

Homoeopathic pathogenetic trial of *Withania somnifera*: A multicentric, double-blind, randomised, placebo-controlled trial

Pritha Mehra^{1*}, Anil Khurana², Renu Mittal², Bhopal Singh Arya¹, Rajpal³, Raj K. Manchanda², Karuna Singh¹, Anil K. Vichitra¹, Goutam Rakshit², Jai P. Singh⁴,
Maya Padmanabhan²

¹Dr. D. P. Rastogi Central Research Institute (H), Noida, ²Central Council for Research in Homoeopathy, New Delhi, ³Homoeopathic Treatment Center, Safdurjung Hospital, New Delhi, ⁴Homoeopathic Drug Research Institute, Lucknow, Uttar Pradesh, India

Abstract

Background: Homoeopathic drug proving being the first step in finding the pathogenetic powers of a drug is an integral part of Homoeopathic system of medicine. **Objective:** To elicit the pathogenetic response of *Withania somnifera* in homoeopathic potencies on healthy human provers. **Materials and Methods:** A multicentric, randomised, double-blind, placebo-controlled trial was conducted at four centres under Central Council for Research in Homoeopathy. Proving was conducted on 63 relatively healthy provers. All the provers were given 12 doses of placebo divided into 4 doses/day for 3 days during the first phase of the trial. After randomisation, 43 provers in the intervention group were given *W. somnifera* in 6C and 30C potencies in two phases. In the placebo group, 20 provers were administered unmedicated globules. The symptoms and signs manifested during the trial were noted down by the provers, elaborated by the proving masters and the data compilation on *W. somnifera* was done at proving-cum-data processing cell. **Results:** Out of 43 provers who were on actual drug trial, only 15 provers manifested 39 symptoms. The symptoms have been manifested predominantly in 30C potency. Among the objective findings, the drug has shown its effect on kidney, ovaries and helminthic infestation. **Conclusion:** The pathogenetic response elicited during this trial expands the scope of the use of *W. somnifera* and needs to be further validated by clinical verification study.

Keywords: Double-blind, Drug proving, Homoeopathic pathogenetic trial, Homoeopathy, Pathogenetic effect, Placebo, *Withania somnifera*

INTRODUCTION

Biodiversity of natural resources has served not only for the primary human needs but also for healthcare, since time immemorial. The Indian subcontinent, with the history of one of the oldest civilisations, has diverse biodiversity in flora and fauna due to variations in geographical landscaping.^[1] Among the diverse flora, one of the widely considered medicinal plants is *Withania somnifera*, which is popularly known as *Ashwagandha*. Its uses in Ayurveda and other Indian systems of medicine are mentioned in literature since ancient times. In Ayurveda, it is classified as a rasayana (rejuvenation) and expected to promote physical and mental health, rejuvenate the body in debilitated conditions and increase longevity. Having wide range of activity, it is used to treat almost all disorders that affect the human health.^[2] In traditional system of medicine, it has been recommended for the treatment of aphrodisiac and used as liver tonic, anti-inflammatory agent, astringent and

more recently to treat bronchitis, asthma, ulcers, emaciation, marasmus, insomnia, senile dementia, etc.^[3] *Ashwagandha* is also useful in the treatment of inflammatory conditions, ulcers and scabies when applied locally. The leaves are crushed and applied to lesions, painful swellings and sore eyes. A paste made from the leaves is prescribed for syphilitic sores. The leaves are bitter and given for fever. Rajputs regard the root as useful in rheumatism and dyspepsia. In Punjab, it is useful for lumbar pain and consider aphrodisiac.^[4] In Unani system of medicine, this meticulous herb was used to treat a variety of infectious diseases as well as tremors and inflammation, especially osteoarthritis, rheumatoid arthritis and gout.^[5]

***Address for correspondence:** Dr. Pritha Mehra,
Dr. D. P. Rastogi Central Research Institute (H), A 1/1,
Sector 24, Noida, Uttar Pradesh, India.
E-mail: crrhdp@gmail.com

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This drug is also used in various central nervous system (CNS) disorders, particularly its indication in epilepsy, stress and neurodegenerative diseases such as Parkinson's and Alzheimer's disorders, tardive dyskinesia, cerebral ischaemia and even in the management of drug addiction.^[2]

A lot of research work has been done in Ayurveda and other Indian systems of medicine to understand and explore the medicinal properties and therapeutic utility of *W. somnifera*.

- Three chemotypes of *W. somnifera* have distinct immune modulation properties in the form of delayed type hypersensitivity reaction, proliferation of B- and T-cells and cellular immune response in terms of higher number of antibody-producing cells.^[6]
- A chemically standardised herbal formulation of *W. somnifera* possesses anticancer and Th1 immune upregulatory activities^[7]
- Withaferin A from leaves of *W. somnifera* in preclinical setting was found effective in preserving bone loss by both inhibition of resorption and stimulation of new bone formation before onset of osteoporosis with no uterine hyperplasia in mice^[8]
- Roots of *W. somnifera* are found effective in treating impotency, infertility, stress and the ageing process in men. *W. somnifera* not only reboots enzymatic activity of metabolic pathways and energy metabolism but also invigorates the harmonic balance of seminal plasma metabolites and reproductive hormones in infertile men^[9]
- *W. somnifera* inhibited lipid peroxidation and protein carbonyl content and improved sperm count and motility^[10]
- Administration of aqueous and methanolic extracts of *W. somnifera* successively decreased the marble burying behaviour activity in mice without affecting motor activity, i.e., it has action on obsessive-compulsive disorder (OCD)^[11]
- Immunopotential on oral feeding of standardised aqueous extract of *W. somnifera* resulted in significant increase of antibody titres to *Bordetella pertussis*^[12]
- *W. somnifera* exhibits antioxidant as well as significant antibacterial activities against Gram-negative bacteria, particularly *Salmonella typhi*^[13]
- It has been found to be potentially useful adjunct for the patients undergoing radiation and chemotherapy. It is also used as an immune stimulant in patients with low leucocyte counts in blood^[3]
- It has gamma-aminobutyric acid mimetic effect and was shown to promote formation of dendrites. Thus, it is useful in various CNS disorders^[14]
- It is used traditionally to treat many medical problems including diabetes and has demonstrated therapeutic activity in various animal models as well as in diabetic patients^[15]
- The aqueous suspensions of roots of an Indian drug *Ashwagandha* and the Korean drug Ginseng were tested comparatively for two pharmacological activities, namely,

the anti-stress activity by the 'mice swimming endurance test' and anabolic activity by noting gain in body weights and levator ani muscle in rats. A significant increase in mice swimming time was shown by Ginseng ($P < 0.001$) and *Ashwagandha* ($P < 0.01$) as compared to the control group^[16]

