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Management of Human Ulcerative Colitis by Saturex™: A Randomized Controlled Trial

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Abstract: To evaluate clinical benefit of Satureja Khuzestanica (SK) trade named Saturex in Ulcerative Colitis (UC). A randomized controlled trial was conducted in UC patients. Patients with proliferative retinopathy, significant renal impairment (serum creatinine>3 mg dL^{-1}), documented coronary artery disease, chronic liver disease, diabetic foot ulceration and gangrene and pulmonary infection were excluded from the study. The patients were administered 500 mg SK or placebo supplements once daily while they were maintained on their current treatment for UC. After 4 months, frequency difference of the disease flare up was compared between study and placebo groups. 12/14 (85.5%) of SK patients were in complete remission after 4 months as compared to 6/13 (46.2%) of the patients on placebo. The flare up frequency difference (0.07-0.73) between two groups was significant. Supplementing with SK by preventing disease flare up and keeping the patients in remission state would give the opportunity to physicians to reduce the dose of chemical drugs resulting in lower side effects and better compliance of patients.

Key words: Satureja Khuzestanica, ulcerative colitis, randomized controlled trial, oxidative stress

INTRODUCTION

Ulcerative Colitis (UC) is kind of chronic Inflammatory Bowel Disease (IBD) that causes many disabling symptoms. It is specified by an inappropriate immune response that causes distinctive inflammatory lesions in the colon. Over production of free radicals (Rezaie *et al*., 2007a; Hosseini-Tabatabaei and Abdollahi, 2008), imbalance of pathogenic and normal flora of the bowel (Rahimi *et al*., 2006, 2007a; Elahi *et al*., 2009) and dysregulation of immune system (Nikfar *et al*., 2010a) are involved in induction and aggravation of the disease. Currently, pharmacological management of UC is done by use of aminosalicylate derivatives (Nikfar *et al*., 2009; Rahimi *et al*., 2009a), tumor necrosis factor antibodies (Rahimi *et al*., 2007b, c), probiotics (Elahi *et al*., 2008; Rahimi *et al*., 2008a, b; Nikfar *et al*., 2010b), immunoregulators (Nikfar *et al*., 2010a) and miscellaneous drugs like nicotine (Nikfar *et al*., 2010c), ATP donors (Salari and Abdollahi, 2009) and phosphodiesterase inhibitors (Salari-Sharif and Abdollahi, 2010). Almost all of these compounds have limited use because of their serious adverse effects. For instance, use of aminosalicylate derivatives during pregnancy may be associated with adverse pregnancy outcomes (Rahimi *et al*., 2008c). Due to side effects that are commonly seen with current treatments, new investigations have focused on safe effective compound like those obtained from herbal sources (Rahimi *et al*., 2009b) or traditional medicine (Rahimi *et al*., 2010).

Satureja Khuzestanica (SK) in Traditional Iranian medicine (TIM) has been used for its antiseptic, analgesic and anti-inflammatory effects. The herb is distributed in the Southern part of the Iran belonging to the family Lamiaceae, subfamily Nepetoideae.

The biological activities and effects of SK have been extensively reviewed by Momtaz and Abdollahi (Momtaz and Abdollahi 2008, 2010). Antioxidative effects of SK have been well confirmed because of its main components such as carvacrol and flavonoids. Carvacrol could prevent prostaglandin synthesis by inhibiting cycloxygenase-2 biosynthesis. Carvacrol also disrupts cell wall of gram negative bacteria and destroys Escherichia coli, Listeria monocytogenes and Lactobacillus sakei. Regarding the role of oxidative inflammation and overgrowth of microbes in pathogenesis of IBD, SK was studied in experimental colitis by our team and found that SK relieves rat IBD through its antioxidant, antimicrobial and anti-inflammatory properties very comparable to prednisolone (Ghazanfari *et al*., 2006). Safety profile of SK has been studied and completed in animals (Abdollahi *et al*., 2003) and this herbal compound

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has been examined and found effective in human diabetes (Vosough-Ghanbari *et al*., 2010), rat diabetes (Saadat *et al*., 2004), rat hemorrhagic cystitis Rezvanfar *et al*., 2008, 2010), rat male infertility (Haeri *et al*., 2006) and human periodontitis (Shahab *et al*., 2011).

