Chapter

Plants and Cancer Treatment

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Abstract

In this century, cancer has become one of the major problems and diseases that have caused predominant death, and it will even surpass heart diseases. Since World War I, chemotherapy has become as one of the most important and significant treatments of cancer. Even if it can cure cancer, it is found to cause several critical side effects. Over the past 20 years, many types of new therapies have emerged; some of them were extracted from plants that are found to be effective and safe. Moreover, it has been approved that several plants, herbs, and vegetables can prevent or reduce incidence of cancer in several sites of the human body. Besides, researchers found that they are a great source for developing and producing new, effective, tolerable, and safe anticancer drugs compared with the synthetic ones. As a result of that, researchers recommended future studies to focus more on plant as a source for safe and effective anticancer treatment.

Keywords: cancer, plants, anti-growth, apoptosis, treatment

1. Cancer background

During this century, cancer has become one of the major problems and diseases which has caused predominant death, and it will even surpass heart diseases. Many of the researchers begin to use the term lifetime risk for cancer patients which refer to the time that cancer will progress and developed or the time that the patient will die because of cancer. Cancer does not represent only one disease but it is a group involving about 100 diseases. It is characterized by two things: Firstly there is no control for the growth of cancer cells, and secondly it is the ability of the cancer cells to metastasize and migrate from the original site to different parts of the body. There are two types of tumors which are malignant and benign. Cancer can attack any person, and its occurrence increases as the age of the individual increases too [1, 2]. There are many problems (i.e., side effects) associated with cancer diseases either solid or hematological cancer such as nausea, vomiting, diarrhea, constipation, hypercalcemia, pain, loss of appetite, anemia, fatigue, cachexia, leucopenia, neutropenia, and thrombocytopenia. However the major problems are nausea and vomiting, neutropenia, anemia, thrombocytopenia, and hypercalcemia. Hence due to these reasons, cancer is considered as one of the major diseases that will affect the quality of life [3–6].

2. Chemotherapy background

Chemotherapy was developed and used since the Word War I from the chemical weapon program of the United States of America (USA). Since then chemotherapy

has become as one of the most important and significant treatments of cancer. Its main mechanism of action is by killing the cancer cells which are characterized by their high multiplication and growth rate. It will also kill all the cancer cells that had broken off from the main tumor and spread to the blood or lymphatic system or any part of the body. This killing process of cells is either by a direct effect on deoxyribonucleic acid (DNA) or an effect on the factors involved in mitosis by inhibition of its synthesis or production or uses [7–9]. Chemotherapy drug may lead to complete cure for some types of cancers or may suppress the growth of others or may prevent their spread to other parts of the body. So many types of new therapies have emerged over the past 20 years. Some of them were straight forward, effective, and safe and some have many side effects. However when comparing chemotherapy with other types of treatments, it still remains potentially high risk with many side effects which are difficult to manage. The chemotherapy used required the involvement of various clinical professionals during its various stages of administration, and enormous patient health care is needed to overcome its side effects [7, 10].

3. Chemotherapy side effects

The goal of chemotherapy is to be as effective as possible with tolerable side effects, since the dose of chemotherapy will be toxic to the cancer cells as well as to the normal cells. A proportion of the cancer patients suffer from only mild side effects, whereas others may suffer from serious side effects [10–12].

These side effects are classified as:

1. Acute, which develop within 24 hours after chemotherapy administration
2. Delayed, which developed after 24 hours and up to 6–8 weeks after chemotherapy treatments
3. Short term, combination of both acute and delayed effect
4. Late/long term, which developed after months or years of chemotherapy treatment
5. Expected, which developed among 75% of the patients
6. Common, occurred in 25–75% of the patients
7. Uncommon, happened less than 15% of the patients
8. Rare, occur in only 5% of the patients
9. Very rare, occur on less than 1% of the patients [10–12]

Occurrence of specific side effects will vary according to the chemotherapy used. The most common side effects experienced are nausea and vomiting, anemia, hair lost, bleeding, thrombocytopenia, hyperuricemia, bone marrow depression, alopecia, and mucositis. So different parameters must be taken into consideration to prevent, reduce, and overcome these side effects [10–12].

4. Plants and cancer

Herbal medicine has been used as a major treatment for cancer in various countries in the Middle East and Europe long time ago. Recent reports released by the World Health Organization (WHO) showed that although many advanced countries have considered traditional herbal treatment as an official treatment for cancer, only 5–15% of these herbs have been investigated to detect their bioactive compounds, i.e., anticancer compounds [13–15].

