

doi: 10.30827/ars.v62i4.20843

Artículos de revisión

General aspects about *Allium sativum* – a review

Aspectos generales del *Allium sativum* - una revisión

Arlene Loría Gutiérrez¹  0000-0002-5059-8026

Jeimmy Blanco Barrantes¹  0000-0001-5471-8948

Marta Porrás Navarro¹  0000-0001-5626-1005

María Celeste Ortega Monge¹  0000-0002-8384-9987

María José Cerdas Vargas¹  0000-0001-7296-7980

German L Madrigal Redondo¹  0000-0002-9856-4044

¹Universidad de Costa Rica, Facultad de Farmacia, Instituto de Investigaciones Farmacéuticas (INIFAR), San José, Costa Rica.

Correspondence

German L Madrigal Redondo
german.madrigal@ucr.ac.cr

Received: 18.03.2021

Accepted: 09.09.2021

Published: 20.09.2021

Financing

Universidad de Costa Rica, INIFAR

Conflict of interests

The authors have not reported a conflict of interest

Acknowledgment

We thank INIFAR (Instituto de Investigaciones Farmacéuticas) and Dr. German Madrigal for all the support.

Resumen

Introducción: El ajo ha sido utilizado como alimento y planta medicinal a través de los años. Se le atribuyen cualidades antimicrobianas, antivirales e inmunoestimuladoras, razón por la que es ampliamente recomendado en el tratamiento de enfermedades como asma, bronquitis, influenza, entre otras.

Método: El objetivo de este estudio fue realizar una revisión y análisis de la literatura relacionada con el uso medicinal del ajo, y su potencial como agente terapéutico e inmunoestimulante en diferentes enfermedades y condiciones de salud. La búsqueda de literatura se realizó en las bases de datos de Medline a través del buscador Pubmed, Scielo, Clinical Key y ClinicalTrials.gov, entre otros.

Resultados: La información consultada respalda los beneficios para la salud asociados con el consumo del ajo. La trituración de los bulbos de ajo permite la obtención de aliína, que al sufrir oxidación enzimática, se convierte en alicina. Este compuesto tiene un rol fundamental en las propiedades medicinales del ajo y se dice que la actividad de esta planta medicinal radica en su capacidad de producir alicina. Estudios preclínicos han demostrado el mejoramiento del sistema inmune y se han identificado proteínas específicas asociadas a su efecto inmunoestimulante. En estudios clínicos se han administrado suplementos con derivados de ajo y se ha observado una disminución en la incidencia de influenza y enfermedades respiratorias agudas.

Conclusiones: El ajo ha demostrado tener un potencial clínico muy importante en el tratamiento de gran cantidad de enfermedades. Se han observado efectos inmunomoduladores y en la prevención de enfermedades respiratorias agudas de origen viral.

Palabras clave: Ajo; Inmunoestimulante; Terapéutico; *Allium sativum L.*

Abstract

Introduction: Garlic has been used as a food and medicinal plant through the years. Antimicrobial, antiviral, and immunostimulatory effects are attributed to garlic, so it is widely recommended to treat diseases like asthma, bronchitis, influenza, and some others.

Method: This work's objective was to conduct a literature review and analysis related to garlic medicinal-use, and its potential as a therapeutic agent and immunostimulant in different diseases and health conditions. The literature review was carried out in the databases Scielo, Clinical Key, Medline and ClinicalTrials.gov, among others.

Results: The information consulted supports the health benefits associated with garlic consumption. The crushing of garlic bulbs allows obtaining alliin, which turns into allicin due to enzymatic oxidation. This compound has a fundamental role in the garlic's medicinal properties, and the garlic plant's activity depends on its ability to produce allicin. Preclinical studies have shown the improvement of the immune system, and specific proteins associated with its immunostimulating effect have been identified. In clinical studies, supplements with garlic derivatives have been administered to patients, and a decrease in the incidence of influenza and acute respiratory diseases has been observed.

Conclusions: Garlic has been shown to have a significant clinical potential to treat many diseases, and immunomodulatory effects and viral acute respiratory disease prevention have been observed.

Keywords: Garlic; Immunostimulant; Therapeutics; *Allium sativum L.*

Highlights

Garlic is an herbal medicine traditionally used to treat infections, asthma, bronchitis, influenza, and colds. There is scientific evidence that supports garlic and derivatives to treat different affections. The evidence ranges from *in vitro* studies to human studies (clinical studies).

Alliin and allicin are compounds derived from garlic and are usually incorporated as active pharmaceutical ingredients into formulations due to the biological activity demonstrated.