Therefore, in the present study we evaluated clinical effects in UC patients for the first time.

MATERIALS AND METHODS

The plant was cultivated in Khorramabad and the aerial parts of the plant were collected during the flowering stage. The aerial parts were air dried at ambient temperature in the shade. Tablets were prepared from dried leaves of plant (each tablet contained 500 mg of dried leaves) as described previously (Vosough-Ghanbari *et al*., 2010). The tablets and placebo were provided by Khorraman Herbal Pharmaceutical Co. (Khorramabad).

This study was a randomized, double blind, placebo controlled trial conducted at the clinic of Digestive Diseases Research Center (DDRC) of Tehran University Teaching Hospital between May 2008 and May 2009. UC patients whom their disease had been already confirmed by colonic features (Table 1) and were in remission were included.

Table 1: Criteria used to Score disease activity index (DAI)

Symptoms and signs	Score
Number of defecation	
<4	1
4-5	2
>5	3
Blood in stool	
+/-	1
++	2
+++	3
Body temperature (°C)	
<37	1
37-37.5	2
>37.5	3
Pulse rate (beats min^{-1})	
<80	1
80-90	2
>90	3
Hemoglobin (mg dL^{-1})	
Male>14	
Female>12	1
Male: 10-14	
Female: 9-12	2
Male<10	
Female<9	3
Erythrocyte sedimentation rate (mm h^{-1})	
<15	1
15-30	2
>30	3
C-reactive protein	
-	1
+	2

Exclusion criteria were the followings: proliferative retinopathy, significant renal impairment (serum creatinin>3 mg dL^{-1}), coronary artery disease, chronic liver disease, diabetic foot ulceration/gangrene and pulmonary infection. The DDRC review board approved the study protocol and all participants were asked to sign a written consent before recruiting into study.

Scoring for Disease Activity Index (DAI) was done according to standard measures (Rezaie *et al*., 2006, 2007b) as described in Table 1 on the basis of disease severity in three categories of mild (grade 1, total score = 8-11), moderate (grade 2, total score = 12-15) and severe (grade 3, total score = 16-19). The patients were simply randomized to receive 500 mg SK or placebo supplements once daily for 4 months.

Baseline characteristics of the patients are shown in Table 2. The patients were maintained on their current treatment for UC.

To measure the outcome, frequency of the disease flare up (intermittent periods of active disease) was evaluated and compared between study and placebo groups by the use of two sample z test and was considered to be significant at a p-value of 0.05, or a confidence interval of 95%.

RESULTS

Thirty patients who met the eligibility criteria were enrolled in the study. They were in the age of 22 to 73 years old. Three patients (one in control and two in placebo patients) left the study because of disease flare-up. Baseline characteristics of the patients are summarized in Table 2. As shown, 12/14 (85.5%) of SK treatment when compared to 6/13 (46.2%) of the patients on placebo. The flare up frequency (Fig. 1) difference (0.07-0.7) between the two groups was significant. Only

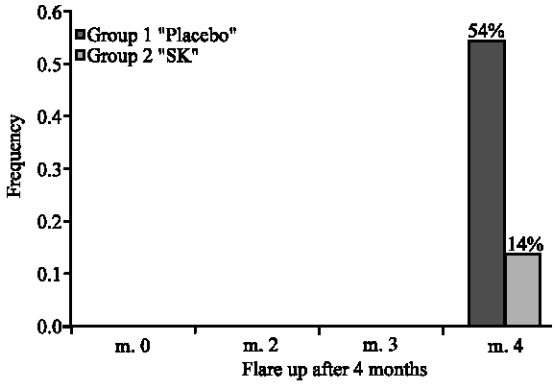

Fig. 1: Frequency of flare up observed in the placebo and SK groups m: months; SK: Satureja khuzestanica

