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DRUG PROVING

Azadirachta indica - *A multicentric double blind homoeopathic pathogenetic trial*

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Objective: To elicit the pathogenetic response of the drug Azadirachta indica in homoeopathic potencies on healthy human volunteers.

Methodology: Drug Azadirachta indica was proved by the Central Council for Research in Homoeopathy through double-blind placebo-controlled method. The study was conducted at 2 centers. The pathogenetic trial of the drug was carried out in three potencies (6C, 30C and 200C) on 27 apparently healthy volunteers who were selected after conducting pre-trial medical examination by the medical specialists and routine laboratory investigations. All the drug samples were coded. In the first phase, volunteers were given 56 doses (04 doses per day for 14 days) of placebo. In the next three phases 56 doses (04 doses per day for 14 days) of the drug in each of the three potencies was given. The symptoms generated during the trial period were noted by the volunteers, cross examined and elaborated by the Proving Masters. The data obtained from both the centers was compiled at proving-cum-data processing cell at CCRH headquarters after de-coding.

Observations: Symptoms more or less related to every part of the body appeared during the course of administration of the drug in each trial-potency.

Conclusion: Pathogenetic responses, (new and reconfirmed), elicited during the trial expands the scope of use of Azadirachta indica and it will benefit the research scholars and clinicians. These symptoms will carry more value when verified clinically.

Keywords: homoeopathy; pathogenetic response; homoeopathic pathogenetic trial; drug proving; azadirachta indica

Introduction

Since antiquity neem has been renowned for healing. The earliest Sanskrit medical writings refer to the benefits of its fruits, seeds, oil, leaves, roots and bark. Neem has been proved experimentally to be a good anti-fungal and anti-bacterial agent. As an anti-viral agent, neem is effective as a preventive but it is useless once the infection is established within the cell. In, India and Bangladesh, villagers apply neem oil to the hair to kill head lice, reportedly with great success.[1] Dentists have found tooth-brushing with neem twigs effective in preventing periodontal diseases.[2] In trials, it has been proved that neem has significant analgesic, antipyretic and anti-inflammatory effects. Interestingly, research at India's Defence Institute of Physiology and Allied Sciences (DIPAS) has shown that neem oil acts as a powerful spermicide and also, it can prevent a fertilized egg from implanting in the wall of the uterus. So, it may be used as an inexpensive birth control method.[1]

Bark used in skin troubles. Leaves considered antiseptic, applied to boils in poultice; decoction given for ulcers and eczema. Flowers tonic and stomachic. Berries purgative, emollient. Seeds yeild a non-drying oil used for skin affections. Nimbidin is the chief bitter principle of the oil.[3]

In small doses, the bark is a bitter tonic, astringent, anti-periodic, anthelmintic, given to children in round-worm and to adults in fever and indigestion; leaves and flowers are alterative and diuretic.[4]

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The bark exudes a clean, bright amber coloured gum which contains a bitter alkaloid named "margosine" in long white needles, as double salt of margosine and soda - a neutral, amorphous resin believed to reside in the inner bark. Seeds contain about 10 to 31% of a yellow bitter fixed oil which is extracted by boiling or by pressure. Roy & Chatterjee (1971) analysed the oil and found the following constituents:- (1) Sulphur 0.427 percent; (2) a very bitter, yellowish substance obtained from the alcoholic extract of the oil, which is supposed to be an alkaloid; (3) resins; (4) glucosides, indefinite; (5) fatty acids.[5]

This common indeginous drug was introduced to Homoeopathy by late Dr. P.C. Majumdar. The drug was first proved by him and one of his pupils, U.C. Bagchi. Later on 2 more provings were made, one by Dr. H. Chakrabarti and another, by his assistant.[1]

Central Council for Research in Homoeopathy (CCRH) undertook systematic Homoeopathic Pathogenetic Trial (HPT) of *Azadirachta indica* as per the approved protocol. SBL Pvt. Ltd. also conducted the proving of the drug on 15 provers through its R&D department with dilutions prepared from the neem leaves.[6]

Taxonomy

Botanical name	:	*Azadirachta indica* A. Juss.[7]
Family	:	Meliaceae[7]
Synonym	:	*Melia azadirachta* linn.[7]
Common names[5]	:	
Sanskrit	:	Ravipriya; Vembaka, Nimba, Arishta
Bengali *Hindi* *Punjabi*	}	Nim or Nimb, Nimgachh
Gujrati	:	Limba
Tamil	:	Vembu
English	:	Neem or Margosa tree; Indian Lilac.
German	:	Indischer Zedrach.
French	:	Azadirae d'Inde

