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- Review -

Biological Constituents of Aged Garlic Extract as Biomarker

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Garlic *(Allium sativum)* are an agronomically important genus because of their sulfur flavour components. The majority of the volatiles flavour principles are generated through the enzymatic hydrolysis of the non-volatile organosulfur compounds. However, these compounds may be possible sources of new novel bioactive and therapeutic principles. Garlic has strong antioxidant activity, and epidemiological studies support the fact that diets rich of garlic may prevent some of the chronic diseases. The health cares of garlic likely arise from a wide variety of components, which may work synergistically. The chemical changes of garlic composition makes it plausible that a variation in processing can lead to acquisition of differential chemical compositions of garlic products. Especially highly unstable allicin can easily disappear during processing and are quickly transformed into a various organosulfur compounds. Various supplements of garlic, particularly aged garlic extract (AGE), are known to possess a promising antioxidant potential and are effective in prevention of chronic diseases because of the bioactive constituents. Although all of active ingredients of AGE are not elucidated, water-soluble components of AGE, including S-allylcysteine, S-allylmercaptane, steroid saponins, tetrahydro-β-carboline derivatives, and fructosyl-arginine, appears to be associated with the pharmacological effects of AGE. Consequently, the allicin free garlic components such as S-allylcysteine, S-allylmercaptane, steroid saponins, tetrahydro-β-carboline derivatives, and fructosyl-arginine can be applicable to standardization of the quality of commercial garlic products. This review provides an insight into garlic's biomarkers and presents evidence that they may either prevent or delay chronic disease associated with aging.

Key words : Aged garlic extract, organosulfur compound, biological constituents, biomarker

Introduction

Garlic (*Allium sativum*) has been used for centuries both as a flavoring and therapeutic agent for the treatments of human diseases and disorders [25]. Although garlic have been using for remedies and food for more than a thousand year, most people used garlic based on their experiences without any knowledge about relationships between biological activities and constituents of aged garlic [23]. Epidemiological, and preclinical studies have shown the close relation between dietary habits including garlic intake, and occurrence of diseases. Garlic has been investigated extensively for health benefits resulting in more than 2,000 publications over the last decade and it is considered one of the best disease preventive foods, based on its varied effects [3].

Many favorable experimental and clinical effects of the consumption of garlic products, including garlic extract, have been reported. These biological responses include reduction of risk factor for cancer [22] and cardiovascular diseases [29], a stimulation of immune function [24], restoration of physical strength [6], resistance to various stresses [9], enhanced foreign compound detoxication [1], potential antiaging effects [14] and heavy metal chelation [37].

Because of the intense interest in garlic, various commercial preparation have become available over the years. These include garlic powder, tablets, oil-macerated garlic, oil of steam-distilled garlic, ether-extracted oil of garlic and etc. In fact, in some products, garlic is soaked, or extracted with water, alcohol, wine or vinegar before use. It has been believed that the medical and beneficial properties may be attributed to specific constituents found in garlic and its extracts, and many studies suggest that organosulfur compounds are responsible for the biological activities. Another such preparation is aged garlic extract (AGE) which is prepared by a unique but natural long-term process of aging extraction for 1 month at 60~70°C. This process causes considerable loss of allicin and increases the concentration of other new component. Garlic products, including enteric coated products, revealed that no allicin was found in blood

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after oral ingestion. Allicin disappeared very rapidly in stomach.

Interestingly, it is therefore not surprising that the composition and quantity of aged garlic extract can produce other compounds, given such chemical diversity as new sources of biactive compounds [19]. It does not explain the cause of the inconsistency, because, as shown in many documents, allicin potential is not a correct biomarker for controlling the quality of garlic supplements [19]. Standardization of aged garlic extract is a key to delivering consistent quality and biological activity of garlic products. Therefore, in the current view, sulfur compounds generate from garlic as biomarkers and these standard biomarkers are very important for ensuring consistent effects.

