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The Efficacy of Some Comestible Natural Products in Treatment of Cancer

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Abstract

Despite the fact that cancer is primarily a preventable disease, recent statistics indicate cancer is the number one killer worldwide. Conventionally, cancer therapy includes surgery, radiation and drugs, separately or in combination. This modality of cancer treatment is still not successful. Therefore, the identification of new cytotoxic drugs with low or none side effects is of great interest worldwide. Since traditional medicines have been used for maintaining health, as well as in the prevention, therapy and remission of cancer, natural products can serve as chemopreventive and chemotherapeutic agent. Here, we describe the efficacy of 3 comestible natural products such as garlic, green tea and cruciferous vegetables in cancer therapy.

Keywords: Efficacy; Garlic; Green tea; Cruciferous vegetables; Cancer; Treatment

Introduction

Cancer is the biggest cause of mortality worldwide, responsible for 8.2 million deaths per year and rising, according to a global scientific report released on the 05th of February 2014 [1]. The causes of this rise in cases of cancer are still unknown. However, factors such as obesity, poor diet, tobacco, radiation, environmental pollutants, lack of physical activity and age increase cancer risk. These factors may cause cancer by damaging genes directly and/or indirectly in combination with existing genetic mutations within cells [2].

For decades cancer treatment has followed 2 beneficial regimens - chemotherapy and radiotherapy. However, these regimens are expensive and have toxic effects [3,4]. Moreover, the appearance of drug resistance makes many well-known and established anticancer drugs ineffective [5]. Therefore, a large number of patients prefer complementary and alternative medicines for treating and managing cancer symptoms and pain [3]. Research on anticancer agents is of particular interest in both developed and developing countries. One of the main strategies has been the isolation of secondary metabolites or the synthesis of analogues from natural sources, based on their use in traditional medicine [6]. In the USA for example, as of 2010, more than 60% of the approved anticancer drugs was of natural origin [7-9]. Increasingly, more medicinal plants are being screened for anticancer properties and may provide modern medicine with effective therapeutic agents. The purpose of this review is to give an overview of the efficacy of some comestible medicinal plants such as garlic, green tea and Cruciferous vegetables from epidemiological data to clinical trials through preclininal data.

Garlic

Epidemiological studies

Garlic, also known as *Allium sativum* is used traditionally for a number of applications including improving performance, protection against toxins and treating cardiovascular disease, diabetes, infections, and cancer [10]. Phytochemical analysis reveals that Garlic contains arginine, oligosaccharides, flavonoids, and selenium, all of which may be beneficial to health [11]. Anticancer effects of garlic are ascribed to sulphur-containing compounds. Initial evidence for the cancer-protective role of *Allium* vegetables emerged from population-based case–control studies [12-16]. They showed an association between increased intake of garlic and reduced risk of stomach, colon, esophagus, pancreas, and breast cancer. For example, in the European Prospective Investigation into Cancer and Nutrition (EPIC) study investigating the effects of nutrition on cancer, the risk of intestinal cancer was reduced in higher intakes of onion and garlic [17]. Similarly, in the Iowa Women's Study, which is a large prospective study, women who consumed the highest amounts of garlic had a 50% lower risk of cancer of the distal colon compared with women who had the lowest level of garlic consumption [18]. Evidence also suggests that increased garlic and scallion consumption may reduce prostate cancer risk (50%) [19] and pancreatic cancer risk (54%) [20]. Moreover, intake of garlic onions and fiber, was inversely associated with the risk of breast cancer in a French case–control study [16].

Preclinical studies

Animal studies: In preclinical studies, Garlic-derived organosulfur compounds including diallyl sulphide (DAS), diallyldisulfide (DADS), and daillyltrisulfide (DATS) (major volatile components of garlic oil), ajoene, S-allyl cysteine (SAC), and garlic extracts are documented to inhibit lung, liver, prostate and skin tumours development in animal models transplanted as well as spontaneous cancers in preclinical animal models without any adverse side effects [21-23]. For example, the effect of DATS at the dose of 2 mg/mouse/twice a week was administered orally at 2-week intervals to A/J female mice has been reported. In this study, the treatment with DATS was done prior to challenge with an environmental carcinogen (benzo(a)pyrene). They

