

Effects of Dietary Honey and Ardeh Combination on Chemotherapy-Induced Gastrointestinal and Infectious Complications in Patients with Acute Myeloid Leukemia: A Double-Blind Randomized Clinical Trial

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Abstract

We aimed to investigate the effects of dietary combination of honey and Ardeh on chemotherapy-induced complications in patients with acute myeloid leukemia (AML).

A total of 107 AML patients who underwent chemotherapy for at least 30 consecutive days were recruited to this double-blind randomized placebo-controlled clinical-trial which was conducted in the Imam Reza and Ghaem teaching hospitals (Mashhad, Iran). They were divided into two age and sex-matched groups: 58 treated and 49 untreated patients. A combination of 50 grams of honey and 150 grams of Ardeh was added to the treated group's diet for 30 consecutive days, three times each day; while the untreated group received their regular diet. Both groups received their standard medication for AML as well. After one month, they were all examined and lab tests were done on them by an internist and laboratory technicians who were blinded to the subject allocations.

Mean value of WBC count in treated group was significantly lower than that of untreated group. Duration of fever and admission in the hospital due to fever were both significantly lower in the treated group ($P=0.014$, $P=0.032$ respectively).

Total gastrointestinal complications were significantly less in the treated group one month after therapy with the special honey and Ardeh compound. No unusual or unexpected side effects were observed.

Honey and Ardeh are easily accessible materials that can be helpfully administered in AML patients receiving chemotherapy, since their useful effects in ameliorating gastrointestinal complications and reducing fever and neutropenia in AML patients have been shown.

Keywords: Honey; Sesame oil; Acute Myeloid Leukemia; Chemotherapy; Gastrointestinal Diseases.

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Introduction

Cancer is the second cause of death worldwide. Hematologic malignancies have a high rate of mortality among different types of cancer due to their progressive nature and poor response to various treatment methods (1). About 40% of young patients with AML are treated by intensive consolidation chemotherapy course (2,3). Due to destruction of the mucosal barrier, chemotherapy usually causes a high risk of gastrointestinal (GI) complications as well as febrile neutropenia and severe infections and thus high mortality rate (4-6).

Usual chemotherapy protocols have many side-effects that can delay patient cure course and lead to over-admission in the hospital. GI complications are common in patients with AML receiving chemotherapy including abdominal pain, nausea and vomiting, diarrhea, constipation, oral candidiasis, esophagitis, dysphagia, odynophagia, typhlitis, enterocolitis, perianal ulcers, appendicitis and life threatening GI tract bleedings(7-10).

Honey is a valuable botanical product, which has been used not only as a great nutrient, but also as a remedy since many centuries ago. The main nutritional components of honey are carbohydrates (80%), mainly fructose and glucose but also about 25 different oligosaccharides, and water(18%)(11). Antibacterial activity of honey has been reported since 1892 particularly against gram-positive bacteria(12, 13). To date, factors contributing to antimicrobial activity of honey identified are the high sugar concentration, hydrogen peroxide, methylglyoxal, the antimicrobial peptide bee defensin-1, phenolics and flavonoids(14), low pH and yet unidentified compounds presumably described as inhibines(15, 16).

Sesame seed is a plant food that is used as a traditional healthy diet in the Middle East countries and Japan. Sesame seed is rich in oil (about 50%) and protein (about 20%) (17).

It is also a rich source of lignans including sesamin, sesamol, sesamolol, sesaminol, sesamololol, and pin which have been isolated from sesame seed and/or sesame seed oil (18, 19, 20). Sesame lignan content is even more than flaxseed, which is already considered

as a major source of lignin (21).

In modern times, sesame oil has been widely used by western herbalists because of its various therapeutic effects including anti-inflammatory, anti-cancer and anti-bacterial (22).

Ardeh is a traditional food which is popular in Middle East countries such as Iran. It is also known as Tahin (in Turkey), Tahineh (in Arabic countries) or sesame paste in other regions—ignoring small differences in processing. Ardeh is prepared by grinding the roasted sesame seeds. In this process, minimum changes in its nutritional content will occur. It is usually consumed as a semi-liquid paste with bread for breakfast(23). Considering a somehow bitter taste of Ardeh, people in some parts of Iran traditionally consume a combination of honey and Ardeh in their routine daily diet. However, little information is available about the effects of dietary honey and Ardeh on chemotherapy-induced complications, if any. Thus, we aimed to evaluate the effects of dietary honey and Ardeh on chemotherapy-induced gastrointestinal and hematologic complications, fever and neutropenia in AML patients.

Experimental

Design and setting

This study is a randomized, double-blind placebo-controlled, parallel group clinical trial, which was conducted between April 2011 and September 2012 in the Imam Reza and Ghaem teaching hospitals' Hematology wards (Mashhad, Iran). Study protocol was approved by Ethics Committee of Mashhad University of Medical Sciences (No. 900931) and written informed consent was obtained from each patient at the event of enrollment.

