

# *Malus domestica* reduces chemotherapy-induced nausea and vomiting: A randomized double-blind placebo-controlled clinical trial

Sharareh Darvishpour<sup>1</sup>, Razieh Avan<sup>2</sup>, Mohammad Azadbakht<sup>3</sup>, Monireh Maham<sup>4</sup>, Jafar Akbari<sup>5</sup>, Ghasem Janbabaei<sup>6</sup>, Ehsan Zaboli<sup>6</sup>, Ali Reza Amirabadizadeh<sup>7</sup>, Ebrahim Salehifar<sup>8</sup>

<sup>1</sup>Department of Clinical Pharmacy, Gastrointestinal Cancer Research Center, Student Research Committee, Mazandaran University of Medical Sciences, Sari, Iran, <sup>2</sup>Department of Clinical Pharmacy, Medical Toxicology and Drug Abuse Research Center (MTDRC), School of Pharmacy, Birjand University of Medical Sciences, Birjand, Iran, <sup>3</sup>Department of Pharmacognosy, Pharmaceutical Sciences Research Center, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran, <sup>4</sup>Department of Clinical Pharmacy, Student Research Committee, Resident of Clinical Pharmacy, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran, <sup>5</sup>Department of Pharmaceutics, Pharmaceutical Research Center, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran, <sup>6</sup>Department of Hematology and Oncology, Gastrointestinal Cancer Research Center, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran, <sup>7</sup>Cardiovascular Diseases Research Center, Birjand University of Medical Sciences, Birjand, Iran, <sup>8</sup>Department of Clinical Pharmacy, Pharmaceutical Sciences Research Center, Hemoglobinopathy Institute, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran.

**Background:** Chemotherapy-induced nausea and vomiting (CINV) is considered as the most common complications of chemotherapy which has a detrimental influence on the quality of life of patients with cancer. We assessed the efficacy of Apple (*Malus domestica*) syrup for reducing CINV. **Materials and Methods:** This study was a randomized, double-blind, placebo-controlled trial carried out in a Hematooncology Clinic affiliated to Mazandaran University of Medical Sciences, Sari, Iran (from October 2017 to August 2018). Subjects were randomly allocated to receive apple syrup or placebo along with their previous antiemetic treatment and chemotherapy regimen, three times a day. Thirty-four patients received apple syrup ( $n = 16$ ) or placebo ( $n = 18$ ). Statistical analysis was conducted using SPSS software Version 21<sup>®</sup> (SPSS Inc., Chicago, IL, USA). A  $P < 0.05$  indicated statistical significance. **Results:** Both acute and delayed nausea grades were significantly lower in *M. domestica* syrup in comparison to placebo syrup ( $P = 0.001$  and  $0.001$ , respectively). The duration of nausea ( $P = 0.04$ ) was lower in intervention group compared to placebo group. **Conclusion:** These findings demonstrated that *M. domestica* syrup can reduce the severity and duration of nausea in cancer patients who received chemotherapy.

**Key words:** Chemotherapy-induced nausea and vomiting, *Malus domestica*, palliative care, quality of life, randomized controlled trial

**How to cite this article:** Darvishpour S, Avan R, Azadbakht M, Maham M, Akbari J, Janbabaei G, et al. *Malus domestica* reduces chemotherapy-induced nausea and vomiting: A randomized double-blind placebo-controlled clinical trial. J Res Med Sci 2021;26:72

## INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) is considered as the most common complications of chemotherapy that has a detrimental influence on the quality of life of patients with cancer.<sup>[1,2]</sup>

The optimal aim of different antiemetic guidelines is prophylaxis.<sup>[3,4]</sup> Generally, in patients receiving highly

emetogenic chemotherapy (HEC), various guidelines recommend administration of an neurokinin-1 receptor antagonist along with a 5-hydroxytryptamine 3 receptor antagonist and dexamethasone.<sup>[5-7]</sup> Sometimes the antiemetic effect of these combination therapies is still insufficient. Hence, complementary therapies are commonly used because of their wide acceptance, low cost, and minimal side effects.<sup>[8]</sup> Few herbal remedies

