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Garlic [*Allium sativum*] and its Beneficial Effect on Cardiovascular Disease: A Review

Manoranjan Adak[1*] • Jaime A. Teixeira da Silva[2]

[1] Department of Biochemistry, National Medical College and Teaching Hospital, Birgunj, Nepal
[2] Faculty of Agriculture and Graduate School of Agriculture, Kagawa University, Miki-cho, Ikenobe 2393, Kagawa-ken, 761-0795, Japan

Corresponding author: * **manoranjanadak@rediffmail.com** or **itsmradak@gmail.com**

ABSTRACT

Garlic [*Allium sativum*] is among the oldest of all cultivated plants and one of the best disease preventive foods. Garlic has been used as a medicinal agent for thousands of years for its antimicrobial, antithrombotic, hypolipidemic, antiarthritic, hypoglycemic and antitumor activity. Major risk factors for cardiovascular diseases, such as high serum total cholesterol, increased LDL oxidation, increased platelet aggregation, impaired fibrinolysis, etc. are controlled by garlic and its preparations. A number of studies have demonstrated that garlic is best known for its lipid-lowering and antiatherogenic activity. Recent studies reported that only aged garlic extract exhibited radical scavenging activity due to the presence of two compounds, S-allyl-L-cysteine and S-allylmercapto-L-cysteine. All bioactive components in garlic preparations, including S-allyl-L-cysteine, have been shown in a number of *in vitro* studies to inhibit the hepatic activities of lipogenic and cholesterogenic enzymes. Clinical trials showed a positive effect of garlic on almost all cardiovascular conditions; however, a number of negative studies have recently cast doubt on the efficacy of garlic, especially its cholesterol-lowering effect. This review has attempted to bridge the gap between the experimental and clinical studies and to discuss the possible mechanisms of such therapeutic actions of garlic.

Keywords: aged garlic extract, allicin, S-allyl-L-cysteine, antiatherogenic, hypertension, platelet aggregation

CONTENTS

INTRODUCTION

Garlic and its preparations have been widely recognized as agents for prevention and treatment of cardiovascular disease (CVD) and other metabolic diseases, atherosclerosis, hyperlipidemia, thrombosis, hypertension, diabetes and cancer (Lawson 1998; Ackerman *et al.* 2001; Adak 2009). Additional claims have been made on its hypoglycemic effects, antimicrobial, antifungal, antiprotozoal, and antioxidant properties (Prasad *et al.* 1995; Amin and Kapadnis 2005). Over the centuries, garlic has acquired a special recognition in the folklore of many cultures as a formidable prophylac-

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tic and therapeutic agent (Moyers 1996). The medicinal use of garlic has a long history. In 1550 BC it was first documented in the *Egyptian Cordex Ebers* that garlic is a useful medicine for heart disease, tumors, and headaches (Woodward 1996). Garlic is also mentioned in the Bible and has been a traditional treatment in many countries, particularly the Near East, China, and India (Dragster *et al.* 2006). The majority of garlic is water (65%), and the bulk of the dry weight is composed of fructose-containing carbohydrates, followed by sulfur compounds, protein, fiber, and free amino acids (Lawson 1996). It also contains high levels of saponins, phosphorus, potassium, sulfur, zinc, moderate levels of selenium and Vitamins A and C, and low levels of calcium, magnesium, sodium, iron, manganese, and B-complex vitamins; garlic also has a high phenolic content (Vinson *et al.*2001). Most of its popularity is based on modern medicine due to its widespread use around the globe resulting from scientific research that suggests cardiovascular benefits associated with intake of garlic as a conventional food and as a dietary supplement (Bordia 1981; Lau *et al.* 1983; Banerjee and Maulik 2002; Rahman and Lowe 2006). Epidemiological studies have shown that diets rich in fruits, herbs and spices are associated with a low risk of CVD (Banerjee and Maulik 2002). It has also been suggested that the benefits of fruit and vegetable consumption appear to be primarily related to CVD and not cancer (Hung *et al.* 2004).

Atherosclerosis and coronary artery disease remain the number one killers in the world (Balk *et al.* 2006; Nicholas *et al.* 2006; O'Keefe *et al.* 2007; Nair *et al.* 2008). It is now recognized that hyperlipidemia is associated with an increased incidence of premature ischemic heart disease (McCance 1983). Hypercholesterolemia is highly correlated with the risk of CVD because it contributes to heart attacks, strokes and atherosclerosis (Lipid Research Clinics 1984). Elevated high-density lipoprotein (HDL) levels may exert a protective effect against coronary artery disease (Lewis 1983). The lipid hypothesis, formulated many years back, proposed that the reduction of plasma cholesterol would lead to a fall in coronary heart disease (Kannel *et al*. 1979). Dietary therapy is an important step in the treatment of hyperlipidemia (Cooper *et al*. 1982; Margetts *et al.* 1986; Kestin *et al.* 1989). Garlic is one such agent. Garlic has been shown to decrease hepatic cholesterol synthesis, which may explain in part the hypocholesterolemic effect of garlic in humans and animals (Steiner *et al.* 1996; Liu and Yeh 2000). Bordia *et al*. (1975) reported that the essential oils of garlic and onion reduce serum cholesterol levels noticeably. Similar effects of garlic were found in cholesterol-fed rats where total plasma and liver cholesterol were reduced by about 30% (Myung *et al*. 1982). Sklan *et al*. (1992) observed depressed hepatic cholesterol levels in chickens fed 2% garlic for 14 days. Various garlic extracts exhibited hypocholesterolemic effects on chickens, mainly through the inhibition of the key enzymes in cholesterol and lipid synthesis (Qureshi *et al*. 1983). In the US and Western Europe, garlic is one of the most popular herbal medicines used to reduce various risks associated with CVD. A survey estimated that the use of garlic as an alternative therapy among adults in the US increased from 33.8% in 1990 to 42.1% in 1997 (Eisenberg *et al.* 1998). The annual prevalence of dietary supplement use increased from 14.2% in 1998-1999 to 18.8% in 2002. Although use did not change among younger subjects, it doubled for men and women 65 years or older. The median age was stable over time; the proportion of female subjects varied from 54.0 to 58.3%. Overall, 15.9% of subjects had used one or more supplements during the previous week; the prevalence of use varied, with a low of 12.3% in 2000 and a high of 19.8% in 2001 (Kelly *et al* .2005). In 2002, approximately 38.2 million adults in the United States (US) used herbals and supplements (Kennedy 2005). US consumers spent $27 billion in 1997 and over $34 billion in 2000 on alternative medicines and expenditures continue to rise (Bent and Ko 2004). In Germany, 73% of Germans greater than 16 years old have used at least one form of alternative medicine (Nahin *et al.* 2007). The National Center for Complementary and Alternative Medicine (NCCAM 2005) announced the release of its new 5-year strategic plan to research and educate physicians and patients about the benefits and disadvantages of certain alternative medicines. In 2008, the FDA's Center for Food Safety and Applied Nutrition (CFSAN) reported that of the six most commonly used dietary botanical supplements, ginseng has the most adverse effects, followed by *Echinacea* (41%) and garlic 20% (Barnes *et al.* 2004; Gardiner *et al.* 2007; Wallace *et al.* 2008).

CVD is a major problem throughout the globe. The Global Burden of Disease Study reported that in 1990 there were 5.2 million deaths from CVDs in economically developed countries and 9.1 million deaths from the same causes in developing countries (Murray and Lopez 1997). The WHO (2005) reported that about 250,000 people die each year under the age of 65 from sudden myocardial infarction, without ever being hospitalized. Of an estimated 58 million deaths globally from all causes in 2005, CVD accounted for 30%. This proportion is equal to that due to infectious diseases, nutritional deficiencies, and maternal and perinatal conditions combined (WHO 2005). Between 2006 and 2015, deaths due to noncommunicable diseases (half of which will be due to CVD) are expected to increase by 17%, while deaths from infectious diseases, nutritional deficiencies, and maternal and perinatal conditions combined are projected to decline by 3% (WHO 2005). It is important to recognize that a substantial proportion of these deaths (46%) were of people under 70 years of age, in the more productive period of life; in addition, 79% of the disease burden attributed to CVD is in this age group (WHO 2007). Almost half the disease burden in low- and middle-income countries is already due to noncommunicable diseases (Lopez *et al.* 2006). It has been predicted that by the year 2020 there will be an increase by almost 75% in the global CVD burden (Ramachandran *et al.* 2001). In the USA, about 40% of all deaths in 1997, or about one million people, were attributed to CVD (Friedewald 2002). The Centers for Disease Control and Prevention reported in 2006 that more than 910,000 people in the US die of CVD each year and currently more than 70 million Americans have one or more forms of CVD. The average annual rates of first major cardiovascular events rise from three per 1,000 men at ages 35–44 to 74 per 1,000 at ages 85–94. For women, comparable rates occur 10 years later in life (American Heart Association 2009). Many of the risk factors for CVD are modifiable through lifestyle changes. In fact, it has been estimated that 70% of CVD can be prevented or delayed with dietary choices and lifestyle modifications (Forman and Bulwer 2006).

Three water-soluble, sulfur-containing compounds found in garlic [S-allyl-L-cysteine (SAC), S-ethyl-L-cysteine (SEC), S-1-propenyl-L-cysteine (SPC)]; reviewed in Jones *et al.* 2007; Kamenetsky *et al.* 2007; Roos *et al.* 2007; Siess *et al.* 2007; Zheng *et al.* 2007)] decreased cholesterol production in cultured rat liver cells by 40-50%. The garlic compound ajoene has β-hydroxy β-methyl glutaryl CoA (HMG-CoA) -reductase reducing activity as well (Banerjee and Maulik 2002). Clinical trials reported varied results regarding garlic's lipid-lowering effects (Neil *et al.* 1996; Steiner *et al.* 1996; Isaacsohn *et al.* 1998). Dried garlic powder 900 mg/day (Kwai; Lichtwer Pharma GmbH, Berlin, Germany; standardized to provide 1.3% alliin/tablet) led to a 13% reduction in serum triglycerides (Warshafsky *et al.* 1993; Silagy and Neil 1994). An *in vitro* study demonstrated that water-soluble garlic extracts reduced hepatocytes cholesterol synthesis by inhibiting HMG-CoA reductase (Qureshi *et al.* 1987). However, the regulatory mechanisms of HMG-CoA reductase activity by garlic compounds is not yet clear but some authors suggested that regulation of HMG-CoA reductase might occur at the transcriptional or post-transcriptional level (Anderson *et al.* 1995). This review represents an overall view of the efficacy of garlic in CVD conditions in both humans and animals with possible mechanisms.

HISTORICAL ASPECTS OF GARLIC

Garlic has been grown worldwide from Mediterranean climates to Siberia. There is evidence that the Greek physicians, Hippocrates, Galen, and Hildegard von Bingen prescribed herbal medicine, garlic to athletes for increasing stamina (Bradley 1992). Ancient Egyptians used it as a form of currency; its medical as well as magical powers were listed in the medical text *Codex Ebers* (*ca*. 1550 BC) especially for the working class involved in heavy labor (Bergner 1996; Lawson 1998). Arabian herbalists used garlic to treat abdominal pain, infantile colic, diarrhea, diabetes and tuberculosis (Ghazanfar 1994).

According to the Bible, the Jewish slaves in Egypt were fed garlic and other allium vegetables, apparently to give them strength and increase their productivity. The Talmud, a Jewish religious text dating from the 2nd century AD, prescribes the patterns of behavior, including the consumption of garlic for the treatment of infection with parasites and other disorders (Moyers 1996).

There is evidence that during the earliest Olympics in Greece, garlic was fed to athletes before their sport competition for better performance (Green and Polydoris 1993; Lawson 1998). Hippocrates, widely regarded as the father of Medicine, made garlic a part of his therapeutic armamentarium, advocating its use for pulmonary complaints, as a cleansing or purgative agent, and for abdominal growths, particularly uterine (Moyers 1996).

Roman soldiers and sailors perceived garlic as an aid to strength and stamina (Green and Polydris 1993). With the emergence of Rome as a leading power, Greek medicine and its traditions gradually were transferred to Rome. Medicine in Rome was greatly influenced by the writings of Pliny the Elder, a Greek physician who wrote the five-volume *Historica Naturalis* (Bergner 1996; Moyers 1996) and 23 uses for garlic were listed for a variety of disorders. Among these was that garlic was believed to confer significant protection against toxins, disorders of the gastrointestinal tract, for treatment of animal bites, for alleviation of joint disease, seizures, and other hepatic degradative diseases (Block 1985; Pinto and Rivlin 1999).

In ancient Chinese medicine, garlic is described as a forbidden food for *Buddhist* monks because of its reputation as a sexual stimulant, to aid respiration and digestion, most importantly diarrhea and worm infestation (Woodward 1996). Evidence also suggests that garlic was frequently used in combination therapy. Fatigue, headache and insomnia were often treated with garlic. There are also indications that garlic was used to treat and improve male potency (Kahn 1996). It is believed that garlic was introduced in Japan later than in China, probably 2000 years ago (Kahn 1996).

The leading Indian ancient medical texts, *Charaka-Samhita* and *Bower Manuscript* dating from around the 2nd century BC to the 2nd century AD, recommends garlic for the treatment of heart disease, arthritis, fatigue, parasitic disease, digestive disorder and leprosy (Rivlin 1998). Its medicinal properties are also found in the *Buddhists* literature in the late 19th century. In *Ayurvedic* medicine, garlic is used to treat respiratory problems, ulcers, colic and flatulence, and oil drops are used to treat earache (Kapoor 1990). Some religious groups did not permit the consumption of garlic or onions, rather as the Greeks and Romans prescribed garlic in the temples (Moyers 1996). Garlic either was not permitted or fancied by the upper Brahmin classes, whereas in other castes, it was applied externally to help repair cuts, bruises and infections, and it comprised one of a number of perceived aphrodisiacs available from natural plant sources (Kahn 1996).

Garlic became available in Europe after the Roman legions moved north. During Medieval times, knowledge of the therapeutic use of plants, particularly garlic, was gained and transmitted through the monks. The leading text of the middle ages was the *Hortulus* manuscript from shortly after 800 AD, described the medicinal properties of garlic (Moyers 1996). Outdoor workers were advised to consume garlic to prevent heat stroke (Khan 1996; Moyers 1996). Another leading physician during the latter part of the 12th century, the Abbess of Rupertsberg, St. Hildegard von Bingen (Bergner 1996; Kahn 1996), gave garlic a prominent role in her medical writing. Curiously, she concluded that raw garlic was more effective than cooked garlic, perhaps because the latter has less pungency then the former. In the Medical School at Salerno, one of the most influential centers of medical learning at the time, food played an important role in the treatment of disease as well as in the protection of good health. Garlic was classified as a "hot food" to be consumed during the winter to limit the development of pulmonary or breathing disorders (Moyers 1996). Garlic was also utilized against massive debilitation and later in the Great Plagues (Bergner 1996; Woodward 1996).

With the onset of the Renaissance, increasing attention was paid in Europe to the medical uses of plants. So-called "physic" gardens were established at leading universities to grow plants of medicinal value. Garlic was one of the major plants grown for this purpose A leading physician of the 16th Century, Pietro Mattioli of Siena, prescribed garlic for digestive disorders, infestations with worms and renal disorders, as well as to help mothers during difficult childbirth (Moyers 1996).

King Henry IV of France in the late 16th and early 17th centuries used garlic to protect from evil spirits and probably from disease. Moving closer to contemporary times, it is worth recalling that bulbs similar to garlic grew freely in the woods of North America and that Native Americans used garlic in their tea. Later in the 19th century, garlic formed an important part of the Shaker medical armamentarium as a stimulant, expectorant and tonic. Garlic is professed large groups of the population accepted all therapeutic properties (Moyers 1996).

The *Home Book of Health*, authored by John Gunn in 1878, featured garlic prominently; it was recommended as a diuretic, for treatment of infections, as a general tonic and for asthma and other pulmonary disorders. In the early part of the 20th century, in the volume *Health Remedies*, *a Complete Medical Work and Family Guide*, garlic was promoted for diseases of the lung in children and adults (Moyers 1996).

In England, however, garlic remained the food of the working class, a view that did not prevent the wealthier English from enjoying the therapeutic properties of garlic, i.e., it was recommended for constipation, toothache, dropsy, animal bites and the plague. Its purported beneficial effects in treating dropsy suggest that it was thought to improve cardiovascular function, mechanisms of which are only now under study. Doctors carried cloves of garlic with them at all times to protect themselves from the odor of disease (Moyers 1996).

Louis Pasteur demonstrated garlic's antiseptic activity in 1858, and Albert Schweitzer used it to treat dysentery in Africa (Peirce 1999). Garlic was also used topically to prevent wound infections during World War II (Tattelman 2005).

The name *Allium sativum* is derived from the Celtic word "all", meaning burning or stinging, and the Latin *sativum* meaning planted or cultivated (McGee 2004). The English word, garlic, is derived from the Anglo-Saxon "garleac" or spear plant, referring to the toast flowering stalk. Garlic has a characteristic pungent, spicy flavor that mellows and sweetens considerably with cooking (Gernot 2005). A bulb of garlic, the most commonly used part of the plant, is divided into numerous fleshy sections called cloves which are used as seed, for consumption (raw or cooked), and for medicinal purposes. Historical aspects of garlic are summarized in brief in **Table 1**.

Table 1 Historical prospective of the use of garlic (based on Rivlin 2001).

Period	Importance	References
Ancient Egypt	Garlic as part of the daily diet	Green and Polydoris 1993
	Medical text Codex Ebers gives remedies based on the use of garlic	Bergner 1996
	Well-preserved garlic cloves were found in the tomb of King Tutankhamen	Kahn 1996
		Lawson 1998
		Weiss and Fintelmann 2000
Biblical	Garlic as part of the daily diet	Bergner 1996
	On leaving Egypt, slaves missed their "fish, cucumbers, melons, leeks, onions and garlic"	Moyers 1996
	Talmud recorded many benefits of garlic, and recommended it for married couples	
Ancient Greece	Garlic found in the palace of Knossos in Crete	Green and Polydoris 1993
	Soldiers were fed garlic to give them courage, and garlic was associated with war	Bergner 1996
	During the first Olympic games, garlic was taken by athletes before they competed	Moyers 1996
	Used to protect the skin against poisons or toxins	Lawson 1998
	Hippocrates, the Father of Medicine, used garlic	
Ancient Rome	Garlic was fed to troops and to sailors for strength	Green and Polydoris 1993
	In Historica Naturalis garlic was prescribed for digestion, animal bites, arthritis and convulsions	Bergner 1996
	Later garlic was used for respiratory ailments and for parasites	Riddle 1996
		Pinto and Rivlin 1999
Ancient China and Japan	Garlic used as a food preservative	Kahn 1996
	Formed part of the daily diet with raw meat	Moyers 1996
	Prescribed as aid to digestion and respiration, to provide energy and lift depression	Woodward 1996
	May have been used to improve male potency	
Ancient India	In medical text Charaka-Samhita, garlic was used to treat heart disease and arthritis	Kahn 1996
	In another ancient medical text, known as the Bower manuscript	Moyers 1996
	(named after its discoverer), garlic was used for fatigue, parasites, digestive diseases and leprosy	Steiner *et al.* 1996
		Ide and Lau 1997
Middle Ages	Christian monks preserved knowledge of benefits of plants, including garlic	Bergner 1996
	The Hortulus manuscript described use of garlic	Kahn 1996
	Garlic recommended raw rather than cooked by the Abbess of Rupertsberg	Moyers 1996
	The medical school of Salerno taught dietetics utilizing garlic prominently	Woodward 1996
	Garlic used as a treatment for the Great Plagues	
The Renaissance	"Physic" gardens were opened in Padua, Pisa, Zurich, Bologna and other cities	Moyers 1996
	Dr. Pietro Mattioli of Siena advised garlic for digestive disorders, kidney stones and expelling afterbirth	
	Henry IV of France baptized in water containing garlic	
	The English included garlic in their medicine chests, and it was used for toothache, constipation, dropsy and plague	
Early America	Native Americans used garlic in a tea to treat flu-like symptoms	Moyers 1996
	Garlic was used in Shaker herb catalogs as a Stimulant, expectorant and tonic	
	Dr. John Gunn used garlic in the Home-Book of Health as a diuretic, expectorant and treatment for worms	
	Dr. Joseph Richardson, author of Health Remedies, used garlic for all lung diseases	

BOTANY OF GARLIC

Plant description

Garlic is a bulbous perennial herb, closely related to the onion. It has a tall, erect flowering stem that reaches 2-3 feet in height. Two distinctive botanical varieties of garlic are *Allium ophioscorodon* L. and *Allium sativum* L. The variety *ophioscorodon* is characterized by an initially coiled, tall woody scape with relatively few brownish-purple cloves per bulb. The *sativum* variety is common garlic, produces a weak flower stalk and has a bulb with many pure white or pink-blushed bulblets (Pooler 1993). The edible bulb, bulblets or cloves are enclosed in a whitish skin and grouped between membranous papery scales. The leaves are grass-like, long, narrow, and flat. The white flowers are grouped together in a globular head, or umbel, and are enclosed in a kind of leaf (Grieve 1995). Small bulbils may be produced to replace the flowers. The development of these aerial bulbils may be a result of domestication (Bozzini 1991).