Subjects

Using the NCSS (Number Cruncher Statistical System) statistical software, and the Equivalent proportion formula; we calculated sample size for the power of 80% and confidence interval of 95%, as to be 40 for each group. We enrolled 107 subjects instead of 80 for the purpose of increasing the power and prevent unwanted drop offs.

These 107 AML patients (52 male, 55 female)

Table 1. Demographic and clinical characteristics

Group	Treated	Untreated	
Age (mean±SD)	34(13-72)	29.7(12-65)	p=0.3
Gender (Male/Female)	28/30	24/25	

were recruited to the study. Subjects were all AML cases (except AML M3 subtype) with early stages of disease, which were scheduled to undergo chemotherapy courses. Diagnosis was confirmed by immunophenotyping and morphology. Anthropometric data was gathered by direct examination and history taking.

All subjects were randomly allocated to two age and sex-matched groups with the allocation ratio of 1:1: treated (58) receiving special honey and Ardeh treatment in addition to their routine diet; and untreated (49) receiving placebo instead of honey and Ardeh (Figure 1). The mean age of the treated and untreated groups were 34(13-72) and 29.7(12-65), respectively ($p=0.3$; Table 1).

Exclusion criteria included AML M3 subtype because these patients were treated with a different protocol, recent antibiotic therapy for any reasons, receiving granulocyte colony stimulating factor (G-CSF), documented active infection such as pneumonia, etc. and other co-morbidities including diabetes mellitus, cardiovascular disorders and chronic pulmonary and/or renal diseases.

Medication

In treated group, patients received a compound containing 50 grams of honey and 150 grams of Ardeh, for 30 consecutive days, three times each day; coinciding with the start of their chemotherapy course which was about 30 days. Besides, the standard therapies for cancer were given to both groups.

Based upon modern scientific literature, the best bee's honey is made by *Apis mellifera* (Family: Apidae) (24) which is the predominant honey-bee in Iran. Honey used in this study was obtained from *A. mellifera* honey-bees raised in North Khorasan, Iran.

Before the first dose and During treatment, patient were all examined for probable GI complications by an Internist and also before and one month after the first dose, lab tests such as CBC count, blood culture, urine culture

and chest X-ray were done. The internist and laboratory technicians were blinded to the subject allocations.

Neutropenia was defined as an absolute neutrophil count of <500 per.

Fever was defined as any single axillary temperature of 38.3°C or two axillary temperatures greater than or equal to 38°C recorded at least four hours apart.

Statistical Analysis

Data were expressed as mean \pm standard deviation (SD) by the 95% confidence interval. Two tailed P-values <0.05 was considered significant. All statistical analyses were performed by Statistical Package for Social Sciences (SPSS) software 20th release, using paired samples t-test.

Results

In the baseline, mean values of anthropometrics data and WBC count in 58 treated and 49 untreated groups did not differ significantly ($p>0.05$; Table 2).

In respect to evaluation of infection in the patients, 1 and 3 positive blood cultures, 2 and 7 positive urine cultures and 9 and 13 positive chest X-rays in treated and untreated groups were detected respectively. Duration of fever and admission in the hospital due to fever were both significantly lower in the treated group ($p=0.014$, $p=0.032$ respectively; Table 3).

Most GI complications were significantly ameliorated more in treated group than in untreated group, one month after starting the treatment in compare with the therapy start time (Table 4).

Some other GI complications such as hematochezia, melena, perianal fistula and ulcers and odynophagia were not statistically analyzed because of few numbers.

In 1 year follow up, number of patients who died due to neutropenia was lower in treated group, in comparison with the untreated group

