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Review

A Comprehensive Review on the Health Benefits of Black Garlic

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Abstract

Black Garlic (*Allium sativum*) and its derivatives have been documented to have multiple biological impacts on health promotion and treatment of various diseases. The transformation of fresh garlic to Black Garlic results in modifications in the biological activity of bioactive compounds caused by fermentation. In the past few decades, extensive pre-clinical investigations have shown the therapeutic potential of BG against a wide variety of human diseases. Nowadays black garlic is most commonly used as a flavoring agent in many cultures and is consumed in large quantities particularly in Korea, Japan, and Italy. When administered as a supplement, black garlic is most often taken raw or in an enteric-coated tablet. It is primarily used as a supplement in treating cardiovascular disease, particularly atherosclerosis. Other uses include protection against viruses such as the common cold. Considering the above facts in view, this review provides comprehensive information on the process of black garlic production and its health benefits.

Keywords: Black garlic, *Allium sativum*, flavoring agent, cardiovascular disease, viruses.

Introduction

Garlic, *Allium sativum*, is part of the Liliaceae family and has a long history in folk medicine in a variety of cultures across the world. Although many of these cultures developed independently of each other, the wide availability and durability of garlic in a variety of conditions have produced similar uses of garlic in several different locations and times in history. Garlic is native to the Tien Shan and Pamir-Alai mountains of southern central Asia. Because of its compact and durable structure, garlic is thought to have been a food source for the nomadic hunter-gatherers more than 10,000 years ago (Cumo, 2017). As garlic made its way around the globe, one of the earliest references to its usage comes from the ancient Egyptians, who used garlic to strengthen their slaves for manual labor, including building the pyramids. One of the earliest records of garlic in medicine and the authoritative medical text at the time, the *Codex Ebers*, prescribed garlic as a method of treatment for abnormal growths, circulatory issues, general malaise, and parasitic infestations (Rivlin, 2001).

Black garlic and its production

The people from Asian countries such as Thailand, South Korea, and Japan have produced and used black garlic as a traditional food for centuries, but it has been introduced into global market in recent decades (Fig. 1).

Fig. 1. Black Garlic.

In brief, black garlic is produced by fermentation of whole bulb of fresh garlic at high humidity and temperature which in turn results in garlic to turn black via a set of non-enzymatic browning reactions, including Maillard reaction, oxidation of phenols, and caramelizing. When garlic undergoes fermentation, not only physiochemical characteristics of garlic are altered, but also the concentration of bioactive compounds is also improved (Kimura *et al*., 2017).

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Choi *et al.* (2014) showed that the moisture of garlic and pH decreased along with the fermentation process, whereas the reducing sugar and total acidity were accumulated. On the other hand, color spectra and composition of amino acids of black garlic also were altered as compared with fresh garlic. As the consequence, black garlic has elastic and chewy texture, as well as sweet taste without offensive flavor of garlic. Furthermore, black garlic possesses an abundant amount of antioxidant compounds such as polyphenols, flavonoids, tetrahydro-β-carboline derivatives, and organosulfur compounds, including S-allyl-cysteine and S-allyl-mercaptocysteine, as compared with fresh garlic. Kim *et al.* (2013) suggested that the total polyphenol and flavonoid of black garlic increase 9.3 and 1.5-folds, respectively, after a program heat schedule as compared with fresh garlic. The concentration of S-allyl-cysteine, one of the most important organosulfur bioactive compounds of garlic, also increases in black garlic from 4.3- to 6.3-folds depending of heating treatment (Bae *et al.*, 2014).

Antioxidant Activity of Black Garlic

Black garlic is believed to protect the body from free radicals. An imbalance between antioxidant levels and free radicals can lead to various diseases (Ende *et al.*, 2011). Black garlic is reported to have a higher antioxidant content compared to garlic (Jang *et al.*, 2018). The antioxidant effect of black garlic is related to the bioactive compound content in it (Azizah *et al.*, 2020). Free radicals are a form of reactive oxygen compounds that have unpaired electrons. Free radicals are often termed Reactive Oxygen Species (ROS). ROS include hydroxyl radical (•OH), superoxide radical (O2•-) singlet oxygen (1O2) and hydrogen peroxide (H_2O_2) (Ende *et al.*, 2011). Hydrogen peroxide is a relatively non-radical form of oxygen compounds (Jang *et al.*, 2018). Reactive Oxygen Species (ROS) attacks various molecules such as DNA, RNA, proteins, lipids, cofactors in enzymes, interferes with and destroys normal cell metabolism. The impact of the formation of ROS can be prevented by antidote to ROS by antioxidants. Free radicals can be controlled and resisted by donating electrons from antioxidants (Ende *et al.*, 2011). The antioxidant effect of black garlic is reported to be related to its chemical content in the form of flavonoids, alkaloids (Azizah *et al.*, 2020) phenolic (Jang *et al.*, 2018). Flavonoids and phenolics have antioxidant effects because these compounds have a 0H- group attached to an aromatic carbon ring that has the ability to donate hydrogen atoms, thus playing an important role in the level of antioxidant power (Prasonto *et al.*, 2017).
Antioxidant activity of garlic could be affected by processing (Querioz *et al.*, 2009). Aged black garlic recently available on the market in Korea is one of garlic products expected to have strong antioxidant capacity. It is produced by ageing whole garlic at high temperature (70°C) and high humidity (90% RH) (Jang *et al.*, 2008; Kang *et al.*, 2008). During ageing process, unstable compounds of fresh garlic including alliin are converted into stable compounds including s-allyl cysteine (SAC), the water soluble compound with potent antioxidant effect (Imai *et al.*, 1994; Corzo-Martinez *et al.*, 2007). It was reported that aged black garlic showed stronger antioxidant activity *in vitro* than garlic (Jang *et al.*, 2008).