This study was a bibliographic review of clinical and preclinical studies about garlic, and greater emphasis is placed on studies investigating the immunostimulating effect of garlic. The main contribution of this work is the information and scientific evidence compilation and presentation in a single document that presents the beneficial effects of garlic for health.

In this work, a bibliographic review was carried out on the general aspects of garlic, and its immunostimulating activity was given main importance. The review's objective is to provide the information necessary to facilitate the formulation processes of natural medicinal products based on garlic. This work is considered a starting point for developing new formulations and products with garlic and its derivatives for the treatment of different health conditions.

Introduction

Medicinal plants have been used since ancient times in the treatment of various diseases. Commonly, these plants have been associated with therapeutic purposes. In addition, their active ingredients are used as a raw material for the development of medicines. However, in many cases these plants are used without noticing the adverse effects or contraindications; for this reason, it is fundamental to have access to scientific information that supports the proper use of medicinal plants and their derivatives.

One of the most used plants either for culinary reasons or as a medicinal plant is garlic. Multiple studies have shown the medicinal properties of the bulb of this plant, such as antimicrobials, expectorants, antiseptics, and antifungals. It is also an easily accessible plant that has been commonly used in the treatment of respiratory diseases such as asthma and bronchitis.

This literature review aims to investigate the benefits of garlic as a potential therapeutic agent and immunostimulant in different diseases and health conditions.

Garlic

The garlic's scientific name is *Allium sativum* L. (Liliaceae)⁽¹⁾. It can also be found as camphor of the poor, nectar of the gods, majo, poor's molasses, rustic molasses, smelly rose⁽²⁾. However, the common name by which it is known in Costa Rica is garlic. The bulb is used for medicinal effects. Alliin and allicin are usually used as active ingredients in different formulations⁽¹⁾.

Garlic is one of the oldest medicinal foods and one of the most researched plants in the world. Due to its wide recognition and cultivation, there is little chance of adulteration with other species. However, garlic used in dietary supplements is handled more carefully than garlic used in commodity spices, it is to preserve the activity of allinase, and subsequently, allicin performance since allinase is sensitive to heat and bruise decomposition⁽³⁾. Likewise, garlic has a strong smell and a pungent flavor that characterizes it⁽²⁾.

Garlic is a herbaceous plant with bulbs composed of numerous fibers divided and wrapped in whitish skin. In addition, it contains 4-6 segments with a characteristic spicy flavor. This perennial herb has a cylindrical stem 50 cm high and sparse, flat leaves 2-3 cm wide. It has sparse flowers in a lilac / pink corolla, and in some cases, the flowers are replaced by bulbs^(3,4). It should be noted that the flowers are rarely open and can wilt in the bud. The flowers are on thin pedicels, consisting of six-segment perianth approximately 4-6 mm long. The fruit is a small loculicidal capsule, and the seeds are rarely produced⁽²⁾.

Garlic is from Siberia and was domesticated in Central Asia. Nomadic tribes have spread it, as it has been cultivated and used in all cultures for more than 5,000 years. It was introduced in America in the XV century⁽¹⁾.

Garlic is grown in loose, rich, silty-sandy, humid, deep, drained soil; mountainous areas with the temperate or cold climate at 1,000-2,400 meters above sea level. It is propagated by bulbils that are sown in full sun; requires abundant water and fertilization. As they mature, the bulbs are dug up and stored in a cool, ventilated place, often cured with smoke that decreases weight loss and partially inhibits germination; teeth become dehydrated ground or flaked⁽¹⁾.

Taxonomy⁽⁵⁾

Kingdom: Plantae

Subkingdom: Viridiplantae

Infrakingdom: Streptophyta

Division: Tracheophyta

Subdivision: Spermatophytin

Class: Magnoliopsida

Superorder: Liliales

Order: Asparagales

Family: Amaryllidaceae

Genus: *Allium*

Species: *A. sativum*

Composition

Allium sativum bulb contains sulfur compounds such as ajoene and derivatives, allicin, allyl-methyl trisulfide and derivatives, diallyl disulfide and derivatives, dimethyl sulfide, allyl-methyl disulfide and derivatives, dimethyl thiosulfonate and derivatives, amino acids derived from cysteine and anthocyanins, sulphurated amino acids: alliin (by enzymatic oxidation it becomes allicin, intermediate in the formation of allyl disulfide derivatives, final constituents of essential oil), 5-butyl-cysteine sulfoxide and derivatives, lipids such as cerebrosides, steroids, prostaglandin A, B, E, and F; alkaloids such as phosphatidylcholine, nicotinic acid, diterpenes (gibberellin A-3 and A-7); carbohydrates such as allium fructans; saponins: derivatives of erubioside, sativoside, and tigonine⁽⁴⁾.

