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Review Article

Unleashing the power of garlic polyphenols: Insights into extraction, identification, structural characteristics and bioactivities

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ABSTRACT

Garlic has long been recognized as a nutrient-rich food and a traditional remedy throughout history. One of the key effective components of garlic is its polyphenols, which exhibit various bioactivities, including anti-cancer, immune-enhancing, and antioxidant properties. Garlic polyphenols consist of flavonoids, such as quercetin, kaempferol, apigenin, and phenolic acids, including caffeic acid, ferulic acid, and gallic acid. Given its significant marketing potential and development prospects, garlic polyphenols have garnered substantial interest from researchers worldwide. This review aims to provide comprehensive and up-to-date information on the extraction, identification, structural characteristics, and bioactivities of garlic polyphenols. Further, it presented compelling evidence for the use of polyphenols as medicinal foods.

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Extraction
Garlic polyphenols
Organ-protective
Structural characteristics

1. Introduction

Plant-derived secondary metabolites, known for their antioxidant properties, are attracting significant attention from various industries. These industries are seeking natural and safe methods to enhance the nutritional profile and qualities of food, as well as to add flavors and improve taste (AM Abdel-Rahman et al., 2022; Kazeminia et al., 2022; Mohammadhosseini and Jeszka-Skowron, 2023). In recent years, extensive research has focused on numerous plant varieties that have significant antioxidant potential. Notably, garlic (*Allium sativum*) has emerged as one of the most prominent ones. The oldest medical book, the Ebers Papyrus, contained text related to the medicinal uses of garlic. Garlic is perhaps the most widely mentioned herb in literature and is continuously researched for its various medicinal properties. It belongs to the family Liliaceae, and its scientific name is *Allium sativum* L. It has been used since 1550 B.C. for headaches, bites, heart disease, and gut parasites (Agarwal, 1996). Researchers further explored garlic's other medicinal properties, such as its antitumorigenic effects (Milner, 1996), its potential as an antidiabetic agent (Eidi et al., 2006), and its antiaging properties (Pazyar and Feily, 2011). Garlic contains various sulfur compounds (alliin, allicin, γ-glutamyl peptides), amino acids, polyphenols, and other secondary metabolites (Agarwal, 1996; Kim et al., 2018; Venditti and Bianco, 2020; Zhang et al., 2020). Advancements in technology have led to the availability of various garlic formulations in the market, such as garlic powder, garlic pills, and aged garlic (Gardner et al., 2007). Now, garlic is not only of interest for its medicinal properties, but the food industry is also recognizing its importance.

Till date, approximately 8,000 plant polyphenols have been identified. These polyphenols are found in red wine, grapes, green tea, garlic, and various aromatic

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herbs. They consist of aromatic rings with one or more hydroxyl groups (Leri et al., 2020). Plant polyphenols, with a molecular weight ranging from 500 to 4000 Da, have low toxicity and exhibit higher bioactivity (Quideau et al., 2011). Plant polyphenols include flavonoid and non-flavonoid compounds. Flavonoids include flavonols, flavononols, and flavones, while non-flavonoids encompass anthocyanins, procyanidins, phenolic acids, stilbenes, and tannins (Leri et al., 2020). Garlic contains the highest amount of polyphenols among commonly consumed vegetables, and the polyphenol content in garlic varies depending on the genotype of the variety, cultivation practices, and growing conditions (Martins et al., 2016). Garlic polyphenols include phenols such as gallic acid, vanillic acid, chlorogenic acid, caffeic acid, coumaric acid, ferulic acid, and flavonoids such as quercetin, apigenin, luteolin, epicatechin, and rutin (Kovarovic et al., 2019). Garlic polyphenols are associated with providing antioxidant activity, which reduces oxidative stress and helps prevent various diseases in the body (Ansary et al., 2020).

Although research on garlic polyphenols has gained attention nowadays, to date, no review has been conducted on this topic. In this review article, the extraction, structure, and bioactivities are summarized. This review will provide a reference for further research and the enhanced utilization of garlic polyphenols in the food and medicinal industries.

2. Extraction of polyphenols

To study the structure and biological activities of polyphenols, a standardized method for polyphenol extraction is essential. In this review article, we have summarized the reported methods of polyphenol extraction. Initially, in the early stages of polyphenol extraction, conventional methods were used, which involved the use of various solvents and different temperatures. However, as technology advanced, more sophisticated techniques were developed for polyphenol extraction. Earlier, we explored conventional methods, which are summarized below.

Researchers have explored the use of different solvents, namely *n*-hexane, methanol, and dichloromethane, at varying temperatures of 60, 80, and 100 °C. Employing methods such as Soxhlet and Soxtec extraction, remarkable success was achieved with methanol solvent at 100 °C, resulting in the recovery of 24.42% of phenolic compounds (Ahmad et al., 2020). In pursuit of improved extraction techniques, Fratianni et al. (2016) employed a solvent mixture consisting of acetone, ethanol, and ultrapure water in specific proportions (70:15:15) to prepare garlic samples for polyphenol extraction. This resulted in 87-90 µg GAE/g TPC. Similarly, in the realm of solvent selection, Gu et al. (2019) successfully employed 30% ethanol for extract preparation, while Phan et al. (2019) utilized the freeze-drying technique to prepare dried garlic skin samples at -50 °C for 48 hours. They then performed polyphenolic extraction using 80% methanol via ultrasonication. Other researchers, such as Tigu et al. (2021) and Yang et al. (2020), employed ethanol (20% and 30%, respectively), in their extraction protocols. Gorinstein et al. (2008) investigated the effects of various cooking techniques (boiling, frying, and microwaving) on defatted vegetables. The vegetables were then extracted using a 50 mg aliquot with 5 mL of 1.2 M HCl, followed by 50% methanol to isolate polyphenols. Gorinstein et al. (2008), Gu et al. (2019), Phan et al. (2019), Yang et al. (2020), and Tigu et al. (2021) have isolated various polyphenols with different concentrations, which are further compared for their quantities. The available knowledge of the best extraction techniques, including the method of extraction, and factors that affect the extraction procedure, such as time, temperature, and solvents, is shown in Table 1.

Most of the studies utilized response surface methodology. Response surface methodology was developed to optimize extraction parameters by considering not only a single independent variable but also the interactive effects of independent variables (Pilkington et al., 2014). This technology was previously used to optimize the extraction process of polyphenols in tomatoes and apples (Li et al., 2012; Musa et al., 2016).

Currently, ultrasound-assisted extraction is the well-established method for extracting polyphenols, which yields the maximum total polyphenol content (TPC) and total flavonoid content (TFC). Ultrasound-assisted extraction increases the penetration of solvent by deteriorating the cell membrane. Extraction factors, such as extraction temperature, duration of extraction, solvent used, solid to liquid ratio, and processing prior to extraction, significantly affect the percentage yield of polyphenols. The temperature range was 59 to 110 °C, and the maximum total phenolic content was observed at 59 °C (Ciric et al., 2020). Ciric et al. (2020) also studied the effect of extraction temperature, time, methanol concentration, and solvent-to-solid ratio on the extraction of polyphenols. They found that the optimized solvent-to-solid ratio was 20 mL/g, with a methanol concentration of 71% and a duration of 13.5 min. These conditions resulted in the maximum yield, *i.e.*, 1.422 mg RUT/g TFC and 19.498 mg GAE/g TPC in the fresh sample, compared to the studies conducted by Ma et al. (2021), Tomsik et al. (2016), and Romilda and Rajesh (2016).

