





Potassium Alum Vaginal Suppository: Irritation Assessment in Rabbit

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Abstract

Background and objective: Potassium alum, called “Zaj-e-abyaz” in Iranian traditional medicine, is used vaginally in traditional clinics as an astringent agent for uterine fibroids. Before evaluating its efficacy, it is necessary to prepare a suitable dosage form and assess the possible irritation in animal model which was the aim of the current research. **Methods:** Vaginal suppositories were prepared using 400 mg potassium alum, 200 mg honey and different proportions of poly ethylene glycol (PEG) 600, 1000 and 4000 in each suppository. The best formulation was used for evaluation of possible irritation in rabbit. The suppositories were used in rabbit’s perineum daily for 5 consecutive days in 3 albino rabbits and the appearance of the vaginal opening and perineum for signs of erythema and edema were recorded every day. The final results were calculated as the primary irritation index (PII). **Results:** The best formulation contained potassium alum 20%, honey 10%, PEG 600 18%, PEG 1000 12%, PEG 4000 30% and water 10%. According to the animal test, the irritation of the vaginal mucus membrane was considered moderate in rabbits. **Conclusion:** Regarding the results, potassium alum could not be used in form of suppository in PEG vehicle and other formulations should be prepared for acquiring the least irritation.

Keywords: Iranian traditional medicine; potassium alum; uterine fibroids; vaginal suppository

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Introduction

Uterine fibroids are common benign smooth muscle tumors of the uterus [1]. About 20-40% of women will develop one or more uterine fibroids during their reproductive life time [2]. Many of them will experience associated symptoms or health concerns which have different outcomes such as diminished quality of life, disturbance of usual activities and roles, lost work time, and healthcare wasting. Various options are considered for uterine fibroids

treatment according to cost, invasiveness, recovery time, risks, possibility of long-term resolving of symptoms, need for future care for uterine fibroids, and effect on later childbearing. Interventions include hopeful management, medications to ameliorate or resolve symptoms or decrease size of uterine fibroids, procedures (uterine artery occlusion via embolization, ligation, or coagulation), fibroid ablation (e.g., high intensity focused ultrasound,

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radiofrequency), and surgery (endometrial ablation, hysterectomy and myomectomy) [1]. Some of interventions are effective for diminishing fibroids size and improving symptoms. Some medications and procedures also improve quality of life. Among various interventions for fibroids treatment, traditional medicine has a special place; traditional healers use some medications in uterine fibroids [3-5], one of them is "Zaj-e-abyaz" (potassium aluminum sulfate, potassium alum, $KAl(SO_4)_2 \cdot 12H_2O$) which is a mineral drug and is used in traditional medicine of different countries for various conditions [6-8]. The substance, which is frequently referred to as just "alum", is the most significant member of the general family of substances known as alums [7]. It is a white and bright crystal with no odor, styptic, some sour in taste and soluble in water along with astringent property. This drug was prepared in Asian countries for the first time and is an ancient drug [6]. It is found in the grocery stores for pickling and in baking powder and also used in leather tanning, water purification, as a flocculants in after shaves and a styptic for small shaving-related bleeding. Since the 1920s, alum has been the main adjuvant used to boost the effectiveness of immunizations [8,9]. According to Iranian traditional medicine (ITM), Persian medicine, alum has hot and dry temperament with severe astringent effect. It is used in spoiling excess flesh of the wound and chronic ulcers such as uterus, and mouth ulcers [10]. In Unani medicine, it is used in vaginal diseases [6]. In Iran, some traditional healers use alum for decreasing uterine fibroids size. In this case, alum powder is used along with honey in hard gelatin capsules and is used vaginally. This form of application is not approved and it is essential to prepare an appropriate dosage form for vaginal use which was the first aim of the current investigation. After the formulation process, the vaginal dosage

form should be evaluated for possible irritation in vivo which has been the second aim of the study.

Material and Methods

Ethical consideration

This research was performed according to guideline of ISO 10993-10:2010 [11] and approved by the ethics committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran with code of IR.SBMU.AEC.1402.028.