Scientific classification

Botanical name: *Allium sativum* L. Pharmacopeia name: *Allii sativi.* Latin name: *Allium sativa*. Kingdom: *Plantae*; Division: *Magnoliophyta*; Tribe: *Allieae*; Family: *Alliaceae*; Subfamily: *Allioideae*; Class: *Liliopsida*; Order: *Asparagales*; Genus: *Allium*; Species: *sativum*.

Common names: Arab countries (thum); China (da-suan, ta-suan); Fiji (lashun); France (ail, aje, cebilhoums); Germany (knoblauch, knoblauchzweibel); India (akashneem, lashun, lusna, rashun, tellagaddalu, velluli); Iran (poor man's treacle, seer); Italy (aglio); Japan (taisan); Jordan (thoum); Korea (taesan); Mexico (majo); Morocco (tuma); Nepal (lob, banlasun, lasun); Nigeria (alubosa elewe); Oman (thom); Portugal, Brazil and other Portuguese-speaking countries (alho); Spain, Peru and other Spanish-speaking countries, e.g. in Latin America (ajo); Thailand (dra thiam, kra thaim); Tunisia (ail, tum); Turkey (sarimsak); West Indies (l'ail, lai). Other name: garlic clove.

CULTIVATION OF GARLIC

Garlic is easily grown year-round in a rich, moist, sandy soil or clay soil in mild climates. During cold climates, cloves can be planted in the ground in 6 inches apart and 2 inches deep about six weeks before the soil freezes, and harvested in late spring. A sunny spot is best and weeding recommended while occasionally gathering the soil up around the roots (Grieve 1995). A look at the effects different fertilizers can have on garlic showed that phosphorous can decrease plant height, average bulb weight, and marketable yield. Farmyard manure can also decrease the average bulb weight and marketable yield but increase the plant height (Seno *et al.* 1995). Use of a green manure crop such as buckwheat tilled in a few weeks before planting is recommended to improve soil physical properties. Well composted manure applied and incorporated at a rate of 20 tons to 30 tons per acre has also been shown to be ideal as a soil amendment, especially on low organic matter soils. The optimum soil pH for garlic is between 6 and 7. Liming is recommended if the pH is less than 5.8. Rates to apply should be based on soil test recommendations. Prior to planting, soils should be well tilled to provide a loose growing bed for bulb growth (Rosen *et al.* 2008). Field trials carried out on three commercial varieties of garlic grown under two different climatic conditions of Western Europe confirmed this observation and suggested an important role of the cropping temperature, soil status and water stress conditions. Experiments performed under fully controlled conditions, *in vitro* and in the greenhouse, showed that sulfur fertilization as well as light conditions could also have an impact on the organo-sulfur composition of garlic bulbs. The effect of increasing mineral sulfur should be considered in relation to other mineral fertilizing components, like nitrogen and selenium, as well as to other sulfur sources, from the soil and from the atmosphere, as garlic seems to be able to use atmospheric sulfur (Huchette *et al.* 2007).

In one study, bulbs planted in the autumn increased total yield by 3.13 tons/ha and marketable yield by 2.93 tons/ha as compared, with bulbs planted in the spring. Trimming can also affect yield. Trimming an upright shoot can increase total yield by 10.07 tons/ha and 0.42 tons/ha for marketable yield (Orlowski *et al.* 1994). Therefore, if planting for higher yield, planting in the autumn and trimming the shoots can be very advantageous for greater bulblet production. Time of planting is critical since both optimum shoot and bulb development require a cold treatment. Ideally, roots should be developing and shoots should be emerging from the clove but not above the soil at the time of the first hard freeze (28°F). Garlic shoots will emerge from the ground in late March or early April. Unless given a proper cold treatment prior to planting, garlic planted in the spring will often produce weak shoots and poorly developed bulbs (Rahim and Fordham 2001). Lack of scape development in hard neck garlic and bulbing in all garlic is usually due to an inadequate cold treatment. Garlic roots and shoots can tolerate freezing conditions provided that sudden drops in temperature do not occur. Therefore, within three to five weeks after planting, rows should be covered with a three- to four-inch layer of weed seed-free straw mulch to moderate soil temperatures and minimize excessively fluctuating temperatures in the winter and early spring. This mulch also will help control weeds during the growing season. Irrigation is essential on sandy soils and may be beneficial in some years on finer textured soils. Enough irrigation should be provided so that the available water holding capacity does not drop below about 50%. The most critical stage for irrigation is during bulbing (mid-May to late June or early July). Lack of irrigation or rainfall during this stage will result in smaller bulbs and earlier maturity. Irrigation should be stopped about two weeks before harvest to avoid stained bulb wrappers and diseases (Rosen *et al.* 2008).

Garlic competes poorly with weeds. Unless weeds are controlled early, they can easily overtake young garlic plants, causing significant yield losses. However, pests do not attack garlic plants but they can suffer from pink root, which is a disease that stunts the roots and turns them pink or red (Rosen *et al.* 2008). China is so far the largest producer of garlic with approximately 10.5 billion kg/year, accounting for over 75% of world output. India (4%) and South Korea (3%) follow, with the United States (2%) in fourth place (FAO 2005).

STORAGE AND CULINARY USE OF GARLIC

Different varieties of garlic will mature at different times. In general, garlic varieties mature in the following order from early to late: Tuban, Asiatic, Artichoke, Rocambole, Creole, Glazed Purple Stripe, Purple Stripe, Marbled Purple Stripe, Porcelain, and Silverskin. Harvesting too early will result in small bulbs that do not store well while harvesting too late will force the cloves to pop out of the skins, making them susceptible to disease and resulting in unmarketable bulbs. The washed or unwashed garlic blubs along with shoots should be tied in bundles of 10 to 15 and allowed to dry in a well-ventilated room. After three to four weeks of curing, the shoots and roots should have dried down. Clean bulbs by removing the outermost skins, being careful not to expose any cloves. Any remaining soil should be brushed away (Rosen *et al.* 2008).

In the US, dry garlic bulb is stored about at 18°C or 64°F whereas commercially it is stored at 0°C. It traditionally hung; soft neck varieties are often braided in strands called "plaits" or grapes. Garlic is often kept in oil to produce flavor red oil. Untreated garlic kept in oil at room temperature can support the growth of deadly *Clostridium botulinum*. Peeled cloves may be stored in wine or vinegar in the refrigerator (www.TheGarlicStore.com; Hardenburg 2004).

Garlic is a fundamental component in many or most dishes of various regions including Eastern Asia, South Asia, South-East Asia, the Middle East, Northern Africa, Southern Europe, and parts of South and Central America due to its pungent flavor. The flavor varies in intensity and aroma with cooking methods. Oils are often flavored with garlic cloves. In France, the young bulbs are pickled for 3–6 weeks in a mixture of sugar, salt and spices. In Eastern Europe, the shoots are pickled and eaten as an appetizer. Immature scapes are tender and edible (Meer *et al.* 1997). Garlic leaves are a popular vegetable in many parts of Asia. Mixing garlic with eggs and olive oil produces *aioli*. Garlic, oil, and a chunky base produce *skordalia*. Blending garlic, almond, oil and soaked bread produces *ajoblanco*.

CHEMISTRY OF GARLIC

Garlic bulbs contain about 65% water, 28% carbohydrates (mainly fructans), 2.3% organosulfur compounds, 2% protein (mainly alliinase), 1.2% free amino acids (mainly arginine), 1.5% fiber, 0.15% lipids, and small amounts of phytic acid (0.08%), saponins (0.07%), and β-sitosterol (0.0015%) (Lawson 1996). The majority of compounds present in garlic are water-soluble (97%) with small amounts of oil-soluble compounds also present (0.15–0.7%). About 33 sulfur-containing compounds in intact garlic are mainly organosulphur compounds and these are the S-alkyl-L-cysteine sulfoxides [alliin (ALN, 1%), methiin (0.12%), isoalliin (0.06%), and cycloalliin (CA, 0.1%)] and the *γ*-L-glutamyl–SACs [*γ*-glutamyl-S-*trans*-1-propenylcysteine (0.6%) and *γ*-glutamyl-S-allylcysteine (0.4%)].These sulfoxides, except CA, are converted into thiosulfinates (such as allicin) through enzyme reactions when raw garlic is cut or crushed. Thus, no thiosulfinates are found in intact garlic. γ-glutamyl-SACs are converted into SAC through an enzymatic transformation with γ-glutamyl transpeptidase when garlic is extracted with an aqueous solution (Matsuura 1997). SAC, a major transformed product from γ-glutamyl-SAC, is a sulfur amino acid detected in the blood that is verified as both biologically active and bioavailable. Other sulfur compounds are allylpropyl disulfide, DATS (DATS), vinyldithiines, S-allylmercapto-cysteine (SAMC), etc. (Newall *et al.* 1996). It also contains high levels of phosphorus, potassium, sulfur, zinc, moderate levels of selenium and low levels of calcium, magnesium, sodium, iron, manganese, and B-complex, Vitamins A and C vitamins (Lu *et al.* 1996). Active principles of garlic and their biological properties are summarized in **Table 2**.

Allicin derived from garlic

Diallyl disulfide (DADS) or diallyl thiosulfinate is believed to be an important contributor of smell and taste of garlic. These thiosulfinates does not exist as such in intact garlic. The disruption of garlic bulbs by bruising, crushing, chewing, or mincing causes the formation of thiosulfinates such as allicin through the enzymatic reaction of sulfur-substituted cysteine sulfoxides, compartmentalized in the cyto-

Table 2 Active principles of garlic and their biological activity.

Biological activity	Active principles	Reference
Anti-platelet	alliin	Hanley and Fenwick 1985
	allicin	Block and Ahmad 1984
	allyl-1.5-hexadienyl-trisulphide	Block and Ahmad 1984
	allyl methyl trisulphide	Block and Ahmad 1984
	S-allyl 2-propene thiosulphinate	Block and Ahmad 1984
	ajoene	Ariga *et al*. 1981
	diallyl disulphide	Ariga *et al.* 1981
	diallyl trisulphide	Apitz-Castro *et al.* 1984
	1.5-hexadienyl-trisulphide	Apitz-Castro *et al.* 1983
	methyl allyl trisulphide	Ariga *et al.* 1981
	2-vinyl-1.3-dithiene	Apitz-Castro *et al.* 1983
	3-vinyl-1.2-dithiene	Block 1985
		Wojcikowski *et al.* 2007
Fibrinolysis	methane-thiol-3,4-dimethylthiophene; methyl cysteine sulphoxide; propyl allyl disulphide; propyl cysteine sulphoxide	Augusti and Benaim 1975
Blood lipids and cholesterol	alliin	Kamanna and Chandrasekhara 1984
	allicin	Kamanna and Chandrasekhara 1984
	propyl disulphide	Bordia 1975
	allyl diallyl disulphide	Bordia *et al.* 1975
	S-methyl-L-cysteine sulphoxide	Liu and Yeh 2002; Turner *et al.* 2004; Lei *et al*. 2008
Blood sugar	allicin ajoene	Hanley and Fenwick 1985
	diallyl disulphide diallyl trisulphide	Amonkar and Reeves 1971; Yoshida *et al.* 1987
Antibiotic	Allicin; diallyl disulphide	Hanley and Fenwick 1985

plasma with ALNase in the vacuole, via sulfur-substituted sulfenic acids as a highly reactive intermediate. Other thiosulfinates, including ally methyl-, methylallyl-, and *trans*-1-propenyl-thiosulfinate, were found in the garlic homogenates, and, like allicin, they are all unstable (Lawson *et al.* 1991). Allicin is further metabolized to vinyldithiines within hours at room temperature or cooking (Blania and Spangenberg 1991). During cooking garlic removes allicin by opening thermo-transient receptor potential (TRP) channel*s* that are responsible for the burning sense of heat in foods and spiciness (Lindsey *et al.* 2005). When allicin itself was kept at 208°C for 20 h, it decomposed to DADS (66%), diallyl sulfide (14%), DATS (9%), and sulfur dioxide (Brodnitz *et al*. 1971). Allicin easily binds to protein and fatty acid in the plasma membrane, is thus trapped before absorption, and cannot circulate in the blood (Freeman and Kodera 1995). Biological and chemical stability of garlic-derived allicin studied recently and reported that allicin was more stable in 20% alcohol than in water and unstable in vegetable oil (Fujisawa *et al.* 2008).

ALNase is the key enzyme that facilitates the transformation of cysteine sulfoxides to thiosulfinates. It is present in unusually high amounts in garlic cloves: at least 10% of the total protein content (10 mg/g fresh weight).The purified enzyme possesses a pH optimum of 6.5 with S-methyl-L-cysteine (SMC) as substrate and pyridoxal phosphate as a cofactor (Mazelis and Crews 1968). The gene coding for the enzyme has been cloned, and upon translation, found to consist of 448 amino acids with a protein molecular mass of 51.45 kDa and together with a carbohydrate content of 5.5-6%, gives 55000 kDa (Rabinkov *et al.* 1994).

Organosulfur volatiles in garlic

Over 20 organosulfur volatiles have been identified in crushed garlic, steam-distilled garlic oil and garlic essential oil include DAS, DADS, DATS, methylallyl disulfide (MADS), dipropyl disulfide (DPDS), methylallyl trisulfide, 2-vinyl-4H-1, 3-dithiin, 3-vinyl-4H-1, 2-dithiin, and (*E*,*Z*)-ajoenes, which are responsible for the characteristic smell and taste of garlic. The major sulfides in garlic oil include DAS (57%), allylmethyl (37%), and dimethyl (6%) mono- to hexasulfides, in some cases, together with a small amount of allyl 1-propenyl and methyl-1-propenyl di-, tri-, and tetrasulfides (Lawson *et al.* 1991). DATS is the most abundant in fresh garlic oil, but commercially available garlic oil products have an increased amount of DADS (Jirovetz *et al.* 1992). Vinyldithiins, especially 2-vinyl-4H-1, 3-dithiin, are rich in the oil macerate of raw garlic (Iberl *et al.* 1990). Apitz-Castro *et al*. (1983) first isolated ajoene from the ether fraction of garlic extract as a potent anti-thrombotic agent.

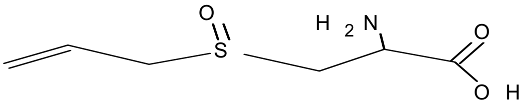
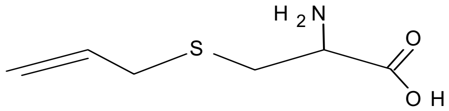
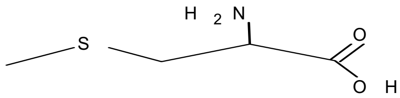
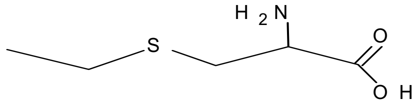
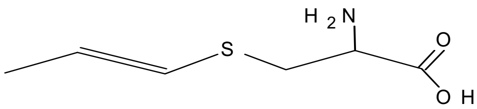
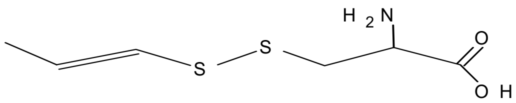
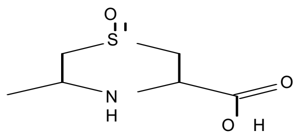
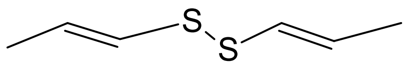
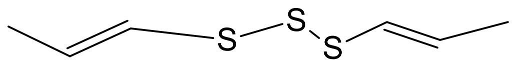
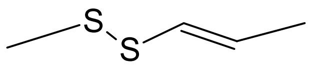
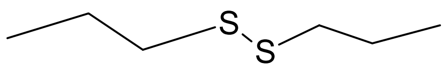
Alcoholic and aqueous garlic extracts contain primarily SAC derived from γ-glutamyl-SACs. SAC and SPC, together with a small amount of SMC and some of its constituents are found in aged garlic extract (AGE). Some water soluble and fat-soluble garlic-derived compounds are cited in **Table 3**. These cysteine derivatives are colorless crystals and are odorless and stable in the solid state or aqueous solution under neural or slight acidic conditions (Kodera *et al.* 2002).

Metabolism of organosulfur compounds

ALN (10 mg/mouse) was administered orally in mouse, after 10 min, ALN was observed in the stomach (7.2%), intestine (22.4%), and liver (2.5%) without the production of allicin and its derivatives as DADS, vinyl dithiins, and allyl-SS conjugated compounds (Guo *et al.* 1990). In another experiment, ALN showed lower plasma concentration with a bioavailability of 16.5% within 4 h after oral ingestion of 60 mg/kg ALN in rats (Guo *et al.* 1990). Freeman *et al.* (1995) reported that ingestion of allicin causes instability and metabolites in the blood. They found that allicin quickly disappeared from whole blood within a few minutes while DAS and allyl mercaptan were formed.

Egen-Schwind *et al.* (1992) reported a remarkable first-pass effect of allicin in the isolated perfused rat liver. DADS quickly form after infusion of allicin in a low concentration. Later, the formation of allyl mercaptan was observed in the collected bile as well as the liver tissue. Although allicin is reported to be metabolized in stomach acid to release DAS, DADS, and other volatiles that are postulated to be metabolized by glutathione or S-adenosyl methionine to form allyl methyl sulfide (AMS) from human breath after consumption of raw garlic (Rosen *et al.* 2001). Blood concentration of AMS and its bioavailability have not yet been studied, and therefore, AMS has not been well established as a metabolite of allicin. Since digestion takes several hours and release of AMS several hours more, the effect of eating garlic may be present for a long time (Nagae *et al.* 1994).

Table 3 Chemical structure of garlic-derived compounds.