Chemical changes of garlic

Garlic is famous for its undesirable odor, arising from allicin and other oil-soluble sulfur components. The major component of garlic is water (65%), and the bulk of the dry weight is composed of fructose containing glucides, followed by sulfur compounds. Major compounds present in garlic are 97% water-soluble constituents with small amount of 0.7~0.15% oil soluble compounds. Garlic contains unique organosulfur compound, which provides its characteristic flavor and odor, and most of its effective biological activities. The strong odor of fresh garlic and its ability to generate unpleasant gastric side effects have caused many to favor dietary garlic supplements as an optimal choice for increasing garlic intake [20]. In fact, over 90% of investigations on garlics, active principles have focused on the sulfur compounds of which comprises 85% of alliin and two main γ-glutamylcysteines [38]. Alliin considered the parent substance of the therapeutically active sulfur components of garlic. Once garlic is cut or crushed, compounds in the intact garlic are converted into hundreds of organosulfur compounds in a short time. When garlic is crushed, cut or chewed, alliin is exposed to the enzyme allinase and thiosulfinated allicin is formed [29]. According to the clinical study, theoretical amounts of allicin delivered to the intestinal tract from enteric-coated garlic powder still do not reach the blood stream. Even whether the garlic products contains allicin or not, allicin is not detected in the blood stream (Fig. 1). Therefore, allicin is not bioavailable and cannot reach target organs via circulation.

When allicin itself was kept at 20°C for 10 hr, it decomposed to diallyl disulfide (DADS), diallyl sulfide (DAS), diallyl trisulfide (DATS) and sulfur dioxide [6] (Fig. 2).

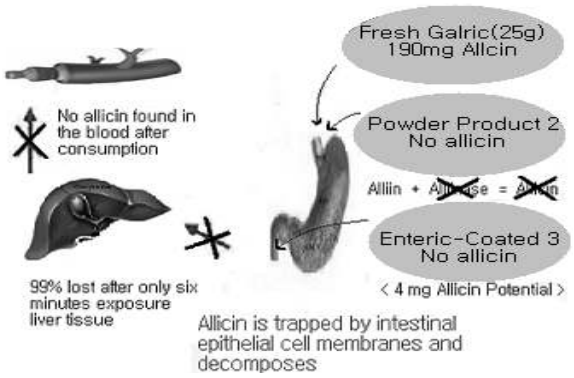

Fig. 1. Fate of allicin. No allicin is found in the blood after oral consumption of 90 mg allicin [23]. According to the clinical study, theoretical amounts of allicin delivered to the intestinal tract from enteric-coated garlic powder still do not reach the blood stream. Even if any allicin were to reach the liver from the intestinal tract, it would be transformed in liver tissue. Whether the garlic preparation/product contains allicin or not, allicin is not detected in the bloodstream in the body. Therefore, allicin is not bioavailable and cannot reach targed organs via circulation.

One of the main sulfur containing compounds in intact garlic are converted into S-allyl -cysteine (SAC) through an enzymatic transformation with γ-glutamyltranspeptidase when garlic is extracted with water. Although freshly crushed, garlic may contain limited amounts of allicin, while no

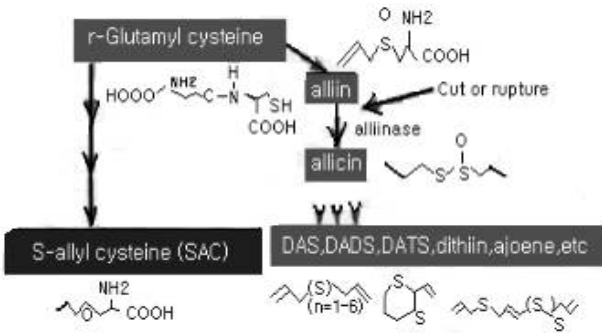

Fig. 2. Chemical change in garlic. Intact garlic bulbs contain high amounts of γ-glutamylcysteines. These reserve compounds can be hydrolyzed and oxidized to form alliin [41], which accumulates naturally during storage of garlic bulbs at cool temperatures. Allicin and other thiosulfinates instantly decompose to other compounds, such as diallyl sulfide (DAS), diallyl disulfide (DADS) and diallyltrisulfide (DATS), dithiins and ajoene. At the same time, γ-glutamylcysteines are converted to S-allylcysteine (SAC) via a pathway other than the alliin/allicin pathway. SAC contributes heavily to the health benefits of garlic.

commercially available processed garlic products contain allicin. These results indicate that allicin does not contribute to the *in vivo* effects of garlic. Allicin and allicin potential is not a correct biological biomarker for controlling the quality of garlic product [5,23]. As mentioned above, garlic changes it characteristics because of the complexity of its intrinsic chemistry, which are very important for biological effects. However, some studies shed doubt on the efficacies of garlic, and careful examination of such research can help clarify the processing of garlic. For example, aged garlic extract. Although many garlic preparations are commercially available, confusion remains because of the inconsistency of clinical study results and the lack of scientific studies on individual products.