Antidiabetic Activity of Black Garlic

It is well known that tight control of hyperglycemia and dyslipidemia is associated with the reduced risk for complications in diabetic patients (DCCT Research Group, 1993; UKPDS Group, 1998; American Diabetes Association, 1999;). In addition, there is accumulating evidence that antioxidants may be useful in the prevention of diabetic complications (Sinclair *et al.*, 1992; Lean *et al.*, 1999; Ceriello, 2006). Hyperglycemia in the diabetic state generates more reactive oxygen species (ROS) and free radicals (Maritim *et al.*, 2003) and the resulting oxidative stress plays a key role in the pathogenesis and progression of diabetes and diabetic complications (Kaneto *et al.*, 2005). It has been reported that both antioxidant nutrients and antioxidant phytochemicals can give an advantage in alleviating diabetes and diabetic complications (Sinclair *et al.*, 1992; Lean *et al.*, 1999,). Several studies have reported that garlic (*Allium sativum* L.) could have hypoglycemic (Eidi *et al.*, 2006; Al-Qattan *et al.*, 2008; Seo *et al.*, 2009) and antioxidant effects (Banerjee *et al.*, 2003). Consumption of 80% ethanol extract of garlic decreased serum glucose (Eidi *et al.*, 2006) and injection of garlic extract attenuated hypoglycemia and structural nephropathy progression in streptozotocin (STZ)-induced diabetic rats (Al-Qattan *et al.*, 2008). Consumption of diet containing 5% garlic powder significantly decreased serum glucose and total cholesterol in db/db mice, an animal model of type 2 diabetes (Seo *et al.*, 2009). Garlic extract showed 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity (Querioz *et al.*, 2009) and superoxide dismutase (SOD) activity *in vitro* (Jang *et al.*, 2008). Aqueous extract of garlic (500 mg/kg/d IP) increased total serum antioxidant levels in STZ-treated diabetic rats (Drobiova *et al.*, 2009). Hyperglycemia in the diabetic state increases oxidative stress and antioxidant therapy can be strongly correlated with decreased risks for diabetic complications. The purpose of this study is to determine antioxidant effect of garlic and aged black garlic in animal model of type 2 diabetes (Lee *et al.*, 2009). The antioxidant activity of garlic and aged black garlic was measured as the activity in scavenging free radicals by the trolox equivalent antioxidant capacity (TEAC) assay.

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Three week-old db/db mice were fed AIN-93G diet or diet containing 5% freeze-dried garlic or aged black garlic for 7 weeks after 1 week of adaptation. Hepatic levels of lipid peroxides and activities of antioxidant enzymes were measured. TEAC values of garlic and aged black garlic were 13.3 ± 0.5 and 59.2 ± 0.8 µmol/g wet weights respectively. Consumption of aged black garlic significantly decreased hepatic thiobarbituric acid reactive substances (TBARS) level compared with the garlic group which showed lower TBARS level than control group ($p<0.05$). Activities of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) of garlic and aged black garlic group were significantly elevated compared to the control group. Catalase (CAT) activity of aged black garlic group was increased compared with the control group. These results show that aged black garlic exerts stronger antioxidant activity than garlic *in vitro* and *in vivo*, suggesting garlic and aged black garlic, to a greater extent, could be useful in preventing diabetic complications.

