REVIEW ARTICLE

Analysis of Clinical Trial Registry of India for Evidence of Anti-Arthritic Properties of *Withania somnifera* (Ashwagandha)

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ABSTRACT

Background • *Withania somnifera* (Ashwagandha) is an herb with anti-inflammatory properties used in managing arthritis. There is significant clinical data in the public domain on the effects of Ashwagandha and this study was aimed at compiling and analysing these data in a structured manner. The major sources of evidence data were clinical trials and systematic review of extant literature.

Methodology • Retrospective database search was conducted in the Clinical Trial Registry of India for trials registered from April 2008 to March 2020, and published literature related to the anti-arthritic effects of *Withania somnifera* were reviewed.

Results • In all, 77 registered clinical trials were analysed and common among them were interventional, single-centre, randomized, double-blind, two-arm studies with Placebo being the comparator. Similar findings were observed in the 10 published clinical trials on arthritis evaluated for this study. While industry- and government-sponsored trials were identified, government funded sites with approvals from Institutional Ethics Committees were preferred. Most trials were registered as Phase 2 with the highest number of sites in the state of Maharashtra. The solid dosage form was most preferred.

Conclusion • While the effects of *Withania somnifera* on various disorders are being investigated by several clinical trials, the ones evaluated for this study provide insight on its potential in managing arthritis when given for a specific duration. Evidence shows a dosage of 6 gm in powder form or extracts in tablets, or 500 -1000 mg capsule consumed for a duration of 8 – 12 weeks may be useful in managing symptoms of arthritis in patients. (*Altern Ther Health Med.* 2021;27(6):58-66)

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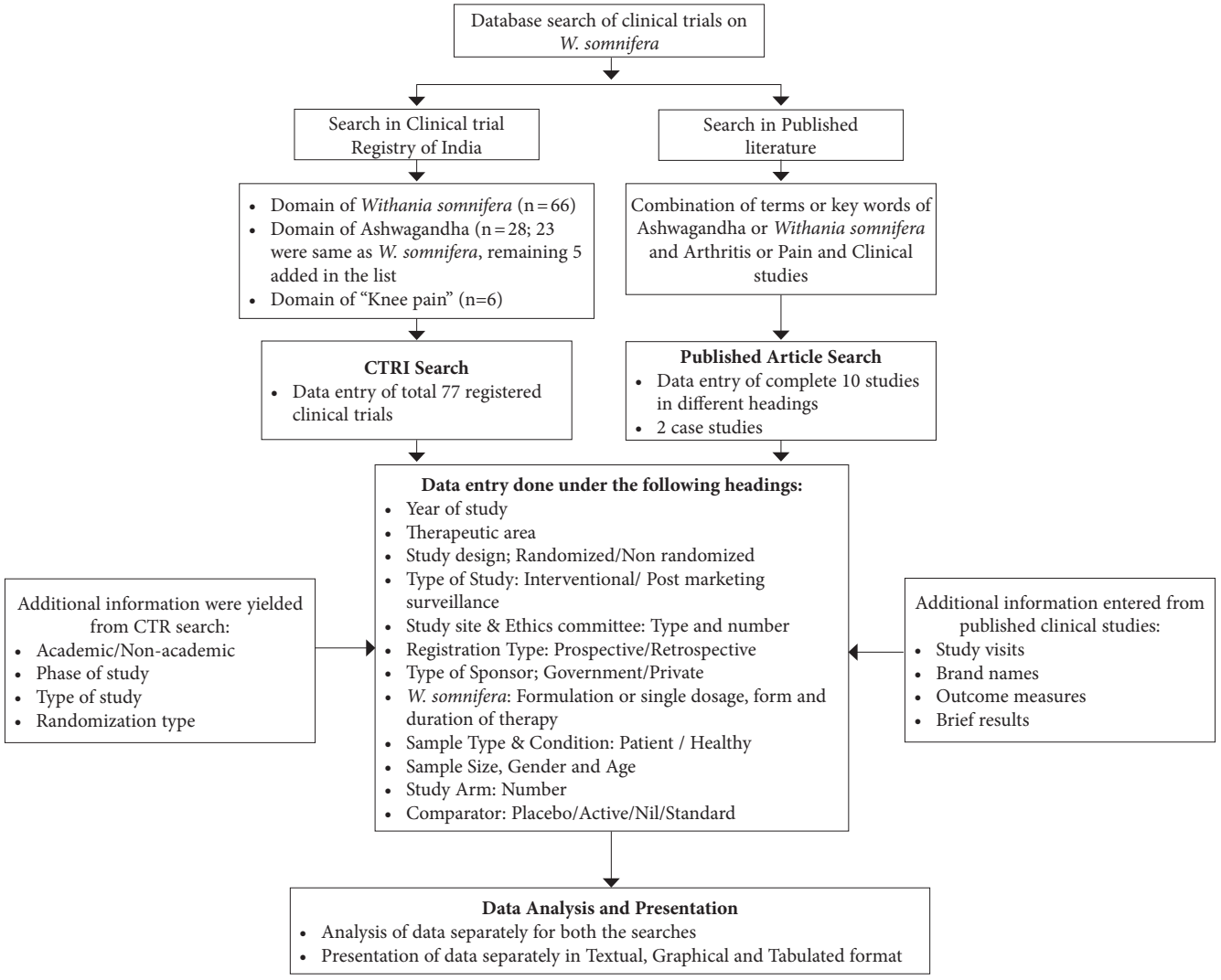
INTRODUCTION