Description

A large evergreen tree, up to 15m in height, with trunk straight or crooked. Leaves alternate, imparipinnately compound, 20 to 28 cm long, crowded near the ends of branches; leaflets 9 to 12, sub-opposite, 2.5 to 11 cm by 1 to 3.5 cm, obliquely lanceolate, sometimes falcate, bluntly serrate, smooth, inequilateral at base, dark green, bitter in taste. Flowers small, numerous, shortly stalked, arranged in long, slender, lax, axillary panicle; bracts minute, deciduous; calyx 5 spreading, rounded blunt, ciliate; corolla 5, white imbricate, spreading, oblong-spathulate, somewhat twisted with a cunduplicate claw, smooth outside, finely pubscent within; stamens 10, filaments fused into a long cylindrical erect tube, anthers erect, introse, oblong 2-lobed; ovary 3-locular, with 2 ovules in each locule, stigma 5-lobed. Fruit: a drupe, ovoid, dark yellow. Seed solitary.[8]

Distribution

Widespread in India**,** widely distributed throughout Indo-Malayan region and also in tropical Africa.[8]

Part used

Bark[8]

Objective

To elicit the pathogenetic response of the drug *Azadirachta indica* on apparently healthy human volunteers in homoeopathic potencies.

Materials and Methods

Location and duration of study

The proving was conducted at Drug Proving Research Unit (Homoeopathy), Ghaziabad in 1988 and at Homoeopathic Drug Research Institute, Lucknow in 1989.

Participants

Total 27 apparently healthy volunteers from above mentioned two centers, between the age group of 18 to 50 years, comprising of 18 males and 9 females, were enrolled in this study. The status of health of these volunteers was ascertained on the basis of the findings of the Pre-trial Medical Examination (PME) conducted by a panel of medical specialists (General Physicians, Psychiatrists, Cardiologists, Ophthalmologists, ENT Specialists, Dermatologists, Gynaecologists, Radiologists) and their routine laboratory investigations at both the centers were done to ascertain their health status. After recommendation of experts, healthy volunteers were enrolled in the Homoeopathic drug proving programme.

Drug

Azadirachta indica was procured in 6C, 30C and 200C potencies from M/s Hahnemann Publishing Co. Pvt. Ltd., Kolkata, West Bengal, India, in 30ml sealed phials of each dilution. Globules (number 30) were medicated with these attenuations at the CCRH headquarter and sent to both the centers in coded phials (verum) along with placebo (control).

Placebo

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

Study Design

The study was a randomized double blind placebo controlled trial.

Method

Before commencing the study, all provers were screened strictly by the experts and apparantly healthy provers between the age group of 18-50 years, both male and female were included in the drug proving trial. Pregnant and lactating mothers were excluded.

'Written informed consent' from each volunteer was obtained before starting the proving. PME was conducted to confirm health status of the volunteers. Volunteers declared healthy, were enrolled in the study. The study was conducted at two centers. According to Drug Proving Protocol, the sample size included 30% volunteers under control group at each center. So, out of 27 volunteers, 18 were kept on drug (verum) and 9 were kept on placebo (control) in all four phases. All the volunteers were assigned code numbers and the coded drugs of different potencies (including placebo) were supplied in separate glass phials bearing code numbers of the respective volunteers; keeping both provers and proving masters blind about what provers were consuming (drug or placebo).

The study consisted of four phases. Each Phase consisted of 56 doses of drug or placebo.

Phase-I: Placebo phase - It is useful in generating volunteer's response to placebo and therefore symptoms generated by the volunteer in this stage act as control for subsequent phases.

Phase-II: In 2nd phase, the trial was conducted with 200C potency.

Phase-III: In 3rd phase, the trial was conducted with 30C potency.

Phase-IV: In 4th phase, the trial was conducted with 6C potency.

The volunteers were asked to take 4-6 globules of a particular potency of the coded drug, four times a day, dry on tongue.

The volunteers were instructed to note down the details of their feelings/changes in mind and body, in 'Prover's Day Book Proforma' daily after taking the coded drug/placebo.

