to the start of the study were randomized into the study.

b. Exclusion Criteria

Patients with severe OA (ARA functional class IV), on alternative system of medicine, any psychiatric disorder or who have been using systemic/intra-articular steroids within 12 weeks of study and hyaluronic acid in the last 9 months, or potential candidates for imminent joint replacement and patients with uncontrolled hypertension or diabetes, hepatic or renal impairment, pregnant or lactating females, or with a recent trauma of the involved knee were excluded from the study.

3.3. Study interventions

The study medications included capsules of *W. somnifera* in the strengths of 125 mg and 250 mg and identical placebo capsules, supplied by Natreon, Inc, New Jersey, USA.

A *W. somnifera* capsule consists of standardized aqueous extract of roots and leaves of *W. somnifera* (Sensoril[®]) containing not less than 10% Withanolide glycosides, not less than 32% oligosaccharides and not more than 0.5% of Withaferin-A and is standardized by HPLC (Fig. 1). The excipients used in these capsules include microcrystalline cellulose, croscarmellose sodium, silicon dioxide, magnesium stearate and gelatin from the capsule shell.

3.4. Study procedure

The study was conducted in the Department of Clinical Pharmacology and Therapeutics. The patients were randomized by the principal investigator using a computer generated simple randomization sequence with a block size of 20 patients per group. Case record numbers and sequentially numbered containers were used for random allocation sequence. The study was performed in a double-blinded manner, with both the study patients and the investigator blinded to study interventions. The participant flow chart is shown in Fig. 2.

A run-in period was allowed between screening visit (Visit 1) and randomization visit (Visit 2) to ensure that the were weaned off all medications 7–10 days prior to randomization. At the baseline/randomization visit (Visit 2, Day 0), all eligible were randomized to receive either *W. somnifera* 250 mg or *W. somnifera* 125 mg or identical placebo capsules for 4 weeks, with one capsule of the study medication to be taken twice daily after food with a glass of water. Paracetamol 650 mg tablets were used as and when required as rescue medication. The subsequent visits were scheduled at 4 weeks interval (Visit 3-after 4 weeks of treatment initiation, Visit 4 -after 8 weeks of treatment initiation and Visit 5- after 12 weeks of treatment initiation). The study and rescue medications were dispensed at visits 2, 3 and 4 and compliance to study medications was checked by pill count method during the subsequent visits. The total duration for which the patients received study medications was 12 weeks.

All the efficacy variables, pill count, use of rescue medication and Physician's Global Assessment were evaluated in the subsequent visits. Adverse reactions/serious adverse effect (ADR/SAE) monitoring was done throughout the course of study. Safety lab were done before and after treatment and as and when required.

3.5. Outcomes

The primary outcome measure was percentage change in the Modified Western Ontario and McMaster University Osteoarthritis Index (mWOMAC, Ref. www.copcord.org/images/WOMAC.pdf) score at the end of 12 weeks from baseline.

