



The Negative Effects of *Inula Viscosa* L. Use on a Cancer Treatment

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Abstract

Herbal products are frequently used and supplied through Internet and herbalists. Incorrect use of herbal products generally may cause adverse effects even death. The aim of the study was to raise awareness about negative effects of the use of herbal products on cancer treatments by reporting a case. Also, it was targeted to underline the importance of physicians being alert on the use of herbs as alternative medicine especially among cancer patients. A 40 years old female patient was admitted to the hospital due to high fever, fatigue and somnolence. According to her medical history, myometrial sarcoma and its surgical operation were recorded. Continuous neutropenia without any chemotherapeutic treatment made the case suspicious. Then she finally confessed that she used an herbal product as a cancer drug. The sample was sent for toxicological analysis. After extraction, the preparative thin layer chromatography was applied to the sample; then purified substance was analyzed by Gas Chromatography-Mass Spectrometry. One of the major compounds found was Inuviscolide which indicates the presence of *Inula viscosa* L. Regular use of this plant possibly gave rise to myelosuppression and apoptosis of neutrophils. In herbal medicine, *Inula viscosa* L. has many properties such as anti-cancerous, antibacterial, cytotoxic. Finally, the use of *Inula viscosa* L. without consulting physician caused a severe medical condition as well as a delay in the antitumor therapy.

Keywords: *Inula Viscosa*; Herbal Medicine; Cancer; Intoxication; Toxicology; Complementary and Alternative Medicine

Introduction

In all over the World, there is an enormous demand for natural herbs as a complementary and alternative medicine (CAM). Although it is widely common in developed countries such as United Kingdom, natural based remedies are point of interest in developing countries as well [1,2]. In Turkey, the idea of treating a disease with an herbal mixture is definitely not new. Plants and herbal mixtures have been using since ancient times for medical purposes. Except for the plants that are officially sold under the name of herbal products on the market, there are some plants sold underhandedly without subjecting to any regulations.

The use of herbal remedies is fundamentally based on the belief that drugs in the market have more side effects than their therapeutic effects. This perception can be explained by the

misconception that due to their natural origins, herbal products are safe and free from side effects. However, as mentioned in a study, word "safety" and "natural" don't mean the same [2-4].

People prefer CAM mostly for diseases where treatment is not always possible such as cancer as well as to treat other simple symptoms such as fever and inflammation [2,10-12]. According to the latest data released from World Health Organization (WHO), cancer is the second most fatal disease worldwide. In 2015, it was responsible for approximately 9 million deaths [13]. For this reason, every promising way has been trying including herbs in order to heal. Some plants have promising potential to act as an anti-cancer agent because of their cytotoxic effects and even aid to slow down or stop the existing tumor(s) in some cases [14]. For this purposes plant's seed, leaf and their extracts can be used or mixed with other plants as well [15].

While global use of herbal medicine carries on growing, introduced products raise many concerns regarding public health and safety. Due to the increasing number of intoxication cases related with the use of these products [5], regulatory status and quality control issues become more of a focus lately. In general, due to the fact that drugs and herbal products are not subject to the same regulations; efficacy, regulatory status and toxicological evaluation of herbal products are mostly missing prior to market introduction [6]. Hence, missing scientific data regarding to possible toxic effects of these herbal products and their therapeutic doses creates a massive health problem because very little information is available for commonly used plants [6,7]. Since herbs generally consist of multiple ingredients, herb-drug interactions and toxic effects may not always be illuminated, even in countries where toxicity and safety of these products are regularly controlled [6,8]. Another aspect related to herbal products is that cultivation differences such as geographical properties, soil type, temperature, water availability, storage and possible environmental pollution in the area may also alter chemical ingredients of these herbs which have direct impact on the mechanism of action and toxicity. [6,9].

Except for herbal medicines available on the market, there are herbs not subjected to any regulation, whose dosage or content are not mentioned, are sold underhandedly. These are the real dangers because they are sold easily by herbalists or via Internet with biased or misleading information about dosage, ingredients, usage, benefits etc.

In this study, the aim was to raise awareness about negative effects of the use of herbal products on cancer treatments by reporting a case. Also, it was targeted to underline the importance of physicians being alert on the use of herbs as alternative medicine especially in cancer patients.