- *If sign(s) symptoms(s) appeared*

The volunteers were asked to stop taking the coded drug as soon as they felt any change or any sign(s) and/or symptoms(s) developed during the trial.

The volunteer noted down the sequence of the appeared 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. Intake of drug remained suspended till the sign(s) and/or symptoms(s) totally disappeared. Any change in normal routine of the prover in respect of daily habits pertaining to diet, living conditions etc./any treatment taken was also noted in the Prover's Day Book Proforma.

After disappearance of sign(s) and/or symptom(s) produced by the drug, the volunteer has to wait further for a further period of 07 days before taking the remaining doses of that potency following the same dose schedule as stated above. In case of further appearance of new sign(s) and/or symptom(s), the same procedure as stated above was followed till the consumption of all 56 doses of that potency by the volunteer.

If the prover was experiencing the same symptom(s) what he/she had already shown, he/she was asked to stop the current quota and to switch over to the next quota after a washout period of 14 days.

Each prover was interrogated everyday by Proving Master about the appearance of new symptom(s) or progress of symptoms and this information was noted in 'Symptom Elaboration Proforma' with respect to appearance and dis-appearance of symptoms, their location, sensation/character, modalities, concomitants, extension of symptoms, causation, clinico-pathological findings and other treatment taken.

- *If no sign(s)/ symptoms(s) appeared*

If no symptom was observed, the volunteers noted down as 'No Symptom' against the date and time of intake of the respective dose of the drug/placebo.

Before commencing the administration of subsequent potencies (subsequent Phase) of the drug, the volunteers remained on a washout/rest period (it should be a symptom free period between two phases of drug trial in which a volunteer does not take any drug) for 14 days and started taking next potency in the same procedure as mentioned above, till completion of 56 doses.

The same procedure was followed for the 3rd and 4th phases.

Each volunteer was interrogated by the Proving Master to verify the sign(s) and/or symptom(s) recorded by the volunteer. The symptoms recorded in 'Prover's Day Book Proforma' were verified by the Proving Master and completed through further interrogation with the volunteer in respect of their location/ sensations/ modalities and concomitants, if any, in 'Symptoms Elaboration Proforma'.

During the course of the trial, the volunteers were referred for specific laboratory investigation(s) to rule out any pathological cause of appearance of symptom(s). Since laboratory tests were performed to identify any correlation between the subjective and objective changes during the course of proving, the expert opinion of the honorary consultant(s) was obtained, wherever needed.

After completion of trial of all potencies, the volunteers underwent Terminal Medical Examination (TME).

On completion of all the respective Phases of the trial, the compilation of data recorded in 'Prover's Day Book Proforma', 'Symptoms Elaboration Proforma', 'Pathological Report Sheets' and 'Terminal Medical Examination sheets', was done at the Council's headquarters by the Drug Proving-cum-Data Processing Cell. After decoding, the sign(s) and/or symptom(s) generated by the volunteers kept on the drug were separated from those generated by the volunteers kept on placebo. The sign(s) and/or symptom(s) which were common to both the groups i.e. placebo as well as drug groups were not taken into consideration while compiling the symptomatology of the drug.

Management of adverse effects – A vial of antidote was sent with each quota to each center. In this trial homoeopathic potencies of *Camphor* were used as antidote as it is believed that *Camphor* can antidote nearly every vegetable medicine.[9] Proving master was to give antidote to the volunteer if symptoms continued for a long time or intensity was much to cause discomfort. Proving Master was also directed to take advice of honorary consultants and to get laboratory investigations done, if required.

Pathogenetic effects

Pathogenetic effects were deduced

(i) from comparison of symptoms developed in placebo phase with symptoms during intervention phases (Intraprover comparison)

(ii) from comparison of symptoms developed by provers on control (for all four phases) with provers on actual drug trial (Interprover comparison)

Results

The following symptoms were observed during the trial.

- *agg.*: aggravation, *amel.*: amelioration
- Symptoms produced during the pathogenetic trial of the drug were compared with the homoeopathic literature cited in the reference and those symptoms which were found in the literature, are shown in **bold**, superscribed with a numerical that refers to the respective literature.

Mind

- **Irritability**[6], no desire to talk.
- Irritability, rage & fury, *agg.* noise.
- **Anxiety**[10,11], apprehensive of some evil with palpitation.

Vertigo

- **Vertigo**[10], *agg.* standing & walking, with constipation.

