World Applied Sciences Journal 38 (3): 183-190, 2020
ISSN 1818-4952

DOI: 10.5829/idosi.wasj.2020.183.190

Utilization of Herbal, Complementary and Alternative Medicines for Treatment in Cancer Patients

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Abstract: Cancer is associated with complicated pathogenesis and carcinogenesis (tumorigenesis or oncogenesis) and is charaterized by abnormal regulation of cell-growth and cell-death. Cancers are categorized into different types which may occur separately in females, males and in both. However, the prevalence rate of cancer is growing in the global wide. The treatment for cancer is confirmed as different types of radiation, therapies and recently enlisted surgery. Apart from these, herbal as well as complementary and alternative medicine (CAM) have been documented in the global wide studies. One of the beneficial applications of herbal plant is widely used in cancer treatment. The herbs are used to replace the anti-cancer drugs, radiations and chemotherapies in the cancer treatment. Some of the well-known and confirmed useful herbs for cancer treatments are *Oldenlandia diffusa, Curcuma longa, Astragalus membranaceus, Panax ginseng, Ganoderma lucidum* and *Glycyrrhiza glabra*. The CAM is documented in limited studies and CAM is considered as standard medical treatment without any scientific evidence. The growth of CAM treatment towards cancer was increased enormously but robust scientific data about the effectiveness and interaction with limited conventional medical treatments. This review recommends herbal medicine contain pharmacological components which have therapeutic effects. Enormous research shows herbal medicines are used for the human treatment.

Key words: Cancer · Herbal Medicines · Therapeutic Factors · Complementary and Alternative Medicine

INTRODUCTION

Cancer is connected with a system of complicated pathogenesis; tumorigenesis is characterized through abnormal regulation of cell-growth and cell-death [1]. The accurate analysis of cancer pathogenesis is still not yet clear. However, cumulative evidence proposes genetic and environmental factors are involved in cancer development. Right now, large number of studies has shown that genetic abnormalities play a critical role in malignant transformation [2]. Cancer is an unembellished metabolic disorder and globally known for the leading cause of death which involves unrestrained proliferation of common cells which is caused due to genetic modifications and the instabilities does results in the generation of malignant cells and initiation of metastasis or tissue invasion [3]. Cancer is known as hyperproliferative disorder that insists on transformation, invasion, apoptosis dysregulation, proliferation, metastasis and angiogenesis [4]. Cancer is defined as irregular division of human cells through uncontrolled manner which affects at any age of the human. However, the risk is depending upon aging and all cancers drains through a process of progressive loss of regular growth control [5]. Cancer is connected as one of the risk complications for human diseases such as type 2 diabetes, gestational diabetes, insulin resistance, metabolic syndrome, polycystic ovarian syndrome, non-alcoholic fatty liver disease. The relation between different forms of diabetes and cancer is documented globally [6-8]. Globally, death rate of cancer in 2018 was estimated to be around 9.6 million [9]. Conservative evaluation specifies cancers as breast, lung, liver, colorectal, stomach and cervix cause 13% of global deaths per annum [10, 11]. Mainstream cancer treatments are chemotherapy, radiotherapy and surgeries also with

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emergent targets of cancer immunotherapies [12]. Conventional therapies for cancer management have numerous side-effects due to the lack of specificity [13]. Anti-cancer drugs can cause side-effects due to toxic effects in normal cells or tissues with multiple symptoms [14]. Chemotherapies endures as a mainstream therapy for multiple cancers. Nausea and vomiting are common side-effects for chemotherapy and trios of chemotherapy-induced nausea and vomiting are categorized as anticipatory, acute and delayed nauseas [15]. Human therapies depend on plants with the supplementation of conventional complementary treatment on human issues of health and plant compounds plays a role in handling human diseases [16]. Previous studies have confirmed as Chinese herb medicines interim as adjuvant therapy which enhance the efficacy and lowers the side-effects during the cancer treatment with chemo and radio therapies [17]. In this review, the aim is to compare between the herbal medicine with the complementary and alternative medicines towards the treatment in the cancer patients.