Now, from 100 g of bulb (117 kcal), you will find: 67.8% water, 3.5% protein, 0.3% fat, 27.4% carbohydrates, 0.7% fiber, 1% ash, 18 mg calcium, 88 mg phosphorus, 1.5 mg iron, 18 mg sodium, 373 mg potassium, 0.24 mg thiamine, 0.05 mg riboflavin, 0.4 mg niacin, and 10 mg ascorbic acid⁽⁴⁾.

It should be noted that the antimicrobial activity is attributed to alliin, a sulfoxide that by alliinase action is converted to allicin and allyl and ajoene disulfide. Antimicrobial activity is also attributed to alixin and garlicin that are obtained by severe bulb treatments. Ajoene is an antithrombotic factor whose action involves fibrinogen receptors on platelets and prevents platelet aggregation; It reduces arachidonate metabolism by inhibiting the enzymes' prostaglandin synthetase and 5-lipoxygenase and has shown a promising role in the treatment of leukemia. Fructosans inhibit adenosine deaminase by participating in the regulation of the processes in which adenosine is involved⁽¹⁾.

Traditional use

Garlic has been used as herbal medicine to treat asthma, bronchitis, influenza, and colds⁽¹⁾. Besides, it serves as a treatment for respiratory infections⁽²⁾. It is commonly used to treat bronchopulmonary diseases as expectorant antiseptic and asthma. Likewise, it is used as a hypotensive, diaphoretic, and vermifuge⁽⁶⁾.

The most commonly used form of garlic extraction is maceration⁽⁷⁾. There are several variants to this method, depending on the amount of plant material and the concentration of the extract required, however, all methods of this type have in common that the extraction solvent can be water (aqueous extract), alcohol (ethanolic extract) or a hydroalcoholic combination.

One way of making the macerated garlic extract is by using the garlic bulb (bulb extract) since these are the parts of the garlic with the highest biological activity. For the preparation, the garlic is peeled, cut into slices, and stored for 40 days at a temperature of 60-70°C, then suspended in a hydroalcoholic solution. After this time, the processed garlic is suspended in an anaerobic maceration for 18 weeks, at the end of which period they are filtered and rotavaporated; the liquid extract obtained should be kept refrigerated⁽⁸⁾. Another way to make this liquid extract is in cold in a conical flask for 72 hours⁽⁷⁾.

Spray drying is another way of making garlic extracts, this technique is performed on the liquid extracts, to obtain a dry extract in a solid matter form. It consists of atomizing it in the form of small drops in a dry medium, dehydrating it employing hot air, and turning it into powder or tiny spheres⁽⁷⁾.

Toxicology

Studies carried out found that the LD50 of the bulb by oral and subcutaneous route to rats of both sexes was higher than 30 mL/kg. The aqueous extract from the bulb elicited *in vitro* uterotonic activity on the pregnant female mouse's uterus. Furthermore, the bulb extract (2g/kg) administered in rats five times a week for six months showed no toxic effects. Externally, poultices with high concentrations of bulb extract can cause skin necrosis and allergenic activity. The latter has been verified with the internal administration of the aqueous extract orally in rats and sensitive humans⁽⁴⁾.

Similarly, the oral bulb can irritate the urinary tract in people with specific sensitivity. A dose of 350 mg/person (both sexes from 30 to 62 years old) administered twice a day did not produce toxic manifestations. No information evidences the safety of its medicinal use in children, pregnancy, or lactation⁽⁴⁾.

In another study, it was shown that the ethanolic extract is not mutagenic in *S. typhimurium*. The LD50 of mouse allicin is 60 mg/kg IV and 120 mg/kg SC; the LD50 of the oil is 50-78 mg/kg IV; the LD50 of neoallicin is 70 mg/kg IV and 600 mg/kg orally. Oral administration is not genotoxic by testing the micronucleus in the bone marrow and inducing changes in sister chromatids in spermatogonia. Due to prolonged traditional use, daily consumption does not pose any health risk⁽¹⁾.

Contraindications

Conditions and diseases such as hyperthyroidism, active bleeding and, thrombocytopenia are contraindicated. Do not prescribe the oil during pregnancy⁽¹⁾. It is contraindicated in patients with a known garlic allergy. Besides, other contraindications include acquired immunodeficiency syndrome (AIDS), surgery, and diabetes mellitus⁽⁹⁾.

Until more data becomes available, people with *diabetes mellitus* have to be careful when taking dietary supplements containing garlic and follow their normally recommended blood glucose control strategies. Because garlic components inhibit platelet aggregation, care must be taken in patients receiving anticoagulant or thrombolytic therapy⁽⁹⁾. Despite this, garlic's safety level is reflected in its worldwide use as a condiment in food⁽²⁾.

