Taiwanese Journal of Obstetrics & Gynecology 60 (2021) 9–12

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Review Article

Non-pharmacological interventions for the prevention of postoperative ileus after gynecologic cancer surgery

Kemal Gungorduk [a, *], Isa Aykut Ozdemir [b]

[a] Department of Gynecology and Oncology, Muğla Sitki Koçman University Education and Research Hospital, Muğla, Turkey
[b] Department of Gynecology and Oncology, Bakirkoy Sadi Konuk Research and Training Hospital, Istanbul, Turkey

ARTICLE INFO

Article history:
Accepted 22 September 2020

Keywords:
Postoperative ileus
Coffee consumption
Gum chewing
Gynecology
Surgery

ABSTRACT

Postoperative ileus (POI) is characterized by impaired gastrointestinal motility after surgery. POI is a major concern for surgeons because it increases hospital stay, the cost of care, and postoperative morbidity in patients who have undergone extensive gynecological oncological surgery. Although several interventions have been proposed and investigated, no effective treatment for the prevention and management of POI has been established. The present review summarizes the current evidence on non-pharmacological interventions, including coffee consumption and chewing gum, used to prevent and treat POI. We obtained studies from MEDLINE, Cochrane Database of Systematic Reviews, ISI Web of Science, and SCOPUS databases.

Introduction

Postoperative ileus (POI) is a common complication of abdominal surgery that leads to prolonged hospital stay and patient discomfort, and poses a significant economic burden to society in terms of costs associated with increased use of healthcare resources and lost productivity [1–3]. Moreover, POI may delay postoperative treatments, such as chemotherapy in patients who underwent surgery for malignancies. The incidence of POI within the first week after surgery is estimated to be between 3% and 50%; this variability is attributed to the lack of consensus on what constitutes an abnormal duration before the recovery of intestinal motility [1–3].

The pathogenesis of POI is multifactorial and not completely understood; however, it is thought to involve the interplay between local trauma and the systemic stress response (due to adrenergic activity) to surgery [1–3]. Women who have undergone surgical staging for gynecologic cancer are at high risk of POI due to the complexity of the procedure.

Given the seriousness of POI, a significant amount of research has focused on its prevention; however, consensus has not been reached on the optimal strategy for preventing POI. None of the pharmaceutical agents investigated, including alvimopan, neostigmine, ghrelin agonists, metoclopramide, and multimodal analgesic regimens, has been completely effective in preventing ileus, and all have various limitations and costs [4–7]. For instance, opioid receptor antagonists significantly enhance the recovery of gut function, but the drugs are expensive and not readily available worldwide.

In this review, we summarize the evidence for the use of non-pharmacological interventions to prevent POI to guide future research into their usefulness (Table 1).

Prevention is better than treatment

Coffee consumption

Coffee is a popular beverage that has multiple effects on the human body. The prokinetic effect of coffee is well known. A recent meta-analysis of six clinical trials conducted by Kane et al. [8] revealed that coffee intake shortly after surgery facilitated the recovery of gastrointestinal function in patients who underwent abdominal surgery. Coffee intake shortened the times to first passage of stool (mean difference [MD], −9.38 h; 95% confidence interval [CI], −17.60 to 1.16; $P = 0.03$), first flatus (MD, −6.96 h; 95% CI, −9.53 to −4.38; $P < 0.00001$), and first solid food intake (MD, −9.52 h; 95% CI, −18.19 to −0.85; $P = 0.03$). Furthermore, no adverse effects were associated with coffee consumption in the early postoperative period.

Several mechanisms may underlie the effect of coffee consumption on POI: coffee promotes the release of gastrin, which has been shown to increase colonic spike and motor activity [9]; and the colonic response to coffee may be mediated by exorphins, which stimulate colonic motility via opiate receptors in the brain

* Corresponding author. Muğla Sitki Koçman University Education and Research Hospital, Muğla, Turkey.
E-mail address: drkemalgungorduk@gmail.com (K. Gungorduk).

https://doi.org/10.1016/j.tjog.2020.11.002

Table 1
Characteristics of included studies.