Withania somnifera (L.) Dunal, commonly known as Indian ginseng, winter cherry or Ashwagandha, is a shrub of the Solanaceae family found throughout the drier parts of Southeast Asia. As a result of its pharmacological and medicinal properties, *Withania somnifera* (*W. somnifera*) is used to treat various diseases including arthritis.[1-4] Ayurveda links arthritis to the health of the joints, gut and the immune system.[5] Strengthening the immune system by use of *Rasayana* (rejuvenator) herbs is one of the mainstays of Ayurvedic management.[6] *W. somnifera* is well known for its *Rasayana* (rejuvenator and immunomodulatory) properties and effectiveness in treating inflammations.[4, 7-8]

Clinical trials and the systematic reviews of literature generate high-quality research data which support innovations in clinical practice.[9] These data can be obtained in a structured way through systematic searches of Clinical Trial Registries and published manuscripts. The Clinical Trials Registry-India (CTRI) has been in existence for decades and has developed a structured compilation of

Figure 1. PRISMA diagram of database search on *Withania somnifera* clinical studies



information on clinical trials related to the field of biomedical sciences, including AYUSH (Ayurveda, Yoga, Naturopathy, Unani, Siddha, Sowa-Rigpa and Homoeopathy) and other alternative systems of medicines. Academicians, researchers, Government, and Industries regularly register their trials and search for data from this repository.[10,11]

However, despite several proactive steps by Government agencies,[10,12,13] there remains a gap in conducting good quality clinical trials and producing impactful publications on Ayurvedic medicines.[14] The present study, which analysed the clinical trial registry for trials involving the use of *W. somnifera,* was conducted to understand the anti-arthritic profile of the herb through various published clinical studies.

METHODOLOGY

The study was a retrospective database review and analysis of the Clinical Trial Registry of India-CTRI (www.ctri.nic.in).[15] Hence, the approval of the Institutional Ethics Committee was not required. All trials registered from April 2008 to March 2020 were evaluated with a search filter of '*Withania somnifera*' and 'Ashwagandha'. No other filters were used concerning the clinical trial design or phase. For published studies, comprehensive searches were conducted using various keywords and combinations (MeSH terms or All Fields) such as *Withania somnifera* OR Ashwagandha AND arthritis OR anti-inflammatory AND Clinical trials OR studies, in databases like PubMed, DHARA portal (Digital Helpline for Ayurveda Research Articles), Google Scholar and Cochrane. All information gathered were tabulated under various headings. Descriptive statistics was used to identify trends.

Limitations of This Study

Only clinical trial data retrieved from CTRI (India) were used for this study while other trial databases were excluded. In addition, no sophisticated statistical tool was applied, and percentage analysis was done to identify preferences. The data on published literature related to arthritic conditions was compiled and discussed without doing meta-analysis. All other therapeutic areas were excluded.

Table 1. Year wise distribution of the Clinical Trials registered in CTRI

Year	No. of Trials	Type of Subject		Type of Comparator				Sponsor		Type of Study center		Type of Registration		Phases of Clinical Trial								
		Healthy	Patient	Placebo	Active	Nil	Standard	Govt	Pvt	Govt	Pvt	Prospectively	Retrospectively	1	1 or 2	2	2 or 3	3	3 or 4	4	PMS	N/A
2008	4	1	3	4				4		9	3	4				4						
2009	2		2	1	1			1	1	1	1	2				1	1					
2011	3	1	2	2	1				3	1	2	3			2					1		
2012	8	3	5	1		6	1	7	1	7	1		8			6		1	1			
2013	3	2	1	3				3		3		1	2									3
2014	2	1	1	2					2	1	1		2							1	1	
2015	5	1	4	3	1	2		2	3	4	1	2	3			3					1	1
2016	8	4	4	7	1			2	6	5	3	3	5		1	1					6	
2017	8	3	5	3	3	2		4	4	6	2	1	7		1	4						
2018	6	2	4	1	5			3	3	4	2	6		2		2		1			1	
2019	20	8	12	6	9	4	1	11	9	9	11	19	1	2	1	4	2	2		2		7
2020	8	2	6	3	4	1		2	6	3	5	8			1	1	2	2	1			1
Total	77	28	49	36	25	15	2	39	38	53	32	49	28	4	6	26	7	6	2	4	9	13
Percentage		36.36	63.64	46.75	32.47	19.48	2.60	50.65	49.35	68.83	41.56	63.64	36.36	5.19	7.79	33.77	9.09	7.79	2.60	5.19	11.69	16.88

Abbreviations: Govt, Government; Pvt, Private; PMS, Post marketing surveillance; N/A, Not applicable.