Warnings

The juice and oil irritate the mucosa and the conjunctiva⁽¹⁾. Additionally, consuming large amounts of garlic can increase the risk of postoperative bleeding. Also, ingesting fresh garlic bulbs, extracts, or oil on an empty stomach can cause heartburn, nausea, vomiting, and diarrhea⁽²⁾.

Side effects

Case reports have highlighted the possibility that the use of garlic may cause allergic reactions (allergic contact dermatitis, generalized urticaria, angioedema, pemphigus, anaphylaxis, and photoallergy), impaired platelet function, and clotting (with a possible risk of bleeding)^(10,11) and burns (when fresh

garlic is applied to the skin, particularly under occlusion dressings). It should be noted that garlic can cause bad breath or body odor, so many people decide not to consume it⁽¹⁰⁾. The oral bulb can irritate the urinary tract in people with specific sensitivity⁽⁴⁾. Furthermore, the use of garlic in some cases evokes asthmatic attacks after inhalation of the drug powder⁽²⁾.

The most common effects associated with the use of garlic in therapeutic doses are mild gastrointestinal, such as nausea, bloating, flatulence, dyspepsia, nausea, vomiting, diarrhea, and pyrosis. Severe gastrointestinal adverse effects can also be found, such as small bowel obstruction, epigastric and esophageal pain, hematemesis, and hematochezia. It can also cause hypotensive effects, heart attack, and Meniere's disease⁽¹⁰⁾.

Pregnancy and lactation

Garlic is safe during pregnancy in amounts that are generally eaten in food. However, garlic supplements or large amounts of garlic should be avoided during pregnancy due to a possible increased risk of bleeding or stimulation of uterine contractions⁽¹²⁾. During lactation, there are no known contraindications. The excretion of the components of garlic in breast milk and its effect on the newborn has not been established⁽²⁾.

Interactions with other drugs

Garlic causes a harmful effect related to kidney damage and nephrotoxicity combined with statins⁽¹³⁾. Clinical evidence suggests that taking garlic may result in pharmacokinetics or pharmacodynamic interactions that could represent a potential risk to patients taking conventional medications, particularly in subjects treated with anticoagulants. Blood clotting time has been reported to double for patients taking warfarin and garlic supplements⁽¹⁰⁾.

Additionally, interactions with antiretroviral therapies may occur. A severe drug interaction has been reported between garlic and an HIV protease inhibitor, saquinavir; this interaction may compromise antiretroviral therapy's effectiveness and lead to higher drug resistance rates against the acquired immunodeficiency virus. Other conventional medications that could interact with garlic include the anti-diabetic chlorpropamide and the pain reliever paracetamol⁽¹⁰⁾.

Dosage and administration

Studies report the use of 4-12.3 mg/day of garlic oil orally.

Adults: The World Health Organization (WHO) recommends 2 to 5 grams of fresh garlic, 0.4 to 1.2g of dry powder, 2 to 5 mg of oil, 300 to 1,000 mg of extract, equivalent to 2- 5 mg alliin/day.

6-10 mg alliin (approx. 3-5 mg alliin) daily, typically contained in one clove of garlic or 0.5-1.0 g of dry garlic powder⁽⁶⁾.

2 to 4 grams of the dry bulb or 2 to 4 milliliters of tincture (1:5 dilution in 45% ethanol) orally three times a day for upper respiratory tract infections⁽⁶⁾.

Pediatrics: dry extract is recommended as a single dose (100 – 200 mg) once or twice a day. The daily dose is 100-400 mg. The herbal substance powder or the liquid extract of garlic is not recommended in children and adolescents under 18 years of age⁽¹⁴⁾.

Geriatric: liquid extract is recommended as a single dose (110 – 220 mg) 4 times a day. The daily dose is 440 – 880 mg. The dry extract is recommended as a single dose (100 – 200 mg) once or twice a day. The daily dose is 100 – 400 mg⁽¹⁴⁾.

Methods

We performed a literature review and analysis of Garlic medicinal use. The databases consulted in the searching process were Medline, Scielo, Clinical Key, and the consulted languages were English and Spanish using the following Medical Subject Heading (MeSH) terms and keywords: Ajo or garlic or Al-

lium sativum L, Inmunoestimulante, Sistema immune or Immune System and Inmunoestimulador or Immunostimulator. Moreover, we searched the United States Patent and the ClinicalTrials.gov website to find patents and Clinical trials about garlic's medicinal use.

The eligibility criteria of consulted material include original studies describing preclinical (*in vivo* and *in vitro*) and clinical studies about garlic's pharmacological use. Moreover, we included information from review papers, scientific communications, books, monographs, and pharmacopeia. Furthermore, studies describing the medicinal use of garlic combined with another component were excluded.