Author/year	Country	Number Of Participants	Surgical procedure	Intervention	Time of first flatus (h)	Time to first bowel movement (h)	Time to tolerance of solid food (d,h)	Time to first defecation (h)	Postoperative Ileus Rate (%)	Complication
Gungorduk 2017	Turkey	114	Laparotomy	coffee vs. no treatment	29.7 ± 4.9[a] vs. 41.6 ± 10.9[a]	35.6 ± 5.4[a] vs. 47.5 ± 11.7[a]	3.5 ± 1.2[a] vs. 4.8 ± 1.6[a]	42.0 ± 6.8[a] vs. 59.8 ± 14.6[a]	13.8 vs. 51.8	none
Gungorduk 2020	Turkey	98	Laparoscopy	coffee vs. hot water	19 (13–35)[b] vs. 25 (15–42)[b]	22 (15–38)[b] vs. 28 (16–47)[b]	2 (2–5)[b] vs. 3 (2–8)[b]	30 (22–54)[b] vs. 38 (26–65)[b]	2.0 vs. 14.9	none
Ertas 2013	Turkey	149	Laparotomy	gum chewing vs no treatment	34.0 ± 11.5[a] vs. 43.6 ± 14.0[a]	41.5 ± 15.7[a] vs. 50.1 ± 15.9[a]	4.0 ± 0.8[a] vs. 5.0 ± 0.9[a]	49.6 ± 18.7[a] vs. 62.5 ± 21.5[a]	16.3 vs. 49.4	none
Nanthiphatthanachai 2020	Thailand	86	Laparotomy & Laparoscopy	gum chewing vs. no treatment	24.7 (2.2–86.5)[b] vs. 35.4 (7.2–80.9)[b]	4.3 (3.2–23.3)[b] vs. 4.3 (1.7 11.5)[b]	–	72.6 ± 34.3[a] vs. 79.6 ± 27.4[a]	35.0 vs 47.7	None
Phutsisen 2019	Thailand	90	Laparotomy	cassia alata linn tea vs warm water	26.4 ± 1.1[a] vs 34.9 ± 2.2[a]	–	20.0 ± 4.3[a,c] vs. 20.3 ± 4.6[a,c]	46.9 ± 2.1[a] vs 66.7 ± 3.8[a]	0 vs. 8.9	none
Ozdemir 2020	Turkey	85	Laparotomy & Laparoscopy	preoperative walking vs.no treatment	32.5 ± 10.4[a] vs. 40.6 ± 16.9[a]	33.2 ± 14.7[a] vs. 42.0 ± 16.8[a]	3.4 ± 0.7[a] vs. 4.3 ± 0.8[a]	62.8 ± 26.7[a] vs. 91.4 ± 51.8[a]	14.0 vs. 42.9	none

[a] Data is presented as mean ± SD.
[b] Data are presented as median (min–max).
[c] Data are hour (h).

and gut walls. Exorphins are found in regular and decaffeinated coffee [10,11], and coffee stimulates motor activity in the colon by antagonizing adenosine receptors [12].

Güngördük et al. [13] conducted a randomized, controlled trial (RCT) of coffee consumption after laparotomy with hysterectomy and staging in 114 women with gynecologic malignancies. To date, this is the only investigation of the effectiveness of coffee consumption for the prevention of POI after gynecologic oncology surgery. After surgery, 58 patients consumed coffee three times daily, and 56 received routine postoperative care without coffee consumption. In the coffee consumption group, compared with the control group, the time to flatus was reduced by 12 h (mean [SD], 30.2 [8.0] vs. 40.2 [12.1] h, res; $P < 0.001$), the time to tolerance of solid food was shortened by 1.3 days (3.4 [1.2] vs. 4.7 [1.6] days; $P < 0.001$), the time to first bowel movement was reduced by 12 h (43.1 [9.4] vs. 58.5 [17.0] h; $P < 0.001$), and the length of hospital stay was shortened by 1 day (7.4 [2.9] vs. 6.1 [1.1] days; $P = 0.003$). A previous multivariant analysis revealed that coffee consumption after surgery was an independent protective factor for POI [9].

