Evaluation of the efficacy of *Thymus kotschyanus* extract as an additive treatment in patients with ulcerative colitis: a randomized double-blind placebo-controlled trial

Fatemeh Vazirian1 · Sara Samadi1 · Mohammadreza Abbaspour1,2 · Amirmahdi Taleb3 · Hadi Bagherhosseini4 · Hooman Mosannen Mozaffari5 · Amir Hooshang Mohammadpour1,6 · Seyed Ahmad Emami7

Received: 28 December 2021 / Accepted: 5 April 2022 / Published online: 20 June 2022
© The Author(s), under exclusive licence to Springer Nature Switzerland AG 2022

Abstract

**Background** Ulcerative colitis (UC) is one of the chronic diseases which is increasing in prevalence and patients suffer from illness flare-ups. UC standard regimen treatment has various side effects besides the efficacy, so there is an interest in administering complementary medicine to reduce adverse effects and increase the efficacy, as well. The aim of this study was to evaluate the efficacy and anti-inflammatory effect of *Thymus kotschyanus* as an additive treatment in a randomized double-blind placebo-controlled trial of UC patients.

**Methods** Thirty UC out-patients with mesalazine regimen treatment that fulfilled the inclusion criteria were participated in a 12 week trial and were randomly chosen for the treatment and control group. Fifteen patients were administered a placebo as a control and 15 patients were received *Thymus kotschyanus* extract by a dose of 0.5 g in a day in the treatment group. Laboratory tests were performed at baseline and week 12. The primary outcome was a reduction in fecal calprotectin as the main intestine inflammatory marker. Likewise, reduction in SCCAI, SIDBQ, and SEO indices were considered as secondary aims.

**Results** Fecal calprotectin was decreased by 54.74% in the treatment group, as compared with the placebo group at week 12 (*p* = 0.02). A significant reduction in SCCAI was also shown between the two study groups (*p* = 0.01). *Thymus kotschyanus* extract was safe and no severe side effects were reported.

**Conclusion** Administration of *Thymus kotschyanus* revealed improvement in UC symptoms by the intestinal anti-inflammation effect of the plant and could be suggested as a potential additive treatment in UC patients. The study protocol has been registered under the identification code: IRCT20200402606965N2.

**Keywords** Ulcerative colitis · UC patients · *Thymus kotschyanus* · Lamiaceae · Inflammation · SCCAI · Calprotectin

Amir Hooshang Mohammadpour and Seyed Ahmad Emami equally contributed as corresponding authors.

Amir Hooshang Mohammadpour
ah_mp@ymail.com

Seyed Ahmad Emami
EmamiA@mums.ac.ir

1 Department of Clinical Pharmacy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran
2 Targeted Drug Delivery Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran
3 Deputy for The Secretariat of the Council for Basic Medical Sciences, Health and Graduate’s Education, Treatment and Medical Sciences, Ministry of Health, Tehran, Iran
4 Department of Gastroenterology and Hepatology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
5 Gastroenterology and Hepatology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
6 Pharmaceutical Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran
7 Department of Traditional Pharmacy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran
Introduction

