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The Chemical Constituents and Pharmacological Effects of Single-Clove and Multi-Clove Garlic: A Comprehensive Overview

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Abstract

Allium sativum L. (garlic) is one of the most important medicinal plants which has been used in traditional medicine for decades. There are four different varieties of garlic. One of them is called single clove garlic which differs from multi clove garlic in morphology and active constituents. Garlic contains a variety of chemical constituents including sulfur-containing phytoconstituents that cause pungent odor and taste, phenolic compounds, and saponins. Several researchers have reported on its broad-spectrum therapeutic efficacy. It has been reported as a prophylactic in cardiovascular diseases due to its antihypertensive and anti-hyperlipidemic, and to boost the immune system in addition to its antimicrobial, antibacterial, antifungal, antiviral, anticancer, and antioxidant activities. This review summarizes the difference between single and multi-clove garlic in botanical, phytochemical, ethnomedicinal, and pharmacological properties.

Keywords: *Allium sativum, single clove garlic, organosulfur compounds, phytochemical constituents, biological activities*

1. Introduction

Garlic, scientifically known as Allium sativum L., is a widely consumed food ingredient and nutraceutical that belongs to the Amaryllidaceae family [1]. The Amaryllidaceae family consists of about 1,100 species and 75 genera, which are distributed in tropical and subtropical regions worldwide[2]. Many plants in this family have a history of medicinal use, particularly for neurological injuries [3]. Garlic, in particular, is one of the oldest cultivated plants and has been used for over 4,000 years as a spice, food, and folk remedy [4].

Garlic is native to Asia but is also found in Europe, America, and Africa. The largest agricultural area for garlic cultivation is in Asia, with China being a major producer and represents 75% of its total production [5]. The name "Allium sativum" is derived from the Celtic word "all," meaning stinging or burning, and the Latin word "sativum," meaning cultivated or planted[6].

The genus Allium, which includes garlic, is the largest genus in the Amaryllidaceae family, consisting of approximately 700 species [7]. Garlic ranks second in importance to onions in terms of worldwide production among Allium species [8].

Unlike onions, which require specific soil conditions and pH levels, garlic can thrive in a wide range of weather conditions. It grows best in cold and moist conditions (with temperatures between 13 and 24°C) during the vegetative stage, while warm and dry weather is needed for bulb formation and maturity. Garlic can also grow at elevations of 1000-1300 meters above sea level [9].

Garlic is used both fresh in cooking and in

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dehydrated products as a condiment in the food industry [10]. Aged garlic extract (AGE) is another well-studied form of garlic preparation. AGE is produced by soaking sliced raw garlic in 15-20% aqueous ethanol for up to 20 months at room temperature, followed by filtration and low-pressure, low-temperature concentration. This process results in odorless and non-irritating sulfur compounds that are safe for consumption [11]. Aged garlic extract has higher concentrations of total phenolic and flavonoid [12] compounds compared to fresh garlic extract, giving it increased antioxidant activity [13].

The garlic bulb is composed of multiple cloves, each enclosed by garlic skin (inner peel), and surrounded by a paper-like, transparent peel (outer peel) [14], which corresponds to 25% of the total industrial production of garlic[15].

The Amaryllidaceae family consists of 59 genera and more than 800 species [16]. Over 600 structurally diverse alkaloids have been isolated from this family [16,17], with isoquinoline alkaloids being exclusive to plants in this family [16,18].Gracilines and plicamines are two subgroups of amaryllidaceae alkaloids that have been identified [19].

Garlic contains various bioactive constituents responsible for its distinctive aroma, including organosulfur compounds, polyphenols, saponins, minerals, and vitamins [20,21]. Phytochemical screening of multi-clove garlic extract has identified the presence of steroids, saponins, alkaloids, flavonoids, glycosides, phenolic compounds, terpenoids, and carbohydrates [22]. Single clove garlic (SCG) is a product of atypical bulb formation under specific conditions and possesses a stronger alliaceous aroma due to increased sulfide levels. Further scientific studies are needed to explore the health benefits of SCG [23,24]. It is worth noting that the chemical composition and bioactive potency of garlic can be influenced by cultivation practices, storage conditions, and processing treatments [25].

The biological activities of the Amaryllidaceae family are primarily attributed to the presence of a unique type of alkaloids. These alkaloids share a common precursor, norbelladine [18,26], and exhibit antimicrobial, antitumor, antiparasitic, anti-inflammatory, and central nervous system disease-fighting properties [26]. Certain species in this family, such as those containing galantamine, have been approved for the treatment of Alzheimer's disease due to its acetylcholinesterase inhibitor action [27,28].