- Pre-treatment with this drug showed significant protection against stress-induced gastric ulcers and has antitumour effect on Chinese Hamster Ovary cell carcinoma. It was also found effective against urethane-induced lung adenoma in mice. In some cases of uterine fibroids, dermatosarcoma, long-term treatment with *W. somnifera* controlled the condition. It has anxiolytic effect and improves energy levels and mitochondrial health. It is an anti-inflammatory and antiarthritic agent and was found to be useful in clinical cases of rheumatoid and osteoarthritis^[16]
- Homoeopathic formulation of potency Q, 30 and 200 showing significant pharmacological effect in animals (Rats) and shows the Pre-clinical effects^[17]
- History and authority for *W. somnifera* is M. Bhattacharya, Homoeopathic pharmacopoeia, published in 1927 as mentioned in HPI, volume VIII.^[18] Further, no details regarding the proving of this drug has been found. There is a definite need to explore and find the pathogenetic effects of this drug in healthy human volunteers, so that further research studies can be taken up to ascertain the therapeutic utility of this drug of great value. Hence, the Council took up this study at four of its centres as per the approved protocol.

Description

As per Homoeopathic Pharmacopoeia of India-Volume VIII,^[18] the botanical name of this drug is *W. somnifera dunal*; synonyms are *Physalis somnifera* Linn, *Physalis flexuosa* Linn, it belongs to *Solanaceae* family found throughout India. Its homoeopathic preparation is from root. This drug is commonly known as Ashwagandha in Hindi and Bengali,^[19,20] Turangi-gandha in Sanskrit and Amukkura, amkulang, amukkuram-kilangu, amulang-kalung, Aswagandhi in Tamil.^[20]

It is an erect, branched, under-shrub, up to 1.5 m high, nearly all parts more or less stellate tomentose; branches flexuous, densely tomentose. Leaves: simply, 5–10 cm long, 2.5–7.0 cm broad, short petioled, sub-opposite or alternate, broadly ovate to oblong, entire, pubescent, main lateral nerves about 6 pairs, prominent; petiole 6–12 mm long. Stem: nodes prominent only on the side wherefrom petiole arises. Flowers: greenish yellow, usually about 5 together, in sub-sessile umbelliform cymes in the axils of leaves, pedicels about 6 mm long. Calyx 5, gamosepalous, campanulate, 5 mm long, the segments becoming linear, acute, with broad base after flowering, increasing up to 18 mm, becoming inflated, nearly globose and enclosing the fruit; corolla 5, gamopetalous, bell-shaped, 0.6–1.2 cm; stamens 5, epipetalous. Fruit: a berry, small,

0.6–0.8 cm in diameter, globose, two chambered, brick red when ripe enclosing within the enlarged calyx; seeds many, small, 2–2.5 mm in diameter, with smooth or pitted testa.^[18] The constituents or alkaloids of this drug are withanolides^[15] and withaferin A.^[8]

MATERIALS AND METHODS

Study design

This is a multicentric, prospective, parallel arm, randomised, double-blind, placebo-controlled study with allocation of verum: placebo: 70:30.

Study setting

The study was conducted at four centres: Dr. D. P. Rastogi Central Research Institute (CRI [H]), Noida (Uttar Pradesh), Dr. Anjali Chatterjee Regional Research Institute (RRI [H]), Kolkata (West Bengal), Homoeopathic Drug Research Institute (HDRI), Lucknow (Uttar Pradesh) and Drug Proving Unit (DPU), Bhubaneswar (Odisha).

Subjects

Volunteers – 15–20 from each centre, of both sexes, aged 18 years and above, from Homoeopathic medical colleges and also from non-homoeopathic background were considered for the study. Detailed physical, pathological and radiological examinations, i.e., pre-trial medical examination (PME), were conducted by the medical experts to ensure the health status of the volunteers after getting written informed consent from them.

Inclusion and exclusion criteria

Individuals of both sexes with age more than 18 years, certified as apparently healthy by the experts, found intelligent enough to record carefully the facts and have not taken any homoeopathic medicine in last 2 months were included in the study.

Volunteers suffering from any acute or chronic disease, colour blindness, anxiety or hysteria, having any addictions, undergoing any kind of medical treatment, undergone surgery in last 2 months, women during pregnancy/ puerperium/lactating and participated in another clinical or proving trial during the last 6 months were excluded from the study.

Sample size

According to the drug proving protocol of the Council, there should be at least 15 provers at one centre, of which 30% will act as control. For the pathogenetic drug trial of *W. somnifera*, a total of 63 volunteers were enrolled as provers.

Proving symptoms

The sign(s) and/or symptom(s) generated in provers of verum (drug) or placebo (control) group were noted down with stage, number of doses after which each of the sign(s) or symptom(s) appeared and the duration for which they persisted. The sign(s) and/or symptom(s) generated by verum group were separated from those generated by provers of control group. The sign(s) and/or symptom(s) which were produced by

provers in the placebo as well as verum group in 1st phase were not considered as proving symptoms. Further, the symptoms were classified as recent symptom, new symptom (NS), old symptom (OS), alteration in present or old symptom (AS) and unusual symptom (US). After compilation of proving data, the old symptoms were discarded and new symptoms as reported in the records were considered as proving symptoms.

Duration of study

Proving period:

- One year at HDRI, Lucknow and DPU, Bhubaneswar in 2010–2011
- One year at DDPRCRI (H), Noida and DACRRI (H), Kolkata in 2012–2013.

Ethics and consent

The Council's Ethical Committee approved the study protocol. Written informed consent was received from all the volunteers prior to enrolment in the study.