Herbal Medicines in Cancer Treatment: Herbal medicinal plants are in usage since foundation of human civilization and more apparent from the ancient script [18]. Herbal medicine offers a wide range of potential benefits for patients opting chemotherapy [19]. The world health organization (WHO) defines herbal plants are used in the human health for treating, prevention or diagnosis of illness [20]. Herb is used for the reference for non-woody plant and its parts such as flower, stigma, stem, bark, seed and leaf. Herbal plants have a substantial potential source for therapeutics; accomplished the impressive role in health care system. Almost, 67% global population be contingent on herbal medicines due to its cultural acceptability. Plant-consequential drugs were discovered with traditional and therapeutics studies [21, 22]. Prophet Muhammad used the pomegranate, miswak, henna, ginger, garlic, fenugreek, costus and black seeds for treating human diseases [23]. The input of plants role towards medicine for human diseases were neglected because of precise biochemical and pharmacological mechanisms [24]. Natural plant compounds achieved fame in pharmacological and clinical effects in cancer disease [25]. Previously documented studies confirmed the fact as herbal plants extract revealed anti-cancer activities in both the *in vitro* and *in vivo*. Herbal medicines tend to have anti-cancer effects which enhances through the immune system further persuades cell differentiation, inhibits the telomerase activities and encouraging apoptosis of cancer cells [26]. The firm belief about herbal medicines are natural without any side-effects to cause dependency. Even so, many herbs can be toxic precisely in large quantities of frequent usage. Along with herb; synthetic drugs interactions can be controversial [27]. Before 1500 years ago Kampo has introduced traditional herbal medicine from China who established distinctly. National Health Insurance has approved this medicine in Japan after examining in animal model and clinical trials to evaluate side effects of chemotherapy [28, 29]. Chinese herbal medicines (CHM) have lower side effects with superior effectiveness in humans including cancers. Among cancers, breast cancer is one of the commonly ripen cancer throughout the world. The disease itself begins malignant cells form in the breast tissues. The therapy of CHM has an exceptional therapeutic effect to lower the chemotherapy and surgery known as side-effects which will boost the immunity in the body. Meta-analysis results displayed combined combination of CHM with western medicine as effective and safe therapies in the breast cancer women after the surgery or chemotherapy [30].

Numerous herbs and remedies have been documented for cancer therapy from south and eastern regions of Asia.

Some of the common and most effective herbs used in the cancer treatments are as follows; *Oldenlandia diffusa*, *Curcuma longa*, *Astragalus membranaceus*, *Panax ginseng*, *Ganoderma lucidum* and Licorice [31]. The details of the included plant herbal species are defined in Table 1.

Oldenlandia diffusa (Rubiaceae family) is an annual herb known to have pharmacological effects which involves immune regulation, antioxidant and anti-cancer. With the active components in this herb can affect induce apoptosis of colorectal, prostate, cervical, gastric and other tumors which can lowers the proliferation and metastasis of liver cancer cells through chemokine receptor inhibitors. Based on the history of this anti-cancer drug, the clinical usage of a decent inhibitor effect on numerous types of cancers and used in the combination of other drugs to enhance its anti-cancer properties and it is known as one of the best herbs for anti-tumor therapies [11, 31, 32].

Curcuma longa (Zingeiberaceae family); commonly termed as turmeric known to be perennial herb and its active ingredient is curcumin used in spice and pigment. For the treatment purpose, curcumin was used as a single decoction in human diseases such as cancers, diabetes and cardiovascular diseases. It mainly inhibits migration

Table 1: List of plant herbal species involved in this study

Plant scientific name	Name of the family	Role of plant	Specific cancer
Hedyotis diffusa	Rubiaceae	Herbal medicine	Liver cancer
Curcuma longa	Zingeiberaceae	Herbal medicine	NSCLS and prostrate cancers
Astragalus propinquus	Fabaceae	Herbal medicine	Breast cancer
Panax ginseng	Araliaceae	Herbal medicine	Breast and lung cancers
Ganoderma lingzhi	Ganodermataceae	Herbal medicine	Breast, lung and prostate cancers
Glycyrrhiza glabra	Fabaceae	Herbal medicine	Metastatic prostrate cancer

Table 2: Applications of ginsenosides in anticancer activities [66].

