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AN ANALYSIS OF CLINICAL TRIALS ON *WITHANIA SOMNIFERA* (ASGAND) REGISTERED IN THE CLINICAL TRIAL REGISTRY OF INDIA (CTRI)

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ABSTRACT *Withania somnifera* is one of the most studied herbs used in the traditional system of medicine in India. Despite the fact that many pharmacological studies have been conducted on *Withania somnifera* worldwide, there is still a lot to meet the level of evidencebased medicine. Study design is an important aspect to generate evidence. In the present study, an attempt has been made to gather methodological quality and characteristicsof the clinical studiesregistered in Clinical Trial Registry of India (CTRI) having *Withania somnifera* as an interventional drug. CTRI is an open registry of all the studies related to the field of clinical research in India. Only a few clinical trialsin a limited number of problems/diseases have beenfound registered in CTRI.Extensive studiesshould becarried outto validatethe therapeutic efficacy of *Withania somnifera* against various diseases.

KEYWORDS : *Withania somnifera*; Asgand; CTRI; Traditional; Randomization

INTRODUCTION

Withania somnifera is one of India's most studied medicinal plants widely used in the Ayurveda and Unani system of Medicine. It is known as *Ashwagandha* in Ayurveda and *Asgand* in the Unani system of medicine.Its action and therapeutic propertiesare well described in the literature(1). The major chemical constituents responsible for multiple medicinal applications identified in the Withania somnifera arewithanolides(2). To date, more than 125 withanolides occurring both in free form and glycosides are well known(3).Despite the fact that many pharmacological studies have been conducted on plant extract and chemical constituents of Withania *somnifera*, there is a lack of scientific evidence to achieve evidence based medicine.

Evidence-based medicine can be achieved by well designed study integrated with clinical expertise, and patient values(4,5). Clinical trials/designs are an important aspect of achieving evidence based medicine(6).Although clinical trials of the *Withania somnifera* have been undertaken but can still be explored and utilizedto meet the level of evidence based medicine. The present study has been conducted to identify the scope of evidence basedmedicine in *Withania somnifera* and obtain a holistic view of the methodological characteristics of the studies available in CTRI.

MATERIALAND METHODS

The study was conducted on clinical trialsthat were registered in CTRI (www.ctri.nic.in)uptomid-August2021. All filters with regard to phase, type, recruitment status and place of trial etc.were left blank. The search was made with the keyword "*Withania somnifera*", a total of 37trials were found registered Search was also made with the keyword "*Ashwagandha*" and "*Asgandh*", a total of 109 and 04trials respectively were found registered.After elimination of duplicates and the fact that *Withania somnifera* has been used as a single drug in the treatment, total 52 relevanttrials were selected for the study. The following information was collected for each of the obtained clinical trials: number of centres (single/multicenter), type of primary sponsor (government/private/combined), study design (randomized/ single/ double-blinded), type of participants (healthy/patients), type of health condition, phase of clinical trial (Phase 1/2/3/4), and method of randomization.

RESULTS

Number Of Clinical Trials

Total 52clinical trials were selected for the study registered in CTRI for *Withania somnifera* as mode of treatment. About 84.60 % studies were single centricand only 15.4 %were foundmulti-centric. The registered studies primarily sponsored by the Government research centres,and medical colleges/universities were 34.6 % and pharmaceutical companies, neutraceuticals and private medical collegeswere 65.4 %.

Characteristics of Registered Clinical Trials

Considering the study design,34 (65.4%) were double blinded, 2 (3.8%) were single blinded and 10(19.3%) was open label. Sixtrials (11.5%) did not describe blinding technique. Most of the studies demonstrated that the *Withania somnifera* was given for prophylactic treatment or to improve the quality of life. The details of diseases or problems on which the action of *Withania somnifera* was studied is given in table-1, An Almost equal number of trials was found in phase II, III, IV and Post Marketing Surveillance phase. Eight (15.3 %) trials belonged to Phase II, 07trials belonged to PhaseIII (13.4 %) while 06 trials (11.5 %) belonged to Phase IV. On the other hand, 06 (11.5 %) trials were registered in Post Marketing Surveillance phase. Fifteen trials (28.8%) did not mention the phase. Only one trial was registered with phase I. The exact phase of the trials was unclear in9(17.3 %)trials.

