

## MULTICENTRIC, PLACEBO-CONTROLLED, RANDOMISED DOUBLE-BLIND EVALUATION OF A NEW HERBAL CREAM IN VAGIAL INFECTIONS

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**Received: 27 December, 1994**

**Accepted: 1 March, 1995**

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**ABSTRACT:** *Efficacy and safety of a new herbal cream containing aqueous extracts of Azadirachta indica, Curcuma longa, Pongamia glabra, Glycyrrhiza glabra and Santallum album were evaluated in a multicentric, randomized, double-blind, placebo-controlled study. With active drug treatment, there was significant improvement in various signs like redness, oedema and symptoms like itching, burning, discharge and discomfort, compared to placebo treatment. Microscopic examination of smear and culture showed significant reduction of offending organisms after treatment with active drug. In patient's global evaluation, active drug was rated 70% as very good and in investigators evaluation 82% as very effective and effective. The overall efficacy was as high as 76% with active drug as against only 24% with placebo. Both active drug and placebo were well tolerated.*

### INTRODUCTION

India has a living tradition of health science-Ayurveda, used for millennia. It has large base of medicinal plants to choose remedies from. Experience and research on indigenous medicinal plants of India have been sizeable and innumerable therapeutic modalities and several leads exist for clinical use and pharmaceutical development (1).

At least one third of all women of child bearing age suffer from one or more vulvo-vaginal infections. Vaginosis may be non-specific caused by *Gardnerella vaginalis* or specific by *Candida trichomonas* or mixed infection (2). The goal of drug treatment of vaginal infections is to restore normal vaginal flora and alleviate symptoms of burning, itching, discharge etc (2). Drug treatment of vaginal infections may be systemic and/or local. Local treatment for

trichomoniasis is with imidazole cream (metronidazole) and for moniliasis by polyene –antifungal pessaries (nystatin) for at least 14 days. *Candida glabrata* is best treated with gentian violet. With anti-fungal creams like miconazole, clotrimazole, nystatin etc. 0-6.6% of patients have reported irritation which may necessitate changing drug therapy (2). Terconazole has been reported to cause headache in 26% of patients. Local treatment of non-specific vaginitis with bactericidal creams like triple sulphur or any antibiotic pessary are known to cause local irritation and reaction. Gentian violet has permanent purple staining characteristics. These adverse effects have prompted the search of newer, safer and effective alternative therapy for treatment of vaginal infections. Indigenous drugs in form of pastes have been used by Siddha

and Ayurveda physicians for treating a number of infections. *Azadirachta indica* (neem) has astringent, local stimulant, antiseptic, antibacterial and antispirocheta properties (1,3,4). Its effectiveness in skin diseases and its ability to inhibit growth of fungi, like *Tinea rubrum* is well established in ayurvedic literature. The extract from *Pongamia glabra* (karanja) seeds has been shown to possess antiseptic, stimulant and healing properties (5). *Curcuma longa* (haridra) has antibacterial and anti-inflammatory properties (6,7). It is used in skin diseases. Anti-inflammatory and anti-arthritis properties of *Glycyrrhiza glabra* (yasti madhu) are well established (8,9). It has anti-inflammatory activity similar of hydrocortisone. It is used in all types of leucorrhoea and other uterine conditions. *Santalum album* (sandal oil) is astringent and disinfectant to mucous membranes of genitor-urinary and bronchia tract (10,11). In skin disease it reduces itching, heat, inflammation and pruritus and gives good aroma. In the present study, *Azadirachta indica*, *Curcuma longa*, *Pongamia glabra*, *Glycyrrhiza glabra* and *Santalum album* prepared in an aqueous base cream, was evaluated for its efficacy in the treatment of vaginal infections.

