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PREPARATION AND CLINICAL EVALUATION OF SOME ANTI-ANORECTAL DISEASE DRUGS OBTAINED FROM MEDICINAL PLANTS

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ABSTRACT

The hydroalcoholic extracts of dried ligulate florets of *Calendula officinalis L.*, dried leaves of *Plantago major L.*, and dried aerial parts of *Vinca major L.* were prepared and used as the main active ingredients of two types of anti-anorectal disease ointments and suppositories. Benzocaine was used in one of the formulations, while a mixture of belladonna dry extract and ephedrine sulfate was used in the other. The effects of both prepared formulations were investigated in patients suffering from anorectal diseases, using relevant placebos for comparison.

The results indicated that the prepared drugs were significantly effective in the treatment of anorectal diseases. Formulations containing benzocaine proved to be more effective in patients suffering from hemorrhoids, while formulations containing belladonna dry extract and ephedrine sulfate were more effective in anal fissure and proctitis.

Keywords: Anti-Anorectal Disease Plants; *Calendula officinalis; Plantago major; Vinca major.*

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INTRODUCTION

In addition to hemorrhoids, anorectal disease encompasses other serious disorders such as anal fissure, anal fistula, proctitis, abscess, condyloma latumi, condyloma acuminata, cryptitis, malignant neoplasm, and polyps.[1-4] The common symptoms of anorectal disorders are: itching, burning, pain, inflammation, irritation, swelling and discomfort which may be relieved by self-medication if they are not manifestations of more serious anorectal disease. Bleeding, seepage, protrusion, prolapse and thrombosis are more serious symptoms of anorectal disease. These symptoms should not be self-medicated because a more serious disorder may be masked.[1]

The main pharmacologic agents used for relief of anorectal disease symptoms are: local anesthetics, vasoconstrictors, protectants, counterirritants, astringents, wound healing agents, antiseptics, keratolytics, and anticholinergics.[1]

In this research, considering the above mentioned types of pharmacological agents which are usually used for relief of anorectal disease symptoms, four formulations were designed, prepared, and their clinical effects investigated. The main active ingredients which have been used in these formulations were the hydroalcoholic extracts of three standard medicinal plants, namely: *Calendula officinalis, Plantago major,*

and *Vinca major*.

Calendula officinalis is an annual herb which is cultivated widely in Iran.[5] It contains saponins,[6,7] flavonoids,[6,8] coumarins,[9] carotenoid,[10] and polysaccharides.[11] It has spasmolytic, anti-inflammatory, anti-hemorrhagic, styptic, and antiseptic properties.[7]

Plantago major, a plant growing wild in different parts of Europe, Asia (including Iran) and north of Africa, contains iridoids,[12] mucilage,[7,13] gum, and the glucoside aucubin.[13] It has anti-hemorrhagic activity.[7,13]

Vinca major, which is a semi-procumbent shrub with tailing or somewhat ascending stems,[7] is cultivated widely in different parts of Iran.[5] It contains alkaloids and tannins with astringent and anti-hemorrhagic properties.[7]

MATERIALS AND METHODS

Plant materials

Dried ligulate florets of standard *Calendula officinalis L.* (family: *Compositae*) and dried leaves of standard *Plantago major L.* (family: *Plantaginaceae*) were obtained commercially from Isfahan, Iran. Aerial parts of standard *Vinca major L.* (family: *Apocynaceae*) were collected from the Agricultural Experimental Station of the Faculty of Pharmacy and Pharmaceutical Sciences-Isfahan University of Medical Sciences, Isfahan, Iran.

The identity of the above mentioned standard plant materials was confirmed by examining them macroscopically and microscopically and analyzing their active ingredients according to pharmacopoeial procedures.[7]

Preparation of plant extracts

Hydroalcoholic extracts of plant materials were prepared by perculation method.[14] Each extract was then evaporated under reduced pressure until its concentration was equivalent to one part of plant material (by weight) per one part of menstruum (by volume).

Ointments

Two types of ointment formulations were designed,[15] and then prepared by fusion method.[16,17] A placebo for each formulation was also prepared by the same method. Formulations of the ointments and their placebos were as follows:

Ointment Formulation Type A: Concentrated hydroalcoholic extracts of: dried ligulate florets of *Calendula officinalis* (10 ml), dried leaves of *Plantago major* (10 ml), and dried aerial parts of *Vinca major* (10 ml); benzocaine (3.3 gm); white soft petrolatum (45.5 gm); cholesterol (3 gm); stearyl alcohol (12 gm); white bees wax (6.7 gm) (total weight = 100 gm).

