Review

Garlic as an anti-fatigue agent

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More than three thousand publications in the past have confirmed the efficacy of garlic for the prevention and treatment of a variety of diseases, acknowledging and validating its traditional uses. Garlic is also used for the treatment of fatigue, although the mechanism involved remain unclear. The anti-fatigue function of garlic may be closely related to its many favorable biological and pharmacological effects. In animal studies, garlic has been shown to promote exercise endurance. Differences in the methods of processing garlic result in differences in the intensity of its anti-fatigue effect, and the most favorable form of processing has been shown to be extraction of raw garlic followed by its natural aging for a long period in a water-ethanol mixture. In human studies, it has been confirmed that garlic produces symptomatic improvement in persons with physical fatigue, systemic fatigue due to cold, or lassitude of indefinite cause, suggesting that garlic can resolve fatigue through a variety of actions. Recently, primarily in Japan, attempts have been made to measure the intensity of fatigue objectively and quantitatively using biomarkers. Currently available data strongly suggest that garlic may be a promising anti-fatigue agent, and that further studies to elucidate its application are warranted.

Keywords: Aged garlic extract / Animal / Fatigue / Garlic / Human

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1 Garlic

Garlic (*Allium sativum*) is a herb that is used mainly as a food in many countries [1, 2]. In ancient Egypt, the amount of garlic that was distributed to the laborers who built the pyramids is written in hieroglyphs on the pyramid walls. It can be concluded that garlic was eaten to mitigate fatigue or to prompt recovery from physical exhaustion, thus helping the workers to endure hard labor. In the same way, garlic was given to soldiers and athletes as a tonic in ancient Rome. Recently, the anti-fatigue effect of garlic has been investigated by many researchers, who have reported that it increases physical strength, and promotes recovery from fatigue or stress. However, the individual components of garlic responsible for these effects have not been investigated. Although it has been assumed that the anti-fatigue effect of garlic is related to improvement of peripheral circulation, and anti-oxidation, immunomodulation and nutritional effects, the anti-fatigue effect of garlic may result from the synthetic effect based on many components of garlic, rather than a particular mechanism. Studies based on the "new science of fatigue" have led to the accumulation of a considerable amount of data. Although the pharmacological effects of garlic and its components have received much attention, little is known about the differences in effects resulting from various methods of processing raw garlic. As these various methods yield characteristic components in differing ratios, their pharmacological effects also differ [3]. The reaction is influenced by various methods of processing raw garlic, although enzymes, such as alliinase, and each precursor react. The main methods for processing raw garlic can be classified as (i) garlic powder, obtained after drying of raw garlic; (ii) garlic oil, distilled by steaming raw garlic; (iii) oil macerate, extracted on raw garlic with vegetable oil; (iv) aged garlic extract (AGE),

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Abbreviations: AGE, aged garlic extract; **ATMT,** advanced trail making test; **GSAC,** gamma-glutamyl- S-allyl-L-cysteine; **GSMC,** gamma-glutamyl-S-methyl-L-cysteine; **8-OHdG,** 8-hydroxy-deoxyguanosine; **SAC,** S-allyl-L-cysteine; **SAMC,** S-allylmercapto-L-cysteine; **SMC,** S-methyl-L-cysteine; **TGF-beta,** transforming growth factor-beta

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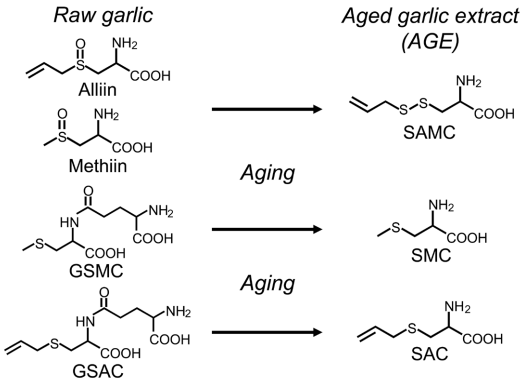

Figure 1. Characteristic organic sulfur-containing components of AGE. SAC, S-allyl-L-cysteine; SAMC, S-allylmercapto-L-cysteine; SMC, S-methyl-L-cysteine; GSAC, gamma-glutamyl-S-allyl-L-cysteine; GSMC, gamma-glutamyl-S-methyl-L-cysteine.

extracted/aged on raw garlic for a long period. These processing methods produce characteristic organic sulfur-containing components. Garlic powder retains alliin and alliinase activity depending on conditions such as the drying temperature. The main components of garlic oil are allyl sulfides, whereas those of oil macerate are allyl sulfides, vinyldithiin and ajoene. AGE is manufactured based on the method described US Pharmacopeia National Formulary (USP NF) and WHO selected medicinal plants monograph. In brief, sliced garlic is soaked with aqueous alcohol and extracted over 10 months at room temperature. As the result, AGE is less irritating and toxic [4, 5], and has many beneficial pharmacological properties [6–11]. AGE contains not less than 0.05% of S-allyl-L-cysteine (SAC) calculated on the dried basis [12, 13]. Moreover, it also contains characteristic water-soluble sulfur compounds, S-allylmercapto-L-cysteine (SAMC) and S-methyl-L-cysteine (SMC) (Fig. 1). These characteristic components are not contained in the raw garlic, and are made from gamma-glutamyl-SAC (GSAC), gamma-glutamyl-SMC (GSMC), alliin or methiin after extracted/aged on raw garlic for a long period. They have been reported to possess anti-oxidative [14–16], cancer preventive [17–19] and hepatoprotective properties [20]. The anti-fatigue effect of garlic differs according to the processing method employed, and it has been demonstrated that AGE is one of the processed products that has the most desirable effects [21, 22].