The polarity of the solvent plays a major role in the extraction procedure of polyphenols. Water extraction, as conducted by Ma et al. (2021), and ethanol extraction, as conducted by Krstic et al. (2023), Romilda and Rajesh (2016), resulted in lower TPC and TFC content as compared to methanolic extraction performed by Ciric et al. (2020).

Krstic et al. (2023) optimized conditions for pressurized liquid extraction, including a 45-75% ethanol concentration, 70-110 °C temperature, and 1-3 min. extraction time, resulting in a yield of 173.96 mg GAE/g TPC. Silva et al. (2012) employed dispersive solid phase extraction, which yielded a polyphenol recovery rate of 78.4% to 99.9% within 8 to 10 min. This method was shown to be efficient. Sato et al. (2006) fermented garlic for 40 days at 70 °C with 85 to 95% humidity before extraction, resulting in 8 mg/g GAE TPC. Finally, it can be concluded that the method proposed by Ciric et al. (2020) is the most effective for extracting

Table 1
Extraction procedure of polyphenols from garlic.

Method	Factors	Optimization techniques	Optimum conditions	Extraction yield	References
Ultrasound assisted extraction	Solvent-to-solid ratio (X1), methanol concentration (X2), extraction time (X3), and extraction temperature (X4)	Response surface methodology and artificial neural network	4-Factor experiment 20.00 mL/g X1, 71.00% X2, 13.50 min X3, and 59.00 °C X4	19.498 mg GAE/g fresh weight of sample total phenolic content 1.422 mg RUT/g fresh weight of sample total flavonoid content	Ciric et al., 2020
Pressurized liquid extraction (PLE)	Ethanol concentration (A), number of cycles (B), extraction time (C) and temperature (D)	response surface methodology (RSM)	A: 45-75% B: 1-3 C: 1-3 min D: 70-110 °C	173.96 Total polyphenol content [mg GAE/100 g]	Krstic et al., 2023
Ultrasound-assisted extraction	Extraction temperature (A), extraction time (B), ultrasonic frequency (C)	Water: ethanol: acetone (2/3:1/6:1) extraction	A: 20 °C B: 15 min C: 60 Hz	5.84 mg GAE/g	Cavalcanti et al., 2021
Water extraction	Extraction temperatures (A), solid-to-liquid ratios (B), and extraction times (C)	Single factor experiment and response surface methodology	A: 99.96 °C B: 1:4.38 g/mL C: 2.72 h	TP:2.69 mg GAE/g TF:1.79 mg QE/g	Ma et al., 2021
Dispersive solid phase extraction	Extraction solvents (A), solid-to-liquid ratios (B), and extraction times (C)	QuEChERS-dSPE/UHPLC-PDA method	A: Acetonitrile and ethyl acetate (50:50 v/v)+buffered salts B: 1:1 g/mL C: 8-10 min	78.4 to 99.9% polyphenols recovery	Silva et al., 2012
Short term fermentation	Extraction solvents (A), extraction temperature (B), and extraction times (C), humidity (D)	Single factor experiment	A: 80% ethanol B: 70°C C: 40 days D: 85-95%	TP: 8000 µg/g GAE	Sato et al., 2006
Methanolic extraction	Solid-to-liquid ratios (A), extraction time (B)	Single factor experiment	A: 1g/20 mL B: 60 min	gallic acid (75.8 to 322.5 mg·100 g-1)	Cinkmanis et al., 2018
Ultrasound-assisted extraction	Extraction temperature (A), extraction time (B), ultrasonic power (C)	Ethanol 30-70% response surface methodology	A: 40-80 °C B: 40-80 min C: 19.2 to 38.4 W/L	TP (1.60 g GAE/100 g DW), TF (0.35 g CE/100 g DW)	Tomsik et al., 2016
Ethanolic extraction	Extraction temperatures (A), solid-to-liquid ratios (B), and extraction times (C)	Two-factor central composite design (CCD) combined with response surface methodology (RSM)	A: 47.1 °C B: 1:30 g/mL C: 6 hours	TPC:0.243 mg GAE/g TFC:0.987 mg QE/g	Romilda and Rajesh, 2016

polyphenols, as it yields the highest total polyphenol content (TPC). In scientific investigations aimed at isolating garlic polyphenols, various solvents, including methanol, ethanol, ethyl acetate, water, and acetone, have been utilized. Notably, methanol has consistently demonstrated superior efficacy, resulting in the highest yield of polyphenols (Ciric et al., 2020).

3. Identified garlic polyphenols and their quantification

Several scientific studies have examined the composition of garlic polyphenols using advanced analytical techniques. Ahmad et al. (2020) quantified gallic acid, rutin, and quercetin in garlic samples using UHPLC-DAD. Azzini et al. (2014) investigated four Italian garlic varieties and found that apigenin and myricetin were the most abundant flavonoids across all varieties, while β-carotene and quercetin were present as minor compounds.

Farag etal. (2017) utilized UPLC/PDA/ESI-ion trap MS analysis to identify caffeic acid and ferulic acid in methanolic extracts of *A. sativum*. Nagella et al. (2014) identified β-resorcinol, gallic acid, pyrogallol, quercetin, rutin, and protocatechuic acid in garlic samples. Fratianni et al. (2016) utilized UPLC with a diode array detector to detect gallic acid, hyperoside, ferulic acid, chlorogenic acid, and epicatechin in two garlic varieties from southern Italy. Parvu et al. (2010) identified *p*-coumaric and ferulic acid in five different species of *Allium*.

Gorinstein et al. (2008) analyzed raw Polish garlic using HPLC and identified quercetin (8 mg/100 g of dry matter) as the major compound. They also found smaller quantities of protocatechuic acid, sinapic acid, vanillic acid, caffeic acid, and *p*-hydroxybenzoic acid. Gu et al. (2019) utilized LC-ESI-QTOF/MS and detected the presence of several compounds in garlic samples. These compounds include protocatechuic acid (2.39 mg/100 g of sample), catechin (0.69 mg/100 g of sample), epicatechin (2.7 mg/100 g of sample), quercetin (2.36 mg/100 g of sample), kaempferol (11.6 mg/100 g of sample), as well as chlorogenic acid, caffeic acid, and *p*-coumaric acid.

Kim et al. (2013) conducted a study on black garlic and discovered various phenolic acids, including gallic acid, vanillic acid, chlorogenic acid, caffeic acid, ferulic acid, and coumaric acid. They also identified several flavonoids, such as catechin, epicatechin, epigallocatechin, quercitrin, myricetin, resveratrol, morin, and quercetin. Phan et al. (2019) analyzed Australian garlic skin using UHPLC-PDA-MS and identified vanillic acid, caffeic acid, *p*-coumaric acid (8 mg/100 g of sample), sinapic acid, and ferulic acid (15.2 mg/100 g of sample).

Recinella et al. (2022) investigated hydroalcoholic and water extracts of garlic and found catechin to be the major polyphenol using HPLC-DAD-MS. Tigu et al. (2021) identified chlorogenic acid (65 μg/mL of sample), *p*-coumaric acid (44 μg/mL), and 4-hydroxybenzoic acid (25 μg/mL) in garlic samples using HPLC-DAD-MS. Yang et al. (2020) employed LC-ES-QTOF/MS and identified 28 phenolic compounds in Australian garlic, including cyanidin 3-*O*-galactoside, delphinidin 3-*O*-glucoside and its derivatives, petunidin 3,5-*O*-diglucoside, eriocitrin, hesperetin 3′-*O*-glucuronide, apigenin 6,8-di-C-glucoside, and more as shown in the structure of polyphenols. Hu et al. (2022) recently identified three new flavonoid glycosides (Dasuanxinoside F-H) in the aerial parts of *A. sativum* using nuclear magnetic resonance spectra.