Ulcerative colitis (UC) is a chronic inflammation in intestines and severe immune reactions are involved in the initiation of UC (Ungaro et al. 2017; Akiho et al. 2015). The immune reaction in UC patients is promoted by unbalanced activation of Th1 and Th2 lymphocytes, followed by increasing the expression of IL-6, IL-13, IL-5, IL-17, and TNF-α (Li and He 2004; Madsen 2002; Sanchez-Munoz et al. 2008). Genetically, less expression of IL-10 is associated with UC prevalence, as well (Tagore et al. 1999). *Thymus kotschyanus* Boiss. and Hohen is a species of the *Thymus* genus from the Lamiaceae family (Jahani et al. 2019). The aerial parts of this plant were traditionally used as a treatment for chronic gastritis and gastrointestinal disorders (Khanavi et al. 2011). Administration of 1–2 g in a day was suggested for general clinical purposes of the plant extract (Basch et al. 2014). Oil components of *Thymus kotschyanus* are comprised of thymol, carvacrol, *para*-cymene, linalool, and geraniol (Tohidi et al. 2018; Hassanzadeh et al. 2011; Morteza-Semnani et al. 2006). By comparison between the anti-inflammatory effect of *Thymus kotschyanus* and indomethacin, the paw’s edema in rats was decreased up to a greater extent after high dosages of the plant administration (Bakhtiarian et al. 2011). Thymol and carvacrol, exert their anti-inflammatory effect by suppressing the transcription of Th1 and Th2 cytokines and reducing the oxidative stress in inflamed tissue. In addition, IL-10, the main anti-inflammatory cytokine, is enhanced by thymol administration (Gholijani and Amirghofran 2016; Costa et al. 2019; Ghasemi et al. 2020). In another animal experiment, thymol was compared with prednisolone in a rat model of UC, which revealed the anti-oxidant activity of thymol in bowel inflammation via inhibiting the COX-2 expression and decreasing nitric oxide level, hence, thymol was more efficient than the corticoid (Tahmasebi et al. 2019). Furthermore, several experimental rat colitis models have indicated the anti-inflammatory effect of thymol and carvacrol in intestines by immune response modification that inhibited TNF-α expression and interfered with the pNF-κB signaling pathway. Also, thymol could reduce colon tissue damage by attenuating nitric oxide production (Algieri et al. 2014; Chamanara et al. 2019; Bukovská et al. 2007; Liu et al. 2018). Thymol administration in young pigs with UC indicated successful achievements in intestine recovery by increasing the mitosis division, as well (Almanea et al. 2019). Due to the known anti-inflammatory and antioxidiant properties of *Thymus kotschyanus* and also the lack of human study on anti-inflammatory effects of thymol in intestine, the present double-blind randomized placebo control trial aimed to analyze the efficacy of *Thymus kotschyanus* in UC patients.

Materials and methods

Plant material and preparation of extract

*Thymus kotschyanus* was gathered from mountains nearby Ardabil city in Iran. The plant was identified in the Department of Pharmacognosy at the School of Pharmacy (Mashhad, Iran) under the voucher number: 13580. Thymus *kotschyanus* leaves (500 g) were cleaned and shade dried, turned into powder using an electrical blender, and then homogenized in ethanol (70%; 750 ml). The mixture was left in a conical flask at room temperature for 2 days and then the plant was extracted by percolation method. The extract was concentrated using a rotary evaporator (Heidolph, Germany) and *Thymus kotschyanus* extraction mixed with microcrystalline cellulose and formulated by the wet granulation method. Then each 500 mg capsule was filled with a mixture of the extraction and microcrystalline cellulose. Each treatment capsule contained 0.167 mg of pure *Thymus kotschyanus* extraction powder. The placebo 500 mg capsule consisted of microcrystalline cellulose powder, but no known active agents, and placebo were identical in taste and appearance to the extract capsule.

Inclusion and exclusion criteria

Inclusion criteria were: (1) ulcerative colitis out-patients (2) age between 13 to 65 years (3) the Simple Clinical Colitis Activity Index (SCCAI) between 5 and 13 (4) taking mesalazine with fixed-dose since one month ago and not exceeding more than 4500 mg mesalazine in a day (5) taking topical mesalazine it should be used at least for 2 weeks with a fixed-dose and not exceed more than 4000 mg in a day (6) if taking topically, mesalazine it should be used at least for 2 weeks with a fixed-dose and not exceed more than 4000 mg in a day (7) hemoglobin higher than 10. Exclusion criteria were: (1) incidence of any adverse reaction of *Thymus kotschyanus* extraction (2) diagnosing concurrent diseases such as diabetes, cardiovascular disease, kidney disease, liver disease, thyroid disease, and bile disease (3) having leukopenia, thrombocytopenia, or other blood coagulation disorders (4) concurrent sepsis or any active infection (5) administering another anti-inflammatory or immunomodulatory or anticoagulant medicine (6) having epilepsy and convulsion (7) pregnancy and lactation, and (8) being reluctant to continue this trial.

