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ALLIUM SATIVUM: FACTS AND MYTHS REGARDING HUMAN HEALTH

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ABSTRACT

Garlic (*Allium sativum L. fam. Alliaceae*) is one of the most researched and best-selling herbal products on the market. For centuries it was used as a traditional remedy for most health-related disorders. Also, it is widely used as a food ingredient – spice and aphrodisiac. Garlic's properties result from a combination of variety biologically active substances which all together are responsible for its curative effect.

The compounds contained in garlic synergistically influence each other so that they can have different effects. The active ingredients of garlic include enzymes (e.g. alliinase), sulfur-containing compounds such as alliin and compounds produced enzymatically from alliin (e.g. allicin). There is a lot of variation among garlic products sold for medicinal purposes. The concentration of Allicin (main active ingredient) and the source of garlic's distinctive odor depend on processing method. Allicin is unstable, and changes into a different chemicals rather quickly. It's documented that products obtained even without allicin, such as aged garlic extract (AGE), have a clear and significant biological effect in immune system improvement, treatment of cardiovascular diseases, cancer, liver and other areas. Some products have a coating (enteric coating) to protect them against attack by stomach acids.

Clinically, garlic has been evaluated for a number of purposes, including treatment of hypertension, hypercholesterolemia, diabetes, rheumatoid arthritis, cold or the prevention of atherosclerosis and the development of tumors. Many available publications indicates possible antibacterial, anti-hypertensive and anti-thrombotic properties of garlic. Due to the chemical complexity of garlic and the use of different processing methods we obtain formulations with varying degrees of efficacy and safety.

Key words: *garlic, Allium sativum, alliin, allicin, cancer, cardiovascular, antioxidant*

STRESZCZENIE

Czosnek (*Allium sativum L. fam. Alliaceae*) jest jednym z najdokładniej zbadanych i najlepiej sprzedających się produktów ziołowych na rynku. Przez wieki był on używany jako tradycyjny środek w leczeniu wielu problemów prozdrowotnych. Ponadto, czosnek stosuje się powszechnie jako składnik żywności – cenna przyprawa czy afrodyzjak. Właściwości prozdrowotne czosnku są wynikiem odpowiedniej kombinacji substancji biologicznie czynnych, które to razem są odpowiedzialne za jego działanie lecznicze. Związki zawarte w czosnku, synergistycznie wpływają na siebie tak, że mogą one razem mieć całkiem odmienny efekty. Aktywne składniki czosnku obejmują min. enzymy (np. alliinaza), związki zawierające siarkę - alliina oraz związki wytwarzane enzymatycznie z alliiny (np. allicyna). Spośród produktów powszechnie sprzedawanych istnieją znaczne rozbieżności w składzie substancji aktywnie czynnych. Ilość allicyny, głównej substancji czynnej oraz charakterystyczny zapach czosnku zależą od sposobu przygotowania. Wynika to z tego, iż allicyna jest niestabilna i zmienia się dość szybko w inne substancje chemiczne. Udowodniono, że produkty uzyskane nawet bez allicyny, takie jak np. ekstrakt z czosnku poddany specjalnemu procesowi starzenia (AGE) mają wyraźny i znaczący wpływ na poprawę systemu odpornościowego, w leczeniu chorób układu krążenia czy na postęp w leczeniu nowotwór wątroby. Niektóre produkty apteczne mają powłoki (powłoka dojelitowa), chroniące substancję czynną przed atakiem kwasów żołądkowych.

Czosnek, był oceniany kliniczne pod względem wielu właściwości, jednak głównie brano pod uwagę leczenie nadciśnienia tętniczego, hipercholesterolemii, cukrzycy, reumatoidalnego zapalenia stawów, przeziębienia czy zapobieganie miażdżycy tętnic czy rozwój nowotworów. Wiele dostępnych publikacji wskazuje na możliwe przeciwbakteryjne, przeciwnadciśnieniowe i przeciwzakrzepowe działanie czosnku. Ze względu na złożoność chemiczną czosnku i stosowanie różnych metod przetwarzania, można otrzymać preparaty o różnym stopniu w zakresie skuteczności i bezpieczeństwa.

