MINI-REVIEW

Preventive and Therapeutic Roles of Ginseng - Focus on Colon Cancer

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Abstract

Colorectal cancer is one of the most prevalent diseases all over the world. Early screening and start of chemotherapy is effective in decreasing mortality. This type of cancer can be controlled to some extent via a healthy diet rich in fruit and vegetables. Ginseng is a plant which has been consumed as a herbal medicine for thousands of years in Asian countries. Several *in vitro* and *in vivo* studies have shown that this plant not only reduces the incidence of colorectal cancer, but also improves patient's status by enhancing the effects of chemotherapy drugs. However, further studies are needed to prove this relationship. We briefly review ginseng and its components such as ginsenosides reported anticancer effects and their mechanisms of action. Understanding these relationships may produce insights into chemical and pharmacological approaches for enhancing the chemo preventive effects of ginsenosides and for developing novel anticancer agents.

Keywords: Ginseng - colon cancer - Rg3 - Rh2 - anticancer compounds

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Introduction

Colorectal cancer is the second leading cause of cancer death in Western countries and the third most common cancer in the world (Nourazarian et al., 2012). In 2010, 715,000 deaths due to cancer incidence have been recorded (Lozano et al., 2013). Although early-stage of cancer treated with surgical resection, often it is treated with combined methods of radiotherapy and chemotherapy (Mano and Duhoux 2008). Chemotherapy has always been with disadvantage effects for patients, adverse effects associated with the medication not only worsen the patient's quality of life, but rather, causes patients to refuse further chemotherapy (Martin et al., 2003). Thus, the need to identify non-toxic chemicals extracted from herbal medicines for cancer treatment is a major goal.

Ginseng is one of the herbs that have a great reputation in the treatment. It is a plant of the *Araliaceae* family named scientifically *Panax ginseng* (Kennedy and Scholey, 2003). Ginseng plays crucial role in maintaining good health and its coordination of activities. There have been many studies on the herb and it is now effective in the treatment and prevention of many chronic diseases and cancers (Bucci 2000; Kim 2008). According to some investigation done ginseng has some anticancer effects by different mechanisms (Yun 2003b; Wen, et al., 2010). The most important of these mechanisms, such as 1- Regulation of cell cycle, (Se et al., 1999) 2- Induction of apoptosis (Se et al., 2009) 3- Inhibition of angiogenesis (Yue et al., 2006) 4- reduce inflammatory responses, (Oh GS et al., 2004; Kimura et al., 2006)

According to previous studies ginseng can be beneficial in the treatment and prevention of colorectal cancer (Yun and Choi 1995; Yun et al., 2001; Yun 2003a). The aim of this study was to review relevant literature on ginseng effects on colorectal cancer.

About Ginseng

The ginseng plant has been used for 5,000 years (Kennedy and Scholey, 2003). The use of this herb has been spread worldwide due to its therapeutic effects. Well-known biochemical and pharmacological effects include anti -aging, anti-diabetic, anti- fatigue, along with promoting the synthesis of DNA, RNA and proteins (Attele et al., 2002; Xie, Mehendale, and Yuan 2005; Christensen 2008; King and Murphy 2010). Studies have also shown that ginseng has beneficial effects on the central nervous system, cardiovascular system, and immune system (Block and Mead, 2003; Qi, et al., 2010) Cancer prevention and inhibition of tumor growth are among other effects (Shin et al., 2000; Shibata 2001; Wang et al., 2007; King and Murphy, 2010). The herb is used as ginseng tea, extract, or raw directly from powdered root (Bucci 2000). Two major species include *Panax ginseng*, or Asian ginseng, and *Panax quinquefolius* L, or American ginseng (Kitts and Hu, 2000; Jia et al., 2009). Ginseng bioactive compounds in Asian and American

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ginseng species contain Triterpene glycosides or saponins, which are generally regarded as ginsenosides (Xie et al., 2009). It has been shown that ginsenosides are the most effective agents in the treatment and prevention of cancer in ginseng. More than 60 different types of ginseng have been identified (Nakamura et al., 2007; Qu et al., 2009). that are in different parts of the plant including roots, leaves and fruits. Because different parts of the plant contain different ginsenosides contents (Xie et al., 2009). Therefore every part of the plant's medicinal activity may be different. Ginsenosides are categorized in three major groups based on triterpene aglycones include panazydol and panaxytriol and oleanolic acid derivatives (Chang et al., 2003; Kim and Lee, 2010).