RESULTS

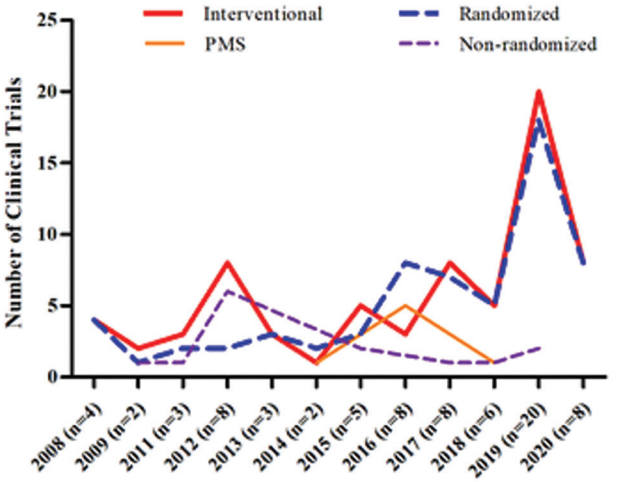
A total of 77 trials conducted from April 2008 till March 2020 were obtained and analysed.

Overall, 66 trials were found for the domain of 'Ashwagandha', 5 for '*Withania somnifera*' and 6 for 'Knee pain'. The year-wise spread of the trials with the type of study, subjects, comparators used, sponsor, study centre, registration phases and randomization are listed in Table 1 and Figure 2.

Characteristics of Registered Clinical Trials

Of the 77 trials conducted within the specified period, 61 (79.22%) were single-centre, 6 (7.79%) were double-centre, 8 (10.38%) were triple-centre and only 2 (2.59%) were four-centre studies. The centres were distributed across India with 12 in Gujarat, 16 in Karnataka, 30 in Maharashtra, 8 in Telangana, 6 in Delhi, 3 in Uttarakhand, 6 in Rajasthan, 4 each in Uttar Pradesh and Himachal Pradesh, 2 in Tamil Nadu, and 1 each in Kolkata, Madhya Pradesh, Jammu and Bihar. Almost an equal number of trials were sponsored by Government and Private institutions. However, the centres were predominantly government-run. (see Table 1).

Figure 2: Year wise distribution of Clinical trials registered in CTRI basis randomization and Type of study



Abbreviation: PMS, Post marketing surveillance.

Randomization and Blinding

Randomized controlled trials accounted for 83.11% of the clinical trials analysed, while the remaining 16.88% were non-randomized in design. Of the 64 randomized trials, 24 were open-labelled and 40 were blinded studies. Among the blinded studies, 55% (n = 22) were double-blind and of these, 13 were participant and investigator blinded, 8 were double-blind double-dummy studies, and 1 study was both participant and outcome assessor-blinded. Of the remaining 18 blinded studies, 6 were single-blinded and of these, the participant was blinded in 4 studies, the outcome assessor was blinded in 1 and 1 was registered only as Single-blind. Among the 12 blinded studies left, 11 trials were quadra-blinded as participant, investigator, outcome assessor and data-entry operator were all blinded. There was also 1 triple-blinded study where participant, investigator and outcome assessor were blinded.

Computer-generated randomization was the most preferred randomization strategy and was employed in 46.75% (n = 36) of the randomized studies. Coin toss, lottery, toss of dice, and shuffling cards were used in 15.58% of the randomized trials, while Random Number Table accounted for 6.49% of the cases, and Stratified randomization and Permuted block randomization fixed were each preferred in 5.19% of the cases. Adaptive randomization such as minimization and others were the least preferred with 1.29% each. However, around 18.18% (n = 14) have not mentioned any technique of randomization and are marked as 'Not applicable'.

Method of Concealment

Around 28.57% (n = 22) used pre-numbered or coded identical containers as the method of concealment. This was followed by 11.68% (n = 9) with case record numbers; 10.38% (n = 8) with open list of random numbers; 7.79% (n = 6) with sequentially numbered, sealed, opaque envelopes; 3.89% (n = 3) each with on-site computer system and alternation, and 2.59% (n = 2) with centralized. Around 31.16% (24 out of 77) trials have not used any method of concealment and are marked as 'Not applicable'.