Procedure

All 63 provers were subjected to three phases of proving at each of the centres. In each phase, 12 doses (one dose = four globules of size number 30) of coded drug or placebo as per randomisation were administered, divided in 4 doses/day for 3 days (if no symptom/sign arises) and provers were asked to stop taking further doses as soon as any symptom or sign appears.

All the provers were given placebo for intra-prover response in Phase I. In Phase II and III, the verum group received the drug in 6C and 30C potency, respectively, whereas placebo group received optically identical placebo.

At each study centre, a proving master supervised the volunteers enrolled in the study. After receiving the informed consent, PME, the baseline characteristics equivalent to homoeopathic interview and the findings with respect to all the systemic examination and laboratory investigations were filled in the proforma. The provers were asked to note down daily the details of their feelings/changes in mental and/or physical level, after taking the coded drug and in the subsequent wash out period of 30 days in 'Prover's Day Book Proforma' before starting the next phases following the same dose schedule. The entries made by the provers were verified by the proving master, and each symptom was completed in respect to their location(s), sensation(s), modalities and concomitants, extension of symptoms, causation, clinicopathological findings and other treatment taken, if any, in 'Symptoms Elaboration Proforma'.

If sign(s)/symptoms(s) appeared, the sequence of the appearance of new sign(s) and/or symptoms(s), their progress and the number of doses after which such sign(s) and/or symptoms(s) appeared, with date, time of onset and duration for which they persisted was noted.

After completion of trial of all potencies, the provers underwent post trial or terminal medical examination (TME). The compilation of data recorded in 'Prover's Day Book

Proforma', 'Symptoms Elaboration Proforma', 'Pathological Report Sheets' and 'TME sheets' was done by the drug proving-cum-data processing cell and after decoding, the sign(s) and/or symptom(s) generated by the provers in verum group were separated from those generated by the provers kept on placebo.

Intervention

Verum group

W. somnifera in 6C and 30C potencies in 100 ml sealed bottles was procured from a GMP certified Homoeopathic drug manufacturer in India. Globules of number 30 were medicated with these attenuations at the CCRH headquarters office.

Placebo group

Placebo was made up of unmedicated globules (number 30) moistened with unmedicated dispensing alcohol (unsuccussed) and was therefore indistinguishable from verum.

Management of severe symptoms

A vial of medicated globules of *Camphora* 30C was sent with each quota to each centre as an 'antidote' to be prescribed in case any of the prover develops sign and/or symptom which affects his/her daily routine.

Proving data analysis

Reporting adhered to the consolidated standards of reporting trials and RedHot. The compiled data of proving symptoms and the changes in the laboratory investigations analysed following the principle of intention to treat (ITT) using Statistical Package for Social Sciences version 20 for Windows (IBM).

RESULTS

From four drug proving centres, a total of 67 volunteers were screened and 63 healthy volunteers were enrolled as provers. Of 63 provers, 43 were on verum and 20 were on placebo. Figure 1 shows the flowchart of the number of volunteers who

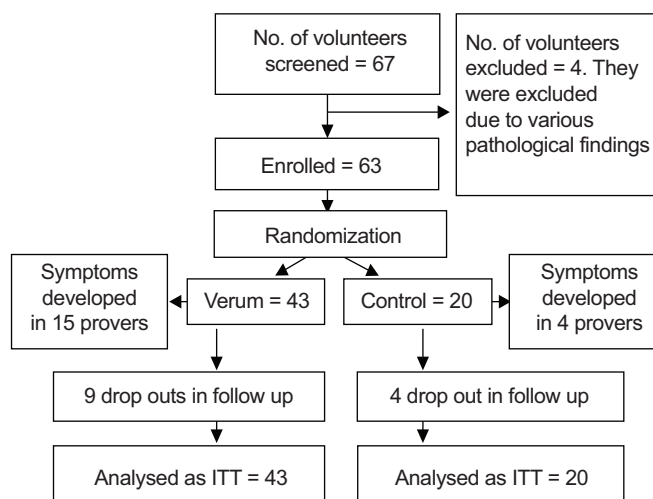


Figure 1: Flowchart of study participants

underwent screening, enrolled, randomised in two groups and dropped out during the study period. The baseline information in both the groups was comparable ($P \geq 0.05$) and well matched as shown in Table 1.

Of total 63 enrolled provers, 50 underwent the TME as 09 and 04 provers from the verum and placebo groups, respectively, were dropped out. The data analysis was done considering the ITT principle with regard to proving symptoms/pathogenetic effects and changes in objective signs, for example, body mass index (BMI), haemoglobin percentage (Hb%), total lymphocyte count (TLC), liver function test and lipid profile.

During the trial 15 out of 43 provers (37.2%) reported 39 symptoms. In the placebo group, out of 20 prover only 4 out of 20 provers (20%) produced 12 symptoms. The symptoms were generated from both the potencies, i.e., 6C and 30C.

The drug has shown the affinity towards head, eye, respiratory system gastrointestinal system, locomotor system, skin and fever. There were 6 symptoms related to head generated with 30C potency predominantly in 5 provers. Similarly, 6 symptoms related to respiratory system were generated in 4 provers in both potencies, 4 symptoms related to fever were found in 3 provers, mostly with 6C potency. In case of gastrointestinal system, 10 symptoms were produced by 8 provers, mostly in 30C potency. Rest all the symptoms were generated in separate individual provers.

Pathogenetic effects

Comparison of symptoms developed in placebo phase to that in intervention phases (inter-prover comparison) is shown in Table 2.