Our recently published randomized control trial demonstrated that postoperative coffee intake after laparoscopic gynecologic surgery (included gynecological cancer surgery) facilitated the recovery of gastrointestinal function by reducing the times to first flatus and first defecation and the time to tolerate a solid diet [14].

Gum chewing

Chewing gum is a form of sham feeding that activates the cephalic–vagal reflex via a mechanism similar to oral food intake, thereby stimulating duodenal, stomach, and rectal motility with a reduced risk of vomiting and aspiration [15]. Furthermore, chewing gum increases the concentration of peptides, including gastrin, neurotensin, and pancreatic polypeptide, in the plasma and increases alkali secretion in the duodenum which, in turn, promotes gastrointestinal function. van den Haijkant et al. [16] reported that chewing gum reduced bowel wall inflammation and subsequently restored motility via a decrease in the inflammatory factors IL-6, IL-8 and TNFRSF1A.

Ertas et al. [17] investigated the effect of chewing gum in an RCT of 149 patients who underwent complete surgical staging for various gynecologic cancers. They found that chewing gum was associated with reduced times to first flatus and defecation and the mean time to first bowel movement. In 2018, Xu et al. conducted a systematic review of 10 studies that investigated the impact of chewing gum on gastrointestinal function following gynecologic surgery. Their findings revealed that chewing gum improved the recovery of bowel function by shortening the times to first flatus (MD, −7.55 h; 95% CI, −10.99 to −4.12; $P < 0.0001$) and first defecation (MD, −12.24 h; 95% CI, −18.47 to −6.01; $P = 0.0001$) and the length of hospital stay (MD, −0.72 h; 95% CI, −1.19 to −0.25; $P = 0.003$) [18]. However, the most recent multicenter RCT, which included 1,941 patients who underwent several types of abdominal surgery, failed to show a benefit of chewing gum on the time to first defecation and the duration of hospital stay; however, the authors did not provide a detailed description of the surgical procedures [19]. In contrast, two recent RCTs in patients who underwent gynecologic surgery, including staging surgery for cancer, found that chewing gum was associated with early recovery of gastrointestinal function [20,21].

Interestingly, Tandeter [22] hypothesized that hexitol sweeteners in sugar-free gum (sorbitol, mannitol, maltitol, and xylitol) may have an additional positive effect on gut function. An RCT in 120 patients who underwent elective laparoscopic gynecologic surgery found that the times to first flatus and first bowel sounds were significantly shorter in the patients who chewed xylitol gum than in the control group [23].

Wu et al. [24] suggested that chewing nicotine gum may have a double stimulating effect on the vagus nerve: via physiological pathways through chewing and via pharmacological pathways through nicotine administration. In an RCT on the effect of nicotine gum on POI, 40 patients who underwent oncological colorectal surgery were randomly assigned to normal gum (n = 20) and nicotine gum (n = 20) groups. Although, time to primary endpoint including time to first feces and time to tolerate solid food for at least 24 h were shorter in the nicotine gum group than in the normal gum group (median, 3.50 days [3.00–4.25] vs. 4.50 [3.00–7.25], respectively) the difference was not statistically significant [25]. Further studies with larger samples are needed to assess the effect of nicotine gum on gastrointestinal recovery after gynecologic oncology surgery.