Head

- Heaviness of head, *agg.* sitting, *amel.* lying down, taking tea.
- **Throbbing**[10,12] pain in head, *agg.* pressure, *amel.* rest, evening.

- Throbbing pain in head, *agg.* raising the head, *amel.* sleep, taking tea.
- Dull, **aching**[10] pain in left side of head, *agg.* movement, *amel.* rest and lying down.
- Throbbing pain in forehead, *agg.* movement, in evening, *amel.* pressure.
- Bursting pain in frontal region, with impaired appetite & fever, *agg.* stooping, morning, sunlight; *amel.* evening, rest, lying down.
- **Heaviness in frontal region**[6], *agg.* morning, ***amel.*** **pressure**[6].
- Tearing pain in forehead, *agg.* midnight, *amel.* pressure.
- Heaviness, dullness in frontal part extending to supra-orbital area, *amel.* by pressure, *agg.* under sun; with pressing pain in eye ball & insomnia.
- Sensation of weight over vertex, *agg.* stooping, morning, *amel.* evening.
- Heat & pressure on vertex, *agg.* midnight, *amel.* tight bandage, taking cold water.

Eyes

- Heaviness of lids, *agg.* in open air.
- Stitching pain in eyes, *amel.* application of cold water.

Ear

- **Buzzing**[10] sound in ear, *agg.* morning, talking
- Hissing sound; *agg.* morning, talking.

Nose

- Bland, **watery**[6,10,11], fluent, coryza, with **sneezing**[6], tickling in nose; headache and thirst for cold water, *agg.* open air, *amel.* warm room.
- Obstruction of nose, followed by thin, watery, fluent discharge with loss of appetite and hoarseness of voice.
- Uneasy, burning sore feeling in nose with redness & rawness of nostrils, *agg.* leaning head downwards, morning, *amel.* rest, sleeping.
- Nose, dry with crust formation, bleeding after removing the crusts with sneezing, *amel.* pressing the nostrils.

Mouth

- Dryness of mouth during sleep.
- Tearing pain in gums, *agg.* hot drinks, *amel.* cold things.
- **Bitter taste**[4,10,11] with desire for salty things.

Throat

- Pain with choking sensation, *amel.* hot drinks.
- Dryness and roughness in throat, *agg.* swallowing solids, *amel.* taking hot drinks.
- **Soreness**[4,10] of throat, *agg.* evening, *amel.* drinking water.
- Irritation in throat with inflammation and redness of upper palate, *agg.* solid things, hot and cold drinks.

Stomach

- Appetite diminished with anxiety and restlessness, with nausea and sour eructation, *agg.* after eating

Abdomen

- Dull pain in abdomen with heaviness and **flatulence**[6], *amel.* eructation.
- Colicky, crampy, intermittent pain while **straining**[6] for stool and after stool, with heaviness and distension in abdomen and **constipation**[6].
- Griping, crampy, colicky **pain around umbilicus**[12].
- Recurrent pain in abdomen, *agg.* before stool, after eating, *amel.* lying down straight.
- Stitching pain in hypochondrium, *agg.* eating.
- Distension of abdomen with heaviness, pressure in epigastrium with rumbling.

Rectum

- **Scanty**[6], **hard stool**[4,6,10,12], urge after eating.
- Loose stool, frequent and painless with anxiety at night.
- **Diarrhoea**[10,12], stool yellowish with whitish frothy mucus with cramping pain in abdomen, *agg.* during stool.

Male

- Spermatorrhoea.

Female

- Menses early and profuse with backache.

Respiratory

- Cough with sensation of constriction in the

chest, *agg.* morning and evening with thick, yellow expectoration.

- **Hoarse voice**[4,10], *agg.* coughing, morning.
- Cough-short, dry, hacking, *agg.* while undressing; with choking sensation in throat.
- Cough, deep spasmodic with salty expectoration, easy to expel with pain in chest and headache.
- Irritation and rawness in larynx, *agg.* during cough, *amel.* hot drinks.
- **Stitching pain in chest**[4,10], *amel.* deep inspiration.

Back

- **Stiffness**[6] with drawing pain in back and neck, *amel.* movement, hot drinks.
- Dull, aching pain in back, ***agg.* sitting**[6], *amel.* lying down.