Male Wistar rats were given garlic to test the garlic hepatotoxicity dose. They were given garlic at doses of 1.0, 2.5, and 5.0 g/kg/day for 28 days. Liver function worsened significantly for each dose after 21, 14, and 7 days respectively. The 1.0 g/kg/day dose caused severe liver damage by day 21. Lower doses (0.1, 0.25, and 0.5 g/kg/day) were then tested. Despite lower amounts, all doses led to liver function decline after 28 days. While 0.1 and 0.25 g/kg/day maintained normal liver histology, one rat showed liver changes at 0.5 g/kg/day. Thus, high garlic doses induced liver damage, while 0.1 or 0.25 g/kg/day are considered safe [29].

1-**Phytochemistry and biological activity of multi-clove garlic (MCG), garlic peel, and single- clove garlic (SCG):**

A-Phytochemistry of multi-clove garlic:

There are various essential phytochemical constituents isolated from multi-clove garlic including sulfur-containing compounds, alkaloids, phenolic compounds, and flavonoid compounds [30].

1- Sulfur-containing compounds:

Mass spectroscopic analysis revealed the presence of nine organosulfur compounds in garlic (Table1) [31]. Additionally, five different organosulfur compounds, namely bis-2-propenyl trisulfide, bis-2-propenyl tetrasulfide, bis-2-propenyl pentasulfide, bis-2-propenyl thiosulfonate, and trans-sulfuric acid allyl ester 3-allyl sulfanyl-allyl ester, were isolated and identified from aqueous ethanol garlic extract using chromatography techniques [32]. Further investigation using high-resolution mass and two-dimensional NMR techniques led to the identification of sulfurous acid ester, trans-sulfurous acid allyl ester 3-allyl sulfanyl-allyl ester 8, and thiosulfate in the garlic extract [33].

During storage at different temperatures, changes in organosulfur contents were observed. When garlic was stored at 4°C for 150 days, γ-glutamyl peptides such as γ-l-glutamyl-S-allyl-l-cysteine and γ-l-glutamyl-S-(trans-1-propenyl)-l-cysteine (GSPC) were converted to sulfoxides, specifically alliin and isoalliin. Conversely, when stored at 23°C, GSPC decreased while cycloalliin increased significantly, instead of isoalliin [34].

The content of individual organosulfur compounds in garlic varied depending on factors such as location, cultivar, and garlic ecotype. Purple-type cultivars showed the highest average contents of γ-l-glutamyl-S-methyl-l-cysteine (GSMC), γ-l-glutamyl-S-(2-propenyl)-l-cysteine (GSAC), alliin, and methiin, but the lowest content of isoalliin [35].

For the rapid and simultaneous quantification of four organosulfur compounds in garlic (alliin, S-allyl-L-cysteine, γ-glutamyl-S-allyl-L-cysteine, and allicin), a suitable method called liquid chromatography-tandem mass spectrometry-selected reaction monitoring (LC-MS/MS-SRM) with electrospray ionization detection was employed [36] . Additionally, different columns were used to separate various sulfur compounds in garlic, such as alliin, methiin, cycloalliin, γ-l-glutamyl-S-(2-propenyl)-l-cysteine, and γ-l-glutamyl-S-(trans-1-propenyl)-l-cysteine [36]. The major organosulfur compounds identified in garlic using RP-HPLC were allyl-L-cysteine (SAC), diallyl-disulfide (DADS), diallyl trisulfide, and allicin (Table 2) [30,37–40].

Alliin is the primary sulfur compound in garlic, which is converted to allicin by the alliinase enzyme. This conversion is responsible for the characteristic aroma and taste of garlic [41]. Aging garlic extract (AGE) is a processed form of garlic that does not contain allicin but instead contains odorless, non-irritating, and safe sulfur compounds such as S-allyl cysteine (SAC), S-allyl mercaptocysteine (SAMC), allixin, and selenium [41].

2- Allkaloids:

Allium sativum extract which is obtained by fermenting powdered garlic bulbs contains secondary metabolite with, alkaloids (3.570%) and saponins (0.696%) for garlic extract using quantitative phytochemical analysis [42]. Saponins that were isolated from garlic bulb were proto-eruboside b, proto-iso-eruboside b, eruboside b, and iso-eruboside b [43].