Case History

A 40 years old female patient, on November 2016, was admitted to General Internal Medicine Service due to high fever, fatigue and she was also neutropenic. The patient was also weak and dehydrated. There were lesions consistent with herpetic stomatitis around her mouth. BP: 100/60 mmHg, HR: 100/minute RR: 36/minute and fever: 39°C, also hemogram and biochemical results were presented in Table 1. Bilateral axillary lymphadenopathy was palpable. The liver edge was palpable more than 2 cm below the costal margin. Her neurologic examination revealed symmetric bilateral weakness of lower limbs. Sensory examination and reflexes were in normal range

Table 1: Hemogram and biochemical results of the patient.

Hemogram results	
Hb	7.4 g/dL
WBC (PNL)	1200/mm ³ (500/mm ³)
Hct	22%
Plt	50 000/mm ³
Biochemical results	
Blood Urea Nitrogen (BUN)	36 mg/dL (< 20)
Creatinine	1.4 mg/dL (< 1.1)
AST	44 U/L (< 40)
ALT	33 U/L (< 40)
Albumin	2.63 g/dL (> 4)
CRP	384 mg/L (N: 0 - 5)
Procalcitonin	2.68 ng/mL (N: 0.5)

She was diagnosed on Feb 2016 as myometrial sarcoma and had an operation on May 2016. Pathological result indicated a high-grade endometrial stromal sarcoma (c-kit positive, Ki - 67: 80%). The patient treated first with local radiotherapy. Two days after the last treatment cycle, she admitted to our Emergency Department as mentioned above. One day later, there was a positive sign for gram-negative bacteria in her hemoculture. In this period, after the consultation of oncology and infectious diseases, pneumocystis and systemic herpes infection were diagnosed, and specific antimicrobial medical treatments were started with Meropenem (3 x 1gr) + Amikacin (1 x 1g) + Vancomycin (2 x 1g) + Acyclovir (3 x 5mg/kg) and fluid resuscitation was also applied. For her oropharyngeal candidiasis, fluconazole (400 mg/day) was started by orally.

Due to patient's persistent febrile neutropenic situation, Granulocyte Colony Stimulating Factor (G-CSF) was also used besides antimicrobials. After repeated interviews with the patient, she confessed an herbal drug use during her radiotherapy sessions without informing physician. Questioned herbal product used by the patient was transferred to the forensic toxicology laboratory of Istanbul University-Cerrahpasa, Institute of Forensic Sciences.

Materials and Methods

Chemicals and equipment

In this study, ethyl acetate, methanol, n-hexane, and dichloromethane (DCM) were purchased from Merck (99,8 - 100%, Darm-

stadt, Germany) with HPLC grade. Ultra-pure water was deionized by passing through a Direct-Q3 UV 3 system (Millipore, Molsheim, France). For preparative thin layer chromatography (P-TLC), TLC Silica gel 60, glass plates with 20 x 10 cm dimensions (Merck, Darmstadt, Germany) were used. For toxicological screening, Agilent HP 7820A Gas Chromatography (GC) system (China) coupled with Agilent MS-Detector 5977E MSD (USA) was used. The system was equipped with 30 m x 0.25 mm fused silica capillary column (HP - 5MS 5% phenyl methyl siloxane, film thickness 0.25 µm - Agilent). Helium was used as carrier gas for chromatography, with 99,999% purity (Okser, Turkey).

Sample preparation and analysis

The received herbal sample with approximately 500 µL volume was blurred reddish brown. Liquid-liquid extraction was carried out by ethyl acetate. In order to achieve the best isolation, three different solvent mixtures were tried prior to P-TLC. The final isolation was performed by dichloromethane: methanol (3:1) solvent system, 100 µL of sample was diluted by 400 µL of ultra-pure water and homogenized by vortex. Then the diluted sample was applied to P-TLC plate, which was shown in Figure 1 to isolate active constituent of the substance. After scratching sample from the plate, the substance was incubated in the mixture of acetone:dichloromethane:methanol and analyzed by Gas Chromatography-Mass Spectrometry (GC-MS). GC-MS separation was achieved with 5:1 split ratio and 1 µL injection volume. Initial temperature was 55°C for 2 minute then from 55 to 280°C at 10°C/min for a total run time of 10.0 minute.