Table 1: Baseline information

Variable	Verum (n=43)	Placebo (n=20)	P
Age (years)	24.1±4.2	25.4±5.5	0.30 [§]
Gender			
Male	21 (48.8)	10 (50.0)	0.93 [¥]
Female	22 (51.2)	10 (50.0)	
BMI (kg/m ²)	22.7±3.4	22.1±5.6	0.62 [§]
Hb (g/dL)	12.3±1.3	12.7±1.2	0.19 [§]
TLC (number of cells/cumm)	6855.8±1239.8	7150.0±1112.4	0.369
ESR (mm after 1 h)	13.0±8.5	12.9±7.9	0.97 [§]
FBS (mg/dL)	72.9±10.3	73.4±9.6	0.89 [§]
Total cholesterol (mg/dL)	161.7±39.5	156.9±24.9	0.67 [§]
SGOT (U/L)	20.0±8.1	21.8±10.1	0.53 [§]
SGPT (U/L)	22.3±8.2	21.8±7.4	0.86 [§]
Alkaline phosphatase (U/L)	110.9±27.6	100.4±31.2	0.36 [§]

[§]Independent t-test, [¥]Chi-square test. Values are expressed in (%), Mean±SD. SD: Standard deviation; BMI: Body mass index; Hb: Haemoglobin; TLC: Total lymphocyte count; ESR: Erythrocyte sedimentation rate; FBS: Fasting blood sugar; SGOT: Serum glutamate oxaloacetate transaminase; SGPT: Serum glutamate pyruvate transaminase

Table 2: Intraprover comparison to deduce the symptoms produced by the drug administered

Section	Placebo (C)	<i>Withania somnifera</i>		Common symptoms found in placebo and verum group (being eliminated)
		6C	30C	
Mind	Cheerful mood			
Head	Aching pain in frontal region; <i>agg.</i> evening, <i>amel.</i> pressure. Pain in head appeared again the next day at 12:30 pm till 9:30 pm	Severe pricking pain in left half of head, starts around 4:30 pm; <i>agg.</i> evening, <i>amel.</i> pressure	Bursting pain in forehead at midpoint between eyebrows. Frontal headache, bursting sensation; <i>amel.</i> tight pressure. Vertigo with frontal headache and heaviness at around 9 am Vertigo with frontal headache and heaviness at around 8:30 am (prover took antidote at 9 am) Heaviness in occipital region (12:00 noon to 12:30 pm)	Affections of frontal region of head; <i>amel.</i> pressure
Eye	Lachrymation with watery discharge from left eye	Itching and redness of left eye		Affections related to left eye
Nose	Nasal discharge from left nostril Nasal obstruction and burning sensation from left nostril	Coryza; <i>agg.</i> early morning	Coryza, watery discharge with sneezing and bodyache; <i>agg.</i> night. Coryza, watery discharge with sneezing and slight lachrymation from right eye; <i>agg.</i> cold air, <i>amel.</i> covering nose	
Mouth		Burning pain (glossitis) in tongue; <i>agg.</i> eating	Apthous ulcer with redness, burning and stinging pain; <i>agg.</i> eating	
Throat		Aching pain in throat; <i>agg.</i> cold drinks, <i>amel.</i> warm drinks	Choking sensation in throat	
Stomach	Appetite increased	Increased thirst Burning pain in stomach; <i>agg.</i> empty stomach	Burning pain in epigastric region; <i>agg.</i> sweet, evening (from 3:30 pm or 4:30 pm to 6 pm), <i>amel.</i> drinking water. Next day, the symptom is accompanied with increased appetite, dizziness and drowsiness as if intoxicated	Increased appetite
Abdomen			Flatulence whole abdomen with bloating; <i>agg.</i> oily, spicy; <i>amel.</i> flatus	
Rectum	Stool, tensmus Constipation with hard stool			
Stool			Stool - loose watery, 4-5 times a day with pain in the right hypochondrium Stool with passage of bright red blood and gripping pain in umbilical region whole night; <i>agg.</i> night	
Cough		Cough without expectoration started after waking up in morning with pain in throat while swallowing. Cough; <i>agg.</i> while lying down, night. Later, cough is accompanied with sleeplessness and restlessness. On 4 th day, there is tickling in throat on coughing. On 5 th day, cough with white expectoration; <i>agg.</i> while lying down. On 6 th day, cough with greenish expectoration; <i>agg.</i> waking up, lying down. It is accompanied with pain in throat. On 8 th day, occasional cough without sputum	Cough with difficult expectoration, scanty mucous sputum; <i>agg.</i> cold air, lying down	

Contd...

Table 2: Contd...

Section	Placebo (C)	<i>Withania somnifera</i>		Common symptoms found in placebo and verum group (being eliminated)
		6C	30C	
Chest		Cough with yellow sputum, expectoration with difficult in expectorating; <i>agg.</i> evening. It is accompanied with weakness Pricking mild pain left side of chest; <i>agg.</i> whole night, <i>amel.</i> pressure		
Back		Sprain in right side of the back		
Extremities	Pain in back of left thigh, popliteal fossa and calf muscles; <i>agg.</i> morning, <i>amel.</i> constant motion, bending leg backward	Aching pain in all joints of the upper limbs more on the right side; <i>agg.</i> motion Tearing pain knee to ankle; <i>agg.</i> walking, bending, <i>amel.</i> rest	Aching pain in right shoulder and left elbow; <i>agg.</i> movement Stitching pain in lower extremities, difficulty to walk	
Fever	High grade fever with weakness, redness of face, head hot, bodyache and soreness associated with diminished appetite, decreased thirst and increased respiratory rate (three doses of antidote was given on 9 th day)	Fever with shivering, aversion covering, with no thirst Fever with throbbing headache whole head Fever with shivering; <i>agg.</i> night, cold drinks, <i>amel.</i> warm	Fever with thirstlessness; <i>amel.</i> warm application	Fever without thirst
Skin		Itching reddish colour measles like eruption in medial aspect of right ankle joint; <i>amel.</i> cold water application		
Generalities	Sore feeling in whole body; <i>amel.</i> rest, at night. It was accompanied with drowsiness			

The symptoms produced in this trial are new symptoms. The qualitative analysis for the proving symptoms generated during this trial, 'coryza, watery nasal discharge with sneezing' occurred twice in the same prover over a gap of few days, while the symptom 'Cough with difficult expectoration' occurred in same prover in both the potencies, i.e., 6C and 30C. Another symptom 'Fever with shivering' occurred in two provers at the same centre in 6C potency. Symptom related to upper extremity developed in the same prover in both potencies. Thus, these can be considered as important pathogenetic effects of this drug.

Comparison of symptoms developed by provers on control (for all phases) with provers on actual drug trial (Interprover comparison) is as follows:

- In mind, rectum and generalities section symptoms were produced in the control group but no symptoms were produced in verum group
- Symptom related to frontal region of head were produced in both groups but with different characteristic, i.e., aching pain in placebo group and pricking, bursting type of pain in verum group
- The symptom related to eye has commonality that the left eye has been affected in both the groups
- Stomach symptom: 'Increased appetite' is overlapping, i.e., present in placebo group and the same symptom was produced in 30C potency of verum group

- Symptom related to fever without thirst is also overlapping in both groups, but other characteristics, concomitants or associated complaints were different.