Study design

This study was conducted as a randomized double-blind placebo-controlled trial in which both patients and trial investigator were blinded. Trial was carried out at the
Imam Reza hospital (Mashhad, Iran) and the School of Pharmacy (Mashhad, Iran) from 2019 to 2021. Outpatients who met the inclusion criteria were qualified to participate in this clinical trial and the diagnosis of ulcerative colitis was confirmed by a relative physician, based on the medical history of patients. Patients were registered based on the mentioned criteria by a trial pharmacist at the school of pharmacy (Mashhad, Iran). Randomization was performed using a computer-generated, randomization formula with A and B sequence, to receive treatment or placebo, which A used for the intervention group and B used for the control group and divided patients into each group. Finally, a research assistant handed over the capsules to the two groups and was not interfered in the other stages of the trial. The intervention group consisted of 15 patients who were randomized by computer and took one extraction capsule three times a day by the effective daily dose of 500 mg of T. kotschyanus. These patients were administered the Thymus kotschyanus extraction capsule for 3 months by a total dose of 45 g of this capsule in the whole time of the trial. 15 patients who were randomized by computer, took one placebo capsule three times a day for 3 months were assigned to the control group. The Ethics Committee of Mashhad University of Medical Sciences (Mashhad, Iran) approved the study protocol. Patients gave written informed consent and were informed about the possible adverse reaction of the treatment prior to the participation. The study protocol has been registered in the Iranian Registry of Clinical Trials (IRCT.ir) under the identification code: IRCT20200406046965N2.

**Efficacy measures**

Qualified patients were interviewed and informed of the details of the trial and patients were asked about symptoms and SCCAI score was recorded at the starting point of the trial (week 0). Patients completed the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) for their quality of life. At the same visit, blood count, routine biochemistry including serum albumin concentration, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), and stool calprotectin were measured and SEO index was recorded. Patients were instructed to continue the main therapy (mesalazine) with a steady dose and take the trial capsule as complementary medicine. In addition, they were guided to contact the trial pharmacist for any unexpected adverse effects. Afterward, patients were followed up by the trial pharmacist at weeks 4 and 8, and any change in the symptoms and occurrence of any adverse effect were asked. Finally, patients were reviewed to calculate the SCCAI and to record compliance with the study medication at week 12. Blood count and stool calprotectin and routine trial biochemistry were checked and SIBDQ and SEO index were recorded.

**Outcome measures**

The primary outcome was a reduction in calprotectin as the specific bowel inflammation marker after 12 weeks, a rational time scale for evaluation of mucosal healing (Maaser et al. 2018).

The secondary outcomes are included as a reduction in SCCAI index score, remission and improvement changes in SIBDQ scores and SEO index which consist of changes in laboratory measures of hemoglobin, ESR, CRP, and albumin. Possible adverse effects of the trial medications were also recorded.

**Statistical analysis**

We estimated that a sample size of 15 patients per group was required to calculate the difference between calprotectin and SCCAI with 80% power and 0.05 significance level.

Statistical calculations were evaluated using computer software programs (Microsoft Excel and SPSS version 16.0). The Levene’s test and t-test were used to compare the groups at week 0 and week 12 according to hemoglobin, ESR, CRP, albumin, calprotectin, WBC, platelet, and SEO index. Mann–Whitney U test and Wilcoxon W test showed the comparison between SIDBQ and SCCAI at week 0 and week 12. A two-sided p value of <0.05 was considered statistically significant in all comparisons.

**Results**

**Population study**

Thirty patients fulfilled the trial criteria and entered the study by the protocol and all of the patients completed a 12 week trial duration (Fig. 1). Fifteen patients (7 men and 8 women) with an average age of 39 (22–58) received allocated intervention in the treatment group. In the placebo group, 15 patients (9 men and 6 women) with an average age of 37.2 (23–55) received the placebo capsule. In the treatment group, 5 patients were administered topical 5-ASA beside the oral 5-ASA and in the placebo group, 3 patients were administered topical 5-ASA beside the oral 5-ASA (Table 1). Complain of bloating was reported as a side effect of the Thymus kotschyanus during the study.

**Comparison of SEO index among study groups**

Although there was no significant difference between the study groups in relation to ESR, CRP, and albumin at
baseline, hemoglobin values were statistically significant between the two groups of study ($p=0.003$). Overall, the SEO index indicated no notable difference between the study groups ($p=0.157$). At week 12, the assessment of the SEO index and its related parameters showed no significant difference between study groups (Table 2).

