

Review

Bioactive Compounds from *Allium* Species: Chemical Features and Molecular Mechanisms in Polycystic Ovary Syndrome—A Narrative Review

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Abstract

Polycystic ovary syndrome (PCOS) is a complex endocrine and metabolic disorder characterized by hyperandrogenism, insulin resistance, oxidative stress, and chronic low-grade inflammation, while conventional therapies are often limited by adverse effects and sub-optimal adherence. This narrative review aims to evaluate the chemical composition and mechanistic effects of bioactive compounds derived from *Allium* species in the context of PCOS. A comprehensive analysis of the literature was performed, focusing on organosulfur compounds and polyphenols, with emphasis on their structure, reactivity, transformation pathways, and biological activity, integrating findings from preclinical and clinical studies. The evidence indicates that key compounds, including allicin, ajoene, and diallyl sulfides, exert biological effects through modulation of redox balance, inhibition of inflammation-related signaling, and regulation of insulin signaling pathways, while also influencing steroidogenesis and androgen synthesis. Polyphenolic compounds contribute primarily through antioxidant mechanisms related to their structural features. However, the current evidence remains limited by the scarcity of large-scale, long-term human clinical trials, particularly in women with PCOS, which restricts definitive conclusions regarding clinical efficacy, optimal dosing, safety, and long-term therapeutic applicability. Overall, *Allium*



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species represent a promising source of multitarget bioactive compounds for PCOS management, and understanding the chemical basis of their activity is essential for optimizing their therapeutic potential and guiding future research.

Keywords: polycystic ovary syndrome; *Allium*; insulin resistance; oxidative stress; phytotherapy; phytochemicals

1. Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder characterized by reproductive and metabolic abnormalities. Current therapeutic approaches are largely symptom-oriented and often require long-term treatment, while patient adherence may be limited by adverse effects and treatment burden. Consequently, increasing attention has been directed toward complementary and alternative therapeutic strategies, including plant-derived bioactive compounds with multitarget biological activities [1]. Species of the *Allium* genus are rich sources of organosulfur compounds, flavonoids, and phenolic constituents whose chemical properties are closely associated with a wide range of biological activities [2]. This review focuses on the major bioactive compounds identified in *Allium* species, their chemical characteristics and biological activities, and their potential beneficial effects on PCOS, as evidenced by available preclinical and clinical studies.

2. Materials and Methods

2.1. Literature Search Strategy

A comprehensive literature search was conducted to identify relevant studies on the phytochemical composition, chemical properties, and biological effects of *Allium* species in the context of polycystic ovary syndrome (PCOS). The search was performed using the electronic databases PubMed, Scopus, and Web of Science, supplemented by manual screening of reference lists from relevant articles. The literature search included all records available in the selected databases up to December 2025.

Search terms included combinations of keywords and controlled vocabulary (MeSH terms), such as “*Allium*”, “*Allium sativum*”, “*Allium cepa*”, “organosulfur compounds”, “allicin”, “ajoene”, “diallyl sulfide”, “polycystic ovary syndrome”, “PCOS”, “insulin resistance”, “oxidative stress”, “inflammation”, “steroidogenesis”, and “phytochemicals”. Boolean operators (AND, OR) were applied to refine the search and ensure comprehensive coverage of the topic.

2.2. Eligibility Criteria

Studies were included if they met the following criteria: original research articles (clinical trials, in vivo, or in vitro studies) or relevant review articles; studies investigating *Allium* species or their isolated bioactive compounds; studies addressing chemical properties, structure–activity relationships, or biological mechanisms relevant to PCOS or associated metabolic and endocrine disturbances; articles published in English.

Exclusion criteria were: studies not directly related to *Allium* species or PCOS; conference abstracts, editorials, and letters without sufficient experimental or analytical data; duplicate publications; studies lacking clear methodological description or scientific relevance.

2.3. Study Selection and Data Extraction

The selection process was conducted in two stages. First, titles and abstracts were screened to exclude irrelevant studies. Subsequently, full-text articles were assessed for eligibility based on predefined criteria. Data were extracted manually and included study design, type of *Allium* preparation or compound, dosage, experimental model, duration of treatment, and main outcomes related to metabolic, hormonal, and oxidative stress parameters.

For chemical and phytochemical aspects, particular attention was given to studies describing molecular structure, chemical reactivity, transformation pathways, and analytical characterization of bioactive compounds.