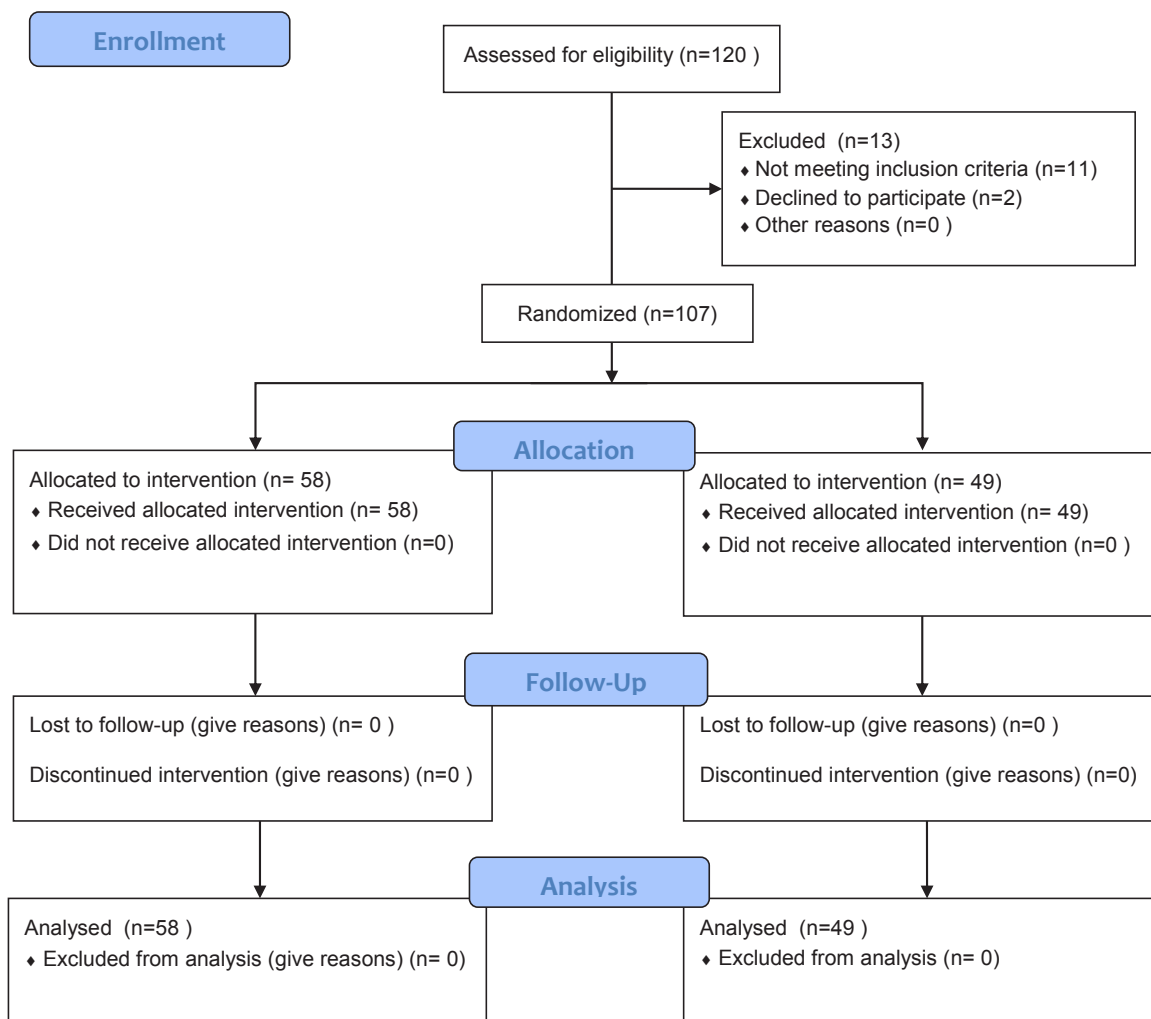


Figure 1. CONSORT Flow Diagram.

(9.7 % and 42.9 %, respectively) (P-value = 0.001). No unusual or unexpected side effects were observed.

Discussion

This trial was designed to test the hypothesis that combination of honey and Ardeh could ameliorate the chemotherapy induced gastrointestinal complications and reduce fever and neutropenia in AML patients.

Complementary medicine is a growing, cost-benefit, useful field in medicine even in modern era. It seems there is a gap between traditional beliefs and scientific researches in this field. Lack of clinical-trials, make it difficult to decide

which beliefs are truly effective and which are not. Considerable compliance of patients to complementary and traditional medicine and, hope for better and more efficient therapies are some of the reasons why more researches should be done in this field.

Anti-febrile effects

Gastrointestinal mucositis and hematologic dissemination of the normal microbial flora may explain febrile episodes in neutropenic patients. Zidan *et al.* have showed that the use of honey in patients who are at high risk of developing neutropenia as a result of chemotherapy decreases the risk of pancytopenia (25). In our study, febrile period which is mostly a

Table 2. WBC count in subjects before and after receiving honey and Ardeh diet.

WBC Count	Group	Untreated	Treated	
Before		18141.1 ± 8084.6	16605.1 ± 4657.7	p=0.24
After		12688.7 ± 1386.4	7634.5 ± 1421.4	P<0.001
p-value		0057	0.003*	

Data expressed as mean ± SD

*Significant

consequence of neutropenia in patients receiving chemotherapy, diminished significantly ($p<0.05$) and as a result, duration of admission decreased significantly ($p<0.05$).

Anti-bacterial effects

The use of broad-spectrum antibiotic prophylaxis will cause several side-effects including: colonization of pathogen in oral cavity (26) developing antibiotic-resistance in pathogens and fungal overgrowth (27). Thus, finding ways to reduce antibiotic use will be very helpful.