For the Medline database, using the keywords "garlic" and "immunity", 29 results were found and only 4 articles were used. The keywords, "garlic" and "cold", were also used, where 7 results were found, and only 3 were used. In addition, with the keywords "garlic" and "antiviral", 9 results were found and only 2 articles were used. Additionally, the keywords "garlic", "immunomodulatory", and "protein" were used, 8 results were found; however, only 1 article was used.

To define the different garlic extracts, a search was performed in the Scholar Google database, using the keywords "extract" and "garlic", 16 articles were found, of which only 2 were used.

Results

Preclinical Studies

Garlic is well-known for improving the immune system. A preclinical study was done to examine the protein fraction changes during garlic aging and identify immunomodulatory proteins. The modifications that occur in garlic during the aging process were studied by protein quantification and gel electrophoresis. Purification and identification of immunomodulatory proteins have been achieved by Q-Sepharose chromatography and mitogenic activity. In the study, only two main proteins (range of 12–14 kDa by SDS-PAGE) were observed in aged garlic extract (AGE). The purified protein components QA-1, QA-2, and QA-3, showed immunomodulatory and mannose-binding activity; QA-2 showed the highest mitogenic activity. The QA-2 and QA-1 proteins' identity with the ASA I and ASA II garlic lectins, respectively, was confirmed by hemagglutination analysis. QA-3 exhibited mitogenic activity but not hemagglutination activity⁽¹⁵⁾.

Another study was done on the enteric-coated garlic supplement, which is a kind of garlic preparation based on garlic oil and garlic powder compressed in tablets, with a remarkable improvement in normal mice's immunocompetence. In the study, garlic oil was extracted from the fresh garlic bulb by steam distillation and complexed with 2-hydroxypropyl-beta-cyclodextrin using a method of high-energy ball milling to then incorporate the inclusion complex with enteric-coated powder and reduce its gastrointestinal irritant. Based on the maximum tolerance dose test, mice that took an enteric-coated garlic tablet by gavage at a dose of 3 g/kg body weight did not show symptoms of acute toxicity⁽¹⁶⁾.

In this study, experimental animals were randomly assigned. Different doses of garlic tablets for 30 consecutive days were given orally. Furthermore, their immune functions were comprehensively analyzed. Compared to the control, the garlic tablet significantly improved ConA-induced splenic lymphocyte proliferation, serum hemolysin production, the number of hemolytic pest-forming cells, peritoneal macrophages phagocytic activity, and the rate of carbon removal at the dose of 400, 600 mg/kg of body weight. It also improved the DNFB-induced delayed-type hypersensitivity reaction and NK cells' cytotoxicity at the 600 mg/kg body weight dose. In addition, garlic tablets increased serum cytokine secretion (TNF- α , IL-2) in a dose-dependent manner⁽¹⁶⁾.

A study was conducted to evaluate the inhibitory effects of garlic extract on avian infectious bronchitis virus. For this purpose, four groups of chick embryonic eggs were used, where the first group was used for virus titration; the second group was given the mixture of different titrations of virus and garlic extract; the third group received a virus titration and after 8 hours received garlic extract and the last group received different dilutions of garlic extract. According to the results of the study, it was shown that garlic extract influences the garlic virus in the replication phase. In addition, avian infectious bronchitis virus RNA and virus replication were dose-dependently decreased⁽¹⁷⁾.

A preclinical study hypothesized that allicin can alleviate immune dysfunction caused by the reticuloendotheliosis virus (REV). For this purpose, 240 White Leghorn SPF chickens were used and divided into 5 treatment groups and one control group. It was found that treatment with allicin enhanced the proliferation of lymphocytes infected with this virus, demonstrating that allicin helps to alleviate the growth inhibition induced by REV infection and immune system dysfunction. In addition, it was shown that in the groups treated with allicin, the expression of inflammatory cytokines produced by REV infection was decreased. It was also found that allicin significantly reduced the oxidative stress caused by REV infection⁽¹⁸⁾.

In a preclinical study, the effect of the 14 kDa protein isolated from AGE on the maturation and immunomodulatory activity of dendritic cells (DC) was studied to prove its immunomodulatory effects. Biochemical methods were used to purify the AGE protein; the semi-purified 14 kDa protein was run on gel filtration Sephadex G50 and checked for purity by SDS-PAGE. DC was separated from the spleen of BALB / c mice by Nycodenz centrifugation and adhesion to plastic plates. The 14 kDa AGE protein was added to the overnight culture of the DC medium and the expression percentages of CD40, CD86, and MHCII were evaluated by flow cytometric analysis. In addition, T-cell proliferation was measured by the mixed allogeneic lymphocyte reaction (MLR) test. Despite the results, more research has to be done to conclude if the 14 kDa protein isolated from AGE induces DC maturation and increases immunostimulatory activity⁽¹⁹⁾.