These comprehensive scientific investigations provide valuable insights into the diverse polyphenolic composition of garlic and their availability as major or minor compounds, depending on the variety of garlic. Further, it contributes to our understanding of the potential health benefits of this diverse range of polyphenols.

4. Structural characteristics of identified polyphenols

In literature, approximately 42 different garlic polyphenols have been identified. These polyphenols belong to different categories, which are summarized in Table 2, and their structures are given in Fig. 1.

Polyphenols are plant compounds with multiple phenol groups and are categorized into flavonoids, phenolic acids, stilbenes, lignans, and tannins (Pandey and Rizvi, 2009). Phenolic acids are compounds that have a phenolic ring and a carboxylic acid group. These compounds are further classified into hydroxycinnamic acids and *p*-hydroxybenzoic acids. Hydroxycinnamic acids have a three-carbon side chain attached to the benzene ring, which is not present in hydroxybenzoic acids. Hydroxycinnamic acids are more common than hydroxybenzoic acids (Kumar and Goel, 2019). Out of these 41 compounds, 10 belong to phenolic acids, with 3 of them being hydroxybenzoic acids.

Flavonoids have a 15 C skeleton with two phenyl rings and one heterocyclic ring. They can be found in both aglycone and glycosidic forms. Flavonoids are further classified into flavones, flavonols, flavanones, isoflavones, anthocyanins, and flavonoid glycosides (Dias et al., 2021). Among the compounds that were detected, 19 of them belong to the flavonoid group. Isorhamnetin, apigenin, quercetin 3-*O*-glucuronide, and hyperoside are flavones that have a double bond between C2 and C3 of the C ring. Eriocitrin is a flavanone. Flavonoid glycosides such as myricetin 3-*O*-rutinoside, hesperetin 3′-*O*-glucuronide, apigenin 6,8-di-C-glucoside, isorhoifolin, and kaempferol 3-*O*-glucoside have one or more sugar molecules attached to them. Quercetin 3-*O*-(6″-malonyl-glucoside), quercetin, kaempferol, rutin, morin, and myricetin are flavonols. Dihydroformononetin and 3′,4′,7-trihydroxyisoflavan belong to isoflavones that have a saturated C ring and a hydroxyl group at the C3 position.

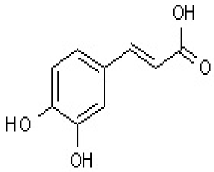
Catechins are a type of flavonoids that have a flavan-3-ol backbone and a catechol (1,2-dihydroxybenzene) structure in the B ring (Fan et al., 2017). Three garlic-identified compounds fall into this category, as mentioned in Table 2. These compounds are lignans, which consist of two phenylpropane units derived from two cinnamic acids connected by a β-β′ bond (MacRae and Towers, 1984). Schisandrin C is the only lignan detected in garlic. Resveratrol and polydatin are natural stilbenes detected in garlic. These compounds have a specific structure known as a stilbene backbone, which consists of two phenyl rings attached by a vinyl linkage (-CH=CH-) (Shen et al., 2009). Galloyl glucose is the only tannin compound detected in garlic. This compound involves the esterification of the carboxyl unit of gallic acid with the hydroxyl group of a glucose molecule (Khanbabaee and Van Ree, 2001). Cyanidin 3-*O*-galactoside, delphinidin 3-*O*-glucoside, and petunidin 3,5-*O*-diglucoside are anthocyanin compounds that are linked with a glucose moiety. Anthocyanins have two benzene rings, A and B, connected by a C=C bond, and one heterocyclic C ring. The C ring is usually six-membered with an oxygen atom (Wallace and Giusti, 2015).

5. Bioactivities of garlic polyphenols

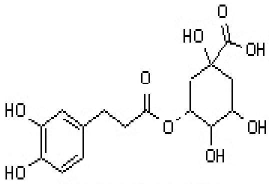
This review study examines the impact of garlic polyphenols on a compound level, with a focus on their biological properties. The investigation encompasses a total of 42 compounds, with the majority of them undergoing thorough examination in both preclinical and clinical settings. Garlic polyphenols have established a reputation for their remarkable antioxidant, anti-inflammatory, anticancer, antiarthritic, neuroprotective, and cardioprotective properties. Table 3 and Fig. 2 delve into comprehensive discussions of their specific biological activities.

5.1. Antioxidant

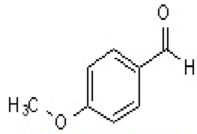
Oxidative stress arises from the impact of free radicals