Ginsenosides	Anti-cancer activities	Molecular mechanisms
Rb1	- Weakly antiproliferative. - Antiangiogenic.	-Inhibits capillary genesis and TNF-α release. -Protect against oxidative stress. -Inhibits tube like structure formation of endothelial cells by regulating pigment epithelium derived factor through estrogen receptor-*β*.
Rb3	- No antiproliferative activity.	Inhibits TNF-α release.
Rg1	- Antiproliferative.	-Inhibits oncogenes (c-myc and fos). -Downregulate nucleophosmin.
Rg3	- Antiproliferative. - Apoptotic. - Antiangiogenic. - Antimetastatic. - Anti-invasive. - Cell-cycle regulation.	-Regulating mitochondrial cytochrome C, poly ADP ribosome polymerase and C9. -Inhibits MMP 2 and 9. -Inhibits MDR and adhesion of metastatic cells to basement membranes.
Rh1	Causes discrepancies of teratocarcinoma cells, strongly apoptotic.	-Inhibits TNF-α and phosphorylation of ERK, JAK1, STAT1 and 3. -Bind to steroid receptor.

and proliferation of cancer cells which occurs apoptosis in the metastatic cells. Curcumin demonstrates huge range of pharmacological properties involves anti-cancerous, anti-angiogenic, anti-inflammatory and anti-oxidative effects. Through the dried product of rhizomes, curcumin was obtained and Asians mainly used in the cooking purpose and also as cosmetics as well as used in the form of traditional Chinese medicine. One of the major roles of curcumin will suppress inflammation affected through regulating polarization of macrophages [33, 34]. Curcumin induces apoptotic effects on non-small cell lung cancer cell lines, prostate cancer, human leukemia and melanoma. During high dose (12g/day), curcumin was confirmed as basic toxicity when preclinical research and phase-I clinical trials [35].

The *Astragalus membranaceus* (Fabaceae family) is enrolled as Chinese medicine in the leguminous plant. Both the astragaloside and astragalus polysaccharide are the main ingredients consists of antiviral and immune functions [36]. This plant is also used in Traditional Chinese medicine in the past 2000 years and well-known with combination of other herbs as ginseng, angelica and poria in clubbed combination. Astragalus Membranaceus inhibits proliferation for cells in breast cancer via PIK3 pathway which induces apoptosis of NSCLC and Leukemia. However, Astragalus Membranaceus induces polarization of M1-type macrophages which activates the anticancer activities and in combination through anticancerous drugs it can increase the cancerous cells inhibitory effects [37]. From these plants prepared medicine can be used as a single medicine and also used to enhance cisplatin [38].

Panax ginseng is a plant belongs to perennial herb in Rhizome of Araliaceae family of *Panax* genus and commonly used in the herbal medicines specifically in cancers [39]. Ginseng is the major active ingredient in ginsenoside in which amino-acids and polysaccharides have documented the pharmacological functions. It has triterpenoids known to be anticancer activities mainly in Rg1-3 and Rh1-2. Ginseng is chemoprophylactic oftenly acts as cellular and molecular targets by various signalling pathways inhibits tumor by regulation of cell-cycle, orientation of apoptosis and inhibition of angiogenesis and invasion. Laboratories and preclinical studies have confirmed the protective achieving role of ginseng in the cancer. The combination of main ingredients of Lizhong decoction and ginseng works very well [31, 40] (Table 2). Initially, ginseng was used as a tonic in Asian countries and based on human studies ginseng was proven to be excellence towards chemotherapy adjuvant due to the low effect of toxic. Required properties such as modulation of immunity, anti-oxidation, apoptosis, anti-inflammation,

Table 3: Country-wide implemented names of *Ganoderma lucidum* [43].

