

Effect of *Sambucus ebulus* topical preparation on uremic pruritusNaghme Jabbar Imani¹, Majid Saeedi^{*1}, Zohreh Hajheydari², Mohammad Ali Ebrahimzadeh³, Katayoun Morteza-Semmani³¹Department of Pharmaceutics, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran²Department of Dermatology, Boo Ali Sina (Avicenna) Hospital, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran³Department of Medicinal Chemistry, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran

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Abstract

Uremic pruritus is a common and distressing symptom that affects more than 40% of patients undergoing hemodialysis. Several medications as well as topical preparation have been used for relief this condition. *Sambucus ebulus* has been shown anti-inflammatory and wound healing effects. In this research, the antipruritic effect of *S. ebulus* fruit extract was evaluated on patients with uremic pruritus. *S. ebulus* fruits were collected from Sari suburb, Iran. Fruits were dried at room temperature and several fractions of extract were prepared. After formulating suitable gel (2%) a randomized, single blind, placebo-controlled clinical trial was performed in 78 patients (40 patients received *S. ebulus* topical gel 2% and 38 patients received placebo gel) for 8 weeks and the changes in hyperuremic induced pruritus severity were evaluated. Sixty one patients completed the study. The Pruritus severity index was reduced in both groups after 8 weeks' treatment. *S. ebulus* topical gel showed more effect than placebo, but this difference was not statistically significant. The results showed that *S. ebulus* topical gel can reduce uremic pruritus severity, and more study with higher extract concentration or more cases is proposed.

Keywords: Uremic pruritus, *Sambucus ebulus*, topical preparation, clinical trial

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Introduction

Uremic pruritus or chronic kidney disease-associated pruritus (CKD-aP) is a common and distressing symptom in patients with end stage renal disease (ESRD) and receiving either peritoneal dialysis or hemodialysis. Although prevalence of pruritus has declined recently by improved hemodialysis techniques, this symptom remains a major and frequent problem in these patients; and more than 40% of patients undergoing hemodialysis suffer from it (1). The most common areas affected are the back, arms, legs and face (2, 3). In general Itching was characterized as worse during dialysis, immediately after that and at night than during the day. These prurituses in combination with other symptoms decreases quality of life and make patient depressed (4). The pathogenesis of uremic pruritus is obscure, Its believed that multi substances cause this problem and it is not dependent on just one factor; some of these risk factors are, parathormone, histamine, divalent ions such as calcium, phosphorus and magnesium, male gender, high pre-dialysis level of BUN, high levels of b2-microglobulin and dialysis filter (1,4,5). There is not any definite treatment; and No drugs have been approved for this problem by the U.S. Food and Drug

Administration. Some common treatments such as antihistamine, topical steroids, emollients, and phototherapy (UVB) are available but have not been investigated rigorously (4).

Sambucus ebulus (Caprifoliaceae) or Dwarf elder is grown naturally in southern and central Europe and southwest of Asia especially Iran and Iraq. It is known as 'Palem' or 'Aghtii' in Iran and distributed in Northern coast of Caspian Sea like Mazandaran province (6). Flavonoids, phenols, steroids, tannins, sambunigrin, glycosides, cardiac glycosides, caffeic acid derivatives, chlorogenic acid, ursolic acid, ebulitins, ebulin and volatile substances of these species were previously reported (6-8). In traditional medicine, extracts of different parts of the herb like leaves, rhizome, root and fruits used in treating some inflammatory cases such as, bee and nettle bites, arthritis and sore-throat, burns and infectious wounds, edema, eczema, urticaria, hemorrhoids, rheumatism (6,7,9). In other studies some effects of *S. ebulus* were investigated Anti-inflammatory and antinociceptive (10), antioxidant (11,12) anticancer (13) and antibacterial (14) effects. Since there is no specific treatment, moreover because of current treatments issues and according to effects and properties of *S.*

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ebulus we aimed to prepare a topical formulation from methanolic extract of this herb, to investigate its effects on uremic pruritus.

Materials and methods

S. ebulus fruits were collected from Sari suburb, Iran in September 2015. The samples were confirmed by Plant systematic specialist and have been deposited in herbarium (Qaemshahr branch, Islamic Azad University, Qaemshahr, Iran). Fruits were dried at room temperature and away from sunlight. 500 grams of powdered sample was fractionated by successive solvent extraction at room temperature by percolation with hexane (2.4 L × 3) then ethyl acetate (2.4 L × 3) and finally methanol (2.4 L × 3). Toxicity in ethyl acetate fraction and safety in methanol fraction have been improved (15). The resulting methanol extract was the concentrated over a rotary vacuum evaporator (30-35 °C) until a solid extract sample was obtained. The resulting crude extracts were freeze-dried.