2.4. Data Synthesis

Due to the heterogeneity of the included studies in terms of design, methodology, and reported outcomes, a narrative synthesis approach was applied. The findings were organized according to the type of compounds (organosulfur compounds, polyphenols, terpenoids, etc.), type of study (preclinical or clinical), and proposed mechanisms of action.

Special emphasis was placed on integrating chemical properties with biological effects, including structure–activity relationships and molecular mechanisms underlying the observed therapeutic potential of *Allium* species in PCOS.

2.5. Quality Considerations

Although a formal systematic review protocol (e.g., PRISMA) was not applied, efforts were made to include high-quality, peer-reviewed studies. Priority was given to randomized controlled trials, well-designed experimental studies, and articles published in journals indexed in major scientific databases. Where possible, findings were interpreted in the context of study design and methodological robustness.

3. The Genus *Allium*: General Characteristics and Relevance

3.1. Botanical Diversity, Distribution, and Traditional Use of *Allium* Species

Allium species have been used since ancient times in human nutrition and traditional medicine, with evidence showing they are among the oldest cultivated plants [2]. These plants are widely used as vegetables and spices, and in modern and traditional medicine as preventive and therapeutic agents. Their global importance is reflected in extensive cultivation and numerous studies on their biological properties [2,3]. The genus *Allium* is one of the largest genera of flowering plants and the most important genus within the family *Amaryllidaceae* (subfamily *Allioideae*), comprising more than 700 species classified into 15 subgenera and 72 sections [4–6].

Regarding geographical distribution, *Allium* species occur throughout the Northern Hemisphere, ranging from the Mediterranean region of Europe through Central Asia to Pakistan and North America. They generally prefer dry climates, sunny and open habitats, and are rarely found in dense vegetation [4,7]. According to FAOSTAT, the largest producers of *Allium* crops in 2021 were China and India, producing over 20 million tons of onions and garlic [8]. In Europe, particularly in the Aegean region of Greece, including the Aegean islands and Crete, as well as in the Balkan Peninsula, the diversity of *Allium* species is comparable to that found in North Africa. Due to the high number of endemic taxa, the Balkan region is considered an important center of diversity. A total of 56 *Allium* species have been recorded in the Balkans, of which 17 are endemic [9–11].

The extensive use of *Allium* species in nutrition, as well as their application as spices and medicinal plants, makes this genus economically significant. Among them, *Allium cepa* plays a dominant role due to its widespread use as a vegetable and culinary spice.

The most widely cultivated species of the genus *Allium* include *Allium cepa* (onion), *Allium sativum* (garlic), *Allium ampeloprasum* var. *porrum* (leek), *Allium fistulosum* (Welsh onion), *Allium tuberosum* (garlic chives), and *Allium schoenoprasum* (chives) [11].

3.2. Morphological Characteristics of *Allium* Species

Allium species are biennial or perennial herbaceous plants with underground storage organs, mainly bulbs, and characteristic structures such as leaves, scapes, flowers, fruits, and seeds [12–14]. Most *Allium* species form bulbs as storage organs, while in some (e.g., leek, *Allium ampeloprasum*) this role is taken over by a pseudostem. They have leafless scapes, variable leaves, umbel inflorescences, and capsules with black seeds, with morphology highly diverse and taxonomically important [15–18].

3.3. Dietary Use and Phytotherapeutic Potential of Selected *Allium* Species

Allium species are valued for their taste, aroma, and nutritional properties, and are widely used in nutrition, cuisine, and traditional and modern medicine. Different plant parts are commonly consumed, while seeds are mainly used as microgreens in modern gastronomy [19]. Various edible parts of *Allium* plants are widely consumed in many cultures and are an important component of the Mediterranean diet due to their rich phytonutrient content. Onion and garlic are mainly used as fresh or dried bulbs, while shallots, leeks, and spring onions are commonly consumed as fresh leaves or young shoots [20,21]. Chinese chives (*Allium tuberosum*, syn. *A. odorum*) have also been used in certain food technologies, including cheese production, where they contribute to improved organoleptic properties and nutritional value [22]. In addition to cultivated species, several wild *Allium* species are traditionally used as food and medicinal plants. Among them, *Allium ursinum* (wild garlic) is especially valued, with its leaves and bulbs commonly consumed and used in traditional medicine across Europe [23].

Over the past decades, *Allium* species have been extensively studied for their biological activity, largely attributed to their high content of organosulfur and other phytochemical compounds [13]. Onion (*Allium cepa*) and garlic (*Allium sativum*) are the most extensively studied *Allium* species, although interest in wild species has recently increased. Their extracts and preparations are widely used as dietary supplements and supportive agents due to their rich nutritional and phytochemical composition [11,20].