Type of Comparator

The randomized trials (n = 64) were designed as placebo-controlled in 56.25% (n = 36) studies, while 35.93% (n = 23) were active controlled, 3.13% (n = 2) were reported to have comparator as standard of care, 1 trial was reported as having both comparator and placebo, and 2 trials were registered as 'Nil'. Among these trials, 87.50% (n = 56) were registered as double-arm, 4.69% (n = 3) were triple-arm, 2 studies each were single-arm and four-arm, and 1 study was six-arm. However, all the 13 non-randomized trials were open-labelled. In all, 76.92% of the trials did not have any comparator as they were single-arm studies. Among the remaining 3 studies, 1 was healthy controlled while the other 2 were active controlled.

Type of Study

Out of the 77 registered trials, 90.9% (n = 70) were interventional trials and 9.09% (n = 7) were registered as post-marketing studies (PMS). 'Type of study' was reported as 'Ayurveda' in 55.84% (n = 43), 'Drug Ayurveda' in 19.48% (n = 15), 'Nutraceutical' in 9.09% (n = 7), and 'Drug' in 2.59% (n = 2). 'Ayurveda Nutraceutical', 'Drug Ayurveda Behavioural', 'Drug Ayurveda process of care changes', 'Drug Siddha' and 'Drug Unani' were each listed once as 'Type of study', while 5 studies were registered without mentioning the type. Around 41.55% (n = 32) studies were done as Postgraduate Thesis work, 50.64% (n = 39) were non-academic and 7.79% (n = 6) did not mention the nature of work.

Type of Diseases

The registered clinical trials involved patients in 63.63% cases (n = 49), while the remaining 36.36% (n = 28) involved healthy volunteers. Among the patient group, musculoskeletal pain and bone-related problems were the most common ailments (n = 12) with 6 cases of Knee Osteoarthritis, 1 case of Cervical spondylosis, 2 cases of Lumbar Spondylosis/ Back pain and 3 cases of Osteopenia/osteoporosis. Stress (n = 3) and anxiety (n = 1), rhinitis (n = 4) and menopausal syndrome (n = 4) each comprised 8.16% of the patient group. Hypertension, Subclinical hypothyroidism, Carcinoma, Ear problem (Hearing Loss, Tinnitus) each comprised 6.12% (n = 3) of the group. Diabetes, Brain-related disorders (Cerebral Palsy and Congenital malformation of the brain), Female infertility, and Malnourishment each accounted for 4.08% (n = 2) of the group, while 1 trial each was registered for Menstrual syndrome, Pulmonary Tuberculosis, Sleeplessness, Depression and non-healing Ulcer.

Ethics Committee (EC)

The majority of trials evaluated for this study were done under the auspices or in affiliation with institutions. Exactly 92.20% (n = 71) of the trials were registered after approval from Institutional Ethics Committees and the remaining studies, 9.09% (n = 7), were approved by independent Ethics Committees. Of the 71, 58 studies were registered with a single Ethics Committee (EC), 8 studies with 3 ECs, 3 studies with 2 ECs, and 2 studies with 4 ECs. Among those registered under independent ECs, 5 studies were registered with 2 ECs 2 studies under single ECs.

Drug, Dosage Form and Route of administration

W. somnifera was administered in isolation in 51.94% (n = 40) of the cases and as part of various combination formulations in the remaining 48.05% (n = 37). The oral route of administration was most preferred with 92.20% (n = 71) cases found, while local, anal and nasal application were used in 3.89%, 2.59% and 1.29% cases respectively. Extracts were found to have been the form of application in 25 studies with root extracts being used in all 25 while a combination of root and leaf extracts were used in 3 of the 25 studies. Both hydro-alcoholic and aqueous extracts were used.

Solid dosage forms were the most preferred for administering the *W. somnifera* intervention. Capsules were used in 29 trials (37.66%), with a dose ranging from 100 mg to 1 gm. In 18 of these 29 cases (62.06%), 100 mg capsules were consumed twice daily. The next most common dosage reported in 19.48% (n = 15) of the trials was in the form of tablets or caplets, also known as *vati*, with strength ranging between 500 mg and 2 gm twice daily. Powder was found to be the third most preferred dosage form used in 11.68% (n = 9) of the cases analysed with dosage ranging between 2-3 gm. The semisolid dosage form of *Awaleha*, a jam-like preparation, was used in 7.79% (n = 6) cases with dosage of 10 - 25 gm daily.