Packaging: Collapsible tin tubes, each containing 15 gm ointment.

Placebo of Ointment Formulation Type A: Hydroalcoholic solution of an approved brown color (30 ml); benzocaine (3.3 gm); white soft petrolatum (45.5 gm); cholesterol (3 gm); stearyl alcohol (12 gm); white bees wax (6.7 gm) (total weight = 100 gm).

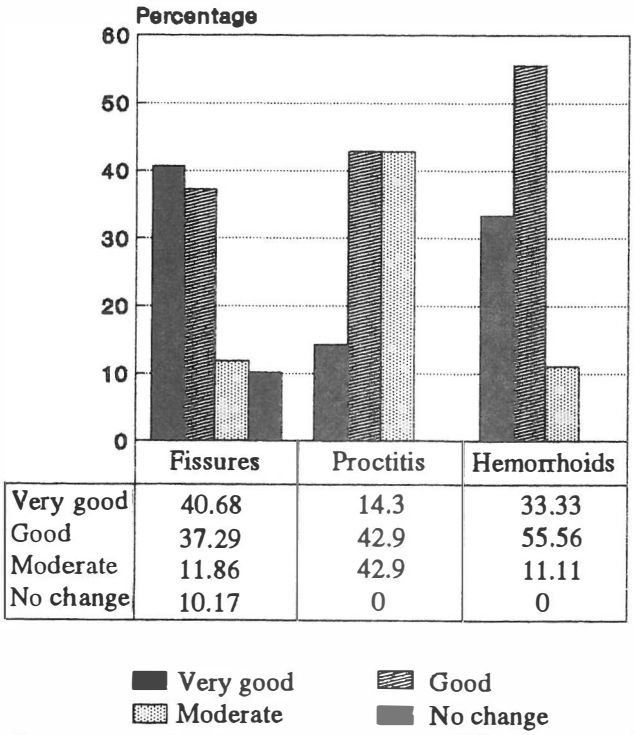
Packaging: Collapsible tin tubes, each containing 15 gm ointment.

Table I. Classification of the patients according to age and sex.

Sex / Age (year)	Male		Female		Total	
	No.	%	No.	%	No.	%
0-5	0	0.00	1	1.04	1	0.59
6-10	2	2.70	0	0.00	2	1.18
11-15	0	0.00	1	1.04	1	0.59
16-20	1	1.35	8	8.33	9	5.29
21-25	2	2.70	11	11.46	13	7.65
26-30	13	17.57	16	16.67	29	17.06
31-35	13	17.57	16	16.67	29	17.06
36-40	13	17.57	17	17.70	30	17.65
41-45	6	8.11	8	8.33	14	8.24
46-50	4	5.40	9	9.38	13	7.65
51-55	6	8.11	4	4.17	10	5.88
56-60	11	14.86	3	3.13	14	8.24
61-65	2	2.70	0	0.00	2	1.18
66-70	1	1.35	2	2.08	3	1.76

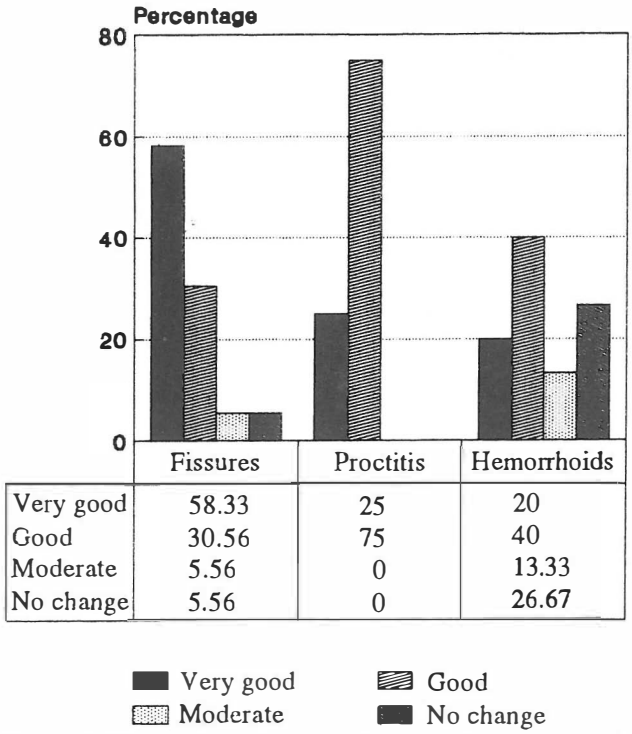
Table II. Percentages of symptom relief with type A formulations.