3.4. Selected *Allium* Species Relevant to Phytotherapeutic Potential

3.4.1. *Allium sativum* (Garlic)

Allium sativum (garlic) is the most extensively studied and one of the most important species of the genus *Allium*. Due to its complex chemical composition, garlic exhibits a wide range of biological activities, including antiviral, antifungal, antibacterial, and antioxidant effects [24]. In conventional medicine, garlic-based supplements are widely used because they contribute to strengthening the immune system, slowing the development and progression of atherosclerosis, improving lipid profiles, and consequently reducing the risk of cardiovascular diseases. The antioxidant properties of garlic may also contribute to the prevention of neurodegenerative disorders such as Alzheimer's disease and dementia. In addition, garlic exhibits carminative and antiseptic effects, supports respiratory health, contributes to the detoxification of heavy metals in the body, and may improve bone health. Garlic preparations are commercially available in various forms, including essential oils, macerates, garlic powder, and other pharmaceutical formulations designed to mask or eliminate the characteristic odor of raw garlic [25,26].

3.4.2. *Allium cepa* (Onion)

Allium cepa (onion) is also used in cosmetology as an ingredient in skin and hair care products. The bioactive components of *A. cepa* have been shown to exert multiple biological effects, including inhibition of pancreatic lipase, suppression of adipogenesis, and enhancement of energy expenditure. Several studies have demonstrated the potential of bulb onion in the management of metabolic disorders associated with obesity, such as hyperlipidemia, hypertension, diabetes, and inflammatory disorders [27,28].

3.4.3. Other Relevant *Allium* Species Include *A. fistulosum*, *A. ampeloprasum*, *A. schoenoprasum*, and *A. ursinum*

Allium fistulosum (Welsh onion) is a perennial species morphologically similar to *A. cepa* but does not form a true bulb. Despite its lower popularity compared to common onion, it exhibits pharmacological activities similar to *A. cepa* and is widely used in traditional medicine [29]. *Allium ampeloprasum* (leek) is valued as a health-promoting vegetable due to its chemical composition, which resembles that of garlic and onion, and its pharmacological properties have been extensively studied [30]. *Allium schoenoprasum* (chives) is a perennial plant with multiple applications, including culinary, medicinal, and ornamental uses. Numerous studies have demonstrated its antioxidant activity, and it has also been reported to be suitable for phytoremediation, particularly for reducing cadmium concentrations in contaminated soils [31,32]. *Allium ursinum* (ramsons or wild garlic) is rich in biologically active compounds and has a long history of use in traditional medicine. It is commonly applied for the prevention and treatment of gastrointestinal, cardiovascular, and respiratory disorders [33]. These species share common beneficial effects, including the potential to lower blood pressure and to alleviate symptoms of various inflammatory conditions [34–36].

3.5. Phytochemical Diversity and Bioactive Constituents of *Allium* Species

Allium species exhibit a complex chemical composition, encompassing diverse phytochemicals. The most important components are organic sulfur compounds, which are primarily responsible for their characteristic smell and numerous biological functions. In addition to sulfur compounds, polyphenols—including phenolic acids and flavonoids—play a significant role and contribute to the specific color of the onion bulb. Carbohydrates, mainly fructose and glucose, are present in the edible parts of onions, while arabinose and galactose are found in the outer skins. Amino acids, particularly arginine and glutamic acid, provide essential nitrogen and contribute to nutritional value. Other bioactive compounds include saponins, vitamins (A, C, B6, and folates), and minerals (Ca, Mg, Zn, Mn, P, K, Na, Fe, Se, Cu, Br, I) [37,38]. The mentioned phytochemical compounds (phenolic and sulfur compounds, fatty acids, and phytosterols) are responsible for the pharmacological properties of *Allium* species, such as anti-inflammatory, antitumor, antioxidant, and antiviral effects [38–41].

The diverse biological activity of *Allium* species arises from their complex phytochemical composition, which comprises over 100 compounds. In addition to organosulfur compounds and polyphenols, which are considered the most important, these species contain flavonoids, phenolic acids, anthocyanins, phytosterols, fatty acids, and terpenoids [42]. These phytochemical constituents are responsible for the pharmacological properties of *Allium* species, including anti-inflammatory, antitumor, antioxidant, and antiviral effects. The structures of the most important bioactive compounds in *Allium* species are presented in Figure 1.