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10.4103/jrms.JRMS\_833\_20

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**Address for correspondence:** Prof. Ebrahim Salehifar, Pharmaceutical Sciences Research Center, Department of Clinical Pharmacy, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Km 18 Khazarabad Road, Khazar sq., Mazandaran Province, Sari, Iran.  
E-mail: esalehifar@mazums.ac.ir, esalehifar52@gmail.com, salehifare@yahoo.com

**Submitted:** 29-Jul-2020; **Revised:** 03-Oct-2020; **Accepted:** 22-April-2021; **Published:** 30-Sep-2021

have been applied to treating CINV. *Achillea millefolium* L., *Cannabis sativa*, *Citrus aurantium*, *Hypericum perforatum* L., *Scutellaria baicalensis*, and *Zingiber officinale* were associated with successful results.<sup>[9,10]</sup>

For 1000 of years, the fruits of *Malus domestica* species, commonly known as apples worldwide, have been cultivated for nutritional and economic value. In the traditional Iranian medicine, apple has been used to increase general well-being, to strengthen cardiovascular, respiratory, and gastrointestinal systems, to improve appetite and also used for its antiemetic and anti-diarrheal effects.<sup>[11-14]</sup> In spite of traditional use of *M. domestica* as an antiemetic, there is no clinical study regarding its efficacy. The aim of this study was to assess the efficacy of *M. domestica* syrup for reducing CINV.

## MATERIALS AND METHODS

### Patients

This study was a randomized, double-blind, placebo-controlled trial carried out in a Hemato-oncology Clinic affiliated to Mazandaran University of Medical Sciences, Sari, Iran (from October 2017 to August 2018). The eligible patients were  $\geq 18$  years of age of either gender, with a documented diagnosis of cancer who experienced nausea and vomiting within the previous cycle (s) of chemotherapy, in spite of standard antiemetic treatment. A cycle means that the patient has a single cancer drug or a combination of drugs and then has a rest to allow his/her body to recover. The patients with uncontrolled or poorly controlled diabetes (because of syrup formulation of study products), nausea or vomiting before chemotherapy administration, existence of special conditions that may induce nausea or vomiting (e.g., brain metastasis, bowel obstruction, hepatitis, or recent abdominal or pelvic irradiation during last week, uremia), and known hypersensitivity to apple or any ingredients of the product were excluded from the study. This study was conducted as a pilot. Then the collected information determined the final sample size. The sample size was determined as a pilot with the first type error of 5% and power of 80%.

### Intervention

The eligible patients were randomly allocated, based on predefined computer-generated codes, to receive either apple syrup or placebo, 10 mL three times a day (half an hour before meals). The dose was selected based on Persian medicine reference.<sup>[11-14]</sup> The syrup was made according to the United States Pharmacopoeia-National Formulary standard (2017).<sup>[15]</sup> Fruits of *M. domestica* were collected from the region of "Damavand city," in Tehran province, Iran, in autumn season 2018. The fruits were