Cassia alata Linn

Cassia alata (syn. *Senna alata* [L.] Roxb.) is a medicinal plant belonging to the Fabaceae family. After cooking, the flowers or leaves are edible and may be used as a laxative; the inflorescence are boiled with chili and consumed for constipation [26]. In 2019, Phutsisen et al. [27] conducted an RCT in 90 patients randomly allocated to receive *Cassia alata* tea (n = 45) or warm water (n = 45) after surgery. Patients in the *Cassia alata* tea group had significantly shorter times to first flatus (MD −8.53; 95% CI −3.69 to −13.38 h) and first defecation (MD −19.83; 95% CI −11.18 to −28.48 h) compared with controls [27]. The common adverse effects of *Cassia alata* Linn consumption are nausea, abdominal pain, and diarrhea, which are usually mild and self-limiting. *Cassia alata* Linn tea [27] and *Cassia alata* Linn infusion have been shown to be well tolerated without side effects [28].

Pre-operative walking

Physical activity has been shown to accelerate rectosigmoid and total colonic transit times [29–31]. Our recent randomized trial published in 2019 included 85 patients who underwent elective total hysterectomy and systematic retroperitoneal lymphadenectomy. We found that walking before surgery shortened the times to bowel motility and the ability to tolerate food and significantly decreased the risk of postoperative paralytic ileus [32]. However, the mechanisms underlying the effect of walking on intestinal motility are not well understood.

Acupuncture and acupressure

Acupuncture has been used to treat postoperative nausea and vomiting as well as various functional gastrointestinal disorders [33]. Abadi et al. [34] investigated the effect of acupressure on POI after cesarean section in 120 women. They found that patients who received two acupressure sessions had shorter times to the presence of bowel sounds and first flatus and shorter postoperative bed rest compared with patients in the control group. Ruan et al. [35] investigated the effects of acupoint massage on gut recovery after gynecologic laparoscopy and found that massage was associated with significantly shorter times to flatus, defecation, and food tolerance, and fewer ileus symptoms [35].

Although the mechanisms underlying the effects of acupuncture and acupressure on gut function are not clear, Ruan et al. [35] hypothesized that acupoint massage stimulates the autonomic nervous system via the vagus nerve, which regulates gastrointestinal motility by modulating the release of various gastrointestinal hormones. Moreover, Ruan et al. reported that acupoint massage increased motilin and cholecystokinin levels, which stimulate gastrointestinal motility by suppressing somatostatin, which suppresses the release of motilin and cholecystokinin. Future research is needed to assess effects of traditional Chinese therapies such as acupuncture and acupressure on gut function after staging surgery for gynecological malignancies.

Chamomile oil

The main mechanism underlying the pathophysiology of POI is local intestinal inflammation triggered by manipulation of the intestine. Chamomile flowers contain a volatile oil containing α-bisabolol, matricin, and other terpenoids that have anti-inflammatory properties [36]. Moreover, Chamomile oil has a neuroprotective effect because it reduces nitric oxide levels [37]. A recent RCT in 142 women who underwent cesarean section found that patients who applied topical chamomile oil to their abdominal region after the surgery experienced earlier spontaneous passage of gas and shorter times to first defecation and food tolerance [38]. Our literature search did not reveal any studies of the effect of topical chamomile oil on POI in women who underwent gynecologic cancer surgery.

Daikenchuto

Daikenchuto (DKT) is a herbal medicine containing zanthoxylum fruit, processed ginger, ginseng, and maltose syrup. Animal studies have shown that DKT stimulates gastrointestinal motility through the cholinergic nervous system via serotonergic receptors and increases intestinal blood flow [39,40]. A secondary analysis of three RCTs in women who underwent open abdominal surgery found that DKT significantly accelerated gastrointestinal system recovery after surgery [41]. A high-quality RCT is needed to assess the efficacy of DKT in patients who have undergone gynecologic cancer surgery.