## MATERIALS AND METHODS

Total hundred female patients, who were symptomatic and diagnosed of having vaginal infection were enrolled in the present, placebo-controlled, randomized, double-blind study. Patients over 45 years, having genital tract carcinoma or those receiving any other systemic or local treatment for vaginal infections were excluded from the study. Each patient gave her informed written consent for participation in this local ethical committee approved study. Patients were randomly divided into two groups. Fifty patients in

first group, mean age  $31 \pm 6$  years received placebo ointment and second group of 50 patients mean age  $29 \pm 4$  years received the ointment containing active drug. Patients were instructed to apply an inch long cream (1gm) twice daily for 7 – 10 days. During the study period no other local or systemic treatment for vaginal infections was allowed. Patients were evaluated for their symptoms and signs for vaginal infections. Redness, edema, ulceration, plaque and discharge as signs and symptoms like pruritus, burning, discharge and discomfort were evaluated before and after 7 – 10 days of treatment. The above parameters were recorded on case record form by the same investigators in 4-points scale as follows: none=0, mild = 1, moderate = 2, severe = 3. In all patients microscopic examination of vaginal smear was also carried out before and after the treatment. The vaginal smear culture was performed before and after the therapy in some patients suspected of vaginal candidiasis on smear examination. Patients were enquired about occurrence of any side effects. Global evaluation, both investigators and patients were recorded at the end of the treatment. ANOVA and paired, "t" test were employed for statistical evaluation.

## RESULTS

In the present, study a total 100 patients were enrolled. Out of 50 patients who received placebo, 46 reported for followup evaluation. In active drug group 44 patients reported for the followup. There was no statistical difference in age and duration of the complaints between the two groups. With active drug treatment, there was significant improvement in various signs and symptoms evaluated than placebo (Tables I & II).

With active drug treatment there was marked decrease in symptoms like pruritus, burning, discharge and discomfort as compared to placebo (fig.1). The decrease in the scores from  $1.81 \pm 0.92$  to  $0.47 \pm 0.6$ ,  $1.27 \pm 0.5$  to  $0.15 \pm 0.36$ ,  $2.2 \pm 0.5$  to  $0.51 \pm 0.36$  and  $1.29 \pm 0.73$  to  $0.32 \pm 0.38$  in pruritus, burning, discharge and discomfort respectively was observed with the active drug.

Redness score decreased from  $1.53 \pm 0.37$  to  $0.28 \pm 0.46$ , edema  $0.76 \pm 0.65$  to  $0.02 \pm 0.2$ , ulceration from  $0.34 \pm 0.51$  to  $0.08 \pm 0.3$  and plaque from  $0.64 \pm 0.7$  to  $0.00$  in patients receiving active drug. The above improvement in signs with active drug as compared to placebo was found to be highly significant statistically ( $p < 0.001$ ) (Fig. 2&3). Microscope examination of the smear as well as culture showed significant reduction of the offending organism after treatment.

In patients global evaluation at the end of the trial 78% rated poor and 22% fair in placebo group while 20% rated very good, 50% good, 14% fair and only 16% rated poor with active drug. Similarly in investigators evaluation, active drug was rated very effective in 32%, effective in 50% and not effective in 18% as compared to only 4% effective and 96% not effective with placebo (Fig 4&5). The over all efficacies were as high as 76% with active drug against only 24% with placebo (Fig.6). Both the active and the placebo creams were well tolerated by all the patients without any side effects.

## DISCUSSION

The pharamacotherapies of various gynecological problems afford varying degrees of clinical efficacy. Significantly high population of women during the child bearing age suffer from one or more

vulvovaginal infections. Local application of anti-fungal creams or imidazole creams and non-specific agents have been shown to be effective in relieving common symptoms like burning, itching and discharge. All these agents have varying degrees of efficacy and are less effective against the local inflammation. In the present study, the extract from five plants, produced significant improvement in alleviating signs and symptoms of vaginitis as compared to placebo.

The goal of drug treatment in these infections is mainly directed to restore normal vaginal flora and to control burning, itching and discharge. As compared to placebo, the test cream significantly reduced pruritus, burning, discharge and discomfort. There was significant reduction in edema, redness and ulceration. This effect may be due to the anti-inflammatory properties of the herbal extract used. Water extract of *Curcuma longa* (turmeric) showed significant anti-inflammatory activity and reduction in edema in experimental animals (12). The antiedema activity of the active principle curcumin was shown to be similar to cortisone and phelybutazone in rats (7). Similarly it has been reported to stabilize the lysosomal membrane, thus preventing inflammatory mediator release (13). The turmeric powder was shown to enhance wound healing (14).