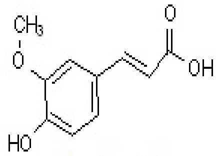
Caffeic acid



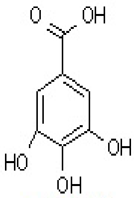
Chlorogenic acid



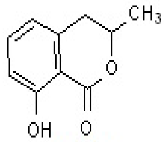
p-Anisaldehyde



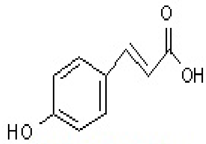
Ferulic acid



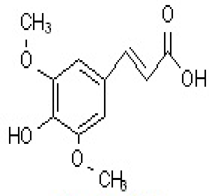
Gallic acid



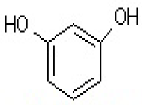
Mellein



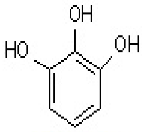
p-coumaric acid



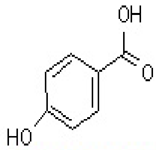
Sinapic acid



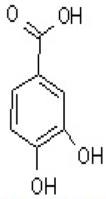
β-resorcinol



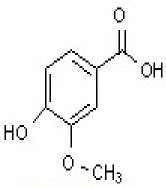
Pyrogallol



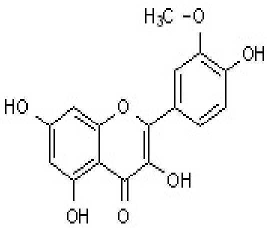
p-Hydroxybenzoic acid



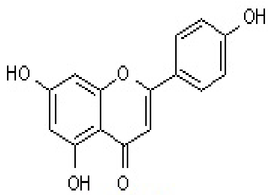
Protocatechuic acid



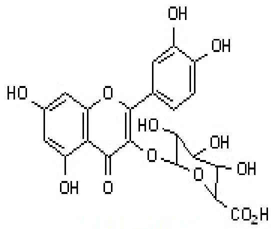
Vanillic acid



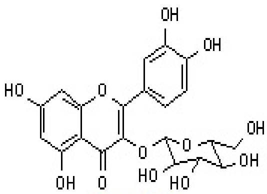
Isorhamnetin



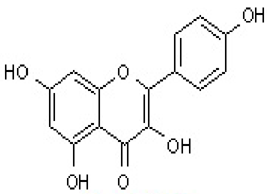
Apigenin



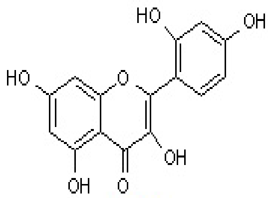
Quercetin
3-*O*-glucuronide



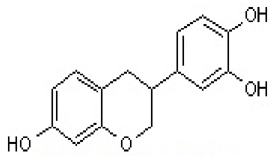
Hyperoside



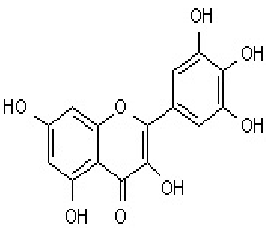
Kaempferol



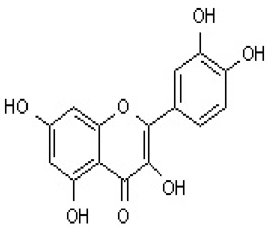
Morin



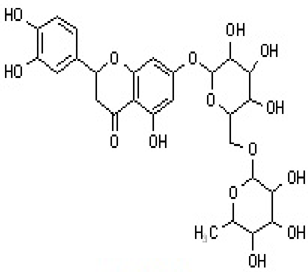
3',4',7-Trihydroxyisoflavan



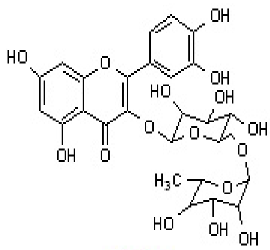
Myricetin



Quercetin



Eriocitrin



Rutin

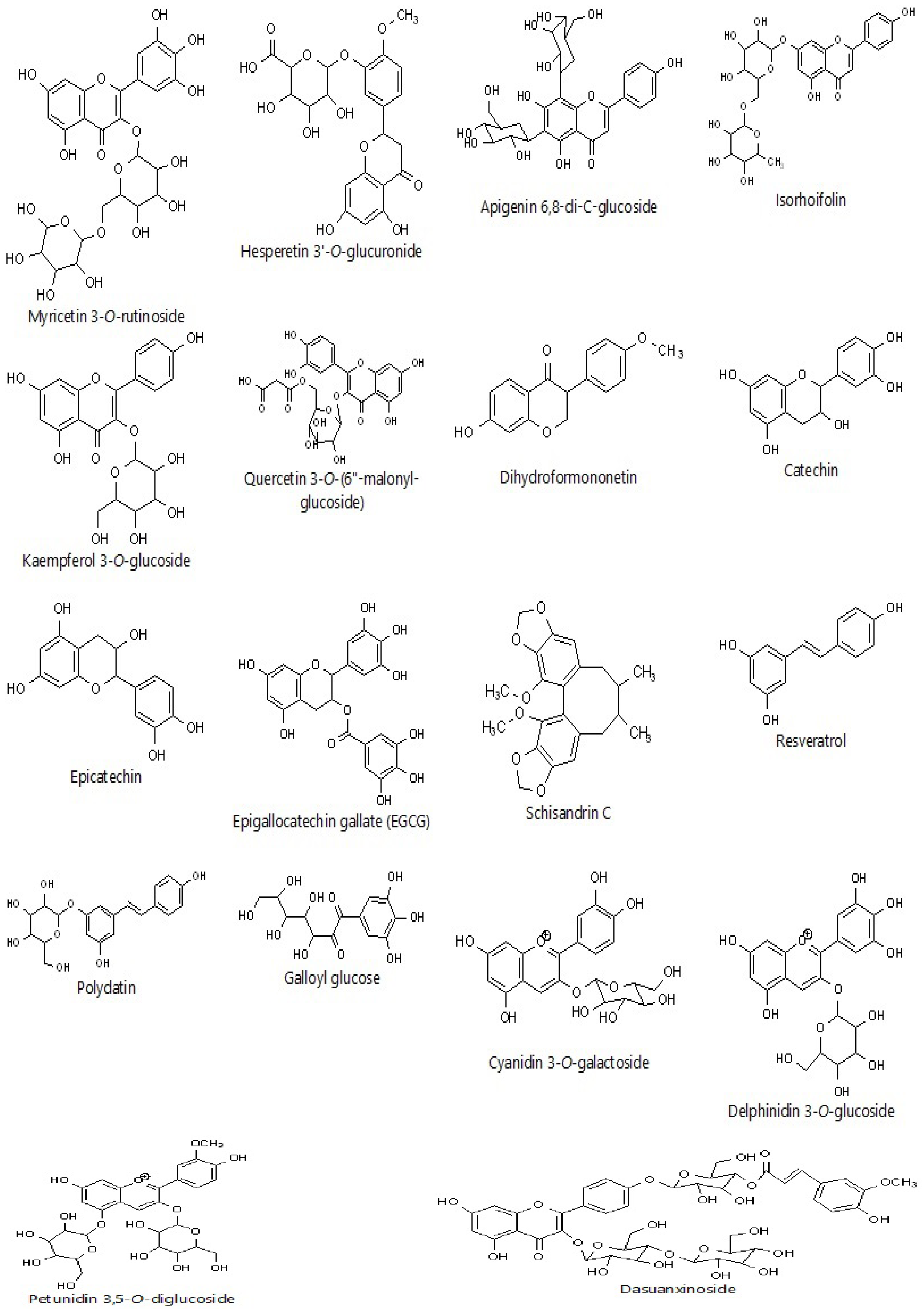


Fig. 2. Molecular structures of garlic polyphenols characterized in the literature.

Table 2
Categorization of phenolic compounds into different groups.

Categories	Compounds
Phenolic acids	Caffeic acid, chlorogenic acid, *p*-anisaldehyde, ferulic acid, gallic acid, *p*-coumaric acid, and sinapic acid
Other phenolic compounds	Mellein, β-resorcinol, and pyrogallol
Hydroxybenzoic acid	*p*-Hydroxybenzoic acid, protocatechuic acid, and vanillic acid
Catechins	Catechin, epicatechin, and epigallocatechin gallate
Lignans	Schisandrin C
Stilbenes	Resveratrol, and polydatin
Tannins	Galloyl glucose
Anthocyanins	Cyanidin 3-*O*-galactoside, delphinidin 3-*O*-glucoside, and petunidin 3,5-*O*-diglucoside
Flavonoids	Isorhamnetin, apigenin, quercetin 3-*O*-glucuronide, hyperoside, kaempferol, morin, 3′,4′,7-trihydroxyisoflavan, myricetin, quercetin, eriocitrin, rutin, myricetin 3-*O*-rutinoside, hesperetin 3′-*O*-glucuronide, apigenin 6,8-di-C-glucoside, isorhoifolin, kaempferol 3-O-glucoside, quercetin 3-*O*-(6″-malonyl-glucoside), dihydroformononetin, and dasuanxinoside F-H