Table 1  Demographic details of patients recruited to the trial

| Parameter | Placebo | Treatment |
|-----------|---------|-----------|
| Gender    | Man     | Woman     | Man | Woman |
|           | 9       | 6         | 9   | 6      |
| Age       | 37.2 (23–55)$^<$ | 39 (22–58)$^<$ |
| 5 ASA     | 15      | 15        |
| Topical 5 ASA | 3      | 3         |

$^<$5 ASA 5-amino salicylic acid
$^<$ data reported as median (IQR)
Comparison of WBC, platelet and calprotectin among study groups

At baseline, analysis of WBC, platelet, and calprotectin results indicated no notable difference between the two groups. At week 12, WBC and platelet indicated no significant difference between the two groups, however, notable difference was observed in calprotectin values by \( p = 0.021 \) between placebo and treatment groups (Table 3).

Comparison of SIDBQ and SCCAI between study groups

No significant difference was observed in SCCAI between the study groups \( (p = 0.393) \), but results indicated a statistically significant difference in SIBDQ between the study groups at baseline \( (p = 0.003) \). At week 12, SIBDQ was resulted in no remarkable difference by \( p = 0.329 \) but, there was a noteworthy difference in SCCAI by \( p = 0.015 \) between the placebo and treatment group (Table 4).

Clinical outcomes among two groups of study

Reduction in SCCAI was reported at week 12. So that there was no statistical significance between treatment and placebo at the baseline (Fig. 2A), but in the last week of the trial, patients showed improvement in clinical symptoms and also analysis approved a significant difference in SCCAI between the two study groups \( (p = 0.01) \) (Fig. 2B).

Although at the first of trial, calprotectin was in the same range between the two study groups and there was no notable difference (Fig. 2C), a significant reduction in stool calprotectin was observed by comparing the placebo and treatment group at week 12 and our primary outcome was achieved \( (p = 0.02) \) (Fig. 2D). SIBDQ, a questionnaire measuring physical, social, and emotional status, showed no significant difference among the two groups at week 12 (Fig. 2E). The other outcome was a reduction in SEO index which consisted of ESR, albumin, CRP, and hemoglobin measurements. There was no statistically significant difference in SEO index between the placebo and treatment group at week 12 \( (p = 0.981) \) (Fig. 2F).

Table 2 Numerical values of SEO index and related parameters assessed between study groups

| Parameter | At baseline | | | At week 12 | | |
|-----------|-------------|---|---|-------------|---|---|
| | Placebo (mean ± STD) | Treatment (mean ± STD) | \( p \) value | Placebo (mean ± STD) | Treatment (mean ± STD) | \( p \) value |
| ESR (mm/h) | 10.13 + 9.69 | 9 + 6.6 | 0.712 | 7 + 3.5 | 8.02 + 5.91 | 0.572 |
| CRP (mg/L) | 1.96 + 2.72 | 1.46 + 1.95 | 0.574 | 2.58 + 3.87 | 1.09 + 1.02 | 0.160 |
| Albumin (g/L) | 4.38 + 0.29 | 4.53 + 0.60 | 0.574 | 4.31 + 0.33 | 4.46 + 0.35 | 0.250 |
| Hemoglobin (g/dL) | 13.78 + 1.83 | 11.78 + 1.50 | 0.003 | 13.64 + 1.79 | 11.63 + 1.38 | 0.003 |
| SEO index | 118.45 + 21.12 | 137.94 + 47.33 | 0.157 | 109.94 + 17.94 | 109.77 + 21.32 | 0.981 |