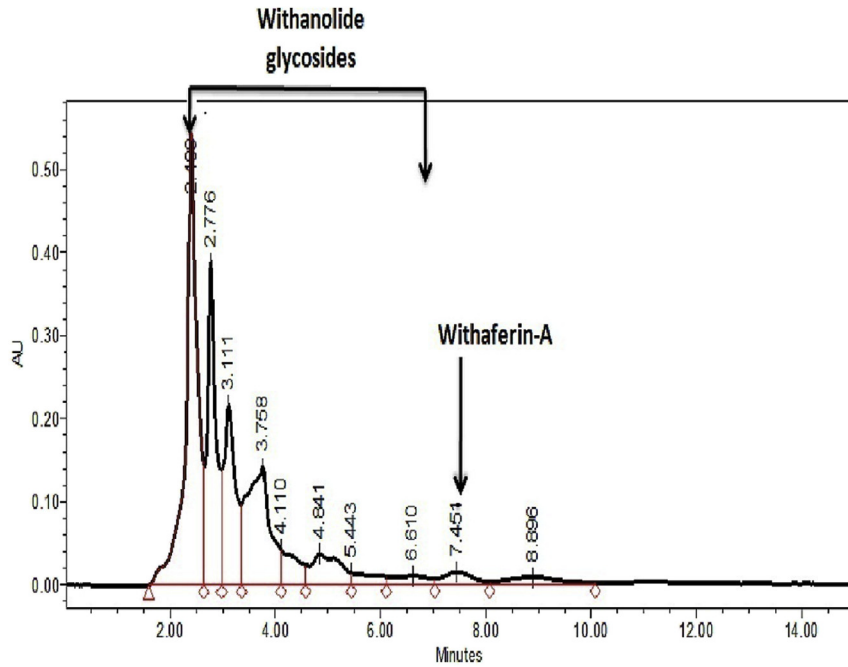


Fig. 1. HPLC Chromatogram of Sensoril®.

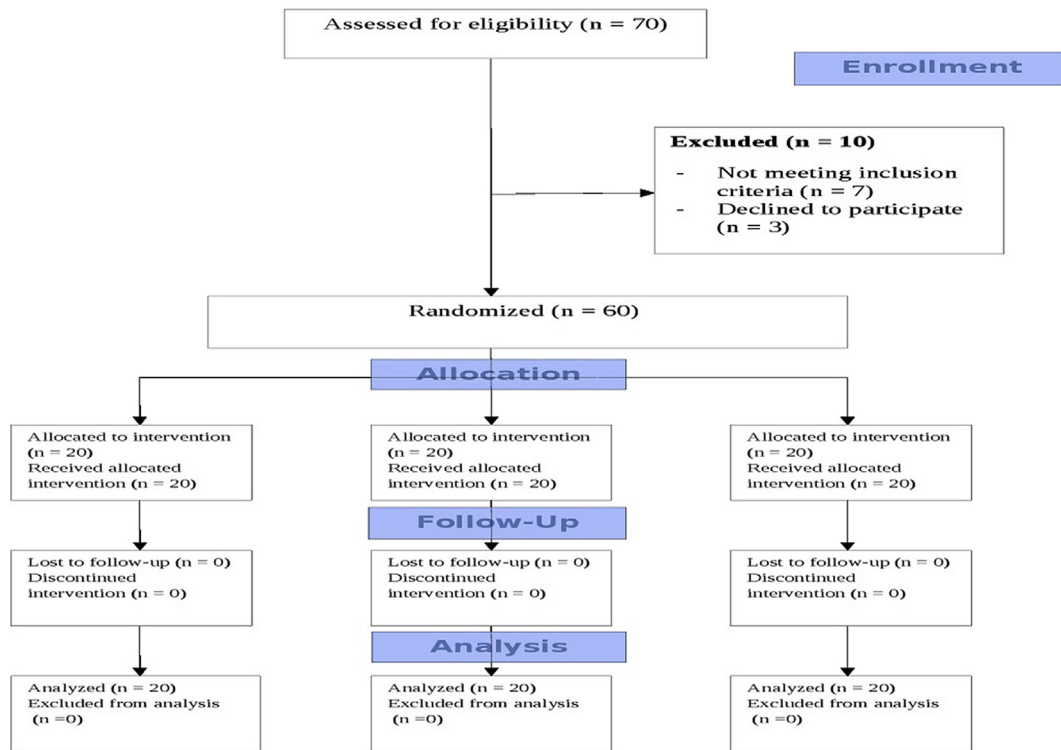


Fig. 2. Participant flow chart.

The secondary outcome measures were percentage changes in mWOMAC score at the end of 4 and 8 weeks, Knee Swelling Index (KSI) as measured by joint circumference (mm) and VAS for pain, disability and stiffness at the end of 4, 8 and 12 weeks, extent of use of rescue medication in treatment groups, Physician Global Assessment scale and tolerability. The Physician Global Assessment was used to classify the patients based on

symptoms. Accordingly, the 5 categories were Excellent (complete relief of symptoms), Good (partial relief of symptoms), Fair (minimal relief of symptoms), Poor (no relief of symptoms) and Very poor (worsening of symptoms). Tolerability was assessed by 3 categories, viz., Good (no side effects), Fair (mild to moderate side effects) and Poor (severe side effects and withdrawal of therapy).