W. somnifera extracts were also used as instillations and topical applications. The medicated butter known as *Ghrit* was applied in 5-10 ml or 10 gm dosage once or twice daily. The oil preparation popularly called *Tail* was used as a local application, for nasal instillation and as a medicated enema known as *basti*. The self-fermented liquid dosage form *arishta* was given in dosage of 10 ml to 25 ml twice or thrice daily. The medicated milk preparation called *Kshir paka* was applied in a dosage of 100 ml once or twice daily while single granules were taken in dosage of 0.5 mg/Kg/day and in formulation as 200 mg/Kg/day. A 40 ml dosage of the decoction *Kwath*, the medicated milk preparation enema *Kshir Basti,* and the Paste *Kalka* were also used for local application.

The duration of therapy ranged from 2 weeks to a maximum of 24 weeks. Fifteen studies applied therapy for a duration between 2 to 4 weeks, 31 studies for between 6 to 8 weeks, 20 studies for 12 weeks, and 10 studies for between

Table 2. Published Clinical Research on Effects of *Withania somnifera* (Ashwagandha) on Arthritis - Therapeutic Area, Study Design, Sample & Study centre Type and Approval

S/N	Study	Therapeutic area	Study Design	Sample (Participants)					Study centre			Type of Sponsor	Approval	
				Type	Size	Age Min	Age Max	Gender	No.	Location	Type		Ethics Committee	Registration
1	Kulkarni RR et.al., 1991[16]	Osteoarthritis	Interventional; Prospective; Double-blind; Randomized	Patient	42	45	51	Both	1	Pune	Govt	Govt	IEC	NM
2	Bikshapathi T and Kumari K., 1999[17]	Rheumatoid arthritis	Interventional; Prospective; Single blind; Non-randomized	Patient	77	12	60	Both	1	Jammu	Govt	Govt	NM	NM
3	Chopra A et.al., 2004[18]	Knee Osteoarthritis	Interventional; Prospective; Double-blind; Randomized	Patient	90	35	75	Both	1	Pune	Govt	Govt	NM	NM
4	Kulkarni MP. et.al., 2011[19]	Knee Osteoarthritis	Interventional; Prospective; Double-blind; Randomized	Patient	36	20	65	Both	2	Mumbai - 2	Pvt	Pvt	Ind EC	CTRI
5	Chopra A et. al., 2011[20]	Knee Osteoarthritis	Interventional; Prospective; Double-blind; Randomized	Patient	245	40	70	Both	4	Pune, Hyderabad, Mumbai - 2	Govt - 2 Pvt -2	Govt	IEC	NM
6	Chopra A et.al., 2012[21]	Knee Osteoarthritis	Interventional; Prospective; Double-blind; Randomized	Patient	92	40	70	Both	2	Pune & Hyderabad	Govt - 1 Pvt -1	Govt	IEC	NM
7	Usharani P et.al., 2013[22]	Pain Threshold	Interventional; Prospective; Double-blind; Randomized	Healthy	12	18	40	Male	1	Hyderabad	Govt	Govt	IEC	NM
8	Kumar G et.al., 2015[23]	Rheumatoid Arthritis	Interventional; Prospective; Open Labeled; Non-randomized	Patient	90	18	60	Both	1	Delhi	Govt	Govt	IEC	CTRI
9	Ramakanth GS. et.al., 2016[24]	Knee Joint Pain	Interventional; Prospective; Double-blind; Randomized	Patient	60	40	70	Both	1	Hyderabad	Govt	Govt	IEC	CTRI
10	Srivastava S. et.al., 2019[25]	Knee Osteoarthritis	Interventional; Prospective; Double-blind; Randomized	Patient	72	40	65	Both	1	Mumbai	Pvt	Pvt	Ind EC	US National Library of Medicine
Case Studies														
1	Mahanta V et.al., 2013[26]	Tennis elbow	Interventional; Prospective; Case study; Open label	Patient	1	38	38	Female	1	Jamnagar	Govt	Govt	NM	NM
2	Singh SK & Rajoria K., 2017[27]	Cervical spondylotic myelopathy	Interventional; Prospective; Case study; Open label	Patient	1	62	62	Male	1	Jaipur	Govt	Govt	NM	NM

Abbreviations: Govt, Government; Pvt, Private; IEC, Institutional Ethics Committee; Ind EC, Independent Ethics Committee; CTRI, Clinical Trial Registry of India; NM, Not Mentioned.

14 to 24 weeks. One study reported having treatment for more than 25 weeks. The most common duration of therapy, however, was 8 weeks for 28 studies (36.36%), followed by 12 weeks for 20 studies (25.97%), and 24 weeks for 8 studies (10.38%).