Therefore, this article focuses on biological properties of main constituents derived from aged garlic extract, which might have an important role in the benefits of garlic to human health.

Commercially available products of aged garlic extracts (AGE)

Garlic supplement products have experienced increasing popularity in the last decade. Market research indicates that garlic products were the most popular herbal supplement in the single herb category. There are many brands of garlic products that provide a convenient way to intake benefits of garlic.

Over the years different garlic products have been studied for their prevention and treatment of various human diseases with clinical trials. The garlic products that have been studied included raw garlic, garlic powder, steam distilled garlic oil, macerated garlic oil, and aged garlic extract (AGE) (Table 1).

All these products differ in their composition, which makes comparing them difficult. It is well known that extraction product such as AGE increases potency generally and safely, and more effectively compared with raw garlic, garlic powder, macerated garlic oil, or others. Although there is no standard intake of garlic, some researcher suggested that daily intake of 1~2 cloves garlic or 1~4 g of intact garlic may have health benefits. The daily dose of garlic powder is 900 mg. However, recommendation is not substantiated with clinical studies. AGE intakes ranging from 1 to 7.2 g have been used with success. Previously, no severe toxic side effects were reported in these clinical studies [9]. AGE has been examined in clinical tests and show no contraindications with several medications including cholesterol lowering agent such as statin, aspirin, doxysorubin etc. AGE is prepared of eliminated toxicity and other strong unpleasant odors of garlic.

Table 1. Garlic products on the market

Type of product	Main compounds and characteristics
Garlic essential oil	Only 1% of Oil-soluble sulfur compounds (DAS, DADS, etc.) in 99% vegetable oil No water-soluble fraction No allicin Not well-standardized No safety data
Garlic oil macerate Oil	Soluble sulfur compounds and alliin No allicin Not well-standardized No safety data
Garlic powder	Alliin and a small amount of oil-soluble sulfur compounds No allicin Not well-standardized Results on cholesterol is not consistent. No safety data
Aged garlic extract (AGE)	Mainly water-soluble compounds (SAC, SAMC, saponins, etc.) Standardized with SAC Small amount of oil-soluble sulfur compounds Various beneficial effects Well-established safety Heavily researched (400 + papers)

Allicin is a highly unstable and reactive compound that rapidly decomposes to other compounds. For this reason no garlic product on the market contains a dete-ctable amount of allicin (<1 μg/g) [13].

Bioavailability of aged garlic extract

Many favorable experiments and clinical studies on the consumption of garlic products, especially of aged garlic extract (AGE), show a wide variety of biological attributes to it. AGE also has more effects against cardiovascular disease [9,30], cholesterol lowering effect [42], antioxidant [15] and blood coagulability [35]. These additional biological effects may be due to conversion compounds that are formed during long term extraction process, called the aging process. AGE is an odorless product resulting from prolonged aging or extraction of fresh garlic at high temperature and humidity. It is highly bioavailable and has biological activity *in vitro* and *in vivo* in both animals and humans [7,10]. AGE contains water soluble allyl amino acid derivatives, which

account for most of its organosulfur content, soluble allyl sulfides, and flavonoids, saponins, essential macro and micronutrients.

The major unique organosulfur compounds in AGE are water soluble S-allylcysteine (SAC), and S-allylmercaptocysteine (SAMC), steroid saponin, fructosyl arginine, a Maillard reaction product [39]. In addition, for tetrahydro-β-carboline derivatives which possess hydrogen peroxide, scavenging activity have recently identified in AGE [18]. Among many garlic products, AGE, demonstrating the benefits of the aging process, can eliminate these undesirable compounds, and water soluble sulfur compounds effectively increase the desirable compounds such as SAC for human benefits [31,32] (Fig. 3).