On the other hand, an in vivo study carried out with Wistar rats evaluated the effects of garlic oil on the serum levels of IFN- γ , TNF- α , and IL-5. Obtaining as a result that the garlic oil increased the levels of IFN- γ and TNF- α to 2 and 3 times those of the control group (which were only treated with corn oil) respectively. It also produced a slight increase in IL-5 levels. In addition, the effect of this oil on IgG and IgM levels was determined, where an increase of approximately 60% in IgG levels was obtained as a result, but a significant increase in IgM levels was not registered⁽²⁰⁾.

Similarly, the effect of garlic oil on mRNA expression levels in interleukins 2, 4, and 5 in rat leukocytes was evaluated and it was determined that it decreases the expression levels of these interleukins in contrast to the control group⁽²⁰⁾.

Clinical Studies

A study at the University of Florida recruited 120 healthy subjects (60 per group) to determine the effect of consuming supplements with AGE (2.56 g/d) on immune cell proliferation and cold symptoms, and flu. After 45 days of AGE consumption, $\gamma\delta$ -T and NK (natural killer) cells thrived better and were more activated than cells in the placebo group⁽²¹⁾. After 90 days, the AGE group showed a reduction in the severity of the cold and flu, a reduction in the number of symptoms, the number of days the participants functioned suboptimally, and the number of days of work school missed^(22,23).

Moreover, a clinical study evaluated the effects of allicor, a long-acting garlic tablets, on acute respiratory viral infection incidence in children. For the first stage, allicor tolerance (600 mg/day) and its effects on ARD morbidity were investigated in a 5-month open study in 172 children and adolescents aged 7 to 16, compared to 468 individuals in a control group; however, this was not observed to induce gastrointestinal side effects in children at any dose, while ARD morbidity was reduced 2 to 4-fold compared to controls. In the second stage, allicor (300 mg/day) effects on morbidity from ASRD were investigated in a 5-month, double-blind, randomized, placebo-controlled trial. This study included 42 children aged 10-12, compared to 41 placebo-treated children and 73 children treated with benzimidazole. For this stage, allicor reduced ARD morbidity 1.7 times compared to placebo and 2.4 times compared to benzimidazole. Furthermore, there was no significant difference in ARD morbidity between the placebo and benzimidazole groups⁽²⁴⁾.

Similarly, a clinical trial regarding the prevention of the common cold was performed with a garlic supplement. A sample of 146 people was used; there were two groups, volunteers who were going to receive a placebo; and the second group of participants received a garlic-containing supplement (allicin) for 12 weeks. The researchers used a five-point scale to assess their health and recorded all infections and symptoms of the common cold⁽²⁵⁾.

Through a clinical study, the effect of garlic (*Allium sativum*) on the gene expression of pro and anti-inflammatory cytokines was evaluated, for which peripheral blood mononuclear cells (PBMC) from donors in optimal health conditions were treated. Treatment with garlic provided satisfactory results since it significantly stimulated the expression of said cytokine in 4 of the 6 study participants. In these donors, an increase in IL-17 transcription was detected thanks to the treatment with garlic⁽²⁶⁾.

Discussion

Aged garlic extract is composed of low molecular weight immunomodulatory proteins, transformed organosulfur compounds, fructans, and some amino acids and their derivatives. According to the aforementioned preclinical studies, the potent immunomodulatory activity of AGE is due to the immunomodulatory proteins garlic agglutinins ASA I and II. Due to the above, garlic can contribute to the treatment and prevention of certain diseases caused by immune dysfunction⁽¹⁵⁾. Also, it was demonstrated that dietary supplementation with garlic tablets could improve the function of the mononuclear phagocytic system, cell-mediated immunity, and humoral immunity of normal mice to varying degrees. In addition, it significantly increased serum cytokine secretions (TNF- α , IL-2) in a dose-dependent manner. Importantly, to see improvements in immune functions *in vivo*, enteric-coated garlic tablets need to be developed as an economical and potential functional food⁽¹⁶⁾.

On the other hand, it was demonstrated that garlic extract has an inhibitory effect on avian infectious bronchitis virus in its replication phase since when garlic extracts were used, a significant decrease of the virus was found in a dose-dependent manner⁽¹⁷⁾. Likewise, allicin, which is one of the main components of garlic, has been shown to significantly reduce immunosuppression induced by the reticuloendotheliosis virus, help reduce inflammation and alleviate oxidative stress produced by this virus. In addition, allicin blocks the ERK/MAPK pathway during infection and has antioxidant activity, which allows it to function as an antiviral⁽¹⁸⁾.

