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DRUG PROVING

Cuscuta reflexa: A Double Blind Homoeopathic Pathogenetic Trial

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Objective: **To elicit the pharmacodynamic response of the drug, *Cuscuta reflexa* (dodder) on healthy human volunteers, in non-toxic doses.**

Methodology: **Drug *Cuscuta reflexa* was proved through a double-blind method. The homoeopathic preparation of the drug was proved in three potencies (6C, 30C and 200C) on 13 volunteers who were selected and declared apparently healthy during their pre-trial medical examination by specialists and through their routine pathological investigations. The volunteers consumed 56 doses (four doses per day for fourteen days) of each potency (6C, 30C and 200C) in three stages for a varying period. The symptoms generated during the trial period were noted by the volunteers and elaborated and cross-examined by the Proving Master. The data obtained from the Drug Proving Center was compiled at drug proving-cum-data processing cell at Central Council for Research in Homoeopathy (CCRH) headquarters after de-coding the drug.**

Observation: **Out of the 9 volunteers who were on actual drug trial, 8 manifested symptoms. The drug was able to produce symptoms in each potency. Only one symptom appeared in more than one prover.**

Conclusion: **Pharmacodynamic responses elicited during the proving trial will add to the literature available on the drug and benefit the research scholars and clinicians. This also needs verification through clinical trials.**

Keywords: homoeopathy; pharmacodynamic effect; homoeopathic pathogenetic trial; drug proving; cuscuta reflexa

Introduction

The plant is acrid, bitter; astringent to the bowels, aphrodisiac, alterative, tonic; useful in diseases of eye and of the heart, in biliousness, and “kapha” (Ayurveda)

The herb has a bitter sharp taste; is an expectorant, carminative, tonic, antihelmintic, purgative; diaphoric, diuretic; purifies the blood and cleanses the body; lessens inflammation; useful in jaundice, pains in the muscles and the joints, heat of the brain, headache, paralysis, diseases of the spleen, vomiting and lumbago.

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The seeds have a bitter bad taste; sedative, emmenagogue, diuretic; useful in the diseases of the liver and spleen, quartan fever, chronic fevers, griping, hiccough; purifies the blood and cleanses the bowels; the infusion is given in ophthalmia, the decoction in biliousness as a purgative (Unani).[1]

The plant contains cuscutalin and cuscutin; cucutalin pharmacologically potent drug; seeds contain pigments amarbelin and cuscutin and a wax and yield a semi-drying oil.[2]

Cuscuta reflexa plant

The plant is regarded as alternative, purgative and antihelmintic. Seeds are carminative and anodyne. Stem is purgative. *Cold infusion* of the seeds is given as a depurative and carminative in pains and stomach-aches. *As poultice* they are also applied locally. Its *seeds* are used along with sarsaparilla to purify blood. *Stems in decoction* are useful in constipation, flatulence,

liver complaints and bilious affections. *Varalians* of the dodder are highly useful in piles. *Externally* they are used against itch and other skin diseases. The *fruits* are used in fever and cough.[3]

Cuscuta reflexa has been proved by CCRH as per a standard protocol.

Literature review[2]

Botanical name: Cuscuta reflexa Roxb.

Family: Convolvulaceae

Common names:

Bengali	:	Algusi, Haldialgusilutta
English	:	Dodder[3]
Hindi	:	Akasbel
Punjabi	:	Nilathari
Sanskrit	:	Amaravela
Marathi	:	Nirmuli
Telugu	:	Sitamma pogu nalu

Description

Stems very long, rather stout, closely twining, branched, glabrous, pale greenish yellow, sometimes dotted with red. Flowers solitary or in umbellate clusters of 2-4 or in short racemes; pedicels short, glabrous, usually curved (rarely 0); bracts 1.5 mm. long, ovate-oblong, obtuse fleshy. Calyx divided almost to the base; lobes 3 mm. long, slightly unequal, broadly ovate, obtuse, glabrous and fleshy. Corolla white; tube 6-8 by 4 mm., almost cylindric; lobes 2.5-3 mm. long, deltoid, acute, reflexed; scales almost at the base of the corolla – tube, large, oblong, subquadrate or some what obovate, fimbriate and incurved at the apex. Stamens in the throat of the corolla- tube; filaments scarcely any; anthers about ½ -exserted beyond the top of the corolla-tube. Ovary ovoid; style simple, very short and thick; stigmas 2, distinct, large thick and fleshy, 1.5 mm. long, ovoid. Capsules 6-8 mm. diam., depressed-globose, glabrous, circumscissille near the base. Seeds 2-4, large, black, glabrous.[1]

Cuscuta reflexa plant

Distribution

Common throughout India, the plant is abundant in Bengal plains. It has no root under the ground but only grows as a parasite twiner on other plants, and hence called akaswel (sky-twiner) or amarwel (immortal twiner), because it grows during the rains and every year the growth is afresh on the same plant.[3]

Part used in Homoeopathy

Twining stem.