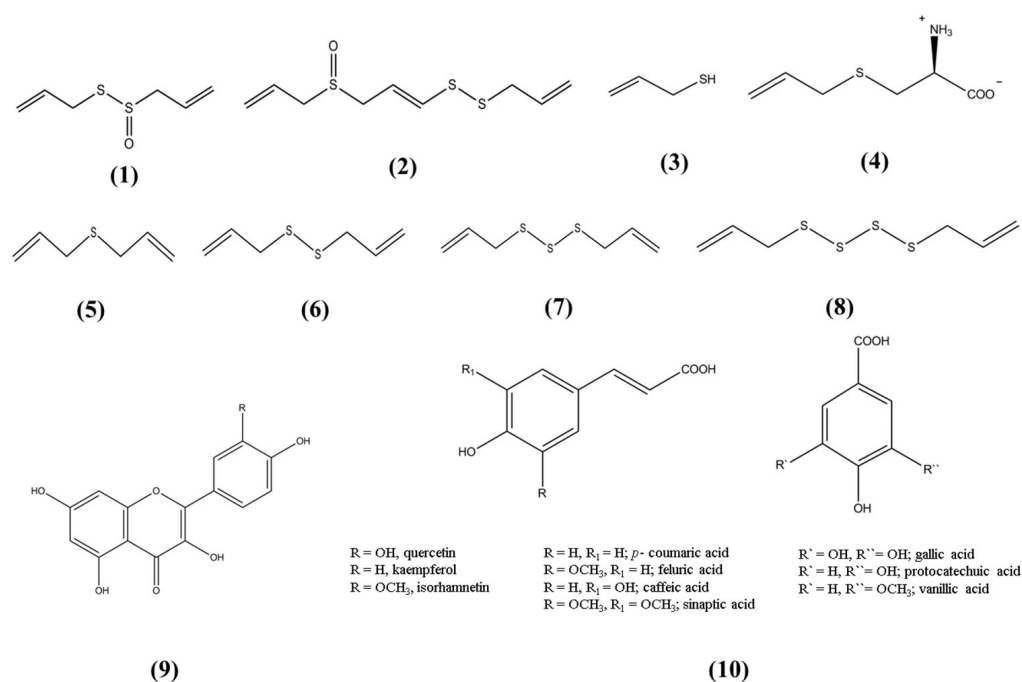


Figure 1. Structures of some of the most important bioactive compounds in *Allium* species: (1) Allicin; (2) Ajoene; (3) Allyl mercaptan; (4) S-allyl cysteine; (5) Diallyl sulfide (DAS); (6) Diallyl disulfide (DADS); (7) Diallyl trisulfide (DATS); (8) Diallyl tetrasulfide (DTS); (9) Flavonoids; (10) Phenolic acids.

3.5.1. Organosulfur Compounds of *Allium* Species

Sulfur-containing compounds are considered the main constituents of *Allium* species. They are responsible not only for the characteristic odor of these plants but, more importantly, for their therapeutic effects. The protective and pharmacological actions of *Allium* species depend on both the type and quantity of sulfur compounds present. The most frequently isolated organosulfur compounds include allicin, ajoene, allyl mercaptan, S-allyl-cysteine, diallyl sulfide, diallyl disulfide, diallyl trisulfide, and diallyl tetrasulfide, which are shown in order in Figure 1 (structures 1–8) [43].

Allicin: Biosynthesis, Stability, and Biological Effects

Allicin (S-(prop-2-en-1-yl)prop-2-ene-1-sulfinothioate; allyl 2-propenethiosulfinate, diallyl thiosulfinate, S-allyl cysteine sulfoxide; C₆H₁₀OS₂) is arguably the most common organosulfur compound isolated from *Allium* species and is characterized by potent biological activity. It contains a thiosulfinate (-S(O)-S-) group, which is critical for its chemical reactivity and inherent instability. Allicin does not exist in intact garlic; rather, it is formed enzymatically from alliin (S-allyl-L-cysteine sulfoxide) by the action of the enzyme alliinase, which is activated upon mechanical disruption of plant cells (e.g., cutting, crushing, or chewing). Chemically, allicin is unstable and rapidly decomposes into secondary sulfur compounds, such as diallyl disulfide, diallyl trisulfide, and ajoene. It appears as a colorless to pale yellow oily liquid, slightly soluble in water but readily soluble in ethanol, ether, and other organic solvents. Allicin is thermolabile; high temperatures, such as during cooking, significantly reduce both its content and biological activity [44]. The biological activities of allicin are broad:

- **Antimicrobial:** Allicin exhibits strong activity against Gram-positive and Gram-negative bacteria, fungi, and viruses. Its mechanism involves reacting with thiol (-SH) groups of microbial enzymes, thereby inhibiting essential metabolic processes and protein synthesis [45].