Conclusions

POI is a common complication of gynecologic surgery. Malignant and benign gynecological diseases may require bowel surgery. Enhanced recovery programs that provide multimodal interventions focusing on the underlying pathology to prevent or treat POI have been shown to reduce morbidity and shorten hospital stay and the time to resumption of normal bowel function. Several meta-analyses have shown that coffee consumption and chewing gum are safe and inexpensive nonpharmacological interventions that decrease the risk of developing POI, alleviate patient discomfort, and reduce hospital stay. Therefore, these interventions should be considered as adjunct treatments in postoperative care. Although the other non-pharmacological interventions included in this review are associated with reduced time to bowel recovery, future well-designed and adequately powered studies are needed to confirm their effect on the gastrointestinal system after surgery.

Declaration of competing interest

The author has no conflicts of interest to disclose.

Acknowledgment

This study did not receive pharmaceutical company support.

References

[1] Vather R, Trivedi S, Bissett I. Defining postoperative ileus: results of a systematic review and global survey. J Gastrointest Surg 2013;17:962–72.
[2] Harnsberger CR, Maykel JA, Alavi K. Postoperative ileus. Clin Colon Rectal Surg 2019 May;32(3):166–70. https://doi.org/10.1055/s-0038-1677003.
[3] Tabata T, Kihira T, Shiozaki T, Tanida K, Kondo E, Nagao K, et al. Efficacy of a sodium hyaluronate-carboxycellulose membrane (Seprafilm) for reducing the risk of early postoperative small bowel obstruction in patients with gynecologic malignancies. Int J Gynecol Canc 2010 Jan;20(1):188–93.