Słowa kluczowe: *czosnek, Allium sativum, alliina, allicyna, nowotwory, choroby układu krążenia, przeciwutleniacz*

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INTRODUCTION

The usage of garlic for medicinal purposes dates back to antiquity, to the year 1550 BC, when it was already a valuable component of food. The Bible mention garlic with regard to the Jews' flight from Egypt. Drawings of garlic were found 3700 years BC in Egyptian tombs. At that time, garlic had such a high commercial value, that it was even considered as a valuable exchange resource. For centuries, garlic has been used in different ways throughout the world. In Roman times, the workers and soldiers chewed garlic before battle, and the Slavs, claimed it to protect against snakebites. In Africa, fishermen smear their bodies with garlic extract to protect against crocodiles. In Europe, it was believed that garlic is able to ward off vampires, demons, evil spirits and have other magical properties. To Poland, it came in the Middle Ages, with a caravan of merchants from the East. Today, garlic is grown almost everywhere and is known with far more than three hundred varieties. There is a wild garlic, green, snake, Siberian. Garlic is a herb with a complex action.

It was used as a cure for heart disease, headaches and cancer. It was believed as having had the bactericidal and fungicidal properties as well as to improve the sexual condition and to cure everything from hemorrhoids to snake bites. Natural medicines are often tried for many conditions based on tradition, anecdotes or marketing, but not all of these indications are supported by reliable or credible scientific research [40].

ABBREVIATIONS

AGE - aged garlic extract; BBB - blood-brain barrier; CYP - cytochrome P450; DADS - diallyl disulfide; DAS - diallyl sulfide; DATS - diallyl trisulfide; EOs - essential oils; EPCs - endothelial progenitor cells; HDACi - histone deacetylases inhibitors; HDL - high density lipoprotein**;** HMG-CoA - 3-hydroxy-3-methylglutaryl-coenzyme A; LDL - low density lipoprotein; MAPK - mitogen-activated protein kinase; NF-kB - c factor kappa B; NO - nitric oxide; NOS - nitric oxide synthase; NPCs - neural progenitor cells; PAEC - pulmonary artery endothelial cell; SAC - S-allylcysteine; SAMC - S-allylmercaptocysteine;

CHEMISTRY OF GARLIC

Garlic contains more than 2000 biologically active substances such as volatile, water-soluble and oil-soluble organosulfur compounds (e.g. DAS, DADS, DATS) along with essential oils, dietary fiber, sugars 32% (included inulin), flavonoids and pectin [7, 49]. The organic sulfur compounds include alliin and scordinin A and B. Recently several novel cyclic sulfoxides called garlicnins were isolated from acetone extracts of garlic [37].

The thiosulfinates (e.g. allicin), ajoenes (e.g. *E*-ajoene, *Z*-ajoene), vinyldithiins (e.g.vinyl-1,3-dithiin, vinyl-1,2-dithiin) and sulfides (e.g. DADS, DATS) are degradation products from the naturally occurring cysteine sulfoxide, alliin (Figure 1).