Active principle glycyrrhetic acid present in *Glycyrrhiza glabra* was shown to have desoxycortisone and ACTH like activity (8). During inflammatory process, free radicle generation and lipid peroxidation play very important role. Both glycyrrhizine (LII) and glycyrrhetic acid (LIII) have potent anti-oxidative effects (15). In Ayurveda use of *Glycyrrhiza glabra* is extensively documented in eye diseases and throat infection (1).

One of the important etiologies of vaginal infection is fungi. Commonly used anti-fungal creams are known to produce local irritation. Post treatment smear examination and culture both showed significant anti-fungal activity in the present study. The chloroform extract of neem oil has been shown to be fungicidal for common skin pathogens (16). The essential oil showed anti-bacterial activity against *S.aureus*, *E.coli* and *S.pyogenes* (3). One of the active ingredients, sodium margosate, present in *A.indica* was shown to kill the protozoa in very low dilution of 1:10, 000. Local application of the present cream significantly reduced the occurrence of trichomoniasis. This activity may be due to the present of *A.indica* in the cream. Significant improvement was demonstrated in clinical trails with fresh leaves of *A.indica* in skin conditions like eczema, scabies and ringworm (17).

In active drug treatment group, the overall efficacy as evaluated by global evaluation by patients and investigators was found to be as high as 76% against only 24% with placebo. The present cream was found to be effective against fungal, protozoal and mixed infections of vagina. One of the ingredients in the cream – *Pongamia glabra* (*karanja*) has antiseptic, antiparasitic effect

and is known to destroy both vegetable and animal parasites in skin diseases (10, 11). The bark of *karanja* has been shown to be powerful astringent (10, 11). For the treatment of ulcer and fistulous sores, juice of *karanja* root with neem is used as paste (10, 11). Similarly, the juice of *karanja* has been shown to be effective in reducing gonococcal urethritis (10, 11). Its efficacy against saprophytic mange was found to be more effective than sulphur or benzyl benzoate ointment (10, 11). Metal complexes of *Pongamia* seeds have been shown to possess anti-microbial activity (10, 11).

Medicinally, sandal wood is applied externally in the form of paste with water, to reduce itching, inflammation and pruritus in skin diseases. Its oil is a astringent and disinfectant to mucous membranes of genitourinary and bronchial tract (11).

Test cream containing five ingredients known to have potent anti-inflammatory, anti-microbial, astringent and disinfectant properties combined in this present evaluation is responsible for significant effectiveness in vaginal infections as compared to the placebo. The cream was well tolerated by all the patients and thus can be recommended as a good, effective local therapy for vaginal infections.