3- Phenolic Compounds:

Garlic is considered one of the richest sources of phenolic compounds among vegetables consumed [44]. The total phenolic content, flavonoids, and phenolic acids in selected garlic cultivars varied depending on the location of cultivation. The total phenolic content ranged from 3.4 mg gallic acid equivalents (GAE)/g of dry matter (dm) to 10.8 mg GAE/g of dm, with a mean value of 6.5 mg GAE/g of dm. The flavonoids myricetin, quercetin, kaempferol, and apigenin were not detected in any of the samples. Caffeic acid and ferulic acid were the major phenolic acids found, with mean values of 2.9 mg/kg of DM and 2.6 mg/kg of DM, respectively [45].

The TPC (total phenolic compounds) levels in garlic varied from 0.21 to 3.33 mg of gallic acid equivalent per gram of fresh matter [46]. The main phenolic compounds identified in garlic included gallic acid, rutin, B-resorcylic acid, protocatechuic acid, and quercetin. Gallic acid, 4-hydroxybenzoic acid, caffeic acid, p-coumaric acid, and trans-ferulic acid were isolated from garlic husk using the carbon dioxide expanded ethanol method [46].

A rapid and simple supercritical fluid extraction and supercritical fluid chromatography coupled with mass spectrometry (SFE-SFC-MS/MS) method was used to extract nine phenolic compounds from garlic. Additionally, a method using SFC-MS/MS was employed to extract 15 phenolic compounds in just 9 minutes at a temperature of 50 °C and with the addition of 30% methanol [47].

4- Flavonoid compounds:

The garlic's flavonoid content was found to be 132 mg kg-1[48]. The concentration of specific flavonoids in garlic was estimated, including epicatechin (1.178 mg×kg-1), rutin (43.43 mg×kg-1), luteolin (0.15 – 22.92 mg × kg-1), hyperoside (0.37 – 20.24 mg×kg-1), quercetin (6.55 – 10.17 mg×kg-1), apigenin (3.2 mg×kg-1), and naringenin (11.75 – 56.71 mg×kg-1)(Table 3) [49].

Phytochemistry of garlic peel:

1- Proteins and sugar:

The phytochemistry of garlic peel reveals interesting findings. Firstly, proteins and sugars are abundant in the outer peel, with 67 proteins identified, including chitinases and proteases. The sugars present include rhamnose, mannitol, sorbitol, and trehalose. Additionally, the outer peel contains higher levels of modified amino acid 5-hydroxylysine, a major component of collagen, compared to the clove and inner peel [14].

2- Phenolic compounds:

The total phenolic contents in garlic peel extract its value ranged from 3910.98 to 14,657.42 mg GAE/100 g of extract [50].

3- Tannins: There was a relation between tannins in garlic peel and ethanol used in the extraction

process. The amount of extracted tannins increased with the increase in the percentage of ethanol used [51].

Phytochemistry of single clove garlic compounds: The phytochemistry of single clove garlic is characterized by high concentrations of organosulfur compounds: allin(68.2 mg/mL) and ajoene differentiated into E-ajoene (101.5 mg/mL), and Z-ajoene (251.4 mg/mL) [52](Table 2).

Table 1. Cyclic organosulfur compounds in garlic leaves [16].

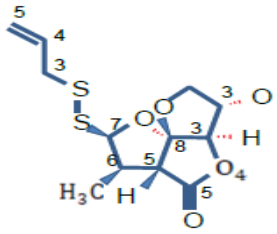
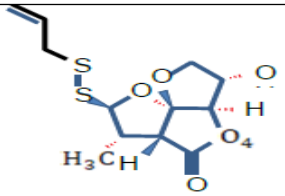
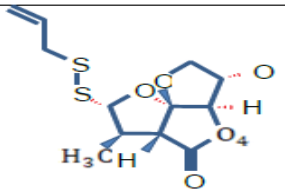
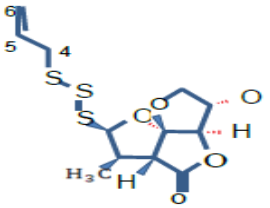
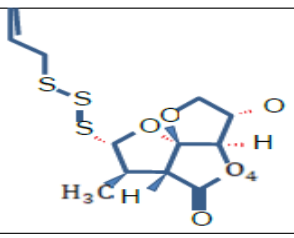
NO	Compound name	Structure
	Foliagarlic disulfane A_1 (1)	
	Foliagarlic disulfane A_2 (2)	
	Foliagarlic disulfane A_3 (3)	
	Foliagarlic trisulfane A1 (4)	
	Foliagarlic trisulfane A2 (5)	

Table 2. Organosulfur compounds in multi clove garlic bulb [52].