Chemicals

Potassium alum was purchased from Tehran market and identified at the Herbarium of Traditional Medicine and Materia Medica Research Center, SBMU, Tehran, Iran with code HMS-580. PEG 600, 1000, 4000 were prepared from Merck Co. (Germany). Honey was from Honey Taj Company (Iran).

Suppository formulation

In traditional clinics, hard gelatin capsules (size 0) containing 400 mg potassium alum with 200 mg honey are used daily for 28 days in 2 consecutive months (14 days in each month). Similar combination was used for preparing vaginal suppository in this study. Since, potassium alum is a polar substance and is soluble in water, polyethylene glycol (PEG) with different molecular weights (600, 1000, 4000) was used as the vehicle for preparation of suppositories (Table 1). Each formulation contained alum (20%), honey (10%), water (10%) and vehicle 60%. First, alum was dissolved in water-honey mixture. Warm PEG complex according to Table 1 was added to the mixture, stirred and poured to suppository making device (2g) until the liquid turned into solid form. The formulation was first prepared with PEG 4000 (100%) and then two other PEG (600 and 1000) were added with different proportions until the suitable formulation was obtained.

Table 1. Different formulations of potassium alum vaginal suppository

No	Alum%	Honey%	Water%	PEG600%	PEG1000%	PEG4000%
F1	20	10	10	0	0	60
F2	20	10	10	6	30	24
F3	20	10	10	6	42	12
F4	20	10	10	24	12	24
F5	20	10	10	24	18	18
F6	20	10	10	24	24	12
F7	20	10	10	18	6	36
F8	20	10	10	18	0	42
F9	20	10	10	18	12	30

Irritation test in rabbit

In order to evaluate irritation potential of potassium alum vaginal suppository, healthy young adult female albino rabbits from a single strain weighing not less than 2 kg were obtained from the Pasteur Institute of Iran. The rabbits were housed singly in stainless steel, wire-mesh cages and kept under standard animal laboratory conditions, 12 h of light and dark cycles, at controlled temperature 22 ± 2 °C, with a relative humidity of $50 \pm 5\%$, and free access to food and water. The animals were checked for vaginal discharge, swelling and/or other evidence of vaginal infection, irritation and/or injury prior to each treatment.

The alum vaginal suppository was placed into the animal's perineum in sterile condition. This procedure was repeated at 24 h intervals every day for five consecutive days. The rabbits were returned to the cage after treatment. No other substances were tested on the rabbits. The animals were observed 24 h after the application and immediately prior to each treatment. The appearance of the vaginal opening and perineum for signs of erythema and edema were recorded. The results of the study were used to determine the appropriate irritation classification. The macroscopic evaluation of potassium alum vaginal suppository was quantified according to the Draize scale (Table 2) [11].

The scores were used to obtain the primary irritation index (PII) as the final result (Table 3).

Results and Discussion

Alum as a mineral drug is widely used in traditional medicine due to its astringent capacity [6,10]. Nowadays, because of high incidence of uterine fibroids and their complications in women, alum is used by some traditional healers for reducing fibroids size.

The results of suppository formulation in the present study showed that due to high polarity of alum and solubility in water, usage of water soluble vehicles such as PEG was necessary. For preparing vaginal suppository, three types of PEG including PEG 600, 1000 and 4000 were applied. According to Table 4 usage of low molecular weight PEG resulted in soft and sticky suppositories. Despite of water soluble property of alum, increasing high molecular weight PEG caused precipitation. By increasing PEG 4000 in the formulation, suppository became harder, and

finally suitable suppository was made using PEG 600 (18%), PEG 1000 (12%) and PEG4000 (30%). This formulation was tested in rabbits for irritating effects.

