



Palliative Care and Phytotherapy in Patients with Cancer

Kanser Hastalarında Palyatif Bakım ve Fitoterapi

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ABSTRACT

Cancer is defined as a complex disease that occurs with the uncontrolled proliferation of cells and develops under the influence of genetic and environmental conditions. Chemotherapy and radiotherapy are frequently used in cancer treatment. Side effects related to these treatments are observed in most of the patients. Palliative care, which is an important part of cancer management today, aims to alleviate the symptoms and side effects of these treatments and to increase the quality of life of the patient. A growing number of patients with cancer are inclined towards complementary and integrative medicine, including herbal medicine. The interest in this field is increasing because it has been shown by preclinical and clinical studies that some phytotherapeutic products can reduce the side effects of chemotherapy and radiotherapy. This review summarizes phytotherapeutic approaches supported by clinical studies for palliative care in cancer patients.

Keywords: Palliative, cancer, phytotherapy

ÖZ

Kanser, hücrelerin kontrollsüz çoğalması ile ortaya çıkan, genetik ve çevresel koşulların etkisi altında gelişen kompleks bir hastalık olarak tanımlanmaktadır. Kemoterapi ve radyoterapi kanser tedavisinde sıklıkla kullanılmakta ve hastaların çoğu buna bağlı yan etkiler gözlenmektedir. Günümüzde kanser yönetiminin önemli bir parçası olan palyatif bakım da bu tedavilerde ortaya çıkan semptomların ve yan etkilerin hafifletilmesini sağlayıp hastanın yaşam kalitesini artırmayı hedeflemektedir. Giderek artan sayıdaki kanser hastası, bitkisel ilaçlar da dahil olmak üzere tamamlayıcı ve entegratif tıbbın önemini vurgulamaktadır. Bazı fitoterapötik ürünlerin kemoterapi ve radyoterapiye bağlı yan etkileri azaltabildiğinin preklinik ve klinik çalışmalarında gösterilmesi sebebiyle bu alana olan ilgi artmaktadır. Bu derleme kanser hastalarında uygulanabilecek palyatif bakımda, klinik çalışmalarla desteklenen fitoterapötik yaklaşımı özetlemektedir.

Anahtar Sözcükler: Palyatif, kanser, fitoterapi

Introduction

Although more people are diagnosed as having cancer today, the life expectancy of patients is increasing with the increase of studies on cancer. Chemotherapy and radiotherapy are effective and comprehensive approaches in cancer management. However, the frequent occurrence of side effects such as oral mucositis, gastrointestinal toxicity, hepatotoxicity, nephrotoxicity, hematopoietic system damage, cardiotoxicity and neurotoxicity limits the clinical use of chemotherapy and radiotherapy (1,2). However, fatigue is a common problem in patients with cancer

(3). Therefore, palliative care, which is one of the strategies to reduce the side effects of chemotherapy and radiotherapy, may be important for these patients. Especially patients with terminal stage cancer often need palliative care. Pressure ulcers are also common in patients who need palliative care, and conventional therapies are often insufficient (4).

In a study conducted on cancer patients, it was shown that 62% of patients used complementary therapies. It was stated that 82% of these patients used at least one herbal product and 30% used herbal products together with chemotherapy drugs (5).

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The purpose of applying palliative care with phytotherapy is to reduce the frequency of symptoms that occur as a result of life-threatening diseases and, as a result, to improve the quality of life. In this review, we will talk about phytotherapeutic approaches supported by clinical studies to increase the quality of life of the person against cancer itself or against the negative conditions that arise as a result of the treatment applied.

The Use of Phytotherapy in Oral Mucositis

Oral mucositis is a common complication that starts with oxidative stress and inflammation and is seen in patients receiving chemotherapy and radiotherapy (6). In addition to disrupting oral nutrition, it also exposes the mucosa to contamination due to disruption of the mucosal barrier against microbial agents and may lead to systemic bacteremia, fungemia and viremia (7).