5. Plants and cancer treatment and prevention

According to the two famous Islamic physicians (Rhazes and Avicenna), diseases need to be treated by using a scheme which consists of three options; the first option will be by using physiotherapy and diet, the second one will be by using drugs, and the last option will be surgery. Drugs used on that time have been classified as simple and compound drugs. Treatment of any disease will start with the simple one to avoid drug–drug interaction; unless it did not work, then physician will use the compound drugs, and when second option failed too, then surgery will be used [15].

Regarding cancer treatment, the Islamic scholar "Avicenna" mentioned that "if it is the start of a cancer, it is possible to make it static and prevent it from growth and hence ulceration" [14].

Researchers mentioned that herbal-based medicines are found to be one of the best choices for treating and/or preventing incidence of cancer. This is mainly because of the varieties of active substances that plants contained which work against many types of cancers in several mechanisms. These compounds can be extracted and can be used alone or in combination with other anticancer treatments. In comparison with synthetic drugs, these natural compounds are found to be naturally available, cheaper, and easy to administered orally and have low or minimal side effects, and they are found to be rich of various biologically active chemotypes [14–16, 19].

Avni and colleagues mentioned there are several plants work as "Chemopreventive agents against many types of cancers like; *Abrus precatorius* on Yoshida sarcoma, *Albizia lebbeck* on sarcoma, and *Alstonia scholaries* on forestomach carcinoma". Other plants characterized by anticancer activity like "*Anacardium occidentale* in hepatoma, *Asparagus racemosus* in human epidermoid carcinoma, *Boswellia serrata* in human epidermal carcinoma of the nasopharynx, *Erythrina suberosa* in sarcoma, *Euphorbia hirta* in Freund virus leukemia, *Gynandropsis pentaphylla* in hepatoma, *Nigella sativa* in Lewis lung carcinoma, *paederia foetida* in human epidermoid carcinoma of the nasopharynx, *picrorhiza kurroa* in hepatic cancers, and *Withania somnifera* in various tumors" [20].

One of the most critical problems associated with cancer treatment is chemotherapy resistance, that's why researchers trying their best to prevent or reduce incidence of resistance by detecting new anticancer agents as an alternate [14].

Thazin and colleagues mentioned that natural compounds extracted from plants have not only the ability to work as anticancer agents but also to restore chemotherapy sensitivity, for example, tetrandrine which is an active alkaloid compound extracted from plant enhances doxorubicin anticancer activity against resistant MCF-1/DOX cells in vivo via modulating P-gp-mediated drug efflux. Another natural compound is quercetin (flavonoid) which restores daunorubicin chemosensitivity in resistant HL-60/DOX and K562/DOX cell lines via suppression of P-gp

expression. Curcumin also increases vincristine chemotherapy activity in SGC7901/VCR cell lines by suppressing ABC transporters such as P-gp, MRP1, and ABCG2 proteins [21].

Jana and colleagues conducted in vitro study to determine the anticancer, antiproliferative, and cytotoxic effect of brassinosteroids (BRs) which are steroids extracted from plants against (MCF-7/MDA-MB-468) breast and (LNCaP/DU-145) prostate cancer cell lines and normal cell line. Results showed that RBs significantly arrested MCF-7, MDA-MB-468, and LNCaP cells in G1 phase of the cell cycle and induced apoptosis in MDA-MB-468, LNCaP, and slightly in the DU-145 cells, without any toxic effect against normal cell lines. These results support the point that RB compounds are a promising source for anticancer drugs [22]. Another in vitro study is conducted to detect the antiproliferative and cytotoxic effect of the aqueous extract of *A. ascalonicum* against Wehi164 (mouse fibrosarcoma cells), Jurkat (human acute T-cell leukemia) and K562 (human erythroleukemia), and human umbilical vein endothelial cells (HUVEC) as a normal cell line. Results showed that the extract showed a significant antiproliferative effect against all cancer cell lines and a dose and time cytotoxic effect against them with a very low cytotoxic effect against a normal cell line. These results showed that the *Allium ascalonicum* plant is a promising source for a potent anticancer treatment for several types of cancers [23].

About cancer prevention, it has been approved that several plants, herbs, and vegetables can prevent or reduce the incidence of cancer in several sites of the human body [14].

