

A Systematic Review of the Role of Medicinal Plants in the Treatment of Chemotherapy Induced Nausea and Vomiting

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Abstract--- Background: Chemotherapy is one of the most common treatments in cancer management. Chemotherapy drugs usually have different side effects. Nausea and vomiting associated with chemotherapy are among the most severe side effects. Due to the limited effect and dangerous side effects of taking anti-nausea drugs, herbal medicine has been chosen by patients as an alternative treatment. The aim of this study was to review the use of medicinal plants in the treatment of nausea and vomiting caused by chemotherapy **Method:** In this study, systematic review using the following keywords: Controlling nausea and vomiting, chemotherapy side effects, chemotherapy-induced nausea, Web of Science, Pub Med, Scopus, SID, Magiran and Iran Doc databases, was performed during 2018 - 2008. In the initial search, 360 articles were found, and after reviewing eligibility criteria, 18 articles were reviewed. **Findings:** The results of this systematic review confirmed the effect of using a variety of herbs that were used as a solution to prevent and treat nausea and vomiting caused by chemotherapy. These herbs included ginger, chamomile, mint, cardamom, garlic and onion, respectively. **Conclusion:** Early diagnosis of side effects in patients can prevent forced discontinuation of treatment or dose reduction to control side effects that will in return reduce treatment efficacy. Therefore, it is possible to improve the condition of patients and reduce the effects of chemotherapy by providing certain requirements and educational programs on how to use these herbs. The interventions were also examined in patients with different types of cancers, while each type of cancer had its own chemotherapy protocols and differed from other protocols in terms of the severity of nausea. Consequently, one could not easily judge the effectiveness of different types of herbs on chemotherapy induced nausea and generalize the results to all types of cancers, therefore further research in this area is recommended by the researcher.

Keywords--- Controlling Nausea and Vomiting, Chemotherapy Side Effects, Chemotherapy-Induced Nausea.

I. INTRODUCTION

Cancer has become a global problem due to the aging population of the world, the increase of risky behaviors like smoking, exposure to chemicals and radiotherapy, poor eating habits, and sedentary lifestyles (1). According to

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World Health Organization, the incidence of cancer in developed countries is twice as high as in developing countries, but the annual number of people who develop such diseases is higher in developing countries with higher fatality (2). Nowadays, significant advances have been made in the treatment of cancer. Various therapies, including chemotherapy, radiotherapy, surgery, hormone therapy, immunotherapy, biological therapies, and cryotherapy, are used to manage cancer (3). The application of chemotherapy medicines is generally associated with various serious and non-serious side effects (4). The purpose of monitoring the side effects is to identify the unknown immune-related safety problems, and to quantify the risk factors associated with drug use (5). Information associated with such side effects can be used to formulate treatment guidelines, to make decision on public health policies, and to be applied in pharmacokinetic research (6).

Evaluating the side effects of chemotherapy drugs in the hospital provides a broader perspective of the cause, severity, and preventability of these side effects and may prevent the recurrence of similar side effects in similar patients (7). Early diagnosis of side effects in patients can also improve the patients' acceptance of their treatment and prevent forced discontinuation of treatment or drug dose reduction in order to control the side effects which will reduce the effectiveness of treatment (8). The most common of these side effects are nausea with or without vomiting, diarrhea, hair loss, darkening of the skin and nails, bone marrow suppression, mucositis, ovarian dysfunction, hyperuricemia, neuropathy, cardiomyopathy, hemorrhagic cystitis, kidney problems, and electrolyte disturbances(9). Chemotherapy induced nausea and vomiting are among the most severe side effects and major concerns of patients with cancer, with a prevalence of about 96% -54% (10). This side effect worsens during the first 24 hours (acute phase) after chemotherapy and has devastating effects on patients' personal and professional lives (11).

Chemotherapy Induced Nausea causes severe problems for patients, and in some cases the severity of these problems causes patients to stop the treatment (12). It would cause physiological, electrolyte imbalances, changes in immune system, nutritional disorders, and even esophageal rupture, it would also affect the patients' quality of life (13). Despite the extend use of antiemetics such as serotonin and neurokinin receptor antagonists, the patients still experience nausea and vomiting (14). Moreover, not controlling nausea and vomiting can lead to high direct and indirect costs. Direct costs include the increase in hospital stays and additional costs related to medical and outpatient care, whereas indirect costs are the loss or reduction of the income of the patients, family members and care providers (15). On the other hand, the widespread use of industrial antiemetic drugs is associated with different side effects such as extra pyramidal, hypertension, headache, etc. (16). Due to the limited effect and dangerous side effects of taking these drugs, the tendency towards non-chemical and non-industrial treatments has increased. One of the basic and low-risk measures in this field is the use of herbal medicine as the most active part of alternative medicine, which has attracted a lot of attention during the past decade. According to World Health Organization, about 80% of the world's population uses herbal compounds for treatment (17). Certain factors such as intervening in choosing the right type of treatment, avoiding drugs toxicity, lack of health insurance, high costs of drugs and most importantly, the interest in using preventive measures, have increased the demand for alternative medicines (18). Although clinical trials on new drugs provide information about their serious side effects, these reports are inadequate and may not accurately reflect the patients' experiences (19). It was important for the researcher to