Type of Sample

Overall, the sample size varied from 12 to 180. Around 28 studies reported sample sizes ranging from 12 to 50, 37 studies had between 40 and 100, 6 had a sample size of 100, and 15 were found to have a sample size of 180. The minimum age range across the clinical trials was from 2 to 65 years. The majority of studies, 67.53% (n = 52), reported a minimum age between 18 and 35 years, and 16.88% (n = 13) reported a minimum above 40 years, whereas 3 studies had minimum ages between 2-5 years, and 9 studies between 8 to 16 years. The maximum age range of participants was from 10 to 99 years. For the majority of studies, 51.94% (n = 40), the maximum age was 60 years and above. In 42.85% (n = 33), the maximum age was between 30 to 55 years and the remaining 4 studies had a range of 12 to 16 years. Participants of both genders received the *W. somnifera* intervention in around 79.22% (n = 61) cases, while 14.28% (n = 11) involved exclusively female participants and 6.49% (n = 5), exclusively male.

Published Clinical Evidences of the Anti-Arthritic Activity of *W. somnifera*

A total of 12 published studies narrating interventional prospective trials were retrieved following a search using the keywords '*W. somnifera*' and 'Arthritis' or 'Pain'. The evidence had a scattered picture from 1991 up till 2019 with two publications each for the years 2011 and 2013. Among them, 10 were controlled clinical trials and 2 were case studies. Details of the therapeutic area, characteristics of the sample, study design, study centres, and approvals are described in Table 2. Details regarding the treatment arm, comparator, duration of therapy, visits intervals, dosage, and brand names along with the outcome measures and inference of the study are mentioned in Table 3.

DISCUSSION

This study found that *W. somnifera* has been clinically tested on diverse therapeutic areas such as degenerative arthritis, especially osteoarthritis of the knees; stress and stress-related disorders; respiratory system ailments; gynaecological disorders such as menopause and menstrual disorders; autoimmune disorders, especially thyroiditis and type 1 diabetes; and others. A good number of trials are also being conducted on the healthy population to understand the effects of *W. somnifera* on strength, stamina, endurance, performance, quality of life, and sexual wellness, in order to

Table 3. Published Clinical Research on Effects of Ashwagandha on Arthritis - Treatment, Dosage, Outcome and Inference

S.No.	Study	Treatment				*Withania somnifera*				Outcome measured	Inference
		Arm	Comparator	Duration (Weeks)	Study Visits	Type	Form	Dose/day	Brand		
1	Kulkarni RR et.al., 1991[16]	2	Placebo	12	Every 1 week	Combination, Cross-over	Capsule	6 capsules	Articulin-F (Eisen Pharmaceutical)	Severity of pain, Morning stiffness, Ritchie articular index, Joint and Disability score	Significant drop in severity of pain ($P < .001$) and disability score ($P < .05$) in Test group with no significant change in radiological assessment in both the groups
2	Bikshapathi T and Kumari K., 1999[17]	1	Nil	6	Every 2 weeks	Single	Powder	9 gm	N/A	Morning stiffness, Pain, Tenderness and Swelling. Symptoms of anorexia, loss of appetite, constipation, and functional abilities of grip power, pressing power, writing time and walking time	Pain, swelling and tenderness started improving along with functional abilities, morning stiffness and digestive impairment after two weeks of treatment. Results were better in mild to moderately severe disease and chronicity of disease less than 1 year and 1 to 2 years duration.
3	Chopra A et.al., 2004[18]	2	Placebo	32	0, 2, 4, 8 and 4 weekly thereafter till week 32	Combination, Parallel group	Capsule	4 capsules	RA-11 (Artex Mendar)	Pain VAS and modified WOMAC	The mean reduction in pain VAS ($P < .05$) and improvement in the WOMAC scores ($P < .01$) at week 16 and week 32 in the active group was significant.
4	Kulkarni MP. et.al., 2011[19]	2	Placebo	12	Every 3 weeks; follow-up 6 weeks	Combination, Parallel group	Capsule	4 capsules	Lanconone (Enovate Biolife)	WOMAC, Pain and stiffness on VAS, range of motion—goniometry, timed up and go, unilateral anterior reach (UAR) and medial step down	Significant reduction of WOMAC scores ($P < .05$) for pain, stiffness, and physical function, and VAS scores for pain and stiffness ($P < .01$) in test group compared to placebo. The effect persisted over a follow-up period of 4 and 6 weeks
5	Chopra A et. al., 2011[20]	7	Placebo and active	16	2,4, then every 4 weeks	Combination, Parallel group	Capsule	2400 mg in combination	N/A	Pain VAS, WOMAC	No significant differences for pain (weight bearing) and WOMAC questionnaire (knee function). Placebo response was high
6	Chopra A et.al., 2012[21]	4	Active	6	1,4 and 6	Combination, Parallel group	Capsule	I. 5400 mg in combination II. 9600 mg in combination	N/A	Pain VAS, WOMAC	Improvement was seen in pain VAS and WOMAC pain score. Urinary C-TAX (cartilage collagen breakdown product) assay, however, was maximum (NS) in comparative group. Lower dose group I showed numerically superior improvement compared with higher dose group II.
7	Usharani P et.al., 2013[22]	1	Placebo	3 hrs	Wash out of 2 weeks followed by cross over	Single, Cross-over	Capsule	1000 mg	Sensoril (Natreon, Inc.)	Mean Pain Threshold Time	Mean Pain Threshold Time increased from 43.99 ± 6.79 to 49.89 ± 7.07 sec ($P < .05$). No significant change observed with placebo.
8	Kumar G et.al., 2015[23]	1	Active	3	Every 2 weeks	Single, Cross-over	Powder	10 g	Ashwagandha powder (Dabur)	American College of Rheumatology (ACR) 20 response. ACR50, ACR70 responses, disease activity score (DAS), 28 score and ACR parameters. Safety assessments LFT, KFT and urine mercury level	Decrease of RA factor, significant change in tender and swollen joint counts, global assessment score, pain assessment score, patient self-assessed disability index score and ESR level. However, increased urinary mercury levels was observed after treatment.
9	Ramakanth GS. et.al., 2016[24]	3	Placebo	12	Every 4 weeks	Single, Parallel group	Capsule	250 - 500 mg	N/A	Modified WOMAC, Knee Swelling Index (KSI), Visual Analogue Scale (VAS)	Significant reductions in mWOMAC [($P < .001$ in 500 mg & ($P < .05$) in 250 mg], KSI and VAS scores for pain, stiffness and disability [($P < .001$ in 500 mg & ($P < .01$) in 250 mg] compared to baseline and placebo
10	Srivastava S. et.al., 2019[25]	2	Placebo	8	Every 4 weeks	Combination, Parallel group	Capsule	1000 mg	Lanconone (Enovate Biolife)	WOMAC pain, stiffness, and physical function, EQ-5D-5L questionnaire, Systemic inflammatory marker (HS-CRP) and self-assessment of treatment satisfaction	Reduction in joint pain severity score ($P < .001$) compared to placebo. Improvement in stiffness and physical function on WOMAC resulting in significant improvement in the quality-of-life standards and higher treatment satisfaction ($P < .001$)
Case Study											
1	Mahanta V et.al., 2013[26]	1	Nil	3	Indoor	Combination	Powder	8 gm	N/A	Pain, stiffness, restricted movements	Considerable relief in pain and movement of the elbow joint
2	Singh SK & Rajoria K., 2017[27]	1	Nil	8	Indoor	Combination	Powder	500 mg	Aghat	Symptoms of CSM and Chile's modified Japanese Orthopaedic Association (mJOA) score for cervical spondylotic myelopathy	Symptoms showed substantial improvement