Table- 1: Percentage Distribution Of Diseases/Problems/Topics

S. No	Problem studied/disease	No. of studies (Total-52)	Percentage distribution (%)
1.	Stress, anxiety	12	23.1
2.	Muscle Strength/ Health Promotion	06	11.5
3.	Menstrual problem and sexual wellness	05	9.6
4.	Covid 19	06	11.5
5	Cardio-respiratory endurance	04	7.6
6.	Cognition impairment	02	3.8
7.	Hypothyroidism related	02	3.8
8.	Pulmonary tuberculosis	01	1.9
9.	Insomnia	02	3.8
10.	Non-restorative sleep	01	1.9
11.	Cancer	01	1.9
12	Digestive system	01	1.9
13	Immuno-modulation	01	1.9
14	Non healing Ulcer	01	1.9
15	Cerebral Palsy	01	1.9
16	Life style disorders	02	3.8
17	Bioequivalence	01	1.9
18	Metabolic disorders	01	1.9
19	Rheumatoid arthritis	01	1.9
20	Osteoarthritis	01	1.9

Methodological Quality Of Registered Clinical Trials

A total of 90.4 %(47/52) trialswere registered using the randomization

designwhile 9.6 % (5/52) were non-randomized trials. Among randomization studies, the method of randomization sequence generation is given in table-2.

Table- 2: Percentage Distribution Of Method Of Randomization

S. No	Randomization Sequence	No. of studies (total-47)	Percentage distribution (%)
1.	Computer generated randomization	30	63.8
2.	Stratified block randomization	05	10.6
3.	Random Number Table	03	6.3
4.	Permuted block randomization	06	12.7
5.	Coin toss, lottery etc	02	4.2
6.	Not mentioned or other	01	2.1

DISCUSSION

The purpose of this manuscriptis to collect and assess thedata from human clinical trials registered in CTRI havingWithania somnifera as an interventional drug. A well designed and executed clinical trial is necessary to deliver safe and effective therapies and this can only be possible by understanding the key concepts involved in the clinical trials. It has been found in our study that most of the trials were randomized (90.3%), double blinded (65.4 %) and single centric (84.6 %). The preferred method used for randomization is computer generated randomizationfor the random assignment of participants to treatment groups in clinical trials. Most of the investigators choose randomized controlled trials in their studies as it effectively removes selection bias for the interventions. Information bias of the outcome, co-interventionsetc.are the limitations of randomized controlled trials(7). It is very important to select a method that will produce interpretable and valid results for the study(8).The phases of a clinical trial are important that deal with testing of safety and maximum tolerated dose of a drug, human pharmacokinetics and pharmacodynamics(7). In the current study,28.8 % of trials did not describe the phase whereas 17.3 % of trials were unclear whether they belonged to phase I, II or III. In the Post Marketing Surveillance (PMS) phase, 11.5 % of trials were found to be registered. PMSstudy isto verify the safety, tolerability and effectiveness of a marketed drug in a particular populationper the locally approved label in Phase IV of drug development.Before launch of any drug, the regulatory authorities have evaluated a huge amount of data from animal and human trial studies which demonstrated that the drug is safe, powerful, effectual and competent(9). It hasbeen observed that a maximum 23.1 % of studies were registered on stress, anxiety and general wellness followed by muscle strength/health promotion and menstrual diseases registered in CTRI. The medicinal properties of *Withania somnifera were* also well described in the Unani and Ayurvedasystems of medicine and in both systems,it is considered the best adaptogenic, rejuvenator and general health tonic(10,11).In Unani Literature, it has been described as useful in various diseases such as polyarthritis (Waja-ul-Mafasil), rheumatoid arthritis (Hudar), lumbago (Wajaul-Qutn), painful swellings (Tawwarum-e-Alami), spermatorrhoea (Jaryan-e-Mani), asthma (Zeeq-un-Nafas), leucoderma (Bars), general debility (Zof-e-Aam), sexual debility (Zof-e-Bah)(12,13). Similarly inAyurveda, it has been utilized for centuries as a "Rasayana" and an adaptogen(14).