- Antioxidant and Anti-inflammatory: Allicin scavenges free radicals and reduces reactive oxygen species (ROS) levels. It also induces endogenous antioxidant enzymes, including superoxide dismutase (SOD), catalase, and glutathione peroxidase. Allicin reduces the expression of pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6) and enzymes such as COX-2 and iNOS, inhibiting NF- κ B and MAPK signaling pathways and alleviating inflammation [46].
- Anticancer: Allicin can induce apoptosis, arrest the cell cycle, and inhibit tumor cell proliferation. It also modulates angiogenesis and metastasis through the regulation of genes such as *Bax*, *Bcl-2*, *p53*, and *VEGF* [47].
- Cardioprotective and reproductive support: Allicin lowers LDL-cholesterol and triglycerides, increases HDL, inhibits platelet aggregation, and prevents lipid oxidation, thus reducing the risk of atherosclerosis and cardiovascular diseases. Preliminary animal studies indicate allicin may help restore regular estrous cycles and improve the health of ovarian tissues [45,48].
- Metabolic Effects and Hormonal balance: Allicin exerts hypoglycemic effects by improving glucose tolerance, stimulating insulin secretion, and enhancing insulin sensitivity in peripheral tissues. Studies suggest allicin may help decrease elevated testosterone levels and increase Sex Hormone-Binding Globulin (SHBG), which helps neutralize excess free androgens [48,49].

Following enzymatic activation, alliin is rapidly converted into allyl sulfenic acid, a highly reactive and transient intermediate that plays a central role in allicin formation. Due to its instability, allyl sulfenic acid does not accumulate but instead undergoes spontaneous condensation of two molecules, resulting in the formation of allicin (diallyl thiosulfinate).

This conversion represents a key biochemical step that determines the initial chemical profile of garlic following tissue disruption. The efficiency of this process is influenced by several physicochemical factors, including pH, temperature, and the surrounding matrix, which can affect enzyme activity and intermediate stability. The formation of allicin, therefore, reflects a tightly coupled enzymatic–chemical sequence rather than a simple one-step transformation [50,51].

This biosynthetic pathway, including the formation and reactivity of allyl sulfenic acid, is illustrated in Figure 2.

Due to its highly reactive thiosulfinate functional group, allicin is chemically unstable and readily undergoes a series of transformation reactions, leading to the formation of a variety of secondary organosulfur compounds. These reactions include nucleophilic substitution, redox processes, and sulfur transfer reactions, which are strongly influenced by environmental conditions such as temperature, pH, solvent, and the presence of lipids or other nucleophiles.

In aqueous environments, allicin can decompose into relatively more stable compounds such as diallyl disulfide (DADS) and diallyl trisulfide (DATS), which retain biological activity but exhibit lower electrophilicity. In contrast, under conditions involving heat or non-polar solvents, such as lipid-rich matrices, allicin undergoes rearrangement and condensation reactions leading to the formation of ajoene, typically as a mixture of E and Z isomers. These transformation pathways significantly affect the chemical stability, bioavailability, and biological activity of the resulting compounds [44,52].

Overall, the conversion of allicin into secondary organosulfur derivatives represents a dynamic chemical process that determines the ultimate biological effects of *Allium* species. These transformation pathways and their dependence on physicochemical conditions are summarized in Figure 3.