[4] Drake TM, Ward AE. Pharmacological management to prevent ileus in major abdominal surgery: a systematic review and meta-analysis. J Gastrointest Surg 2016 Jun;20(6):1253–64.
[5] Tan EK, Cornish J, Darzi AW, Tekkis PP. Meta-analysis: alvimopan vs. placebo in the treatment of post-operative ileus. Aliment Pharmacol Ther 2007;25:47–57.
[6] Beck DE, Sweeney WB, McCarter MD. Prospective, randomized, controlled, proof-of-concept study of the Ghrelin mimetic ipamorelin for the management of postoperative ileus in bowel resection patients. Int J Colorectal Dis 2014;29:1527–34.
[7] Wongyingsinn M, Baldini G, Charlebois P, Liberman S, Stein B, Carli F. Intravenous lidocaine versus thoracic epidural analgesia: a randomized controlled trial in patients undergoing laparoscopic colorectal surgery using an enhanced recovery program. Reg Anesth Pain Med 2011;36:241–8.
[8] Kane TD, Tubog TD, Schmidt JR. The use of coffee to decrease the incidence of postoperative ileus: a systematic review and meta-analysis. pii: S1089-9472 J Perianesth Nurs 2019 Dec 16;(19):30365. X.
[9] Boekema PJ, Samsom M, van Berge Henegouwen GP, Smout AJ. Coffee and gastrointestinal function: facts and fiction. A review. Scand J Gastroenterol Suppl 1999;230:35–9.
[10] Rao SS, Welcher K, Zimmerman B, Stumbo P. Is coffee a colonic stimulant? Eur J Gastroenterol Hepatol 1998;10(2):113–8.
[11] Bueno L, Fioramonti J, Honde C, Fargeas MJ, Primi MP. Central and peripheral control of gastrointestinal and colonic motility by endogenous opiates in conscious dogs. Gastroenterology 1985;88:549–56.
[12] Johnston KL, Clifford MN, Morgan LM. Coffee acutely modifies gastrointestinal hormone secretion and glucose tolerance in humans: glycemic effects of chlorogenic acid and caffeine. Am J Clin Nutr 2003;78(4):728–33.
[13] Güngördük K, Özdemir İA, Güngördük Ö, Gülseren V, Gokçü M, Sancı M. Effects of coffee consumption on gut recovery after surgery of gynecological cancer patients: a randomized controlled trial. Am J Obstet Gynecol 2017 Feb;216(2):145.e1–7.
[14] Gungorduk K, Paskal EK, Demirayak G, Köseoğlu SB, Akbaba E, Ozdemir IA. Coffee consumption for recovery of intestinal function after laparoscopic gynecological surgery: a randomized controlled trial. Int J Surg 2020 Aug 24;82:130–5.
[15] Fanning J, Hojat R. Safety and efficacy of immediate postoperative feeding and bowel stimulation to prevent ileus after major gynecologic surgical procedure. J Am Osteopath Assoc 2011 Aug;111(8):469–72.
[16] van den Heijkant TC1, Costes LM, van der Lee DG, Aerts B, Osinga-de Jong M, Rutten HR, et al. Randomized clinical trial of the effect of gum chewing on postoperative ileus and inflammation in colorectal surgery. Br J Surg 2015 Feb;102(3):202–11. https://doi.org/10.1002/bjs.9691.
[17] Ertas IE, Gungorduk K, Ozdemir A, Solmaz U, Dogan A, Yildirim Y. Influence of gum chewing on postoperative bowel activity after complete staging surgery for gynecological malignancies: a randomized controlled trial. Gynecol Oncol 2013 Oct;131(1):118–22.
[18] Xu C, Peng J, Liu S, Qi DY. Effect of chewing gum on gastrointestinal function after gynecological surgery: a systematic literature review and meta-analysis. J Obstet Gynaecol Res 2018;44(5):936–43.
[19] de Leede EM, van Leersum NJ, Kroon HM, van Weel V, van der Sijp JRM, Bonsing BA, Kauwgomstudie Consortium. Multicenter randomized clinical trial of the effect of chewing gum after abdominal surgery. Br J Surg 2018;105(7):820–8.
[20] Nanthiphatthanachai A, Insin P. Effect of chewing gum on gastrointestinal function recovery after surgery of gynecological cancer patients at Rajavithi Hospital: a randomized controlled trial. Asian Pac J Cancer Prev 2020 Mar 1;21(3):761–70. https://doi.org/10.31557/APJCP.2020.21.3.761.
[21] Turkay Ü, Yavuz A, Hortu İ, Terzi H, Kale A. The impact of chewing gum on postoperative bowel activity and postoperative pain after total laparoscopic hysterectomy. J Obstet Gynaecol 2019 Oct 14:1–5.
[22] Tandeter H. Hypothesis: hexitols in chewing gum may play a role in reducing postoperative ileus. Med Hypotheses 2009 Jan;72(1):39–40. https://doi.org/10.1016/j.mehy.2008.06.044. Epub 2008 Sep. 9.
[23] Gong Y, Zhang Q, Qiao L, Lv D, Ruan J, Chen H, et al. Xylitol gum chewing to achieve early postoperative restoration of bowel motility after laparoscopic surgery. Surg Laparosc Endosc Percutaneous Tech 2015 Aug;25(4):303–6. https://doi.org/10.1097/SLE.0000000000000174.