It has been traditionally used to promote "youthful vigour" by enhancing muscle strength, endurance, and overall health. Several studies showed strong evidencethat*Withania somnifera* a robust antidepressant, anti-stress, moderate mood behaviours and modulates physical and mental health, whichprovidesdefence against disease and adverse environmental factors and to halt the ageing process(15).Surprisingly, it has been noticed that only one study has been found registered in CTRI to study the role of *Withania somnifera* for immune-modulation studies. There are lots of animal and pre-clinical studies demonstrating the positive effect of *Withania somnifera* stimulating cell-mediated immunity and it could be a potential therapeutic candidate in several immunosuppressed clinical trials(16).Muralikrishnan et al 2010, showed that the administration of 400 mg/kg body weight of *Withania somnifera* extract once a week for four weeks orally in Azoxymethane induced colon cancer animals leads to the alteration in the levels of leucocytes, lymphocytes, neutrophils, immune complexes and immunoglobulins IgA, IgG and IgM. These results suggested that the immunomodulatory effects of *Withania somnifera* could be useful in the treatment of colon cancer(17). in vitro study Lung adenocarcinoma cells were given a dose of Withania somnifera (L.) Dunal extract, and the generation of reactive oxygen species (ROS), a marker of the apoptotic effects, was evaluated. Additionally, the cell lysates were used for immunofluorescence and immunoblotting to examine how the extract affected the expression of CTLA 4, HIF-1, TNF, and PECAM-1. Both immune cells showed a significantly increased phagocytic and pinocytotic impact at increasing treatment concentrations. The W. somnifera (L.) Dunal treatment elevated the formation of ROS and decreased the expression of CTLA-4, HIF-1, TNF-, and PECAM-1 in lung cancer cells. This study demonstrated that the ethanol extract of W. somnifera (L.) Dunal has an immunomodulatory impact, enhancing the cell death of lung cancer cells through ROS(18).In another studyHabb-e-Asgandh, a formulation used in the Unani System of medicine, is used to treat conditions including arthritis, however, there are no current studies on how it might be used to treat chronic myeloid leukaemia. Therefore, using the Chronic Myeloid Leukemia cell line K562, the anti-leukemic effectiveness of Habb-e-Asgandh was evaluated either single or combination with the common chemotherapeutic imatinib. This innovative research proved that Habb-e-Asgandh has in vitro anti-leukemic potential. This formulation increases imatinib more effectively, even at low concentrations, suggesting that Habb-e-Asgandh could be used as a novel adjuvant treatment in the future to treat Chronic Myeloid Leukemia more effectively(19). In another study,the total WBC count, bone marrow cellularity and α-esterase were increased after administration of five doses ofWithania root extract (20 mg/dose/animal; i.p.) in Babl/c mice(20).A study found the effect of ethanol extract of Withania somnifera root standardized for one of its components (withaferin A) on fatty acid synthesis using LNCaP and 22Rv1 human prostate cancer cells. Key fatty acid metabolism enzymes, such as ATP citrate lyase, acetyl-CoA carboxylase 1, fatty acid synthase, and carnitine palmitoyltransferase 1A, showed a statistically significant decrease in protein levels in extract of Withania somnifera root treated cells compared to solvent control, according to Western blotting and confocal microscopy. The mRNA levels of ATP citrate lyase, acetyl-CoA carboxylase 1, fatty acid synthase, and carnitine palmitoyltransferase 1Awere also lower in extract of Withania somnifera root treated cells in comparison with control. According to these findings, fatty acid production in human prostate cancer cells is an exception that the extract of Withania somnifera root inhibits(21).A study by Sara Moghimi illustrates how a high dose of W. somnifera increased the lifespan of a Drosophila paralytic mutant while remaining safe for fecundity and fertility. As anticipated, CBZ reduced the lifespan of the Drosophila paralytic mutant at a higher dose (40 g/ml), and it also had an impact on the fecundity and fertility of the flies. Studies prove that W. somnifera was superior to CBZ in controlling epileptic phenotype(22).To reduce stress and improve general human well being, Withania somnifera has been used traditionally. 24 dogs with stress and anxiety received either a placebo or 15 mg/kg of Ashwagandha root extract once daily during a 4-week, randomised, double-blind, placebo-controlled research. The Canine Behavioural Assessment and Research Questionnaire, the Canine Brief Pain Inventory scale, the Body Condition score, and the Urinary Cortisol to Creatinine Ratio were used as outcome measures. Consuming root extract of Withania somnifera for four weeks has been associated with a large decrease in the urine cortisol to creatine ratio, as well as symptoms of fear, anxiety, and interference with pain(23).