Materials and Methods

Location and duration of study

The drug was proved at Drug Proving Research Unit (H), located at Kolkata during 2002-03.

Design

The study was conducted through placebo controlled 'Double Blind Technique.' Before commencing the study, all volunteers were screened according to the drug proving protocol of CCRH. Ethical approval was obtained and written informed consent from each volunteer was obtained before commencing the study. Pre-trial Medical Examination (PME) was conducted to confirm health status of the volunteers. The volunteers declared as healthy were enrolled in the study. Out of thirty eight volunteers, twenty five (25) were kept on drug (verum) and thirteen (13) were control volunteers. 30% volunteers were selected as control in randomized fashion according to CCRH protocol. All volunteers were assigned code numbers and the coded drugs (including placebo) of different potencies were supplied in separate phials bearing code numbers pertaining to respective volunteers.

Participants

In total, 13 apparently healthy volunteers from the above mentioned center, between the age group of 18 to 50 years, comprising of 07 males and 06 females, were enrolled in this study. Pre-trial Medical Examination (PME) and Terminal Medical Examination (TME) of the volunteers were carried out by General Physicians, Psychiatrists, Cardiologists, Ophthalmologists, ENT Specialists, Dermatologists, Gynaecologists, Radiologists and their routine laboratory investigations were done at the center to ascertain their health status.

Drug

Cuscuta reflexa was procured in 6C, 30C and 200C potencies from Homoeopathic Drug Research Institute (HDRI), Lucknow; in 450 ml. sealed phials of each dilution. Globules (number 30) were medicated with these attenuations at headquarters office and sent to Drug Proving Research Unit (H), Kolkata in coded phials (verum) along with placebo (control).

Placebo

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

Study Design

The study was a randomized double blind placebo controlled trial.

Objective

To ascertain its effects on healthy human being, as well as its indications for application in homoeopathic system of medicine, a systematic trial (homoeopathic pathogenetic trial) with its higher dilution (6C, 30C & 200C).

Methods

Before commencing the study, all provers were screened strictly on the basis of Inclusion and Exclusion Criteria of "drug proving protocol" of CCRH.

Inclusion criteria includes:

1. The prover must be between 18-50 years of age, either males or females.
2. The provers should be apparently healthy. He/she should not show severe psychic or physical symptoms or in need of any kind of medical treatment. Pre-trial Medical Examination (PME) should confirm healthy status of the prover.
3. The prover must be intelligent enough to record the subjective symptoms generated by the drug during proving. Facts must be recorded very carefully.

Exclusive criteria includes:

1. Persons suffering from any chronic disease and under any kind of medical treatment.
2. Hysterical or anxious persons as such individuals display a high incidence of 'Placebo effects'.
3. Those who suffer from hypersensitivity diseases such as asthma, allergies, food hypersensitivities.
4. Pregnancy, puerperium, breast-feeding.
5. Colour blindness.
6. Age of less than 18 years.

'Written informed consent' from each volunteer was obtained before starting the proving. Pre-trial Medical Examination (PME) was conducted to confirm health status of the volunteers. Volunteers declared healthy, were enrolled in the study. The study was conducted at 01 center. According to the CCRH Drug Proving Protocol, the sample size included 30% control at the center. So, out of 13 volunteers, 09 were kept on drug (verum) and 04 were on placebo (control). 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 are consuming (drug or placebo).

The study consisted of *four stages,* of which first was pre-trial observation ('run-in') period with placebo and after that three subsequent potencies viz. 200C, 30C and 6C. Each potency of the drug was given in 56 doses. The drug/placebo was taken by the volunteers as 4 doses per day till the appearance of symptoms. So the duration of each stage varied according to presentation and duration of symptoms.

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, after taking drug in 'Prover's Day Book Proforma' daily.

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

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

The volunteers noted down the sequence of the new sign(s) and/or symptoms(s), their progress and the number of doses after which the sign(s) and/or symptom(s) appeared with date, time of onset and

duration for which they persisted in Prover's Day Book Proforma. Intake of drug remained suspended till the sign(s) and/or symptoms(s) totally disappeared. There is also a column for any change in normal routine of the Prover in respect of daily habits pertaining to diet, living conditions, any treatment taken, etc. in the Prover's Day Book Proforma.

After disappearance of sign(s) and/or symptom(s) developed by the drug, the volunteer waited for a further period of 07 days before resuming the intake of remaining doses of that potency. The volunteer took the remaining doses of the drug following the same dose schedule as stated above. In case of further appearance of new sign(s) and/or symptom(s) or re-appearance of the earlier sign(s) and/or symptom(s), the same procedure (as stated above) was followed till the consumption of 56 doses of that potency by the volunteer.