ESR Erythrocyte sedimentation rate, CRP C-reactive protein

Table 3 Numerical values of WBC, platelet and calprotectin assessed between study groups

| Parameter | At baseline | | | At week 12 | | |
|-----------|-------------|---|---|-------------|---|---|
| | Placebo (mean ± STD) | Treatment (mean ± STD) | \( p \) value | Placebo (mean ± STD) | Treatment (mean ± STD) | \( p \) value |
| WBC (× 10³ /mm³) | 7.56 + 1.59 | 7.50 + 1.54 | 0.920 | 7.84 + 1.44 | 7.94 + 1.37 | 0.84 |
| Platelet (× 10³ /mm³) | 300.60 + 60.54 | 288.20 + 63.15 | 0.587 | 305.33 + 58.04 | 312.53 + 53.51 | 0.72 |
| Calprotectin (mg/kg) | 131.06 + 37.33 | 143.93 + 64.46 | 0.510 | 145.06 + 119.87 | 65.66 + 37.42 | 0.02 |

WBC White blood cells

Table 4 Numerical values of SIDBQ and SCCAI assessed between study groups

| Parameter | At baseline | | | At week 12 | | |
|-----------|-------------|---|---|-------------|---|---|
| | Placebo (median) | Treatment (median) | \( p \) value | Placebo (median) | Treatment (median) | \( p \) value |
| SCCAI | 10 | 11 | 0.393 | 7 | 6 | 0.015 |
| SIBDQ | 42 | 57 | 0.003 | 39 | 43 | 0.329 |

SCCAI Simple clinical colitis activity index, SIBDQ short inflammatory bowel disease questionnaire
Adverse effects of the trial medications

Adverse effects recorded among patients taking *Thymus kotschyanus* and placebo were minor, similar, and not clearly related to the study medications. One of the patients in the treatment group complained about a mouth ulcer and the other one reported bloating, but they were not withdrawn from the trial in case of these minor adverse effects.

Discussion

Since the standard treatment regimen for UC can potentially cause different incidences of adverse effects over a long time, administering an efficient complementary medicine would reduce the adverse effects (Algieri et al. 2014). *Thymus kotschyanus* could be used as an additive medicine since it can alleviate abdominal pain and flatulence in patients with intestinal disorders (Navaei et al. 2012). According to our findings, the anti-inflammatory effect of *Thymus kotschyanus* extract was indicated through a reduction in calprotectin and SCCAI at week 12 by 54.39% and 45.46%, respectively. Several studies using thymol in models of colitis in rats have demonstrated the potential recovery effect of thymol on the damaged colon which was similar to our findings on human samples (Tahmasebi et al. 2019; Algieri et al. 2014; Liu et al. 2018). Furthermore, in the other animal study on young pigs with colitis the same results were obtained showing that thymol could reduce bowel inflammation through enhancing the mitosis division in intestine cells (Almanea et al. 2019). To the best of our knowledge, the evaluation of the anti-inflammatory effect of *Thymus kotschyanus* on UC patients has not been previously assessed in a randomized double-blind placebo-controlled clinical trial. One of the mechanisms involved in the promotion of UC is attributed to the imbalanced Th1/Th17 response-related inflammatory cytokines that can damage the bowel tissue. The imbalanced T helper cells activation leads to an increase in the expression of IL-5, IL-6, IL-13, TNF-α and IL-17 as inflammatory markers (Sanchez-Munoz et al. 2008). In addition, IL-17 can play a role in the recruitment of neutrophil and Th1 in bowel tissue and exacerbates the tissue damage (Algieri et al. 2014). *Thymus kotschyanus* extract can potentially down-regulate the imbalanced Th1/Th17 activation by its components, thymol and carvacrol, which reduce inflammation by decreasing TNF-α and IL-6 and IL-17 in intestines, followed by increasing IL-10 expression as the main anti-inflammatory cytokine (Gholijani and Amirghofran 2016). The other mechanism related to the UC progression is the stimulation of the immune system by the nuclear factor κB (NF-κB (Sanchez-Munoz et al. 2008), which