Determination of total phenolic compounds and flavonoid contents

Total phenolic compound contents were determined by the Folin-Ciocalteu method. The extract sample (0.5 mL) was mixed with 2.5 mL of 0.2 N Folin-Ciocalteu reagent for 5 min and 2.0 mL of 75 g/L sodium carbonate was then added. The absorbance of reaction was measured at 760 nm after 2 h of incubation at room temperature. Results were expressed as gallic acid equivalents. Total flavonoids were estimated using our recently publish papers (16). In other words, 0.5 mL solution of extract in methanol were mixed with 1.5 mL of methanol, 0.1 mL of 10% aluminum chloride, 0.1 mL of 1 M potassium acetate, and 2.8 mL of distilled water and left incubated at room temperature for 30 minutes. The absorbance of the reaction mixture was measured at 415. Total flavonoid contents were calculated as quercetin from a calibration curve.

Preparation of the formulations

The extract was dissolved in solvent system containing tween 80, preserved water (methyl paraben 0.18% and propyl paraben 0.02%) and ethanol. Several concentrations of HPMC (2-6%) and carbopol (0.3-1%) were used as gelling agent. The polymer was dispersed in this solution for overnight. The system was homogenized and neutralized by triethanolamine in formulations containing carbopol as gelling agent. The

formulations were kept in 4 °C, 25 °C and 40 °C for physical stability evaluation (viscosity, syneresis, swelling, color change) during 2 weeks (17). The selected formulation for clinical trial was controlled microbiologically based on USP 30 (United States Pharmacopoeia 30) (18).

Clinical assessments

The study was a randomized, single blind, placebo-controlled clinical trial and approved by the Research Ethics Committee of the council of Mazandaran University of Medical Sciences (IRCT 2016102810203NF). Seventy eight patients with uremic pruritus after giving written informed consent divided into two group randomly case group and control group. Patients were included if they had end-stage renal disease, were on hemodialysis for at least 3 months, 18 years old or older, experience at least 3 episodes of itching in last 2 weeks, xerosis without edema, despite medication intake in the last month of treatment, no evidence of improvement was observed. Patients with systemic disease such as cholestatic liver disease, hepatitis B and C, HIV, thyroid disorder, patients with skin disorder such as eczema and atopic dermatitis, lactating and pregnant women, patients with allergy to *Sambucus ebulus* gel, patients who received cholestyramine and UVB therapy, patients with psychotic illness or other communications problems were excluded from the study (5).

The following demographic, clinical and laboratory characteristics including age, gender, duration of dialysis, duration of itching, other systemic disease (Etiology of ESRD), Medications including, oral antihistamines and local steroids, and values of the most recent laboratory studies (haemoglobin, calcium, phosphorus, parathyroid hormone (PTH), pre and post-dialysis creatinine, pre and post- dialysis blood urea nitrogen, albumin, liver enzymes, adequacy of dialysis expressed as K_t/V , uric acid, fasting blood sugar) were recorded.

Case group's patients used *S. ebulus* gel and control group's patients used placebo gel twice a day for 8 weeks. Each person received cetirizin 10mg/day. At the first visit, 4th week, 8th week, the pruritus severity was determined using a scale ranging from 1 to 48 where 48 was the most severe itch imaginable (Table 1), xerosis in pruritus area (xerosis related to uremia) and bleeding from scratching were obtained. A detailed pruritus history was obtained at each visit to assess 24 hours

pruritus rate, severity, distribution, number and duration of pruritus episode, pruritus induced sleep disorder. Pruritus was graded by the 30-item inventory of pruritus developed by researchers through deep relevant review of literature about pruritus and itching (19-21).

Table 1 Pruritus-pointing system

Item	Morning	Afternoon	Night	Total
Period	1	1	1	3
Severity	5	5	-	10
Distribution	5	5	-	10
Frequency	5	5	-	10
Sleeping	-	-	10	10
Waking up	-	-	5	5
Total	16	16	16	48

At each visit drug sides effect including edema, erythema, burning, itching and pigmentation (hyperpigmentation and hypopigmentation) were investigated.

Statistical analysis

Quantitative data between two groups were compared by T-student test and qualitative data was compared by Chi-square and Fisher's exact test. In all cases, $p < 0.05$ was taken as statistically significant.