Other chemical compounds extracted from *Panax ginseng* include alkanes, alkynes and sterols, fatty acids, mono- triterpene, phenylpropanoids, kairomones, carbohydrates (sugars and polysaccharides), amines, flavonoids, organic acids and vitamins. Also amino acids, nucleic acids, various enzymes and inorganic compounds (including germanium) are obtained from ginseng (Chang et al., 2003). There are concerns about toxicity of ginseng. Studies show toxicity due to improper use or overdose causes hypertension, sleep disorder, nervousness, diarrhea and depression (Coon and Ernst, 2002; Kiefer and Pantuso, 2003). Thus, due to poisoning effects of ginseng, care should be taken of overuse of the plant.

Effect of Ginseng on Colorectal Cancer

Numerous studies have been conducted on the effects of ginseng in colorectal cancer; most of these studies have been carried cell line. Treatment of HT-29 cells with a fermented ginseng extracts using high concentration of effective ginsenosides causing enhanced the anti-proliferative and the anti-invasive activity against human colon cancer cells (Park et al., 2011).in other study treatment of HCT116 and SW480 colorectal cancer cells with ginsenoside Rh2 activated the p53 pathway and significantly increased the levels of the pro-apoptotic regulator, Bax and decreased the levels of anti-apoptosis regulator Bcl-2. The anti-cancer effect of Rh2 was enhanced by antioxidants (Li et al., 2011).also treatment of HT-29 colorectal cancer cells with Ginseng polysaccharide fraction shown the increased in antiproliferative effect (Cheng et al., 2011). P 21 functioned to arrest HCT116 wild-type cells treated with water- extracted ginseng, while p21-deficient cells underwent cell death in a ginseng constituent-dependent manner (King and Murphy 2010). Treatment of HCT116 and SW480 colorectal cancer cells with steamed and unsteamed American ginseng berries increased the antiproliferative effects (Wang, Xie, et al., 2009). In a study carried out by Li and Colleagues treatment of HCT116 and SW480 colorectal cancer cells with 4h-steamed American ginseng root extract induced mitochondrial damage, increased reactive oxygen species (ROS), and apoptosis in colorectal cancer cells. The anti-cancer effect of steamed ginseng was enhanced by antioxidants or inhibitors of the NF-κB pathway (Li et al., 2010)

Previous studies have shown that *Panax ginseng* has anticancer activity (Shin et al., 2000; Shibata, 2001; Wang and Yuan 2008; Kim and Lee, 2010). An epidemiological study on 1000 subjects in Korea showed reduced the risk of a number of cancers including colorectal cancer in those taken Asian ginseng compared with those who did not use it (Yun and Choi 1995; Yun, Choi, and Yun 2001). Studies on ginsenosides especially Rg3 and Rh2 showed that they are most effective anti- cancer compounds identified in ginseng (Kim et al., 2004; Helms 2004; Li et al., 2009; Liu et al., 2009; Lee et al., 2009).

East Asian countries Asian *Panax ginseng* is steamed and is called red ginseng, red ginseng air dried is called white ginseng .Studies have shown that anti-cancer effects of red ginseng are stronger than white ginseng (Wang, Xie, et al., 2009; Xie et al., 2009). The steaming process alters ginseng content and is a good way to convert all kinds of ginsenosides to strong anticancer compounds such as Rg3 and Rh2 (Xie, 2009). In one study it was shown that the extract, Rg3 and Rh2 amount was minimal in not steamed extracts (0.06 %), followed by boiling for 4 hours ginsenosides Rg3 and Rh2 contents increased up to 7.8% and 1.2 %, respectively (Wang et al., 2009). The antiproliferative effect of American ginseng on cancer cells also increased significantly by boiling (Wang et al., 2007). In another study the effects of two types of boiled and not boiled ginseng on the cell line of Colorectal Cancer including HCT-116 and HT-29 and SW-48 showed that the boiled roots of the herb, although with less total ginsenosides content than the not oiled extract, it showed significantly more powerful antiproliferative effect than not boiled type (Xie et al., 2009). Some studies have also been conducted on the effects of ginsenosides on Colorectal Cancer that show that ginsenosides Rb3 has no significant antiproliferative effect in colorectal cancer cells, but Rg3has a strong antiproliferative effect on these cells (Xie et al., 2009; He et al., 2011).