conduct a systematic review of the literature by using author's experiences and experts opinions to study the effects of medicinal plants on chemotherapy induced nausea and vomiting.

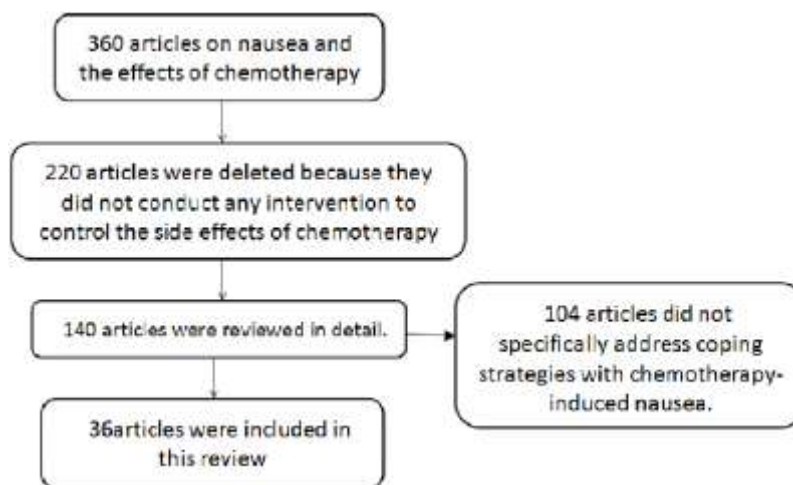
II. METHOD ANALYSIS

In this structured review, all the studies conducted inside and outside the country were reviewed during 2008-2018 using the following keywords: Controlling nausea and vomiting, chemotherapy side effects, chemotherapy induced nausea and meta-analysis of the databases including Mag Iran –med lib-SID-Iran medex as well as English databases such as CINHAI-Pub med scopus ,and the data were analyzed using meta-analysis method (random effect model). All data of the selected articles were collected and analyzed without considering the place and place of publication and the method of work. After reviewing and collecting all articles, duplicate and unrelated articles were deleted. In the next step, the articles were examined based on eligibility criteria, which was the interventional studies that examined different types of medicinal plants as a solution for the prevention and treatment of chemotherapy induced nausea.

The output criteria included data from case reports, posters, conferences and descriptive and review articles. This study had several limitations; the limited number of databases for extracting full-text articles had limited the availability of most of the articles, despite the relevance with the title, the language, and their interventional essence. Another limitation was that most articles were related to acupressure and electrical stimulation, and there may have been articles with various interventions on chemotherapy-induced nausea and vomiting which could not be reviewed due to inaccessibility of the full text or their non-English language. All the necessary ethical issues regarding the correct use of the extracted articles and the criteria related to their publication were taken into account.

III. FINDINGS

After searching the databases and extracting a large number of articles based on the title and abstract, 360 articles were reviewed, of which 220 were deleted because they did not have any intervention to deal with the side effects of chemotherapy. Altogether, 140 articles were examined more accurately, of which 122 articles did not specifically address chemotherapy-induced nausea. Finally, 18 articles were reviewed (PRISMA chart).



PRISMA Chart

IV. DISCUSSION

According to what was mentioned earlier, ginger, chamomile, mint, cardamom, garlic and onion were used to prevent and treat nausea caused by chemotherapy. In the following, we will analyze the articles. The table below shows some of the details of such studies (Table 1).