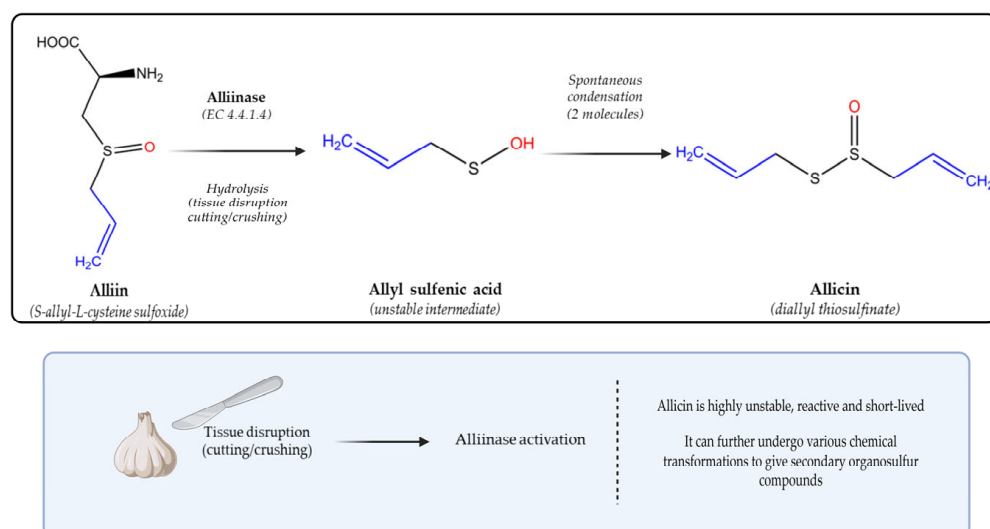


Figure 2. Enzymatic biosynthesis of allicin from alliin in *Allium sativum*. Blue—allyl group; Red—oxygen; Black—other atoms. Upon mechanical disruption of garlic tissue (e.g., cutting or crushing), the enzyme alliinase (EC 4.4.1.4) catalyzes the conversion of alliin (S-allyl-L-cysteine sulfoxide) into allyl sulfenic acid, a highly reactive and short-lived intermediate. This intermediate rapidly undergoes spontaneous condensation to form allicin (diallyl thiosulfinate), the principal bioactive organosulfur compound responsible for many of the biological effects of garlic. The process is strongly dependent on tissue integrity and environmental conditions.

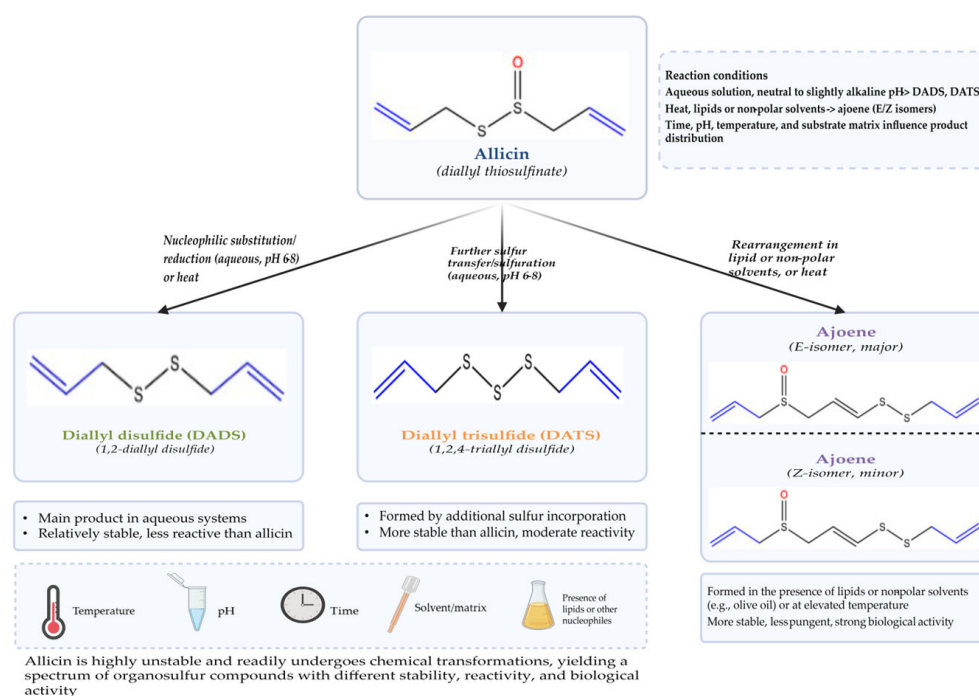


Figure 3. Decomposition and transformation pathways of allicin into secondary organosulfur compounds. Owing to its electrophilic thiosulfinate (S(=O)–S) group, allicin readily undergoes nucleophilic substitution, redox, and sulfur transfer reactions, resulting in the formation of structurally diverse derivatives. In polar (aqueous) environments, allicin decomposes into diallyl disulfide (DADS) and diallyl trisulfide (DATS), whereas in non-polar or lipid-rich media, it undergoes condensation and rearrangement reactions yielding ajoene as a mixture of E- and Z-isomers. These condition-dependent transformations modulate the chemical stability, reactivity, and biological activity of the resulting compounds.

