

Analgesic Effect of *Ziziphora Tenuior* Essential Oil and Lubricant Gel in Patients Referring for Colonoscopy: A Randomized Double-Blind Clinical Trial

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ABSTRACT

Background:

Colonoscopy is a diagnostic tool of choice to examine the lower part of the gastrointestinal tract, which includes the colon and the beginning of the ileum. Colonoscopes are used for diagnostic and therapeutic purposes. Colonoscopy is also accompanied by abdominal pain. Accordingly, the purpose of this study was to evaluate the analgesic effect of *Ziziphora tenuior* essential oil and lubricant gel in patients undergoing colonoscopy using a randomized double-blind clinical trial.

Materials and Methods:

In this clinical trial, 100 patients who were candidates for colonoscopy were selected through convenience sampling and were randomly divided into two groups. The control group (n = 50) used lubricant gel (placebo) and the treatment group (n = 50) used the gel containing *Ziziphora tenuior* essential oil (the compounds of the *Ziziphora tenuior* essential oil were identified by injection of the sample into a gas chromatography-mass spectrometry (GC-MS) device). The patients' satisfaction and pain were assessed using a standard questionnaire and the collected data were analyzed by descriptive and inferential tests (t test).

Results:

The GC analysis revealed 42 different compounds in the essential oil. Six of the identified compounds comprised more than 60% of the compounds presented in the oil including pulegone (26.65%), alpha-terpinyl acetate (9.53%), geraniol (7.11%), menthone (5.74%), thymol (5.51%), and alpha-terpineol (3.24%) in decreasing order. The mean value of pain and the duration of colonoscopy in the control group (6.56 + 1.89) were significantly different from the corresponding value for the case group (4.25 + 1.2) ($p < 0.0001$).

Conclusion:

The use of the mix of *Ziziphora tenuior* essential oil and lubricant gel as a safe and inexpensive analgesic drug during colonoscopy is recommended.

Keywords: *Ziziphora tenuior*, Colonoscopy, Pain, Colorectal Cancer

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INTRODUCTION

Colonoscopy is performed for diagnostic and therapeutic purposes. Both the colon and the terminal ileum can be examined during colonoscopy (1,2). Colonoscopy is the gold standard for screening or care evaluation of colon and rectal cancer (CRC). Gastrointestinal bleeding, lower gastrointestinal symptoms, and abnormal imaging findings are among the colonoscopic indications (3-6). Cases such as IBD (Inflammatory bowel disease), finding cancers with early CRC, finding the precise location of lesions during surgery, and evaluation of terminal ileum

are other important applications of colonoscopy (5,6). Colonoscopic therapeutic applications include foreign body surgery, sigmoid volvulus treatment, false colon obstruction, and balloon dilatation in cases of regional strictures (7,8). Colonoscopy in the United States has increased to 52.5% since 2000, with most of the cases being performed at outpatient centers. Numerous studies have shown that although the use of propofol anesthetic well induces colonoscopy tolerance, analgesia in the anus and abdomen plays a special role in colonoscopy, and especially in outpatient recto-sigmoidoscopy. Inducing anal and intestinal analgesia by medicinal herbs and lubricating gels will be very helpful in replacing complicated intravenous drugs such as propofol, opioids, and benzodiazepines (7-10).

Plant therapy is one of the treatments that have been considered since ancient times. In recent years, many studies have been done about the effects of medicinal plants on various conditions including pain. For instance, a study by Ranjbari and colleagues showed that *Ziziphora tenuior* had considerable analgesic effects (11,12).

Ziziphora tenuior is one of the traditional medicinal plants belonging to the Lamiaceae family. The plant has dense bushes and is 20 to 50 cm high. Its leaves are small, crossed, more or less lanceolate without a petiole. It also has small, full flowers in white, pink, and purple. Its medicinal effects can be used in the treatment of gastrointestinal disorders such as diarrhea and stomach ache (13). In addition, *Ziziphora tenuior* has antibacterial (14), antioxidant (15), intestinal disinfection (16), and sputum (anti-sputum??), and anti-cold effects (17). Also, one of the main active chemical compounds of this plant is pulegone with well-known analgesic and anti-inflammatory effects (18) that can be used for the treatment of fever, menstrual cramps, and gastric tonus (19). Some reports also suggest the analgesic effects of Lamiaceae family due to the presence of compounds such as carvacrol, flavonoids, and steroids (20). Therefore, given the analgesic effect of this plant, in the present study, we investigated the analgesic effect of the mixture of *Ziziphora tenuior* essential oil and lubricant gel in patients referred for colonoscopy using a randomized double-blind clinical trial.