Root and leaves extracts of *Withania somnifera* showanalgesic, anti-inflammatory and chondroprotective effects.Similarly,several reports are suggesting the positive role of *Withania somnifera* in joint pain. Treatment of knee joint pain with *Withania somnifera,* in a randomized, double-blind, placebo-controlled, cross-over study patients showed a significant drop in severity of pain and disability score. In this study, sixty patients with knee joint pain were randomized and given daily twice the 250 mg and 125 mg dose of *Withania somnifera* for 12 weeks respectively and it was compared to baseline and placebo. Significant reductions were observed in knee joint pain, stiffness and disability(24).It has also been found in the study the 06 clinical trials were registered with *Withania somnifera* as an interventional drug for the prophylactic treatment for the managementof COVID-19. The recent in-silico studies showed thatthe Withaferin-A, and Withanone, the active constituents of *Withania somnifera* inhibit the activity of TMPRSS2, viral protease (3 CLpro and PLpro) and the interaction site of viral S protein with host receptor ACE-2 and thus prevents the entry of SARS-COV2 to the host cells(25).The Withania somnifera may have a potential to become a therapeutic target against the management of covid-19 disease. Hence more clinical trials should be taken up with the *Withania somnifera* in the near future. We found lots of published clinical studies conducted on *Withania somnifera* in different diseases

and all these are not included in the study as our main purpose is to access the quality methods of clinical trials registered only in CTRI. Furthermore, as per data available in CTRI it was found that 65.4 % studies were primarily sponsored by the pharmaceutical companies and private medical colleges while only 34.6% studies were funded by government research institution/councils. Government organizations should sponsor and fund to conduct clinical trials using*Withania somnifera* as a treatment drug to achieve the level of evidence based medicine.

CONCLUSION

Only a few clinical trials were carried out to evaluate the safety and efficacy of the *Withania somnifera* against in limited number of problems/diseases. The area of *Withania somnifera* should be broadened and more focus should be given to quality.Extensive well designed clinical trials with *Withania somnifera*, hence, are needed to confirm its therapeutic potential in patients with immunomodulation, anti-cancerous, rheumatologic conditions, asthma, anxiety and other infectious diseases More studies should also be needed to establish evidence based dataforits prophylactic agent for the prevention and treatment of novel corona virus disease (COVID-19).