Furthermore, results suggest that AGE consumption may improve immune cell function and be responsible for reducing the severity of reported colds and flu. These results also suggest that the immune system works well with AGE supplements, with less subsequent inflammation^(22,23). Correspondingly, the consumption of allicin was proven as an effective tool for the nonspecific prevention of acute respiratory infections in children; also, it did not show side effects⁽²⁴⁾. In the same manner, in a clinical trial, the active treatment group had significantly fewer colds than the placebo group, while the placebo group recorded significantly more days of viral exposure and a significantly longer duration of symptoms. Thus, volunteers in the active group were less likely to catch a cold and recover faster if infected, meaning that a supplement containing allicin may prevent the common cold virus effects⁽²⁵⁾.

Through the results obtained, it is concluded that garlic oil can modulate the immune response in rats. It should be noted that the decrease in IFN- γ levels due to the administration of garlic oil is an indicator of the effect it exerts against the deviation of the immune response. In addition, this oil can stimulate the activity of basal macrophages. Finally, it was determined that this oil has immunomodulatory properties due to the balance that is exerted on the elevation of IgG and IgM⁽²⁰⁾.

The results indicated that the garlic extract did not impair the proliferation of both human CD8 + and CD4 + T cells. Furthermore, no significant effects were found on IL-4 gene expression, but IL-17. The foregoing refers to the fact that the results obtained determined the inhibition of the pro-inflammatory cytokine (IL-17), which could be beneficial to regulate its potential and thereby control various autoimmune and inflammatory diseases. IL-17 plays a very important role in inflammation of the Central Nervous System as in multiple sclerosis, since it has a close relationship with active lesions. It is also part of the pathogenesis of rheumatoid arthritis, and high levels of this cytokine have been found in various types of tumors. Therefore, this plant has great potential for the treatment of inflammatory diseases and cancer, due to the inhibition of IL-17⁽²⁶⁾.

Conclusion

Garlic is shown to have significant clinical potential in treating a wide variety of diseases. Different studies have indicated that garlic is attributed a potentiating effect on the mononuclear phagocytic system, which is related to an improvement in the body's immune functions. Likewise, proteins that have a link with the immunomodulatory properties related to garlic have been identified. In a study on the effect of garlic tablets (allicor) in the child population, the efficacy of treatment in preventing acute respiratory viral infections was determined. Garlic has also been linked in other studies for reducing the severity of symptoms of the common cold in experimental subjects.

Although garlic is believed to be a safe substance, it is necessary to clarify that garlic supplements are contraindicated in pregnant women due to a possible uterine contraction stimulation. Nor is the use of garlic powder and liquid extract recommended for those under 18 years of age. Also, because the components described in garlic inhibit platelet aggregation, special care must be taken in its administration to patients with anticoagulants or thrombolytic therapies.

Bibliography

1. Vanaclocha B, Cañigueral S. Fitoterapia, Vademécum de prescripción. 5ª ed. Barcelona: Elsevier; 2019.37p.
2. World Health Organization. WHO monographs on selected medicinal plants. Vol 1. Geneva; 1999. p.16-26.
3. Upton R, Graff A, Jolliffe G, Langer R, Williamson E. American Herbal Pharmacopeia. Estados Unidos de América: CRC Press Taylor & Francis Group; 2011.
4. Germosén L. Farmacopea Vegetal Caribeña. 2ª ed. Santo Domingo: Tramil; 2005. p.36-40.
5. Integrated Taxonomic Information System [Internet]. Itis.gov. 2020. Available from: <https://www.itis.gov/>
6. *Allii sativi* bulbus (Garlic). ESCOP Monographs: The Scientific Foundation for Herbal Medicinal Products; 2019
7. Santander A. Proceso de elaboración de un ungüento con acción antifúngica a partir un extracto seco de ajo (*Allium sativum* L.). Bachelor's thesis, Machala: Universidad Técnica de Machala. 2021.
8. Chaupis D, Rojas J, Gasco M, & Gonzales G. Efecto hipotensor del extracto de ajo (*Allium sativum*) macerado por 18 semanas en un modelo experimental *in vivo*. Revista Peruana de Medicina Experimental y Salud Pública. 2014; 31(3), 461-466.
9. *Allium sativum* drug monograph [Internet]. Gold Standard Drug Database; 2018 [Accessed 2 May 2020]. Available from: https://www-clinicalkey-com.ezproxy.sibdi.ucr.ac.cr/#!/content/drug_monograph/6-s2.0-2221
10. Borrelli F, Capasso R, Izzo A. Garlic (*Allium sativum* L.): Adverse effects and drug interactions in humans. Molecular Nutrition & Food Research. 2007;51(11):1386-1397. doi 10.1002/mnfr.200700072
11. Puell L, Bravo F, Del Solar M, Salomón M, Ramos C, Alca E. Dermatitis de contacto alérgica debido al ajo (*Allium sativum* L.). Folia Dermatología. 2007; 18(2): 72-76
12. O'Mathuna D, Larimore W. Alternative Medicine: The Christian Handbook. Zondervan; 2006. p.346-349.
13. Kansara M, Jani A. Possible interactions between garlic and conventional drugs: a review. Pharmaceutical and Biological Evaluations. 2017;4(2):73. doi:10.26510/2394-0859.pbe.2017.12
14. European Medicines Agency. European Union herbal monograph on *Allium sativum* L., bulbs. [monografía en Internet]; 2016 [Accessed April 24, 2020]. Available from: <https://www.ema.europa.eu/>