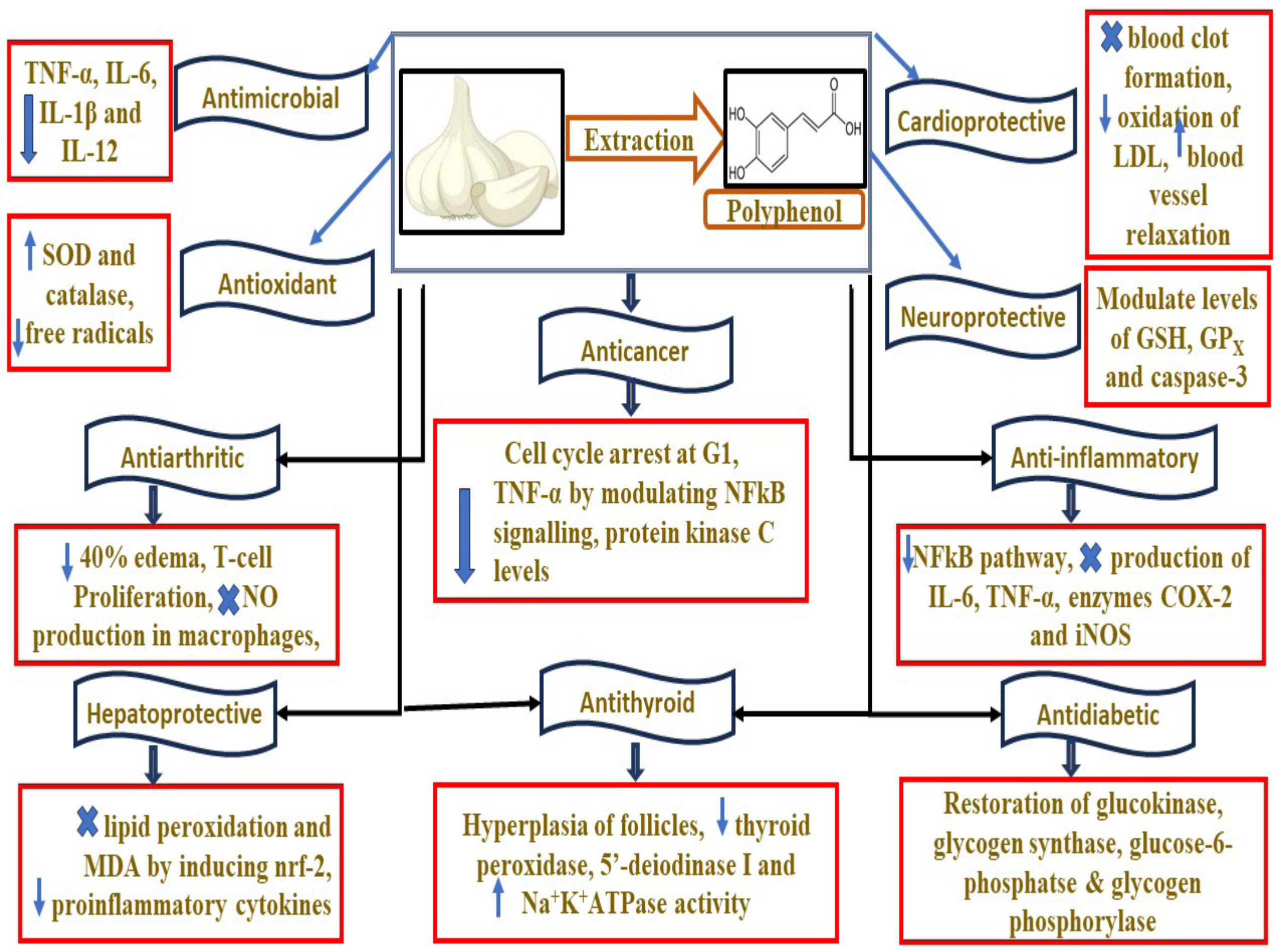


Fig. 2. Biological activities of garlic polyphenols.

Table 3
Representation of the biological activity and the mechanism of action of phenolic compounds.

Sr. No.	Compound	Biological activity	Mechanism of action	References
1	Isorhamnetin	Anticancer	Blocking phosphatidylinositol-3-kinase AKT-mTOR signalling pathway (Protecting from cardiac hypertrophy)	Khaled, 2020
		Anti-inflammatory	Inhibited LPS stimulated expression of iNOS and cox-2 in BV2 cells, downregulated TNF-α, IL-1β, Inhibited NFkB signalling	
		Anti-Tuberculosis, antioxidant, antiviral, antimicrobial	Suppressed TNF-α, IL-6, IL-1β and IL-12	
		Hepatoprotective	Inhibited apoptosis and autophagy via P38-PPAR-α pathway.	
2	Apigenin, rutin	Anticancer	Inhibited cell cycle progression at G0/G1, G2/M phase, Inhibited NFkB signalling, Inhibition of Wnt/β-catenin and STAT3 pathway	Gullon et al., 2017; Zhou et al., 2017; Salehi et al., 2019
		Organ protective	Decrease chemical induced toxicity	
		Anti-inflammatory	Decrease in inflammation by suppressing cox-2 and NFkB pathway	
		Anti-osteoporosis	Reduction of dendritic cell maturation, inflammatory cytokine secretion, and matrix metalloproteinase production	
		Anti-atherogenic	Increase in NO, decrease in cell adhesion molecules, decrease in inflammatory cytokines	
3	Caffeic acid	Antioxidant	Reduces oxidative stress	Jiang et al., 2005
		Anti-inflammatory	Inhibited production of pro-inflammatory cytokines and prostaglandins	
		Anticancer	Induce apoptosis in cancer cells, inhibited formation of new blood cells to prevent tumor growth	
		Cardioprotective	Preventing blood clot formation, decrease oxidation of LDL, improving blood vessel relaxation	
		Neuroprotective	Reduce neuroinflammation, promote neuronal survival by preventing oxidative damage	
		Antimicrobial	Antibacterial, antifungal, antiviral	
		Anti-diabetic	Reducing blood glucose level, protecting pancreatic β cells, improving insulin sensitivity	
4	Quercetin and quercetin 3-O-glucuronide, quercetin 3-O-(6”-malonyl-glucoside)	Antioxidative	Reduce production of oxygen radicals by 50%, suppressed plasma NOX levels	Materska, 2008; Razavi et al., 2009; Patan et al., 2015; Wang et al., 2016; Salehi et al., 2020; Nile et al., 2021
		Anti-inflammatory	Reduced IL-6, IL-8, and TNF-α	
		Anti-cancer	Cell cycle arrest at G1, reduced TNF-α by modulating NFkB signalling, decrease protein kinase C levels	
		Cardioprotective	Decrease lipid peroxidation, attenuate atherosclerosis	
5	Catechin	Antidiabetic	Restoration of glucokinase, glycogen synthase, glucose-6-phosphatse & glycogen phosphorylase	Ganeshpurkar and Saluja, 2020
		Organ protective	Hepatoprotective, nephroprotective, neuroprotective	
		Antiulcer	Reduction in TBARS levels	
		Antimicrobial	Antibacterial, anti-fungal	
		Antithyroid	Hyperplasia of follicles, reduction in thyroid peroxidase, 5’-deiodinase I and increase in Na+K+ATPase activity	