3.6. Sample size

The sample size calculation was based on the assumption that there will be a decrease of 10% in total mWOMAC score from baseline to end of treatment. A sample size of 60 evaluable cases would provide an 80% power to estimate the reduction of total mWOMAC score at 5% level of significance at the end of the study. Anticipating 15% dropouts, we enrolled 70 to get 60 evaluable cases for the study.

3.7. Statistical analysis

Primary and secondary end points were analyzed as average change in the response from baseline. Student's 't' test and ANOVA were used to compare the mean change from baseline to post-treatment period within and between study medications and placebo groups, respectively, at 80% power. A $p < 0.05$ was used to test the significance. All statistical analysis was performed using the GraphPad Prism Software 4 (GraphPad Software Inc., San Diego, California, USA).

4. Results

A total of seventy patients were recruited and screened over a period of 10 months (4/7/2014 to 16/5/2015), out of which 60 eligible patients (43 males, 17 females) with a mean age of 57.78 ± 4.49 years were enrolled into the study. Patients were divided into three groups of 20 each and were randomized to receive *W. somnifera* 250 mg, *W. somnifera* 125 mg or identical placebo capsules, one capsule twice daily for 12 weeks. All patients completed 12 weeks of treatment.

The demographic characteristics of all the three study groups are shown in Table 1. There were no significant differences between the treatment groups in baseline characteristics including age, weight and body mass index, indicating a homogenous population.

The mWOMAC scores at the end of 12 weeks are shown in Table 2(a) and the mean percentage reduction in mWOMAC scores

are shown in Fig. 3. The baseline values of the mWOMAC score were comparable in all the three groups without any statistically significant difference between them. There was a significant reduction in the mWOMAC score at the end of 12 weeks from baseline in *W. somnifera* 250 mg group (A) ($p < 0.001$) and *W. somnifera* 125 mg group (B) ($p < 0.05$). The mean percentage reduction in the mWOMAC score at the end of 12 weeks showed significant differences between *W. somnifera* 250 mg (A) and *W. somnifera* 125 mg groups (B) ($p < 0.001$), *W. somnifera* 250 mg (A) and placebo groups (C) ($p < 0.001$) and *W. somnifera* 125 mg (B) and placebo groups (C) ($p < 0.01$).

The KSI scores at the end of 12 weeks are shown in Table 2(a) and mean percentage change in KSI scores are shown in Fig. 4. The baseline values of the KSI scores were comparable in all the three groups without any statistically significant difference between them. There was a significant reduction in the KSI score at the end of 12 weeks from baseline in *W. somnifera* 250 mg group (A) ($p < 0.001$) and *W. somnifera* 125 mg group (B) ($p < 0.05$). The mean percentage reduction in the KSI scores in all the three groups at the end of 12 weeks showed a significant difference between *W. somnifera* 250 mg (A) and *W. somnifera* 125 mg (B) groups ($p < 0.001$) and *W. somnifera* 250 mg (A) and placebo (C) groups ($p < 0.001$).

The VAS score for pain, stiffness and disability are shown in Table 2(b) and the mean percentage changes in these scores are shown in Figs. 5–7, respectively. The baseline values for pain, stiffness and disability measured by VAS were comparable in all the

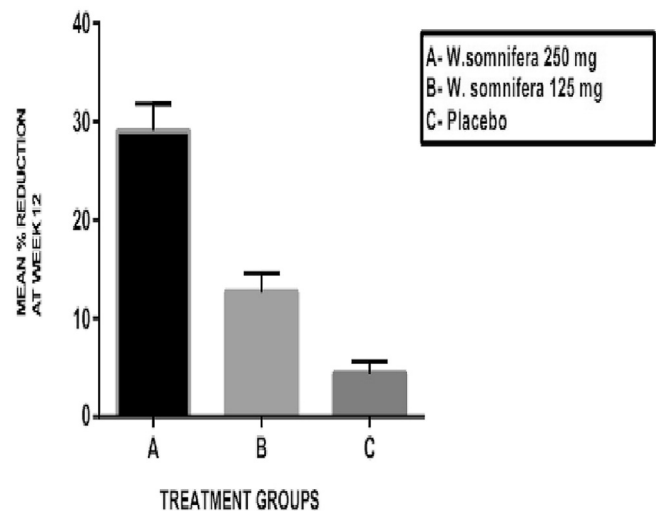


Fig. 3. Mean percentage change in modified WOMAC score at the end of 12 weeks.