An in vitro study is conducted by a group of researchers trying to detect the ability of ethyl acetate extract of onion (EEO) to cause inhibition for cancer growth and cause apoptosis in human breast cancer MDA-MB-231. Results showed that EEO cause apoptosis for MDA-MB-231 breast cancer cell line and prevent incidence (i.e., growth) of breast cancer by inhibiting fatty acid synthase (FAS) production and accumulation in adipose tissues [24].

Another in vitro study is conducted by Arif and colleagues to detect the antitumor effect of *Aloe vera* crude extract (ACE) alone and in combination with cisplatin on human breast carcinoma cell line (MCF-7) and human cervical carcinoma cell line (HeLa) [25]. **T**he cytotoxic potential of ***Aloe vera*** crude extract alone or in combination with cisplatin in human breast (MCF-7) and cervical (HeLa) cancer cells was studied by cell viability assay, nuclear morphological examination, and cell cycle analysis. Effects were correlated with the modulation of expression of genes involved in cell cycle regulation, apoptosis, and drug metabolism by RT-PCR. "Results showed that exposure of cells to ACE resulted in considerable loss of cell viability in a dose- and time-dependent fashion, which was found to be mediated by through the apoptotic pathway as evidenced by changes in the nuclear morphology and the distribution of cells in the different phases of the cell cycle. Interestingly, ACE did not have any significant cytotoxicity towards normal cells, thus placing it in the category of safe chemopreventive agent. Further, the effects were correlated with the downregulation of cyclin D1, CYP 1A1, and CYP 1A2 and increased expression of bax and p21 in MCF-7 and HeLa cells. In addition, a low-dose combination of ACE and cisplatin showed a combination index less than 1, indicating synergistic growth inhibition compared to the agents applied individually. In conclusion, these results signify that *Aloe vera* may be an effective antineoplastic agent to inhibit cancer cell growth and increase the therapeutic efficacy of conventional drugs like cisplatin. Thus promoting the development of plant-derived therapeutic agents appears warranted for novel cancer treatment strategies" [25].

6. Anticancer plant-derived drugs

About two-thirds of the anticancer treatments are extracted from plants, and these drugs are divided into several classes depending on their pharmacological effect: antimitotics [vinca alkaloids (e.g., vincristine and vinblastine), podophyllotoxins (e.g., etoposide and teniposide), and taxanes (e.g., paclitaxel, docetaxel)], topoisomerase inhibiters [Topo I (e.g., topotecan and irinotecan), Topo II (e.g., ellipticine and podophyllotoxins)], ROS inducers (e.g., EGCG2 and thymoquinone), angiogenesis inhibitors (e.g., flavopiridol), histone deacetylases (HDAC) inhibitors (e.g., sulforaphane and pomiferin), and mitotic disruptors (e.g., roscovitine) [3, 4, 15].

An *in vitro* study is conducted by Maram and colleagues to detect the antitumor effect of *Aloe vera* (*A. vera*) and *Calligonum* extracts on hepatocellular carcinoma (HepG2) cells. Viability, apoptosis, and DNA damage of these cells have been tested after exposure to different concentrations of the two extracts. Results showed that the extracts of these two plants could have an antitumor effect against HepG2 cells. Thus, these two plants can be promising sources for future anticancer treatment [26].

Nadia and colleagues conducted an *in vitro* study in which the main aim was to detect the anticancer effect of ethyl acetate extract of *Crataegus azarolus* against HCT-116 and HT-29 human colorectal cancer cell lines. Results showed that the extract demonstrated strong cytotoxic and anti-growth activities via several mechanisms. Moreover, its apoptotic effect is associated with the elevation of p21 expression but not through p53 activation. As a result of that, authors concluded that this compound can be used as anticancer for treating colorectal cancer [27].

7. Secondary metabolites extracted from plants used as anticancer agents

Overtime researchers detected that plants found to be enriched with natural compounds called secondary metabolites these metabolites characterized by several points that make them effective antitumor agents. These compounds can be classified into "three main groups which are: terpenoids (polymeric isoprene derivatives and biosynthesized from acetate via the mevalonic acid pathway), phenolics (biosynthesized from shikimate pathways, containing one or more hydroxylated aromatic rings), and the extremely diverse alkaloids (nonprotein nitrogen-containing compounds, biosynthesized from amino acids such as tyrosine, with a long history in medication)" [16]. Yearly several new metabolites are extracted from plants, but limited numbers of them have been used to synthesize new potent anticancer agents.