In recent years, the knowledge on the antibacterial compounds in honey has been expanded. Direct antimicrobial effects of honey have been widely used in wound healing by applying certain honey combinations in wound dressings (28). A great deal of its GI ulcer healings may be explained in this way. Additionally, favorable effects of honey on multidrug resistant bacteria have been observed (29).

An anti-microbial role has been demonstrated for sesame as well (30). Sesame seed lignans have other demonstrated activities such as modulation of fatty acid metabolism, improvement of liver functions, inhibition of cholesterol absorption, vitamin-E sparing and anti-hypertensive and anti-aging effects (18).

In our study, lower documented infections were observed in treated group. This may indicate that honey and Ardeh combination may

reduce need to antibiotics in cancer patients. However, it seems more precise *in-vitro* and *in-vivo* researches should be done to approve this claim.

Effects on gastrointestinal complications

Chemotherapy induced GI complications are common in AML patients undergone chemotherapy (8, 31). Application of either fresh or old natural bee honey has been showed to be effective in managing vomiting, diarrhea, constipation, mucositis, or infectious states such as throat infection, tuberculosis or worm infestation (24, 32).

In our study, overall comparison of the number of GI complications between two groups showed a significant difference in recovery from the complications in favor of the group who consumed honey and Ardeh. It should be mentioned that nausea and vomiting, which is one of most prevalent and annoying complications induced by chemotherapy, declined significantly ($p<0.05$). In this way, not only the quality-of-life of patients could be increased brightly, but also the risk of malnourishment is lowered obviously.

Anti-neoplastic effects

Recently, anti-oxidant activity of honey came into limelight. Anti-oxidant agents have been proven as a preventive and curative factor against different diseases, such as cancer, inflammatory disorders, coronary diseases, neurological

Table 3. Fever and admission in the treated and untreated groups.

	Treated group	Untreated group	P-value
Duration of fever (days)†	5 ± 1.51	11.61 ± 7.39	0.014*
Duration of admission(days) †	13.66 ± 4.64	24.95 ± 14.96	0.032*

† Data expressed as mean ± SD. Analysis performed by paired samples t-test.

*Significant

Table 4. Frequency of gastrointestinal complications in the patients before and after honey and Ardeh diet.

	Treated group		Untreated group		P-value
	Before	After	Before	After	
Oral ulcers	24	5	22	17	P<0.05*
Oral candidiasis	13	2	11	3	0.541
Diarrhea	7	0	8	5	P<0.05*
Nausea/Vomiting	32	9	28	21	P<0.05*
Abdominal Distention	6	1	4	4	P<0.05*
Abdominal Pain	10	2	8	7	P<0.05*
Dysphagia	6	0	6	2	0.227
Constipation	8	1	5	3	0.119
Total	115	21	101	64	P<0.05*

Data expressed as N (%). Analysis performed by Fisher's exact test.

*Significant

degeneration, and aging. Since honey is rich in phenolic compounds and other anti-oxidants such as glucose oxidase, catalase, ascorbic acid, flavonoid, carotenoid derivatives, organic acids, Maillard reaction products, amino acids and proteins; it has gained great vitality (33-36).

Some of the mechanisms suggested for anti-cancer properties of honey are inhibition of cell proliferation, induction of apoptosis, and cell-cycle arrest (37).

In modern medicine, numerous benefits of sesame oil are confirmed by botanists such as anti-cancer, anti-bacterial, anti-inflammatory, lipid and cholesterol-lowering effects and preventive effects on chemotherapy-induced phlebitis (22, 38- 41). Previously, it has been recognized that the sesame lignans can be effectively converted into entrolactone (ENL) (19) which has anti-cancer and anti-oxidant effects (42-45). The anti-oxidant effect may be due to inhibition of γ -tocopherol metabolism (46, 47).

We obviously observed lower mortality rate in treated group, which may in part, be related to anti-neoplastic effects of honey and Ardeh combination beside their anti-bacterial and anti-oxidant properties.

Up to our knowledge, this is the first human trial evaluating the effects of honey and Ardeh combination diet on chemotherapy induced complications in AML patients.

In other parts of our project we have demonstrated the useful effects of honey and

sesame in gynecologic diseases, atherosclerosis prevention, diabetic myopathy, gastric ulcers, etc.

Further studies on different types of honey and different proportions of honey and Ardeh in their combination are suggested. Evaluation of effects of honey and Ardeh on other hematologic disorders and other complications will broaden our knowledge about the benefits of these precious materials.

Conclusion

Since the useful effects of honey and Ardeh in ameliorating gastrointestinal complications and fever have been shown, they can be administered in AML patients who undergone chemotherapy as a helpful adjuvant. This combination is an inexpensive, natural and easily accessible diet with high degrees of patient compliance that will improve patients' lifestyle and reduce their need to antibiotics, anti-emetics and extra costs.

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