MATERIALS AND METHODS

Sampling

This study was a clinical trial and after obtaining the code of ethics IR.BMSU.REC.1396.719, a total number of 100 patients (aged below 50 years) as candidates for colonoscopy referring to the gastrointestinal ward of Baqiyatallah Hospital in Tehran for 8 months (spring 2018 to spring 2019) were selected as the participants. They were randomly placed into the control and treatment groups. The inclusion criteria were being suspected of having polyps, intestinal diseases, and unclear bleeding. The exclusion criteria were lack of mental health, complete alertness, drug use, and anxiolytic and analgesic use. The patients were matched for age and sex and were randomly assigned to either a control (50) or a treatment (50) group 30 minutes before colonoscopy.

Plant collection and identification

The leaves and branches of *Ziziphora tenuior* were collected from Pariz (a town in Sirjan) in August 2018 and dried at 25 °C in the shade, then powdered by mechanical grinding. The dry powder was kept in the freezer in the nylon bags until testing.

Essential oil preparation

The leaves and branches of the *Ziziphora tenuior* were dried in shade and ground by a grinding machine. Then, the essential oil was extracted by water distillation in a Clevenger apparatus for 3 hours. The ratio of essential oil to the dry weight of the plant was 5%. The essential oil was stored in dark glass for subsequent use.

Colonoscopy

The control group received a placebo (lubricant gel with no medicinal herb) and the treatment group received the drug (lubricant gel with 2% *Ziziphora tenuior* essential oil). Then, 50 mL of the prepared solution in a prefilled syringe, either *Ziziphora tenuior* or placebo, was gently delivered into the cecum and directly sprayed on the bowel wall through the working channel of the colonoscope. Afterward, the pain pediatric questionnaire was completed for each patient by a nurse who was unaware of the study (21).

Plant compounds

First, *Ziziphora tenuior* essential oil was prepared and then the compounds were isolated by GC/MS

Table 1: Vital sign summary

Phonotype	Group	Mean (SD)	p value
Heart rate	Treatment	72.74 ± 5.57	0.023
	Control	74.26 ± 7.96	
Systolic BP	Treatment	133.64 ± 11.36	0.092
	Control	136.26 ± 10.87	
Diastolic BP	Treatment	73.52 ± 7.39	0.11
	Control	75.02 ± 8.64	
O ₂ Sat	Treatment	92.24 ± 10.64	0.052
	Control	94.2 ± 8.9	

BP: blood pressure

device (HP-6840/5973) in the central laboratory of Ferdowsi University of Mashhad. The constituting elements were identified by comparing their mass spectra with the existing standard spectra.

Statistical analysis

The collected data were analyzed using independent samples t test by GraphPad Prism V6 statistical software at the significance level of 0.05. All results were presented as mean ± SD.

RESULTS

Figure 1 shows a chromatogram of *Ziziphora tenuior* essential oil. A total of 42 chemical compounds were identified in the essential oil. Of these, six were the most common chemicals in *Ziziphora tenuior* essential oil including pulegone (26.65%), alpha-terpinyl acetate (9.53%), geraniol (7.11%), menthone (5.74%), thymol (5.51%), and alpha-terpineol (3.24%) (figure 1).

The mean age of the patients in the control group was 48.96 ± 6.59 years and in the treatment group was 49.25 ± 7.2 years. Vital signs were not different between the two groups (table 1). The results showed that mean pain intensity was 6.56 ± 1.89 among the patients in the control group and 4.25 ± 1.25 in the treatment group, showing a statistically significant difference (p < 0.0001) (figure 2). However, the duration of colonoscopy was not significantly different between the two groups.

The frequency of abdominal pain was more than three times in the control group, but in some patients in the treatment group was more than one time, which showed a statistically significant difference between the two groups (p < 0.0001).

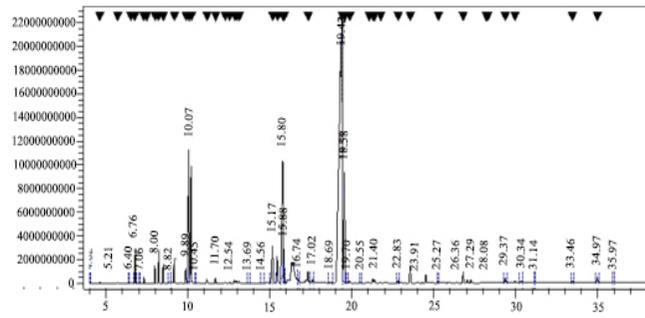


Fig.1: Chromatography of *Ziziphora tenuior* essential oil

The duration of abdominal pain in the treatment group was less than 1 minute in 80% of the patients, while 60% of the patients in the control group suffered from abdominal pain for 1 to 3 minutes.