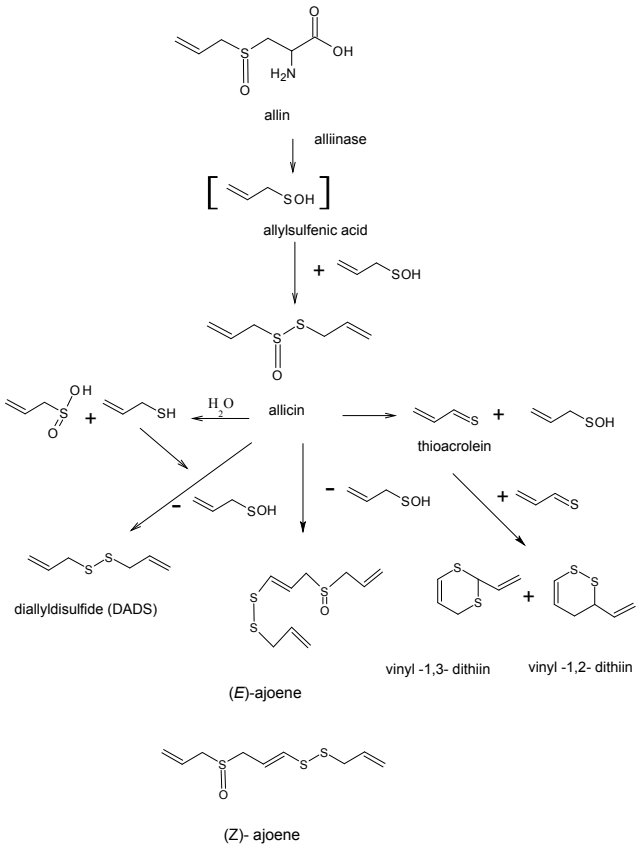

Figure 1 Schematic metabolism of alliin

When the garlic bulb is crushed, minced, or otherwise processed, alliin is released from compartments and interacts with the enzyme alliinase. Hydrolysis and immediate condensation of the reactive intermediate (allylsulfenic acid) forms allicin (diallyl thiosulfinate), a substance that is a stronger antibiotic then penicillin or tetracycline. Allicin itself is an unstable product and will undergo additional reactions to form other derivatives, depending on environmental and processing conditions. Extraction of garlic cloves with ethanol below 0 °C gave alliin; extraction with ethanol and water at 25 °C led to allicin; and steam distillation (100 °C) converted the alliin totally to diallyl sulfides. Sulfur chemical profiles of Alium products reflect the processing procedure: bulb, mainly alliin; dry powder, mainly alliin; volatile oil, almost entirely DAS, DADS, DATS; oil macerate, mainly vinyl-1,3-dithiin, vinyl-1,2-dithiin, *E*-ajoene, and *Z*-ajoene. Diallyl disulfide can be readily oxidized to allicin with hydrogen peroxide or peracetic acid.

Allicin in turn can hydrolyze, giving diallyl disulfide and trisulfide [54].

The content of alliin is also affected by processing treatment: whole garlic cloves (fresh) contained 0.25–1.15% alliin, while material carefully dried under mild conditions contained 0.7–1.7% alliin [18, 31].

Other elements which can be found in 100 g of product are vitamin C - 31 mg, B_1 - 0.2 mg, PP, B_2, B_3, provitamin A and minerals: 400 mg of potassium, 25-28 mg of magnesium, 100 mg of calcium, and trace elements of iron , copper, nickel, cobalt, chromium, selenium, and germanium. Although selenium and germanium are present in trace amounts, it is very important in reducing the division of cancer cells, inhibiting their growth or even destroying cancer cells. Garlic oil is a yellowish liquid which is insoluble in water and has a strong garlic odor.

Table 1. Forms of garlic - products and stability

Product	Main ingredient and its characteristic
Raw fresh garlic	Up to 65% of fresh garlic is water. Contains 4–12 mg of alliin per gram. Fresh garlic contains only alliin and not allicin. The natural allicin potential is assumed to be 2.5 – 5.1 mcg/g of alliin.
Garlic essential oil	No data as to the safety of usage. The content is not well standardized. It does not contain allicin. It does not contain a water-soluble fraction. Contains only 1% soluble in the oil fraction of sulfur compounds (DAS, DADS) and 99% of vegetable oil.
Oil garlic extract – macerate	Soluble sulfur compounds and alliin. It does not contain allicin. The content is not well standardized. No data as to the safety of usage.
Dried garlic - garlic powder in special capsules	Includes both alliinase and alliin and low levels of sulfur compounds soluble in oil. On an equivalent weight, dry garlic powder has a higher level of alliin (3x) than fresh garlic. Temperatures above 70 °C inactivates the enzyme alliinase, which is responsible for converting alliin into allicin. It does not contain allicin. The content is not well standardized. Effects on cholesterol is not well known.
Aged garlic extract - AGE (Water-alcohol garlic extract)	Mainly contains water-soluble compounds S-allylcysteine (SAC), SAMC and saponins. Standardized for the content of SAC. Contains small amounts of oil soluble sulfur compounds (DADS). Different beneficial effects. Safety of therapy is well documented. Well known, more than 400 scientific studies Aged garlic does not contain allicin.