Name	Structure	Abbreviation	Solubility
Alliin		ALN	Water
S-Allyl-L-cysteine		SAC	Water
S-Methyl-L-cysteine		SMC	Water
S-Ethyl-L-cysteine		SEC	Water
S-1-Propenyl-L-cysteine		SPC	Water
S-Allylmrecapto-L-cysteine		SAMC	Water
Cycloalliin		CA	Water
Diallyl disulphide		DADS	Fat
Diallyl trisulphide		DATS	Fat
Methylallyl disulphide		MADS	Fat
Dipropyl disulphide		DPDS	Fat

Available forms and typical dosages of garlic

Market research conducted in the US showed that garlic products were the most popular of all 91 dietary supplements (Wyngate 1998). Garlic supplement products have experienced increasing popularity in the last decade. There are several brands of garlic products on store shelves that provide a convenient way to obtain the health benefits of garlic. One may contain more of an active ingredient than another. These are classified into five groups: fresh cloves of garlic, garlic powder, aged garlic extract, garlic essential oil and garlic oil macerate (see **Table 4**).

The European Scientific Co-operative on Phototherapy recommends a daily 6-10 mg of ALN (or 3-5 mg of allicin) or in 500-1000 mg of garlic powder (Efendy *et al.* 1997). Typical adult dosages are recommended as (Blumenthal 1998): Raw garlic cloves: 0.5-2 raw cloves (2-6 g), up to three times daily (TID). Garlic pills: 0.5 to 1.3% ALN (600-900 mg) daily divided into three doses. Garlic powder: 0.4-1.2 g daily divided into three doses. Oil extract of garlic: 1-2 capsules daily or 0.03-0.12 ml three times daily (TID); Juice: 2-4 ml TID; Syrup: 2-8 ml TID; Tincture (1:5, 45% alcohol): 2-4 ml TID.

CVD

CVD is a complex and multifactorial disease refers to disorders of the cardiovascular system – the heart and the body's blood vessels (Hokenson and Austin 1996; Grundy 1999; Vanhecke *et al.* 2006). Included under this designation are such diverse medical conditions as heart attack (myocardial infarction), stroke, coronary heart disease, cerebrovascular disease, atherosclerosis, hypertension, arrhythmia, and rheumatic heart disease. CVD is associated with several factors, including raised serum total cholesterol, raised low-density lipoprotein (LDL), an increase in LDL oxidation (free radical damage), increased platelet aggregation (clumping), increased plasma fibrinogen, coagulation factors, hypertension, alterations in glucose metabolism and smoking (McGill *et al.* 2000; Wood 2001; Bhatt *et al.* 2006). The oxidative modification of LDL by reactive oxygen species (ROS) is also now considered an important mechanism in the development of atherosclerosis, as is the pathogenesis of hypertension (Dhawan and Jain 2004). There is also considerable evidence supporting the involvement of platelets in the development of atherosclerosis (Keaney 2000). Several studies suggested that CVD is also associ-

Table 4 Different garlic product in the market and main compounds.

Product name	Main compounds and characteristic
Fresh cloves of garlic	Highest amount of allicin
	Not well studied yet
	Alliin and small amount of oil-soluble sulfur compounds
	Used on warts and to draw out corns
	Helps lower blood sugar levels and to treat all kinds of digestive disorders
Garlic powder	No allicin
	Not well- standardized and no safety data
	Result on cholesterol is not consistent
	Lipid lowering effect (Igor *et al.* 2008)
Aged garlic extract (AGE)	Mainly water-soluble compounds (SAC, SAMC, saponins, etc.)
	Standardized with SAC
	Small amount of oil-soluble compounds
	Sliced raw garlic stored in 15-20% ethanol for 20 months
	Various beneficial effects (Shah *et al.* 2006)
	Well-established safety and less toxic
	N-α-(1-deoxy-D-fructose-1-yl)-L-arginine, antioxidant (Ryu *et al.* 2001)
	Potential suppressive effect on colorectal adenomas (Tanaka *et al.* 2006)
	Improve thermal vascular function (Budoff *et al.* 2008)
Garlic essential oils	Prepared by steam distillation process
	Only 1% oil-soluble compounds and 99% vegetative oil
	Diallyl disulfide (55-57%, DADS), diallyl trisulfide (35-37% DATS) and dimethyl mono to hexa sulfides (Fenwick and Hanley 1985)
	No water soluble fraction and no allicin
	Not well-standardized and no safety data
	Antithrombotic and antiplatelet aggregation (El-Sabban 2009)
Garlic oil macerate	Soluble sulfur compounds included alliin, dithiins, ajoene (Iberl *et al.* 1990)
	No allicin
	Encapsulated mixtures of whole garlic cloves ground into vegetable oil
	Not well-standardized
	No safety data

Abbreviations : Alliin(ALN), S-Allyl-L-cysteine (SAC), S-Methyl-L-cysteine (SMC), S-Ethyl-L-cysteine (SEC), S-1-Propenyl-L-cysteine (SPC), S-Allylmrecapto-L-cysteine (SAMC), Cycloalliin (CA), Diallyl disulphide (DADS), Diallyl trisulphide (DATS), Methylallyl disulphide (MADS), Methylallyl disulphide (MADS), Dipropyl disulphide (DPDS).

ated with several genetic and environmental factors, including elevated lipid levels, platelet aggregation, hypertension, smoking, diet, exercise and stroke (Joshipura *et al.* 1999; Zyriax *et al.* 2005; He *et al.* 2006). High intakes of fruits and vegetables are also associated with decreases in cardiovascular risk markers including total and LDL cholesterol (Hung *et al.* 2004; Dragsted *et al.* 2006), blood pressure (Appel *et al.* 1997). Many of the risk factors for CVD are modifiable through lifestyle changes and about 70% of CVD can be prevented or delayed with dietary choices and lifestyle modifications (Forman and Bulwer 2006).

CVD is a major cause of death. The Global Burden of Disease Study reported that in 1990 there were 5.2 million deaths from CVDs in economically developed countries and 9.1 million deaths from the same causes in developing countries (Murray and Lopez 1997). CVD killed 945,836 people in 2000, comprising 39.4% of all deaths, and 150,000 of these deaths occurred in people under the age of 65 (Rodgers *et al.* 2000). It has been predicted that by the year 2020 there will be an increase by almost 75% in the global CVD burden (Ramachandran *et al.* 2001). In the US, about 40% of all deaths in 1997, or about one million people, was attributed to CVD (Friedewald 2002). The Center for Disease Control and Prevention reported in 2006 that more than 910,000 people in the US die of CVD each year and currently more than 70 million Americans have one or more forms of CVD. It was estimated for 2006 that CVD and stroke costed the US approximately $403 billion in health care expenditures and loss of productivity (Cook *et al.* 2006). Among the major risk factors for CVD that can be addressed are cigarette smoking, high blood pressure, obesity, diabetes, physical inactivity, and high blood cholesterol level (Wood 2001). Chronic inflammation is another risk factor more recently associated with CVD (Wattanapitayakul and Bauer 2001; Carreiro-Lewandowski 2004; Margolis *et al*. 2005).

Some biomarkers are thought to offer a more detailed risk of CVD. However, the clinical value of these biomarkers is questionable (Wang *et al.* 2006). Currently, two biomarkers that may reflect a higher risk of CVD include C-reactive protein (CRP) (Koenig *et al.* 1999; Mendall *et al.* 2000; Ridker *et al.* 2000, 2001; Albert *et al.* 2002; Torres and Ridker 2003b; Best *et al*. 2005) and interleukin-6 (IL-6) (Cesari *et al*. 2003; Petersen and Pedersen 2005). Some other biomarkers are higher fibrinogen, elevated homocysteine, elevated blood levels of asymmetric dimethylarginine and elevated blood levels of B-type natriuretic peptide (BNP) thought to offer a useful for diagnosis of CVD (Cook *et al.* 2007). CRP is an inflammatory serum protein measuring inflammation, and it has been linked to risks of future CVD at all levels of LDL cholesterol (Ridker *et al.* 2002; Albert *et al*. 2003; Hoffmeister *et al*. 2005). IL-6 may be predictive of low-level inflammation leading to cardiovascular and other chronic diseases and has been shown to be a useful independent biomarker of atherosclerosis (Cesari *et al*. 2003; Larsson *et al.* 2006).

1. Types of CVDs

Aneurysm, atherosclerosis, arrhythmia, cardiomyopathy, endocarditis angina cerebrovascular accident (stroke), cerebrovascular disease, congenital heart disease congestive heart failure, high blood pressure (hypertension), hypertrophic cardiomyopathy mitral valve prolapsed disease, hypotension, diastolic dysfunction, dilated cardiomyopathy, coronary heart disease (coronary artery disease), myocardial infarction (heart attack), myocarditis, rheumatic heart disease, valve disease, venous thromboembolism (New World Encyclopedia Online 2008).

2. Foods for CVD

Research has shown that a diet like dark chocolate, almonds, fish, wine, fruits, vegetables, olive oil and garlic can increase life expectancy and decrease the risk for CVD (Franco *et al.* 2004). Eating oily fish twice a week may help reduce the risk of sudden death and arrhythmias (Studer *et al.* 2005). A low level of magnesium in a healthy diet may prevent heart disease. Excess calcium can cause a magnesium deficiency, and magnesium can reduce excess calcium (Rosanoff and Seelig 2004). In 2007, researchers of the Albert Einstein College of Medicine of Yeshiva University found that 80% of people more likely to die of CVD due to 25% higher intake of sodium in their diet than the normal (Cook *et al.* 2007).

3. Lipid profiles

The National Heart, Lung, and Blood Institute panel provides information about plasma concentrations of lipid constituents (NHLBI 2007): Total cholesterol: 200 mg/dl or less; LDL cholesterol (30-39 years): 100 mg/dl or less; HDL cholesterol (male): 40 mg/dl or more; HDL cholesterol (female): 50 mg/dl or more; Very low-density (VLDL) cholesterol: 35 mg/dl or less; Triglycerides: 150 mg/dl or less.

4. Atherosclerosis

Atherosclerosis is a complex disease, characterized by an extensive inflammatory, fibro-fatty, proliferative response to damage of the arterial wall particularly muscle cells, monocyte-derived macrophages, T-lymphocytes and platelets (Schwartz *et al.* 1993). It is commonly referred to as a hardening in the wall of arteries, in large part due to accumulation of macrophage white blood cells and promoted by LDL without removal of adequate free fats and cholesterol from macrophage by high-density lipoprotein. This can lead to the formation of multiple plaques within the arteries (Stitzinger 2007). Atherosclerosis can affect any artery in the body, including arteries in the heart, brain, arms, legs, and pelvis. As a result, different diseases may develop based on which arteries are affected (NHLBI 2007).

Coronary artery disease (CAD): This is when plaque builds up in the coronary arteries. These arteries supply oxygen-rich blood to heart. When blood flow to heart reduced or blocked, it can lead to chest pain and heart attack. CAD also is called heart disease, and it is the leading cause of death in the United States (Wilson *et al.* 1998).

Carotid artery disease: This happens when plaque builds up in the carotid arteries. These arteries supply oxygen-rich blood to brain. When blood flow to brain is reduced or blocked, it can lead to stroke (Castelli 1988).

Peripheral arterial disease (PAD): This occurs when plaque builds up in the major arteries that supply oxygen-rich blood to the legs, arms, and pelvis. When blood flow to these parts is reduced or blocked, it can lead to numbness, pain, and sometimes dangerous infections (Golomb *et al.* 2006).

Current theories suggest that atherosclerosis begins with injury to the lining of the arteries, leads to CVD, and is the leading cause of death in men over age 45. Based on both cross sectional and longitudinal epidemiology studies, there are statistically significant correlations between the prevalence of atherosclerosis and several other diseases like diabetes, hypercholesterolemia, hypertension, hyperhomocysteinemia (Bergmann and Sano 2006; Saczynski *et al.* 2007). Various anatomic, physiological and behavioral risk factors for atherosclerosis are known (Blankenhorn and Hodis 1993). Hyperlipidemia, hypertension and cigarette smoking together increases the risk seven times than age, sex, obesity, alcohol consumption, intake of *trans* fat and genetic abnormalities (Sen *et al.* 2002; O'Keefe *et al.* 2007). Among all risk factors of atherosclerosis, dyslipidemias is thought to be most potent that greatly increase the risk of CVD (Anderson 1991; Donnell 1998). The increased level of blood cholesterol is a major risk factor for CVD and death in both men and women (Lewington and Clarke 2005; Ghosh *et al.* 2006; Kumar *et al.* 2009). In addition to the role of cholesterol in A-β lipoprotein generation, interactions of cholesterol with A-β lipoprotein and its role in the pathogenesis of Alzheimer's disease have been shown i.e. A-β affects cholesterol dynamics in neurons, and altered cholesterol metabolism in turn leads to neurological diseases (Michigawa 2006). An epidemiological study by Kin *et al.* (2007) provides compelling evidence that carotid atherosclerosis is associated with brain atrophy. Another evidence that lipid peroxidation may also be a major factor in the aging process and hypercholesterolemic diets may lead to microglia activation and beta amyloid [A-β] plaque deposition (Sparks *et al.* 1994).

5. Garlic's effect on factors associated with CVD

Garlic and its derivatives are traditionally known as effective preventive and treatment for CVD risk factors, atherosclerosis, hyperlipidemia, thrombosis, hypertension, diabetes, and other metabolic diseases (Chang and Johnson 1980; Auer *et al.* 1990; Santos and Johns 1995; Ackermann *et al.* 2001; Omar *et al.* 2007). Numerous clinical trials were conducted on garlic to measure cardiovascular effects with both healthy persons and patients with hyperlipidemia and hypercholesterolemia. These studies indicated that garlic could lower total cholesterol and affect other cardiovascular risk markers (Gardner *et al.* 2001; Turner *et al.* 2004). Meta-analyses of clinical trials documented its use for lowering cholesterol in hyperlipidemia (Warshafsky *et al.* 1993) and in treating hypertension (Silagy and Neil 1994b). Several randomized, double-blind, placebo controlled trials investigating garlic's effect on blood lipids have shown that garlic lowers serum cholesterol when used for a period of 4-16 weeks in hyperlipidemic patients and beyond that period (>20 weeks) garlic's effects on lipids is unknown (Banerjee and Maulik 2002).

Designs of these studies varied widely in sample size and subject composition as well as the type of garlic preparation administered to subjects (Turner *et al*. 2004). Thus, it is difficult to draw any meaningful conclusions from them. So, a brief description of the clinical trials investigating garlic's effects on blood cholesterol, platelet aggregation and blood pressure are presented in the following sections.

HIGH CHOLESTEROL AND LIPID-LOWERING EFFECTS

Some cholesterol is necessary to maintain normal body functions like cell membranes, transports nutrients into and waste products out of cells, and hormones, etc., but too much of the wrong kind leads to trouble. All this cholesterol is transported through either low-density lipoprotein or high-density lipoprotein. LDL-cholesterol is bad for health whereas HDL-cholesterol is good because it works to eliminate excess blood cholesterol so it does not collect in the arteries. Research on animals and humans in the 1980s and early 1990s seemed to indicate that garlic had much promise for lowering cholesterol (Kamanna and Chandrasekhara 1982; Kleijnen *et al.* 1989; Gebhardt 1993).

Animal studies

Garlic's ability to significantly lower total blood cholesterol has been shown in animal studies, suggesting that it may provide some protection against CVD (Isaacsohn *et al.* 1998; Superko and Krauss 2000; Santo *et al.* 2007). In rats, both garlic and garlic oil exhibited significant lipid lowering effects, primarily through a decrease in hepatic cholesterogenesis (Kamanna and Chandrasekhara 1982). Several groups of investigators studied the effects of long term (>6 months) feeding of garlic and its preparations (2% garlic powder in diet) on experimental atherosclerosis induced by a high-cholesterol diet in rabbits (Jain 1977; Mand *et al.* 1985; Rajasree *et al.* 1999), reported a statistically significant reduction in atheromatous lesions, particularly in the aorta, that averaged about 50%. A recent study has been documented that aqueous extract of raw garlic exerted cholesterol-lowering activity, especially LDL-cholesterol in normo-lipidemic rats (Mokni *et al.* 2009).

Chronic studies (4 weeks) of garlic on lipid metabolism in rats were also encouraging. Garlic (1–4% in the diet) administration in hypercholesterolemic rats induced by a high-cholesterol diet significantly reduced serum lipid profiles except serum HDL-cholesterol (Chi 1982). Chickens whose diets were supplemented with garlic powder had significant reductions of plasma and tissue cholesterol and plasma triacylglycerols through by decreased HMG-CoA-reductase activity and cholesterol-7-α-hydroxylase activity (Konjufca *et al.* 1997).

In rats in which endothelial injuries of the carotid artery were induced and then fed a cholesterol-rich diet, those given garlic supplementation had a significant inhibition of hypercholesterolemia (Heinle and Betz 1994). Similarly, in rabbits given arterial endothelial injuries and then fed a high cholesterol diet, those assigned to garlic supplements (Kyolic) had a significant reduction in the development of fatty streaks and plaques and cholesterol accumulation in vessel-wall, thus providing protection against the onset of atherosclerosis (Efendy *et al.* 1997).

In several studies in rabbits fed a high cholesterol diet, garlic or allicin supplementation significantly decreased tissue cholesterol, lowered LDL concentrations, raised HDL concentrations, inhibited hypercholesterolemia, and reduced atheromatous changes in the aorta by 50% (Jain and Konar 1978; Bordia and Verma 1980; Mirhadi *et al.* 1991; Eilat *et al*. 1995).

Other studies have indicated that garlic and its constituents inhibit human squalene monooxygenase and HMG-CoA reductase, enzymes involved in cholesterol biosynthesis (Gebhardt 1993; Gupta and Porter 2001). This inhibition of HMG-CoA reductase by garlic has also been confirmed in a recent study (Augusti *et al.* 2005). It has also been shown that three water-soluble sulfur containing compounds (SAC, SEC, SPC) present in aged garlic extract are less cytotoxic and more efficient in inhibiting cholesterol biosynthesis than the lipid-soluble sulfur compounds such as diallyl sulfide (DAS) (Yeh and Liu 2001). The garlic compound ajoene has HMG-CoA-reducing activity as well (Gebhardt *et al.* 1994).

Human studies

Several clinical reports and meta-analyses have revealed the cholesterol-lowering effects of garlic and its preparations (Robbers and Tyler 1999; Ashraf *et al*. 2005; Yeh and Yeh 2006; Gardner *et al.* 2007; Sobenin *et al.* 2008; Khoo and Aziz 2009). There is no reasonable explanation for this inconsistency with research results that demonstrate the cholesterol-lowering effects of garlic. It may be the wrong use of allicin as standardize potential marker (Schardt and Schmidt 1995). However, the above meta-analysis excluded the results of several clinical studies of the effects of AGE on cholesterol. AGE has consistent effects on risk factors for CVD, including cholesterol and others (Yokoyama *et al.* 1988; Steiner and Lin 1994; Munday *et al.* 1999; Budoff *et al.* 2004). In some of these studies, blood SAC level was measured in the subjects as a compliance marker for the standardization of garlic products (Steiner and Li 2001; Budoff *et al.* 2004).

Some case series and controlled trials in healthy adults given garlic supplements along with cholesterol-rich diets suggest that garlic can reduce mean serum cholesterol levels and increase fibrinolytic activity (Bordia and Bansal 1973). These studies were mostly randomized, double blind, placebo-controlled using garlic powder at 600-900 mg/day rather than raw garlic of 4-16 weeks in hyperlipidemic patients showed a significant decrease in serum cholesterol and serum triglyceride (Nitiyanant *et al.* 1987; Vorberg and Schneider 1990; Silagy and Neil 1994). Only about one-third of these studies were reported a consistent decrease of LDL-cholesterol (11-26%) level. A few studies using garlic powder (having low allicin yields) failed to show any lipid lowering effects (Luley *et al.* 1986).