Country	Language	Local name	Other features
Korea	Korean	Seon-cho; Yeong ji cho	Ja-ji=Purple; Heuk-ji=Black; Cheong-ji=Blue; Baek-ji=White; Hwang-ji=Yellow.
China	Chinese	Lingzhi; Zhi	Red or purple or propitious or divine or plant mushrooms .
Japan	Japanese	Reishi	Zuiso mushroom; plant of propitious and immortality.
Vietnam	Vietnamese	Linh chi	Reishi mushroom.
Spain	Spanish	Pipa	-
France	French	Polypore/ganoderme luisant	-
Germany	German	Glanzender lackporling	-
Catalonia	Catalan	Pipa and Paella	-
-	English	Ganoderma, shiny poly	-

anti-proliferation and anti-angiogenesis effects. Based on animal and *in vivo* studies, the profits of ginseng- active elements in ornamental antitumor activity used in the application of anticancer drugs [41]. This herb is applied in breast and lung cancer treatment purposes [42].

Ganoderma lucidum is also known as Curtis belongs to Ganodermataceae family (polyporales) is confirmed as an annual wood-degrading Basidiomycota; recurrently dimidiate in the form of a stipulated shelf, pileus or hat. It has been documented between 40 to 200 mm in diameter, which is rounded irregularly, fan-shaped and oval is frequently stipulated centrally (Table 3). *Ganoderma lucidium* is recorded as oldest Chinese herbal medicine called as *Shen-Nong-Ben-Cao-Jing* [43]. It is documented as a specific type of fungus in both food and medicine. These active components involve amino-acids, triterpenoids, proteins, alkaloids, steroids and polysaccharides; are known to be self-possessed of three-dimensional structures similar to either DNA or RNA. These drugs are taken as a single or as a tonic for food intake for the lung cancer. *Ganoderma lucidum* can be consuming in their daily life in various cancer patients as lung, breast and prostate cancers as a herbal medicine [44, 5].

Licorice is derived from dried roots and rhizomes of genus *Glycyrrhiza* is define as *gancao*. Licorice or *Glycyrrhiza* is one of old medicinal plant termed as Chinese licorice belongs to the Fabaceae (Leguminosae) family. Licorice root is known to be old, common and most frequent employed botanicals in Chinese medicine. Globally, licorice distributes around 30 different species of licorice and Glycyrrhiza's (i) *uralensis*, (ii) *inflata bat* and (iii) *glabra* L. are prearranged as licorice in the Chinese Pharmacopoeia [46]. The major active ingredient of licorice is glycyrrhizic acid; well-known saponin structure [47]. Glycyrrhizin can persuade apoptosis of cells in the oral cancer by growing the Bax/Bcl-2 ratios and upregulates the cleavages of Caspase 3/9 and PARP [48]. Licorice is known to be a perineal plant, cultivated in India, China, Russia, Spain and Persia and it extract from the roots which is very sweet and common source used in both traditional and herbal medicines [49]. Licorice roots consists of triterpenes, alkaloids, phenolic acids, polysaccharides, falvones, polyamines, flavans, flavonoids, chalcones and isoflavonoids. Licorice major components are glycyrrhizin which is also known as glycyrrhizic acid is known to hydrolyze in the intestine of glycyrrhetic acid through β-glucuronidase. Licorice can be used to treat in metastatic prostate cancer [50].