Table 3 Continued

Sr. No.	Compound	Biological activity	Mechanism of action	References
6	Chlorogenic acid	Antioxidant	Scavenge ROS	Upadhyay and Mohan Rao, 2013; Naveed et al., 2018
		Cardioprotective	Suppressing p-selectin expression on platelets, inhibit COX-I and COX-II enzymes	
		Neuroprotective	Modulate levels of GSH, GPX and caspase-3	
		Anti-arthritic	Reduce 40% edema, inhibition of NO production in macrophages, suppression of T-cell Proliferation	
7	Epicatechin, galloyl glucose, polydatin	Antioxidant	Showed in vitro antioxidant activity, induction of antioxidant enzymes, decrease in plasma lipid peroxide	Zhang et al., 2009; Cao et al., 2014; Bernatova, 2018; Prakash et al., 2019; Karami et al., 2022
		Anti-inflammatory	Inhibit lipoxygenase, COX-2 and NF-kB pathway	
		Antimicrobial	Against S. aureus	
		Antidiabetic	β-Cells regeneration in pancreas	
		Antitumor	Inhibit cancer progression pathways	
8	Epigallocatechin gallate (EGCG)	Antioxidant	Reduced oxidative stress in vitro studies	Krupkova et al., 2016; Eng et al., 2018
		Anti-inflammatory	Inhibited phosphorylation of p38, JNK, NFkB	
		Antitumor	Exhibited toxic effects in cancer cell lines, modulate membrane receptor activity	
9	Ferulic acid	Antioxidant	Increase level of glutathione and activity of superoxide dismutase, glutathione peroxidase	Kim and Park, 2019; Stompor-Goracy and Machaczka, 2021
		Anti-inflammatory	control GSK-3β/NFkB/CREB pathway, decrease MPO, ALT, AST activity	
		Antitumor	Increase levels of caspase-8 and -9 to induce apoptosis in cancer cells	
		UV-protective	Topical application prevents photodamage	
		Antibacterial	Disintegrate membrane permeability and outer membranes of bacteria	
10	Gallic acid, p-coumaric acid, pyrogallol, sinapic acid, schisandrin C	Anti-inflammatory	Decrease levels of IL-2, IFN-γ, TNF-α, IL-4 & IL-5	Niciforovic and Abramovic, 2014; Badhani et al., 2015; Lima et al., 2016; Pei et al., 2016; Kahkeshani et al., 2019; Nasser et al., 2020
		Organ protective	Inhibited lipid peroxidation and MDA by inducing nrf-2, reduces proinflammatory cytokines	
		Anticancerous	Via modulating pro-oxidant and antioxidant balance, regulate cyclin A, cyclin D1, and cyclin E	
11	Mellein	Antibacterial, antifungal	Very less studied on compound level	Reveglia et al., 2020
12	Hyperoside, myricetin, resveratrol	Antioxidant	Scavenge free radicals	Bhat et al., 2001; Park et al., 2016; Semwal et al., 2016; Wang et al., 2022; Xia et al., 2022
		Anti-inflammatory	Suppress NFkB pathway, inhibit production of IL-6, TNF-α, inhibit enzymes COX-2 and iNOS	
		Anticancer	Inhibition of cell proliferation, and programmed cell death of cancer cells	
		Cardiovascular	Inhibit platelet aggregation, improving endothelial function	
		Neuroprotective	Reduces neuroinflammation by decreasing oxidative stress	

Table 3 Continued

Sr. No.	Compound	Biological activity	Mechanism of action	References
13	Kaempferol, kaempferol 3-O-glucoside, morin, cyanidin 3-O-galactoside, delphinidin 3-O-glucoside	Antioxidant	Enhance the activity of SOD and catalase	Sari et al., 2019; Taiwo et al., 2019; Liang et al., 2021; Bangar et al., 2022; Balaga et al., 2023
		Anti-inflammatory	Suppression of NFkB pathway	
		Anticancer	Inhibition of angiogenesis to stop supply to tumor cells	
		Cardiovascular	Improved endothelial function, lower blood pressure	
		Neuroprotective	Prevent neuronal inflammation and damage in brain	
14	p-Hydroxybenzoic acid, protocatechuic acid, Vanillic acid	Antioxidant	Inhibit lipid peroxidation, reducing oxidative stress	Masella et al., 2012; Khan et al., 2015; Kaur et al., 2022; Wang and Jiang, 2022
		Anti-inflammatory	Reducing activation of inflammatory pathways like NFkB and MAP kinases	
		Anticancer	Inhibit growth of cancer cells	
		Antimicrobial	Disrupting cellular membranes of microbes	
		Neuroprotective	Reducing neuroinflammation	
15	Eriocitrin	Anti-obesity, antioxidant,	Inhibit adipogenesis, prevent excess fat deposition	Yao et al., 2022
		anti-inflammatory,		
		hepatoprotective,		
		cardioprotective		
16	Dihydroformononetin	Estrogenic activity, anticancer, antidiabetic, anti-inflammatory	Help to prevent deficiencies associated with estrogen in postmenopausal women	Kolodziejczyk-Czepas, 2012
17	β-Resorcinol	Skin lightening	Inhibit melanin production by inhibiting tyrosinase	Durairaj, 2005
		Antifungal	Effective against skin infection causing fungi Trichophyton and Candida	
		Preservative	Used as preservative because of antimicrobial activity	

on the cellular membrane, which leads to detrimental effects on the structure and function of cells. Oxidative stress is implicated in various diseases, including neurodegeneration, cardiovascular disorders, and type 2 diabetes. Extensive research has been conducted on all identified polyphenols to investigate their antioxidant properties, both *in vitro* and *in vivo*. These polyphenols possess a hydroxyl group in their chemical structure, which contributes to their potent antioxidant properties.

In a study by Masella et al. (2012), the antioxidant activity of protocatechuic acid was examined. The authors demonstrated that protocatechuic acid exhibits robust DPPH scavenging activity *in vitro*. Additionally, in *in vivo* studies, it was found to enhance the activity of GPx (glutathione peroxidase), SOD (superoxide dismutase), and catalase, which are enzymes involved in antioxidant defense. Furthermore, protocatechuic acid has been shown to reduce the production of oxygen radicals and suppress plasma NOx (NADPH oxidase) levels. Similarly, other polyphenols that have been identified, such as isorhamnetin, caffeic acid, quercetin, and its derivatives, have been found to possess potent antioxidant activities through similar mechanisms, as summarized in Table 3. These mechanisms involve scavenging of free radicals and modulation of antioxidant enzyme activity.

5.2. Antimicrobial

Several scientific studies have investigated the efficacy of garlic polyphenols as potent agents against various harmful bacteria, fungi, and viruses (Ushimaru et al., 2012). Fratianni et al. (2016) conducted research on the antioxidant, antimicrobial, and antifungal properties of polyphenols found in garlic. Their findings revealed that extracts containing these polyphenols demonstrated significant effectiveness against bacteria such as *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*, as well as fungi like *Aspergillus versicolor* and *Penicillium citrinum*.

In light of the recent global pandemic caused by the SARS coronavirus 2, Nguyen et al. (2021) investigated the impact of black garlic extract and its polyphenols on the virus. Their study specifically focused on the main protease Mpro, which is responsible for viral replication. Various polyphenols displayed inhibitory effects, with genistein, myricetin, quercetin, rutin, kaempferol, chlorogenic acid, caffeic acid, ferulic acid, and gallic acid exhibiting 48, 80, 74, 45, 16, 61, 50, 46, and 7% inhibition, respectively. Through structure-activity relationship analysis, it was determined that hydroxyl groups at specific carbon positions in the B-ring and C-ring, as well as double bonds and glycosylation, contribute to the inhibitory effects of flavonoids on Mpro. Durairaj (2005) explained the antimicrobial properties of β-resorcinol, which make it suitable for use as a preservative. It has been proven to exhibit antifungal activity against *Trichophyton* and *Candida*, which are known to cause skin infections. Hydroxybenzoic acids, such as *p*-hydroxybenzoic acid, protocatechuic acid, and vanillic acid, have been identified as compounds that exhibit antimicrobial activity by disrupting the microbial membrane (Masella et al., 2012; Kaur et al., 2022; Wang and Jiang, 2022). Wang and Jiang (2022) conducted a study on *p*-hydroxybenzoic acid and found that it exhibited antimicrobial activity against both Gram-positive and Gram-negative bacteria, including *E. coli*, *P. aeruginosa*, *B. subtilis*, and *S. aureus*. Khaled (2020) studied that the compound isorhamnetin is effective against different species of *Staphylococcus*, *Bacillus*, and *Salmonella*. It can be used to prevent food contamination. Kim and Park (2019) studied the enhancement of antibacterial efficiency against *Acinetobacter baumannii* by combining ferulic acid with quinoline antibiotics. Gullon et al. (2017) explained the antimicrobial activity of rutin against *P. aeruginosa*, *A. baumannii*, *S. aureus*, and *C. krusei*. In conclusion, garlic polyphenols exhibit strong antimicrobial activity. These can be used as therapeutic agents against various disease-causing microbes and as preservatives in food to prevent contamination.