Table 1: Some of the Reviewed Details in the Study

Effect	Outcome Criteria	Cancer Type	Plant	Authors
Daily consumption of one gram of capsules containing ginger root powder can reduce the number of nausea and vomiting cases caused by chemotherapy.	Visual Analogue Scale(VAS)	Breast and Leukemia	Ginger	Najafi, Montazeri, Qanbari, Keyhani, Sanati Lete ‘Zick‘ ‘Leopold‘ anusirivithaya‘ Sontakke
It reduces chemotherapy induced nausea, but it does not have a significant effect on reducing the vomiting caused by chemotherapy	Visual Analogue Scale(VAS)	Breast Colorectal Lungs Leukemia Testicles	<u>Chamomile</u>	Borhani and Sanati
It reduced nausea in patients, but in case of vomiting, ice containing mint extract had no effect.	Visual Analogue Scale(VAS)	Breast	Mint	Ahdadi
Inhaled aromatherapy of cardamom has helped standard antiemetic drugs reduce the severity of chemotherapy induced nausea, but has failed to help reduce the number of nausea and vomiting during acute phase of chemotherapy.	Visual Analogue Scale(VAS)	Gastrointestinal	Cardamom	Khalili and Potter
They can stimulate the digestive process by absorbing AGE from small intestine, and increase the rate of food absorption and reduce the time it takes for food to pass through the gastrointestinal tract and finally help to improve nausea and vomiting	Visual Analogue Scale(VAS)	-	Garlic and onion	Fakhaar

Ginger

Ginger is a medicinal plant effective in treating nausea and vomiting and does not cause any special side effects and is used in German pharmacopoeia in the preparation of anti-nausea medications. The main pharmacological activity of ginger (*Zingiber officinale*) is related to its active components: gingerols and shagaols. These compounds have antiemetic, antitussive, antipyretic, antiinflammatory, antihypertensive, anti-cancer, anti-prostaglandin and anti-gastrointestinal effects. Ginger products have an antiemetic effect through several mechanisms. For example, gingerols and shagaols reduce gastric contractions but increase gastrointestinal activity. These compounds also have anti-serotonin effects with Free radical anti-inflammatory actions.

In the study conducted by Ebrahimi et al. (20), the only side effect of ginger reported by some patients was heartburn, which did not have any statistically significant difference between the two groups. As a result, it can be concluded that ginger is uncomplicated and safe. Clinical trials have yielded conflicting results on the effects of

ginger on chemotherapy-induced nausea, making it difficult to judge its effectiveness. Sontakke (21) showed that the anti-nausea effect of ginger is almost similar to Metoclopramide. Ryan and Lete (22,23) also confirmed its positive anti-nausea effects, while Zick and Manusirivithaya (25,24) rejected its effectiveness.

In the case of using ginger for cancer patients, a study by Sontakke et al. (21) on 50 patients with cancer showed that ginger control nausea and vomiting more effective than Metoclopramide. However, there are other studies with contradictory results. Leopold et al. (26) in their study on 180 women undergoing laparoscopy of the genital tract indicated that ginger had no effect on nausea and vomiting after the surgery and no difference in the severity of nausea and vomiting was observed between the recipients and the control group. Also, a study by Manusirivithaya et al. on 43 patients undergoing chemotherapy with the aim of determining the anti-vomiting effects of ginger on chemotherapy induced nausea and vomiting showed that ginger is effective in reducing chemotherapy induced nausea and vomiting in the delayed phase (24).

Such results could be due to the small size of the statistical population, the limited number of samples and lack of high quality product, because the features of previous studies can affect their results. For example, each conducted study examined the effects of ginger on patients with different types of cancers, while each type of cancer has its own chemotherapy protocol. Hence, we should not easily conclude the effectiveness of ginger on chemotherapy-induced nausea and generalize the results to all cancers. In the study that conducted by Ebrahimi et al. (20), ginger had a great effect on controlling nausea and vomiting in patients with breast cancer and undergoing treatment with one-day chemotherapy courses. On the other hand, this positive effects has been mentioned in other studies (27-31).

Therefore, by thoroughly comparing and generalizing all the results, it is suggested to conduct more extensive researches on patients with different types of cancer and on cancer patients under several days of chemotherapy courses. Based on the obtained results, it can be stated that daily consumption of one gram of capsules containing ginger root powder can reduce chemotherapy induced nausea and vomiting. Consequently, it would be possible to improve the condition of patients and to reduce the complications caused by chemotherapy by providing appropriate facilities and educational programs on how to consume the capsules of this plant.

Chamomile

Chamomile belongs to the family Asteraceae and has a special place in ancient medical and medicinal texts as well as in Iranian and Islamic traditional medicine with different medicinal properties in treatment of diseases related to nervous, digestive and respiratory systems. In pharmaceutical science, different species of this plant and the compounds in its herbal essence have been identified. Borhani et al. (32) studied the effect of this medicinal plant on nausea and vomiting caused by chemotherapy. According to their results, chamomile extract reduces chemotherapy induced nausea, but does not have a significant effect on reducing vomiting caused by chemotherapy. On the other hand, Sanaati et al. (33) showed in their study that ginger and chamomile have no effect on the severity of chemotherapy induced nausea in patients with breast cancer and is only effective in the number of times they vomit, which is not in accordance with the results of this study and it might be related to their research method or differences in characteristics of subjects.