In a single blind, placebo-controlled study, 40 hypercholesterolemic adults were assigned to either placebo for one month or garlic powder (1200 mg) capsules with fish oil (1800 mg of eicosapentanoic acid [EPA] + 1200 mg of docosahexanoic acid [DHA]) daily for one month, resulted in an 11% decrease in cholesterol, a 34% decrease in triglycerides, and a 10% decrease in LDL levels, as well as a 19% decrease HDL risk (Morcos 1997).

In a double-blind placebo controlled trial among 115 hypercholesterolemic adults assigned to a low fat, low cholesterol diet and different formulated garlic preparation (dried powder, aqueous extracts, raw, oil) with different dosages showed an approximate 10% reduction in total cholesterol levels (Silagy and Neil 1994). Negative results were also noted in two other studies of hypercholesterolemic patients (n = 40 and n = 28) on a low-fat diet who were supplemented with 900 mg daily of Kwai garlic powder and placebo (Simons *et al.* 1995). These results indicate that in patients following a low fat, low-cholesterol diet, and garlic supplementation may have little additional lipid-lowering effect. The efficacy of a garlic-ginkgo combination product (Allium Plus®) was analyzed in a randomized, placebo-controlled, double-blind study of 43 patients with elevated total cholesterol levels (230-390 mg/dl) showed an improvement of their total cholesterol level (Kenzelmann and Kade 1993). Another meta-analysis (Neil *et al.* 1996) revealed that there was no significant difference in the mean concentrations of serum lipids, lipoproteins or apo A_1 or B amongst the groups receiving garlic (900 mg/day of dried garlic powder standardized to 1.3% allicin) and placebo. In this meta-analysis, garlic was less effective in reducing total cholesterol than suggested by previous meta-analyses. Another meta-analysis revealed that garlic reduced total cholesterol significantly compared to placebo, but results from six of the studies analyzed showed non- significant differences between garlic and control groups (Stevinson *et al.* 2000; Banerjee and Maulik 2002). These meta-analyses show that garlic intake (powder tablets or aged extract) for 4-12 weeks by hypercholesterolemic subjects moderately reduces (<20 mg/dl) total cholesterol. In a placebo-controlled trial in 35 renal transplant patients, those given garlic supplements (680 mg bid) for 6 weeks had a significant reduction in total serum cholesterol and LDL-cholesterol compared with placebo-treated patients (Lash *et al.* 1998). But in a placebo-controlled randomized trial in 30 pediatric patients with familial hypercholesterolemia, eight weeks of supplementation with 900 mg daily of garlic (Kwai) had no significant impact on fasting cholesterol levels or LDL (McCrindle *et al.* 1998). Alder *et al.* (2003) published a systematic review of the effectiveness of garlic as an antihyperlipidemic agent. They included 10 studies and found that in 6 studies garlic was effective in reducing serum cholesterol levels. The average drop in total cholesterol was 9.9%, LDL 11.4%, and triglycerides 9.9%. Earlier meta-analysis has also confirmed that garlic is superior to a placebo in reducing total cholesterol levels (Ackermann *et al.* 2001; Stevinson *et al.* 2004).

In a placebo-controlled trial of 25 patients with moderate hypercholesterolemia, those assigned to a steam-distilled garlic oil preparation (5 mg twice a day) for 12 weeks did not have significantly lower serum lipoprotein levels, total cholesterol, LDL-cholesterol, HDL-cholesterol, or triglycerides (Berthold *et al.* 1998).

In a randomized, controlled double blind study of 152 adults, supplementation with 900 mg daily of standardized garlic powder (Kwai) for 4 years reduced plaque volume in the carotid and femoral arteries by 9-18%, decreased LDL-cholesterol by 4%, increased HDL concentration by 8%, and lowered blood pressure by 7% (Siegel *et al.* 1999). A double-marked placebo-controlled randomized study reported that garlic powder tablets beneficial effects on blood lipid levels in mild hyperlipidemic patients, namely lower total cholesterol and LDL-cholesterol (11-13%) and raised HDL-cholesterol (11.5%) (Sobenin *et al.* 2008).

Garlic oil appears to be less efficacious than garlic powder, presumably because the oil does not contain allicin, the active ingredient in the garlic powder (Berthold *et al.* 1998). The available data suggests that garlic is superior to placebo in reducing total cholesterol levels. However, the size of the effect is modest, and the robustness of the effect is debatable. Therefore, the cholesterol-lowering effect of garlic remains to be firmly established.

HYPERTENSION

A general definition of hypertension is a systolic blood pressure (SBP) of 140 mm Hg or higher or a diastolic blood pressure (DBP) of 90 mm Hg or higher or both. It is a prominent risk factor for the development of cardiovascular morbidity and mortality, affecting an estimated 1 billion individual's worldwide (Chobanian *et al.* 2003). By prevention and proper management of hypertension decreases the incidence of related morbidity and mortality. In 1993, Joint National Committee reported that a downward shift of 3 mm Hg in SBP decreases the mortality from stroke by 8% and from ischemic heart disease by 5%. Life style modification like low fat diets, low-fat dairy products, vegetables and fruits are definitive therapy for some and adjunctive therapy for all persons with hypertension (Joint National Committee 1997). Based on current information, garlic powder and its preparations are considered for recommendation as adjuncts in the treatment of hypertensive patients (Turner *et al.* 2004).

Animal studies

Garlic extracts reduce blood pressure in rats and dogs (Korotkov 1996). In experimental animals, intravenous injection of garlic extracts produced slight reductions in both systolic and diastolic pressures whereas oral administration of garlic extracts bringing blood pressure back to the normal range (Chanderka and Jain 1973). Blood pressure in dogs was significantly reduced for several hours following intragastric administration of a small dose (2.5 mg/kg) of garlic powder (Banerjee 1976). Garlic (100 mg/kg) administration for 5 days resulted in a complete inhibition of acute hypoxic pulmonary vasoconstriction in rats (Fallon *et al.* 1998).

Chronic oral administration of allicin lowered blood pressure and pulmonary vasodilatation in hypertensive rats (Kaye *et al.* 2000). Single as well as multiple doses of aqueous garlic extract reduced thromboxane-B_2 and prostaglandin-E_2 level in hypertensive rats (Al-Qattan *et al.* 2001). In rabbits, intravenous administration of garlic extracts elicited a dose-dependent diuretic-natriuretic response and a gradual decrease in heart rate, but not in arterial blood pressure (Pantoja *et al.* 1996). Recent studies have been established that blood pressure reducing properties of garlic linked with production of hydrogen sulphide (Benavides *et al.* 2007) and enzyme ALNase which has angiotensin-II inhibiting and vasodilating effects in animal cell (Al-Qattan *et al.* 2006).

Human studies

Several clinical trials of garlic's effects on blood pressure have been performed since Leoper and DeBray (1921) recognized garlic's ability to lower blood pressure. Damrau (1941) reviewed the earlier literature, including his own investigations on 26 patients. Blood pressure reduction was observed in 85% of the patients, the average decline being 12.3 mm Hg systolic blood pressure (SBP) and 6.5 mm Hg diastolic blood pressure (DBP), over one-quarter of the subjects experienced a decline in SBP of 20 mm Hg or more. Piotrowski (1948) reviewed some of the early clinical studies in which garlic was administered under controlled conditions to hypertensive patients. Two-fifths of 100 patients exhibited a 20 mm Hg or greater decline in SBP generally within 1 week after initiation of treatment with 0.6 to 1.2 g daily of dialyzed, alcoholic garlic extract. Studies with a dried garlic powder tablets (Kwai) showed a significant reduction in SBP as well as DBP with 0.6 g garlic powder/day and in a randomized double blind trial, a beneficial effect of garlic on blood pressure and blood lipids in mildly hypertensive subjects was demonstrated (Harenberg *et al.* 1998). Pektov (1997) also cited several studies, mostly from the Soviet Union and Bulgaria, which indicate that garlic and its extracts exhibit moderate hypotensive effect involving a drop in SBP of 20–30 mm Hg and in DBP of 10–20 mm Hg. Another study in China on 70 hypertensive patients who were given garlic oil equivalent to 50 g of raw garlic/day, 47 patients showed moderate to marked reduction in blood pressure (Bordia *et al.* 1986).

In a randomized, controlled trial (415 subjects, >4 weeks in duration) were identified using a dried garlic preparation (Kwai) and found that most studies had no significant hypotensive activity (Mulrow *et al.* 2000). Only three trials were specifically conducted in hypertensive subjects. Of the seven trials that compared the effect of garlic with that of placebo, three showed a significant reduction in SBP and four in DBP (Silagy and Neil 1994b). The overall pooled mean difference in the change in SBP was 5-7% greater in the subjects who were treated with garlic then in those treated with placebo. A meta-analysis suggests that garlic powder preparation may be of some clinical use in subjects with mild hypertension. The Rahman and Lowe (2006) review of garlic and CVD concluded that while some studies reported a reduction in blood pressure, others did not and the reductions reported were not significant. Ried *et al.* (2008) studied a systematic review and meta-analysis, reported that that garlic preparations are superior to placebo in reducing blood pressure in individuals with hypertension.

PLATELET AGGREGATION

Platelet aggregation is a leading cause of thrombosis and myocardial infarction (Schiffer *et al.* 2004; Fauci *et al.* 2009). The prostaglandin, prostacyclin (PGI_2), produced by endothelial cells lining the blood vessels, prevents the adherence of platelets to the blood vessels. Therefore, disc-shaped blood platelets come into contact with foreign surface, collagen in the injured vessel wall and form plaques that inhibit flow of blood. This process is platelet activation. ADP and thrombin also accelerate platelet activation. The activated platelets change shape, put out pseudopodia, discharge their granules, and stick to other platelets, initiating the process of platelet aggregation. An important plasmalogen, 1-alkenyl, 2-acetylglycerol- 3-phosphocholin is referred to as platelet activating factor (PAF) and causes spontaneous blood platelet aggregation (Ali *et al.* 1990). Studies have shown that fresh garlic, garlic powder and garlic oil have great potential in inhibiting platelet aggregation (Sharma and Sunny 1988). Several garlic compounds, ALN, ajoene, allicin, vinyldithiines and DADS contribute to the antithrombotic effect (Makheja *et al.* 1979). These effects appear to be important contributors to garlic's beneficial effects in atherosclerotic conditions.

Animal studies

Pretreatment of rabbits with an aqueous extract of garlic (500 mg/kg) significantly inhibited aggregation induced by ADP, epinephrine, collagen, thrombin, arachidonate, and PAF in a dose-dependent manner *in vitro* and inhibited biosynthesis of prostacyclin in rat aorta (Ali *et al.* 1990). Thromboxane-B_2 synthesis was significantly reduced in animals pretreated with garlic and then injected with a lethal dose of either collagen or arachidonic acid. These observations indicate that garlic may be beneficial in the prevention of thrombosis (Kiesewetter *et al.* 1990). In rabbits, an aqueous extract of garlic demonstrated a dose-dependent inhibition of thromboxane production, but there was no impact on prostacyclin synthesis (Apitz *et al.* 1983). A dose-dependent inhibition of cyclooxygenase activity and collagen-induced platelet aggregation was observed in rabbit platelets treated with raw garlic *in vitro*, but boiled garlic was found to be of little effect. This finding indicates that garlic may be beneficial in the prevention of thrombosis if ingested raw rather in a cooked form (Ali and Mohammad 1986). Fresh garlic extract is effective in reducing thromboxane formation by platelets both *in vivo* and *in vitro* animal models of thrombosis. This study suggested that garlic should be taken more frequently in order to achieve beneficial effects in the prevention of thrombosis (Ali and Thomson 1995). Garlic extract also inhibited prostaglandin synthetase (96%) and lipoxygenase (100%), thereby decreasing thromboxane synthesis and inflammatory cytokines (Thomson *et al.* 2000).

Human studies

In human studies a positive response to garlic has been observed. In randomized, controlled trials in healthy adults with garlic supplementation (600–800 mg daily) has reduced platelet aggregation and enhanced fibrinolysis (Boullin 1981; Ali and Mohammad 1986). In another study, 14 adult volunteers given one clove (approximately 3 g) of fresh garlic daily for 26 weeks, there was an approximately 80% reduction in serum thromboxane (Ali 1995). In a randomized, double-blind, placebo controlled crossover study of 12 healthy adults, dried garlic powder supplementation (900 mg daily) led to significantly higher total fibrinolytic activity and tissue plasminogen activator activity within 2-4 hours of garlic ingestion. Platelet aggregation was also significantly lower after 7 and 14 days of garlic treatment (Legnani *et al.* 1993). Another study using aged garlic extract for 13 weeks in duration on 23 normolipidaemic subjects showed a significant decrease in both the total percentage and initial rate of platelet aggregation (Rahman and Billington 2000). Raw garlic, garlic oil and other extract of garlic have been shown to inhibit platelet aggregation in *vitro* induced by ADP, collagen, arachidonate, epinephrine and calcium ionophore (Srivsatava 1986). Chronic intake of garlic powder and garlic oil also inhibits platelet aggregation (Steiner *et al.* 1998; Thomson *et al.* 2000). Wojcikowski *et al.* (2007) reported that platelet aggregation induced by adrenaline was reduced slightly but significantly ($P < 0.05$; 12% reduction).

POSSIBLE MECHANISMS

The pharmacologic effects of garlic are attributed to allicin, ajoene, and other organosulfur constituents and medicinal value of garlic is best known for its antiatherosclerotic and antiatherogenic effects (Orekhov and Grunwald 1997; Ali *et al.* 2000). As the most plausible explanation of the defense mechanism operative in the garlic, allicin modifies the ALNase molecule at its -SH groups, leading to inactivation of this allicin-producing enzyme (Ankri *et al.* 1997). Bhusan *et al.* (1979) studied the effect of raw garlic on normal blood cholesterol in humans. They reported that allicin can combine with -SH groups, the functional part of CoA, a necessary part of the biosynthesis of cholesterol.

Animal studies have shown that supplementation of garlic in the diet depressed the hepatic activities of lipogenic and cholesterogenic enzymes such as malic enzyme, glucose-6-phosphate dehydrogenase and (HMG-CoA) reductase (Mathew *et al.* 1996). One comprehensive study of hydrophilic and hydrophobic compounds of garlic demonstrated that the cholesterol-lowering effects of garlic extract result mainly water-soluble sulfur compounds causes inhibition of hepatic cholesterol synthesis (Yeh and Lin 2001). The results of this study indicated squalene monooxygenase as one of the target enzymes through which garlic inhibits cholesterol biosynthesis (Gupta and Porter 2001). Mehrzia *et al.* (2006) examined the acute effects of a partially purified fraction from garlic on plasma glucose and cholesterol levels in rats, and confirmed that aqueous extract of garlic contained an active fraction different from SAC sulfoxide, exerting both glucose and cholesterol lowering activity. The mechanism of action seemed to involve a specific inhibitor of nitric oxide (NO) production, which increased time and dose dependently. *In vitro* studies revealed that water-soluble organic sulfur compounds, especially SAC present in AGE and DADS present in garlic oil, are also potent inhibitors of cholesterol synthesis (Amagase 2006). Weiss *et al.* (2006) demonstrated that AGE retards the progress of coronary artery calcification by improves homocysteine-induced endothelial dysfunction in macro- and micro-circulation. Yeh *et al.* (2005) reported that garlic extract attenuates increased amounts of homocysteine exerts several proatherosclerotic effects. Thus, the decrease in levels of elevated homocysteine by garlic ingestion suggests its protective role against CVD.

Uptake of oxidized LDL (ox-LDL) by vascular endothelial cells is a critical step in the initiation and development of atherosclerosis. Adhesion molecules are up regulated by ox-LDL and numerous inflammatory cytokines and play a pivotal role in atherogenesis. Lei *et al.* (2008) reported that diallyl sulfide (DAS), DADS, and DATS, three major organosulfur compounds of garlic oil, reduce adhesion molecule expression induced by ox-LDL.

In addition to lowering lipid levels, garlic has a positive and well-established mechanism of platelet aggregation inhibitory effect in both healthy subjects and subjects with CVD (Banerjee 1976; Steiner and Li 2001). It is well known that prostaglandin is an inhibitor of platelet aggregation and is used in the treatment of atherosclerosis (Kikura *et al.* 2000; Koga *et al.* 2002). It has also been reported that when PGE_1 aggregated platelets, it caused them to disaggregate (Kikura *et al.* 2000). This activity is in part, regulated by cyclic adenosine monophosphate (cAMP). Endothelial cells contain prostacyclins synthetase, which produces prostaglandin I_2 from endoperoxides; whereas platelets contain thromboxane synthetase, which produces thromboxane (TXA_2) (Smith 1989). The formation of TXA_2 in platelets induces platelet aggregation, which is accompanied by the platelet-release reaction whereby serotonin and other granule components are expelled from platelet stores. TXA_2 also induces a rise in the concentration of ionized calcium in the platelet cytosol and a decrease in platelet cAMP formation by inhibiting adenylyl cyclase. Prostaglandin I_2 binds to specific receptors on the surface of the platelets and stimulates adenylyl cyclase. The resulting increase in platelet cAMP leads to calcium reuptake by the dense tubular system and thereby inhibits platelet activation, platelet granulation secretion, and thus platelet aggregation. In confirmation, PGE_1, a known stimulator of platelet cAMP, caused significant inhibition of platelet aggregation when these were pre incubated with PGE_1 up to a concentration of 250 mg/ml and stimulated with ADP (Willoughby *et al.* 2002). AGE and its constituents were shown to exert inhibitory effects on platelet aggregation at all levels of supplementation in the course of one study but they failed to draw any concrete mechanism of action (Steiner *et al.* 2001). Samson *et al.* (1982) suggested that the antiaggregation effect might be related to intraplatelet mobilization of calcium. Inhibition of epinephrine-induced aggregation by garlic extract may suggest that it may be inhibiting uptake of calcium into platelets thereby lowering cytosolic calcium concentrations. Hussein (2003) reported the relaxant effect of garlic on the skeletal muscle due to blockade of nicotinic receptor at the neuromuscular junction. This investigation provides new documents about its direct action on the myocardium, its increase to the smooth muscle mortality and its relaxant to the smooth muscle concentration. The biologically active chemical constituents as well as the rich-minerals contents help in the manifestation of its mode of action on the excitable tissues. They could affect directly the cell membrane probably through the receptors coupling to G-proteins, which regulates the ion channels physiology as in the myocardium and indirectly through inactivation of the cholinergic muscarinic receptors of the smooth muscle.

AGE is reported to enhance NO production and it is likely that the platelet-derived NO contributes to the process of platelet disaggregation (Morihara *et al.* 2002). The inhibition of phosphoinositide-3-kinase (PI3-kinase) has been shown to cause platelet disaggregation, and the incubation of platelets with PI3-kinase inhibitors leads to a dose-dependent increase in platelet NO and cAMP levels (Morihara *et al.* 2002). AGE could also be reducing thromboxane formation because fresh garlic extract has been shown to do this (Thomson *et al.* 2000), or it is binding to thromboxane A_2 receptors in a similar manner to that observed with the inhibitory effects of flavonoids on platelet function (Guerrero *et al.* 2005). Srivastava *et al.* (1986) reported that aqueous extract of garlic inhibits platelet aggregation induced by ADP, epinephrine, collagen. Sendl *et al.* (1992) demonstrated that chloroform/acetone extracts of fresh garlic inhibit cyclo-oxygenase activity, reduced formation of thromboxane, inhibit phospholipase activity, and lipoxygenase activity in platelets.