Severe stomatitis results in discontinuation of cancer chemotherapeutics and an increased risk of local and systemic infections. *Chamomile* (*Matricaria recutita*) is widely used for its antioxidant, antimicrobial and anti-inflammatory effects. Due to these properties, it is considered to be a useful option in cases such as oral mucositis or recurrent aphthous stomatitis. According to a randomized clinical trial in which 36 patients with recurrent aphthous stomatitis were included, it was reported that a significant reduction in pain and burning sensation was achieved in the group using chamomile mouthwash (Matica Drop®, Barij Essence Co.) containing 0.09-0.17 mg of kamazulene per milliliter compared to placebo. As a result of this study, it was stated that chamomile mouthwash treats pain and burning sensation without any side effects, and can be used safely in patients with recurrent aphthous stomatitis (8).

Aloe vera gel has been used in dermatological ailments for centuries due to its wound healing and antibacterial effects. According to a randomized controlled clinical study conducted by Mansouri et al. (9) on 64 patients with Acute lymphoid leukemia and Acute myeloid leukemia, it was stated that the severity and degree of pain of stomatitis were significantly reduced in the aloe vera mouthwash group compared to the control group. Therefore, the authors recommend the use of solutions containing aloe vera gel in patients receiving chemotherapy to improve nutritional status and maintain oral hygiene.

Turmeric (*Curcuma longa rhizome*) is a spice and herb that is known to have many health benefits and has traditional uses. Recent pharmacological studies have shown that curcumin in turmeric has strong antioxidant, antimicrobial, anti-inflammatory and anticancer activities (10). According to a study conducted in 20 patients with cancer who received chemotherapy and radiotherapy, the patients were randomly divided into two, one group was given the standard preventive oral care, 0.2% chlorhexidine mouthwash, while the other group was given a freshly prepared 0.004% curcumin mouthwash. Patients were expected to gargle three times a day for 20 days. It was reported that rapid wound healing was achieved in the group receiving curcumin mouthwash and it was better than chlorhexidine mouthwash in terms of patient compliance in the treatment of radiotherapy-chemotherapy-induced oral mucositis (11).

Black mulberry molasses is a traditionally widely used food ingredient in the treatment of mucositis in Turkey. Recently, a randomized controlled clinical trial was published in which 80 patients with head and neck cancer undergoing radiotherapy who used black mulberry molasses were included (12). As a result of this study, it was stated that the use of black mulberry molasses together with radiotherapy might be an effective treatment for the prevention of radiation-induced mucositis in patients with head and neck cancer (12).

Propolis is a natural product rich in flavonoids and known for its antiulcer, antibacterial, antifungal and anti-inflammatory effects (13). Studies have been reported showing that the use of water-based propolis extract as a mouthwash (14,15) effectively treats chemotherapy and radiotherapy-induced oral mucositis in patients with head and neck cancer and in patients with leukemia (16,17). On the other hand, according to the results of a double-blind, randomized, placebo-controlled study, it was stated that propolis was not recommended for severe oral mucositis in pediatric patients (18).

Calendula [(*Calendula officinalis*) (*C. officinalis*)] has long been used in traditional medicine and since 2008 has been recognized as an herbal medicinal product by the European Medicines Agency. Both the flowers and leaves of the calendula are used in folk medicine today as an anti-inflammatory and antispasmodic drug, in the treatment of minor burns, bruises and rashes. It is also used in alleviating the discomfort caused by gastric ulcer, oral and pharyngeal mucosa inflammation (19).

In a randomized controlled clinical study involving 40 patients with head and neck cancer who received radiotherapy, the effectiveness of mouthwash containing 2% ethanolic flower extract of *C. officinalis* on oropharyngeal mucositis was evaluated. It was concluded that *C. officinalis* was effective in reducing the density of oral mucositis, but could not completely prevent its formation (20).

Radiodermatitis and Phytotherapy

Radiodermatitis is defined as a skin lesion caused by excessive exposure to ionizing radiation, which can lead to dehydration of the skin and serious complications (ulceration, local infection). In patients with breast cancer and head and neck cancer, the skin area in the treatment area is more sensitive and has more skin folds. Therefore, it is a major risk factor for the development of radiodermatitis.