Another such preparation is aged garlic extract (AGE), which is processed by one month under the conditions of 80°C temperature with 70% humidity. This black garlic is extract with water and then filtered under concentrated reduced pressure at low temperature and is marketed in both dry and liquid forms. This manufacture process causes considerable loss of allicin and increases the concentration of other new sulfur-base and water soluble compounds. The major compounds such as polyphenol, S-allylcysteine (SAC), S-allylmercaptocysteine (SAMC), fructosyl arginine (FA), and steroid saponin is used to standardize AGE [23,31]. Several clinical and publications reports that neither aged garlic extract nor dehydrated garlic powder for human benefits. These research data have caused serious confusion in academic and in the public health, because alliin and allicin potential is not correct biomarker for showing the quality of garlic products. As mentioned above, garlic changes it properties because of the complexity of its chemistry, during aging process, and standardization biomarker compound are very useful for consistent activities. Therefore, standardization is a key to delivering parameters of biological effects of garlic products to consumers.

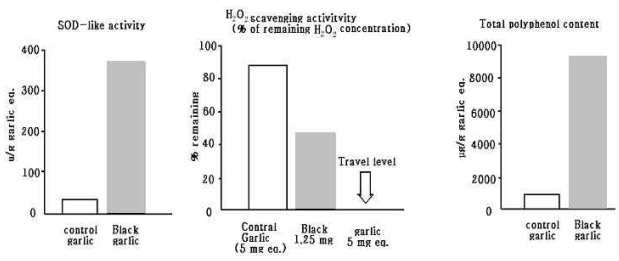

Fig. 3. SOD-like activity, hydrogen peroxide scavenging activity and total polyphenol content of garlic extract [4]. Hydrogen peroxide scavenging activity is expressed as the % of remaining hydrogen peroxide concentration in which the concentration of the solvent control (80% EtOH alone) is regarded as 100%.

S-allylcysteine (SAC)

SAC content in the intact garlic is a small amount of 20 ~30 μg/g fresh weight, however, SAC is increased in a aging/extraction procedure through hydrolysis of γ-glutamyl-S-allylcysteine which exists in raw garlic as a precursor of SAC [35].

Studies on the pharmacokinetics of SAC in a number of animal species show SAC is easily absorbed from the gastrointestinal tract distributed in plasma, liver and other organs with a bioavailability of 98% in rat [6,17]. Recently, SAC major a sulfur-containing amino acid compound has been reported to have antioxidant activity, anticancer promoting effect, and hepatopathic activity [13,14]. N-acetyl SAC has been identified as a metabolite of SAC in the urine of dogs and humans. These indicated that SAC could be transformed by N-acetyltransferase.

SAC is a very stable compound, although, numberous sulfur containing compounds in garlic transformed/ decomposed compounds appear after cleavage of the C-S bond fresh or processed garlic. However, SAC in AGE would be absorbed without any decomposition from changes in gastrointestinal pH after administration [35]. The pharmacokinetic study in human was performed by oral administration of garlic product, which contains. show the concentration of SAC in plasma after oral administration of garlic supplement by health volunteers (Fig. 4).

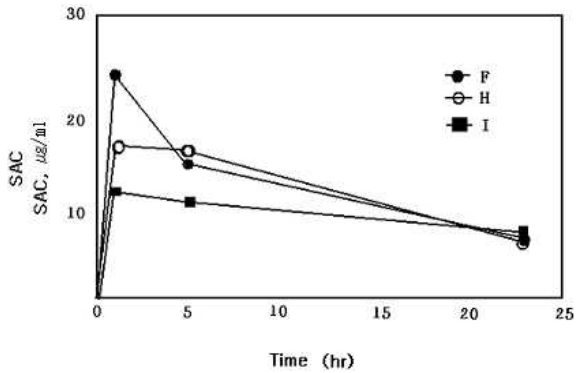

Fig. 4. SAC content in human volunteers orally consuming garlic supplement containing SAC [28]. Volunteer F: age, 46; sex, male; body weight, 64 kg; SAC consumed, 0.82 mg. Volunteer H: age, 38; sex, male; body weight, 63 kg; SAC consumed, 0.67 mg. Volunteer I: age, 45 ; sex, male; body weight, 65 kg; SAC consumed, 0.67 mg.

These results of SAC stability in the plasma fraction of SAC was almost 100% at 3 hr after the addition of SAC to this fraction, however, recovery from the red blood was 87% at 3 hr [5]. Therefore, high level of SAC in human plasma, might have an important role in the benefits of garlic to health. The S-allyl group in SAC had the highest potency for colon cancer prevention and was almost stable than the other groups, S-methyl, S-propyl and disulfide derivatives [20]. The importance of the S-allyl group on the survival of neurons by using S-allyl group, analogue or derivatives, then only derivatives of S-allyl group were effective [4]. This results indicated that the S-allyl group reacts effective role in disease prevention.