Results

Baseline characteristics

The extract was standardized by its total phenol and flavonoids contents as the main therapeutical compounds in this plant. The total phenolic content was 190.37 mg gallic acid equivalent/g of extract by reference to standard curve (Abs. = 0.0054Conc. + 0.062, $r^2 = 0.999$). The total flavonoid content was 24.6 mg quercetin equivalent/g of extract, by reference to standard curve (Abs. = 0.0063Conc. - 0.0075, $r^2 = 0.999$).

A total of 78 patients were recruited in the present study by a single investigator, 61 participants completed this study 17 patients were excluded from the efficacy analyses. Two patients suffered from allergic reactions one in control group and one in case group and 13 patients (7 persons in case group and 6 persons in control group) discontinued treatment due to personal reasons, one patient in each group

discontinued study because of death. All of the 61 subjects (31 patients in case group and 30 patients in control group) completed 8 weeks treatment (Fig. 1).

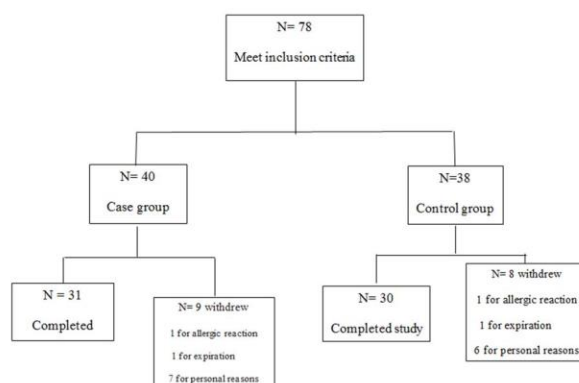


Figure 1 Profile of randomized controlled trial

The basic demographic, clinical and laboratory Data characteristics of the participants are summarized in (Table 2) Patients in control group were older than case group, and had higher duration of hemodialysis, duration of itching, FBS, ALT, AST, ALP, albumin, post-dialysis creatinine, K_t/V , PTH than patients in case group but there were no significant differences among these factors between patients in two groups. Case group had significant higher level of phosphorus, hemoglobin and pre-dialysis BUN compared with control group.

Efficacy

At baseline, no significant difference was observed between groups in mean pruritus severity scores ($P = 0.2630$). This similarity was observed between groups in the number of patients (%) with xerosis in the pruritus area ($P = 0.5077$) and number of patients (%) who making themselves bleed from scratching ($P = 0.443$) too.

Pruritus severity

At baseline (Fig. 2), the mean scores of pruritus severity in two groups were 20.53 ± 9.08 and 23.44 ± 10.36 , respectively. Patients in both groups experienced significant decrease in pruritus severity scores in comparison with baseline at 4th week 10.07 ± 6.78 ($P < 0.0001$) and 9.74 ± 9.749 ($P < 0.0001$) and at 8th week 7.43 ± 7.75 ($P < 0.0001$), 7.04 ± 9.81 ($P < 0.0001$). There was no significant difference in mean of pruritus severity between two groups at 4th and 8th week ($P = 0.8831$ and $P = 0.8656$ respectively).

Table 2 The basic demographic, clinical and laboratory Data characteristics of the participants