Table 2. Draize scale for scoring of irritation

Erythema and eschar formation	Score
No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4
Edema formation	
No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (raised approximately 1.0 mm)	3
Severe edema (raised more than 1.0 mm extending beyond the area of exposure)	4

Table 3. Descriptive rating for mean primary irritation index (PII)

Primary irritation index (PII)	Classification
0	Negligible
$0 < \text{PII} \leq 2$	Slight
$2 < \text{PII} \leq 5$	Moderate
$5 < \text{PII}$	Severe

Table 4. Physical characteristics of different formulations of potassium alum vaginal suppository

No	Characteristics
F1	Hard
F2	Precipitation
F3	Precipitation
F4	It became hard immediately
F5	Soft
F6	Soft
F7	Sticky
F8	Fragile
F9	Suitable

The scores from rabbits with respect to observation time are presented in Table 5. In the present study, potassium alum, produced moderate mucosal irritation, erythema and edema when applied to the vaginal tissue of rabbits. This side effect is due to severe astringent effects of the drug which makes it unsuitable for vaginal indication in the form of suppository or even capsule which is used by traditional healers. Because after dissolving the capsule gelatin in vaginal area, alum is released immediately and will cause irritation similar to suppository.

It seems that usage of oils in the formulation may diminish the irritation which maybe a reason for soaking alum capsules in olive oil by some traditional healers before use. On the other hand, formulation of long acting formulations may be another choice in order to prevent releasing high concentration of the drug and possible irritation.

Table 5. Mucosal responses observed in female rabbits 24 h after each treatment

Female rabbits	Evaluation					
	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	
1	Erythema	0	1	2	1	2
	Edema	0	0	0	0	0
2	Erythema	1	2	2	1	0
	Edema	3	3	3	1	2
3	Erythema	0	0	0	0	0
	Edema	0	0	0	0	0

Despite several studies on biological effects of alum, no investigation has been conducted on uterine fibroids. Antibacterial properties of alum on various bacteria strains have been proved [12,13]. Alum has anti hemorrhagic activity as well. It was also successfully used as haemostatic agent in patients with tonsillectomy [14]. The efficacy of alum in intravesicular irrigation was established in continuous and severe urinary bladder hemorrhage [15,16]. During a research, alum was used in patients of malignant hemopathies who developed cyclophosphamide-induced hemorrhagic cystitis by continuous irrigation of the bladder. In these patients, hematuria ceased with 75% success rate [17]. During a research done by Altaei et al for ulcer healing activity of alum in form of mouth wash, it was found that solutions of 3, 5, 7% alum showed lesion healing and decrease of healing duration in patients with aphthous ulceration [18]. It seems that the mentioned properties in somehow is related to the high astringent effect of alum which has been well defined in traditional medicine [10].

Despite of effectiveness of alum in some conditions, it may cause side effects as same as other drugs. According to Unani medicine, it may cause irritation of the skin and mucus membrane [6]. The drug contains aluminum which may be absorbed from vaginal mucosa and cause systemic side effects. Several studies reported aluminum toxicity. Perl et al studied three cases of senile dementia and three non-demented elderly controls, foci of aluminum were detected within nuclear region of a high percentage of neuron [19]. Aluminum can be deposited in bone and CNS particularly in renal failure patients [20-22]. Some people are allergic to Aluminum products and show symptoms due to contact to Aluminum products [6]. Overall, alum as a drug may cause side effects mostly due to aluminum content. It might cause vaginal irritation which was established in the current investigation. It is

not an appropriate choice for uterine fibroids in immediate release dosage forms in water soluble vehicles.

Conclusion

Alum vaginal suppository along with honey was prepared using PEG with suitable formulation characteristics. However, alum suppository is a vaginal irritant and induces erythema and edema, so it is not recommended to be administered vaginally alone, and needs to be modified to prepare a suitable formulation without irritant effects.

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Author contributions

Sareh Sangy, Mojgan Tansaz and Homa Hajimehdipoor designed the study. Leila Ara, Samira Sangy and Mehdi Mazinani contributed to performing the experiments.

Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the accuracy and integrity of the paper content.

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Abbreviations

ITM: Iranian traditional medicine; PEG: polyethylene glycol; PII: primary irritation index; CNS: central nervous system