washed and crushed and the seeds were separated. Due to the oxidation of the its compounds in the presence of oxygen, the crushed apple is placed in 96% boiling ethanol to neutralize its oxidizing enzymes, and then it macerated in hydroalcoholic solution (1:5) for 24 h. The extract was evaporated by rotary evaporator and then freeze-dried of apple powder was prepared. It was further standardized its flavonoid content as based on quercetin. The apple syrup and placebo were manufactured by the pharmaceuticals laboratory of Pharmacy faculty of Mazandaran University of Medical Sciences, Iran. Each 100 mL of apple syrup included 20 g lyophilized extract of apple fruit, 10 g Honey, 0.5 g ethyl alcohol, 0.02 g propylparaben, 0.18 g methylparaben and water to 100 mL. The placebo was prepared as like as apple syrup without lyophilized extract of apple fruit. Both apple syrup and placebo were filled in 250 ml amber glass bottles without any apparent difference. The treatment was initiated 1 day before the 1<sup>st</sup> day of chemotherapy administration (day-1) and lasted until 6 day (day + 6) after that. All patients received antiemetic medications including granisetron 0.01 mg/kg intravenous (IV), dexamethasone 8 mg IV, metoclopramide 10 mg IV and aprepitant 125 mg oral, 30 min before chemotherapy. Furthermore, aprepitant 80 mg daily and metoclopramide 10 mg three times a day, orally on days 2-3 was administered. Participants were enrolled in either apple syrup or placebo syrup by the block randomization allocation sequence with a block size of 4. The physicians, assessor, and patients were blinded to the randomization and treatment assignment. Medications were prepackaged in bottles labelled with random codes generated by a computer. Preparation, packaging, and labeling of the drugs performed by the third person under the supervision of the senior manager of the project. Packaging of the drugs was exactly identical in both arms of the study. The bottle's contents only could be recognized through a key which was solely accessible for the senior supervisor. Recording and processing patients' data also performed using the codes.

CINV is classified into two phases: the acute phase and the delayed phase. Acute CINV appears within 1-2 h of chemotherapy administration and often lasts for up to 24 h. The delayed phase of CINV initiates on day 2 after chemotherapy and can continue up to 5 days. The grade of nausea is divided into five levels according to the criteria of the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) v3.0: 1-Loss of appetite without alteration in eating habits 2-Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 h 3-Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or total parenteral nutrition indicated  $\geq 24$  h 4-life-threatening consequences and 5-death.<sup>[16]</sup>

### Ethical approval

The study protocol was approved by Mazandaran University of Medical Sciences Ethical Committee (IR.MAZUMS.REC.95-2254) and registered in Iranian Registry of Clinical Trials (IRCT201709142027N10). Written informed consent was gathered from all participating patients before enrollment into the study.

### Endpoint and assessments

The primary outcome was considered as reduction in the incidence of nausea and vomiting and the secondary outcomes were decrease in the duration of nausea and vomiting and adverse events rate.

The severity of nausea and vomiting was assessed based on the NCI-CTCAE criteria v. 3.0.<sup>[16]</sup>

### Statistical analysis

Bivariate outcomes and normally distributed continuous outcomes were assessed using the Chi-square analysis and independent sample *t*-test, respectively. The Mann–Whitney U-test was used for nonparametric outcomes. *P* < 0.05 indicated statistical significance. Statistical analysis was conducted using the SPSS software version 21® (SPSS Inc., Chicago, IL, USA).

## RESULTS

Forty patients were eligible for enrolment and randomized to receive apple syrup or placebo syrup. Of these, 34 patients completed the study and remained in the final analysis [Figure 1]. Demographic characteristics of patients were not significantly different. The common types of cancer were breast, gastrointestinal, and ovarian cancers [Table 1]. Relative to the differences in the emetic

potential of chemotherapy regimens, the majority of patients in the study treated with HEC regimen (88.2%). In apple syrup and placebo groups, the most common chemotherapy regimens were anthracycline-based (50.2% and 55.5%) and platinum-based (18.9% and 33.5%), respectively.

The grade of acute and delayed nausea in the study cycle of chemotherapy was significantly lower in *M. domestica* syrup as compared to placebo (*P* = 0.001 and *P* = 0.001, respectively) [Figure 2]. The severity of both acute and delayed vomiting in the previous cycle was not significant between two groups (*P* = 0.14 and *P* = 0.65, respectively). In the study cycle, the grade of both acute and delayed vomiting was not significantly different between groups (*P* = 0.11, *P* = 0.40).