## SYMPTOM EVALUATION

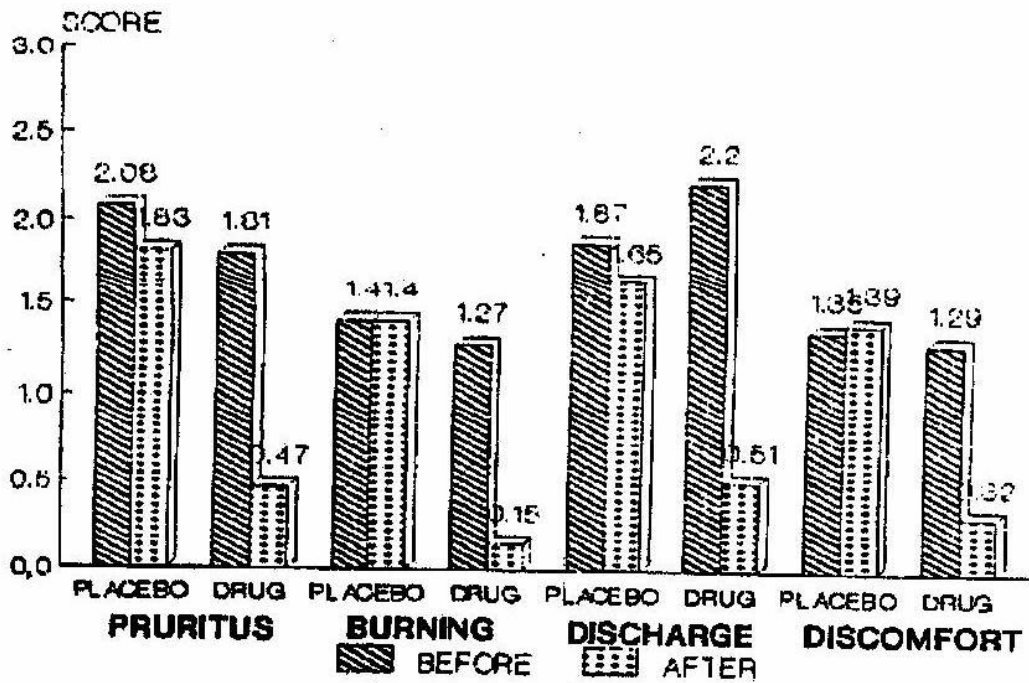


Fig- 1

**Effect of active drug cream and placebo cream on symptoms**

## SIGNS EVALUATION

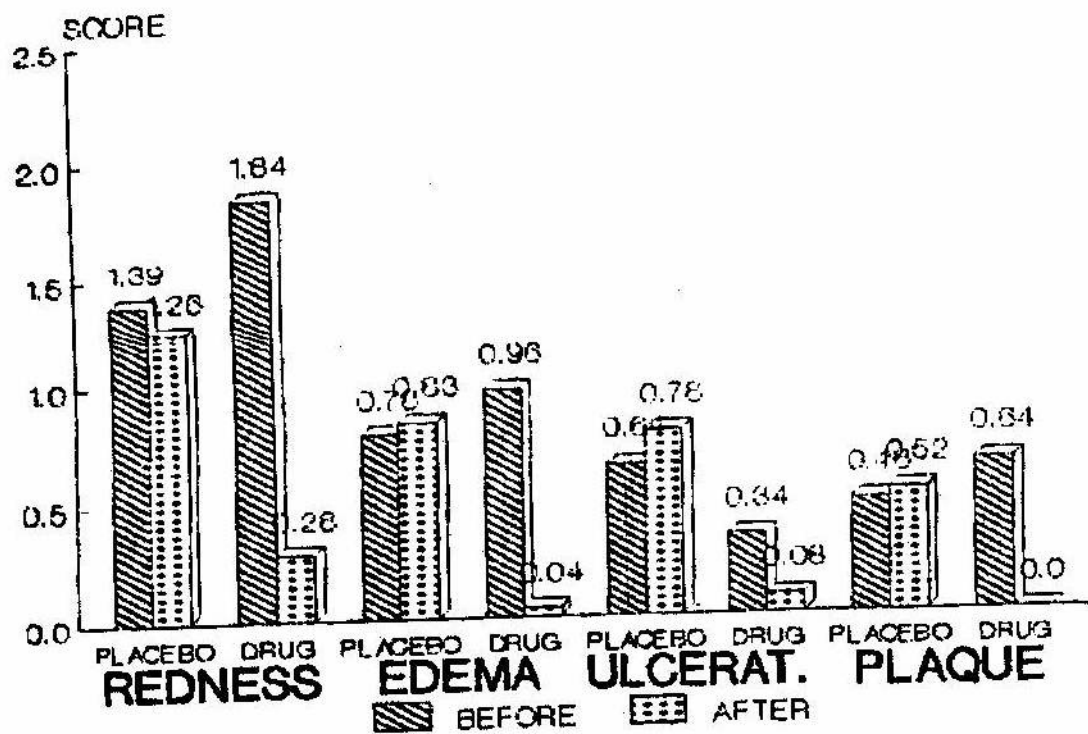


FIG-2

Effect of active drug cream and placebo cream on signs

# PATIENTS' EVALUATION

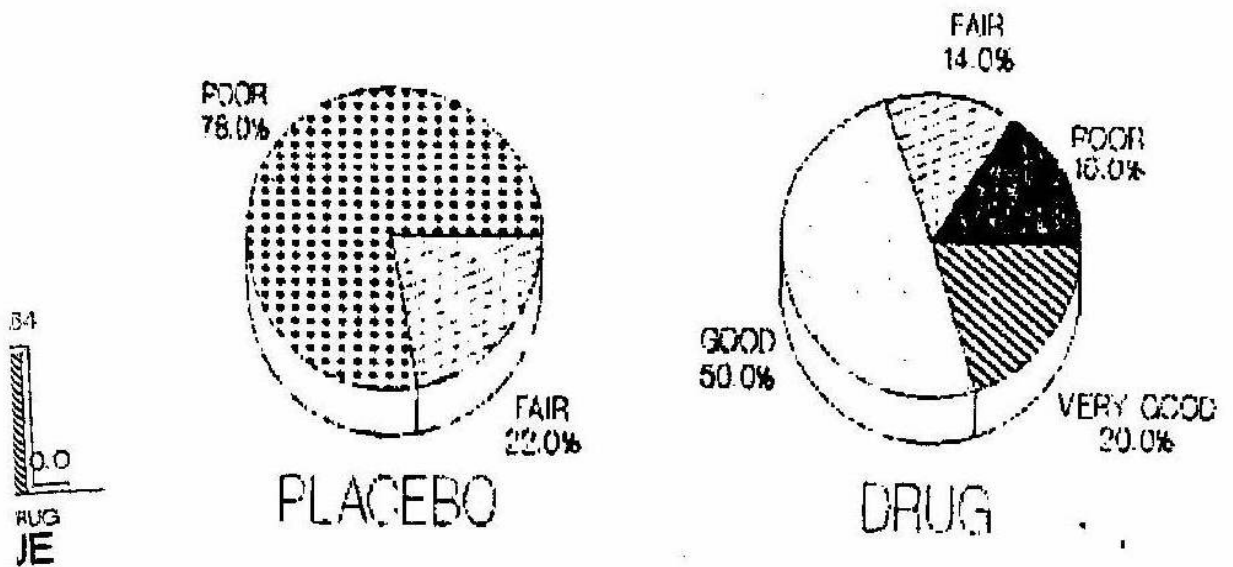


FIG - 3

Percentage of global evaluation rating with active drug and placebo cream

## INVESTIGATOR'S EVALUATION

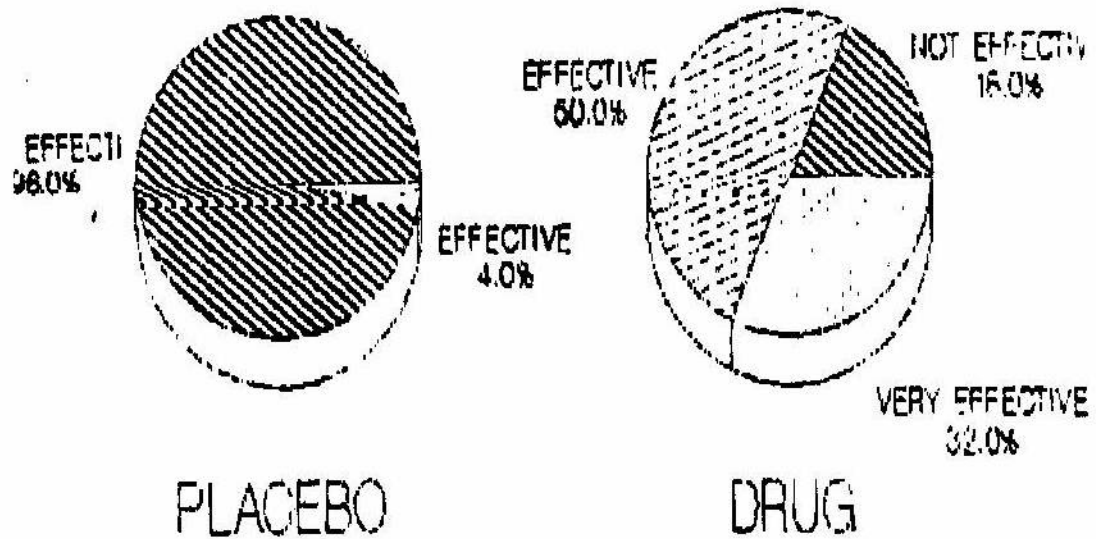


FIG - 4

Percentage of global evaluation rating with active drug and placebo cream



# RELIEF %

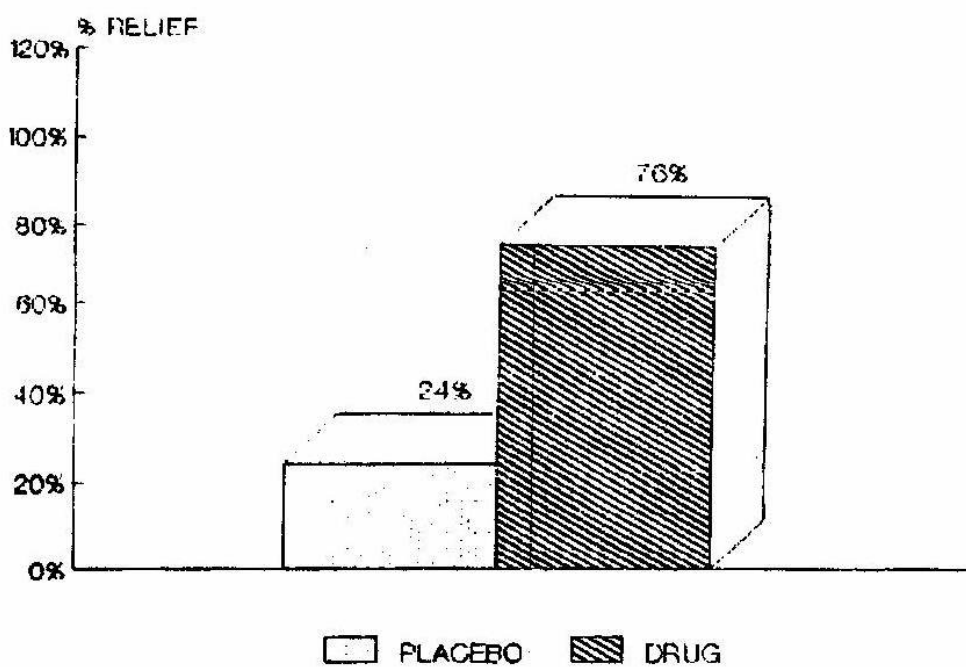


