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Ginseng phytochemicals as therapeutics in oncology: Recent perspectives

Fatima Majeed[a], Fozia Zahur Malik[a], Zaheer Ahmed[a,**], Asma Afreen[a], Muhammad Naveed Afzal[b], Nauman Khalid[c,d,*]

[a] Department of Home and Health Sciences, Allama Iqbal Open University, Islamabad, Pakistan
[b] School of Health Sciences, University of Management and Technology, Lahore 54000, Pakistan
[c] School of Food and Agricultural Sciences, University of Management and Technology, Lahore 54000, Pakistan
[d] Center of Chemistry and Biotechnology, Deakin University, Waurn Ponds, Victoria, 3217, Australia

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ABSTRACT

During the last few decades, cancer has mushroomed as a major health issue; and almost all drugs used for its therapy are very toxic with lethal side effects. Complementary and alternative medicines gain popularity among health professionals in recent era owing to its preventive mechanism against side effect chemotherapeutic drugs. Efforts are focused by scientists to isolate compounds from medicinal plant that have chemotherapeutic attributes; and ability to neutralize the side effects of chemotherapy. Ginseng is an oriental medicinal recipe from Araliceae family and Panax species. The chemotherapeutic effect of ginsenoside is resultant of its appetites, antiproliferative, anti-angiogenic, anti-inflammatory and anti-oxidant properties. The anticancer effect of ginseng is proven in various types of cancer, including; breast, lung, liver, colon and skin cancer. It increases the mitochondrial accumulation of apoptosis protein and downregulate the expression of anti-apoptotic protein. It also aids in the reduction of alopecia, fatigue and nausea, the known side effects of chemotherapeutic drugs. The aim of the present review is to provide the brief review of the recent researches related to mechanism of action of ginseng in different types of cancer as complementary and alternative medicine on different body organs.

1. Introduction

Cancer is a disease which involves abnormal growth of cells with the potential to proliferate and spread into the surrounding tissues. It is a genetic disease which can be inherited by parents or by deoxyribonucleic acid mutation by certain carcinogenic substance e.g., tobacco smoke, pesticide residue; and ultraviolet rays from sun [1]. Human body is constituted of variety of cells; where epithelial cell constitutes 70% of total number of body cell. Epithelial cells are among those which are majorly affected by cancer owing to malignant progression. The tumor cell can be proliferated to the surrounding tissues by mean of lymph nodes, organ and body tissue and called as metastasis. The metastasis occurs in cancerous cell due to downregulating of tumor suppressor gene i.e. P53 [2]. According to global burden of cancer study, 14.1 million new cases and 8.2 million mortality occurred due to cancer throughout the world in 2012 [3].

Complementary and Alternative Medicine (CAM) is termed as a healthcare practice, products, and therapies that are typically not - part of conventional medicine e.g., acupuncture, dietary supplements, massage therapy, and yoga. These are used with or without standard medical care [4]. In clinical practice, dietician can help oncology patient to the effective use of CAM products to prevent the chemotherapeutic effects [5]. From last few years, CAM gain popularity in tumor patient due to enhancement in body immunity against cancer or improvement in physical and mental health [6]. In industrialized countries, 25–50% people used CAM [7]. Chemo preventive effect of CAM may be the resultant of its apoptotic, anti-proliferative, anti-angiogenic, anti-inflammatory and antioxidant properties. Ginseng ability to kill tumor cell and relative nanotoxicity to normal cell make it attractive candidate for used as CAM product. There is no recent review available on the ginseng role on organ specified anti-cancer property. So, purpose of this review is to provide recent knowledge related to the anti-cancer activity of ginseng on different body organs i.e., breast, colon, liver, lung and skin.