According to a randomized double-blind controlled clinical study evaluating the efficacy of *C. officinalis* on radiodermatitis and head and neck cancer, a lotion prepared with 4% *C. officinalis* oil (olive oil maceration) was applied to one group, while the other group was treated with a lotion rich in essential fatty acids (EFA). The incidence of grade 1 dermatitis was 40.73% in the EFA group and 25% in the *C. officinalis* group. In addition, after the last radiotherapy session, the incidence of grade 2 or 3 radiodermatitis was 21.43% in the *C. officinalis* group, while this rate nearly doubled in the EFA group (46.16%). According to the results of this study, it was reported that *C. officinalis* was effective in the prevention and treatment of radiodermatitis (21).

There is a randomized, double-blind, phase III, clinical study examining the efficacy of *C. officinalis* on breast cancer after radiotherapy. This study evaluated the efficacy of grade 2 or higher radiation-induced acute dermatitis on 254 patients with breast cancer (22). When the *C. officinalis* oil-containing cream applied group was compared with the trolamine-administered group, it was stated that grade 2 and higher acute dermatitis formation was significantly lower in the *C. officinalis* group. In addition, it was reported that patients receiving *C. officinalis* had less interruption of radiotherapy and no allergic reaction, and *C. officinalis* significantly reduced radiation-induced pain. Therefore, it has been emphasized that *C. officinalis* oil may be a good non-steroidal agent for the prevention of radiation-induced dermatitis in patients with breast cancer (22). In addition, a recent meta-analysis indicated that trolamine was ineffective in the prevention and treatment of radiation dermatitis (22). Therefore, the efficacy of *C. officinalis* here needs to be supported by other clinical studies.

Aloe vera gel is widely used in the treatment of radiation dermatitis. The part of the plant used topically is a clear, viscous gel-like structure that appears when the leaves of the plant are cut. A study on 60 patients with cancer (breast, head and neck, pelvis cancer) evaluated the effectiveness of aloe vera gel on radiodermatitis. Patients were asked to apply aloe vera lotion to half of the radiotherapy application area. No lotion was applied to the other half. The lotion contained aloe vera as well as lanolin oil, glycerol stearate, collagen, tocopherol, allantoin and paraben. The lotion containing aloe vera gel was applied to one side of the radiotherapy treated area for 6 weeks. It was reported that from the 4th week to the end of the evaluation period, the decrease in the degree of dermatitis on the side where aloe vera gel was applied was statistically significant, and the highest statistical difference was seen in the 5th and 6th weeks of radiotherapy, when the patients received high radiation dose (23).

The Use of Phytotherapy against Cancer-Associated Fatigue

Cancer-related fatigue (CRF) is one of the most common symptoms that occurs during cancer treatment. Fatigue complaints are frequently reported in 80% to 96% of patients receiving chemotherapy and 60% to 93% of patients receiving radiotherapy (24). CRF is a different condition from fatigue caused by excessive physical activity or flu-related fatigue. In cases of CRF, fatigue occurs during normal activities and becomes pathological and seriously affects the patient's quality of life (25). Although the underlying mechanism of CRF is not fully understood, factors such as proinflammatory cytokine network, dysfunction in the hypothalamo-pituitary adrenal axis, circadian rhythm disruption, and mitochondria dysfunction are thought to cause CRF (26,27).

Ginseng is an herb that has been used in Asian countries for thousands of years. There are 2 main types of ginseng: *Asian/Korean ginseng* [*Panax ginseng*] (*P. ginseng*) and *American ginseng* (*Panax quinquefolius*). Both types have similar ingredients. *P. ginseng* is the most studied species in terms of its antioxidant, anticancer, and anti-inflammatory properties (28).

According to a study of quality of life in patients with cancer conducted by Kim et al. (29), patients were observed for 12 weeks and the effectiveness of 3000 mg *P. ginseng* daily over placebo was compared. It was reported that there was a significant improvement in mental and physical functionality in the group given *P. ginseng* compared to the placebo. It was stated that the improvement in quality of life might occur as a result of the anxiolytic effect of ginsenosides by binding to gamma aminobutyric acid receptors (30).

In a randomized double-blind multicenter study conducted by Barton et al. (31), the effectiveness of American ginseng on CRF was investigated. Patients who were diagnosed as having cancer in the last two years and received or completed treatment were included in the study. The effects of 2,000 mg of *Panax quinquefolius* containing 3% ginsenoside on CRF were compared against placebo. As a result of 8 weeks of observation, it was reported that the fatigue scoring in 2,000 mg of *Panax quinquefolius* daily group was found to be significantly lower compared to placebo.