One of the provers of verum group developed intense headache and vertigo for 2 days, and required an antidote immediately on the very same day. Another prover from placebo group, developed high-grade fever that continued for 9 days and was prescribed three doses of the antidote. There was complete recovery thereafter in both cases. The duration of other symptoms ranged from 15 min (choking sensation in throat) to 8 days (symptoms related to cough and skin of face). There was spontaneous and complete remission of all these pathogenetic effects.

The characteristics of both groups at TME were again checked for any change but were found to be well matched [Table 3].

Statistical analysis was performed using independent *t*-test, related to laboratory investigational values of provers in the verum group who produced symptoms as compared with those who did not develop any symptom/sign [Table 4]. The values in the table reflect that there is statistically significant difference in the erythrocyte sedimentation rate (ESR) values and rest of the parameters are well

matched. There is increase in the BMI, Hb, TLC and fasting blood sugar (FBS) and decrease in ESR, total Cholesterol and serum glutamate pyruvate transaminase (SGPT) values in the provers who produced symptoms. Among the provers who did not produce any symptom, there is no change in BMI, decrease in Hb, ESR, FBS, total Cholesterol and SGPT and there is increase in serum glutamate oxaloacetate transaminase values.

Apart from these changes, other parameters were also looked into and the objective findings are shown in Table 5.

DISCUSSION

Proving of *W. somnifera* was conducted twice, first in 2010–2011 and then in the year 2012-13 following the same protocol. The number of symptoms generated during the second proving was comparatively more, which could be due to the sensitivity of the provers, environmental factors, better sensitisation of the provers to HPT, etc.

On searching the homoeopathic literature, neither the drug proving study nor any Materia Medica reflecting the complete symptomatology has been found. Thus, this pathogenetic trial is the first systematic scientific study in homoeopathic system of medicine, for this drug substance to understand its pathogenetic effects.

Symptoms generated in both groups were analysed and the organ affinity has been found for head, eye, respiratory system gastrointestinal system, locomotor system, skin and fever. 30C potency has produced more symptoms as compared to 6C potency. On qualitative analysis, important symptoms which can be considered as the effect of the drug mainly pertaining to upper respiratory tract infection and fever usually occurs due to inflammation were found. per the classification mentioned in the protocol, all the symptoms are considered as new symptoms and the one related to coryza and cough are the effects of the drug substance may be considered as characteristic symptoms.

This pathogenetic trial has developed symptoms in all the above mentioned sections in both verum and control groups except those in mind, rectum and generalities which were only covered by placebo group. Symptom related to head were produced in both the groups with different characteristic in which 'affection of frontal region of head; *amel.* pressure is common, therefore of less importance and the fever symptoms were differing due to the associated complaints but we cannot give importance to fever without thirst as it was common in both the groups. Affections related to left eye was common but associated symptoms were quite different. Thus, these symptoms may be considered for clinical verification and if these get relieved in the patients then can be considered as the proving symptoms else discarded. Coryza was also present in both groups but control group did not have any modalities. Stomach symptom: 'increased appetite' is prominent in control as well as verum group, so cannot be reflected as proving symptom.

Table 3: Characteristics at end of study

Variable	Verum (n=43)	Placebo (n=20)	P
BMI (kg/m ²)	22.3±3.3	22.1±6.4	0.62 [§]
Hb (g/dL)	12.2±1.6	12.8±1.1	0.14 [§]
TLC (number of cells/cumm)	6902.3±1117.5	7405.0±1306.0	0.12 [§]
ESR (mm after 1 h)	9.6±6.2	9.9±7.8	0.97 [§]
FBS (mg/dL)	76.5±10.2	71.8±9.1	0.89 [§]
Total cholesterol (mg/dL)	141.3±33.0	141.8±26.6	0.67 [§]
SGOT (U/L)	14.8±5.7	13.0±3.7	0.53 [§]
SGPT (U/L)	19.2±7.2	18.6±5.0	0.86 [§]
Alkaline phosphatase (U/L)	92.5±8.2	83.0±10.8	0.36 [§]

[§]Independent t-test, [¶]Chi-square test. Values are expressed in (%), Mean±SD. SD: Standard deviation; BMI: Body mass index; Hb: Haemoglobin; TLC: Total lymphocyte count; ESR: Erythrocyte sedimentation rate; FBS: Fasting blood sugar; SGOT: Serum glutamate oxaloacetate transaminase; SGPT: Serum glutamate pyruvate transaminase

Table 4: The change in investigation values (variables) for the verum group provers who produced symptoms with those who did not produce any symptom

Variable	Symptom produced		P
	Yes (n=16)	No (n=27)	
BMI (kg/m ²)	-0.02±0.84	0.00±0.00	0.88
Hb (g/dL)	-0.11±0.90	0.26±1.35	0.32
TLC (number of cells/cumm)	-150.0±1327.65	14.81±499.77	0.56
ESR (mm after 1 h)	5.81±8.68	1.31±4.01	0.03
FBS (mg/dL)	-8.14±12.01	0.25±2.49	0.06
Total cholesterol (mg/dL)	27.62±35.42	8.93±18.59	0.07
SGOT (U/L)	0.00±0.00	-0.47±1.32	0.18
SGPT (U/L)	0.26±1.03	0.11±1.11	0.69

BMI: Body mass index; Hb: Haemoglobin; TLC: Total lymphocyte count; ESR: Erythrocyte sedimentation rate; FBS: Fasting blood sugar; SGOT: Serum glutamate oxaloacetate transaminase; SGPT: Serum glutamate pyruvate transaminase

Conventionally, *W. somnifera* has been used as an anti-inflammatory agent,^[3-5] and in this pathogenetic trial also, some symptoms developed which can be related to inflammatory conditions such as burning pain in tongue (glossitis), itching and redness of left eye (conjunctivitis), rhinitis, burning pain in stomach (gastritis), enteritis, etc., Fever has been reported in the present study which is in corroboration with the pharmacological studies.^[12,13]

According to traditional use of medicine, it has also been recommended for the treatment of bronchitis^[3] and in this study also we found chest and respiration-related symptoms which are quite similar to this condition, i.e., mild pricking pain in left side of chest, cough in morning with pain in throat while swallowing, cough is accompanied with sleeplessness and restlessness, cough with difficult yellow sputum.