DISCUSSION

The results of the present study showed that the administration of the lubricant gel containing *Ziziphora tenuior* essential oil increases patients' satisfaction after colonoscopy. Research shows that extract and essential oil of *Ziziphora tenuior* can induce analgesia and muscle expansion and relaxation (11,12,22). Vojdani and colleagues (23) also concluded that taking peppermint extract for 8 weeks reduced pain in patients with irritable bowel syndrome compared with the placebo group. Various studies have shown that medicinal plants belonging to the Lamiaceae family decrease the calcium flux by affecting the calcium channels in neurons. As a result, neuronal excitability and synaptic transmission are reduced, thereby alleviating pain (24).

The present study also showed that the essential oil of *Ziziphora tenuior* collected from southeast of Iran (Sirjan) contained 42 chemical compounds, the most important of which are pulegone (26.65%), alpha-terpinyl acetate (9.53%), geraniol (7.11%), menthone (5.74%), thymol (5.51%), and alpha-terpineol (3.24%).

The diversity of geographical conditions in Iran has created a rich source of plant species diversity. One of these species is *Ziziphora tenuior*, which belongs to the Lamiaceae family. *Ziziphora tenuior* is found in various parts of Iran, especially in the north and northwest, and has many therapeutic benefits. Our studies in recent years have demonstrated the

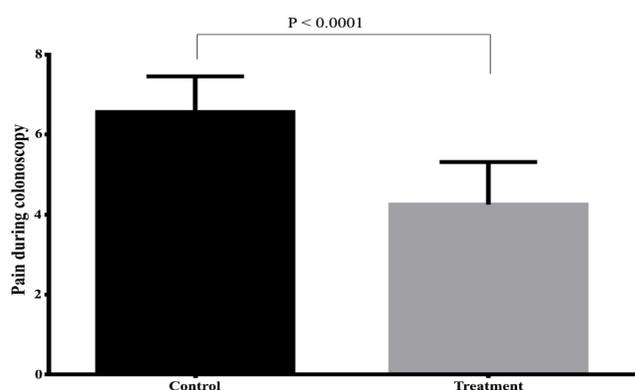


Fig.2: The analgesic effects *Ziziphora tenuior* essential oil (treatment) compared with the lubricant gel (control)

analgesic effects of *Ziziphora tenuior* in rats (12). Other studies by other researchers have found that the presence of compounds such as thymol, carvacrol, flavonoid, polyphenol, limonene, and alpha-terpineol in the Lamiaceae family are likely to reduce pain by affecting the opioid system (25,26).

Pulegone is the most frequent and main compound of *Ziziphora tenuior* essential oil with its well demonstrated analgesic and anti-inflammatory effects (27). As a case in point, a study by De Sousa and colleagues indicated that the analgesic effects of Pulegone and limonene in *Mentha villosa* belonging to the Lamiaceae family were greater than the effects of monoterpenes in visceral pain testing (28). Besides, Chiou and Yao (29) showed that inflammation induced by lens protein in the eyes was significantly reduced by administering Pulegone as a plant compound.

Imagawa and co-workers compared the effects of peppermint oil, hyoscine, and glucagon antispasmodics on upper gastrointestinal endoscopy. The results showed that the administration of peppermint oil to the elderly was effective in reducing spasm during esophageal, gastric, and duodenal endoscopy (30).

Another study by Ishani Shah and colleagues showed that peppermint oil could reduce pain and help with colonoscopy by reducing intestinal spasm during colonoscopy (21). Similarly, in our study, the use of *Ziziphora tenuior* increased the rate of patients' and physicians' satisfaction by reducing colonic spasm. Although the administration of *Ziziphora tenuior* essential oils in this study was effective in reducing pain and increasing patients' and physicians'

satisfaction, and herbal remedies usually have fewer complications, their potential side effects should be taken into account.

CONCLUSION

The administration of *Ziziphora tenuior* essential oil to patients undergoing preoperative colonoscopy reduces abdominal pain and increases patients' satisfaction after colonoscopy. Also, our randomized double-blind clinical trial design can have closer results to the clinical tests than other studies.

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CONFLICT OF INTEREST

The authors declare no conflict of interests related to this work.

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