Results	Very good		Good		Total
Symptoms Relieved	No.	%	No.	%	% of relief
Pain	25	41.67	23	38.33	80.00
Bleeding	27	55.10	15	30.62	85.72
Burning	22	43.14	16	31.37	74.51
Discomfort	15	44.12	13	38.24	82.36
Itching	15	48.39	10	32.26	80.65
Inflammation	11	39.29	10	35.71	75.00
Swelling	4	23.53	8	47.06	70.59
Seepage	5	41.67	2	16.67	58.34



	Fissures	Proctitis	Hemorrhoids
Very good	40.68	14.3	33.33
Good	37.29	42.9	55.56
Moderate	11.86	42.9	11.11
No change	10.17	0	0

Figure 1. Effects of type A preparations on different anorectal diseases.



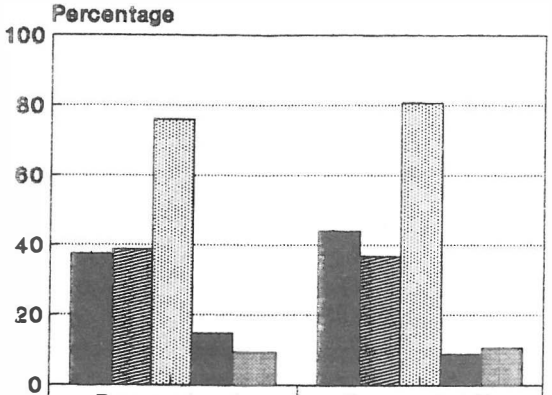
	Fissures	Proctitis	Hemorrhoids
Very good	58.33	25	20
Good	30.56	75	40
Moderate	5.56	0	13.33
No change	5.56	0	26.67

Figure 2. Effects of type B preparations on different anorectal diseases.

Ointment Formulation Type B: Concentrated hydroalcoholic extracts of: dried ligulate florets of *Calendula officinalis*
major (10 ml), and dried aerial parts of *Vinca major* (10 ml); ephedrine sulfate (0.2 gm); belladonna dry extract (0.7 gm); white soft petrolatum (45.5 gm); cholesterol (3 gm); stearyl alcohol (12 gm); white bees wax (6.7 gm) (total weight = 100 gm).
Packaging: Collapsible tin tubes, each containing 15 gm ointment.
Placebo of Ointment Formulation Type B: Hydroalcoholic solution of an approved brown color (30 ml); ephedrine sulfate (0.2 gm); belladonna dry extract (0.7 gm); white soft petrolatum (45.5 gm); cholesterol (3 gm); stearyl alcohol (12 gm); white bees wax (6.7 gm) (total weight = 100 gm).
Packaging: Collapsible tin tubes, each containing 15 gm ointment.

Suppositories

Two types of suppository formulations were prepared by fusion method.[16,17] A placebo of each formulation was also prepared by the same method. Formulations of the suppositories and their placebos were as follows:
Suppository Formulation Type A: Concentrated hydroalcoholic extracts of: dried ligulate florets of *Calendula officin*
major (0.2 ml), and dried aerial parts of *Vinca major* (0.2 ml); benzocaine (75 mg); cetostearyl alcohol (50 mg); white bees wax (50 mg); cocoa butter (1.16 gm) (total weight = 1.55 gm).
Packaging: Plastic (P.V.C.) molds, each containing 1.55 gm of the formulation.
Placebo of Suppository Formulation Type A: Hydroalcoholic solution of an approved brown color (0.6 ml); benzocaine (75 mg); cetostearyl alcohol (50 mg); white bees wax (50 mg); cocoa butter (1.16 gm) (total weight = 1.55 gm).
Packaging: Plastic (P.V.C.) molds, each containing 1.55 gm of the formulation.
Suppository Formulation Type B: Concentrated hydroalcoholic extracts of: dried ligulate florets of *Calendula officinalis*
major (0.2 ml), and dried aerial parts of *Vinca major* (0.2 ml); ephedrine sulphate (3 mg); belladonna dry extract (9 mg); cetostearyl alcohol (50 mg); white bees wax (50 mg); cocoa butter (1.25 gm) (total weight =1.55 gm).
Packaging: Plastic (P.V.C.) molds, each containing 1.55 gm of the formulation.
Placebo of Suppository Formulation Type B: Hydroalcoholic solution of an approved brown color (0.6 ml); ephedrine sulfate (3 mg); belladonna dry extract (9 mg); cetostearyl alcohol (50 mg); white bees wax (50 mg); cocoa butter (1.25 gm) (total weight =



	Preparation A	Preparation B
Very good	37.33	43.86
Good	38.67	36.84
Total	76	80.7
Moderate	14.67	8.77
No change	9.33	10.53

Very good Good
Moderate No change
Total

Figure 3. Overall efficacy of type A and B preparations on anorectal disorders.