Symptoms such as increased thirst, dizziness, drowsiness and increase in fasting blood glucose levels corroborate with its

Table 5: Objective parameters and findings during pre-trial medical examination and terminal medical examination

Group (V/P)	Symptoms produced (yes/no)	PME findings	TME findings
V	Yes	USG - left renal calculi - 3.1 mm	NAD
V	Yes	USG - left renal concretions Urine examination - NAD	USG-NAD Urine examination - calcium oxalate crystals
V	Yes	USG - right ovarian cyst (2.5 cm×2.7 cm)	NAD
V	Yes	USG - right ovarian cysts (3.01 cm×1.67 cm and 4.18 cm×4.34 cm×4.64 cm)	NAD
V	No	Stool examination - ova of <i>E. vermicularis</i> Urine examination - NAD	Stool examination - NAD Urine examination - calcium oxalate crystals
V	No	NAD	Stool examination - <i>E. histolytica</i> Urine examination - amorphous phosphate crystals USG - left ovarian cyst (3.2 cm×3.7 cm)
C	Yes	Left renal cortical cyst (USG)	NAD
C	No	Right renal calculus - 4.9 mm (USG)	NAD

V: Verum group; C: Control group; NAD: Nothing abnormal detected; *E. vermicularis*: *Enterobius vermicularis*; *E. histolytica*: *Entamoeba histolytica*; TME: Terminal medical examination; PME: Pre-trial medical examination; USG: Ultrasonography

pharmacological action and therapeutic activity in diabetic patients.^[15,17]

This drug has been used for dyspepsia and considered as a liver tonic.^[3,4] Symptoms developed in this study, pertaining to liver and gastric affection are loose watery stool (4–5 times a day) with pain in the right hypochondrium, stool with gripping pain in umbilical region and flatulence with bloating.

Similarly, the symptoms generated affecting the locomotor system are aching pain in all joints of the upper limbs, aching pain in right shoulder and left elbow tearing pain from knee to ankle, stitching pain in lower extremities causing difficulty in walking in corroboration with the uses of this drug as mentioned in complementary and alternative medicine for various bone and joint affections.^[5,8,14]

In Unani medicine, this herb is being used to treat a variety of infectious diseases.^[5,6] In the present study, symptom of itching, reddish vesicular eruptions also appeared after administration of this drug.

In the literature, it has been mentioned that this drug can be used as an immune stimulant in patients with low white blood cells (WBCs). In this study also, the change has been found in the TLC but not statistically significant. Apart from this, the increase in WBC count can be better noted by clinical verification in patients. BMI has also increased in provers of verum group who have produced symptoms. Although this was not statistically significant, the history that this drug is effective in weight gain needs to be further verified as far as the utility of Homoeopathic medicine is concerned. Apart from these findings, there are changes in other biochemistry investigations done for the provers but these are within the normal range. Thus, the proving substance in this study has not caused any pathological changes in the provers and the proving process is safe. Clinical verification study using this drug in patients with pathological findings may be taken up

to assess that the changes in haematological and biochemistry parameters.

There were no symptoms noted regarding its traditional use in OCD, impotency, infertility, increase in sperm count and motility. To explore the additional therapeutic use of this drug, there is a need to undertake re-proving of the drug in large doses and/or longer repetition.

Apart from the subjective symptoms, the objective findings reflect that the drug has an effect on the left-sided renal calculi, ovarian cysts and helminthic invasion. However, there is one prover in verum group and one in control group in whom the renal calculus has disappeared as per ultrasonography report of TME and this can be attributed to the small size of the calculus. The dissolution of renal concretions (curative effect) and appearance of calcium oxalate and amorphous phosphate crystals in urine during TME may be considered as the curative effect in the first case and pathogenetic effect of the drug in the other two cases. Similarly, in case of ovarian cysts and helminthic invasion, the curative and pathogenetic effect of the drug has been noted. Thus, these effects of the drug have left the clues to explore the utility of this drug in such metabolic disorders and helminthic affections.

On re-proving the symptoms and objective findings of this pathogenetic trial, *Phosphorus* is covering maximum rubrics and can be considered as closest chemical analogue [Figure 2].

In one of the articles,^[20] it has been mentioned that placebo proving occasionally seem to produce similar symptoms to the proving symptoms, thus casting further doubt on the use of this medium in proving and has attributed it to nocebo effect. Thus, few of the symptoms and signs overlapping in both the groups can be due to nocebo effect.

Two provers received antidote during the trial for the increased severity of symptoms which lead to complete recovery and no residual effect was found thereafter.