[24] Wu Z, Boersema GS, Jeekel J, Lange JF. Nicotine gum chewing: a novel strategy to shorten duration of postoperative ileus via vagus nerve activation. Med Hypotheses 2014 Sep;83(3):352–4.
[25] Lambrichts DPV, Boersema GSA, Tas B, Wu Z, Vrijland WW, Kleinrensink GJ, et al. Nicotine chewing gum for the prevention of postoperative ileus after colorectal surgery: a multicenter, double-blind, randomized, controlled pilot study. Int J Colorectal Dis 2017 Sep;32(9):1267–75.
[26] Monkheang P, Sudmoon R, Tanee T, Noikotr K, Bletter N, Chaveerach A. Species diversity, usages, molecular markers and barcode of medicinal Senna species (Fabaceae, Caesalpinioideae) in Thailand. J Med Plants Res 2011;5(26):6073–181.
[27] Phutsisen J, Kietpeerakool C, Jampathong N, Chumworathayi B, Temtanakitpaisan A, Aue-Aungkul A, et al. Effects of *Cassia alata* Linn on bowel function recovery following surgery for gynecological cancer: a randomized controlled trial. Compl Ther Med 2019 Dec;47:102222. https://doi.org/10.1016/j.ctim.2019.102222. Epub 2019 Oct 21.
[28] Thamlikitkul V, Bunyapraphatsara N, Dechatiwongse T, Theerapong S, Chantrakul C. Randomized controlled trial of *Cassia alata* Linn for constipation. J Med Assoc Thai 1990;73(4):217–22.
[29] De Schryver AM, Keulemans YC, Peters HP, Akkermans LM, Smout AJ, De Vries WR, et al. Effects of regular physical activity on defecation pattern in middle-aged patients complaining of chronic constipation. Scand J Gastroenterol 2005 Apr;40(4):422–9.
[30] Cheskin LJ, Kamal N, Crowell MD, Schuster MM, Whitehead WE. Mechanisms of constipation in older persons and effects of fiber compared with placebo. J Am Geriatr Soc 1995 Jun;43(6):666–9.
[31] Rao SS, Beaty J, Chamberlain M, Lambert PG, Gisolfi C. Effects of acute graded exercise on human colonic motility. Am J Physiol 1999 May;276(5):G1221–6.
[32] Özdemir İA, Comba C, Demirayak G, Gülseren V, Erdogan SV, Aslanova F, et al. Impact of pre-operative walking on post-operative bowel function in patients with gynecologic cancer. Int J Gynecol Canc 2019 Oct;29(8):1311–2131.
[33] Liu L, Yuan X, Yang L, Zhang J, Luo J, Huang G, et al. Effect of acupuncture on hormone level in patients with gastrointestinal dysfunction after general anesthesia: a study protocol for a randomized controlled trial. Medicine (Baltim) 2020 Apr;99(14):e19610.
[34] Abadi F, Shahabinejad M, Abadi F, Kazemi M. Effect of acupressure on symptoms of postoperative ileus after cesarean section. J Acupunct Meridian Stud 2017 Apr;10(2):114–9.
[35] Ruan D, Li J, Liu J, Li D, Ji N, Wang C, et al. Acupoint massage can effectively promote the recovery of gastrointestinal function after gynecologic laparoscopy. J Invest Surg 2019 Mar 27:1–5.
[36] Saneian H, Tavakkol K, Adhamian P, Gholamrezaei A. Comparison of Lactobacillus Sporogenes plus mineral oil and mineral oil alone in the treatment of childhood functional constipation. J Res Med Sci 2013 Feb;18(2):85–8.
[37] Zargaran A, Borhani-Haghighi A, Salehi-Marzijarani M, Faridi P, Daneshamouz S, Azadi A, et al. Evaluation of the effect of topical chamomile (*Matricaria chamomilla* L.) oleogel as pain relief in migraine without aura: a randomized, double-blind, placebo-controlled, crossover study. Neurol Sci 2018 Aug;39(8):1345–53.
[38] Khadem E, Shirazi M, Janani L, Rahimi R, Amiri P, Ghorat F. Effect of topical chamomile oil on postoperative bowel activity after cesarean section: a randomized controlled trial. J Res Pharm Pract 2018 Jul-Sep;7(3):128–35.
[39] Kono T, Kaneko A, Hira Y, Suzuki T, Chisato N, Ohtake N, et al. Anti-colitis and -adhesion effects of Daikenchuto via endogenous adrenomedullin enhancement in Crohn's disease mouse model. J Crohns Colitis 2010;4:161–70.
[40] Muraoka I, Takatsuki M, Soyama A, Yamaguchi I, Tanaka S, Tanaka T, et al. Efficiency of herbal medicine Dai-kenchu-to on portal blood flow in rat models. Ann Med Surg 2015;4:211–4.
[41] Kono T, Shimada M, Nishi M, Morine Y, Yoshikawa K, Katsuno H, et al. Daikenchuto accelerates the recovery from prolonged postoperative ileus after open abdominal surgery: a subgroup analysis of three randomized controlled trials. Surg Today 2019 Aug;49(8):704–11.