corroborate the *Rasayana* (rejuvenator) effects attributed to the herb in Ayurveda practice.[1,8]

It was found that while registering clinical trials in Ayurveda was not very common in the early years covered in this study, the number of registered trials increased in the later years.[28,29]

It is noted that 20 trials were found to have been registered in 2019, the highest among the range of years investigated, while 8 studies had already been registered by March 2020. This finding is consistent with that of an earlier study which was interventional, single-centred, randomized and blinded in design.[28]

The double-blind method with both participant and investigator blinded was the most preferred design. For the single-blind studies, the participant-blinded design was preferred. Computer-generated randomization method and Pre-numbered or Coded Identical Container were the most used methods of concealment. However, many studies did not use any method and reported method of concealment for the trial as 'Not applicable'. This occurrence can be minimized through structured planning of trials prior to initiation.

Two-arm studies were most common where a placebo was used as the comparator, and there was a correlation between these studies and the preferred use of solid dosage forms such as tablets, capsules, powders, etc. It was also found that studies involving semisolid dosage forms, such as jelly (*avaleha*), medicated butter (*Ghrit*), medicated oils (*Tailam*), and self-fermented liquid (*Arishta*), were often open-blinded arguably as a result of the difficulty in preparing suitable comparators.[30]

Due to factors such as access to infrastructure, manpower, and patient pool, along with the reputation of Government, most trials were planned and organised in establishments owned or run by the Government. Moreover, following the directives of the Drugs Controller General of India (DCGI) on registration with Ethics Committees,[31] only Institutional Ethics Committees can approve and monitor all the phases of a Clinical trial, further giving government institutions an edge. This is consistent with findings of this study where 92% of the trials investigated were conducted in the Government sector.

The state-wise distribution of the clinical studies was found to be in line with the findings from other analyses of Ayurvedic clinical trials where Gujarat, Maharashtra, and Karnataka were found to have the highest number of sites.[29] This indicates there may be need to enhance awareness among scholars as well as sponsors and to encourage multi-site trials with distribution in all the four zones of the country.