en/documents/herbal-monograph/draft-european-union-herbal-monograph-allium-sativum-l-bulbus_en.pdf

15. Chandrashekar P, Venkatesh Y. Identification of the protein components displaying immunomodulatory activity in aged garlic extract. *Journal of Ethnopharmacology*. 2009;124(3):384-390. doi: <https://doi.org/10.1016/j.jep.2009.05.030>
16. Gu B, You J, Li Y, Duan C, Fang M. Enteric-coated garlic supplement markedly enhanced normal mice immunocompetence. *European Food Research and Technology*. 2009;230(4):627-634. doi: 10.1007/s00217-009-1202-1
17. Mohajer T, Ghalyanchi A, Karimi V, Barin A, Sadri N. The effect of *Allium sativum* (Garlic) extract on infectious bronchitis virus in specific pathogen-free embryonic egg. *Avicenna J Phytomed*. 2016;6(4):458-267.
18. Wang L, Jiao H, Zhao J, Wang X, Sun S, Lin H. Allicin Alleviates Reticuloendotheliosis Virus-Induced Immunosuppression via ERK/Mitogen-Activated Protein Kinase Pathway in Specific Pathogen-Free Chickens. *Front Immunol*. 2017;8:1856.
19. Ahmadabad HN, Hassan ZM, Safari E, Bozorgmehr M, Ghazanfari T, Moazzeni SM. Evaluation of the immunomodulatory effect of the 14kDa protein isolated from aged garlic extract on dendritic cells. *Cellular Immunology*. January first of 2011;269(2):90-5.
20. Mohamed E, Baiomy A, Ibrahim Z, Soliman M. Modulatory effects of levamisole and garlic oil on the immune response of Wistar rats: Biochemical, immunohistochemical, molecular and immunological study. *Molecular Medicine Reports*. 2016;14(3):2755-2763. doi: 10.3892/mmr.2016.5551
21. ClinicalTrials.gov: The Effect of Aged Garlic Extract Supplementation on Immune System [Internet]. Percival (MD): National Library of Medicine (US); [Updated November 13, 2013; Accessed May 2, 2020]. Available from: <https://clinicaltrials.gov/ct2/show/NCT01390116>
22. Percival S. Aged Garlic Extract Modifies Human Immunity. *Nutrition Journal*. 2016;146(2):433S-436S. doi: 10.3945/jn.115.210427.
23. Nantz M, Rowe C, Muller C, Creasy R, Stanilka J, Percival S. Supplementation with aged garlic extract improves both NK and $\gamma\delta$ -T cell function and reduces the severity of cold and flu symptoms: a randomized, double-blind, placebo-controlled nutrition intervention. *Clinical Nutrition*. 2012; 31(3):337-344. doi: 10.1016/j.clnu.2011.11.019.
24. Andrianova I, Sobenin I, Sereda E, Borodina L, Studenikin M. Efecto de las tabletas de ajo de acción prolongada “allicor” sobre la incidencia de infecciones virales respiratorias agudas en niños. *Therapeutic archive journal*. 2003;75(3):53-6.
25. Josling, P. Prevención del resfriado común con un suplemento de ajo: una encuesta doble ciego controlada por placebo. *Advances in Therapy*. 2001;18(4):189-93.
26. Moutia M, Seghrouchni F, Abouelazz O, Elouaddari A, Al Jahid A, Elhou A et al. *Allium sativum* L. regulates *in vitro* IL-17 gene expression in human peripheral blood mononuclear cells. *BMC Complementary and Alternative Medicine*. 2016;16(1). doi: 10.1186/s12906-016-1365-9