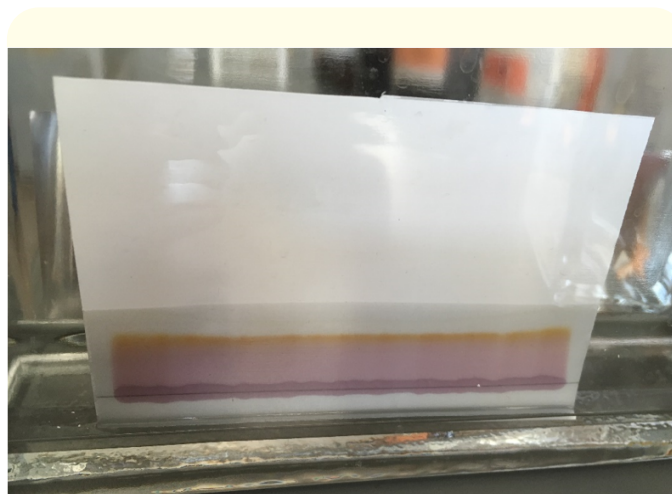


Figure 1: Migration of questioned herbal drug on P-TLC plate.

Results

After evaluation of analysis results on GC - MS, one of the major active constituents found was Inuviscolide, which has been isolated from the questioned herb, as can be seen in Figure 2. Compatible with patient's statement, the constituent indicates the presence of *Inula viscosa* L. [11,16,17]. The plant is a member of Asteraceae family [18,19], which grows mostly in Mediterranean countries such as Syria, Turkey and Morocco [14,18,20,21]. *Inula viscosa* L. has a well-known alternative medicine use due to its antiseptic [22,23], anti-inflammatory [24], anti-microbial [25], anti-fungal [20] and cytotoxic [14,17] effects. In Turkey, *Inula viscosa* L. grows regularly and there are total of 27 species including 7 endemics [18,26,27].

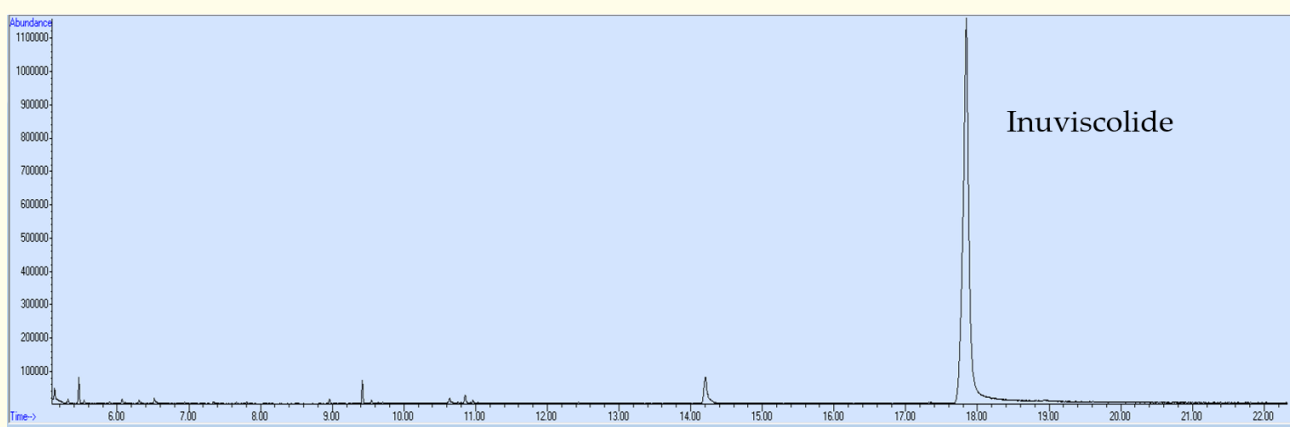


Figure 2: GC-MS Chromatogram of the question sample resulting with Inuviscolide finding as the major component.

Discussion

In spite of the fact that many improvements have been achieved on cancer treatments and survival rates in the last decade, due to the loss of faith in conventional medicines and disturbing side effects in radiation therapy/chemotherapy, patients are looking for alternatives [11,28]. The primary reasons behind of high prevalence of herbal medicines are disease related symptoms which cannot be resolved by prescribed drugs, disturbing side effects of conventional drugs, medication prices and the perception of herbs being harmless [3,4,6,29].