![Clinical outcomes analysis among two groups of study. A Simple Clinical Colitis Activity Index (SCCAI) at baseline, B SCCAI at week 12, C calprotectin at baseline, D calprotectin at week 12, E Inflammatory Bowel Disease Questionnaire (SIBDQ) at week 12, F SEO index at week 12](image-url)
can inhibit apoptosis and induce inflammation cytokines by leukocytes migration (Liu et al. 2017). The Thymus kotschyanus extract’s potential to inhibit this mechanism is attributed to the thymol, which can down-regulate the stimulation of the NF-kB pathway and reduce inflammation (Chamanara et al. 2019; Liu et al. 2018). Furthermore, overproduction of nitric oxide (NO) which is mediated by inflammatory cytokines can react as a pro-inflammatory factor and cause more damage to the bowel in UC settings (Guslandi 1998). Moreover, Thymus kotschyanus extract inhibits the expression of NO through its thymol component (Tahmasebi et al. 2019). Particularly, in this trial, calprotectin was measured as the main sensitive marker of inflammation in the intestines which is excreted in feces because of neutrophil migration to intestines (Pathirana et al. 2018). Our findings demonstrated a significant reduction in calprotectin and SCCAI in UC patients. The current study is among the first human clinical trials to assess the potential effects of Thymus kotschyanus extract in UC patients and the use of a fecal indicator protein to measure inflammation in the intestines instead of invasive diagnostic methods, hence, patients showed more compliance in this trial. Nevertheless, the current findings are based on a relatively small sample of participants which could affect the overall results and also we just included the UC patients, whereas the trial could include Crohn’s patients to have bigger sample size. Additionally, more clinical trials can be conducted that preferably measure the bowel inflammation with colonoscopy beside assessing the fecal calprotectin to indicate sigmoidoscopic and histological appearances and evaluate Mayo clinic score.

In conclusion, the anti-inflammatory effects of Thymus kotschyanus extract may effectively reduce the adverse effects of the standard regimen in UC patients and can be applied as a beneficial additive treatment for the disease in clinical settings. The results of this trial would be in support of further research on the therapeutic future of Thymus kotschyanus extract in UC.

Author contributions All authors contributed to the study conception and design. AHM and HMM are the guarantors of the article. FV and AHM performed the research, MA and AT collected and analyzed the data, SS and HB designed the research study and wrote the paper. AHM and HMM revised the manuscript and SAE and HMM contributed to the design of the study. All authors reviewed and approved the manuscript.

Funding This work was supported by the Mashhad University of Medical Sciences [grant number: 980801].

Data availability Enquiries about data availability should be directed to the authors.

Declarations

Conflict of interest The authors have no conflict of interest to disclose.

References

Akiho H, Yokoyama A, Abe S, Nakazono Y, Murakami M, Otsuka Y et al (2015) Promising biological therapies for ulcerative colitis: a review of the literature. World J Gastrointest Pathophysiol 6(4):219–227

Algieri F, Rodriguez-Nogales A, Garrido-Mesa N, Zorrilla P, Burkard M, Pischel I et al (2014) Intestinal anti-inflammatory activity of the Serpilly herba extract in experimental models of rodent colitis. J Crohns Colitis 8(8):775–788

Almamea A, Abd El-Aziz GS, Ahmed MMMJB (2019) The potential gastrointestinal health benefits of Thymus vulgaris essential oil: a review. Biomed Pharmacol 12(04):1793–1799

Bakhtiarian A, Aarabi Moghaddam F, Zamani MM, Ghamami SG, Farahanikia B, Khamvai M (2011) Anti-inflammatory effect of Thymus kotschyanus Boiss. & Hohen. Extract on rat’s hind paw edema induced by Carrageenan. JIMP 10(37):25–32

Basch E, Ulbricht C, Hammerness P, Blevins A, Sollars D (2004) Thyme (Thymus vulgaris L.) Thymol. J Herbal Pharmacother 4:49–67

Bukovská A, Cikoš Š, Juhás Š, Il’kóvá G, Rehák P, Koppel J (2007) Effects of a combination of thyme and oregano essential oils on TNBS-induced colitis in mice. Mediat Inflamm 2007:023296

Chamanara M, Abdollahi A, Rezayat SM, Ghazi-Khansari M, Dehpour A, Nassireslami E et al (2019) Thymol reduces acetic acid-induced inflammatory response through inhibition of NF-kB signaling pathway in rat colon tissue. Inflammopharmacology 27(6):1275–1283

Costa MF, Duarte AO, Rabelo TK, Barreto RSS, Guimarães AG (2019) Effects of carvacrol, thymol and essential oils containing such monoterpenes on wound healing: a systematic review. J Pharm Pharmacol 71(2):141–155