Extremities

- Pain in muscles in lower limbs with violent twitching, *agg.* movement, *amel.* pressure.
- Cutting pain in legs, *agg.* motion, *amel.* pressure.
- Heaviness in calf muscles, *amel.* pressure.
- Heaviness in shoulder joints to elbows, *agg.* hanging down the arms, *amel.* flexing and pressure.
- Pulsating pain in the knee joints, *agg.* walking, cycling, *amel.* warm application, rest.

Skin

- Itching on legs with redness and dry eruptions, followed by burning sensation, *agg.* undressing, evening, after scratching.

Fever

- **Fever with chill**[10], **restlessness**[6], bitter taste, thirstlessness, weakness, tongue coated thick and white.

Discussion

Fifty seven symptoms appeared in the volunteers on verum group in 2nd, 3rd and 4th phase. The drug produces irritability, throbbing pain and heaviness in head. Appetite is diminished and there is colicky, crampy, griping pain in abdomen (*Colo.*). Cough and backache was also produced by the drug during the trial. Pain in the neck and back can be compared with *Actea racemosa*. As shown in literatures, neem has great action on skin diseases and the trial has confirmed it by producing red, itchy, dry eruptions, itching followed by burning. It was able to produce fever with chill, so it can be thought to be useful in malaria or pyemic fever. Many symptoms mentioned under different anatomical regions have been reappeared, wich are mentioned in other literature sources.[3,9,11] A subsequent proving Sharda Boiron Ltd.[6] also reflected similar symptoms and mentioned in the bold like irritability, flatulence, fever with chill and stiffness of back. As per the symptoms elicited during the proving, the drug will be of therapeutic use in the clinical conditions of hypertension, rhinitis, dysentery, chronic dyspepsia, laryngitis, skin complaints, lumbago and intermittent fever.

Conclusion

The symptoms appeared (new and re-confirmed) during the trial will add to the available literature on this medicine and benefit the research scholars and clinicians. These pathogenetic symptoms need further verification through clinical applications in different settings.

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References

1. Shultz Eugene B., Bhatnagar Deepak, Jacobson Martin *et. al.* Medicinals. Neem- A Tree For Solving Global Problems. National Academy Press, Washington D.C., 1992: 60-70.
2. Elvin-Lewis M. Plants used for teeth cleaning throughout the world. *Journal of Preventive Dentistry.* 6 1980:61-70.
3. Ambasta SP. The Useful Plants of India. Publication & Information Directorate, Council of Scientific & Industrial Research, New Delhi, 1986: 63-64.
4. Ghosh SC. Azadirachta indica or Melia azadirachta. Drugs of Hindoosthan, 9th edition. Hahnemann Publishing Co. Pvt. Limited, Kolkata, 2007: 68-82.

5. Nadkarni KM. Melia Azadirachta, Linn. Indian Materia Medica: Vol-I. Second reprint of Third Revised and Enlarged Edition. Bombay Popular Prakashan, Mumbai, 1991: 776-784.
6. Pathogentic Trial (Drug Proving) of Azadirachta indica folia. Online document at: http://www.sblglobal.com/azadirachta_indica.html accessed on 01.09.2010.
7. Chopra RN, Nayar SL & Chopra IC. Azadirachta. Glossary of Indian Medicinal Plants. Council of Scientific & Industrial Research, New Delhi, 1956: 31-32
8. Govt. of India, Ministry of Health and Family Welfare, Homoeopathic Pharmacopoeia of India, Eighth Volume, The Controller of Publication, New Delhi, 2000: 16-17.
9. Allen HC. Camphora. Allen's Keynotes Rearranged and Classified with Leading Remedies of the Materia Medica and Bowel Nosodes, 10th Edition. Azad Rai. B. Jain Publishers (P) Ltd., New Delhi, 2005: 77-78.
10. Anshutz EP. Azadirachta indica. New, Old & Forgotten Remedies, 2nd Edition. B. Jain Publishers (P) Ltd., New Delhi, 1996: 47-50.
11. Boericke W. Azadirachta indica or Melia Azadirachta. Boericke's New Manual of Homoeopathic Materia Medica with Repertory, 3rd Revised & Augmented edition based on Ninth edition. B. Jain Publishers (P) Ltd., New Delhi, 2007: 976-977.
12. Clarke JH. Azadirachta indica. A Dictionary of Practical Materia Medica, Vol. I, Reprint edition. B. Jain Publishers (P) Ltd., New Delhi, 2006: 235-236.