Ajoene: A Stable Bioactive Metabolite of Allicin

Ajoene ((E)-1(prop-2-enylsulfanyl)-3-prop-2-enylsulfanylprop-1-ene; $C_9H_{14}OS_3$) is one of the most important secondary organosulfur compounds derived from allicin, characterized by unique chemical and biological properties. It contains three sulfur atoms and one sulfinate group (-SO-), making it a typical organosulfur compound with high biological reactivity. Ajoene is formed by the spontaneous condensation of allicin in aqueous or ethanolic solutions, particularly during the standing of garlic extracts or in the presence of oil. It is considerably more stable than allicin, which is highly unstable, and is therefore often regarded as the active metabolite responsible for the biological effects of garlic. It is characterized by low water solubility and an almost neutral nature, due to its high pKa value (~14.9) and very low acidity. Structurally, ajoene exists as a mixture of E and Z isomers, whose ratio and configuration contribute to its overall chemical and biological properties. Its formation from allicin is gradual, so its concentration depends on the method of extract preparation. In addition to the effects previously described for allicin, ajoene exhibits a broad spectrum of biological effects, such as antimicrobial, anti-inflammatory, and anticancer properties. These activities are primarily attributed to its sulfur-containing structure, which enables thiol–disulfide exchange reactions and modulation of redox-sensitive signaling pathways. Further, ajoene exhibits potent antiplatelet properties. It inhibits platelet aggregation by blocking fibrinogen phosphorylation and reducing the activity of thromboxane synthase. Moreover, it interacts with the platelet receptor GPIIb/IIIa, making it a significant natural antiplatelet agent [53].

S-Allyl-L-Cysteine (SAC): A Key Marker of Aged Garlic Extract

Garlic's third major organosulfur compound is S-allyl-L-cysteine (SAC; (2R)-2-amino-3-prop-2-enylsulfanylpropanoic acid; $C_6H_{11}NO_2S$). Chemically and pharmacologically, it differs considerably from allicin and ajoene. Unlike these compounds, which are unstable, highly reactive, and short-lived, SAC is stable, water-soluble, and safe, making it the primary bioactive marker of aged garlic extract. SAC is characterized by high thermal stability (melting point ~220 °C) and good solubility in aqueous systems, while being practically insoluble in most organic solvents such as ethanol, acetonitrile, and ethyl acetate. It is formed from the precursor γ -glutamyl-S-allyl cysteine present in fresh garlic and is particularly abundant and stable in aged garlic extracts, where it can remain unchanged for up to two years. SAC exhibits excellent bioavailability (>90%) and is rapidly absorbed after oral intake. SAC exhibits high bioavailability and, due to its long plasma half-life, provides a consistent pharmacokinetic profile [49,54]. Beyond its potent antioxidant properties (neutralizing free radicals and restoring cellular nitric oxide levels, which may help improve the microenvironment of maturing oocytes), SAC demonstrates a broad spectrum of pharmacological effects, including neuroprotective, hepatoprotective, nephroprotective, anticancer, cardioprotective, antihypertensive, and antidiabetic activities (SAC has demonstrated insulin-sensitizing and antidiabetic properties in models of gestational diabetes). Neuroprotective effects have been demonstrated in models of neurodegeneration, where SAC protects dopaminergic and cholinergic neurons, and mitigates neuroinflammation and damage induced by oxidative stress and mitochondrial dysfunction. SAC suppresses pro-inflammatory cytokines (such as TNF- α and IL-1), which are typically elevated in PCOS [54].

Allyl Mercaptan: Reactive Thiol Metabolite and Epigenetic Modulator

The fourth important organosulfur compound in garlic is Allyl mercaptan (prop-2-ene-1-thiol; C_3H_6S), also known as allyl mercaptan, or 2-propenyl mercaptan or 3-mercaptopropene, belongs to allyl sulfur compounds with an allyl sulfur functional group.

It is a highly reactive thiol metabolite formed during the metabolism of allicin and thiosulfonates. Its short-lived reactivity and capacity to modify proteins via –SH groups render it an important anticancer and antimicrobial metabolite of garlic. It is a volatile compound with limited water solubility and exhibits weak acidic properties, with a pKa of approximately 9.83. Unlike SAC, allyl mercaptan is unstable and therefore rarely used directly in supplements; its effects are predominantly exerted in vivo as a metabolite of allicin and ajoene. Literature evidence indicates that this metabolite directly influences lipid metabolism, acting as an inhibitor of cholesterol biosynthesis and secretion in Hep-G2 cells at very low concentrations [55,56]. Allyl mercaptan is rapidly metabolized, while allyl methyl sulfide persists for over 30 h, indicating a significant systemic effect [57]. Among the volatile sulfur compounds of *Allium* species, it is also considered one of the most significant antidiabetic compounds, which may improve fasting blood sugar and insulin resistance [58].