Peppermint

peppermint is commonly used as a flavoring in food, tea, toothpaste, washing solutions and medicines. Menthol in mint acts as a gastric sedative, which reduces nausea and vomiting by relaxing gastrointestinal muscles and numbing the stomach wall. Mint with its calming effect and special scent has a psychological effect and reduces nausea and vomiting. In a study by Haddadi et al. (34), ice containing mint extract was used as a non-invasive, simple, inexpensive method with no side effects along with drug therapy to improve the nausea of breast cancer patients. The cold causes vasoconstriction in the peripheral parts of gastrointestinal tract (esophagus and stomach) and reduces the entry of chemotherapeutic agents into these areas, which results in reducing gastrointestinal irritation and nausea and vomiting. In their study, the intervention reduced nausea in patients, and the patients were satisfied, but in the case of vomiting, no effect was observed by using ice containing mint extract. Therefore, it is recommended to use it in conditional nausea (before starting chemotherapy) and delayed nausea and also on other cancer groups.

Cardamom

The scientific name of cardamom is "Elettaria cardamomum". The main chemical components of cardamom include cineole, limonene, terpenyl acetate, sabinene and linalool. Cardamom belongs to ginger family and is commonly known as the queen of spices. Cardamom is used to relieve indigestion, cough and itching, to prevent and treat gastrointestinal disorders, sore throats, lung congestion and oral infections. Also, one of its uses is to relieve nausea and vomiting. Inhaled aromatherapy of cardamom can help antiemetic medications to reduce the severity of chemotherapy induced nausea(35). Relatively, Khalili et al. used cardamom scent for this purpose. According to their findings, inhaled aromatherapy of cardamom could help with standard anti-nausea and vomiting medications in reducing the severity of chemotherapy induced nausea, but failed to reduce the number of times one experienced nausea and vomiting during acute chemotherapy course. Potter et al.(36) mentioned that deep inhaling of bergamot essential oil reduced nausea followed by stem cells infusion ;however, aromatherapy with bergamot failed to reduce nausea in children and teenagers under stem cells injection.

Garlic and Onion

Scientific evidence indicates that the medicinal and biological effects of garlic and onion are due to their high amount of sulfur compounds which create the special taste of garlic and onion. There are plenty of flavonoids in onions, while they are not found in garlic. Biological properties of garlic and onion constituents such as lectin, prostaglandin, fructan, pectin, adenosine, vitamins B6, B2, B1, E, nicotinic acid, fatty acids, glycolipids, phospholipids and essential amino acids have been studied for decades. So far, the biological importance and medicinal properties like antifungal, antibacterial, anti-tumor, antithrombotic and hypocholesterolemic effects of saponins such as B-chlorogenicin have been recognized. Garlic and onions, in addition to the above mentioned biological activities, can protect patients against the side effects of antitumor drugs such as vomiting, nausea, gastritis, gastric ulcer, bleeding and intestinal ulcer by absorbing AGE from the small intestine. Onion consumption can also stimulate digestive process and increase the rate of food absorption and reduce the time it takes for food to pass through the gastrointestinal tract, and therefore help improve nausea and vomiting (37).

V. CONCLUSION

Early detection of side effects in patients can improve patients' treatment acceptability and prevent forced discontinuation of treatment or dose reduction to control the side effects that would in return reduce the effectiveness of treatment. According to Pakdel et al., who considered different body systems, the most common side effects in patients with gastric cancer were gastrointestinal side effects, especially nausea and vomiting. In addition, in some patients, no treatment was performed to control this complication, while as mentioned, many of these complications could be minimized by early diagnosis and appropriate dose adjustment based on body level, weight and the patient's kidney and liver function using preventive measures. Therefore, it is possible to improve the condition of patients and reduce the adverse effects of chemotherapy by providing appropriate facilities and educational programs on how to use these plants. Researchers have studied patients with different cancers, and each type of cancer has its own chemotherapy protocol and differs from other protocols in terms of the severity of nausea. Finally it is not easy to judge the effectiveness of different medicinal plants on chemotherapy induced nausea and to generalize the results to other cancers, so further research is recommended by the researcher.

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