2 Improvement of peripheral circulation

Waste substances arising from muscle use are excreted into the blood, and cause fatigue or muscle pain. The peripheral circulation accounts for 90% of total blood vessels in the body, and its role is to distribute cells or organs via the blood, to smooth metabolite of organ, and to remove waste substances. In this way, the peripheral circulation plays an important role in maintaining physical strength or prompting recovery from fatigue by supplying oxygen, nutrients and water, or removing wastes. The effects of garlic on the peripheral circulation have been reported to include a decrease of blood pressure through vascular relaxation [23], enhancement of blood flow by altering the blood's lipid components or stickiness [24], acceleration of fever production [25], protection against vascular injury by free radicals [7], inhibition of blood coagulation or adhesion of blood platelets [26] and removal of thrombi by increasing the activity of the blood fibrinolytic system [27].

3 Anti-oxidative effects

Moderate exercise is useful for preventing lifestyle-related diseases or enhancing physical strength, but excessive exercise itself can be a form of stress and cause fatigue or various types of damage to the body due to the production of increased level of free radicals. Under exercise conditions that lead to fatigue, the concentration of lipid peroxide in the liver or muscles increase, and the pentane content in expiration enhances [28–30]. The anti-oxidative effects of garlic have been reported to include enhancement of superoxide dismutase activity [31], a decrease of the serum lipid peroxide level [32], and trapping of hydroxyl radicals [33]. The degree of the anti-oxidative effect is also influenced considerably by differences in the methods used to process garlic [14].

4 Immunomodulation effects

Physical or mental stress can lead to perturbation of the immune system or immune responses, and this can be one cause of fatigue. Many *in vitro* studies and clinical studies have shown that natural foods or components derived from plants stimulate or regulate the immune response, or exert an anti-stress effect [34]. Immunomodulation effects of garlic have been reported to inhibit the decrease of spleen weight and spleen cell number caused by psychological stress [35], to enhance natural killer activity [36], and to suppress contact hypersensitivity [37]. It is also known that influenza or infection can have a marked effect on the immune system, leading to fatigue. Further studies of this issue are warranted.

5 Nutritional effects

Exercise or work decreases glycogen reserves, which are a source of energy in the liver or muscles, leading to a lack of energy supply or oxygen to the muscles, and thus inducing muscle fatigue. Thus, it can be assumed that a supply of

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nutrients such as carbohydrate, lipid, and phosphate would prevent such fatigue. Similarly, a supply of protein or amino acids is important for maintaining the protein content of organs, and it is also essential to provide vitamins B1, B2, C and sodium, which are needed as metabolic components of blood and body fluids. It has been reported that garlic possesses many nutritional components such as magnesium, iron, copper, zinc, sulfur compounds, amino acids, vitamins and carbohydrate [38]. These constituents undoubtedly contribute to recovery from fatigue period.

6 Animal studies of anti-fatigue effects

A number of anti-fatigue studies using animal models have reported differences in the effect of garlic with regard to differences in the methods of processing. Morihara *et al.* [8] investigated the mechanism responsible for the ameliorating effect of AGE on physical fatigue in rats subjected to repeated endurance exercise on a mechanical treadmill. They considered that AGE might facilitate the turnover of aerobic glucose metabolism, attenuate oxidative stress, and promote oxygen supply based on vasodilation. Ushijima *et al.* [22] examined the effect of raw garlic juice, heated garlic juice, dehydrated garlic powder and AGE on physical strength and recovery from fatigue. They found that raw garlic and AGE prolonged the treadmill running time of mice and enhanced the speed of recovery of rectal temperature after immersion in cool water. It was suggested that the mechanism of the effect was related to improvement of peripheral circulation, an anti-stress action, and improvement of nutrition. However, the effect of raw garlic was not dose dependent, and a high dose did not attenuate the effect. Saxena *et al.* [21] investigated the effect of raw garlic juice and garlic oil on swimming endurance in rats, and found that garlic prolonged swimming time before fatigue, and enhanced normal endurance, although the mechanism responsible was unclear. Sookvanichsilp *et al.* [39] examined the effects of garlic on physical performance and learning behavior using the maze model, rope model, rotarod model and step-down model, and found that it had beneficial effects in the rope model and step-down model only at low doses. They also provided some evidence to support the beneficial effect of long-term garlic consumption on physical performance and learning behavior in normal subjects. However, it must also be noted that chronic administration of raw garlic has diverse toxic effects, including anemia, weight loss and growth reduction [4, 5].