The garlic component, DATS, is reported to inhibit platelet aggregation and calcium mobilization in a concentration-dependent manner without increasing intracellular cAMP and cGMP levels. DATS also had no effect on thromboxane A_2 production and no effect on inositol-1,4,5-triphosphate formation. Hence, it is possible that AGE acts in a similar fashion and suppresses calcium mobilization at a step distal to the formation of inositol-1, 4, 5-triphosphate (Qi *et al.* 2000). Another speculation is that AGE may inhibit phospholipase A_2, thus reducing levels of lysophosphatidic acid, which causes platelet aggregation and increases intracellular calcium ions (Xu *et al.* 2003). About antiplatelet action of ajoene several authors suggested that ajoene strongly inhibits the metabolism of arachidonic acid by both cyclooxygenase and lipoxygenase pathways (Apitz *et al.* 1986). Jamaluddin *et al.* (1988) reported that ajoene interacts with a purified hemoprotein implicated in platelet activation. Apitz-Castro *et al.* (1983) suggested that garlic's inhibitory effect might be mediated through modification of the physiochemical properties of the plasma membrane, rather than by affecting the arachidonic or calcium metabolism of platelets. Stephen *et al.* (1987) assessed the fatty acids in plasma and phospholipids in RBC and suggested that garlic may affect the levels of polyunsaturated fatty acids which known to influence platelet aggregation.

The antihypertensive effects of garlic have been studied but remain controversial. In a 1994 meta-analysis by Silagy *et al.* (1994) assesses the effect of garlic on hypertension, showed significant reductions in systolic blood pressure (>7.7 mm Hg reduction), and diastolic blood pressure (>5 mm Hg reduction) with garlic treatment compared with placebo. Mechanism of antihypertensive action of garlic is due to its prostaglandin-like effects, which decrease peripheral vascular resistance (Rashid and Khan 1985). Kim *et al.* (2000) reported that direct action of garlic on rat pulmonary artery due to nitric oxide induce protection against hypoxic pulmonary vasoconstriction. Other researchers noticed that the administration of NO synthase inhibitor inhibited the vasodilatory effect of garlic and they concluded that garlic blocks hypoxic pulmonary hypertension *in vivo* and there is a combination of endothelium-dependent and independent mechanisms for its effect in pulmonary arterial rings (Fallon *et al.* 1998). The intraocular pressure-lowering effect by garlic-derived compound, SAMC in rabbits could involve the elevation of anti-naturitic peptide (ANP) levels in aqueous humor which was enhanced modestly by topical, bilateral pretreatment with a reducing agent, tris(2-carboxyethyl)phosphine without alteration of pupil diameter but alteration of sulfhydryl reactivity does not seem to be a major mechanism of action for SAMC (Chu *et al.* 1999).

One more study *in vitro* indicated that γ-glutamyl cysteines in garlic might lower blood pressure by inhibiting angiotensin-converting enzyme (Qidwai *et al.* 2000). Garlic modulates the production, function of both endothelium derived relaxing and constricting factors, and this may contribute to its protective effect against hypoxic pulmonary vasoconstriction (Kim *et al.* 2000).

One hypothesis was explained by the fact that NG-nitro-L-arginine methyl ester (L-NAME) a nitric oxide inhibitor abolished the vasodilatory effect of garlic (Kaye *et al.* 2000). But another study reported that pulmonary vasodilatory effect of allicin is independent of the synthesis of NO, ATP-sensitive (K^+) channel, activation of cyclooxygenase enzyme (Nakagawa *et al.* 1980).

ADVERSE EFFECTS OF GARLIC

Garlic has been used as a medicinal agent for thousands of years and it is taken for granted that garlic is safe in a wide range of doses. However, excessive intake can have harmful effects. Prolonged feeding of raw garlic juice in rats at a dose of 5 ml/kg led to weight loss, anemia, hepatic and pulmonary toxicity and sometime resulted in death due to stomach injury (Joseph *et al.* 1989). Raw-garlic preparations containing allicin can cause chemical burns on the skin, contact dermatitis, and bronchial asthma (Burden *et al.* 1994). Chronic administration of garlic powder (50 mg/day) resulted in inhibition of spermatogenesis in rats due reduction of sialic acid concentration in the testes, epididymis and seminal vesicles along with decreased leydig cell which antiandrogenic effect of garlic (Joseph *et al.* 1989).

Aqueous garlic extract (200 g/l) with drinking water for 10 days exhibited significantly higher levels of serum glutamate oxlaoacetate transaminase (SGOT) due to liver injury (Banerjee *et al.* 2001). Chen *et al.* (1999) reported that treatment of rats with fresh garlic homogenate for 7 days caused a significant decrease in liver catalase activity in doses of 2 and 4 g/kg. Other authors reported a significant loss of normal cellular function of heart, liver and kidneys after 30 days feeding of raw garlic homogenate at 1000 mg/kg/day dose (Rabinkov *et al.* 2000).

Garlic oil fed at a dose of 100 mg/kg after 24-h fasting has also been found to be lethal due to acute pulmonary edema with severe congestion (Banerjee *et al.* 2001). Garlic oil with diallyl-disulfide (200 mg/kg b.wt.) significantly reduced body weight gain of rats (Holzgartner *et al.* 1992).

Though toxicity reports cannot be explained to its fullest extent but the sulphoxides present in the garlic extract can undergo exchange reaction with the tritable SH-groups of enzymes like alkaline phosphatase (Banerjee *et al.* 2001), papain, and alcohol dehydrogenase (Blumental *et al.* 2000) and other proteins in the body spontaneously at physiological pH and temperature, inhibiting their activity. These enzyme interactions with garlic components may be a reason for its toxicity.

Relatively few non-specific side effects were reported in human clinical trials using garlic and its preparations included heartburn, nausea, vomiting, diarrhea, flatulence, bloating, mild orthostatic hypotension, flushing, tachycardia, headache, insomnia, decrease in serum protein and calcium levels, sweating and dizziness as well as offensive body odor (Piscitell *et al.* 2002). Consumption of excessive amounts of garlic, especially on an empty stomach, can cause gastrointestinal upset, flatulence, and changes in the intestinal flora (Fugh-Berman 2000).

CONCLUSION

Garlic has many health benefits and its therapeutic effects have been studied extensively in the last few decades. Many clinical and preclinical studies have shown that garlic and its preparations help in preventing or reducing the risk of CVDs. Various chemical constituents have also been identified. Each compound is closely related to and responsible for the various biological effects, and it is unnecessary to retain allicin or its degraded odorous oil-soluble sulfur compounds in the garlic product. This clearly indicates that while garlic preparations are traditionally recognized as a source of sulfur compounds, much more interesting compounds than allicin may be actually responsible for cardio protective function. However, certain issues regarding the proper use of garlic, i.e. use of different preparations available, dose, duration and interaction with generic drugs should be optimized. Further research should also be carried out to identify specific compounds from garlic or garlic products that are responsible for most of its biological effects and to draw a proper mechanism of action.

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REFERENCES

Ackerman RT, Mulrow CD, Ramírez G, Gardner CD, Morbidoni L, Lawrence VA (2001) Garlic shows promise for improving some cardiovascular risk factors. *Archives of Internal Medicine* **161**, 813-882

Adak M (2009) Beneficial effect of garlic (*Allium sativum*) on cancer. *Jamahiriya Medical Journal* **9 (3)**, 169-170

Agarwal RK, Dewar HA, Newell DJ, Das B (1977) Controlled trial of the effect of cycloalliin on the fibrinolytic activity of venous blood. *Atherosclerosis* **27**, 347-351

Ajayi GO, Adeniyi TT, Babayemi DO (2009) Hepatoprotective and some haematological effects of *Allium sativum* and vitamin C in lead-exposed Wistar rats. *International Journal of Medicine and Medical Sciences* **1 (3)**, 64-67

Albert CM, Ma J, Rifai N, Stampfer MJ, Ridker PM (2002) Prospective study of C-reactive protein, homocysteine, and plasma lipid levels as predictors of sudden cardiac death. *Circulation* **105 (22)**, 2595-2599

Albert MA, Glynn RJ, Ridker PM (2003) Plasma concentration of C-reactive protein and the calculated Framingham Coronary Heart Disease Risk Score. *Circulation* **108 (2)**, 161-165

Alder R, Lookinland S, Berry JA, Williams M (2003) A systematic review of the effectiveness of garlic as an antihyperlipidemic agent. *Journal of the American Academy of Nurse Practitioners* **15**, 120-129

Ali M (1995) Mechanism by which garlic (*Allium sativum*) inhibits cyclooxygenase activity. Effect of raw versus boiled garlic extract on the synthesis of prostanoids. *Prostaglandins, Leukotrienes and Essential Fatty Acid* **53**, 397-400

Ali M, Mohammed SY (1986) Selective suppression of platelet thromboxane formation with sparing of vascular prostacyclins synthesis by aqueous extract of garlic in rabbits. *Prostaglandins, Leukotrienes and Essential Fatty Acid* **25**, 139-146

Ali M, Thomson M (1995) Consumption of a garlic clove a day could be beneficial in preventing thrombosis. *Prostaglandins, Leukotrienes and Essential Fatty Acids* **53**, 211-212

Ali M, Thomson M, Afzal M (2000) Garlic and onions: Their effect on eicosanoid metabolism and its clinical relevance. *Prostaglandins, Leukotrienes and Essential Fatty Acids* **62**, 55-73

Ali M, Thomson M, Alnaqeeb MA, Al-Hassan JM, Khater SH, Gomes A (1990) Antithrombotic activity of garlic: its inhibition of the synthesis of thromboxane-B2 during infusion of arachidonic acid and collagen in rabbits. *Prostaglandins, Leukotrienes and Essential Fatty Acids* **41**, 95-99

Al-Qattan KK, Khan I, Alnaqeeb MA, Ali M (2001) Thromboxane-B2, prostaglandine-E2 and hypertension in the rat 2-kidney 1-clip model: a possible mechanism of the garlic induced hypotension. *Prostaglandins, Leukotrienes and Essential Fatty Acids* **64**, 5-10

Al-Qattan KK, Khan I, Alnaqeeb MA, Ali M (2003) Mechanism of garlic (*Allium sativum*) induced reduction of hypertension in 2K-1C rats: a possible mediation of Na/H exchanger isoform-1. *Prostaglandins, Leukotrienes and Essential Fatty Acids* **69 (4)**, 217-222

Al-Qattan KK, Thomson M, Al-Mutawa'a S, Al-Hajeri D, Drobiova H, Ali M (2006) Nitric oxide mediates the blood-pressure lowering effect of garlic in the rat two-kidney, one-clip model of hypertension. *Journal of Nutrition* **136 (3)**, 774S-776S

Al-Qattan MM (2009) Garlic burns: case reports with an emphasis on associated and underlying pathology. *Burns* **35 (2)**, 300-302

Amagase H (2006) Clarifying the real bioactive constituents of garlic. *Journal of Nutrition* **136**, 716S-725S

American Heart Association (2009) Heart Disease and Stroke Statistics - 2009 Update. Dallas, Texas: American Heart Association, 2009. Available online: http//www:americanheart.org/statistics

Amin M, Kapadnis BP (2005) To study antimicrobial activity of shallot in comparison with that of garlic. *Indian Journal of Experimental Biology* **43 (8)**, 751-754

Amonkar SV, Reeves EL (1971) Mosquito control with active principle of garlic. *Journal of Economic Entomology* **63**, 1172-1175

Anderson JA, Leonard DA, Cusack KP, Frye LL (1995) 15-Substituted lanosterols: post-transcriptional suppressors of 3-hydroxy-3-methylglutaryl coenzyme A reductase. *Archives of Biochemistry and Biophysics* **316**, 190-196

Anderson KM, Odell PM, Wilson PW, Kennl WB (1991) CVD risk profiles. *American Heart Journal* **121**, 293-298

Ankri S, Miron T, Rabinkov A, Wilchek M, Mirelman D (1997) Allicin from garlic strongly inhibits cysteine proteinases and cytopathic effects of *Entamoeba histolytica. Antimicrobial Agents and Chemotherapy* **41**, 2286-2288

Apitz-Castro R, Cabrera S, Cruz MR, Ledezma E, Jain MK (1983) Effects of garlic extract and of three pure components isolated from it on human platelet aggregation, arachidonate metabolism, release reaction and platelet ultra structure. *Thrombosis Research* **32**, 155-169

Apitz-Castro R, Ledezma E, Escalante J, Jain MK (1986) The molecular basis of the antiplatelet action of ajoene: direct interaction with the fibrinogen receptor. *Biochemistry and Biophysics Research Communication* **141**, 145-150

Apitz-Castro R, Escalante J, Vargas R, Jain MK (1986) Ajoene, the antiplatelet principle of garlic, synergistically potentiates the antiaggregatory action of prostacyclin, forskolin, indomethacin and dypiridamole on human platelets. *Thrombosis Research* **42**, 303-311

Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM, Lin PH, Karanja N (1997) A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *New England Journal of Medicine* **336 (16)**, 1117-1124

Ariga T, Oshiba S, Tamada T (1981) Platelet aggregation inhibitor in garlic. *Lancet* **1**, 150-151

Ashraf MZ, Hussain ME, Fahim M (2005) Antiatherosclerotic effects of dietary supplementations of garlic and turmeric: Restoration of endothelial function in rats. *Life Science* **77 (8)**, 837- 857

Ashraf R, Aamir K, Shaikh AR, Ahmed T (2005) Effects of garlic on dyslipidemia in patients with type-2 diabetes mellitus. *Journal of Ayub Medical College, Abbottabad* **17 (3)**, 60-64

Auer W, Eiber A, Hertkorn E, Hoehfeld E, Koehrle U, Lorenz A, Mader F, Merx W, Otto G, Schmid-Otto B (1990) Hypertension and hyperlipidemia: Garlic helps in mild cases. *British Journal of Clinical Practice* **69**, 3-6

Augusti KT, Benaim ME (1975) Effect of essential oil of onion (allyl propyl disulphide) on blood glucose, free fatty acid and insulin levels of normal subjects. *Clinica et Chimica Acta* **60**, 121-123

Augusti KT, Chackery J, Jacob J, Kuriakose S, George S, Nair SS (2005) Beneficial effects of a polar fraction of garlic (*Allium sativum* Linn) oil in rats fed with two different high fat diets. *Indian Journal of Experimental Biology* **43**, 76-83

Bagga S, Thomas BS, Bhat M (2008) Garlic burn as self-inflicted mucosal injury – a case report and review of the literature. *Quintessence International* **39 (6)**, 491-494

Balk EM, Lichtenstein, AH, Chung M, Kupelnick B, Chew P, Lau J (2006) Effects of omega-3 fatty acids on serum markers of cardiovascular risk: A systematic review. *Atherosclerosis* **189**, 19-30

Banerjee AK (1976) Effect of aqueous extract of garlic on arterial blood pressure of normotensive and hypertensive rats. *Artery* **2**, 369-373

Banerjee SK, Maulik M, Manchanda SC, Dinda AK, Das TK, Maulik SK (2001) Garlic-induced alteration in rat liver and kidney morphology and associated changes in endogenous antioxidant status. *Food and Chemical Toxicology* **39**, 793-797

Banerjee SK, Maulik SK (2002) Effect of garlic on cardiovascular disorders: A review. *Journal of Nutrition* **1**, 1-4

Barnes P, Powell-Griner E, McFann K, Nahin R (2004) Complementary and alternative medicine use among adults United States, 2002. *Advanced Data* **27 (343)**, 1-19

Bartimaeus ES (2002) Toxicological effects of garlic (*Allium sativum*) on some haematological and biochemical parameters in rats. *Global Journal of Environmental Science* **2 (1)**, 11-16

Benatuil L, Apitz-Castro R, Romano E (2003) Ajoene inhibits the activation of human endothelial cells induced by porcine cells: implications for xenotransplantation. *Xenotransplantation* **10 (4)**, 368-373

Benavides GA, Squadrito GL, Mills RW, Patel HD, Isbell TS, Patel RP, Darley-Usmar VM, Doeller JE, Kraus DW (2007) Hydrogen sulfide mediates the vasoactivity of garlic. *Proceedings of the National Academy of Science USA* **104 (46)**, 17977-17982

Bent S, Ko R (2004) Commonly used herbal medicines in the United States: a review. *American Journal of Medicine* **116**, 478-485

Bergner P (1996) *The Healing Power of Garlic*, Prima Publishing, Rocklin, CA, pp 3-26

Bergmann C, Sano M (2006) Cardiac risk factors and potential treatments in Alzheimer's disease. *Neurology Research* **28 (6)**, 595-604

Berthold HK, Sudhop T, von Bergmann K (1998) Effect of a garlic oil preparation on serum lipoproteins and cholesterol metabolism: a randomized controlled trial. *Journal of American Medical Association* **279**, 1900-1902

Best LG, Zhang Y, Lee ET, Yeh JL, Cowan L, Palmieri V, Roman M, Devereux RB, Fabsitz RR, Tracy RP, Robbins D, Davidson M, Ahmed A, Howard BV (2005) C-reactive protein as a predictor of cardiovascular risk in a population with a high prevalence of diabetes: the Strong Heart Study. *Circulation* **112 (9)**, 1289-1295

Bhatt DL, Steg GP, Ohman ME, Hirsch AT, Ikeda Y, Mas JL, Goto S, Liau CS, Richard AJ, Röther J, Wilson PWF (2006) International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *Journal of the American Medical Association* **295 (2)**, 180-189

Bhushan S, Sharma SP, Singh SP, Agrawal S, Indrayan A, Seth P (1979)

Effect of garlic on normal blood cholesterol level. *Indian Journal of Physiology and Pharmacology* **23**, 211-214

Blania G, Spangenberg B (1991) Formation of allicin from dried garlic (*Allium sativum*): a simple HPTLC method for simultaneous determination of allicin and ajoene in dried garlic and garlic preparations. *Planta Medica* **57**, 371-375

Blankenhorn DH, Hodis HN (1993) Atherosclerosis-reversal with therapy. *The Western Journal of Medicine* **159 (2)**, 172-179

Block E (1985) The chemistry of garlic and onions. *Scientific American* **252**, 94-114, 119

Block E, Ahmad S (1984) Ajoene: a potent antithrombotic agent from garlic. *Journal of American chemical Society* **106**, 8295-8296

Blumenthal M (1998) The complete German Commission E monographs: therapeutic guide to herbal medicines. Austin: American Botanical Council.