If the Prover is experiencing the same symptoms what he/she has already shown, he/she is asked to stop the current quota and to switch over to the next quota after a washout period of 14 days.

Management of adverse effects – A vial of antidote is sent with each quota to each center. Proving master gives antidote to the volunteer if any adverse effect is seen in the prover. Proving Master is also directed to take advice of honorary consultants and to get laboratory investigations done if required.

Each Prover was interrogated everyday by Proving Master about the appearance of new symptoms or progress of symptoms and noted it in 'Symptom Elaboration Proforma' w.r.t. Appearance and disappearance of symptoms, Location, sensation/character, Modalities, Concomitants, Extension/Direction Radiation of symptoms, Causation, Clinico-pathological findings, Remarks/ other treatment taken.

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

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

Before commencing the administration of subsequent potencies (subsequent stage) of the drug, volunteers remained on a rest period (it is a symptom free period between 2 stages of drug proving 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.

Same procedure was followed for the 3rd potency.

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 Masters and completed with the details related to their location/ sensation/ modalities and concomitants, if any, in 'Symptoms Elaboration Proforma'.

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

After completion of trial of all potencies, the volunteers were examined by the specialists again. This is called 'Terminal Medical Examination' (TME).

On completion of all the respective stages of the proving, 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 headquarters by the Drug Proving-cum-Data Processing cell. After decoding the proved drug, 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.

Pathogenetic effects

Pathogenetic effects (Proving symptoms) are defined as all changes in clinical events and laboratory findings reported by volunteers during an HPT and recorded in the final report. The incidence of pathogenetic effects per volunteer is defined as the total number of findings claimed in the trial divided by the total number of subjects. So incidence in this proving was 7.78 findings per volunteer.

The criteria for selection of pathogenetic effects was both intraprover (i.e. pathogenetic effects produced by prover in 1st run-in pre-trial observation period with placebo and in subsequent stages on verum) and interprover (i.e. comparison of pathogenetic effects produced in provers on verum with provers who remained throughout on placebo)

Results

In this study, out of 09 volunteers who were on actual drug, 08 volunteers manifested symptoms.

The following symptoms were observed during the drug proving

- In parenthesis, the first number after every symptom denotes number of volunteers who produced that particular symptom and the second number denotes the potency used.
- *agg.*: aggravation, *amel.*: amelioration

Vertigo

- Vertigo with pain in neck and hands with constant nausea (1, 200C).
- Vertigo on standing, on empty stomach, walking; *amel.* after eating, rest (1,30C).

Head

- Dull headache with fever (1, 200C).
- Throbbing pain in right side of head with mild fever (1,6C).
- Frontal headache; *agg.* in evening with fever and bodyache (1, 200C).
- Violent cutting pain in occiput with heaviness; *agg.* in cold air; *amel.* by drinking hot tea (1,30C).
- Severe throbbing pain in temporal regions; *agg.* after sleep in afternoon (1,6C).
- Pain in right side of temple, as if beaten by hammers (1,30C).
- Throbbing pain extends to right parietal region; *agg.* on waking up in morning; *amel.* after eating (1,30C).

Eyes

- Burning pain in eyes with lachrymation (1,200C).
- Burning pain in eyes with coryza and lachrymation (1,6C).
- Redness and burning pain in both eyes with headache (2, 6C).
- Stye on lower eyelid with redness and pus (1,200C).

Nose

- Running nose, *agg.* in rainy cold weather, fanning (1,200C).
- Sneezing, running nose, *agg.* in open air, going outside, *amel.* in warm room (1,6C).
- Sneezing without discharge from nose, but with burning sensation in nose and throat (1,200C).

Face

- Pain in mandibular joints, *agg.* while chewing (1,30C).
- Reddish small eruptions on face with severe itching (1,30C).

Mouth

- Bleeding from gums while brushing the teeth in morning (1,30C).
- Gums tender and teeth of lower jaw sensitive (1,30C).
- Vesicular eruptions inside lower lip (1,6C).
- Tingling sensation in mouth when drinking cold water, eating sweets, *amel.* holding hot water, tea in mouth (1,30C).

Throat

- Pricking pain in throat, *agg.* by swallowing liquid, *amel.* by drinking hot liquid (tea) (1,30C).
- White patches on both the tonsils (1,30C).
- Soreness of throat with mild cough (1,6C).
- Soreness of throat, *agg.* from cold drinks, *amel.* in morning with little expectoration (1,6C).

Stomach

- Loss of appetite (1,30C).
- Loss of appetite, thirst for water (1,6C).
- Vomiting tendency, *agg.* at night (1,6C).
- Vomiting just after taking food (1,6C).
- Constant nausea with pain in neck and hands (1,200C).

