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THERAPEUTIC USE OF GARLIC (*Allium sativum* L.): NEW POSSIBILITIES*

VESNA LALOŠEVIĆ, SLOBODAN VLAJIĆ, STEVAN MAŠIREVIĆ, STANISLAV SIMIN, ANA TAKAČ, LJILJANA KURUCA[1]

SUMMARY: Garlic (Allium sativum L.) has been seriously investigated in purpose to find an alternative measure for control of various diseases in humans and animals. Use in cardiovascular therapeutics has an even longer history over 3000 years to ancient time. The active chemical in garlic is allicin, which is produced when raw garlic is crushed, allowing the enzyme alliinase to act on the stable precursor alliin. Antidiabetic, antibiotic and perhaps anticancer effects of garlic are well-accepted over the world because there is a range of scientific literature to support this. Garlic also has hepatoprotective, antioxidant, and anthelmintic effect. The other pharmacological effect includes the anticoagulant, anti inflammatory, immunomodulatory and wound healing action of garlic.

***Keywords**: Allium sativum, garlic extract, allicin, pharmacological activities.*

INTRODUCTION

Garlic (*Allium sativum* L.) is a hardy annual monocotyledon plant, and one of the oldest cultivated vegetable crops. Over the years it has been seriously investigated in purpose to find an alternative measure of control of various human and animal diseases. It is well known fact that this plant has been used for centuries in fight against various infections (Onyeagba et al., 2006). The data about the medicinal properties of this cultivated plant has been found in the oldest records of Herodot and the founder of medical class, Hipocrates (Jones and Mann, 1963; Rabinowich, 1990). The Egyptians used it to treat diarrhoea, then ancient Greeks

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[1]Lalošević Vesna, PhD, full professor, University of Novi Sad, Faculty of Agriculture, Department of veterinary medicine, Serbia. Vlajić Slobodan, MSc, Maširević Stevan, PhD, full professor University of Novi Sad, Faculty of Agriculture, Department of phytomedicine, Serbia. Simin Stanislav DVM, MSc, research associate, University of Novi Sad, Faculty of Agriculture, Department of veterinary medicine, Serbia. Takač Ana, dipl. ing., Kuruca Ljiljana, DVM, MSc, University of Novi Sad, Faculty of Agriculture, Department of veterinary medicine, PhD student granted by Ministry of Science, R. Serbia.
Corresponding author: Lalošević Vesna, e-mail: lvesna@polj.uns.ac.rs, phone: +38121/450-494.

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used it to treat intestinal diseases, while the ancient Japanese and Chinese used it to treat headache, flu, sore throat and fever (El-mahmond, 2009). The antimicrobial properties of garlic were first described by Pasteur in 1858, and it was used as an antiseptic to prevent gangrene during World War I and World War II. Since then, research has demonstrated its effectiveness against bacteria, protozoa, fungi and some viruses (Jaber and Al-Mossawi, 2007). Nowadays, garlic is increasingly used as an alternative medicine for treating various diseases in human medicine, to prevent and treat cardiovascular disease by lowering blood pressure and cholesterol and as a preventive agent for cancer. Garlic inhibits platelet aggregation and enhances fibrinolytic activity, reducing clots on damaged endothelium (MacDonald et al., 2004).

In phytopharmacy it is used in the form of various macerate and fermented extracts, for the suppression of certain plant pathogens.

The garlic particularly has influence on certain genera of bacteria, even in dilutions from 85,000 to 125,000 (Lazić et al., 2001).

Chemistry of garlic

Allicin (diallylthiosulfinate), the best known active compound of garlic, is the product from the secondary metabolism of amino acids containing sulfur, and it is not the the initial substance of garlic plant, but occurs after bulbs injury under the interaction of the amino acid alliin with the enzyme alliinase (Kastori 2010, Miron et al., 2002). Alliin is the primary odorless, sulfur-containing amino acid, a precursor of allicin; it is converted into thiosulfinates through enzyme reactions when raw garlic is cut or crushed.