SAC is one of the potential compound obtained from AGE and this compound was increased in the manufacture of garlic. SAC could be used as health claim of biomarker of garlic product that are used neutraceutical and medical application of human benefits.

Allyl mercaptan

Garlic and garlic compounds are metabolized in the intestine and liver, but allicin and some of its transformed constituents, such as diallyl disulfide and ajoene, have never been found in the blood, indicating that they are converted to other compounds [11,19]. Some studies have suggested that pure garlic-related organosulfur compounds such as allicin, ajoene, disulfides and perhaps the trisulfides are metabolized primarily to allyl mercaptan shortly after entering the blood [21].

Allicin also has been shown to transform to diallyl sulfide and allyl mercaptan in the isolated perfused rat liver, with the former being rapidly metabolized to allyl mercaptan [8]. However, the physiologic role of allyl mercaptan is well unknown, despite the fact that allyl mercaptan is the major metabolite of garlic compounds. Allyl mercaptan reduces cholesterol synthesis in the rat hepatocytes by the enzymes, 3-hydroxy-3-methyl-glutar-yl coenzyme A (HMG-COA) [18]. Based on well viability, various content ratio up to 100 μg /ml, were chosen as nontoxic levels of allyl mercaptan to carry out subsequent studies.

Allyl mercaptan indicated in a marked inhibition of cholesterol in the cells, and also decreased significantly in cholesterol secretion [21]. The effecting allyl mercaptan of ^{3}H-acetate into cholesterol with or without 1 ml oleic acid treatment, allyl mercaptan significantly decreased cholesterol in cells [21,23].

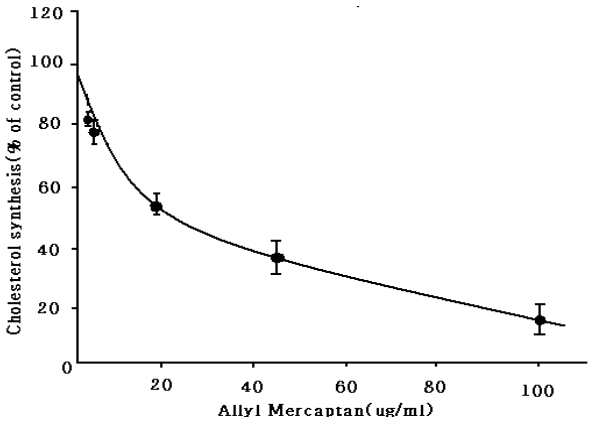

Fig. 5. Effects of various concentrations of allyl mercaptan on cholesterol synthesis in Hep-G2 cells [12]. The cells were incubated in a serum-free Dulbecco's modified Eagles; medium containing 5, 10, 25, 50, and 100 μg/ml of allyl mercaptan and ^{3}H-acetate (1 uci/ml) for 4 hr. Values are mean±SEM (n=6).

Allyl mercaptan treatment of cells incubated with oleic acid indicated in a significantly reduction in the cholesterol synthesis in cells and cholesterol secretion (Fig. 5).

The results is in agreement with the report that allyl mercaptan exerts an inhibitory effect on cholesterol synthesis in rat heptatocytes and inhibition of cholesterol synthesis by allyl mercaptan could be due to the decreased activity of HMG-COA reductase in rat [42]. Although it is rather difficult to interpret the relevance of current data to dietary effect of garlic *in vivo*, allyl mercaptan, which is a major metabolite of garlic compounds circulating in the blood, could be partly responsible for the cholesterol-lowering effect of garlic. In conclusion, allyl mercaptan is effective in suppressing the synthesis and excretion of cholesterol.

Steroid saponins, non-sulfur compounds

Saponins have characteristic properties, including the production of a stable foam when shaken with water, a bitter taste, and hemolytic activity. Steroid saponins has been detected in AGE. Steroid saponins from garlic led to the isolation named sativoside-B_1, and to the discovery of a known furostanol saponin, proto-desgalactotigonin [18,27]. On the other hand, eruboside-B, a spirostanol saponin corresponding to proto-eruboside-B, was isolated from garlic bulbs [15].