Characteristic	Case group (n=31)	Control group (n=30)	P value
Age (y)	55.9 ± 11.7	59.97 ± 13.88	0.2217
<i>Sex (%)</i>			
F	16 (51.61%)	14 (46.66%)	0.7997
M	15 (48.38%)	16 (53.33%)	
Duration of hemodialysis	25.4 ± 16.65	36.16 ± 25.49	0.0566
Duration of itching	14.43 ± 15.16	27.29 ± 27.74	0.0679
<i>Previous treatment (%)</i>			
Oral antihistamine	9 (29.03%)	7 (23.33%)	0.1923
Topical steroid	4 (12.9%)	3 (10.0%)	
<i>Etiology of ESRD (%)</i>			
Diabetes mellitus	17 (54.83%)	19 (63.33%)	
Hypertension	23 (74.19%)	19 (63.33%)	
Ischemic heart disease	4 (12.9%)	7 (23.33%)	
Kidney stone	2 (6.45%)	1 (3.33%)	
Multiple myeloma	-	1 (3.33%)	
Cystic kidney disease	-	2 (6.66%)	
Genetic	1 (3.22%)	1 (3.33%)	
Nephrotic syndrome	-	1 (3.33%)	
FBS (mg/dl)	128.6 ± 104.66	141.08 ± 82.92	0.6783
Alanine transaminase (U/L)	14.33 ± 8.37	20.41 ± 11.68	0.0661
Aspartate transaminase (U/L)	20.56 ± 8.68	23.91 ± 10.16	0.2821
Alkaline phosphatase (U/L)	341.04 ± 183.88	451.08 ± 235.8	0.1069
Albumin (g/dl)	4.06 ± 0.5	4.1 ± 1.01	0.8747
Calcium (mg/dl)	8.72 ± 1.17	8.4 ± 1.52	0.4602
Phosphorus (mg/dl)	5.62 ± 1.47	4.38 ± 1.33	0.008*
Hemoglobin (g/L)	11.65 ± 1.95	9.28 ± 2.75	0.0032*
Creatinine Pre-dialysis (mg/dl)	7.14 ± 2.38	6.47 ± 2.5	0.3908
Creatinine Post-dialysis (mg/dL)	2.16 ± 1.23	3.08 ± 1.97	0.0845
BUN Pre-dialysis (mg/dL)	111.3 ± 38.33	84.56 ± 36.56	0.0298*
BUN Post-dialysis (mg/dl)	34.59 ± 19.93	34.4 ± 18.09	0.9746
K _t /V	1.059 ± 0.319	1.067 ± 0.299	0.9339
Parathyroid hormone (pg/dl)	338.92 ± 337.61	391.58 ± 361.56	0.6367
Uric acid (mg/dl)	5.84 ± 2.27	5.33 ± 2.33	0.4875

*Data are expressed as mean ± standard deviation for normally distributed continuous variables; as number (percentage) for categorical variables. *P<0.05. BUN, blood urea nitrogen; ESRD, end stage renal disease; K_t/V is a measure of dialysis adequacy.

Xerosis in pruritus area

At baseline (Fig. 3) the number of patients (%) suffered from xerosis in case and control groups were 77.41% and 86.66% respectively (P= 0.5077). There was no significant reduction of xerosis in two groups

(P = 0.9189, P = 0.9022 respectively) during treatment.

Bleeding from scratching

Numbers of patients who making themselves bleed from scratching in both groups at the baseline, 4th and

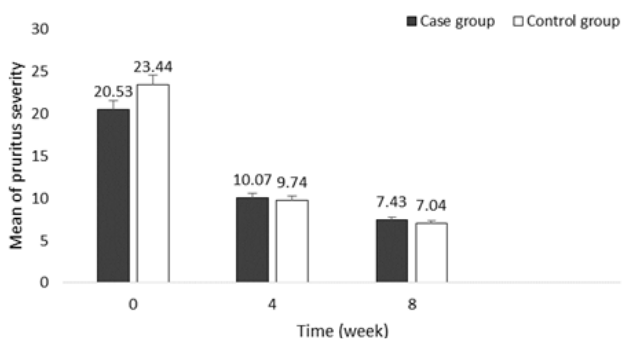


Figure 2 Mean of pruritus severity changes from baseline to weeks 4 and 8

8th week were shown in (Fig. 4). There was no significant difference between two groups at the baseline ($P = 0.443$), and there were no significant intra groups differences in both groups in 4th week ($p = 1$, $p = 0.1196$) and 8th week ($p = 0.1581$, $p = 0.007$).

Discussion

The aim of this Randomized, placebo-controlled study was to compare the effect of *S. ebulus* fruits extract topical gel 2% with placebo on uremic pruritus. Less than half of patients were previously treated unsuccessfully with antihistamines and topical steroids, but previously antihistamine’s non effectiveness has been investigated and they make a good feeling in patinets with mild sedative effect (3). Topical gel was chosen as selected dosage form. This topical preparation is not greasy and spread readily on the skin. The low oily effect of this dosage form make it more compliant rather than other topical preparations. In this study a significant reduction in pruritus severity was observed after 4 and 8 weeks but the difference between both groups was not statistically significant. Rayner et al. was investigated the effect of gabapentin and pregabalin on uremic pruritus in 71 patients in 2013.