Conflict Of Interest

Authors declare no conflict of interest

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REFERENCES

1. Gupta G, Rana A, Rana A, Rana A. Withania somnifera (Ashwagandha): A Review. Pharmacogn Rev. 2007;1(1).
2. Lopresti AL, Smith SJ, Malvi H, Kodgule R, Wane D. An investigation into the stress-relieving and pharmacological actions of an ashwagandha (Withania somnifera) extract: A randomized, double-blind, placebo-controlled study. Medicine [Internet]. 2019 Sep 1 [cited 2023 Aug 17];98(37).
3. Vyas VK, Bhandari P, Patidar R. A comprehensive review on Withania somnifera Dunal. Journal of Natural Remedies. 2011;11(1):1–13.
4. Masic I, Miokovic M, Muhamedagic B. Evidence Based Medicine - New Approaches and Challenges. Acta Informatica Medica. 2008;16(4):219.
5. Sridharan K, Sivaramakrishnan G. Clinical trials in Ayurveda: Analysis of clinical trial registry of India. J Ayurveda Integr Med. 2016 Jul 1;7(3):141–3.
6. Parveen A, Parveen B, Parveen R, Ahmad S. Challenges and guidelines for clinical trial of herbal drugs. J Pharm Bioallied Sci [Internet]. 2015 Oct 1 [cited 2023 Aug 17];7(4):329–33.
7. Umscheid CA, Margolis DJ, Grossman CE. Key Concepts of Clinical Trials: A Narrative Review. Postgrad Med. 2011 Sep 13;123(5):194–204.
8. Suresh K. An overview of randomization techniques: An unbiased assessment of outcome in clinical research. J Hum Reprod Sci. 2011;4(1):8.
9. Suvarna V. Phase IV of Drug Development. Perspect Clin Res. 2010 Apr;1(2):57–60.
10. Chaudhary SP. An Ayurvedic Review Of Ashwagandha From Samhitha And Nighantus [Internet]. Vol. 4, Prakash. World Journal of Pharmaceutical Research. 2015. Available from: https://www.researchgate.net/publication/311806429
11. Uddin Q, Samiulla L, Singh VK, Jamil SS. Phytochemical and Pharmacological Profile of Withania somnifera Dunal: A Review. J Appl Pharm Sci. 2012(01):170–5.
12. Rampuri NG. Khazain ul Advia. Vol. Vol. I. Lucknow; 1920. 230–231 p.
13. Khan M azam. Muhit-i Azam. Vol. First. New Delhi: CCRUM; 2012. 319–320 p.
14. Kulkarni SK, Dhir A. Withania somnifera: An Indian ginseng. Prog Neuropsychopharmacol Biol Psychiatry. 2008 Jul;32(5):1093–105.
15. Chandrasekhar K, Kapoor J, Anishetty S. A prospective, randomized double-blind, placebo-controlled study of safety and efficacy of a high-concentration full-spectrum extract of Ashwagandha root in reducing stress and anxiety in adults. Indian J Psychol Med. 2012 Jul;34(3):255–62.
16. Malik F, Singh J, Khajuria A, Suri KA, Satti NK, Singh S, et al. A standardized root extract of Withania somnifera and its major constituent withanolide-A elicit humoral and cell-mediated immune responses by up regulation of Th1-dominant polarization in BALB/c mice. Life Sci. 2007 Mar 27;80(16):1525–38.
17. Muralikrishnan G, Dinda AK, Shakeel F. Immunomodulatory Effects of Withania Somnifera on Azoxymethane Induced Experimental Colon Cancer in Mice.2010;39(7):688–98.
18. Sajida, Prabhu A. Withania somnifera deploys immunomodulation and exerts anticancer effects on lung adenocarcinoma cells. South African Journal of Botany. 2022 Dec 1;151:47–65.
19. Gupta N, Gurung SK, Das D, Nafees S, Sharma A. Anti-tumor efficacy of Habb-e-Asgandh as an adjuvant therapy in chronic myelogenous leukemia in vitro. J Herb Med. 2022 Sep 1;35:100584.
20. Davis L, Kuttan G. Immunomodulatory activity of Withania somnifera. J Ethnopharmacol. 2000 Jul 1;71(1–2):193–200.
21. Kim SH, Singh KB, Hahm ER, Lokeshwar BL, Singh S V. Withania somnifera root extract inhibits fatty acid synthesis in prostate cancer cells. J Tradit Complement Med. 2020 May 1;10(3):188–97.
22. Moghimi S, Harini BP. A comparative study of the efficiency of Withania somnifera and carbamazepine on lifespan, reproduction and epileptic phenotype – A study in Drosophila paralytic mutant. J Ayurveda Integr Med. 2022 Apr 1;13(2):100534.
23. Kaur J, Seshadri S, Golla KH, Sampara P. Efficacy and safety of standardized Ashwagandha (Withania somnifera) root extract on reducing stress and anxiety in domestic dogs: A randomized controlled trial. Journal of Veterinary Behavior. 2022 May 1;51:8–15.
24. Ramakanth GSH, Uday Kumar C, Kishan P V., Usharani P. A randomized, double blind placebo controlled study of efficacy and tolerability of Withaina somnifera extracts in knee joint pain. J Ayurveda Integr Med. 2016 Jul 1;7(3):151–7.
25. Kashyap VK, Dhasmana A, Yallapu MM, Chauhan SC, Jaggi M. Withania somnifera as a potential future drug molecule for COVID-19. Future Drug Discov. 2020 Oct 1;2(4):FDD50–FDD50.