Blumenthal M, Goldberg A, Brinckmann J (2000) *Herbal Medicine: Expanded Commission Monographs*, Integrative Medicine Communications, Newton, MA, pp 139-147

Bordia A, Bansal HC (1973) Letter: Essential oil of garlic in prevention of atherosclerosis. *Lancet* **2**, 1491-1492

Bordia A (1981) Effect of garlic on blood lipids in patients with heart disease. *American Journal of Clinical Nutrition* **34**, 2100-2103

Bordia A, Bansal HC, Arora SK, Singh SV (1975) Effect of the essential oils of garlic and onion on alimentary hyperlipemia. *Atherosclerosis* **21**, 15-19

Bordia A, Verma SK (1980) Effect of garlic feeding on regression of experimental atherosclerosis in rabbits. *Artery* **7**, 428-437

Bordia A, Joshi HK, Sandya YK, Bhu N (1977) Effect of essential oil of garlic on serum fibrinolytic activity in patients with coronary artery disease. *Atherosclerosis* **28**, 155-159

Bordia A, Joshi HK, Sandya YK, Bhu N (1986) The effect of essential oil of garlic on hyperlipemia and platelet aggregation – an analysis of 308 cases. Cooperative Group for Essential oil of Garlic. *Journal of Traditional Chinas Medicine* **6**, 117-120

Borrelli F, Capasso R, Izzo AA (2007) Garlic (*Allium sativum* L.): adverse effects and drug interactions in humans. *Molecular Nutrition and Food Research* **51 (11)**, 1386-1397

Boullin DJ (1981) Garlic as a platelet inhibitor. *Lancet* **1**, 76-77

Bozzini A (1991) Discovery of Italian fertile tetraploid line of garlic. *Economic Botany* **45**, 436- 438

Bradley PR (1992) British herbal compendium: a handbook of scientific information on widely used plant drugs/published by the British Herbal Medicine Association and produced by it Scientific Committee. Bournemouth, Dorset

Brodnitz MH, Pascale JV, van Derslice LJ (1971) Flavor components of garlic extract. *Journal of Agricultural and Food Chemistry* **19**, 273-275

Budoff M, Takasu J, Flores FR, Niihara Y, Lu B, Lau B, Rosen RT, Amagase H (2004) Inhibiting progression of coronary calcification using aged garlic extract in patients receiving statin therapy: a preliminary study. *Preventive Medicine* **39**, 985-991

Budoff M J, Ahmadi N, Gul K, Hajsadeghi F, Usman N, Nuguri V, Flores F, Nasir K, Naghavi M (2008) Aged garlic extract improves vascular function in asymptomatic individuals with subclinical atherosclerosis. *The Federation of American Societies for Experimental Biology* **22**, 442-445

Burden AD, Wilkinson SM, Beck MH, Chalmers RJG (1994) Garlic-induced systemic contact dermatitis. *Contact Dermatitis* **30**, 299-300

Carreiro-Lewandowski E (2004) Update on selected markers used in risk assessment for vascular disease. *Clinical Laboratory Science* **17 (1)**, 43-49

Castelli WP (1988) Cholesterol and lipids in the risk of coronary artery disease; the Framingham Heart Study .*Canadian Journal of Cardiology* **4**, 5A-10A

Cesari M, Penninx BW, Newman AB, Kritchevsky SB, Nicklas BJ, Sutton-Tyrrell K (2003) Inflammatory markers and onset of cardiovascular events: results from the Health ABC study. *Circulation* **108 (19)**, 2317-2322

Chanderkar AG, Jain PK (1973) Analysis of hypotensive action of *Allium sativum* (garlic). *Indian Journal of Physiology and Pharmacology* **17**, 132-133

Chan KC, Yin MC, Chao WJ (2007) Effect of diallyl trisulfide-rich garlic oil on blood coagulation and plasma activity of anticoagulation factors in rats. *Food and Chemical Toxicology* **45 (3)**, 502-507

Chang HS, Yamato O, Sakai Y, Yamasaki M, Maede Y (2010) Acceleration of superoxide generation in polymorphonuclear leukocytes and inhibition of platelet aggregation by alk(en)yl thiosulfates derived from onion and garlic in dogs and humans. *Prostaglandins, Leukotrienes and Essential Fatty Acids* **70 (1)**, 77-83

Chang HS, Yamato O, Yamasaki M, Maede Y (2005) Modulatory influence of sodium 2-propenyl thiosulfate from garlic on cyclooxygenase activity in canine platelets: possible mechanism for the anti-aggregatory effect. *Prostaglandins, Leukotrienes and Essential Fatty Acids* **2 (5)**, 351-355

Chang MLW, Johnson MA (1980) Effect of garlic on carbohydrate metabolism and lipid synthesis in rats. *Journal of Nutrition* **110**, 931-936

Chen HW, Sheen LY, Kung YL, Liu CT, Lii CK (1999) Effects of garlic oil and its organosulfur compounds on the activities of hepatic drug metabolizing and antioxidant enzymes in rats fed high- and low-fat diets. *Nutrition and Cancer* **35**, 160-166

Chi MS (1982) Effect of garlic products on lipid metabolism in cholesterol-fed rats. *Proceedings of the Society for Experimental Biology and Medicine* **171**, 174-178

Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr., Jones DW, Materson BJ, Oparil S, Wright JT Jr. (2003) The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *Journal of American Medical Association* **289 (19)**, 2560-2572

Chu TC, Han P, Han G, Potter DE (1999) Intraocular pressure lowering by S-allylmercaptocysteine in rabbits. *Journal of Ocular Pharmacology and Therapeutics* **15 (1)**, 9-17

Cook S, Togni M, Schaub MC, Wenaweser P, Hess OM (2006) High heart rate: a cardiovascular risk factor? *European Journal of Heart* **27 (20)**, 2387-2393

Cook NR, Cutler JA, Obarzanek E, Lee MN, Appel LJ (2007) Long term effects of dietary sodium reduction on CVD outcomes: observational follow-up of the trials of hypertension prevention (TOHP). *British Journal of Medicine* **334**, 885-888

Cooper RS, Goldberg RB, Trevisan M, Tsong Y, Liu K, Stamler J, Rubenstein A, Scanu AM (1982) The selective lipid-lowering effect of vegetarianism on low-density lipoproteins in a cross-over experiment. *Atherosclerosis* **44**, 293-305

Das I, Saha T (2009) Effect of garlic on lipid peroxidation and antioxidation enzymes in DMBA-induced skin carcinoma. *Nutrition* **25 (4)**, 459-471

Damru F (1941) The use of garlic concentrate in vascular hypertension. *Medical Resources* **153**, 249-251

Dhawan V, Jain S (2004) Effect of garlic supplementation on oxidized low-density lipoproteins and lipid peroxidation in patients of essential hypertension. *Molecular and Cellular Biochemistry* **266**, 109-115

Donnell CJ, Kannel WB (1998) Cardiovascular risk of hypertension: lesson from observation studies. *Journal of Hypertension* **16 (Suppl)**, 3-7

Dragsted LO, Krath B, Ravn-Haren G, Vogel UB, Marie VA, Bo Jensen P, Loft S, Rasmussen SE, Sandstorm TL, Pedersen A (2006) Biological effects of fruit and vegetables. *Proceedings of the Nutrition Society* **65 (1)**, 61-67

Durak I, Kavutcu M, Aytac B, Avci A, Devrim E, Ozbek H, Ozturk HS (2004) Effects of garlic extract consumption on blood lipid and oxidant/antioxidant parameters in humans with high blood cholesterol. *Journal of Nutritional Biochemistry* **15 (6)**, 373-377

Edwards QT, Colquist S, Maradiegue A (2005) What's cooking with garlic: is this complementary and alternative medicine for hypertension? *Journal of the American Academy of Nurse Practitioners* **17 (9)**, 381-385

Efendy JL, Simmons DL, Campbell GR, Campbell JH (1997) The effect of the AGE 'Kyolic'on the development of experimental atherosclerosis*. Atherosclerosis* **132**, 37-42

Egen-Schwind C, Eckard R, Kemper FH (1992) Metabolism of garlic constituents in the isolated perfused rat liver. *Planta Medica* **58**, 301-305

Eilat S, Oestraicher Y, Rabinkov A, Ohad D, Mirelman D, Battler A, Eldar M, Vered Z (1995) Alteration of lipid profile in hyperlipidemic rabbits by allicin, an active constituent of garlic. *Coronary Artery Disease* **6**, 985-990

Eisenberg DM, Davis RB, Ettner SL, Appel S, Wilkey S, Van Rompay M, Kessler RC (1998) Trends in alternative medicine use in the United States, 1990-1997. *Journal of the American Medical Association* **280**, 1569-1575

El-Sabban F (2009) Garlic as an antithrombotic and antiplatelet aggregation agent. *Journal of Chinese Clinical Medicine* **4 (5)**, 288-289

Fallon MB, Abrams GA, Abdel-Razek TT, Dai J, Chen SJ, Chen YF, Luo B, Oparil S, Ku DD (1998) Garlic prevents hypoxic pulmonary hypertension in rats. *American Journal of Physiology* **275**, 283-287

Fauci A, Braunwald E, Kasper LD, Hauser SL, Longo DL, Jameson JL, Loscalzo J (2009) Harrison's principle's of internal medicine. In: Konkle BA (Ed) *Disorder of Platelets and Vessel Wall* (17th Ed, Vol 1), McGraw Hill Medical, New York, pp 718-724

Fenwick GR, Hanley AB (1985) The genus *Allium*. Part 2. *Critical Reviews in Food Science and Nutrition* **22**, 273-277

Food and Agricultural Organization of United Nations (2005) Economic and Social Department: The Statistical division. Available online: http://www.fao.org/es/ess/top/commodity.html?

Forman D, Bulwer BE (2006) CVD: Optimal approaches to risk factor modification of diet and lifestyle. *Current Treatment Options of Cardiovascular Medicine* **8 (1)**, 47-57

Franco OH, Bonneux L, de Laet C, Steyerberg EW, Mackenbach J (2004) The Polymeal: A more natural, safer, and probably tastier (than the Polypill) strategy to reduce CVD by more than 75%. *British Journal of Medicine* **329**, 1447-1450

Freeman F, Kodera Y (1995) Garlic chemistry: stability of S-(2-propenyl)-2-propene-1-sulfinothiate (allicin) in blood, solvents and simulated physiological fluids. *Journal of Agricultural and Food Chemistry* **43**, 2332-2338

Friedman T, Shalom A, Westreich M (2006) Self-inflicted garlic burns: our experience and literature review. *International Journal of Dermatology* **45 (10)**, 1161-1163

Friedewald WT (2002) CVDs. In: Breslow L (Ed) *Encyclopedia of Public Health*, Macmillan Reference USA/Gale Group Thomson Learning, New York

Fugh-Berman A (2000) Herb–drug interactions. *Lancet* **355**, 134-138

Fujisawa H, Suma K, Origuchi K, Kumagai H, Seki T, Ariga (2008) Biological and chemical stability of garlic-derived allicin. *Journal of Agricultural* *and Food Chemistry* **56 (11)**, 4229-4235

Gallicano K, Foster B, Choudhri S (2003) Effect of short-term administration of garlic supplements on single-dose ritonavir pharmacokinetics in healthy volunteers. *British Journal of Clinical Pharmacology* **55**, 199-202

Gardiner P, Graham R, Legedza AT, Ahn AC, Eisenberg DM, Phillips RS (2007) Factors associated with herbal therapy use by adults in the United States. *Alternative Therapeutic Health Medicine* **13**, 22-29

Gardner CD, Lawson LD, Block E Kiazand A, Balise RR, Kramer HC (2007) Effect of raw garlic vs commercial garlic supplements on plasma lipid concentrations in adults with moderate hypercholesterolemia: a randomized clinical trial. *Archives of Internal Medicine* **167 (4)**, 325-326

Gardner CD, Chatterjee LM, Carlson JJ (2001) The effect of a garlic preparation on plasma lipid levels in moderately hypercholesterolemic adults. *Atherosclerosis* **154**, 213-220

Gebhardt R (1993) Multiple inhibitory effects of garlic extracts on cholesterol biosynthesis in hepatocytes. *Lipids* **28**, 613-619

Gebhardt R, Beck H, Wagner KG (1994) Inhibition of cholesterol biosynthesis by allicin and ajoene in rat hepatocytes and HepG2 cells. *Biochimica et Biophysica Acta* **1213**, 57-62

Gernot K (2005) Spice pages: Garlic (*Allium sativum*, garlic). Available online: http://www.uni-graz.at/~katzer/engl/Alli_sat.html

Ghazanfar SA (1994) *Handbook of Arabian Medicinal Plants*, CRC Press, Boca Raton, FL pp 74-76

Ghosh J, Mishra TK, Rao YN, Aggarwal SK (2006) Oxidized LDL, HDL cholesterol, LDL cholesterol levels in patients of coronary artery disease. *Indian Journal of Clinical Biochemistry* **21**, 181-184

Golomb BA, Dang TT, Criqui MH (2006) Peripheral arterial disease: Morbidity and mortality implications. *Circulation* **114**, 688-699

Gravas S, Tzortzis V, Rountas C, Melekos MD (2010) Extracorporeal shockwave lithotripsy and garlic consumption: a lesson to learn. *Urological Research* **38 (1)**, 61-63

Green OC, Polydoris NG (1993) *Garlic, Cancer and Heart Disease: Review and Recommendations*, GN Communications Chicago, IL, pp 21-41

Grieve M (1995) A modem herbal: Garlic. Available online: www.botanical.com/mgmh/g/garlic

Grundy SM (1999) Primary prevention of coronary heart disease, integrating risk assessment with intervention. *Circulation* **100**, 988-998

Guerrero JA, Lozano ML, Castillo J, Benavente-Garcia O, Vicente V, Rivera J (2005) Flavonoids inhibit platelet function through binding to the thromboxane A2 receptor. *Journal of Thrombosis and Haemostasis* **3**, 369-376

Guo Z, Müller D, Pentz R, Kress G, Siegers CP (1990) Bioavailability of sulphur containing ingredients of garlic in the rat. *Planta Medica* **56**, 692-693

Gupta N, Porter TD (2001) Garlic and garlic-derived compounds inhibit human squalene monooxygenase. *Journal of Nutrition* **131**, 1662-1667

Hanley AB, Fenwick GR (1985) Cultivated alliums. *Journal of Plant Foods* **6**, 211-238

Hardenburg RE, Watada AE, Wang C-Y (2004) *The Commercial Storage of Fruits, Vegetables, and Florist and Nursery Stocks*, USDA Handbook No. 66, p 59

Harenberg J, Giese C, Zimmermann R (1998) Effect of dried garlic on blood coagulation, fibrinolysis, platelet aggregation and serum cholesterol levels in patients with hyperlipoproteinemia. *Atherosclerosis* **74**, 247-249

He FJ, Nowson CA, MacGregor GA (2006) Fruit and vegetable consumption and stroke: meta-analysis of cohort studies. *Lancet* **367 (9507)**, 320-326

Heinle H, Betz E (1994) Effects of dietary garlic supplementation in a rat model of atherosclerosis. *Arzneimittelforschung* **44**, 614-617

Hiyasat B, Sabha D, Grotzinger K, Kempfert J, Rauwald JW, Mohr FW, Dhein S (2009) Antiplatelet activity of *Allium ursinum* and *Allium sativum*. *Pharmacology* **83 (4)**, 197-204

Hoffmeister A, Rothenbacher D, Kunze M, Brenner H, Koenig W (2005) Prognostic value of inflammatory markers alone and in combination with blood lipids in patients with stable coronary artery disease. *European Journal of Internal Medicine* **16 (1)**, 47-109

Hokenson JE, Austin MA (1996) Plasma triglyceride level is a risk factor for CVD independent of high-density lipoprotein cholesterol level: a meta analysis of population based prospective studies. *Journal of Cardiovascular Research* **3**, 213-229

Holzgartner H, Schmidt U, Kuhn U (1992) Comparison of the efficacy and tolerance of garlic preparation vs. bezafibrate. *Arzneimittelforschung* **42**, 1473-1477

Huchette O, Auger J, Arnault I, Barandiaran X, Chovelon V, Kahane R (2007) Garlic cultivation for high health-value. *Medicinal and Aromatic Plant Science and Biotechnology* **1 (1)**, 16-20

Hung HC, Joshipura KJ, Jiang R, Hu FB, Hunter D, Smith-Warner SA, Colditz GA, Rosner B, Spiegelman D, Willett WC (2004) Fruit and vegetable intake and risk of major chronic disease. *Journal of National Cancer Institute* **96 (21)**, 1577-1584

Hussein AA (2003) Mechanism of action on the Egyptian garlic '*Alliums sativum*' on excitable tissues. *Pakistan Journal of Biological Sciences* **6 (8)**, 782-788

Iberl B, Winkler G, Knobloch K (1990) Products of allicin transformation: ajoenes and dithiins, characterization and their determination by HPLC. *Planta Medica* **56 (a)**, 202-211

Ide N, Lau BH (1997) Garlic compounds protect vascular endothelial cells from oxidized low-density lipoprotein-induced injury. *Journal of Pharmacy and Pharmacology* **49**, 908-911

Isaacsohn JL, Moser M, Stein EA, Dudley K, Davey JA, Liskov E, Black HR (1998) Garlic powder and plasma lipids and lipoproteins, a multicenter, randomized, placebo-controlled trial. *Archives of Internal Medicine* **158**, 1189-1194

Jain RC (1977) Effect of garlic on serum lipids, coagulability and fibrinolytic activity of blood. *American Journal of Clinical Nutrition* **30**, 1380-1381

Jain RC, Konar DB (1978) Effect of garlic oil in experimental cholesterol atherosclerosis. *Atherosclerosis* **29**, 125-129

Jamaluddin MP, Krishnan LK, Thomas A (1988) Ajoene inhibition of platelet aggregation: possible mediation by a hemoprotein. *Biochemical and Biophysical Research Communications* **153**, 479- 486

Jirovetz L, Jäger W, Koch HP, Remberg G (1992) Investigation of volatile constituents of the essential oil of Egyptian garlic (*Allium sativum*) by means of GCMS and GC-FTIR. *Zeitschrift für Lebensmittel Untersuchung und Forschung* **194**, 363-365

Jones MG, Collin HA, Tregova A, Trueman L, Brown L, Cosstick R, Hughes J, Milne, Wilkinson MC, Tomsett AB, Thomas B (2007) The biochemical and physiological genesis of alliin in garlic. *Medicinal and Aromatic Plant Science and Biotechnology* **1 (1)**, 21-24

Joseph PK, Rao KR, Sundaresh CS (1989) Toxic effects of garlic extract and garlic oil in rats. *Indian Journal of Experimental Biology* **27**, 977-979

Joshipura KJ, Ascherio A, Manson JE, Stampfer MJ, Rimm EB, Speizer FE, Hennekens CH, Willett WC (1999) Fruit and vegetable intake in relation to risk of ischemic stroke. *Journal of American Medical Association* **282 (13)**, 1233-1239

Kahn G (1996) History of garlic. In: Koch HP, Lawson LD (Eds) *Garlic: The Science and Therapeutic Application of Allium sativum L. and Related Species*, Williams and Wilkins, New York, pp 25-36

Kamanna VS, Chandrasekhara N (1982) Effect of garlic (*Allium sativum* Linn) on serum lipoproteins and lipoprotein cholesterol levels in albino rats rendered hypercholesterolemic by feeding cholesterol. *Lipids* **17**, 483-488

Kamanna VS, Chandrasekhara N (1984) Hypocholesteremic activity of different fractions of garlic. *Indian Journal of Medical Research* **79**, 580-583

Kamenetsky R, Khassanov F, Rabinowitch HD, Auger J, Kik C (2007) Garlic biodiversity and genetic resources. *Medicinal and Aromatic Plant Science and Biotechnology* **1 (1)**, 1-5

Kannel WB, Casetlli WP, Gordon T (1979) Cholesterol in the prediction of atherosclerosis disease. New perspectives based on the Framingham study. *Annals of Internal Medicine* **90**, 85-91

Kapoor LD (1990) *Handbook of Ayurvedic Medicinal Plants*, CRC Press, Boca Raton, pp 149-150

Kaye AD, De Witt BJ, Anwar M, Smith DE, Feng CJ, Kadowitz PJ, Nossaman BD (2000) Analysis of responses of garlic derivatives in the pulmonary vascular bed of the rat. *Journal of Applied Physiology* **89**, 353-358

Keaney JF Jr. (2000) Atherosclerosis: from lesion formation to plaque activation and endothelial dysfunction. *Molecular Aspects of Medicine* **21**, 99-166