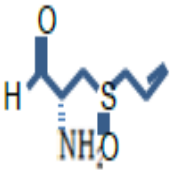
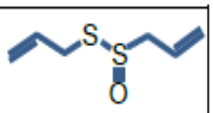
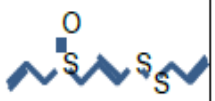
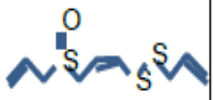
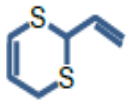
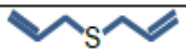
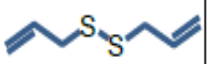
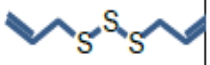
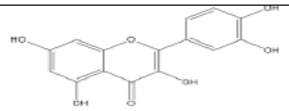
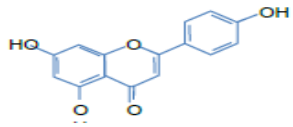
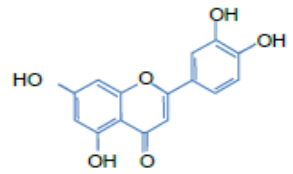
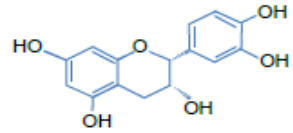
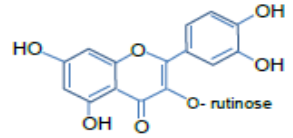
no	Compounds	Molecular formula	Structure
	Allin	$C_6H_{11}NO_3S$	
	Allicin	$C_6H_{10}OS_2$	
	E-Ajoene	$C_6H_{14}OS_3$	
	Z-Ajoene	$C_9H_{14}OS_3$	
	2-vinyl-4H-1,3-dithiin	$C_6H_8S_2$	
	Diallyl sulfide (DAS)	$C_6H_{10}S$	
	Diallyl disulfide (DADS)	$C_6H_{10}S_2$	
	Diallyl trisulfide (DADS)	$C_6H_{10}S_3$	
	Allyl methyl sulfide (AMS)	C_4H_8S	

Table 3. Flavonoids in the multi-clove garlic bulb [11].

NO	Compound name	Structure
1	Quercetin	
2	Apigenin	 Apigenin
3	Luteolin	 Luteolin
4	Epicatechin	 Epicatechin
5	Rutin	 Rutin

Bioactivity of multi-clove garlic:

1- Traditional uses:

Garlic has been traditionally used for various purposes. Apart from being a popular spice, garlic is known for its sedative and antipyretic properties. It is also used to treat indigestion, respiratory and urinary tract infections [53].

2- Anti -bacterial activity:

Crude extract of fresh peeled garlic had antibacterial activity against S. aureus and E.coli.[54]. Garlic powder had a good effect on food poisoning caused by bacteria such as Salmonella enteritidis , Candida albicans, and methicillin-resistant Staphylococcus aureus (MRSA) [55].

Garlic and heat-treated garlic juices had bactericidal effects on food-poisoning bacteria.[56]. Aqueous extract of garlic had a broad spectrum antimicrobial activity against H. pylori. [56]. The aqueous extracts of garlic had more anti-bacterial effects on Bacillus subtilis and E. coli than ethanolic extracts [57].

Fresh garlic extract had antibacterial effects at different concentrations o (5%,10%,20%, and 100%) on dental plaque bacteria which is the major cause of dental caries as Streptococcus mutants, Streptococcus sanguis, Streptococcus salivarius, Pseudomonas aeruginisa, and Lactobacillus)[58].

3- Antifungal activity:

Garlic extract had antifungal activity against Candida, Trichophyton, Cryptococcus, Trichosporon, Torulopsis, Aspergillus, and Rhodotorula species by inhibiting their growth and germination through irreversible changes in fungal cells [59].

4- Antiviral activity:

In terms of antiviral activity, garlic extracts have been effective against influenza B, Parainfluenza virus type 3, human rhinovirus type 2, human cytomegalovirus (HCMV), and herpes simplex type 1 and 2 [44]. This antiviral activity is attributed to organosulfur compounds such as allicin, allyl methyl thiosulfinate, and ajoene, which enhance the production of neutralizing antibodies and prevent adhesive interactions and leukocyte fusion [60].

5- Anti-cancer activity:

Garlic also exhibits anti-cancer activity through various mechanisms, including the regulation of carcinogen metabolism, inhibition of cell proliferation, induction of apoptosis, suppression of angiogenesis, and inhibition of cell migration. It has been reported to reduce the negative effects of anticancer therapies as well [38].