2. Composition of ginseng

Ginseng usage in oriental medicinal recipes is thousands years old; but majority of the people standpoint that ginseng cultivation started around three hundred years ago [8]. There are many kinds of ginseng in

* Corresponding author at: School of Food and Agricultural Sciences, University of Management and Technology, Lahore 54000, Pakistan.
** Corresponding author at: Department of Home and Health Sciences, Allama Iqbal Open University, Islamabad, Pakistan.
E-mail addresses: zaheer.ahmed@aiou.edu.pk (Z. Ahmed), nauman.khalid@umt.edu.pk (N. Khalid).

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the world, and all are belonged to the *Araliaceae* family in the *Panax* species. The name *Panax* originates from the Greek words means all-healing whilst ginseng comes from Chinese word "*Jen Sheng*" means man-root. The faith is established that ginseng can be beneficial for all aspects of the human body due to the humanoid shape of the root and rhizome of plant [9]. Many species of ginseng are used all over the world, but two most common used species are *Panax ginseng* (Chinese ginseng) and *Panax quinquefolius* (American ginseng). Ginseng is also classified according to their preparation method into fresh ginseng (sliced and eaten without any treatment), white ginseng (dried after peeling) and red ginseng (dried after steaming) [10].

Ginseng used as herbal medicine in the Eastern Asia, especially in Korea and China. A case control study was conducted in South Korea which included 4587 individuals, aged 39 years and older from 1987 to 1991. The result showed that the incidence of death among ginseng user is 60% less as compared to non-ginseng user [11]. Another clinical study was performed in Korea from 1987 to 1992 that shows ginseng user have reduced relative risk (0.40) in comparison to non-ginseng user (0.28) [12]. A case-control study was conducted in Korean Cancer Control Hospital on 1987 pairs, which told that the ginseng help to reduce the risk of cancer among ginseng consumer as compared to non-consumer [13].

The meta-analysis of different research studies shown that ginseng use might be linked with the lower risk of cancer. In a study, the result of reduced cancer risk by ginseng consumption in China had no significant inverse relationship in comparison to Korea. The effect of ginseng as a reduced cancer risk factor is only confirmed in Korea, China and United State. The difference in ecology and population distribution, we cannot manipulate the result from rest of the world. There is need of other study to verify its impact in other countries [14]. In December 1997–December 2008, a randomized, double-blinded, placebo-controlled trial were conducted in four hospitals of Zhejiang Province, China which included 643 chronic atrophic gastritis patients and divided randomly into two groups; Placebo and treatment group. All patient in treatment group take 1g of ginseng extract powder orally in every week for three years and to figure out the impact, the patients were followed up for 8 years. During the study, 16 cases of different type of cancer were diagnosed in placebo group while 8 in treatment group. The treatment group decreased the risk of cancer development (RR = 0.54) in comparison to the placebo group, which has non-significant difference as p value was 0.13 [15].

The pharmacological active ingredient is present throughout the ginseng plant. The main anti-cancer ingredient in ginseng is ginsenoside, which mainly present in root. The root content of ginseng is highly regarded which makes ginseng one of the most expensive and popular herb all over the world [16]. Ginseng root is recognized as king or lord of herb. The three key ingredients of ginseng are saponins, polysaccharides and phenolic compounds [17].

2.1. Saponins

Saponins are main components of ginseng and are recognized as primary pharmacologically active components; ginsenosides is alternative name for saponins [18]. Ginsenoside from ginseng are categorized into two different groups; based on their chemical structure known as oleanane type (five ring structure) and dammarane type (four ring structure). The dammarane type ginsenoside are the major components of ginseng which can be further categorized into two groups based on aglycone bond i.e. 20(S) protopanaxatriol (Re, Rg1, Rh1 and Rg2) and 20(S) protopanaxadiol (Rg3, Rd, Rb3, Rc, Rb1, Rb2). There are 50 types of ginsenosides, separated from the roots of ginseng plant [19]. The oleanane type ginsenoside are anabolic compound of B-amyrin, which are found rarely in ginseng e.g., Ro that is acidic in nature. Many new ginsenoside named as 25-OH-PPD and 25-OH-PPT were recently separated from ginseng berries [20].