Recently the isolation and structure determination of new steroid saponins named proto-isoeruboside-B and isoeruboside-B, which are elucidated to be the C-25 epimers of pro-eruboside-B and eruboside-B [28]. Steroid saponins and sapogenins could be considered reliable chemical structure

biomarkers for the identification of garlic and garlic products. Among the biological activities of steroid saponins islated from the AGE, eruboside-B exhibited antifungal activity for C*andida albicans* [16], cardiovascular disease [26], and cytotoxic activities *in vitro* [28]. Crude saponins from methanol garlic extracts lowered total plasma cholesterol and LDL cholesterol without changing HDL cholesterol levels in hypercholesterolemic animal models [40]. Saponins in garlic are reported to exhibit various biological effects, including cholesterol reduction, and probably effects synergistically with organosulfur compounds.

Tetrahydro-β-carboline derivatives

Formation of tetrahydro-β-carboline derivatives (THβCS) were not detect in raw garlic, but they were generated at the beginning of the aging extraction process with intrinsic natural enzyme or high temperature during the aging process of garlic [12]. These compounds are naturally occurring substances chemically produced during food processing, extraction, and storages. THβCS have been identified in soy sauces, beers, wines, chocolate, and cocoa. THβCS are chemically synthesized by condensation between tryptophan and acetaldehyde or pyruvic acid. Acetaldehyde, a precursor of 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (MTCC), is believed to occur from alcohol [12]. On the other hand, in natural aging process of garlic, one is the alliin-allicin pathway, which is the most common pathway in garlic, and another is via the Maillard reaction process. Therefore, THβCS were detected in AGE, but not in raw and other processed garlic such as sliced, baked, boiled, crushed, and aging processes. These alkaloids have been demonstrated to exhibited antioxidant properties [1], and to inhibit platelet aggregation [41], and monoamine oxidase [37], and metal chilating, and reducing properties [34], monoamines oxidases [37], monoamine uptake [34], and binding to benzodiazepine receptor [34].

In the present review, AGE was fractionated using hydrogen peroxide scavenging assay, and THβCS were identified. THβCS was stronger than common antioxidant, ascorbic acid.

The intracellular level of inducible nitric oxide synthase (INOS) play an important role in determining nitric oxide (NO) production rates in activated macrophages and several other cell types. The high amounts of NO is associated with acute and chronic inflammation and atherosclerosis through cytotoxicity and injury to the surrounding cells and tissues, THβCS exhibited inhibition at low concentrations. THβCS formed at the beginning of the natural aging process, and the contents increase during the aging. These data suggest that not only organosulfur compounds but also THβCS formed during the natural aging process may contribute to the biological effects of AGE (Fig. 6).

Fructosyl arginine

The amino-carbonyl (Maillard) reaction takes place during food processing, cooking or storages of food and produced to a complex mixture of reaction products. Maillard reaction products are very heterogeneous and complex, and their exact composition remains mostly unknown. More recently, the antioxidant activities of Maillard reaction products was shown *in vivo* study [33]. Feeding rats of Maillard reaction products from arginine, lysine or glycine and sugars significantly inhibited TBARS formation in the liver [24]. It is believed that the observed activities were derived from melanoidine-brown nitrogenous polymer with high molecular weight. However the Maillard reaction also produces compounds of low molecular weights fructose-arginine [39]. A low molecular weight Maillard reaction products is lated shown to lower blood pressure and to improve microcirculation in rabbits. Fructose-arginine, water soluble compound, brown color of Maillard reaction product derived from AGE, was used to determine its antioxidant activity toward oxidation of LDL. Fructose-arginine inhibited Cu^{2+} induced LDL oxidation. Fructose-arginine on oxidized LDL induced injury in vascular endothelial cells by measuring