6- Antioxidant activity:

Garlic demonstrates potent antioxidant activity. Essential oil extracted from garlic rhizomes displays strong antioxidant potential [60], and the antioxidant activity of fresh garlic and its commercialized products is attributed to phenolic and organosulfur compounds [22]. The mechanism of garlic's antioxidant activity lies in its ability to promote internal antioxidant activities and reduce oxidative

adverse effects by increasing endogenous antioxidant synthesis or reducing the production of oxidizers such as oxygen-free radical species [22].

7- Anti- inflammatory activity:

Garlic extracts and their phytochemical constituents have also been found to possess anti-inflammatory properties by inhibiting the emigration of neutrophilic granulocytes into epithelial tissues [61].

8- Anti-hyperlipidemic:

Garlic has been shown to have a positive effect on lipid levels, reducing cholesterol, triglyceride, and low- density lipoprotein levels [62]. Compounds like allicin (allyl 2-propenethiosulfinate) and vinyl-dithiin oils in garlic contribute to its blood lipid-reducing effects, making it beneficial for cardiovascular health [61,63].

9- Anti platelet aggregation:

Garlic could inhibit platelet aggregation due to presence of its antioxidant compounds, so garlic has cardiovascular protective activity. [64].

10- Antihypertensive activity

Garlic has also been found to lower hypertension by reducing oxidative stress, increasing the production of nitric oxide and hydrogen sulphide, and inhibiting angiotensin [65].

11- Therapeutic effects on female reproductive system

Garlic is believed to offer benefits for women's reproductive health, potentially improving hormonal balance, alleviating PMS symptoms, and supporting fertility. Its components like allicin and ajoene are thought to influence different aspects of the female reproductive system, including menstrual cycle regulation, hormone balance, fertility, and reproductive disorders[66].

12- Anti-parasite activity

Garlic extract and certain components combat giardiasis effectively. Whole garlic extract displayed potent activity with an IC (50) of 0.3 mg/ml. Allyl alcohol and allyl mercaptan were particularly effective, disrupting the parasite's membrane potential. Microscopic analysis revealed that both whole garlic and allyl alcohol induced structural changes in the parasite, whereas allyl mercaptan exhibited a distinct effect, mainly causing an increase in distended vesicles, implying a different mechanism of action[67].

13- Anti-diabetic activity:

Garlic extract affects blood sugar, cholesterol, and other markers in both normal rats and rats with diabetes. They gave different doses of garlic extract to the rats for 14 days and measured various blood markers. The results showed that garlic extract significantly reduced levels of blood sugar, cholesterol, and other markers in diabetic rats but not in normal rats. In fact, garlic extract was even more effective than a commonly used diabetes medication called glibenclamide[68].

Pharmacological activity of garlic peel (garlic skin):

Garlic peel, even at low levels, it enhances the haematological parameters and resistance of catfish to certain bacteria, leading to a decrease in the mortality rate of catfish [69]. Moreover, the outer peel of garlic contains substances that inhibit the germination and post-germination growth of S. alba and B. juncea [14].

Effect of garlic peel on microbial growth:

The extract from the outer peel of garlic had a stimulating effect on the growth of E. coli and S. aureus, while the extract from the inner peel only promoted the growth of E. coli [14]. However, extracts from all parts of the garlic bulb, including the outer peel, inner peel, and clove, exhibited strong inhibitory effects on the germination and growth of the pathogenic fungus Fusarium.

Pharmacological activity of single clove garlic:

1- Hepatoprotective and antioxidant:

In the case of Single clove garlic (SCG), it exhibits more hepatoprotective and antioxidant activity compared to multi-clove garlic (MCG) by surpassing the ccl4 which cause injury to the liver in mice and it also efficient in treatment of oxidative liver toxicity in male mice [67] . Anti-oxidant activity of SCG was due to phenolic compounds [70,71].

2- Antibacterial activity:

Antibacterial activity of single clove garlic (solo garlic) extract obtained by organic solvent extraction had antibacterial activity using agar diffusion and dilution method. [72].

3- Decreasing cholesterol level (hypolipidemic and hypocholesterolemic activity):

Organosulfur compound allicin in single clove garlic suppress the synthesis of cholesterol in liver which cause diminishing the levels of serum cholesterol [73].

Single-clove garlic could treat degenerative disorders caused by a high-fat diet and decrease liver and spleen weight [24,74].

2. Conclusion:

The present study concluded that there is the big difference between single-clove garlic and multi-clove garlic. The reported difference is not in morphology only but also extended to include the active constituents and pharmacological properties.

3. Conflicts of interest

"There are no conflicts to declare".

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