Rhodiola Rosea (*Golden root*) roots have been used for centuries as an "adaptogen" to enhance physical and mental performance and combat stress (32,33). Currently, *Rhodiola rosea* (*R. rosea*) extracts are used as dietary supplements in Europe, Asia and the United States for similar indications (34).

R. rosea roots have different effects on the central nervous system depending on the dose. While larger doses have a sedative effect, smaller doses increase the release of monoamines and activate the cerebral cortex and limbic system (35). With *in vivo* studies, it was predicted that *R. rosea* roots could increase the effect of chemotherapy in general and potentially reduce side effects such as fatigue and cognitive impairment (36).

Although there is no direct study of *R. rosea* on CRF, there are several clinical studies evaluating the effectiveness of *R. rosea* in mental and physical fatigue. According to a randomized, double-blind clinical study on stress-induced fatigue conducted by Panossian et al. (37), it was reported that standardized root extracts of *R. rosea* reduced the stress-induced cortisol response and had a significant effect on fatigue levels compared with placebo. *Guarana* (*Paullinia cupana*) is a plant of Brazilian origin. In two randomized, placebo-controlled studies, the positive effects of using guarana extract at doses of 75 mg per day (containing 11-12 mg of caffeine) on memory and cognitive function were reported (38,39). According to a randomized double-blind pilot study evaluating its efficacy on CRF and depression due to its stimulant effects, it was stated that no significant result could be achieved on CRF in the group given 75 mg guarana extract daily compared to placebo (40). In a study that included 77 patients with breast cancer receiving chemotherapy and used a higher dose of guarana compared to the previous study, the effectiveness of guarana on fatigue, anxiety and depression was investigated. As a result of the study, it was stated that guarana was an effective, non-toxic, inexpensive and effective herbal product and had a positive effect on fatigue in patients with breast cancer receiving chemotherapy (41).

Phytotherapy for Wound Healing

Wound formation, which is frequently encountered in patients in palliative care, is an important problem that threatens life and reduces the quality of life. It is stated that wound formation occurs in 35% of palliative care patients (4). These wounds include pressure ulcers, venous or arterial leg ulcers, diabetic ulcers, and malignant fungating ulcers (42).

Aloe vera gel is a widely used plant due to its antibacterial, antiviral, and anti-inflammatory effects (43-45). It has been reported that aloe vera gel is more successful in chronic wounds than in acute wounds (46). In previous studies, aloe vera gel preparations have been reported to have wound-healing properties by increasing macrophage and fibroblast activity (46,47). Aloe vera can inhibit the inflammatory process by reducing leukocyte adhesion and limiting the activity of proinflammatory cytokines such as tumor necrosis factor- α and Interleukin-6 (48). Thanks to the glucomannan in the aloe vera gel content, it increases the production of collagen by stimulating the Fibroblast growth factor. Aloe vera contributes to wound healing not only by increasing collagen production at the wound site, but also by increasing collagen cross-links, providing tissue integrity thanks to the amino acids and minerals such as zinc in its content (47,48).

There is a case report in which a patient with a 30x10 cm ulcer in the pretibial region was treated with surgical debridement and antibiotic therapy, and after 160 days, there was no response to the treatment, and aloe vera gel was applied. The mucilage structure in the aloe vera leaves was collected and mixed with a preservative and lubricant and applied to the ulcerated area. It was reported that with the tissue healing at the end of the 58th day, a decrease in pain, exudate and erythematous tissue was achieved (47).

It was reported that aloe vera gel reduced the healing time to 9 days in first and second degree burns (49). It is stated that once or twice a day aloe vera gel dressing may be a more effective method than existing treatments (vaseline dressing, silver sulfadiazine 1% ointment and framycetin cream). In this way, it allows to reduce the healing time, to prevent infection in the wound area, and to relieve redness and itching (49).

According to a randomized double-blind controlled trial using a cream formulation containing aloe vera gel and olive oil, and including 61 patients with chronic wounds (41 pressure ulcers, 13 diabetic wounds, and 6 venous ulcers), patients were randomly divided into two and treated with phenytoin. It was reported that the cream containing aloe vera gel and olive oil significantly accelerated the biological healing of chronic wounds and helped to reduce the severity of pain with a higher efficacy than the cream containing phenytoin (50).