7 Anti-fatigue study in humans

Recently, clinical studies of garlic have revealed many intriguing findings [40, 41]. Verma *et al.* [41] investigated the effect of six weeks of garlic oil administration on cardiac performance and exercise tolerance in 30 patients with coronary artery disease. After an initial treadmill stress test, the subjects were administered garlic oil in the form of four capsules twice a day for 6 weeks, and treadmill stress tests were repeated. Garlic significantly reduced the heart rate at peak exercise, and significantly reduced the work load on the heart, resulting in better exercise tolerance in comparison with the initial test. Kawashima *et al.* [42] examined the effect of AGE on fatigue in athletes given an exercise load by using a subjective or objective fatigue test. They found that AGE ameliorated the subjective symptoms caused by fatigue and enhanced the threshold of knee reflection. Kimoto *et al.* [43] investigated whether intake of AGE for 2 weeks influenced the level of urinary 8-hydroxy-deoxyguanosine (8-OHdG) and the total oxygen uptake during daily regular or temporary intense exercise. They found that AGE decreased the content of 8-OHdG in urine, and increased the total oxygen uptake during intense exercise. Based on these findings, they considered that AGE might prevent the accumulation of oxidants as a result of oxidative stress during exercise. Moreover, many clinical studies of garlic product containing AGE have reported that they exert significant effects against systemic fatigue accompanying the common cold, or fatigue accompanying unidentified complaints [44, 45]. Ishii *et al.* [40] examined the anti-fatigue action of garlic in a 4-week human trial, in which AGE was administered to subjects twice a day after meals in the morning and evening. Fatigue was evaluated at 0, 2 and 4 weeks of AGE administration using the advanced trail making test (ATMT) for measuring the performance of brain function associated with mental fatigue. It was found that AGE decreased "brain-age" time-dependently and significantly, as calculated using several indicators of fatigue defined by the ATMT, indicating that AGE attenuated fatigue induced or accumulated as a result of various factors in humans.

8 Latest findings in the science of fatigue

Fatigue is an alarm signal for rest recognized by the brain, but not by muscles or other organs. In order for fatigue to be recognized by the brain, it needs to develop or progress as a result of various triggers. The intensity of fatigue increases with stress, heavy work responsibility, or worsening of a cold or chronic disease, while the recognition of fatigue is masked by a sense of work-related motivation, responsibility, or success. Therefore, a crucial aspect of research on fatigue is how to evaluate the subjective symptoms of fatigue more objectively and quantitatively. Recent studies of fatigue have clarified the mechanism by which fatigue is recognized (Fig. 2). This mechanism involves neurotransmitters such as serotonin in the brain [46–49], cytokines such as transforming growth factor-beta (TGF-beta) [50], hormones such as dehydroepiandrosterone sulfate (DHEA-

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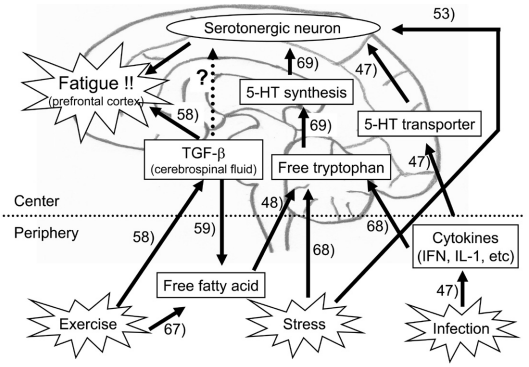

Figure 2. Mechanism of fatigue. Each number represents a reference number. TGF-beta, transforming growth factor; IFN, interferon; IL-1, interleukin; 5-HT, 5-hydroxytryptamine.

S), or oxidative stress [51, 52]. New fatigue-associated animal models are being actively studied and developed to clarify the influences of mental, environmental, and immunological factors, or their combinations, such as the water immersion model [53, 54], ultraviolet irradiation model [55], viral-like injection model [46, 47], and death from overwork model [56, 57]. Fatigue-associated biomarkers are being actively investigated, and are classified as immunochemical/biochemical biomarkers and physiological biomarkers. The former include TGF-beta [58–60], peripheral interferon [61], herpesvirus [62], DHEA-S and acylcarnitine [63–65], and the latter include performance of a task with ATMT [66] and autonomic nerve imbalance with accelerated plethysmography (second derivative of photoplethysmogram). Recently, a garlic preparation has been reported to prevent the reduction of swimming time in a water immersion rat model, and the decrease of spontaneous motor activity in a viral-like infection rat model, in addition to up-regulating performance of an ATMT task in humans [40]. Although research on the association of biomarkers with the anti-fatigue effect of garlic and its preparations is still ongoing, further studies will be warranted to elucidate the optimal areas for its application.

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