Chronic inflammation is associated with increased cancer risk (Qi et al., 2010) . Studies have shown that ginseng plays a role in inflammation reduction and thereby reduces the risk of cancer (Keum et al., 2003; Hofseth and Wargovich 2007). In another study it was shown that the anticancer effect of steamed ginseng is enhanced with antioxidants (Li et al., 2010).

Ginseng more than its role in reducing the risk of cancer, improves the condition of patients in cancer treatment. This herb is effective in improving patients undergoing chemotherapy and reduces chemotherapy side effects (Wang et al., 2007). Also, studies have concluded that noto ginseng root extract enhances two chemotherapy drugs, 5-fluorouracil and irinotecan activities (Fishbein et al., 2009; Li et al., 2009), such that cell growth is enhanced by noto ginseng root extract combined with 5-fluorouracil and showed a greater reduction than drug used alone (Wang et al., 2007).

Ginseng Mechanism of Action in the Treatment of Colorectal Cancer

Although the mechanism of Ginseng on inhibition of colorectal cancer cells is unclear, several previous studies, such as being an antioxidant, being carcinogens

metabolism regulator, anti-inflammation and apoptosis have been suggested as possible mechanisms (Xie et al., 2009). Apoptosis is the main mechanism of ginseng (Lee et al., 2000). Ginseng anticancer effect of Asian boiled ginseng probably is not directly due to cancer cells destruction and instead may be due to the induction of apoptosis. Apoptosis is a selective process to physiologically destroy cells to maintain balance between cell proliferation and cell death. Ginseng herb induces apoptosis via two different paths: Intrinsic mitochondrial-mediated, pathway and extrinsic death receptor-mediated, pathway.

In the first method ginseng alters mitochondrial membrane permeability and increases cytochrome C relase into the cytosol, activates Caspase 3 and 9, and breaks poly ADP ribose polymerase. Also cyclin kinase activity during induced apoptosis by ginsenosides may be related to mitochondrial membrane potential depolarization.in the second path ginsenosides increases death receptor DR4 expression and activate caspase 3 and 8 (Qi, Wang, and Yuan 2010).

Reports have indicated that ginseng or ginsenosides may have direct anticancer effects (Wang and Yuan 2008; King and Murphy, 2010)Several ginsenosides like Rh2, Rg3, Rk1 exhibited anti-proliferative and anti-angiogenesis effects in vivo and *in vitro* (Iishi et al., 1997). in terms of the mechanisms these ginsenosides inhibit NF-kB pathway and inhibits cell proliferation and induces apoptosis in cancer cells. This beneficial effect of ginsenosides might be due to cell cycle arrest in cancer. It seems that the G1 phase and G1/S checkpoint are blocked by different mechanisms of ginsenosides (Qi, Wang, and Yuan 2010; Park et al., 2011) .this cell arrest is involved with tumor suppressor proteins up-regulation of P53 and P21 tumors and down regulation of cyclin and CDK including the CDK 2, cyclin E and D1 in G1 phase and G1/S checkpoint (Park et al., 2011).

In one study it was shown that red ginseng has the cancer-preventive properties and metastasis through inhibition of the MMP pathway (matrix metalloproteinase) (Seo and Kim, 2011).

Conclusions

According to the studies reviewed, it seems that Asian and American ginseng both play important roles in colorectal cancer treatment, especially if steamed or boiled. It seems that the bioactive compounds in ginseng, ginsenosides Rg3 and Rh2 produce the most anticancer effects; however, there is a need for further studies in this field to confirm this.

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