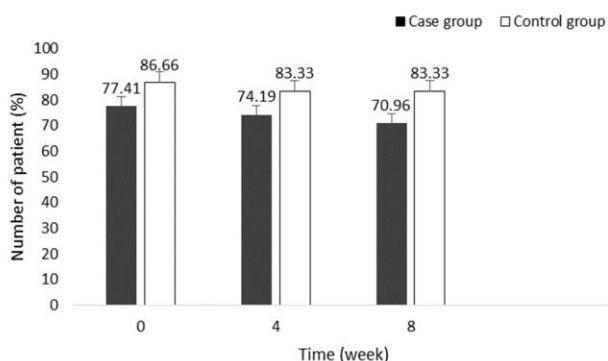


Figure 3 Number of patients (%) suffered from xerosis in pruritus area from baseline to 4 and 8 weeks

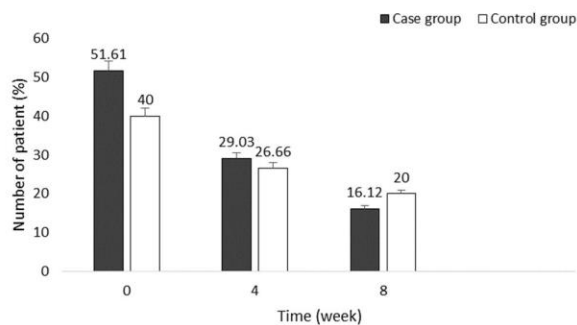


Figure 4 Number of patients (%) making themselves bleed from scratching from baseline to 4 and 8 weeks

Starting dose of gabapentin was 100 mg after dialysis or daily. Patients who experienced side effects with gabapentin were treated with pregabalin, starting dose 25 mg after dialysis or daily. Gabapentin or pregabalin relieved itching in 60 patients (85%), median follow-up 2 months. Unless renal elimination and side effects of these medicine must be considered (22). Nalfurafine, a selective agonist of kappa receptor has been approved for resistant pruritus. This open-label prospective study examined the effects of 52week oral administration of 5 µg/day nalfurafine hydrochloride in 211 hemodialysis patients and produced a long-term without significant safety problems (23). As microinflammatory processes may be involved in the pathogenesis of uremic pruritus, in another study 22 Patients applied Tacrolimus 0.01% ointment twice a day for 4 weeks, a strong reduction of pruritus severity was obtained but the differences between case and control groups wasn’t statistically significant (24).

In previous studies were investigated wound healing and anti-inflammatory effects of different part of *S. ebulus* extract. In one study Suntar et al. reported Wound healing potential of *S. ebulus* ointment prepared with leaves methanol extract at 1% concentration. A flavonoid derivative “quercetin 3-O-glucoside” was isolated and determined as one of the active component (9). According to Ebrahimzadeh et al. (in 2006) *S. ebulus* aerial parts and roots hexane extract showed statistically significant inhibition of edema induced by carrageenan at all doses (8). Jabbari et al. (in 2016) designed a study to compare the efficacy of *S. ebulus* gel which prepared from leaves water extract versus diclofenac in patients with knee osteoarthritis and there were significant differences between the efficacy of *S. ebulus* gel and diclofenac gel, regarding WOMAC

(Western Ontario and McMaster Universities Osteoarthritis Index) pain score, total WOMAC score and VAS score of pain. These effects of *Sambucus ebulus* may related to its different active ingredients such as quercetin-3-O-glucoside, ebullitin, ebullin1, flavonoid and anthocyanin components (25).

A large number of patients suffered from xerosis related to CKD (Chronic Kidney Disease), it is likely that xerosis has the synergistic effect with other pathogens on pruritus severity. In this study there were no significant differences in xerosis between two groups and no significant improvements were obtained in both groups in this parameter at the end of the study. A study was performed on 100 patients with moderate to severe uremic xerosis. Case group applied an emulsion combining glycerol and paraffin twice a day for 7 days on one allocated lower leg, and the emulsion preparation (comparator) on the other lower leg. A significant improvement of the uremic pruritus and quality of life of the patients at end of the study ($P < 0.001$, intragroup analysis) were investigated (26). Due to this synergistic effect it would be better if we used oil-based production. In number of patients who making themselves bleed from scratching in both group at the baseline there was no significant difference. No change was obtained in case group between 4th and 8th week, and a minor change was obtained in control group between 4th and 8th week but it is not statistically significant.

This study showed statistically similar results in two groups. It seems that some antipruritic effects of placebo were related to its hydrating, anesthetics and cooling effects.

Conclusion

The present study showed that *S. ebulus* gel reduced the pruritus severity and improved symptoms but no significant difference was observed between *S. ebulus* and placebo gel, although further studies are needed to confirm the results.

Acknowledgment

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Declaration of interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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