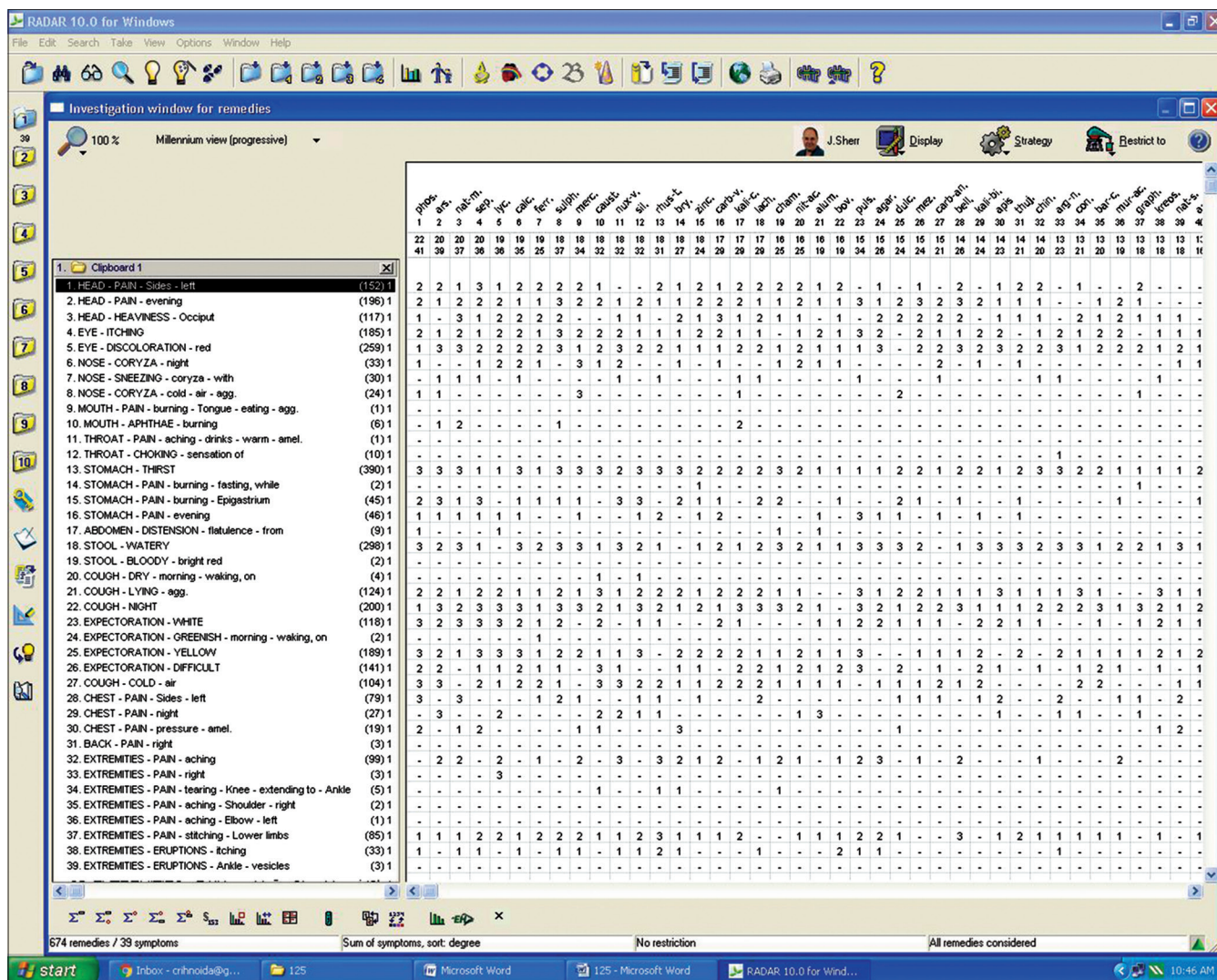


Figure 2: Repertorisation chart

Although the findings mentioned under results and as interpreted in discussion reflect that this could be the effect of the drug proving substance, to establish the causality relationship, the tools such as modified Naranjo’s probability scale may be used.

CONCLUSION

The pathogenetic response elicited during the proving trial expands the scope of use of the drug *W. somnifera* in Homoeopathy as no proving study or Homoeopathic literature reflecting the complete symptomatology has been found. To authenticate, the signs and symptoms generated during this trial should be subjected to clinical verification which will confirm its therapeutic utility. The research scholars and clinicians may also contribute their experiences or take up further research studies with this drug.

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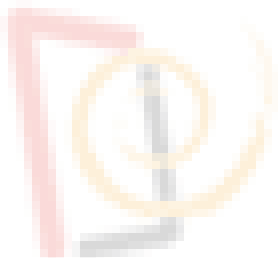
Conflicts of interest

None declared.

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होम्योपैथिक पैथोजेनेटिक ट्रायल ऑफ विथानिया सोमनिफेरा: एक बहु केन्द्रीक, डबल ब्लाइंड, यादृच्छिक, प्लासिबो नियंत्रित परीक्षण

पृष्ठभूमि: होम्योपैथिक औषध प्रमाणन, होम्योपैथिक औषधि की रोगजनक क्षमता को खोजने में पहला कदम है, यह होम्योपैथिक चिकित्सा प्रणाली का अभिन्न अंग है।

उद्देश्य: स्वस्थ मनुष्य में होम्योपैथिक पोटेंसिज़ में विथानिया सोमनिफेरा की रोगजनक प्रतिक्रिया को प्राप्त करना।

सामग्री और विधि: केन्द्रीय होम्योपैथी अनुसंधान परिषद् के चार केन्द्रों पर 63 अपेक्षाकृत स्वस्थ व्यक्तियों पर एक बहु-केन्द्रीक, यादृच्छिक, डबल ब्लाइंड, प्लासिबो नियंत्रित परीक्षण किया गया। सभी व्यक्तियों को परीक्षण के पहले चरण में 3 दिन के लिए प्रतिदिन 4 खुराक के हिसाब से कुल 12 खुराक दी गई। यादृच्छिककरण के बाद, संबंधित समूह में 43 व्यक्तियों को 6 सी और 30सी पोटेंसिज़ की विथानिया सोमनिफेरा दो चरणों में दी गई। प्लासिबो समूह में 20 व्यक्तियों को अनमेडिकेटेड ग्लोब्यूलस प्रदान किये गये। परीक्षण अवधि के दौरान प्रकट लक्षण और संकेत प्रेरकों द्वारा लिये गये तथा इन्हें अन्वेषक द्वारा विस्तारित किया गया। विथानिया सोमनिफेरा पर डेटा संकलन का कार्य प्रमाणन-सह-डेटा-प्रसंस्करण प्रकोष्ठ में किया गया।

परिणाम: वास्तविक औषधि परीक्षण के अंतर्गत 43 व्यक्तियों में से केवल 16 व्यक्तियों ने 39 लक्षण दर्शाए। लक्षण मुख्य रूप से 30सी पोटेंसी में प्रकट हुए हैं। वस्तुपरख निष्कर्षों में, औषधि ने गुर्दे, अंडाशय और हेलमेंथिक इन्फेक्शन पर अपना प्रभाव दिखाया।

निष्कर्ष: इस परीक्षण के दौरान प्राप्त रोगजनक प्रतिक्रिया विथानिया सोमनिफेरा के उपयोग की गुंजाइश को बढ़ाती है तथा नैदानिक सत्यापन अध्ययन द्वारा इसकी और अधिक पुष्टि की जानी चाहिए।