Black Garlic and Obesity

Obesity has become a major public health problem. Obesity-related problems are linked to a variety of metabolic syndrome symptoms including high blood pressure, dyslipidemia, insulin resistance, and glucose intolerance. Various approaches might be employed in human obesity prevention and control. Since a perfect cure or prevention of obesity still remains to be established and the majority of the anti-obesity drugs could have adverse effects, an exploration into the identification of new materials has shown a growing interest. BG extracts have been reported for their activity in reducing body weight, adipose tissue mass, serum triglyceride, total cholesterol, low-density lipoprotein, and plasma malondialdehyde in mice with high-fat-diet-induced obesity (Lee *et al*., 2010; Chang *et al*., 2017). The fermentation of garlic by lactic acid bacteria ameliorated diet-induced obesity in db/db C57BL/6J mice by decreasing body weight (18%), lowered epididymal (36%), retroperitoneal (44%), and mesenteric adipose tissue mass (63%), respectively. Moreover, fermented garlic extract by lactic acid bacteria also down-regulated mRNA protein expression of proliferator-activated receptor γ (PPARγ), CCAAT-enhancer-binding proteins, and lipogenic proteins, including sterol-regulatory element-binding protein-1C (SREBP-1C), fatty acid synthase (FAS), and stearoyl-CoA desaturase-1 (SCD-1) (Lee *et al.,* 2016).

Anticancer Activity of Black Garlic

Garlic has been long recognized for its medicinal properties and has been used for sterilization and anti-inflammation throughout history. Allicin, the main active ingredient of garlic, is currently extensively investigated for antitumor therapy (Rajput *et al*., 2012). Black garlic is a type of fermented garlic. Numerous *in vivo* and *in vitro* studies demonstrated that aged black garlic possesses strong antioxidant and anticancer properties and may inhibit the proliferation of a variety of tumor cell lines by altering the cell cycle and inducing apoptosis (Shirzad *et al*., 2011; Cha *et al*., 2012; Kaschula *et al*., 2012). However, the underlying mechanisms have not been fully elucidated. A previous epidemiological investigation indicated that the development and progression of colon cancer is a complex, multistep and multifactorial process (Hammoud *et al*., 2013). The PI3K/Akt pathway is involved in intracellular signal transduction and mediates numerous cellular processes, including cell proliferation, migration and apoptosis. Dong *et al*. (2014) reported aged black garlic extracts (ABGE) may regulate the function of the PI3K/Akt pathway through upregulating PTEN and downregulating Akt and p-Akt expression, as well as suppressing its downstream target, 70-kDaribosomal protein S6 kinase 1, at the mRNA and protein levels. The HT29 cells growth inhibition rate at ABGE concentrations of 20, 50, and 100 mg/mL. ABGE inhibited the growth and induced apoptosis in HT29 cells through the inhibition of the PI3K/Akt pathway. Numerous studies demonstrated that allicin, an organosulfur compound obtained from garlic, has the ability to promote the apoptosis of tumor cells, cause cell cycle arrest and improve the antioxidant activity. Qian *et al*. (2004) reported the tumor cure rate by black garlic water extracts attained 50% against Meth A fibrosarcoma of BALB/c mouse by intratumor injection of 1 mg extracts, three times every other day. By contrast, fresh garlic extracts (FGE) used as a reference, failed to induce tumor-free animals, even though the reduced tumor size to 60% to compare with the tumor mass in a non-treated control mouse. That garlic organo-sulfur compounds test (5-100 µM) worked to protect against DNA damage (Belloir *et al*., 2006). Park *et al*. (2014) reported U937 cells were exposed to various concentrations of hexane extract aged black garlic (HEABG) for 24 h or 10 µg/mL of HEABG for the indicated times. The MTT assay was used to examine the effect of HEABG on cell viability. Resulted showed that the viability of HEABG-treated cells decreased in time and concentration-dependent manners. Consistent with these effects, after treatment with HEABG, U937 cells showed changes in morphology, including blebbing of the cell membrane and shrinkage of the cells, in a time-dependent manner. Gastric cancer is one of the most common human malignant tumors. Epidemiological investigations have provided evidence that gastric carcinogenesis is a complex, multistep and multifactorial event (Nagaoka *et al*., 2009). Wang *et al*. (2012) reported that ABGE treatment inhibits the growth of SGC-7901 cells by inducing apoptosis *in vitro*. Flow cytometry (FCM) with PI staining revealed that the apoptosis rates of SGC-7901 cell line treated with 10, 50 or 100 mg/ml ABGE for 48 h were 10.9±3.9%, 16.7±4.8%, and 22.7±5.8, respectively and were significantly higher than

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that in the negative control. ROS are also involved in the pathogenesis of gastric malignancies. To date, the correlation between the administration of ABGE and its effect on the status of SOD and GSH-Px has yet to be fully investigated. The activities of SOD and GSH-Px were significantly increased by the administration of ABGE in an animal model (Wang *et al*., 2012).

Conclusion

This review provided comprehensive information on the process of black garlic production and its health benefits namely its antioxidant potential, antidiabetic activity, anticancer activity and its role on reducing obesity. There are numerous therapeutic as well as medicinal applications of black garlic and more research is required to exploit the complete potential of black garlic in future.

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