Table 1 Demographic data.

	<i>W. somnifera</i> 250 mg (A)	<i>W. somnifera</i> 125 mg (B)	Placebo (C)
No. of Subjects	20	20	20
Gender (M/F)	13/7	14/6	16/4
Age (Yrs)	58.92 ± 6.07	55.42 ± 3.69	58.95 ± 3.73
BMI(Kg/m ²)	23.79 ± 2.99	23.82 ± 1.86	24.15 ± 2.17

Table 2a Summary of results – I.

	mWOMAC score			Knee swelling index		
	<i>W. somnifera</i> 250 mg (A)	<i>W. somnifera</i> 125 mg (B)	Placebo (C)	<i>W. somnifera</i> 250 mg (A)	<i>W. somnifera</i> 125 mg (B)	Placebo (C)
Baseline	53.1 ± 2.90	51.15 ± 2.39	50.45 ± 2.11	423.25 ± 9.63	415.5 ± 20.76	408.5 ± 15.05
End of 4 weeks	48.6 ± 2.41#	49.95 ± 2.11	49.97 ± 2.04	415.25 ± 9.66#	413.75 ± 19.65	404.6 ± 15.30
End of 8 weeks	43.4 ± 2.47*	47.4 ± 1.91	49.31 ± 2.11	404.75 ± 10.44*	409.25 ± 19.61	401 ± 15.61
End of 12 weeks	37.65 ± 2.41*	44.6 ± 1.42@	48.24 ± 2.31	396.25 ± 10.98*	405.75 ± 19.21@	399.5 ± 15.55
Absolute change at end of 12 weeks	15.45 ± 1.73*	6.5 ± 1.23#	2.15 ± 0.75	27 ± 6.76*	9.75 ± 3.43 ^{NS}	9 ± 2.62
Mean percentage change at end of 12 weeks	29.07 ± 2.73*	12.7 ± 1.96#	4.27 ± 1.46	6.37 ± 1.58*	2.34 ± 0.78 ^{NS}	2.2 ± 0.65

@ p value < 0.05; #p value < 0.01; *p value < 0.001 compared to baseline; NS- Non-significant. Absolute change in mWOMAC score: * A vs B, A vs C ($p < 0.001$); #B vs C ($p < 0.01$). Mean percentage change in mWOMAC score: * A vs B, A vs C ($p < 0.001$); #B vs C ($p < 0.01$). Absolute change in KSI: * A vs B, A vs C ($p < 0.001$),^{NS} B vs C. Mean percentage change in KSI: * A vs B, A vs C ($p < 0.001$),^{NS} B vs C.

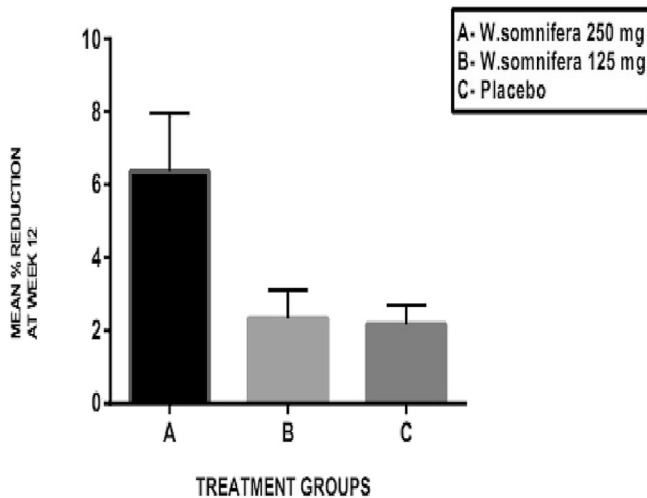


Fig. 4. Mean percentage change in knee swelling index score at the end of 12 weeks.