5.3. Anti-inflammatory

Several studies have consistently reported the immunomodulatory effects of garlic polyphenols and their ability to exhibit anti-inflammatory properties without any adverse effects. Various investigations have examined the anti-inflammatory properties of specific polyphenols found in garlic, and their mechanisms of action appear to be largely similar. Recinella et al. (2022) conducted a study on the anti-inflammatory and antioxidant effects of catechin, a component of garlic extracts. Their findings demonstrated that garlic extracts containing catechins effectively suppressed the expression of cyclooxygenase (COX)-2, tumor necrosis factor (TNF)-α, nuclear factor-kB (NFkB), and interleukin (IL)-6 genes induced by lipopolysaccharide (LPS) in the colon of mice. Additionally, these extracts inhibited the production of prostaglandin (PGE2) and 8-iso-PGF2α, while increasing the ratio of 5-hydroxyindoleacetic acid to serotonin following LPS treatment. Khaled (2020) elucidated the role of isorhamnetin in mitigating inflammatory responses triggered by lipopolysaccharide (LPS) in BV2 glial cells. This compound significantly suppressed the production of proinflammatory mediators, such as nitric oxide (NO) and prostaglandin E2. As a result, the production of TNF-α and IL-1β decreased. It also inhibited the expression of Toll-like receptor 4 (TLR4) and the binding of LPS to TLR4. Gullon et al. (2017) provided an explanation of the anti-inflammatory activity of rutin in conditions such as inflammatory bowel disease, colitis, and ear edema. Rutin was found to reduce brain damage by decreasing the levels of p38-MAPK, NFkB, COX-2, i-NOS, TNF-α, and IL-6. Ganeshpurkar and Saluja (2020) described how catechins can prevent autoimmune myocarditis by reducing the activity of NFkB and the expression of intercellular adhesion molecule-1 (ICAM-1). Prakash et al. (2019) demonstrated that epicatechin significantly reduces inflammation by inhibiting the enzymes cyclooxygenase and lipoxygenase. Collectively, these studies provide scientific evidence for the anti-inflammatory properties of garlic polyphenols that have been identified, as well as their mechanisms of action.

5.4. Anticancer

Cancer remains responsible for approximately 10 million deaths annually. Extensive research has been conducted on the anti-tumor effects of garlic polyphenols, both *in vitro* and *in vivo*. Various mechanisms have been identified to elucidate the anticancer properties of flavonoids, including the inactivation of carcinogens, inhibition of proliferation, cell cycle arrest, induction of apoptosis and differentiation, angiogenesis inhibition, antioxidation, and reversal of multidrug resistance, either individually or in combination.

Khaled (2020) demonstrated that isorhamnetin effectively suppresses colon cancer by modulating the PI3K-Akt-mTOR pathway. Zhou et al. (2017) highlighted the significance of apigenin in the prevention of various types of cancer, including breast cancer, colon cancer, ovarian cancer, cervical cancer, thyroid cancer, and lung cancer. Apigenin exhibited cytotoxic effects on various cancer cell lines at different concentrations. Its antitumor effect was attributed to the suppression of NFkB, which resulted in the downregulation of cell proliferation genes such as cyclin D1 and cox2, as well as antiapoptotic factors like Bcl-2, Bcl-xL, and the angiogenesis factor VEGF in cancer cells. Apigenin was also capable of arresting the cell cycle in the G0/G1 phase, thereby inhibiting leukemia cell proliferation. Rutin was found to induce cell cycle arrest and apoptosis in various cancer cell lines (HT-60, U-937). It also decreases cell adhesion and migration in cancer cells. Additionally, the combination of rutin and lower doses of chemotherapeutic drugs has been shown to prevent the adverse effects of these drugs (Gullon et al., 2017).

Quercetin demonstrated anticancer activity by inhibiting the growth of SK-Br3 and MDA-MB (breast cancer) cells (Wang et al., 2016). It induced death receptors to eliminate lymphoma cells in rats and inhibited protein kinase C to impede the growth of cancer cells. Prakash et al. (2019) observed significant inhibitory effects of epicatechins on breast, lung, oral, colon, liver, and pancreatic cancer. Zhang et al. (2009) conducted a study on the anticancer properties of galloyl glucose. They found that galloyl glucose demonstrated antitumor activity against prostate, lung, breast, and liver cancer by inhibiting angiogenesis, P-glycoprotein, and cell cycle progression. P-glycoprotein overexpression in cancer cells contributes to drug resistance by expelling drugs from the cells. Yao et al. (2022) identified eriocitrin as a promising anticancer compound against breast cancer. They found that eriocitrin downregulated the levels of cyclin D1 and cyclin A, while increasing the levels of TNF-α, IL-1β, and IL-6.

5.5. Organ-protective

Garlic polyphenols have demonstrated diverse organ-protective effects, including cardioprotective, hepatoprotective, and neuroprotective properties. Khaled (2020) discussed the neuroprotective effects of isorhamnetin in diabetic rats induced by streptozotocin (STZ). This compound reduces oxidative stress, apoptosis, and inflammation by suppressing astroglial activation and acetylcholinesterase activity. It also demonstrated hepatoprotective effects by inhibiting autophagy through modulation of the P38/PPAR-α pathway. Additionally, isorhamnetin provides protection against cardiac hypertrophy by blocking the PI3K-AKT pathway. Zhou et al. (2017) explained that apigenin protects the cardiovascular system from hypertension by blocking calcium channels, reducing nitric oxide levels in blood vessels. This promotes relaxation of the vascular endothelium and helps to lower blood pressure. Both apigenin and rutin have shown protective effects against myocardial ischemia-reperfusion injury by increasing Bcl-2 expression, reducing p38 MAPK signaling pathway activation, and decreasing the levels of TNF-α, IL-1β, and IL-6 (Gullon et al., 2017). Apigenin also demonstrated the ability to inhibit liver injury induced by toxic chemicals such as furan and acetaminophen. It prevents oxidative stress-induced liver injury by scavenging reactive oxygen species (ROS) and increasing the levels of antioxidant enzymes such as glutathione (GSH) and superoxide dismutase (SOD). Wang et al. (2016) explained that the intake of quercetin could prevent coronary artery disease by reducing the levels of inflammatory cytokines. Ganeshpurkar and Saluja (2020) highlighted the antihypertensive effects of catechins due to their antioxidant properties. Catechins act as anticoagulants and prevent platelet adhesion by reducing the production of hydrogen peroxide. Administration of catechins, along with vitamin C, restored cardiac contraction and normalized body and heart weight in idarubicin-induced cardiac toxicity. Long-term administration of catechins has also been shown to improve learning ability and brain function. Upadhyay and Mohan Rao (2013) investigated the neuroprotective and hepatoprotective effects of chlorogenic acid. Chlorogenic acid protected neuronal PC12 cells against methylmercury toxicity by regulating the levels of GSH, ROS, GPX, and caspase 3. Additionally, both chlorogenic acid and caffeic acid demonstrated cardioprotective effects by reducing P-selectin expression on platelets and inhibiting the activity of COX-1 and COX-2 enzymes. Prakash et al. (2019) explained the cardiovascular protective effects of epicatechin through the modulation of nitric oxide (NO) levels. Yao et al. (2022) described the anti-atherosclerotic properties of eriocitrin, which increased levels of the NO enzyme and reduced overall body weight. This compound also demonstrated nephroprotective and neuroprotective effects by maintaining various levels of antioxidant enzymes, caspases, and cytokines. Eng et al. (2018) elucidated the role of epigallocatechin in preventing cardiac hypertrophy. It inhibits NFkB and connective tissue growth factor overexpression, thereby reducing collagen synthesis, fibronectin expression, and cardiac fibroblast proliferation.