1.55 gm.)

Packaging: Plastic (P.V.C.) molds, each containing 1.55 gm of the formulation.

Evaluation of clinical effects of the prepared fomulations

The prepared formulations and their placebos were prescribed to 170 patients suffering from anorectal disease. The patients were examined by a specialist before and after treatment at the Vijeh Clinic of Khorshid Hospital in Isfahan, Iran. Out of 144 patients who cooperated with us, 75 patients used type A ointment and suppository formulations, 57 patients used type B ointment and suppository formulations, and 12 patients used the placebos of these formulations. Duration of treatment was at least 6-7 days, and the patients used either one tube of ointment or six suppositories. Ointments were applied locally twice daily (b.i.d.), and suppositories as one suppository h.s.

RESULTS AND DISCUSSION

Out of 170 patients who received the prepared formulations, 96 patients (56.5%) were women and 74 patients (43.5%) men. The prevalence of anorectal disease in women has been reported previously by other investigators.[18] These disorders appear with greatest frequency in subjects 26-40 years of age (see Table I).

Table III. Percentages of symptom relief with type B formulations.

Results	Very good		Good		Total
Symptoms Relieved	No.	%	No.	%	% of relief
Pain	21	55.26	12	31.58	86.84
Bleeding	2	60.00	9	25.71	85.71
Burning	25	69.44	7	19.44	88.88
Discomfort	18	64.29	4	14.29	78.58
Itching	10	43.48	8	34.78	78.26
Inflammation	12	54.55	7	31.82	86.37
Swelling	7	70.00	0	0.00	70.00
Seepage	4	66.67	2	33.33	100

Previously, subjects 20-50 years of age have been claimed to own the greatest frequency of disease.[1]

From an occupational point of view, the greatest frequency of these disorders was among women housekeepers (49.41%). Pregnancy and labor were by far among the most important etiologic factors in women. The gravid uterus causes increased pressure in the middle and inferior hemorrhoidal vessels, while labor intensifies the hemorrhoidal condition, producing intense symptoms after delivery.[1]

Patients who received the prescribed formulations for treatment were mostly suffering from anal fissures, followed in order of frequency by hemorrhoids and proctitis.

The common symptoms of anorectal disorders were, in order of frequency, pain (71.76%), bleeding (66.47%), burning (65.88%), discomfort (50.59%), itching (46.47%), inflammation (35.29%), swelling (20.59%) and seepage (13.53%).

Type A formulations of both ointment and suppository forms were more effective in patients suffering from hemorrhoids (see Fig. 1). This efficacy can be attributed to the presence of benzocaine which acts as a local anesthetic by preventing the transmission of nerve impulses.[19] On the other hand, type B formulations of both drug forms were more effective in anal fissures and proctitis (see Fig. 2). In the latter formulations, benzocaine was replaced with ephedrine sulfate and belladonna dry extract. Ephedrine sulfate is a vasoconstrictor which acts on both alpha- and beta-adrenergic receptors.[19,20] When applied locally in the anorectal area, it causes arteriolar constriction. It relieves local itching because of its slight anesthetic effect, caused by an unknown mechanism.[1] Belladonna dry extract which has anticholinergic action, has been employed previously to relieve the discomfort of hemorrhoids and anal

fistula.[19,20]

When the efficacy of different formulations on the common symptoms of anorectal disorders were compared, type A formulations were shown to be less effective on burning, pain, discomfort, inflammation and seepage, while type B formulations were less effective on itching and swelling. On the other hand, the effects of both formulations were similar on bleeding, since the proportions of anti-hemorrhagic plant extracts were equal in all types of formulations (see Tables II and III).

Placebo ointments and suppositories of both types A and B were ineffective in treatment, but temporarily relieved some of the symptoms, such as pain or itching, depending on the presence of either benzocaine or ephedrine sulfate and belladonna dry extract in the formulations used.

The overall results obtained from the use of the prepared drugs in this investigation are shown in Figure 3. It is notable that the ointment and suppository forms of type B formulations are more effective than type A in the treatment of anorectal disorders.

Out of 92 patients who used the "antihemorrhoid" formulations which are available in the commercial market of Iran, 23 patients (25%) experienced no change in symptoms, while out of 132 patients who used our prepared formulations, this number dropped to 14 (10.60%). The differences between the above mentioned percentages are statistically significant.

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