The median duration of nausea in the study cycle in apple and placebo groups was 0.5 (0.0–4.0) and 4.5 (2.7–5.2) days, respectively. Duration of nausea was significantly decreased in patients received apple syrup as compared to placebo syrup (*P* = 0.04). However, nausea in pervious cycle, vomiting in pervious cycle, and vomiting in study cycle were not significantly different between apple and control groups (*P* > 0.05) [Table 2].

Drinking too much apple juice can cause diarrhea and flatulence, belching, or burping.<sup>[17]</sup> Because of the high sugar content, it may also lead to increased risk of type 2 diabetes mellitus.<sup>[18]</sup> No significant adverse event was reported either by apple syrup or placebo during the study. Only one patient in each group discontinued the study because of noncompliance.

## DISCUSSION

In the traditional Iranian medicine, *M. domestica* has been used for a variety conditions including improvement of appetite and as an antiemetic and antidiarrheal herbal

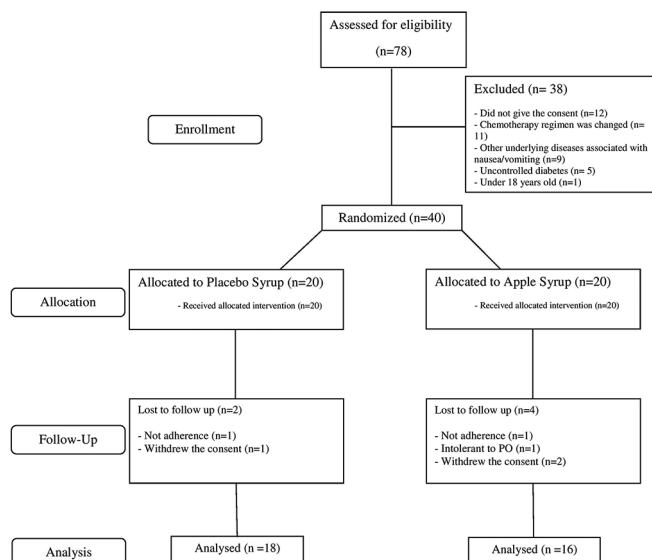


Figure 1: Consort flow diagram

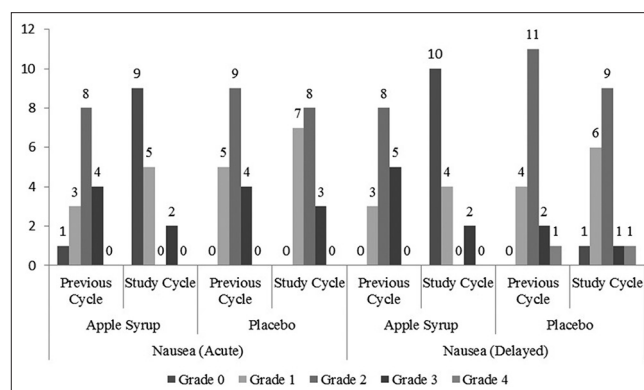


Figure 2: Acute and delayed nausea in apple syrup and placebo syrup the severity of both acute and delayed nausea in the previous cycle was similar between two groups (*P* = 0.69, *P* = 0.42 respectively). In the study cycle, patients received apple syrup favorably had a lower grade acute and delayed nausea (*P* = 0.001)