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authors showed that DATS decreased the tumour multiplicity for about 85% in forestomach [24,25]. It is noteworthy to mention that DATS did not inhibit the pulmonary adenoma formation [24]. We could interpret it as plausible tissue selectivity. However, the study was directed toward the measurement of glutathione-S-transferase activity and the treatment regimen was then conceived in order to trigger its expression. Therefore, the use of different treatment regimens is needed in order to clarify the effects of DATS on other tumour types. Years later, some authors reported the effects of DATS on other cancer types using xenograft models. They showed that oral administration of 6 μmoL DATS/mouse (three times per week) [26] and 40 mg DATS/kg (five times/week) [21] to PC-3 human prostate cancer xenograft-bearing male athymic mice inhibited tumor growth [21,26]. Moreover, 5 μmol DATS/kg (twice/week) to MCF-7 human breast cancer xenograft-bearing female Balb/c nude mice resulted in retardation of the tumour growth [27]. Taken together these data suggest that garlic extracts inhibit several tumours developed in animal models.

***In vitro* studies:** The molecular mechanisms of action underlying the anticancer effect of garlic and its secondary metabolites have also been reported, although not yet fully understood. DATS inhibited oestrogen receptor-α (ER-α) activity in human breast cancer cells [28]. DATS suppressed proliferation and induced apoptosis of human colon cancer cells through oxidative modification of β-tubulin [29]. DATS also induced apoptosis and G1 phase arrest in human colon cancer cells [29,30]. DATS induced apoptosis through modulation of Bcl-2 expression and phosphorylation of JNK and ERK in human prostate PC-3 cells [31]. DATS treatment resulted in apoptotic cell death in breast cancer cells (MCF-7, MDAMB-231, and BRI-JM04) regardless of the p53 or human epidermal growth factor receptor-2 status [32]. DAS on the other hand, decreased the cell growth of HEK 293T keratinocytes through inhibition of cyclooxygenase-2 [33]. In NCI-H460 and NCI-H1299 non-small cell lung cancer cell lines, DAS increased cell death through regulation of the expression of Bcl-2, Bax, and p53 [34].

Clinical studies

At the clinical level, three randomized trials have been performed in order to evaluate garlic intake efficacy on gastric cancer risk, two studies showed a decrease while one showed no reduction. In fact, in the study which involved over 5,000 Chinese men and women at high risk of developing stomach cancer, a 33% and 52% decrease was reported in the risk for all cancers and gastric cancer respectively in the group that received allitridum (200 mg) and selenium (100 mg) compared to the placebo-treated group for 5 years [35]. Conversely, in another study involving individuals with precancerous stomach lesions treated with garlic supplements, there was no improvement in the prevalence of precancerous gastric lesions as well as no decrease in the incidence of gastric cancer [36]. This seems contradictory. There is a challenge to compare data from studies that used different garlic products and amounts in different conditions. However, based on preclinical data, the efficacy of garlic is undeniable and intervention studies are needed to determine potentially effective intakes.

Green Tea

Epidemiological studies

Green tea is one of the most popular beverages around the world. For several decades, numerous epidemiological, preclinical and clinical studies have demonstrated that Green Tea Polyphenols (GTPs), especially epigallocatechin-3-gallate (EGCG) have cancer-preventing effects on various cancers [37]. Wu and Butler [38] reported in a meta-analysis a significant inverse association between green tea consumption and breast cancer incidence [38]. Moreover, in two Japanese cohort studies, high daily green tea intake among patients with breast cancer has been associated with a decrease in risk of recurrence and mortality [39,40].

Preclinical studies

Many studies reported a protective effect of green tea and its secondary metabolites on chemical carcinogens in intestine, lung, liver, prostate, and breast [41]. Li et al. [42] showed that oral administration of 0.6% green tea in water reduced the incidence of dysplasia and oral carcinoma in 7,12-dimethylbenz[a]anthracene (DMBA)-induced oral carcinogenesis in hamster [42]. In two different models of lung tumours namely the 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)- and the Lewis lung carcinoma cells-induced lung tumours, green tea also significantly reduced the number of tumours [43,44]. Green tea also inhibits the growth and the progression of DMBA-induced mammary carcinogenesis [45] and prostate cancer in Transgenic adenocarcinoma of the mouse prostate (TRAMP) [46]. In addition, in a study using the C3(1)/SV40 mouse model which more closely mimics the development and progression of human breast cancers, the administration of 0.5% Polyphenon E in drinking water inhibited mammary tumour growth [47].