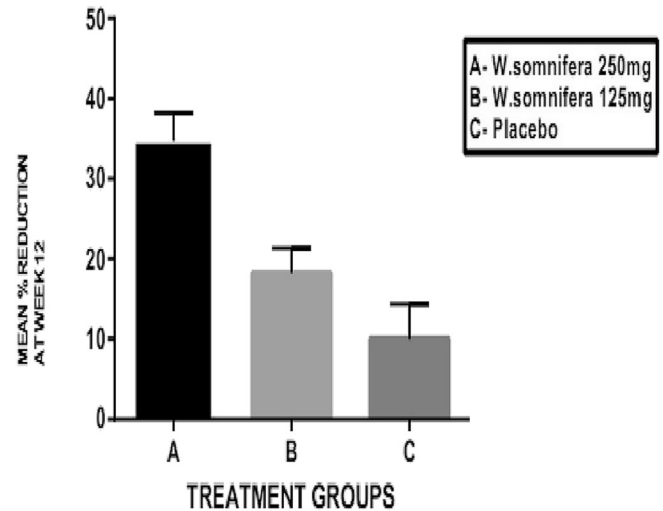


Fig. 5. Mean percentage change in VAS – pain score at the end of 12 weeks.

three groups without any statistically significant differences between them. In *W. somnifera* 250 mg group (A), there was a significant reduction in pain, stiffness and disability ($p < 0.001$) at the end of 12 weeks from baseline. In *W. somnifera* 125 mg group (B), there was a significant reduction in pain ($p < 0.01$), stiffness ($p < 0.01$) and disability ($p < 0.05$). The mean percentage reduction in the pain, stiffness and disability in all the three groups at the end of 12 weeks showed a significant difference between *W. somnifera* 250 mg (A) and *W. somnifera* 125 mg (B) groups ($p < 0.001$) and *W. somnifera* 250 mg (A) and placebo (C) groups ($p < 0.001$) and *W. somnifera* 125 mg (B) and placebo (C) groups ($p < 0.01$).

5. Rescue medication usage

The mean number of rescue medication tablets (Paracetamol 650 mg) was 10, 13 and 17 in *W. somnifera* 250 mg (A), *W. somnifera* 125 mg (B) and placebo (C) groups, respectively.

6. Physician Global Assessment

The Physician Global Assessment was done at the end of 12 weeks. In *W. somnifera* 250 mg group, 15 patients were assessed to

be excellent and 5 were assessed as good by the Physician Global Assessment scale.

In *W. somnifera* 125 mg group, 17 patients were assessed to be good and 3 were assessed as fair and in the placebo group, 1 patient was assessed to be fair and 19 patients were assessed as poor.

7. Results at 4 and 8 weeks

At the end of 4 weeks, patients treated with *W. somnifera* 250 mg twice daily showed statistically significant reductions in the mWOMAC score ($p < 0.01$), KSI ($p < 0.01$), pain ($p < 0.01$), stiffness ($p < 0.01$) and disability ($p < 0.01$) as measured by VAS when compared to baseline. However, patients treated with *W. somnifera* 125 mg twice daily did not show any significant changes at the end of 4 weeks compared to baseline.

At the end of 8 weeks, patients treated with *W. somnifera* 250 mg showed statistically significant reductions in the mWOMAC score ($p < 0.001$), KSI ($p < 0.001$), pain ($p < 0.001$), stiffness ($p < 0.001$) and disability ($p < 0.001$) as measured by VAS, compared to baseline. *W. somnifera* 125 mg (B) showed significant

Table 2b
Summary of results – II.