Usage of Complementary Medicine and Alternative Medicine for Cancers Treatment: Since antient times, medicinal plants have played a major role in a traditional manner of medicine for treating the human diseases. Applications of medicinal plants are used for healing various kinds of infections and contributed as a foundation for motivation of innovative therapeutic agents. Globally, 80% of countries still now depends on traditional usage of medicinal plants [51]. Roots and leaves are the major plant parts used for cancer treatment as well as the usage of plant leaves in alternative medicine might be ascribed to accessibility and facility rather than collection of roots [12]. The involvement of plants for cancer treatment is due to the dysregulation of apoptosis and cancerous cell growth rate is still depends on for controlling the cells to undergo apoptosis through mitochondrial intrinsic pathways which was induced through aqueous extract of *Bryonia dioica* on BL41 cancer cell lines [51]. Globally, more than one-third of the cancer patients use the complementary medicine (CM) and based on World Health Organization, CM is defines as a broad set of healthcare practices that are not a countries routine part of or conventional medicine, which is not completely integrated into the dominant healthcare system [52]. The usage of CM in Europe was 15-73% [53] and 26-39% was documented in the Switzerland [54].

Complementary and alternative medicine (CAM) is defines diagnosis, treatment and prevention that compliments mainstream medicine by contributing to a common or whole by satisfying a demand not met either

orthodoxy or diversifying the conceptual framework of medicine. CAM usage has drastically grown-up since more than a decade and it had gained the medical, economic and sociological importance in the field of medicine [55]. The usage of CAM in cancer patients has begun since 1970's and from the past couple of decades, usage of CAM has increased drastically [56]. The Australian communities have shown the high usage of CAM in public and health specialists. Numerous cancer patients have opted CAM as a preliminary medicine for the symptoms of cancer or oncological treatment. The advantageous and administered interaction between CAM and controversial cancer care is known as integrative oncology [57]. Previous results studies from 2015-NCSME-PR in USA has documented 43% of cancer patients use herbal medicine when compared with 34.6% in other diseased subjects [58]. The practice of CAM has begun to inspire geographically by the results of cultural attitudes towards health and CAM therapies [59]. Patients have started to show interest towards using CAM rather than pharmacological drugs precisely those who are disappointed with available data on the cancer disease. From a study, 69% of post-menopausal women with breast cancer patients were active physically and 87% showed attention towards the nutrition and 46% used CAM. More than 50% of post-menopausal breast cancer patients were treated with aromatase inhibitor are interested in CAM [60]. A study from US have confirmed 33% of cancer patients have applied CAM towards cancer treatment and the subjects diagnosed with cancer have multiple nodes of motivations for seeking CAM which include persistent symptoms and psychological distress and to gain a sense of control over their care [61]. The meaning variations cannot be measured with the usage of CAM in cancer patients. However, the CAM patients were highly to the nonusers to have a past medical history for non-CAM for the involvement in the clinical trials [62]. During the canonical days, the applications of CAM were high and use of family traditions such as meditation, praying, healing with oil and baptism with the use of plant roots [63].

Alternative, complementary and integrative medicines as well as standard medical care are sub-types of CAM. However, CAM are not a part of conventional medical care. Standard anti-cancer treatments such as diet, lifestyle factors and supplements are replaced with alternative medicines. Oriental (ayurvedic) medicine, yoga, herb, diet, relki, nutritional supplementations and acupuncture comes under CAM interventions. Comprehensive range of cancer interventions through CAM are repeatedly favored for anticancer therapies providing patients have complete knowledge and reality of prospective [64]. One of the beneficial sources for cancer patients for opting CAM is to avoid sensible side-effects of radiations during chemotherapies. Another belief with CAM in the cancer patients is benefited with preventing illness, endorsing health, improving immune function and managing cancer symptoms. The growth of CAM treatment towards cancer have been increased enormously but the robust scientific data about the effectiveness and interaction with conventional medical treatments are limited [65].

CONCLUSION

This review concludes the available sources for the cancer patient treatment including herbal medicine and CAM apart from the routine therapies. Maximum studies have confirmed herbal medicine as safe and secure; whereas CAM is considered as standard medical treatment without any scientific evidence. However, acupuncture can be helpful in cancer treatment without any side-effects. The response towards CAM is varied between person to person. Herbal medicine is not only useful in the cancer treatment but also useful in other human diseases as therapeutic factors without any side-effects.

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