Thus, no thiosulfinates are found in intact garlic (Amagase H., 2013). In order to activate the enzyme and start the reaction, oxygen from the air is required. For this reason the tissue must be injured so that leaking juice can come in touch with oxygen.

S-Allyl-L-cysteine (**SAC**) is one of the water-soluble organosulfur compounds in garlic and it has many biological effects: antidiabetic action (Saravanan et al., 2013), suppress of proliferation and metastasis of carcinoma (Ng et al., 2012), influence on placenta or retina (Yu et al., 2012; Chen et al., 2012).

Nonsulfur compounds - steroid saponins, such as eruboside-B isolated from the garlic bulb, exhibit antifungal activity against *Candida albicans* (Nakagawa et al., 1987). Studies report that the crude glycoside fraction (Matsuura H., 2001; Slowing et al., 2001) from methanolic raw-garlic extracts, which mainly contains spirostanol saponins, lowered total plasma cholesterol and LDL cholesterol without changing HDL cholesterol levels in hypercholesterolemic animal models.

Safety of garlic preparations

Although garlic has been safely used in cooking as a popular flavor and has been used traditionally for medicinal purposes, it is commonly known that excessive consumption of garlic can cause diarrhea (Adachi A., 2010) and occasional allergic reactions like dermatitis and bronchial asthma (Jappe et al., 1999; Van der Walt et al., 2013). Garlic fractions induced apoptosis of testicular germ cells and decrease of serum testosterone levels (Hammami et al., 2013). SAC, as one of the active ingredients in garlic preparations, is a safe compound and its biological effects are well researched. The U.S. National Cancer Institute tested the toxicity of SAC

compared with other typical garlic compounds and found that SAC is less toxic than allicin. The oral 50% lethal dose in mice (mg/kg body weight) is 309 in males and 363 in females for allicin and 8890 in males and 9390 in females for SAC. Thus, SAC is 24% less toxic than allicin (Amagase H., 2013).

The different constituents in various garlic preparations, have different safety characteristics and biological and pharmacological activities, which are discussed below.

Cholesterol reduction

Numerous animal studies, as well as *in vitro* ones, have demonstrated the hypolipidemic effects of garlic while clinical trials are highly inconsistent (Zeng et al., 2013). But, it has been demonstrated that 12-month treatment with garlic powder tablets results in the significant decrease of cardiovascular risk by 1.5-fold in men ($p < 0.05$), and by 1.3-fold in women (Sobenin et al., 2010). Also, some studies suggested garlic as effective in reducing total serum cholesterol and low-density lipoprotein cholesterol in individuals with elevated total cholesterol levels (>200 mg/dL). Reduction in total serum cholesterol of 8% has been observed after 2 months application of garlic. This finding is of clinical relevance as it has been associated with 38% reduction of risk of coronary diseases in fifty-year-olds (Ried et al., 2013a).

Antihypertensive potential

Hypertension (systolic blood pressure (SBP) $\geq$ 140 mm Hg; diastolic blood pressure (DBP) $\geq$ 90 mm Hg) is a main risk factor for cardiovascular diseases, it affects about 30% of adults worldwide. Blood pressure reducing properties of garlic have been linked to its hydrogen sulphide production and allicin content – liberated from alliin and the enzyme allinase, which has angiotensin II inhibiting and vasodilating effects, as shown in animal and human cell studies (Londhe et al., 2011). It may be a safe adjunct treatment to conventional antihypertensive therapy (Ried et al., 2013b). Aged garlic exstract significantly reduced interstitial fibrosis in hypertensive rats (Hara et al., 2013). Allicin lowered blood pressure and triglyceride levels in spontaneously hypertensive rats, also (Elkayam et al., 2013). From that reasons garlic has played an important dietary role in human medicine.