Ghasemi G, Alirezalu A, Ghosta Y, Jarrahi A, Safavi SA, Abbas-Mohammadi M et al (2020) Composition, antifungal, phytotoxic, and insecticidal activities of Thymus kotschyanus essential oil. Molecules 25(5):1152

Gholijani N, Amirghofran Z (2016) Effects of thymol and carvacrol on T-helper cell subset cytokines and their main transcription factors in ovalbumin-immunized mice. J Immunotoxicol 13(5):729–737

Guslandi M (1998) Nitric oxide and inflammatory bowel diseases. Eur J Clin Invest 28(11):904–907

Hassanzadeh M, Emami S, Asili J, Tayarani-Najaran Z (2011) Review of the essential oil composition of Iranian Lamiaceae. J Essent Oil Res 23:35–47

Jahani R, Mojab F, Mahboubi A, Nasiri A, Tahamtani A, Faizi M (2019) An in-vivo study on anti-convulstant, antioxidant, and sedative-hypnotic effects of the polyphenol-rich thymus kotschyanus extract; evidence for the involvement of GABA(A) receptors. Iran J Pharm Res 18(3):1456–1465

Khanavi M, Farahanikia B, Rafiee F, Dalili D, Safaripour E, Ajani Y et al (2011) Reversal of resistance in MRSA strains by Thymus kotschyanus essential oil. J Essent Oil Bear Plants 14(6):684–692

Li M-C, He S-H (2004) IL-10 and its related cytokines for treatment of inflammatory bowel disease. World J Gastroenterol 10(5):620–625

Liu T, Zhang L, Joo D, Sun SC (2017) NF-kB signaling in inflammation. Sig Transduct Target Ther 2:17023

Springer
Liu D-M, Zhou C-Y, Meng X-L, Wang P, Li W (2018) Thymol exerts anti-inflammatory effect in dextran sulfate sodium-induced experimental murine colitis. Trop J Pharm Res 17:1803
Maaser C, Sturm A, Vavricka SR, Kucharzik T, Fiorino G, Annese V et al (2018) ECCO-ESGAR guideline for diagnostic assessment in IBD part 1: initial diagnosis, monitoring of known IBD, detection of complications. J Crohns Colitis 13(2):144–164
Madsen K (2002) Combining T cells and IL-10: a new therapy for Crohn’s disease? Gastroenterology 123(6):2140–2144
Morteza-Semnani K, Rostami B, Akbarzadeh M (2006) Essential oil composition of Thymus kotschyanus and Thymus pubescens from Iran. J Essent Oil Res 18(3):272–274
Navaei MS, Taleb A, Isfahani M, Amin G, Faghihi A, Lakeh MM (2012) Study on the phytochemical constituents of Thymus kotschyanus Boiss. Et Hohen and its efficacy on the symptoms’ improvement of irritant bowel syndrome. Res Pharm Sci 7(5):741
Pathirana WGW, Chubb SP, Gillett MJ, Vasikaran SD (2018) Faecal calprotectin. The clinical biochemist. Reviews 39(3):77–90
Sanchez-Munoz F, Dominguez-Lopez A, Yamamoto-Furusho J-K (2008) Role of cytokines in inflammatory bowel disease. World J Gastroenterol 14(27):4280–4288
Tagore A, Gonsalkorale WM, Pravica V, Hajeer AH, McMahon R, Whorwell PJ et al (1999) Interleukin-10 (IL-10) genotypes in inflammatory bowel disease. Tissue Antigens 54(4):386–390
Tahmasebi P, Abtahi Froushani SM, Afzale AN (2019) Thymol has beneficial effects on the experimental model of ulcerative colitis. Avicenna J Phytomed 9(6):538–550
Tohidi B, Rahimmalek M, Arzani A (2018) Variations in chemical composition and bioactive compounds of Thymus kotschyanus Boiss & Hohen populations originated from different collection sites. J Essent Oil Bear Plants 21(3):1272–1283
Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel JF (2017) Ulcerative colitis. Lancet (London, England) 389(10080):1756–1770

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.