* Allicin is highly unstable and very reactive, which causes the fast break down into other compounds. For this reason, there are no products on the market, which would contain a detectable amount of allicin (less than 1 microgram/gram)

The differential effect of allyl sulfides on Ca^{2+} signaling and cell death appears to correlate with the number of sulfur atoms in the structure of these allyl sulfides [20]. Reaction of DADS with liquid sulfur gives a mixture containing diallyl polysulfides with as many as 22 sulfur atoms in a chain [51]. Additional pharmacological effects may be due to the presence of compounds such as SAC, SAMC, saponins, N(alpha)--fructosyl arginine and other substances formed during the lasting extraction process [45].

There is a lot of variation among garlic products sold for medicinal purposes. The amount of the active ingredients depends on the method of preparation. Allicin is unstable, and changes into a different chemical rather quickly (Table 1).

PROPERTIES

Cholesterol and lipids

Garlic consumption helps in fat metabolism, lowering blood cholesterol levels. Increases "good" cholesterol HDL and lowers „bad" LDL cholesterol and triglycerides, protects blood vessels and the heart. Significantly reduces the activity of the enzyme - HMG--CoA reductase and may have an effect on the level of cholesterol hydroxylase and other enzymes - fatty acid synthase and enzymes taking part in pentose-phosphate metabolism [41, 43, 44, 48].

In vitro studies have shown that garlic has specific anti-atherosclerotic effects, by reducing the mRNA expression of inducible nitric oxide synthase (iNOS) and inhibition of oxidized low-density lipoprotein (LDL) induced by lactate dehydrogenase (LDH) and inhibition of oxidized LDL induced by depletion of glutathione.

OXYDATION PROCESSES AND CANCER

Recent scientific studies have shown that certain substances in garlic act as a powerful antioxidant and its sulfur components have anti-tumor properties. Protein fractions purified from fresh garlic bulbs augment CD8(+) T-cell infiltration into the tumor site, inhibiting tumor growth more efficiently than garlic extract [12]. In studies both *in vitro* and on animals, it was shown that organic combinations of sulfur contained in garlic can suppress the incidence of many cancers, such as breast, blood, bladder, gastric, oral cavity, colorectal, skin, uterus, esophagus, and lung cancers [1, 2, 17, 25, 30, 35, 39, 52]. A high intake of garlic reduces the risk of prostate cancer up to 50%. Diallyl trisulfide (DATS) has been reported to possess antioxidant, anti-inflammatory, and anti-carcinogenic properties by down regulating

AKT1/TGF-β-activated kinase-mediated MAPK and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathways [27, 55].

The water-soluble allium derivative, S-allyllmercaptocysteine, inhibits metastases to the lung and adrenal gland by 90% [16]. Also, it was recently concluded that a combination of alliinase with the appropriate monoclonal antibody (e.g. rituximab) offers a new powerful and less toxic therapy for B chronic lymphocytic leukemia B-CLL and other B-cell malignancies [3]. Diallylsulfide, a powerful garlic component, has been reported to inhibit oxidative stress caused by testosterone and to accelerate testosterone metabolism [45].

It has been proven that mainly AGE protects both liver and nervous cells and has strong antioxidant properties, while other formulations may stimulate oxidation. These additional biological properties may be due to the conversion to compounds which are formed during long lasting extraction (AGE), called the aging process [10].

Allyl compounds and isothiocyanates can act as HDACi. They activate epigenetically silenced genes in cancer cells, causing cell cycle arrested and apoptosis [11]. Furthermore, garlic is a seleniferous plant, accumulating selenium from the soil against a concentration gradient. Selenium has many anticancer actions, particularly in control of genes involved in carcinogenesis.

BLOOD VESSELS AND HEART

Garlic has been proven to have a significant effect on the cardiovascular system. It includes areas such as improving lipid balance, affecting blood pressure, the inhibition of platelet function, antioxidant properties and fibrinolytic activity [19, 43, 44, 47, 48].