	VAS, pain			VAS, stiffness			VAS, disability		
	<i>W. somnifera</i> 250 mg (A)	<i>W. somnifera</i> 125 mg (B)	Placebo (C)	<i>W. somnifera</i> 250 mg (A)	<i>W. somnifera</i> 125 mg (B)	Placebo (C)	<i>W. somnifera</i> 250 mg (A)	<i>W. somnifera</i> 125 mg (B)	Placebo (C)
Baseline	67.25 ± 4.48	65.6 ± 4.56	63.8 ± 2.78	60.25 ± 4.11	62.55 ± 4.43	61.8 ± 2.71	50.45 ± 4.35	63.95 ± 4.71	58.6 ± 4.30
End of 4 weeks	60.95 ± 4.22#	63.05 ± 4.67	60.5 ± 3.24	55.8 ± 3.83#	59.45 ± 4.13	58.6 ± 2.85	46 ± 3.98#	61 ± 5.03	55.35 ± 4.06
End of 8 weeks	52.9 ± 3.37*	59.5 ± 4.07	58.65 ± 3.56	49.4 ± 3.28*	56.3 ± 4.05 @	56.7 ± 2.96	40.35 ± 3.64*	57.75 ± 5.03	53.5 ± 4.42
End of 12 weeks	43.9 ± 3.30*	53.3 ± 4.02#	57.4 ± 3.68	41.3 ± 3.54*	50.1 ± 4.12#	55.2 ± 2.98	33.55 ± 3.79*	52.6 ± 5.37@	51.87 ± 4.48
Absolute change at end of 12 weeks	23.35 ± 3.04*	12 ± 2.31#	6.4 ± 1.57	18.95 ± 3.08*	12.45 ± 2.08#	6.6 ± 1.82	17.4 ± 3.08*	11.35 ± 1.56#	6.5 ± 1.79
Mean percentage change at end of 12 weeks	34.73 ± 3.49*	18.29 ± 3.13#	10.08 ± 2.71	31.4 ± 4.26*	19.9 ± 3.15#	10.67 ± 2.93	33.7 ± 3.37*	17.74 ± 3.13#	11.15 ± 3.18

@ p value < 0.05; #p value < 0.01; *p value < 0.001 compared to baseline.

Absolute change in VAS scores:

- Pain: * A vs B, A vs C ($p < 0.001$); #B vs C ($p < 0.01$).
- Stiffness: * A vs B, A vs C ($p < 0.001$); #B vs C ($p < 0.01$).
- Disability: * A vs B, A vs C ($p < 0.001$); #B vs C ($p < 0.01$).

Mean percentage change in VAS scores:

- Pain: * A vs B, A vs C ($p < 0.001$); #B vs C ($p < 0.01$).
- Stiffness: * A vs B, A vs C ($p < 0.001$); #B vs C ($p < 0.01$).
- Disability: * A vs B, A vs C ($p < 0.001$); #B vs C ($p < 0.01$).

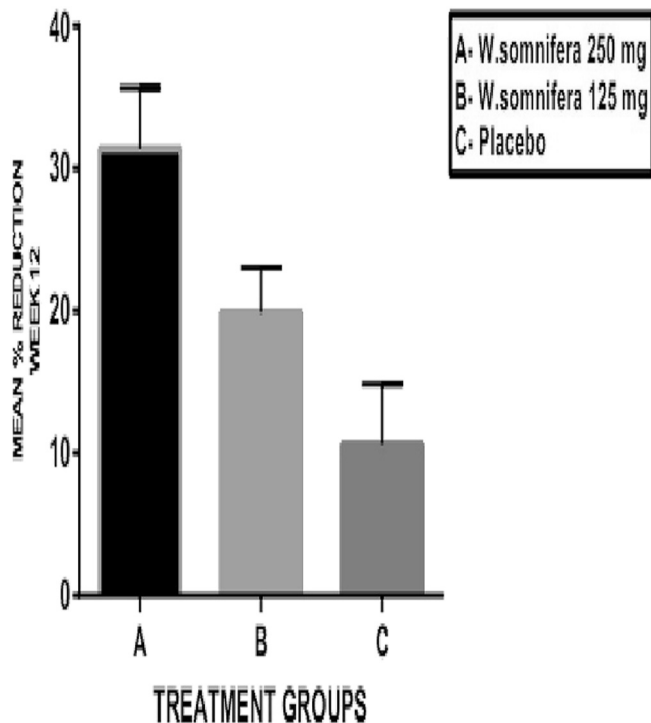


Fig. 6. Mean percentage change in VAS – stiffness score at the end of 12 weeks.