FIG - 5

Overall relief efficacy with active drug cream and placebo

and

**TABLE – 1**

GROUP	AGE	DURATION	PRURITUS		BURNING		DISCHARGE		DISCOMFORT		REDNESS	
			B	A	B	A	B	A	B	A	B	A
PLACEBO (n=46)												
Mean	31.39	6.91	2.08	1.83	1.39	1.39	1.87	1.65	1.35	1.39	1.39	1.26
S.D	5.8	4.7	0.59	0.71	0.72	0.78	0.69	0.65	0.7	0.65	0.65	0.62
ACTIVE DRUG (n=44)												
Mean	29.0	5.7	1.81	0.47	1.27	0.15	2.2	0.56	1.28	0.32	1.53	0.30
S.D ±	4.2	4.02	0.9	0.6	0.58	0.36	0.5	0.36	0.73	0.38	0.37	0.46

**TABLE - 2**

GROUP	EDEMA		ULCERATION		PLAQUE		DISCHARGE		SMEAR		CULTURE		% RELIEF	PATIENT EVALUATION	INVESTIGARO EVALUATION
	B	A	B	A	B	A	B	A	B	A	B	A			
PLACEBO (n=46)															
Mean	0.78	0.83	0.61	0.78	0.48	0.52	1.65	1.74	Mixed 30	Candid 30	7	7	24.23	Poor 78%	Not Effective 96%
S.D ±	0.52	0.65	2.0	2.4	0.66	0.73	0.49	0.8	Candid 4	4			8.6	Fair 22%	Effective 4%
									T. Vaginalis 12	12					
DRUG (n=44)															
Mean	0.76	0.65	0.34	0.08	0.61	0	2.0	0.58 26	Mixed 7 11		Candid -Ve		76.25	Poor 16% Fair 14% Good 50%	Not Effective 18% Effective 50%
SD ±	0.02	0.2	0.51	0.3	0.7	0	0.32	0.46	Candid 9	3				Very Good 20%	Very Effective 32%
									T. Vaginalis 9	3					

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