8. Medicinal plant enhanced chemotherapy and radiotherapy function

As mentioned above one of the crucial problems associated with chemotherapy drug is multidrug resistance (MDR), which happened when cancer cells become insensitive to chemotherapy treatment used for treating it [17]. The main factor that plays a role in the incidence of this phenomenon is the overexpression of ATP-binding cassette (ABC) transporters which their main function is to prevent transportation of chemotherapy drug through the biological membrane of the cell to reach its target [17]. As a result of that, many researchers are working so hard to produce and/or extract efficient and low-toxic inhibitors for ABC drug transporters from natural

sources, i.e., natural products. Their main target is to restore drug sensitivity in MDR cancer cells by improving chemotherapy drug penetration, distribution, and accumulation of the drug inside the tumor cells [17]. Besides that, natural compounds extracted from plants can be used to enhance chemotherapy function in several ways, as clarified in **Table 1**.

Compound	**Dietary source**	**Chemotherapy drug**	**Effect**
			Influence on treatment efficacy
Ginsenosides	Ginseng	Cisplatin 5-Fluorouracil	Enhancement of drug-induced antiproliferative effect Increase in antiproliferative effect
Curcumin	Turmeric	Vinorelbine	Enhancement of chemotherapeutic efficacy
Catechins/theanine	Green tea	Doxorubicin Cisplatin	Enhancement of antitumor activity Increase in reduction of tumor growth
Quercetin	Many foods such as onions, apples, berries, and tea	Doxorubicin Busulfan Cisplatin	Potentiation of growth-inhibitory activity Synergistic antiproliferative activity Increased cytotoxic effect
Genistein	Soy foods	Tamoxifen	Attenuation of inhibitory effect of tamoxifen on tumor cell growth Attenuation of tamoxifen effect on reducing of tumor burden Synergistic growth inhibition
Daidzein	Soy foods	Tamoxifen	Improvement of drug activity to reduce tumor burden
Tangeretin	Tangerine and other citrus peels	Tamoxifen	Complete blocking of growth-inhibitory effect of tamoxifen
			Influence on side effects of chemotherapy
Ginsenosides	Ginseng	Cyclophosphamide	Protection against drug-induced genotoxicity and apoptosis in bone marrow cells and peripheral lymphocytes
Quercetin	Many foods such as onions, apples, berries, and tea	Cisplatin	Protection of normal renal tubular cells from drug toxicity
			Influence on drug resistance
Ginsenosides	Ginseng	Paclitaxel	Chemosensitization
		Doxorubicin	Inhibition of drug efflux from tumor cells

Table 1.
Various natural compounds and their effects on chemotherapy [17, 18].

Plants (family)	Radioprotective/radiosensitizing efficacy
Aegle marmelos (L.) Corr. (Rutaceae)	Reduced decline in hemoglobin level, and leukocytes and lymphocytes counts because of radiotherapy.
Aloe arborescens Mill. (Liliaceae)	Radioprotective efficacy
Alstonia scholaris L. (Apocynaceae)	Radioprotective efficacy
Biophytum sensitivum (L.) DC. (Oxalidaceae)	Prevented γ-radiation-induced DNA damage
Citrus sinensis (L.) Osbeck (Rutaceae)	Significantly counteracted UV-B-induced damage in human keratinocytes
Emblica officinalis L. (Phyllanthaceae)	Significantly caused depletion in lipid peroxidation and elevation in glutathione and catalase levels
Grewia asiatica L. (Malvaceae)	Inhibited γ-radiation-induced glutathione depletion and ameliorating lipid peroxidation
Isatis indigotica Fort. (Brassicaceae)	Reduce the mucosal damage caused by radiation
Mentha piperita and *Mentha arvensis* (Lamiaceae)	Prevented γ-radiation-induced DNA damage
Olea europaea L. (Oleaceae)	Inhibited incidence of skin damage
Panax ginseng L. (Araliaceae)	Prevented γ-radiation-induced DNA damage
Rosmarinus officinalis L. (Lamiaceae)	Prevented γ-radiation
Rubus spp. (Rosaceae)	Prevented UV radiation
Syzygium cumini L. Skeels (Myrtaceae)	Prevented γ-radiation
Tinospora cordifolia (Thunb.)	Prevented γ-radiation
Viscum album L. (Santalaceae)	Palliate radiotherapy side effects
Xylopia aethiopica (Dunal) A. Rich (Annonaceae)	Prevented γ-radiation

Table 2.
Radioprotective/radiosensitizing efficacy of plants against radiotherapy [28].