The molecular mechanisms of action that underpin these anti-tumorigenic effects of green tea extracts are diversified. They involved the alteration of circulating hormones, inhibition of cancer cell proliferation and induction of apoptosis. In fact, green tea extracts favorably influenced several markers of breast cancer risk such as circulating estrogens, androgens, and mammographic density [38]. Epigallocatechin-3-gallate (EGCG) influenced cell growth and inhibited cell proliferation and angiogenesis [48]. Yu et al. [49] also showed that EGCG induced apoptosis of preneoplastic and neoplastic cells [48].

Clinical studies

In human studies using controlled green tea, the efficacy of green has been reported in breast cancer patients in a pre-surgical study, and after the completion of the standard treatment including chemotherapy and radiation [49-51]. In the pre-surgical study investigating markers of cell proliferation (Ki-67) and apoptosis [cleaved caspase-3 (casp-3)] in patients diagnosed with breast cancer, Yu et al. [49] showed a reduction in cell proliferation marker Ki-67 in association with green tea supplementation [49]. Moreover, Nguyen et al. conducted a randomized, double-blind, placebo-controlled trial of Polyphenon E in men with prostate cancer [52]. They showed that there was a trend of reduction in Gleason score, and larger reductions in PSA levels and oxidative DNA damage in the green tea group [52]. Both studies were short-term studies, making the conclusion on the efficacy of green tea in cancer therapy quite elusive. Randomized studies with longer-term follow-up may help to correlate the reduction of markers such as Ki-67 and PSA with improved outcomes.

Cruciferous Vegetables

Epidemiological studies

Cruciferous vegetables (CV) - cabbage, broccoli, brussels sprouts, cauliflower, and other members of the family - are a group of vegetables

named for their cross-shaped flower petals. CV contain a variety of anticancer constituents such as glucosinolates, the precursors of isothiocyanates (ITC) as well as indole-3-carbinol (I3C), both of which may contribute to a reduced risk of a variety of cancers [53-56]. In a case control study in Italy, CV prevented gastric cancer through their cleansing action, removing or diluting the carcinogens from the epithelial surface [57]. In addition, five recent meta-analyses also provided evidence that CV intake was inversely associated with colorectal, gastric, renal, bladder and breast cancers [58-61].

Preclinical studies

In animal studies, oral administration of I3C inhibited the development of cancer in a variety of animal models [62-64]. However, a number of animal studies have found that I3C actually promoted or enhanced the development of cancer in a long-term treatment [65,66]. DIM (3,3′-diindolylmethane), formed by the conversion of I3C in the acidic environment of the stomach, is also an antitumorigenic agent in carcinogen-induced mammary cancer in Sprague–Dawley rats and breast cancer xenografts in nude mice [67,68]. DIM has been shown to induce G1 cell cycle arrest and to increase apoptosis in oestrogen receptor alpha positive and negative breast cancer cells (MCF-7, MDA-MB-231) [69,70]. Chinnakannu et al. reported that DIM increased growth arrest and death of prostate cancer cells [71]. Because of few side-effects of both I3C and DIM in humans and their various potential anticancer properties, further studies in humans should resolve questions about safety issues and demonstrate their efficacy as chemopreventive and/or therapeutic compounds [72,73].

Conclusion

Cancer is the leading cause of death worldwide. Epidemiological and preclinical studies indicate that the consumption of vegetables and fruits with natural chemopreventive agents alone or in a mixture is associated with a reduced risk of cancer development. Focusing on garlic, green tea and cruciferous vegetables, we found that they contain secondary metabolites endowed with chemopreventive and chemotherapeutic activities on various cancers. However, further studies are needed to translate findings in basic research into controlled human clinical trials. These randomised human trials may lead to significant therapeutic outcomes and probably rationalize the use of these comestible medicinal plants as novel anticancer drugs.

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