Some of the beneficial effects of dietary garlic against cardiovascular disorders are mediated via the generation of hydrogen sulfide and nitric oxide in cardiomyocytes and PAEC. Garlic has the potential to protect the heart against myocardial infarction, doxorubicin-induced cardio toxicity, arrhythmia, hypertrophy, and ischemia–reperfusion injury. The induction of cardiac endogenous antioxidants and the reduction of lipid peroxidation by garlic has been reported by several different groups. Other mechanisms, such as regulating ion channels, modulating Akt signaling pathways, histone deacetylase inhibition, and cytochrome P450 inhibition, could also be responsible for the cardio protective effect of garlic [11, 26].

In animal studies the nutraceutical AGE, completely prevent the dietary fat-induced disturbances of BBB and normalized the measures of neurovascular inflammation and oxidative stress [50].

Garlic consumption enhances neovasculogenesis in human endothelial progenitor cells (EPCs) and thereby exerts a preventive effect against ischemic injuries [9].

ORGAN DAMAGE

Animal studies indicate protective effects of garlic in colorectal therapy especially in the treatment of damage caused by methotrexate and 5-fluorouracil [34]. Both, *in vitro* and animal studies demonstrate that AGE protects against liver damage caused by substances from the environment such as bromobenzene and against cardio toxicity caused by doxorubicin [10, 46]. Also DADS may contribute to the protective effects against ethanol-induced liver injury [57].

Garlic protects the brain from a loss of intellectual capacity, memory, depression and has a potentially positive and preventive therapeutic effect in the treatment of Alzheimer's disease [21, 24, 36, 42]. It also improves spatial memory deficits that are associated with aging. Some reports suggest that DADS may have adverse effects on hippocampal neurogenesis and neurocognitive functions, so large amounts of garlic products should be avoided, particularly during the period of neural growth [22].

BONES AND JOINTS

DADS, inhibits the expression of matrix proteases, responsible for damaging the structure of chondrocytes, providing a potential mechanism for the protective effect in patients suffering from osteoporosis [53]. Also its anti-inflammatory properties have been documented.

BACTERIA

In vitro studies show garlic activity against many types of Gram-negative, Gram-positive bacteria including species such as: *Escherichia, Salmonella, Staphylococcus, Streptococcus, Klebsiella, Proteus, Bacillus, Clostridium and Mycobacterium tuberculosis*. The *in vitro* antibacterial activity of essential oils obtained from fresh bulbs of garlic show a good antimicrobial activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli* [6]. Even some bacteria normally resistant to antibiotics (including methicillin-resistant *Staphylococcus aureus)* or strains of bacteria resistant to several antibiotic treatments (*Escherichia coli, Enterococcus spp, Shigella spp*) were sensitive to garlic treatment . The combination of EOs of onion (75%) and garlic (25%) had a synergistic

effect on growth inhibition of *Aspergillus versicolor* and sterigmatocystin STC production [28].

It is believed that the antibacterial activity is caused by garlic components such as allicin and the presence of the allyl group is fundamental for the antimicrobial activity of sulfide derivatives –DADS, DAD, DATS [6, 14]. A feature unique to allicin is the inability to develop resistance to these substances by most bacteria. Also, garlic disinfects the urinary tract, and destroys bacteria which are resistant to antibiotics.

Other *in vitro* data show antibacterial activity against *Helicobacter pylori* infection [29, 33, 38].

FUNGAL, PARASITES AND VIRAL INFECTIONS

Topically, garlic oil is used in the treatment of tinea pedis, tinea cruris, onychomycosis, removing warts and corns [32]. There was even a case of using garlic virginally standalone or combined with yogurt. *In vitro* studies have shown that garlic has antiviral activity against several types of viruses including cytomegalovirus, influenza B virus, herpes simplex virus type 1 and type 2, parainfluenza virus type 3 and human rhinovirus type 2. It is also a good agent in destroying threadworms in human body by removing parasites from the gastrointestinal tract. In some cases was used in a rectal form.

DIABETES

Garlic supplementation together with anti-diabetic medication provides better control of diabetes type 2 patients [4, 23].

DIARRHEA

Garlic is effective against diarrhea caused by products containing castor oil, as well as relieving flatulence, abdominal discomfort or heartburn. Small doses of garlic leads to increase smooth muscle tension of the gastrointestinal tract, however large its doses cause opposite effects.