Antidiabetic potential

Diabetes mellitus is a metabolic disorder characterized by hyperglycaemia resulting from either a defect in the secretion or activity of insulin. Hyperglycaemia leads to an increase in the oxidative stress because of the overproduction of free radicals (Wiernsperger F., 2003). Most of the previous researches in animal models on rats have studied the physiological and biochemical effects of garlic on diabetes.

Oral administration of garlic to alloxan-induced diabetic rats for a month significantly reduced the concentrations of serum lipids and blood glucose. The supplementation of garlic oil for diabetic patients may decrease the incidence of diabetic complications, which may result from an increase of free radical activity in diabetes (Abdultawab and Ayuob, 2013). S-allyl cysteine is a potent agent against lipogenesis and glucose metabolism in alloxan diabetic rabbits (Nasri H., 2013).

From these encouraging results in animal models, garlic extract could have sufficient potential as anti diabetic agent for the patient of type 2 diabetes mellitus.

Antibacterial potential

Various preparations of garlic nowadays exhibit a wide spectrum of activity against Gram–positive and Gram–negative bacteria (Ankri and Mirelman, 1999). The most common bacterial genera that have been investigated in terms of sensitivity to garlic were *Escherichia, Salmonella, Staphylococcus, Streptococcus, Klebsiella, Proteus, Bacillus* and *Clostridium.* More frequent consummation of garlic prevents the development of the *Helicobacter pylori* which causes gastritis in humans and animals (Cellini et al., 1996). Increase of the number of sulphur atoms in the active substance of garlic increases the antibacterial activity against the same bacterium (O'Gara et al., 2000). It was noted that pharmacological components of garlic act synergistically with antibiotics such as streptomycin and chloramphenicol in therapy against *M. tuberculosis* (Gupta and Viswanathan, 1955). In research carried by Vlajić et al. (2013), it was noticed that raw garlic extract has proved to be more effective *in vitro* conditions against isolates of *Salmonella typhimurium* and *Salmonella enteritidis*, which are resistant to ampicillin. The data given by Ankri and Mirelman (1999) indicate that the development of resistance to betalactame antibiotics is 1000 times faster then to allicin, from the garlic. Gram–positive bacteria are less sensitive to garlic extract because of the presence of thick layer of peptidoglycan (Bakri and Douglas, 2005; Indu et al., 2006), however some isolates of Gram–positive bacteria like *S. aureus* originated from swab throat are extremely sensitive (Vlajić et al., 2013).

In the last few years it has been noticed that bacteria have become more significant pathogens of cultivated plants. The sensitivity of phytopathogenic bacteria to garlic is also very important, especially since the usage of antibiotics in therapeutic treatment of plants is prohibited by the Law of Plant Protection. The usage of specific copper compounds produces results only in prophylaxis, since they are the first of all fungicides. Highly sensitive effect to garlic extract was recorded in species *Xanthomonas euvesicatoria*, *X. a.* pv. *phaseoli* and *Erwinia amylovora*, a lower sensitivity was observed in *Pseudomonas syringae.* pv. *syringae* (Vlajić et al., 2012). The existence of hydrophilic capsules or mucoid layers in bacterial cells, in some cases prevents the penetration of allicin in the bacteria (Ankri and Mirelman, 1999).

An accurate determination of the mechanism of garlic action is very complex; the reason for that is the interaction of some various pharmacological active ingredients found in *Allium* species. As the most important organosulphur compounds (Harris et al, 2001.; Kumar et al., 1998; Kyung et al, 2001.), allicin (Ankri and Mirelman, 1999, Chung et al., 2007, Medina et al., 2006), ajoene (Nakagawa et al., 1987) and diallyl sulphide (O'Gara et al., 2000) stand out. Yin and Cheng (2003) observed that diallyl disulphide was more effective in the elimination of important pathogenic microorganisms such as *Escherichia coli* O157: H7 and *Listeria monocytogenes.* However, others have shown that the phenolic compounds also contribute to antimicrobial activity (Benkeblia, 2004). According to Feldberg et al. (1988) allicin from garlic extract, directly or indirectly blocked the synthesis of RNA, whereas had no significant effect on DNA. Therefore it is considered that the primary aim is blocking the formation of RNA.