Kelly JP, Kaufman DW, Kelley K, Rosenberg L, Anderson TE, Mitchell AA (2005) Recent trends in use of herbal and other natural products. *Archives of Internal Medicine* **165**, 281-286

Kennedy J (2005) Herb and supplement use in the US adult population. *Clinical Therapeutics* **27**, 1847-1858

Kenzelmann R, Kade F (1993) Limitation of the deterioration of lipid parameters by a standardized garlic-ginkgo combination product. A multicenter placebo-controlled double-blind study. *Arzneimittelforschung* **43**, 978-981

Kestin M, Rouse IL, Correll RA, Nestel PJ (1989) CVD risk factors in free-living men: comparison of two prudent diets, one based on lactoovo vegetarianism and the other allowing lean meat. *American Journal of Clinical Nutrition* **50**, 280-287

Khoo YS, Aziz Z (2009) Garlic supplementation and serum cholesterol: a meta-analysis. *Journal of Clinical Pharmacy and Therapeutics* **34 (2)**, 133-145

Kiesewetter H, Jung F, Mrowietz C, Pindur G, Heiden M, Wenzel E (1990) Effects of garlic on blood fluidity and fibrinolytic activity: a randomized, placebo-controlled, double-blind study. *British Journal of Clinical Practice* **69**, 24-29

Kikura M, Kazama T, Ilkeda T, Sato S (2000) Disaggregatory effects of prostaglandin E1, amirinone and milrone on platelet aggregation in human whole blood. *Platelets* **11**, 446-458

Kin T, Yamano S, Sakurai R, Kajlani M, Okahashi Y, Nishiura *N* (2007) Carotid atherosclerosis is associated with brain atrophy in Japanese elders. *Gerontology* **53 (1)**, 1-6

Kim P, Ku D, Kim R (2000) Garlic elicits a nitric oxide-dependent relaxations and inhibits hypoxic pulmonary vasoconstriction in rats. *Clinical and Experimental Pharmacology and Physiology* **27**, 780-787

Kleijnen J, Knipschild P, Riet G (1989) Garlic, onions and cardiovascular risk factors. A review of the evidence from human experiments with emphasis on commercially available preparations. *British Journal of Clinical Pharmacology* **28**, 535-544

Koenig W, Sund M, Frohlich M, Fischer HG, Lowel H, Doring A, Hutchinson WL, Pepys MB (1999) C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in CVD) Augsburg Cohort Study, 1984 to 1992. *Circulation* **99 (2)**, 237-242

Kodera Y, Suzuki A, Imada I, Kasuga S, Sumioka I, Kanezawa A, Fujikawa M, Nagae S, Masamoto K (2002) Physical, chemical, and biological properties of S-allylcysteine, an amino acid derived from garlic. *Journal of Agricultural and Food Chemistry* **50**, 622-632

Koga T, Az-Ma T, Yuge O (2002) Prostaglandin E1 at clinically relevant concentrations inhibits aggregation of platelets under synergistic interaction with endothelial cells. *Acta Anaesthesiologica Scandinavica* **46**, 987-993

Konjufca VH, Pesti GM, Bakalli RI (1997) Modulation of cholesterol levels in broiler meat by dietary garlic and copper. *Poultry Science* **76**, 1264-1271

Korotkov VM (1996) The effect of garlic juice on blood pressure. *Vrach Delo* **6**, 123

Koseoglu M, Isleten F, Atay A, Kaplan YC (2010) Effects of acute and subacute garlic supplement administration on serum total antioxidant capacity and lipid parameters in healthy volunteers. *Phytotherapy Research* **24 (3)**, 374-378

Kumar A, Nagtilak S, Sivakanesan R, Gunasekera S (2009) Cardiovascular risk factors in elderly normolipidemic acute myocardial infract patients – a case controlled study from India. *Southeast Asian Journal of Tropical and Public health* **40 (3)**, 581-592

Larsson SC, Hakansson N, Naslund I, Bergkvist L, Wolk A (2006) Fruit and vegetable consumption in relation to pancreatic cancer risk: a prospective study. *Cancer Epidemiology Biomarkers Prevention* **15 (2)**, 301-305

Lash JP, Cardoso LR, Mesler PM, Walczak DA, Pollak R (1998) The effect of garlic on hypercholesterolemia in renal transplant patients. *Transplant Proceedings* **30**, 189-191

Lau BH, Adetumbi MA, Sanchez A (1983) Garlic and atherosclerosis: a review (letter). *Nutrition Research* **3**, 227-237

Lawson L D (1998) Garlic: a review of its medicinal effects and indicated active compounds. In: Lawson LD, Bauer R (Eds) *Phytomedicines of Europe. Chemistry and Biological activity*, Series 691, American Chemical Society, Washington, DC, pp 176-209

Lawson LD (1996) The composition and chemistry of garlic cloves and processed garlic. In: Koch HP, Lawson LD (Eds) *Garlic: The Science and Therapeutic Application of Allium sativum L. and Related Species*, Williams and Wilkins, Baltimore, pp 37-107

Lawson LD, Wood SG, Hughes BG (1991) HPLC analysis of allicin and other thiosulfinates in garlic clove homogenates. *Planta Medica* **57**, 263-270

Lawson LD, Wang ZJ, Hughes BG (1991) Identification and HPLC quantitation of the sulfides and dialk(en)yl thiosulfinates in commercial garlic products. *Planta Medica* **57**, 363-370

Legnani C, Frascaro M, Guazzaloca G, Ludovici S, Cesarano G, Coccheri S (1993) Effects of a dried garlic preparation on fibrinolysis and platelet aggregation in healthy subjects. *Arzneimittelforschung* **43**, 119-122

Lei YP, Chen HW, Sheen LY, Lii CK (2008) DADS and DATS suppress oxidized LDL–induced vascular cell adhesion molecule and E-selectin expression through protein kinase A- and B-dependent signaling pathways. *Journal of Nutrition* **138**, 996-1003

Leoper M, DeBray M (1921) Hypotensive effect of tincture of garlic. *Progress in Medicine* **36**, 391-392

Lewington S, Clarke R (2005) Combined effects of systolic blood pressure and total cholesterol on cardiovascular disease risk. *Circulation* **112**, 3373-3374

Lewis B (1983) Relation of high-density lipoproteins to coronary artery disease. *American Journal of Cardiology* **52**, 5-8

Lipid Research Clinics Coronary Primary Prevention Trial Results (1984) Reduction in incidence of coronary heart disease. *Journal of the American Medical Association* **251**, 351-364

Liu L, Yeh YY (2000) Inhibition of cholesterol biosynthesis by organosulfur compounds derived from garlic. *Lipid* **35**, 197-203

Liu L, Yeh YY (2002) S-alk (en) yl cysteines of garlic inhibit cholesterol synthesis by deactivating HMG-CoA reductase in cultured rat hepatocytes. *Journal of Nutrition* **132 (6)**, 1129-1134

Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL (2006) Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet* **367 (9524)**, 1747-1775

Lu J, Pei H, Ip C, Lisk DJ, Ganther H, Thompson HJ (1996) Effect on an aqueous extract of selenium enriched garlic on *in vitro* markers and *in vivo* efficacy in cancer prevention. *Carcinogenesis* **17**, 1903-1907

Luis DA, Aller R (2008) Garlic and cardiovascular risk. *Anales de Medicina Interna* **25 (5)**, 237-240

Luley C, Lehmann-Leo W, Moller B, Martin T, Schwartzkopff W (1986) Lack of efficacy of dried garlic in patients with hyperlipoproteinemia. *Arzneimittelforschung Drug Research* **36**, 766-768

Macpherson LJ, Geierstanger BH, Viswanath V, Bandell M, Eid SR, Hwang SW, Ardem Patapoutian A (2005) The pungency of garlic: Activation of $TRPA_1$ and $TRPV_1$ in response to allicin. *Current Biology* **15**, 929-934

Mahmoodi M, Islami MR, Asadi Karam GR, Khaksari M, Sahebghadam Lotfi A, Hajizadeh MR, Mirzaee MR (2006) Study of the effects of raw garlic consumption on the level of lipids and other blood biochemical factors in hyperlipidemic individuals. *Pakistan Journal of Pharmaceutical Science* **19 (4)**, 295-298

Makheja AN, Vanderhoek JY, Bailey JM (1979) Inhibition of platelet aggregation and thromboxane synthesis by onion and garlic. *Lancet* **1**, 781

Mand JK, Gupta PP, Soni GL, Singh R (1985) Effect of garlic on experimental atherosclerosis in rabbits. *Indian Journal of Heart* **37**, 183-188

Mathew BC, Daniel RS, Augusti KT (1996) Hypolipidemic effect of garlic protein substituted for casein in diet of rats compared to those of garlic oil. *Indian Journal of Experimental Biology* **34**, 337-340

Matsuura H (1997) Phytochemistry of garlic horticultural and processing procedures. In: Lachance PA (Ed) *Neutraceuticals: Designer Foods III. Garlic, Soy and Licorice*, Food and Nutrition Press, Turnbull, CT, pp 55-69

Margetts BM, Beilin LJ, Vandongen R, Armstrong BK (1986) Vegetarian diet in mild hypertension: a randomized controlled trial. *British Journal of Medicine* **293**, 1468-1471

Margolis KL, Manson JE, Greenland P, Rodabough RJ, Bray PF, Safford M, Grimm RH Jr., Howard BV, Assaf AR, Prentice R (2005) Leukocyte count as a predictor of cardiovascular events and mortality in postmenopausal women: the Women's Health Initiative Observational Study. *Archives of Internal Medicine* **165 (5)**, 500-508

Mazelis M, Crews L (1968) Purification of the alliin lyase of garlic, *Allium sativum* L. *Journal of Biochemistry* **108**, 725-730

McCance KL (1983) Lipoproteins and heart disease. *Nurse Practitioners* **8**, 69-72

McCrindle BW, Helden E, Conner WT (1998) Garlic extracts therapy in children with hypercholesterolemia. *Archives of Pediatrics and Adolescent Medicine* **152**, 1089-1093

McGee H (2004) The onion family: Onions, garlic, leeks. In: *On Food and Cooking* (Revised 2nd Edn), pp 310-313. Available online: http://en.wikipedia.org/wiki/On_Food_and_Cooking

McGill HC, McMahan CA, Zieske, AW, Malcom, GT, Tracy RE, Strong JP (2000) Associations of coronary heart disease risk factors with the intermediate lesion of atherosclerosis in youth. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. *Arteriosclerosis Thrombosis and Vascular Biology* **20**, 1998-2004

Meer QP, Botha JL, Galmarini CR (1997) Old and new crops within edible *Allium*. *Acta Horticulturae* **433**, 17-31

Mehrzia M, Ferid L, Mohamed A, Ezzedine A (2006) Acute effects of a partially purified fraction from garlic on plasma glucose and cholesterol levels in rats: putative involvement of nitric oxide. *Indian Journal of Biochemistry and Biophysics* **43 (6)**, 386-390

Mendall MA, Strachan DP, Butland BK, Ballam L, Morris J, Sweetnam PM, Elwood PC (2000) C-reactive protein: relation to total mortality, cardiovascular mortality and cardiovascular risk factors in men. *European Journal of Heart* **21 (19)**, 1584-1590

Michigawa M (2006) Role of cholesterol in amyloid cascade: cholesterol–dependant modulation of tau phosphorylation and mitochondrial function. *Acta Neurologica Scandinavica* **185**, 21-24

Mirhadi SA, Singh S, Gupta PP (1991) Effect of garlic supplementation to cholesterol-rich diet on development of atherosclerosis in rabbits. *Indian Journal of Experimental Biology* **29**, 162-168

Mokni M, Limam F, Amri M, Aouani E (2006) Acute effects of a partially purified fraction from garlic on plasma glucose and cholesterol levels in rats: Putative involvement of nitric oxide. *Indian Journal of Biochemistry and Biophysics* **43**, 386-390

Mokni M, Limam F, Amri M, Aouani E (2009) Plasma lipid modulating activity of intraperitoneally administered aqueous extract from raw garlic: Acute studies in normo-lipidemic rat. *Journal of Food Biochemistry* **33**, 355-367

Morcos NC (1997) Modulation of lipid profile by fish oil and garlic combination. *Journal of the National Medical Association* **89**, 673-678

Morihara N, Sumioka I, Ide N, Moriguchi T, Uda N, Kyo E (2006) Aged garlic extract maintains cardiovascular homeostasis in mice and rats. *Journal of Nutrition* **136**, 777S-781S

Morihara N, Sumioka I, Moriguchi T, Uda N, Kyo E (2002) Aged garlic extract enhances production of nitric oxide. *Life Science* **71**, 509-517

Moyers S (1996) *Garlic in Health, History and World Cuisine*, Sun Coast Press, St. Petersburg, pp 1-36

Mulrow C, Lawrence V, Ackermann R, Gilbert Ramirez G, Morbidoni L, Aguilar C, Arterburn J, Block E, Chiquette E, Gardener C, Harris M (2000) Garlic: effects on cardiovascular risks and disease, protective effects against cancer, and clinical adverse effects. *Evidence Report Technology Assessment* **20**, 1-4

Munday JS, James KA, Fray LM, Kirkwood SW, Thompson KG (1999) Daily supplementation with Aged Garlic Extract, but not raw garlic, protects low-density lipoprotein against *in vitro* oxidation. *Atherosclerosis* **143**, 399-404

Murray CJL, Lopez AD (1997) Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet* **349**, 1269-1276

Myung SC, Eunsook TK, Stewart TJ (1982) Effects of garlic on lipid metabolism in rats fed cholesterol or lard. *Journal of Nutrition* **112**, 241-248

Nagae S, Ushijima M, Hatono S, Imai J, Kasuga S, **Matsuura H, Itakura Y, Higashi Y** (1994)Pharmacokinetics of the garlic compound S-allylcysteine. *Planta Medica* **60**, 214-217