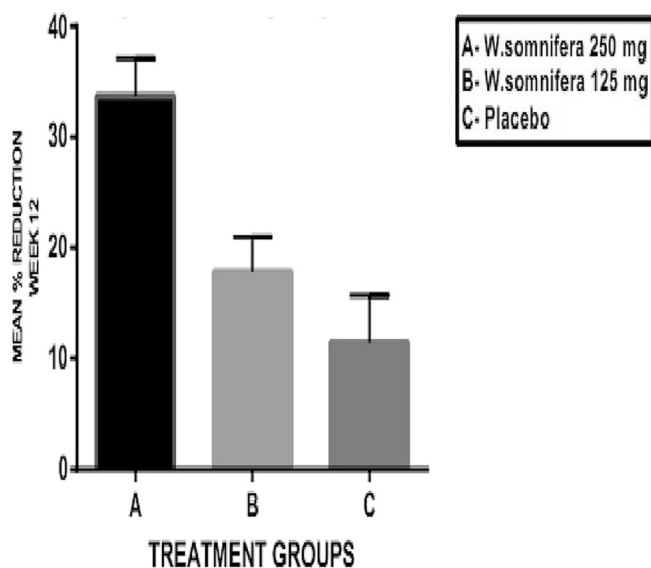


Fig. 7. Mean percentage change in VAS – disability score at the end of 12 weeks.

change from baseline only in VAS stiffness at the end of 8 weeks ($p < 0.05$).

There were no significant changes in the efficacy variables in the placebo group at the end of 4 and 8 weeks. The results at the end of 4 and 8 weeks are summarized in Tables 2(a), 2(b).

8. Safety and tolerability

All safety hematological and biochemical variables were within normal limits in all the three treatment groups at the baseline

recording. Both *W. somnifera* 250 mg and *W. somnifera* 125 mg were well tolerated. In *W. somnifera* 250 mg group, 4 patients complained of nausea and 1 patient developed mild gastritis. In *W. somnifera* 125 mg group, 2 patients complained of nausea and mild headache. None of the patients in placebo group had any adverse effects. No patients in any of the groups discontinued the study.

9. Discussion

W. somnifera has multiple bioactive components which contribute to its biological activity as an analgesic, anti-inflammatory, anti-arthritic and chondroprotective [11]. The chemical analysis of *W. somnifera* shows its main constituents to be alkaloids and steroidal lactones. The biologically active alkaloids include withanine, somniferine, somnine, isopelletierine and anferine, and the steroidal lactones include withanolides and withaferins [12,13]. The roots and leaves of *W. somnifera* have been shown to be rich in withanolides, which resemble steroids in their action and are considered to account for the biological activities of *W. somnifera*. Other components include saponins like sitoindoside VII and VIII and iron. Much of *W. somnifera*'s pharmacological activity has been attributed to Withaferin A and Withanolide D [13]. However, chemical composition of *W. somnifera* extracts vary widely depending on which part of the plant is used as well as the extraction solvent and procedure, and thus are expected to elicit different clinical response. Sensoril® is an aqueous extract of *W. somnifera* roots plus leaves and contains withanolide glycosides, Withaferin-A and oligosaccharides as the major components.

In the present study, the mWOMAC score was reduced significantly at the end of 12 weeks from baseline in both *W. somnifera* 250 mg and *W. somnifera* 125 mg groups, with the reduction being greater in *W. somnifera* 250 mg group. This reduction in mWOMAC scores by *W. somnifera* may be attributed to its analgesic and chondroprotective effects. The analgesic activity of *W. somnifera* is mainly mediated by Withaferin A which has been shown to block the cyclo-oxygenase (COX) pathway involved in the production of prostaglandins, the endogenous pain mediators [14]. The analgesic activity is also due to its action of soothing the nervous system from pain responses [15]. Also it is suggested that serotonin may be involved in the analgesic effects of *W. somnifera* [16]. An experimental study has demonstrated the chondroprotective activity of *W. somnifera* in human cartilage tissue [17].