Regarding radiation therapy, studies found that a substantial fraction of cancers fails to response properly to radiation therapy, and for this case the use of a high dose is recommended, and this will cause incidence of major side effects (like tissue fibrosis, hair loss, myelosuppression, etc.) [28]. This will happen as a result of generation of intercellular reactive species which will cause breakdown for DNA strand and alteration in biomolecules. Moreover, the combination of radiotherapy and chemotherapy can aggravate the situation, for example, renal problems and alopecia will be detected on cancer patients treated with radiotherapy and platinum chemotherapy, while the combination with alkylating agents is found to cause infertility [28]. Therefore, researchers worked so hard to detect compounds from natural and/or synthetic source (s) to overcome radiotherapy damage and side effects. Studies showed that some plants are radioprotectors which are capable of preventing and/or palliating radiotherapy damage and side effects. Other plants are found to be radiosensitizers which are capable of enhancing radiotherapy pharmacological effects i.e., get the desired pharmacological effect with the minimum dose, as shown in **Table 2**.

9. Nutritional approach in chemotherapy and radiotherapy

During this century chemotherapy and radiotherapy remain as the dominant and the most effective treatments against many types of cancers. Extraordinary effort is made by the researchers to improve the efficacy of both of them. The new

vision for doing that is by using natural products (supplements) in concurrent with them [18, 29].

Besides, these supplements will significantly reduce the incidence of many side effects like "oral mucositis, gastrointestinal toxicity, hepatotoxicity, nephrotoxicity, hematopoietic system injury, cardiotoxicity, and neurotoxicity" that can be caused by the use of the pharmacological treatments, and example for these natural supplements are ginseng extract, grape seed extract, and curcumin [18, 30].

Moreover, nutritional supplement can also help in increasing cancer cell apoptosis, reducing multidrug resistance, increasing drug penetration and its concentration inside cancer cells, and reducing incidence of weight loss, malnutrition, and severity of comorbidities. At the same time, they can significantly improve cancer patients' quality of life [18]. As a result of that, clinicians encouraged to administer nutritional supplement in combination with chemotherapy, rather than giving them separately [18].

One of the most important benefits that can be obtained by combining nutritional supplement with chemotherapy is reducing the incidence of drug resistance by inhibiting ABC transporters [example P-glycoprotein (P-gp) and multidrug resistance proteins (MRP-s)] [18]. Currently no synthetic material is found to be efficient and safe for multidrug resistance, but some novel compounds extracted from natural products can help in some ways to solve this crucial problem [18].

An in vitro study is conducted to determine the antiproliferative and apoptotic effect of *B. serrata* plant methanolic extract as a monotherapy and in combination with doxorubicin (DOX) chemotherapy against hepatocellular carcinoma cell lines (HepG2) and (Hep3B). The results showed that the extract of the plant inhibited the proliferation of both cancer cell lines (HepG2 and Hep3B) with IC_{50} values 21.21 ± 0.92 and 18.65 ± 0.71 μg/mL, respectively. About DOX it caused an inhibition for proliferation of both cancer cell lines at IC_{50} values 1.06 ± 0.04 and 1.92 ± 0.09 μg/ML, respectively, while when the extract is used in combination with DOX, results showed that there was a synergistic effect against both cancer cell lines with combination index (CI) of DOX and *B. serrata* extract of 0.53 ± 0.03 to 0.79 ± 0.02. Besides, results showed that the use of the extract alone and in combination with Dox significantly stimulated the activity of caspase-3 and the activation in combination with Dox was higher. A similar result also gotten about the use of the extract with Dox significantly increased the expression of *TNF-α* and IL-6 and reduced the anti-apoptotic protein level which is *NF-κB*. Moreover, the use of the extract showed a significant reduction in liver enzymes SGOT, SGPT, and ALP which have been elevated as a result of the use of Dox alone, i.e., the extract significantly helped in reducing liver toxicity. Also the extract leaded to restored albumin protein level which has been decreased as a result of Dox use. Moreover, the use of the extract with Dox chemotherapy significantly helps in preserving the histological architecture of the liver, which showed a significant change among group of rats receiving Dox chemotherapy alone. All these points confirmed that the use of the extract in combination with Dox will significantly help in improving treatment of hepatocellular cancer and reducing side effects of Dox [31].

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