Nahin RL, Dahlhamer JM, Taylor BL, Barnes PM, Stussman BJ, Simile

CM (2007) Health behaviors and risk factors in those who use complementary and alternative medicine. *BMC Public Health* **25 (41)**, 7217-7223
Nair D, Carrigan TP, Curtin RJ, Popovic ZB, Kuzmiak S, Schoenhagen P, Flamm SD, Desai MY (2008) Association of coronary atherosclerosis detected by multislice computed tomography and traditional risk-factor assessment. *American Journal of Cardiology* **102 (3)**, 316-320
Nakagawa S, Masmoto K, Sumiyoshi H, Kunihiro K, Fuwa T (1980) Effect of raw and extracted aged garlic on growth of young rats and their organs after peroral administration. *Journal of Toxicological Science* **5**, 109-112
National Center for Complementary and Alternative Medicine (NCCAM), National Institutes of Health (2005) Expanding Horizons of Health Care: Strategic Plan 2005–2009. Available online: www.nccam.nih.gov/about/plans/2005/
National Heart, Lung, and Blood Institute (2007) Available online: www.nhlbi.nih.gov/health/dci/Diseases/Atherosclerosis/Atherosclerosis_WhatIs.html and http://www.nhlbi.nih.gov/health/dci/index.html
Neil HA, Silagy CA, Lancaster T Hodgeman J, Vos K, Moore JW (1996) Garlic powder in the treatment of moderate hyperlipidemia: a controlled trial and meta-analysis. *Journal of the Royal College of Physicians London* **30 (4)**, 329-334
Newall CA, Anderson LA, Phillipson JD (1996) *Herbal Medicines: A Guide for Health-Care Professionals*, Pharmaceutical Press, Londonp296
New World Encyclopedia Online (2008) CVD. Available online: http://www.newworldencyclopedia.org/entry/cardiovascular_disease
Nicholas AB, Nicki RC, Brain RW, John AAH (2006) CVD. In: *Davidson's Principles and Practice of Medicine* (20th Edn), Churchill Livingstone, New York, pp 520-644
Nitiyanant W, Ploybutr S, Wasuwat S, Tandhanand S (1987) Effect of the dried powder extract, water soluble of garlic (*Allium sativum*) on cholesterol, triglyceride and high-density lipoprotein in the blood. *Journal of the Medical Association of Thailand* **70**, 646-648
O'Keefe JH, Bybee KA, Lavie CJ (2007) Alcohol and cardiovascular health: the razor-sharp double-edged sword. *Journal of the American College of Cardiology* **50**, 1009-1014
Ong HT, Cheah JS (2008) Statin alternatives or just placebo: an objective review of omega-3, red yeast rice and garlic in cardiovascular therapeutics. *Chinese Medical Journal (English)* **121 (16)**, 1588-1594
Omar SH, Hassan A, Hunjul N, Ali J, Aqil M (2007) Historical, chemical and cardiovascular prospective on garlic: A review. *Pharmacognosy Reviews* **1 (1)**, 80-87
Orekhov AN, Grunwald J (1997) Effects of garlic on atherosclerosis. *Journal of Nutrition* **13**, 656-663
Orlowski M, Rekowska E, Dobromilska R (1994) The effect of yield of garlic (*Allium sativum* L.) of autumn and spring planting using different methods of seed stalk trimming. *Folia Horticulture* **6**, 79-89
Pantoja CV, Norris BC, Contreras CM (1996) Diuretic and natriuretic effects of chromatographically purified fraction of garlic (*Allium sativum*). *Journal of Ethnopharmacology* **52**, 101-105
Pierce A (1999) *The American Pharmaceutical Association Practical Guide to Natural Medicines*, William Morrow and Co., Inc., New York
Petersen AM, Pedersen BK (2005)The anti-inflammatory effect of exercise. *Journal of Applied Physiology* **98 (4)**, 1154-1162
Petkov V (1997) Plants and hypotensive, antiatheromatous and coronarodilating action: *American Journal of Clinical Medicine* **7**, 197-236
Pinto JT, Rivlin RS (1999) Garlic and other allium vegetables in cancer prevention. In: Heber D, Blackburn G, Go ULM (Eds) *Nutritional Oncology*, Academic Press, San Diego, CA, pp 393-403
Piotrowski GL (1948) Ail en therapeutique. *Praxis* **26**, 488-492
Piscitell SC, Burstein AH, Welden N, Gallicano KD, Falloon J (2002) The effect of garlic supplements on the pharmacokinetics of saquinavir. *Clinical Infection Disease* **34**, 234-238
Pooler M, Simon PW (1993) Characterization and classification of isozyme and morphological variation in a diverse collection of garlic cloves. *Euphytica* **68**, 121-130
Prasad K, Laxdal VA, Yu M, Raney BL (1995) Antioxidant activity of allicin, an active principle in garlic. *Molecular and Cellular Biochemistry* **148 (2)**, 183-189
Qidwai W, Qureshi R, Hasan SN, Azam SI (2000) Effect of dietary garlic (*Allium sativum*) on the blood pressure in humans – a pilot study. *Journal of the Pakistan Medical Association* **50**, 204-207
Qi R, Liao F, Inoue K, Yatomi Y, Sato K, Ozaki Y (2000) Inhibition by DATS, a garlic component, of intracellular Ca21 mobilization without affecting inositol-1,4,5-triphosphate (IP3) formation in activated platelets. *Biochemical Pharmacology* **60**, 1475-1483
Qureshi AA, Din ZZ, Abuirmeileh N, Burger WC, Ahmad Y, Elson CE (1983) Suppression of avian hepatic lipid metabolism by solvent extracts of garlic: impact on serum lipids. *Journal of Nutrition* **113**, 1746-1755
Qureshi AA, Crenshaw D, Abuirmeileh N, Peterson DM, Elson CE (1987) Influence of minor plant constituents on porcine hepatic lipid metabolism. Impact on serum lipids. *Atherosclerosis* **64**, 109-111
Rabinkov A, Miron T, Mirelman D, Wilchek M, Glozman S, Yavin E, Weiner L (2000) S-Allyl mercaptoglutathione: the reaction product of allicin with glutathione possesses SH-modifying and antioxidant properties. *Biochimica et Biophysica Acta* **1499**, 144-153
Rabinkov A, Xiao-Zhu Z, Grafl G, Galili G, Mirelman D (1994) Alum lyase (allinase) from garlic (*Allium sativum*): Biochemical characterization and cDNA cloning. *Applied Biochemistry and Biotechnology* **48**, 149-171
Rahim MA, Fordham R (2001) Environmental manipulation for controlling bulbing in garlic. *Acta Horticulture* **555**, 181-188
Rahman K (2007) Effects of garlic on platelet biochemistry and physiology. *Molecular Nutrition and Food Research* **51 (11)**, 1335-1344
Rahman K, Billington D (2000) Dietary supplementation with aged garlic extract inhibits ADP- induced platelet aggregation in humans. *Journal of Nutrition* **130 (11)**, 2662-2665
Rahman K, Lowe GM (2006) Garlic and CVD: a critical review. *Journal of Nutrition* **136 (3)**, 736S-740S
Rajasree CR, Rajmohan T, Agusti KT (1999) Biochemical effects of garlic on lipid metabolism in alcohol fed rats. *Indian Journal of Experimental Biology* **37**, 243-247
Rajasree CR, Rajmohan T, Augusti KT (2009) Antiatherogenic and antiperoxidative effects of garlic and soy proteins in alcohol fed rats. *Indian Journal of Experimental Biology* **47 (3)**, 169-175
Ramachandran A, Snehalatha C, Sivasankari S, Satyavani K, Vijay V (2001) Diastolic dysfunction and hypertension. *New England Journal of Medicine* **344 (18)**, 1401-1404
Rashid A, Khan HH (1985) The mechanism of hypotensive effect of garlic extract. *Journal of Pakistan Medical Association* **35**, 357-362
Riddle J M (1996) The medicines of Greco-Roman antiquity as a source of medicines for today. In: Holland BK (Ed) *Prospecting for Drugs in Ancient and Medieval European Texts*, Harwood Academic Publishers, Amsterdam, The Netherlands, pp 7-17
Ridker PM, Rifai N, Rose L, Buring JE, Cook NR (2002) Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *New England Journal of Medicine* **347 (20)**, 1557-1565
Ridker PM, Hennekens CH, Buring JE, Rifai N (2000) C-reactive protein and other markers of inflammation in the prediction of CVD in women. *New England Journal of Medicine* **342 (12)**, 836-843
Ridker PM, Stampfer MJ, Rifai N (2001) Novel risk factors for systemic atherosclerosis: a comparison of CRP, fibrinogen, homocysteine, lipoprotein (a), and standard cholesterol screening as predictors of peripheral arterial disease. *Journal of the American Medical Association* **285 (19)**, 2481-2485
Ried K, Frank OR, Stock NP, Fakler P, Sullivan T (2008) Effect of garlic on blood pressure: A systematic review and meta-analysis, *BMC Cardiovascular Disorders* **8**, 8-13
Rivlin RS (1998) Patient with hyperlipidemia who received garlic supplements. Lipid management. *Report from the Lipid Education Council* **3**, 6-7
Rivlin RS (2001) Historical prospective on the use of garlic. *Journal of Nutrition* **131**, 951S-954S
Robbers JE, Tyler VE (1999) *Tyler's Herbs of Choice: The Therapeutic Use of Phytomedicines*, Haworth Herbal Press, New York, 287 pp
Rodgers A, Lawes C, McMahon S (2000) Reducing the global burden of blood pressure related CVD. *Journal of Hypertension* **18 (1)**, S3-S6
Roos T, Dirsch V, Buniatian G, Ende C, Günther J, Heise K, Kellert D, Lerche K, Pavlica S, Struck F, Usbeck E, Voigt J, Zellmer S, Princen JMG, Vollmar AM, Gebhardt R (2007) Garlic and CVDs. *Medicinal and Aromatic Plant Science and Biotechnology* **1 (1)**, 25-30
Rosanoff A, Seelig MS (2004) Comparison of mechanism and functional effects of magnesium and statin pharmaceuticals. *Journal of the American College of Nutrition* **23 (5)**, 501S-505S
Rosen RT, Hiserodt RD, Fukuda EK, Ruiz RJ, Zhou Z, Lech J, Rosen SL, Hartman TG (2001) Determination of allicin, s-allylcysteine and volatile metabolites of garlic in breath, plasma or simulated gastric fluids. *Journal of Nutrition* **131**, 968S-971S
Rosen C, **Becker R**, **Fritz VHutchison B**, **Percich J**, **Tong C**, **Wright J** (2008) Growing Garlic in Minnesota. Available online: http://www.extension.umn.edu/distribution/cropsystems/DC7317.html
Ryu K, Ide N, Matsuura H, Itakura Y (2001) *N*-alpha-(1-deoxy-D-fructos-1-yl)-L-arginine, an antioxidant compound identified in aged garlic extract. *Journal of Nutrition* **131**, 972S-976S
Saczynski JS, White L, Peila RL, Rodríguez BL, Launer LJ (2007) The relation between apoA_1 and dementia: the Honolulu–Asia aging study. *American Journal of Epidemiology* **165**, 993-997
Samson RR (1982) Effects of dietary garlic and temporal drift on platelet aggregation. *Atherosclerosis* **44**, 119-120
Sangeetha T, Darlin QS (2006) Preventive effect of S-allyl cysteine sulfoxide (alliin) on cardiac marker enzymes and lipids in isoproterenol-induced myocardial injury. *Journal of Pharmacy and Pharmacology* **58 (5)**, 617-623
Santo SE, Keiss HP, Meyer K, Buytenhek R, Roos T, Dirsch V, Buniatian G, Ende C, Günther J, Heise K, Kellert D, Lerche K, Pavlica S, Struck F, Usbeck E, Voigt J, Zellmer S, Princen JMG, Vollmar AM, Gebhardt R (2007) Garlic and cardiovascular diseases. *Medicinal and Aromatic Plant Science and Biotechnology* **1 (1)**, 25-30
Santos OA, Johns RA (1995) Effects of garlic powder and garlic oil preparations on blood lipids, blood pressure and wellbeing. *British Journal of Clinical Research* **6**, 91-100

Schardt D, Schmidt S (1995) Garlic, clove at first sight? *Nutrition Action Health Letter* **22 (6)**, 3-5

Scharbert G, Kalb ML, Duris M, Marschalek C, Kozek-Langenecker SA (2007) Garlic at dietary doses does not impair platelet function. *Anesthesia and Analgesia* **105 (5)**, 1214-1218

Schiffer B, Bunte C, Witte J, Hoeper K, Boger RH, Schwedhelm E, Drexler H (2004) Comparative effects of At_1-antagonism and angiotension converting enzyme inhibition on markers of inflammation and platelet aggregation in patients with CAD. *Journal of the American College of Cardiology* **44**, 362-368

Schwartz CJ, Valente AJ, Sprague EA (1993) A modern view of atherogenesis. *American Journal of Cardiology* **71**, 9b-14b

Sen S, Oppenheimer SM, Lima JAC, Cohen B (2002) Risk factors for progression of aortic atheroma in stroke and transient ischemic attack patients. *Stroke* **33**, 930-935

Seno S, Saliba GG, de Paula FJ, Koga PS (1995) Utilization of phosphorous and farmyard manure in garlic cultivation. *Horticultura Brasileira* **13**, 196-199

Shah BN, Nayak BS, Patel MA, Mishra AD, Seth AK (2006) Aged garlic extract – a health benefit review. *Pharmacognosy Magazine* **2 (60)**, 90-95

Sharifi AM, Darabi R, Akbarloo N (2003) Investigation of antihypertensive mechanism of garlic in 2K1C hypertensive rat. *Journal of Ethnopharmacology* **86 (2-3)**, 219-224

Sharma CP, Sunny MC (1988) Effects of garlic extracts and of three pure components isolated from it on human platelet aggregation, arachidonate metabolism, release reaction and platelet ultra structure comments. *Thrombosis Research* **52**, 493-494

Siegel G, Walter A, Engel S, Walper A, Michel F (1999) Pleiotropic effects of garlic. *Wiener Medizinische Wochenschrift* **149**, 217-224

Siegel G, Klussendorf D (2002) The anti-atherosclerotic effect of *Allium sativum*: statistics re-evaluation. *Atherosclerosis* **150**, 437-438

Siess MH, Le Bon AM, Teyssier C, Belloir C, Singh V, Bergès R (2007) Garlic and cancer. *Medicinal and Aromatic Plant Science and Biotechnology* **1 (1)**, 31-36

Silagy CA, Neil HA (1994) Garlic as a lipid lowering agent-a meta-analysis. *Journal of the Royal College of Physicians London* **28**, 39-45

Silagy CA, Neil HA (1994b) A meta-analysis of the effect of garlic on blood pressure. *Journal of Hypertension* **12 (4)**, 463-468

Simons LA, Balasubramaniam S, von Konigsmark M, Parfitt A, Simons J, Peters W (1995) On the effect of garlic on plasma lipids and lipoproteins in mild hypercholesterolemia. *Atherosclerosis* **113**, 219-225

Sklan D, Berner YN, Rabinowitch HD (1992) The effect of dietary onion and garlic on hepatic lipid concentrations and activity of antioxidative enzymes in chicks. *Journal of Nutritional Biochemistry* **3**, 322-325

Smith WL (1989) The eicosanoids and their biochemical mechanisms of action. *Journal of Biochemistry* **259**, 315-324

Sobenin IA, Andrianova IA, Demidova ON, Gorchakova TV, Orekhov NA (2008) Lipid-lowering effects of time-released garlic powder tablet in double-blinded placebo-controlled randomized study. *Journal of Atherosclerosis and Thrombosis* **15**, 334-338

Sparks DL, Scheff SW, Hunsaker JC, Liu H (1994) Induction of Alzheimer like beta-amyloid immune reactivity in the brains of rabbits with dietary cholesterol. *Experimental Neurology* **126**, 88-94

Srivsatava KC (1986) Evidence for the mechanism by which garlic inhibitors platelet aggregation. *Prostaglandin, Leukotrienes and Essential Fatty Acids* **22**, 313-321

Steiner M, Khan AH, Holbert D, Lin RS (1996) A double-blind crossover study in moderately hypercholesterolemic men that compared the effect of aged garlic extract and placebo administration on blood lipids. *American Journal of Clinical Nutrition* **64**, 866-870

Steiner M, Li W (2001) Aged garlic extract, a modulator of cardiovascular risk factors: A dose finding study on the effects of AGE on platelet functions. *Journal of Nutrition* **131 (3)**, 980S-984S

Steiner M, Lin RS (1998) Changes in platelet function and susceptibility of lipoproteins to oxidation associated with administration of aged garlic extract. *Journal of Cardiovascular Pharmacology* **31**, 904-908

Steiner M, Lin RS (1994) Cardiovascular and lipid changes in response to aged garlic extract ingestion. *Journal of the American College of Nutrition* **13**, 524

Stephen A, Barrie ND, Jonathan V, Wright MD, Joseph E, Pizzorno ND (1987) Effects of garlic oil on platelet aggregation, serum lipids and blood pressure in humans. *Journal of Orthomolecular Medicine* **2 (1)**, 15-21

Stevinson C, Pittler MH, Ernst E (2000) Garlic for treating hypercholesterolemia. A meta-analysis of randomized clinical trials. *Annals of Internal Medicine* **133 (6)**, 420-429

Stitzinger M (2007) Lipids, inflammation and atherosclerosis. The digital repository of Leiden University. Available online:
https://openaccess.leidenuniv.nl/dspace/bitstream/1887/9729/11/01

Studer M, Briel M, Liemenstoll B, Blass TR, Bucher HC (2005) Effect of different antilipidemic agents and diets on mortality: A systematic review. *Archives of Internal Medicine* **165 (7)**, 725-730

Sumioka I, Hayama M, Shimokawa Y, Shiraishi S, Tokunaga A (2006) Lipid-lowering effect of monascus garlic fermented extract (MGFE) in hyperlipidemic subjects. *Hiroshima Journal of Medical Sciences* **55 (2)**, 59-64

Superko HR, Krauss RM (2000) Garlic powder, effect on plasma lipids, postprandial lipemia, low-density lipoprotein particle size, high-density lipoprotein subclass distribution and lipoprotein (a). *Journal of the American College of Cardiology* **35**, 321-326

Tanaka S, Haruma K, Yoshihara M, Kajiyama G, Kira K, Amagase H, Chayama K (2006) Aged garlic extract has potential suppressive effect on colorectal adenomas in humans *Journal of Nutrition* **136 (3)**, 821S-826S

Tanamai J, Veeramanomai S, Indrakosas N (2004)The efficacy of cholesterol-lowering action and side effects of garlic enteric coated tablets in man. *Journal of the Medical Association of Thailand* **87 (10)**, 1156-1161

Tattelman E (2005) Health effects of garlic. *American Family Physician* **72**, 103-106

Teranishi K, Apitz-Castro R, Robson SC, Romano E, Cooper DK (2003) Inhibition of baboon platelet aggregation *in vitro* and *in vivo* by the garlic derivative, ajoene. *Xenotransplantation* **10 (4)**, 374-379

Thomson M, Mustafa M, Ali M (2000) Thromboxane-B $_2$ levels in serum of rabbits receiving a single intravenous dose of aqueous extract of garlic and onion. *Prostaglandins, Leukotrienes and Essential Fatty Acids* **63**, 217-221

Torres JL, Ridker PM (2003b) High sensitivity C-reactive protein in clinical practice. *American Heart Hospital Journal* **1 (3)**, 207-211

Turner B, Molgaard C, Marckmann P (2004) Effect of garlic (*Allium sativum*) powder tablets on serum lipids, blood pressure and arterial stiffness in normolipidaemic volunteers: a randomized, double blind, placebo-controlled trial. *British Journal of Nutrition* **92 (4)**, 701-706

Vanhecke TE, Miller WM, Franklin BA, Weber JE, McCullough PA (2006) Awareness, knowledge, and perception of heart disease among adolescents. *European Journal of Cardiovascular Prevention and Rehabilitation* **13 (5)**, 718-723

Vinson JA, Su X, Zubik L, Bose P (2001) Phenol antioxidant quantity and quality in foods: fruits. *Journal of Agriculture and Food Chem*istry **49**, 5315-5321

Vorberg G, Schneider B (1990) Therapy with garlic: results of a placebo-controlled, double-blind study. *British Journal of Clinical Practice* **69**, 7-11

Wallace RB, Gryzlak BM, Zimmerman MB, Nisly NL (2008) Application of FDA Adverse Event Report data to the surveillance of dietary botanical supplements. *Annals of Pharmacotherapy* **42**, 653-660

Wang TJ, Gona P, Larson MG,Tofler GH, Levy D, Newton-Cheh C, Jacques PF, Rifai N, Selhub J, Robins SJ, Benjamin EJ, D'Agostino RB, Vasan RS (2006) Multiple biomarkers for the prediction of first major cardiovascular events and death. *New England Journal of Medicine* **355 (25)**, 2631-2639

Warshafsky S, Kamer RS, Sivak SL (1993) Effect of garlic on total serum cholesterol. A meta-analysis. *Annals of Internal Medicine* **119**, 599-605

Wattanapitayakul SK, Bauer JA (2001) Oxidative pathways in CVD: roles, mechanisms, and therapeutic implications. *Pharmacology and Therapeutics* **89 (2)**, 187-206

Weiss R, Fintelmann V (2000) *Herbal Medicine*, Thieme, Stuttgart, pp 156-157

Weiss N, Ide N, Abahji T, Nill L, Keller C (2006) Aged garlic extract improves homocysteine induced endothelial dysfunction in macro- and microcirculation. *Journal of Nutrition* **136**, 750S-754S

Wilson PDF, Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB (1998) Prediction of coronary artery disease using risk factor categories. *Circulation* **97**, 1837-1847

World Health Organization (2005) Available online: www.who.int/ncd/cvd

World Health Organization (2005) Preventing chronic disease: a vital investment. Geneva. Available online:
http://www.who.int/chp/chronic_disease_report/en/

World Health Organization (2007) Prevention of CVD: guidelines for assessment and management of total cardiovascular risk. Available online:
http://www.who.int/cardiovascular_diseases/guidelines/Full%2520text.pdf

Willoughby S, Holmes A, Loscalzo J (2002) Platelets and CVD. *European Journal of Cardiovascular Nursing* **1**, 273-288

Wojcikowski K, Myers S, Brooks L (2007) Effects of garlic oil on platelet aggregation: a double-blind placebo-controlled crossover study. *Platelets* **18 (1)**, 29-34

Wood D (2001) Established and emerging cardiovascular risk factors. *American Journal of Heart* **141**, S49-S57

Woodward PW (1996) *Garlic and Friends: The History, Growth and Use of Edible Alliums*, Hyland House, Melbourne, Australia, pp 2-22

Wyngate PP (1998) One study of vitamins, minerals, herbs and supplements 1998 research conducted by Hartman and New Hope. *Natural Foods Merchandiser*, pp 14-16

Xu YJ, Aziz OA, Bhugra P, Arneja AS, Mendis MR, Dhalla NS (2003) Potential role of lysophosphatidic acid in hypertension and atherosclerosis. *Canadian Journal of Cardiology* **19**, 1525-1536

Yanagita T, Han SY, Wang YM, Tsuruta Y, Anno T (2003) Cycloalliin, a cyclic sulfur imino acid, reduces serum triacylglycerols in rats. *Nutrition* **19**, 140-143

Yeh YY, Lim HS, Yeh SM, Picciano MF (2005) Garlic extracts attenuate hyperhomocysteinemia caused by folic acid deficiency in the rat. *Nutritional Research* **25**, 93-102

Yeh YY, Liu L (2001) Cholesterol-lowering effect of garlic extracts and organosulfur compounds: Human and animal studies. *Journal of Nutrition* **131 (3)**, 989S-993S

Yeh YY, Yeh SM (2006) Homocysteine-lowering action is another potential cardiovascular protective factor of aged garlic extract. *Journal of Nutrition* **136 (3)**, 745S-749S

Yeh GY, Davis RB, Phillips RS (2006) Use of complementary therapies in patients with cardiovascular disease. *American Journal of Cardiology* **98 (5)**, 673-680

Yilmaz HH, Gormez O, Hastar E, Yildirim D, Aksoy MC (2010) Garlic burn in a patient with trigeminal neuralgia: a case report. *European Journal of Dentistry* **4 (1)**, 88-90

Yokoyama K, Yoshi M, Takasugi N, Fuwa T (1988) Effect of garlic extract preparation containing vitamins (Kyoleopin) and ginseng-garlic preparation containing vitamin B1 (leopin five) on peripheral blood circulation of animals. *Oyo Yakuri* **36**, 301-308

Yoshida S, Kasuga S, Hayashi N, Ushiroguchi T, Matsuura H, Nakagawa S (1987) Antifungal activity of ajoene derived from garlic. *Applied Environmental Microbiology* **53**, 615-617

Zheng SJ, Kamenetsky R, Féréol L, Barandiaran X, Rabinowitch HD, Chovelon V, Kik C (2007) Garlic breeding system innovations. *Medicinal and Aromatic Plant Science and Biotechnology* **1 (1)**, 6-15

Zyriax BC, Boeing H, Windler E (2005) Nutrition is a powerful independent risk factor for coronary heart disease in women-The CORA study: a population-based case-control study. *European Journal Clinical Nutrition* **59 (10)**, 1201-1207