C. officinalis flower extracts can be used in inflammatory conditions of the skin such as herpes, sunburns and dermatitis. An observational study of 41 patients with pressure ulcers for more than 3 months evaluated wound healing after spray application of *C. officinalis* flower extract to patients. It was stated that the wound healing rates at 15 and 30 weeks were 63% and 83%, respectively, and the spray containing *C. officinalis* flower extract increased wound healing (51).

St. John's Wort (Hypericum perforatum) is widely grown in our country and there are 84 species in our country. Topical formulations such as oily extracts or ointments prepared with the blooming aerial parts of *St. John's Wort* have been used in the treatment of a wide variety of dermatological problems such as superficial wounds and burns, bruises, contusions. According to the case report of an 83-year-old patient with a pressure ulcer followed in the intensive care unit, the extract obtained from *St. John's Wort* maceration was applied to the patient twice a day for 40 days, and the follow-up was ensured. Macroscopic evaluation of wound size and stages and histopathological examinations were performed. The authors stated that as a result of macroscopic and histopathological examinations, oily maceration of *St. John's Wort* provided significant efficacy in the treatment of pressure ulcers (52).

In another study conducted on 30 patients with bedsores, in addition to routine wound care, half of the patients were treated with *St. John's Wort* oil, while only olive oil was applied to the other half. It was reported that the wound area and wound depth were significantly reduced in the *St. John's Wort* oil applied group compared to the control group (15).

Conclusion and Recommendations

Applying palliative treatment in patients with cancer is very important in order to improve the social and physical condition of the patient, as well as to increase the quality of life. Side effects that may occur due to the disease itself or the drugs used for its treatment can reduce the quality of life of the patient. Therefore, approaches that can prevent or reduce these side effects are very important.

CRF is one of the most common complaints in patients with cancer. *P. ginseng* is the most researched plant species in this field. In addition to the use of adaptogen plants in CRF, regular nutrition, stress management and regular exercise can be added to the treatment plan of patients.

Radiodermatitis and oral mucositis observed in palliative care patients receiving radiotherapy or chemotherapy are complaints that may affect the patient's continuity of treatment. *C. officinalis* is a plant that is used in both radiodermatitis and oral mucositis. It should be noted that topical formulations containing the standardized extract of this plant can be a complementary treatment option in addition to existing treatments in reducing complaints due to chemotherapy or radiotherapy. Indications for chamomile approved by Commission E include inflammation of the mouth and pharynx. For external use, it is recommended to prepare an infusion of 2 teaspoons of chamomile with 2 glasses of water (14). For the same indication, it is recommended to prepare 1-2 g of powdered herb for *C. officinalis* as an infusion in a glass of water (14). Since there are easily accessible plants in our country, the preparation of solutions of infusions prepared from these plants to ensure oral hygiene in the treatment of oral mucositis can be considered as an auxiliary option for treatment.

Another problem frequently encountered in palliative care patients is wound formation, especially pressure ulcers. Aloe vera gel and *St. John's Wort* oil are the herbal products with

the most research in wound treatment. John's wort oil, which is obtained from St. John's Wort and widely grown in Anatolia, has a traditional use in wound healing and its effectiveness has been supported by clinical studies. For this reason, it can make a positive contribution to wound healing by adding it to the existing treatment in palliative care patients.

As seen in the clinical studies mentioned in our review, symptom-oriented use of phytotherapeutic products in palliative care patients can be considered a rational approach. Phytotherapeutic products have high antioxidant capacity due to the bioactive substances in their content. While this may provide support to palliative care patients, it may also cause a decrease in the effectiveness of chemotherapeutics in the chemotherapy group. Although antioxidants are a useful option for the harmful effects caused by chemotherapeutics, their simultaneous use may reduce the therapeutic effect of the anticancer drugs used. For this reason, physician and pharmacist consultation is required for the prophylactic and therapeutic use of phytotherapeutics, which have been used for many years.

Ethics

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Authorship Contributions

Concept: M.N.A., A.A., M.K., Design: M.N.A., A.A., Data Collection or Processing: M.N.A., Analysis or Interpretation: M.N.A., A.A., M.K., Literature Search: M.N.A., Writing: M.N.A.

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