**Table 1: Baseline characteristics of patients**

	Apple syrup (n=16), n (%)	Placebo syrup (n=18), n (%)	P
Age (years), mean±SD	51±3.8	48.6±3.2	0.63
Gender			
Women	12 (75)	11 (61)	0.47
Men	4 (25)	7 (39)	
Smoking			
Yes	2 (12.5)	2 (11)	0.65
No	14 (87.5)	16 (89)	
Alcohol drinking			
Yes	1 (6.2)	0 (0)	0.47
No	15 (93.8)	18 (100)	
Previous surgery			
Yes	3 (18.8)	9 (50)	0.06
No	13 (81.2)	9 (50)	
Previous chemotherapy			
Yes	4 (25)	2 (11.1)	0.38
No	12 (75)	16 (88.9)	
Previous radiation therapy			
Yes	2 (12.5)	1 (5.6)	0.59
No	14 (87.5)	17 (94.4)	
Tumor site			
Breast	6 (37.5)	8 (44.4)	0.61
Lung	1 (6.25)	1 (5.5)	
Gastric	2 (12.5)	4 (22.2)	
Colon	1 (6.25)	0	
Rectal	1 (6.25)	1 (5.5)	
Ovarian	2 (12.5)	1 (5.5)	
Hodgkin lymphoma	2 (12.5)	0	
Pancreas	0	1 (5.5)	
Osteosarcoma	1 (6.25)	0	
CNS cancer	0	2 (11.1)	
BMI (kg/m <sup>2</sup> ), mean±SD	28±1.19	27±1.5	0.62

SD=Standard deviation; CNS=Central nervous system, BMI=Body mass index

**Table 2: Duration of nausea/vomiting in previous and study cycles of chemotherapy**

Variable	Apple group		Placebo group		Z (P)
	Mean±SD	Median (Q1-Q3)	Mean±SD	Median (Q1-Q3)	
Nausea in previous cycle (n)	6.0±4.6	5.0 (4.0-5.75)	5.3±3.6	5.0 (3.0-5.5)	0.39 (0.70)
Nausea in study cycle (n)	3.0±5.1	0.5 (0.0-4.0)	4.6±3.3	4.5 (2.7-5.2)	2.09 (0.04)
Vomiting in previous cycle (n)	2.2±4.9	0.7 (0.0-2.7)	2.1±3.9	0.5 (0.0-2.2)	0.21 (0.83)
Vomiting in study cycle (n)	1.7±5.0	0.2 (0.0-0.5)	1.3±2.6	0.4 (0.0-2.0)	0.98 (0.32)

SD=Standard deviation

medicine, but the information on the use of apple in CINV is very limited. To date, only one published study assessed the efficacy of a colorless, odorless meal that includes apple-sauce for cisplatin-induced nausea and vomiting in 19 cancer patients. The consumption of this predetermined meal reduced cisplatin-induced nausea and vomiting.<sup>[19]</sup>

It seems that several components of the extract of *M. domestica* may be responsible for anti-vomiting effect, especially through neutralizing the reactive oxygen species (ROS).<sup>[20]</sup> Oxidative stress considered as an

overproduction of ROS has been reported to play an important role in the etiology of the emetic reflex. One of the early steps in the development of CINV is based on the formation of free radicals by chemotherapy drugs within the gastrointestinal tract which results to the release of serotonin from enterochromaffin cells located in the intestinal mucosa.<sup>[21]</sup> The antioxidant activity of these compounds in *M. domestica* syrup can modify the disrupted cellular oxido-reductase mechanisms. The limitation of the study was relatively small sample size, although the design was a randomized, double-blinded, placebo-controlled study.

## CONCLUSION

The findings of the study demonstrated anti-emetic function of apple syrup in addition to standard antiemetic treatment, in decreasing the grade and duration of nausea in cancer patients who received moderately to HEC.

### Acknowledgments

This study was supported by a grant from Research and Technology Deputy of Mazandaran University of Medical Sciences. The Research and Technology Deputy of the university did not have any role in the design of the study, data collection, analysis, interpretation of data, and in writing the manuscript. The study protocol was approved by Mazandaran University of Medical Sciences Ethical Committee (IR.MAZUMS.REC.95-2254) and registered in Iranian Registry of Clinical Trials (IRCT201709142027N10).

### Financial support and sponsorship

This study was financially supported by Research and Technology Deputy of Mazandaran University of Medical Sciences.

### Conflicts of interest

There are no conflicts of interest.

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