Although, the usage rate has been increasing continuously, it is known that many undesirable effects may occur among which is fatal or severe with the careless use of herbs [2,3,30]. Since herbs may contain more than one active ingredient, wide ranges of undesirable or adverse reactions are frequently encountered. This requires more effective regulations and standardizations regarding to herbal products. In some countries these are regulated as food supplements or health products, this causes an uncertainty in both classifications of products and quality standards [6]. Adulteration, contamination and mislabeling may also be possible sources for side effects as the natural consequence of the lack of standardization [31].

The more life-threatening danger is the herbs sold underhandedly without controlling by any regulations or official authorities. These plants are sold at relatively high prices by exploiting the hopes of patients, which is the case for *Inula viscosa* L. reported in this study as well. Since many patients prefer to use herbs with the conventional medicine, some may induce or inhibit the mechanism of actions of cytotoxic agents, which can lead to fatal consequences [4,32]. Herb-drug interactions are also need to be taken into consideration to prevent possible adverse effects. Nowadays, due to the increasing number of intoxication cases, the need for toxicity studies of herbs has raised and become inevitable [5]. However, worldwide challenges will be encountered because studies on underhandedly sold herbs are inadequate as yet.

Many researches have been conducted on the frequency of the use of herbs among patients. For example, in a study with total of 217 patients with chronic diseases such as hypertension or diabetes; 63 out of 217 patients were preferred to use herbal products for their diseases [12]. In addition, Soner et al. found the total frequency of herbal medicine use as 48% among 927 patients in the mentioned study [33]. Also, in a survey conducted in 14 European

countries including Turkey revealed that CAM use among cancer patients ranged from 14.8% to 73.1% and herbs was the most common type of CAM [34]. As Tascilar et al. stated many cancer patients from Australia, Canada, New Zealand, US, Japan and China also prefers to use CAM for their treatments [4].

As for the case, despite antimicrobial treatments given, her medical condition did not improve and continuous neutropenia without taking any chemotherapeutic agent made it suspicious. On account of the physician's attention and awareness, herbal product use was persistently questioned and enlightened. The patient confessed to use the herbal product during her radiotherapy sessions without informing her physician. It is thought that regular use of *Inula viscosa* L. with possibly high doses caused to myelosuppression and apoptosis of neutrophils. Consequently, *Inula viscosa* L. had adversely affected the current cancer treatment. Therefore, only after side effects of the plant were removed, patient could only receive one cycle of chemotherapy and then she died. Although it has been proven by some experimental studies that the plant shows cytotoxic effects against some cancer cells [11,14,17], *Inula viscosa* L. had not influenced positively on this patient. Hence, it is believed that further investigations deem necessary on dosage, toxicity and adverse effect of *Inula viscosa* L. and potentially many other herbal CAMs.

Conclusion

First, the belief that herbs and herbal products are harmless should be transformed in a more realistic and reliable manner. It should be taken into consideration that the unconscious use of these plants could generate more harmful effects than plant's therapeutic effects. As can be understood from the case, even if clinical studies of an herb present effective results for a specific disease, the herb is not always suitable for each type of that disease. For this reason, patients should be more cautious about the use of herbal products especially in terminal diseases such as cancer. On the other hand, physicians should raise more awareness on the subject of herbal product use, which will be crucial to save or extend patients' lives. In order to resolve intoxications and undesired adverse reactions, new legislations and standardizations should be established related to herbal medicine market. In addition, considering that most of the sales and advertisements of underhandedly sold products are made over the Internet as in this case, making the necessary regulations covering promotive websites will be an important step in awareness.

Author Contributions

Conceptualization, I.B., S.M., Z.T.; Methodology, Z.T., S.M., M.K., T.T.; Interpretation of results, Z.T., M.A. S.M.; Formal Analysis, I.B., I.S.; Investigation, I.B., M.K., T.T., S.M., Z.T., I.S., M.A.; Data Curation, I.B., M.K., T.T., S.M., Z.T., I.S., M.A.; Writing - Original Draft Preparation, M.K., T.T., S.M., Z.T.; Writing - Review and Editing, I.B., M.A.; Visualization, I.B., M.K., T.T., S.M.; Supervision, I.B., M.A.

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Conflicts of Interest

The authors declare no conflict of interest.

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