Homöopathische pathogenetische Studie von *Withania somnifera*: Eine multizentrische, doppelblinde, randomisierte, placebokontrollierte Studie

Ziel: Um die pathogenetische Reaktion von *Withania somnifera* in homöopathischen Potenzen auf gesunde menschliche Probanden hervorzurufen

Materialien und Methoden: Eine multizentrische, randomisierte, doppelblinde, placebokontrollierte Studie wurde an 63 relativ gesunden Personen an vier Zentren des Zentralrates für die Forschung in der Homöopathie durchgeführt. Alle Probanden erhielten in der ersten Phase des Versuches 12 Dosen Placebo in 4 Dosen pro Tag für 3 Tage. Nach der Randomisierung wurden 43 Probanden in der Interventionsgruppe vergeben. *Withania somnifera* in 6C und 30C Potenzen in zwei Phasen. In der Placebo-Gruppe wurden 20 Probanden unmedizierte Kügelchen verabreicht. Die Symptome und Zeichen, die sich während der Probezeit manifestierten, wurden von den Probanden notiert, die von den Prüfungsmeistern und der Datenkompilierung auf *Withania Somnifera* ausgearbeitet wurden, wurde bei der Prüfung der Cum-Datenverarbeitungszelle durchgeführt

Ergebnisse: Von 43 Probanden, die auf der tatsächlichen Drogenprobe waren, zeigten nur 16 Probanden 39 Symptome. Die Symptome haben sich überwiegend in der 30C-Potenz manifestiert. Unter den objektiven Befunden hat die Droge ihre Wirkung auf Niere, Eierstöcke und helminthischen Befall gezeigt

Fazit: Die pathogenetische Reaktion, die während dieser Studie hervorgerufen wird, erweitert den Anwendungsbereich von *Withania somnifera* und muss durch eine klinische Verifikationsstudie weiter validiert werden.



Patogenesia homeopática de *Withania somnifera*: Estudio multicéntrico, controlado con placebo, aleatorizado **RESUMEN**

Objetivos: Evidenciar la respuesta patogenética de *Withania somnifera* en potencias homeopáticas en voluntarios sanos.

Materiales y métodos: Se efectuó un estudio multicéntrico, controlado con placebo, aleatorizado a doble ciego en 63 personas relativamente sanas en cuatro centros del CCRH (*Central Council for Research in Homoeopathy*, India). En la primera fase del ensayo, todos los voluntarios recibieron 12 dosis de placebo, divididas en 4 dosis al día durante 3 días. Tras la aleatorización, 43 voluntarios del grupo de estudio recibieron *Withania somnifera* a las potencias de 6C y 30C en dos fases. En el grupo de placebo, 20 voluntarios recibieron los glóbulos de placebo (sin medicación). Los voluntarios registraron los síntomas y los signos manifiestos durante el periodo de ensayo. Estos registros fueron evaluados por los directores de la patogenesia y la recogida de datos sobre *Withania somnifera* se efectuó en la célula de tratamiento de *proving-cum-data*.

Resultados: Únicamente 16 de los 43 voluntarios que recibieron el medicamento activo, manifestaron 39 síntomas. Los síntomas se manifestaron sobre todo con la potencia 30C. Entre los hallazgos objetivos, el medicamento presentó un efecto en los riñones, los ovarios y frente a infestaciones helmínticas.

Conclusiones: La respuesta patogenética manifiesta durante este ensayo, amplía el rango de aplicación de *Withania somnifera* y ha de ser validada en posteriores estudios de verificación clínica.

Pathogénésie homéopathique de *Withaniasomnifera*: essai contrôlé contre placebo, randomisé, en double aveugle

RESUME

Objectif: Obtenir la réponse pathogénétique à *Withania somnifera* en dilutions homéopathiques sur des expérimentateurs sains.

Méthodes et matériaux: un essai multicentrique, randomisé et en double aveugle contre placebo a été conduit sur 63 personnes en relative bonne santé dans quatre centres du Central Council for Research in Homoeopathy. Chaque expérimentateur a reçu 12 doses de placebo à prendre en 4 fois par jour sur 3 jours pendant la première phase de l'étude. Après randomisation 43 expérimentateurs du groupe de départ ont reçu *Withaniasomnifera* 6C et 30C en deux phases. Dans le groupe placebo 20 expérimentateurs ont reçu des globules non imprégnés. Les symptômes observés par les expérimentateurs ont été notés par ces derniers, colligés par les coordinateurs du proving et la compilation des données de *Withania somnifera* a été effectuée à l'aide d'une cellule de traitement des données de provings

Résultats: parmi les 43 expérimentateurs ayant reçu le remède verum seuls 16 expérimentateurs ont présenté 39 symptômes; Ces symptômes ont été prédominants dans la dilution 30C. Les résultats objectifs ont été surtout l'action du remède sur les reins, les ovaires, et l'infestation helminthique.

Conclusion: La réponse pathogénétique obtenue par cette essai permet d'élargir le champ d'action de *Withania somnifera* et doit être validée par des vérifications cliniques.



順勢療法療劑睡茄的致病學試驗：一個多研究中心、雙盲、隨機、安慰劑對照試驗

摘要

目標：使用順勢療法層級的睡茄，在健康驗證者中引發致病反應

原料和方法：這是一個多研究中心、隨機、雙盲、安慰劑對照的試驗。於順勢療法研究中央委員會的4個研究中心中，在63位相對健康的人身上進行。在試驗的第一階段，所有驗證者都被給予12劑安慰劑（分為每天4劑，使用3天）。在隨機抽樣之後，在療劑組別的43位驗證者分兩個階段，分別被給予睡茄 6C和30C。在安慰劑組別的20位驗證者被處方無藥效的丸劑。在試驗期間顯示的症狀和徵兆，會被驗證者記錄下來，並由驗證主管詳細說明。對於睡茄的資料編纂，會由驗證數據處理小組完成。

結果：在43名接受真實療劑試驗的驗證者中，只有16名驗證者展現39種症狀。症狀主要展現於30C層級。在這些客觀性發現中，顯示了藥物對腎臟、卵巢和蠕蟲入侵的效果。

結論：這試驗出現的致病反應，擴充了睡茄的使用範圍，需要透過臨床研究去進一步證實。