As a result of the notification from the Ministry of AYUSH in 2012 on the mandatory registration of trials, the majority of clinical trials analysed, 64.93% (n = 50), were reported as registered and a predominant number of these, 33.76% (n = 26), were of Phase 2. However, a considerable number of trials, specifically 16.88% (n = 13), were unclear about their phases, suggesting inadequate design planning. A significant number of trials were also found to have been registered by academic institutions which suggests there is a definite push from educational institutes to conduct structured clinical trials and bring them to the public domain. The registration of trials as Ayurveda as well as drug or nutraceuticals shows the increase in popularity of *W. somnifera* in other parts of the pharmaceutical or nutraceutical sectors. However, there is a need to create certain structured question sets within the CTRI database to capture similarities in research design and composition as there was some lack of clarity particularly in understanding the part and form of the herb used in many trials.

The oral route of administration was preferred the most and commonest duration of therapy was 8 weeks followed by 12 weeks, which is considered easy to implement in clinical practice. However, duration of therapy extended to 24 weeks or more depending on the ailment. The dosage also varied depending on the form of administration. This study shows capsules or 2-3 gm powder in twice-daily dosage and 500-1000 mg tablets with Ashwagandha can be given. The study also suggests *W. somnifera* can be given to both genders across all the age groups from 2 years onwards, corroborating evidence from other clinical studies.[32] However, considering that the average sample size was often below 100, there is need for large population trials.

Consistent with the findings from the registered trials investigated, published studies also involved mostly randomized, double-blind, interventional, prospective studies. In addition, studies were conducted predominantly at single-centre sites set-up by Government with the majority of approvals from the Institutional Ethics Committee. These were mostly Government-sponsored studies whose sites were located in Mumbai, Pune, or Hyderabad. They documented the use of *W. somnifera* in combination with other herbs where parallel design with placebo as a comparator was used. The Capsule dosage form was most preferred, followed by powder.

Evidence suggests the potential role of *W. somnifera* in symptomatic management of arthritis, particularly osteoarthritis. The major tools used to measure progress following treatment were WOMAC scores for joint pain, stiffness, and physical functions, along with Pain VAS. It was found that therapy could be applied for 12 weeks with measurable results. In the management of rheumatoid arthritis, *W. somnifera* when used as a powder in doses of 9 -10 gm/day for 3 to 6 weeks, has been shown to relieve symptoms of inflammatory joint disease. Alongside tender and swollen joint counts, constitutional symptoms were also taken into consideration while evaluating the cases. On average, *W. somnifera* was found to increase the pain threshold level of participants, thereby justifying its use as a pain reliever. Improvement in tennis elbow[26] and neck stiffness[27] were noted when *W. somnifera* was given as part of a combinatorial therapy.

The risk of bias assessment for published clinical studies[33,34] is detailed in Table 4. In general, risk of bias was deemed to be low in view of the various aspects of methodology such randomization, blinding, allocation concealment,[18-21,24,25]

Table 4. Assessment of Risk of Bias for published clinical studies on *Withania somnifera* based on the Cochrane Collaboration tool[33]

S.No	Study	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other bias
1	Kulkarni RR et.al., 1991[16]	Unclear	High	Unclear	Low	Low	Low
2	Bikshapathi T and Kumari K., 1999[17]	High	High	Unclear	Low	Low	Low
3	Chopra A et.al., 2004[18]	Low	Low	Low	Low	Low	Low
4	Kulkarni MP. et.al., 2011[19]	Low	Low	Low	High	Low	Low
5	Chopra A et. al., 2011[20]	Low	Low	Low	Unclear	Low	Low
6	Chopra A et.al., 2012[21]	Low	Low	Low	Low	Low	Low
7	Usharani P et.al., 2013[22]	High	High	Unclear	High	Low	Unclear
8	Kumar G et.al., 2015[23]	High	High	High	High	Low	Low
9	Ramakanth GS. et.al., 2016[24]	Low	Low	Low	Low	Low	Low
10	Srivastava S. et.al., 2019[25]	Low	Low	Low	Low	Low	Low

sample size calculation and justification.[18,20,21,24] Outcome parameters were well-substantiated with data in the results section.[16,17,19,22,24,25] Patients' adherence to protocols throughout the study also indicates that the trials and follow-ups were conducted properly,[16,17,24] and the documentation of the adverse events[16,18,20,21,25] and the reporting of response percentages[17] support this assessment.

CONCLUSION

Evidence shows *W. somnifera* can be used in various dosage forms and durations either in single or combined formulation for the management of a variety of diseases. A dose of 6 gm powder or extracts in tablets, or 500-1000 mg capsules applied for a duration of 8 – 12 weeks is recommended as part of therapy for arthritis, especially in degenerative cases. In addition, while *W. somnifera* (Ashwagandha) is being studied clinically through structured protocol-based research, there is need for large population studies with sample sizes well above 100. Multi-site trials with distribution in all the four zones of the country should also be encouraged.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

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