Another important biological effect of *W. somnifera* is its anti-inflammatory activity which can be determined by its effect on the KSI. The KSI scores were significantly reduced at the end of 12 weeks from baseline in both *W. somnifera* 250 mg and *W. somnifera* 125 mg groups. However, greater reduction was seen in *W. somnifera* 250 mg group. This anti-inflammatory effect of *W. somnifera* has also been attributed to Withaferin A [18]. The possible role of anti-oxidant activity of *W. somnifera* on its anti-inflammatory properties has also been proposed. An experimental study in rats has shown that the anti-inflammatory activity of *W. somnifera* may be due to the inhibition of biological changes like increase in levels of lipid peroxides and glycoproteins and decreased antioxidant status and bone collagen in the affected joint [19]. In the affected joint, reactive oxygen species are known to activate a number of intracellular signaling pathways such as NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells), which further activate the transcription of various pro-inflammatory cytokines (interleukins and TNF α), cell adhesion molecules and COX 2 [20]. Some of the constituents of *W. somnifera* like flavonoids and phenolic acid such as gallic acid, rutein, vanillic acid, quercetin and kaempferol block the distinct signal transduction events necessary for NF- κ B activation and thus inhibit transcription factors such as

NF- κ B, activating protein-1 (AP-1) and nuclear factor-erythroid 2-related factor 2 (Nrf2) [21].

VAS scores for pain, stiffness and disability were used to assess the physical function of the knee joint. *W. somnifera*, in both 250 mg and 125 mg twice daily doses, significantly reduced the pain, stiffness and disability at the end of 12 weeks. However, the extent of reduction of these variables was higher with *W. somnifera* 250 mg twice daily dose. Also, the mean percentage reduction in all the three variables at the end of 12 weeks was significant with *W. somnifera* 250 mg, when compared to *W. somnifera* 125 mg and placebo groups.

The clinical assessment of patients with knee joint pain and discomfort was made by the Physician Global Assessment scale. Accordingly, patients in *W. somnifera* 250 mg group were assessed to have performed better in terms of clinical improvement compared to the other two groups.

Rescue medication in the form of Paracetamol 650 mg was allowed as and when required during the course of the study. We evaluated the usage of rescue medication as one of the outcomes measures of efficacy of *W. somnifera* treatment. The usage of rescue medication was the least in *W. somnifera* 250 mg group and the highest in the placebo group, indicating effectiveness of *W. somnifera* in reducing the symptoms of knee joint pain and discomfort.

The efficacy was also evaluated at 4 weeks and 8 weeks to determine the earliest onset of action. At the end of 4 and 8 weeks, patients treated with *W. somnifera* 250 mg twice daily showed statistically significant reductions in all efficacy variables, compared to baseline. However, patients treated with *W. somnifera* 125 mg twice daily did not show any significant changes at the end of 4 weeks compared to baseline and showed only significant change in VAS stiffness ($p < 0.05$) at the end of 8 weeks, compared to baseline. This suggests that treatment with *W. somnifera* 250 mg twice daily produces earlier and better symptomatic relief thus increasing patient compliance and satisfaction. In addition, the response with *W. somnifera* seems to be linearly dose-dependent.

The safety of *W. somnifera* was evaluated by monitoring the occurrence of any adverse effects. Both *W. somnifera* 250 mg and *W. somnifera* 125 mg were well tolerated and our study did not report any serious adverse effects with either of the doses of *W. somnifera*. This is consistent with the available literature on safety of *W. somnifera* [22]. Gastritis, nausea and headache that were reported were treated symptomatically with standard care of treatment.

10. Conclusions

Treatment with *W. somnifera* 250 mg and *W. somnifera* 125 mg, both taken twice daily in patients with knee joint pain and discomfort for a period of 12 weeks showed significant reduction in the outcome variables of efficacy and safety, when compared to baseline and placebo. On further analysis, *W. somnifera* 250 mg produced better reduction in outcomes when statistically compared to *W. somnifera* 125 mg. Also, this effect was seen earlier (in 4 weeks) in *W. somnifera* 250 mg group than in *W. somnifera* 125 mg group. The need for rescue medication (Paracetamol 650 mg tablets) was the least with *W. somnifera* 250 mg group suggesting its analgesic and anti-inflammatory effects. All the study medications were well tolerated and mild gastrointestinal adverse effects like nausea and gastritis were observed in few patients. None of the patients discontinued the study suggesting the favorable safety profile of *W. somnifera*. Further studies with *W. somnifera*, hence, are needed to confirm its therapeutic potential in

patients with knee joint pain and discomfort and other painful rheumatologic conditions.

Registration of the trial

The trial was registered in the Clinical Trial Registry-India (CTRI) with the reference number REF/2014/08/007385.

Conflict of interest

None.

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