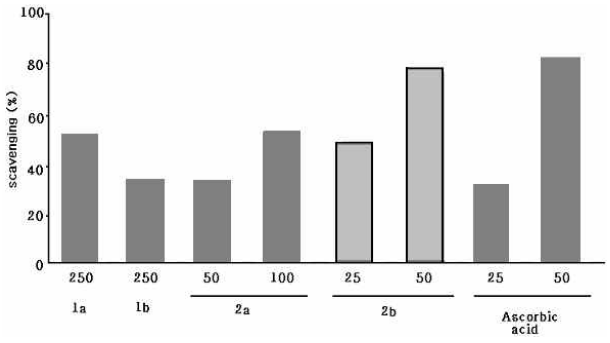

Fig. 6. Scavenging effects of tetrahydro-β-carboline derivatives identified in AGE on hydrogen peroxide [23]. Data represent means±SEM of triplicate samples. 1a : (1R,3S)-1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid. 1b: (1S, 3S)-1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid. 2a: (1R,3S)-1-methyl-1,2,3,4-tetrahydro-β-carboline-1,3-dicarboxylic acid. 2b: (1S,3S)-1-methyl-1,2,3,4-tetrahydro-β-carboline-1,3-dicarboxylic acid.

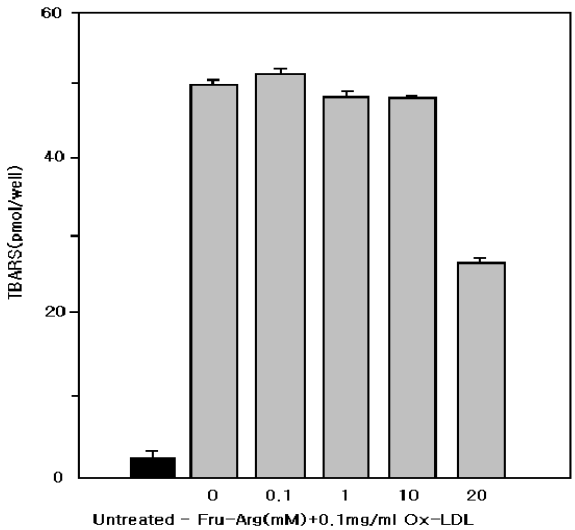

Fig. 7. Effects of fructosyl arginine (Fru-Arg) on oxidized low density lipoprotein (Ox-LDL)-induced lipid peroxidation [16]. Pulmonary arterial endothelial cells were pre-incubated with various concentrations of Fru-Arg at 37°C and 5% CO_2 for 24 hr. Cells were washed with Hanmks' balanced salt solution, incubated with 0.1 mg/ml Ox-LDL for 24 hr, and then thiobarbituric acid reactive substances (TBARS) indicating lipid peroxidation were determined. Data represent means±SE of triplicate samples. Significant difference ($P<0.05$) compared with control exposed to Ox-LDL but without pretreatment with Fru-Arg.

lactate dehydrogenase (LDH) release [36]. LDH is an intracellular enzyme released into the medium upon cell membrane damage. Oxidized LDL caused a significant increase in LDH release (Fig. 7).

There are numerous studies that show Maillard reaction products possess antioxidative activity [27]. The compounds are very important, for the quality of food, because they contribute to the development of flavour, color or browning and to changes in the nutritional value [2]. In most cases, Maillard products are tested whereas only in many cases was antioxidative activity related of structurally defined Maillard products [41]. Antioxidative activities of Maillard reaction products have been studied extensively using amino acids-sugar as arginine, lysine, glycine or histidine with reducing sugars, have been shown to have very strong biological activities *in vitro* or *in vivo*.

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초록 : 숙성마늘 extract의 biomarker로서 생리활성 성분

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마늘은 역학조사에 의하면 각종 질환의 예방과 치료에 효능이 있는 것으로 알려져 있다. 마늘의 주요 성분인 알리신 성분은 매우 불안정하여 쉽게 분해되어 새로운 형태의 유황 화합물로 만들어져 이들 성분들이 상승적으로 작용하여 중요한 생리활성을 갖는 것으로 알려져 있다. 시판되고 있는 여러 종류의 마늘제품 중에서 숙성마늘제품이 다른 제품에 비하여 생리활성이 높은 것으로 보고되었다. 숙성마늘제품은 마늘을 일정한 조건으로 숙성시킬 때 수용성 성분인 S-allylcysteine, S-allylmercaptan, steroid saponins, te-trahydro-β-caboline derivatives 및 fructo-syl-arginine 등이 많이 증가하여 그 효능이 상승적으로 높아지는 것으로 알려져 있다. 따라서 시판 마늘가공품의 품질을 표준화하기 위하여 이들 수용성 성분을 biomarker로서 규격기준을 정해야 할 것이다.