2.2. Polysaccharides

Ginseng have two type of polysaccharides, one of them is composed of starch like glucan known as neutral polysaccharide and other is acidic polysaccharide [21]. Acidic polysaccharide have more anti-tumor and anti-oxidant property as compared to neutral polysaccharides [22]. *Panax ginseng* have immunomodulating glycans, ginsenan PB and ginsenan PA [23]. Korean ginseng root extract have panaxans (M, N, O, P, I, J, K, L, A, B, C, D and E) [24].The red ginseng has 7.5% polysaccharide which is three times higher to the white ginseng (0.63%) due to degradation of sugar molecule in the process of preparation of red ginseng by steaming and drying white ginseng [25]. According to Rapp, Pater, Willan, Cormier, Murray, Evans, Hodson, Clark, Feld and Arnold [26] the acidic polysaccharide of ginseng produced nitric oxide (NO) without changing morphology of RAW264.7 macrophage cells. The production of NO in RAW26.7 cell is due to the upregulation of nuclear transcription factor (Ap-1, ATF-2, STAT-1, CREB and Nf-kB).

2.3. Polyacetylene

The ginseng also contains non-water soluble polyacetylene compound. Takahashi and Yoshikura [27] initially isolated the panoxynol polyacetylene compound from ginseng [28]. The polyacetylenes of ginseng does show effect against cancerous cell but in vivo there is no proven fact present owing to their wobbly chemical nature [19]. Most recently researches demonstrate that ginseng acts as a chemo preventive agent owing to its anti-cancer and anti-oxidant properties. In future, ginseng has potential to be used as chemo preventive agent due to its properties related to apoptosis and anti-proliferative mechanism against cancer.

3. Ginseng role in chemotherapy

It is well established fact that chemotherapy has many side-effects, which impacts the patient's quality of life [29]. Ginseng has the magic to minimize the side effects of chemotherapy including; hair-loss, nausea, fatigue and if exercised in combination with other chemo drugs it leads to augmented anticancer activity. A clinical trial was conducted in BenQ Hospital of China. In which 96 patients of Non-Small Cell Lung Carcinoma (NSCLC) were added from January 2013–January 2016. These were distributed randomly in two groups, each group have 48 patients with average age of 32–66 years. The same foundation treatment was given to both groups. The control received dendritic cell (DC) and treatment group received Ginseng Polysaccharides (GPS) with dendritic cell under thoracoscope. The Functional Assessment of Cancer Treatment- Lung ((FACT-L)) was measured to access the quality of life. The (FACT-L) score was decreased in both groups but control group had higher value as compared to the treatment group. The Serum interferon-γ (INF-γ), interleukin-4 (IL-4), IL-2 and IL-5 were measured in both groups before and after treatments. The expression of Th1 cytokines (IL-2, INF-γ) and the ration of the Th1/Th2 cytokines (INF-γ/IL-4, IL-2/ IL-5) is increased and expression of Th2 (IL-4, IL-5) decreased significantly during foundation treatment. When treated with DC and GPS, the treatment group had higher value of Th1 and ratio of Th1/Th2 and lower value of Th2 as compared to the control group. The result showed the GPS with DC have synergic effect on NSCLC patients [30].

Ginseng helps to boost the antitumor effect of epirubicin and paclitaxel drugs by increasing the mitochondrial accumulation of Bax and Bak that mediate cell death by apoptosis. Alopecia is one of the major stressful and negative psychological effect on patient undergoing chemotherapy [31]. It is reported that Korean red ginseng (KRG) helps to promote the hair growth [32]. Cyclophosphamide is a chemo preventive drug which formed metabolite 4-hydroxycyclophosphamide (4-HC) by liver cytochrome P450 (CYP) enzyme and exhibited an anticancer effect [33]. 4-HC clogged human hair growth by enhancing

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