5.6. Other biological activities

Garlic polyphenols have been found to exhibit various beneficial effects in addition to the aforementioned biological activities. These include hepatoprotective properties, anti-arthritic effects, antidiabetic activity, antiulcer properties, and antithyroid potential. Berginc et al. (2010) conducted a study on the impact of garlic flavonoids, including rutin, tangeretin, and nobiletin, on the hepatic pharmacokinetics of saquinavir and darunavir. The findings suggest that saquinavir and garlic constituents may compete for the same binding site on the efflux transporter, while darunavir and garlic phytochemicals may have a positive synergistic effect by binding to separate binding sites on the transporter. These mechanisms could explain potential changes in plasma profiles that may occur *in vivo* when antiretrovirals and garlic supplements are consumed simultaneously.

Another study by Long et al. (2023) investigated the effects of garlic polyphenols on rheumatoid arthritis (RA). These polyphenols, known for their antioxidant potential, were found to help alleviate pain in RA patients. They exhibited anti-inflammatory effects by reducing the levels of TNF-α, IL-6, and CRP in the serum through the inhibition of cell signaling pathways, including COX-2, as well as the suppression of NFκB activation.

Zhou et al. (2017) conducted research on the impact of apigenin, one of the least studied compounds mentioned in the previous text, on bone turnover. They found that apigenin had a positive effect on bone mineral content and bone density, while also reducing the maturation of dendritic cells.

Ganeshpurkar and Saluja (2020) explained that catechins, another group of compounds mentioned earlier, have been clinically studied to evaluate their effects on patients with type 2 diabetes. Catechins have been found to prevent obesity, reduce lipid peroxidation, maintain low levels of haemoglobin A(1c), and restore the activity of enzymes such as glycogen synthase, glucokinase, and glycogen phosphorylase in diabetic patients. Furthermore, catechins have been shown to have an anti-ulcerative effect by protecting the gastric mucosa.

Moreover, Satoh et al. (2002) investigated the effects of catechins on thyroid function. They observed that catechins reduced the levels of T3 and T4 hormones while increasing the level of TSH. Additionally, catechins were found to decrease the activity of thyroid peroxidase, indicating their potential as antithyroid agents. Furthermore, compounds such as 3′,4′,7-trihydroxyisoflavan, petunidin 3,5-*O*-diglucoside, myricetin 3-*O*-rutinoside, hesperetin 3′-*O*-glucuronide, apigenin 6,8-di-C-glucoside, isorhoifolin, and *p*-anisaldehyde have received limited scientific study at the compound level. This warrants further investigation into their potential benefits and mechanisms of action.

6. Summary and future perspectives

Polyphenols, the active constituents found in traditional herbs, have a wide range of sources and show minimal cytotoxicity. Garlic polyphenols exhibit diverse biological activities, including antioxidative, anti-inflammatory, organ-protective, endocrine function maintenance, and anticancer properties, among others. Various extraction methods exist for obtaining garlic polyphenols, with ultrasound-assisted extraction being particularly efficient. Moreover, the concentration of garlic polyphenols depends on the variety of garlic and the conditions in which it is grown. Hydroxycinnamic acids are the main polyphenols found in garlic. Garlic polyphenols can be categorized based on their structural characteristics, including the position of hydroxyl groups and double bonds between carbon atoms. The structural features of garlic polyphenols influence their biological activities. In-depth investigations have examined the specific biological activities of identified polyphenols, revealing their diverse roles. Additionally, there is potential for studying less explored polyphenols and investigating the synergistic effects of combining two or more polyphenols using animal models. This comprehensive review provides strong evidence supporting the utilization of garlic polyphenols as functional food, therapeutic agents, and industrial products.

To fully utilize the non-toxic and safe properties of garlic polyphenols, it is crucial to actively pursue preclinical and clinical trials using advanced technologies like bioinformatics to verify their reliability and efficacy in humans. Furthermore, there is an expectation that garlic polyphenols could have substantial market, social, and economic implications in the fields of medication, vaccines, and health products. However, comprehensive investigations focusing on the precise structures, structure-activity relationships, activation mechanisms, and clinical trials are necessary to advance the development and application of garlic polyphenols.

Data availability

The data which supported the manuscript are included within the article.

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Author contribution statement

Conceptualization, literature search, and first draft of manuscript were prepared by Monika Monika. Sanjeev Gupta critically analyzed and gave suggestions to finalize the manuscript. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that there is no conflict of interest.

Abbreviations

Akt: Protein kinase B; **ALT**: Alanine aminotransferase; **AST**: Aspartate aminotransferase; **BC**: before christ; **Bcl**: B-cell leukemia/lymphoma 2 protein; **CCD**: Central composite design; **CE**: Catechin equivalent; **COX-2**: Cyclooxygenase-2; **CREB**: cAMP-response element binding protein; **CRP**: C-reactive protein; **Da**: Dalton; **DPPH**: 2,2-Diphenyl-1-picrylhydrazyl; **dSPE**: Dispersive solid phase extraction; **ESI/ES**: Electron spray ionization; **GAE**: Gallic acid equivalent; **GP$_x$**: Glutathione peroxidase; **GSH**: Reduced glutathione; **GSK-3β**: Glycogen synthase kinase-3-beta; **HCL**: Hydrochloric acid; **HPLC**: High performance liquid chromatography; **HT-60**: Human leukemic myeloblast-60; **ICAM-1**: Intercellular adhesion molecule 1; **IL**: Interleukin; **iNOS**: Inducible nitric oxide synthase; **JNK**: Jun N-terminal kinase; **LC**: Liquid chromatography; **LDL**: Low density lipoproteins; **LPS**: Lipopolysaccharide; **MAPK/MPK**: Mitogen activated protein kinase; **MDA**: Malondialdehyde; **MDA-MB**: An epithelial, human breast cancer cell line; **MPO**: Myeloperoxidase; **MS**: Mass spectrometry; **mTOR**: Target of rapamycin; NFkB: Nuclear factor kappa B; **NO**: Nitric oxide; **NO$_x$**: NADPH oxidase; **Nrf-2**: Nuclear factor erythroid 2 related factor 2; PC-12: Adrenal phaeochromocytoma; **PDA**: Photo diode array; **PGE2**: Prostaglandin E2; **PGF2α**: Prostaglandin F2 alpha; **PI3K**: Phosphoinositide 3 kinase; **PLE**: Pressurized liquid extraction; PPAR: Peroxisome proliferator activated receptor; **QE**: Quercetin equivalent; **QTOF**: Quadruple time of flight; **QuEChERS**: Quick, easy, cheap, effective, rugged and safe; **RA**: Rheumatoid arthritis; **ROS**: Reactive oxygen species; **RSM**: Response surface methodology; **RUT**: Rutin; **SARS**: Severe acute respiratory syndrome; **SK-Br3**: Human breast cancer cell line; **SOD**: Superoxide dismutase; **STZ**: Streptozotocin; **T3**: Triiodothyronine; **T4**: Thyroxine; **TFC**: Total flavonoid content; **TLR**: Toll like receptor; **TNF-α**: Tumor necrosis factor-alpha; **TP**: Total phenols; TPC: Total phenolic content; **TSH**: Thyroid stimulating hormone; **U-937**: Monoblast cell line; **UHPLC-DAD**: Ultra-high performance liquid chromatography diode array; **UPLC**: Ultra performance liquid chromatography; **VEGF**: Vascular endothelial growth factor.

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