OTHER

Garlic protects against the effects of environmental pollution, smoking, and can also help in the treatment of urinary tract and bile infections. Garlic opens up the blood vessels, which increases blood flow to other tissues, improves circulation, and relieves spasms. Garlic oil suppressed hematological disorders induced by chemotherapy and radiotherapy in tumor-bearing mice [56].

It is particularly recommended for the elderly, helping to reduce body fat and slow down the aging process. Through strengthening the immune system prevents cold and flu symptoms. Prophylactic use of garlic may decrease the frequency of colds in adults, but has no significant effect on the duration of symptoms [13]. The presence of sulfur-containing compounds mobilizes the body's immune system against infectious agents.

In food and beverages, fresh garlic, garlic powder and garlic oil are used as a flavoring agents. During World War I, garlic was used to dress wounds, abscesses, and boils. The active compounds of garlic help to endure headaches and promote sleep.

SIDE EFFECTS AND CONTRAINDICATIONS

Bleeding

Garlic has antiplatelet properties which increase the risk of bleeding, especially at the time when it is used in combination with anticoagulants and antiplatelal drugs such as aspirin, clopidogrel, ticlopidine, dipyridamole, heparin and warfarin [5]. Then, its necessary to constantly control INR level denoted for warfarin. Because of a demonstrated antiplatelet effect, garlic should be avoided in patients with bleeding disorders and 1-2 weeks prior to surgery. In addition, prolonged bleeding after a shaving cut was reported.

Cytochrom activity

Supplements of garlic, which contain allicin can reduce the expression and activity of cytochrome, which may cause a clinically significant reduction in the plasma concentrations of drugs metabolized by this enzyme. The effect on CYP2C9 was proven without a noticeable effect on CYP3A4 [15]. Until further data become available, it would be reasonable to avoid or take extra caution during concomitant use of allicin with certain drugs metabolized by CYP 3A4, such as protease inhibitors, cyclosporine, ketoconazole, itraconazole, glucocorticoids, oral contraceptives, verapamil, diltiazem, lovastatin, simvastatin and atorvastatin.

Gastrointestinal tract and allergies

Many studies have described adverse effects resulting with the part of the GI tract, such as abdominal pain, bloating, loss of appetite and garlic breath especially after intake of fresh garlic, and advice not to consume in acute gastroenteritis as it may exacerbate the symptoms of the disease. Excessive intake of garlic may also have adverse effects on the liver, especially on the muscle

cells. There have been few cases of allergic reactions (allergic contact dermatitis, generalized urticaria, angioedema, pemphigus, anaphylaxis and allergic to light), a change in platelet function and clotting time. It's not recommended to apply garlic on the skin under occlusive dressings as it can cause burns.

Diabetes

Patients taking drugs for diabetes should be vigilant, as the garlic therapy does not always go hand in hand with insulin therapy.

Hypoglycemia

Following administration of chlorpropamide can also cause hypoglycemia and reduce the bioavailability parameters (t max, C max, AUC) of saquinavir in patients treated with anti-AIDS medicines [8].

Other

Garlic is not recommended in the treatment of cough with blood and fever associated with pneumonia. It should not be used in patients with advanced kidney inflammation [29]. In large doses garlic and its derivatives are dangerous, especially for children (not to be given for children under 10 months of age). Garlic in large quantities should be eliminated from the diet for pregnant women and nursing mothers as it can have adverse effect on hippocampal neurogenesis and neurocognitive functions [22].

Clinical studies have consistently shown that "garlic breath" and the peculiar smell of the body are the most common unpleasant elements after eating garlic.

CONCLUSIONS

In recent years there have been many pre-clinical, clinical and *in vitro* studies on animal models, which focus on the protective effect of garlic against various health related disorders, especially heart disease and cancer. Now it's well known that products obtained even without allicin, such as AGE have clear and significant biological effects in the treatment cardiovascular diseases, cancer, liver problems, improving immune system and in other areas. There are other chemical components which can have synergistic properties altogether. However, the risk of drug interactions with garlic, especially in the elderly and those with chronic diseases, is attracting more and more interest. The observed results and intervention studies conducted on humans are not very consistent so further studies are needed to understand the real health benefits and the effects of garlic on the human body.

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