Table 2: Baseline characteristics of the patients

Characteristics	SK (n = 14)	Placebo (n = 13)
Age (year) (Mean±SEM)	39.85±2.6	40.92±4.20
Number of male/female	6/8	6/7
With/without positive familial history	4/10	2/11
Disease by region		
Proctitis n (%)	1 (7.1)	2 (15.4)
Proctosigmoiditis n (%)	2 (14.3)	6 (46)
Left sided colitis n (%)	7 (50)	4 (30.7)
Pancolitis n (%)	4 (28.6)	1 (7.7)
Extra intestinal n (%)	3 (21.4)	3 (23.1)
Maintenance medication		
5-aminosalicylates	14	13
Azathioprine	2	2
Oral steroids	4	4
Severity of UC		
Mild n (%)	12 (85.70)	11 (84.6)
Moderate n (%)	2 (14.3)	2 (15.4)

three patients (one in the control group and two in the placebo group) withdrew from the study. One patient in control group withdrew due to UC flare-up (severe bloody diarrhea, high fever and abdominal pain). Two patients in placebo group withdraw, one due to severe nausea and one because of abdominal pain.

DISCUSSION

Our study showed SK could help UC patients to remain in remission state and reduced flare up rate. This finding appears to be due to its potent antioxidant components including carvacrol (Momtaz and Abdollahi 2008, 2010). In support, there are many studies indicating usefulness of herbal antioxidants like Zataria (Ashtaral-Nakhai *et al*., 2007), Ziziphora (Ghafari *et al*., 2006; Amini-Shirazi *et al*., 2009), Silymarin (Esmaily *et al*., 2009), Teucrium (Abdolghaffari *et al*., 2010), IMOD (Baghaei *et al*., 2010) or even those synthetized like N-acetyl-cysteine (Ebrahimi *et al*., 2008) and pentoxifylline (Khoshakhlagh *et al*., 2007). In animal studies, SK reduced bowel biomarkers of free radical damage including myeloperoxidase and lipid peroxidation and improved cellular histology and the inflammatory process (Ghazanfari *et al*., 2006). SK when tested in human diabetic patients reduced blood markers of oxidative stress and increased body total antioxidant capacity without occurrence of any toxic or adverse effects (Vosough-Ghanbari *et al*., 2010). Fortunately, no significant adverse effect was recorded in the present study patients and the compound was well tolerated. In another study, the essential oil from SK prevented from malathion-induced free radical damage and toxicity (Rezvanfar *et al*., 2008, 2010) and even improved blood acetylcholinesterase activity, improved hepatic mitochondrial glycogenolysis and gluconeogenesis in subchronically-exposed rats to the toxin malathion (Saadat *et al*., 2004; Basiri *et al*., 2007). Very interestingly, SK improved reproductive potential of normal (Abdollahi *et al*., 2003; Haeri *et al*., 2006) and cyclophosphamide-treated (Haeri *et al*., 2006) male rats through enhancement of body antioxidant potential. These all explains antioxidant potential of SK as one of the mechanisms of actions of SK in management of UC patients (Hasani-Ranjbar *et al*., 2009).

On the other hand, the role of microbes in induction and development of IBD has been confirmed well and there are strong meta-analysis studies indicating that antibiotics can control human IBD (Rahimi *et al*., 2007a; Elahi *et al*., 2009; Nikfar *et al*., 2010a, b). In support as mentioned in introduction, SK has been traditionally used as antiseptic. Interestingly new study indicated that use of SK irrigation reduces human periodontitis (Shahab *et al*., 2011) even better than chlorhexidine. Therefore, another explanation for efficacy of SK in human UC is its antimicrobial effects.

CONCLUSION

To keep patients in remission, derivatives of aminosalicylates are conventionally and chronically used but their use is limited with various side effects. Supplementing with SK by preventing disease flare up and keeping the UC patients in remission state would give the opportunity to physicians to reduce the dose of aminosalicylates and other side effects full drugs, thus would result in better compliance of patients. To our best of knowledge, SK gives its benefit in human UC through its potent antioxidant and antimicrobial properties.

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