- Thirst increased (1,6C).
- Thirst for large quantity of cold water (1,30C).

Abdomen

- Pain in abdomen, *agg.* after taking food(1,6C).
- Severe pressing pain in abdomen, radiates upwards (1,200C).
- Cutting pain in upper part of left side of abdomen (1,30C).

Rectum

- Ineffectual desire for stool; passes with great straining; bleeding after stool (1,6C).
- Much offensive flatus passes with stool (1,30C).
- Diarrhoea at night (1,30C).

Stool

- Stool normal in consistency but blood drops after stool (1,200C).
- Hard stool passed with pain and bleeding from rectum followed by loose watery stool which passes forcefully (1,30C).
- Hard black stool passed with great straining (1,6C).
- Stool small, stony hard (1,6C).
- Sudden, watery, offensive, yellowish stool (1,30C).

Female

- Violent itching in both labial commissures; itching followed by bleeding, burning (1,30C).

Larynx & trachea

- Hoarseness of voice (1,200C).

Respiration

- Difficulty in breathing with nausea and severe abdominal pain (1, 200C).

Cough

- Dry cough with cold and coryza (1,200C).
- Dry paroxysmal cough with stitching pain in chest (1,30C).
- Paroxysmal dry cough with pain in throat, *agg.* talking, *amel.* by drinking cold water (1,30C).
- Cough with little expectoration, *agg.* in morning (1,6C).

Chest

- Electric pain in left side of chest, *agg.* at evening (1,200C).
- Stitching pain in left side of chest, *agg.* walking (1,30C).
- Wheezing in chest with coryza and redness of eyes (1,6C).

Extremities

- Pain between the shoulders, radiates to both hands up to fingers, *agg.* by movement, driving (scooter), lifting weight, *amel.* by rest (1,30C).
- Pain in both hands, radiates from the nape of neck. Pain goes up to little finger, *agg.* by bending neck forward, *amel.* by lying down (1,200C).
- Pain in left shoulder up to left side of neck, radiates to back of hand up to the tips of fingers, *agg.* by cold application, movement, jerk, *amel.* by hot application (1,200C).
- Burning pain behind the left knee, *agg.* from morning to afternoon, *amel.* by applying cold water (1,6C).
- Violent cramping pain in lower extremities, *amel.* by pressure (1,6C).
- Pustular eruptions near right elbow with swelling down to hand with pain, *agg.* by touch, jerk, *amel.* by cold application (1,200C).
- Itching of upper and lower extremities with dryness, *agg.* in open air, putting off clothes, *amel.* by cold water bath and after scratching (1,6C).

Fever

- Fever with chill, loose stool and vomiting (1,6C).
- Feverish feeling with bodyache and frontal headache, *agg.* in evening (1,200C).
- Mild fever with throbbing pain in head (1,6C).

- Great weakness, tired feeling with fever (1,200C).
- Malaise and general weakness with occasional chill and sometimes hot feeling with headache, body ache (1,6C).
- General weakness with fever, loose stool and vomiting (1,6C).

Skin

- Urticarial eruptions on body, hands, lips with severe itching; burning after scratching (1,200C).
- Pustular eruptions with mild fever, cold air unbearable (1,200C).

Generalities

- Weakness and tiredness; *agg.* in morning (1,6C).

Discussion

Drug was able to produce symptoms in 6C, 30C and 200C potencies. No mental symptom was observed. Only one symptom viz. *Redness and burning pain in both eyes with headache* appeared in more than one volunteer. Symptoms like nausea, vomiting and loss of appetite corroborate its toxic effects and symptoms like constipation seem to be its secondary action as its primary action causes purging. Drug seems to be indicated in gastrointestinal disorders, headache, sinusitis, conjunctivitis, cold, coryza, cough and fever. A concomitant symptom of constant nausea with pain in neck and hands was also found. These symptoms may help in clinical application of the medicine.

It is possible that there might have been partial proving of the drug at individual level but it is not published in available homoeopathic literature. However, the Council is open to receive feedback from the physicians or organizations, if they have proved the drug. The Council would be grateful, if they can share their proving data with the Council, for the benefit of homoeopathic profession. Limitation of the study was that enrollment of provers was less as per the requirement of the protocol. However, for further detailed proving it can be proved on larger number of volunteers keeping 30% of the volunteers as controls.

Conclusion

The symptoms observed during the proving indicates that this drug may be useful in the clinical conditions like conjunctivitis, stye, cough, coryza, cervical spondylosis and urticarial eruptions on symptom similarity basis. Symptoms that appeared during the trial will add to the available literature on this medicine and benefit the research scholars and clinicians for clinical use.

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