Anticancer potential

Although the exact mechanism involved in the protective effects of garlic compounds against carcinogenesis has not been clearly understood, at present some

organosulfur compounds derived from garlic, including S-allylcysteine, have been found to retard the growth of chemically induced and transplantable tumors in several animal models (Thomson and Ali, 2003). Some results indicate that mitochondria certainly play a major role in diallyl disulfide-induced apoptosis (Nagaraj et al., 2010). Authors of population-based case-control study which was conducted in a Chinese population from 2003 to 2010 concluded that raw garlic consumption of 2 times or more per week is inversely associated with lung cancer (Jin et al., 2013).

The Iowa Women's Health Study reported that having at least one serving of garlic per week was associated with a 48% reduced risk of distal colon cancer compared to zero servings of garlic (Larsson et al., 2005).

Antiinflammatory potential

The sulfur compounds inhibited the production of nitric oxide (NO) and prostaglandin E (2) (PGE (2)) and the expression of the pro-inflammatory cytokines tumor necrosis factor-α, interleukin-1β, and interleukin-6 in lipopolysaccharide (LPS)-activated macrophages (Lee et al., 2012). By inhibiting Th1 and inflammatory cytokines while upregulating IL-10 production, treatment with garlic extract may help to resolve inflammation associated with inflammatory bowel disease (Londhe et. al., 2011).

Hepatoprotective Potential

SAC significantly induced apoptosis and necrosis of cells MHCC97L *in vitro* and *in vivo* xenograft liver tumor model demonstrated that SAC inhibited the progression and metastasis of HCC tumor (Ng et al., 2012).

CONCLUSION

The human health benefits of consuming garlic are well documented. Garlic (*Allium sativum* L.) used in cardiovascular therapeutics has an even longer history back over 3000 years. Garlic's antidiabetic, antibiotic and perhaps anticancer effects are well-accepted because of the many of scientific literature supporting these effects. Garlic also has hepatoprotective, and antioxidant effect. The other pharmacological effect includes the anticoagulant, antiinflammatory, immunomodulatory and wound healing action of garlic. Garlic has the potential of preventing or curing a man and animals from a large number of diseases.

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TERAPIJSKA UPOTREBA BELOG LUKA (*Allium sativum* L.): NOVE MOGUĆNOSTI

VESNA LALOŠEVIĆ, SLOBODAN VLAJIĆ, STEVAN MAŠIREVIĆ, STANISLAV SIMIN, ANA TAKAČ, LJILJANA KURUCA

Izvod

Beli luk (*Allium sativum*) je dugo istraživana kultura, upravo zbog cilja pronalaženja alternativnih mera kontrole različitih oboljenja kod ljudi i životinja. Njegova upotreba u terapiji kod kardiovaskularnih oboljenja ima dugu istorijsku tradiciju, stariju od 3000 godina. Aktivnu komponentu belog luka čini alicin, koji nastaje nakon ozlede tkiva lukovice pod dejstvom enzima alinaze na alin. Antidijabetički, antibakterijski a verovatno i antikancerogeni efekti belog luka su dokumentovani u naučnoj literaturi. Takođe, primećeno je da beli luk ispoljava hepatoprotektivno i antioksidativno dejstvo. Drugi farmakološki efekti koji su još uvek nedovoljno ispitani, uključuju antikoagulantno, antiinflamatorno i imunomodulatorno dejstvo kao i pozitivan efekat u zarastanju rana. Beli luk ima potencijal primene u lečenju ljudi i životinja od različitih bolesti.

Ključne reči: *Allium sativum*, ekstrakt belog luka, alicin, farmakološki efekti.

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