Diallyl Trisulfide (DATS): Modulation of Redox and Inflammatory Signaling

Diallyl trisulfide (DATS; 3-(prop-2-enyltrisulfanyl)prop-1-ene; $C_6H_{10}S_3$) is a nonpolar organosulfur compound belonging to the trisulfide group, formed as a product of allicin decomposition. It is characterized by poor water solubility and a chemically neutral nature, lacking significant acidic or basic properties. Due to its hydrophobic structure, DATS preferentially localizes within lipid-rich environments, particularly cell membranes, where it can interact with nonpolar regions of lipid bilayers and influence membrane properties such as fluidity. In addition to its potent antioxidant activity, diallyl trisulfide (DATS) exhibits significant metabolic regulatory pathways. Oxidative stress-induced insulin resistance represents a central metabolic disturbance in PCOS, and DATS alleviates this condition by enhancing antioxidant defenses through activation of the Nrf2/HO-1 pathway and by inhibiting pro-inflammatory mediators, including STAT1 and NF- κ B. These mechanisms contribute to improved insulin signaling, reduced hyperinsulinemia, and better glucose homeostasis [59,60]. Furthermore, DATS has been shown to modulate lipid metabolism by decreasing lipid peroxidation and improving dyslipidemia, thereby reducing metabolic stress at both ovarian and systemic levels. By attenuating oxidative and inflammatory burdens, DATS indirectly influences endocrine function, leading to a reduction in androgen excess and normalization of the gonadotropin hormones ratio. These interconnected antioxidant, metabolic, and hormonal effects suggest that DATS may serve as a promising adjunctive therapeutic agent for addressing metabolic dysfunctions; however, confirmation through well-designed clinical studies is still required [59].

Chemical Reactivity of Allicin and Interactions with Thiol-Containing Biomolecules

A key chemical mechanism underlying allicin activity is thiol–disulfide exchange, whereby the thiosulfinate group reacts with cysteine residues in proteins and low-molecular-weight thiols such as glutathione, leading to modification of protein function. This thiol–disulfide exchange mechanism between allicin and biological nucleophiles is illustrated in Figure 4. Allicin readily reacts with glutathione (GSH), forming S-allylmercaptogluthione and altering cellular redox balance. In vivo, allicin and its derivatives are rapidly metabolized into a range of sulfur-containing compounds, including allyl mercaptan and allyl methyl sulfide, which may contribute to systemic biological effects.

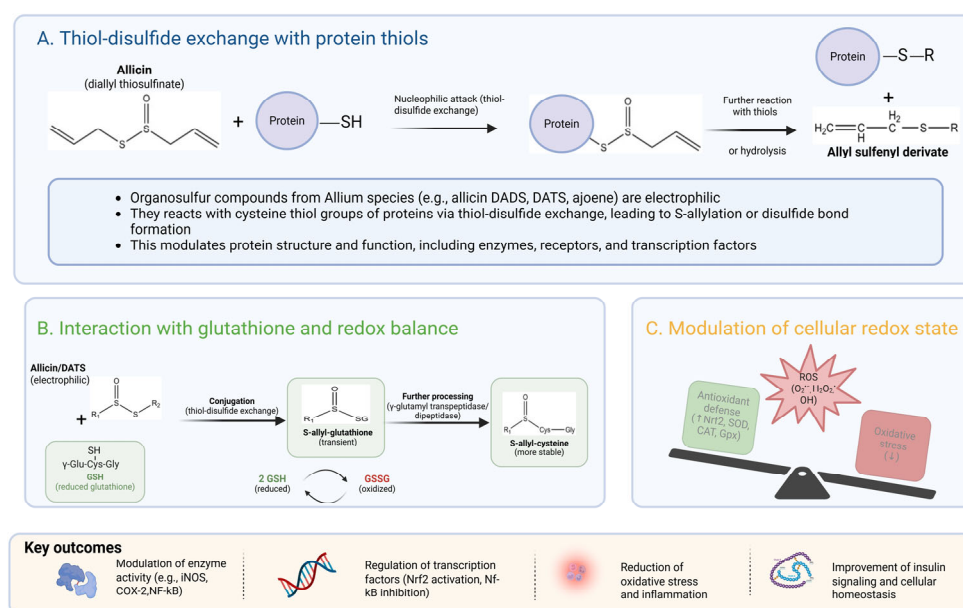


Figure 4. Thiol–disulfide exchange reactions of allicin with biological nucleophiles. The electrophilic thiosulfinate (S(=O)–S) group of allicin reacts with thiol (–SH) groups of cysteine-containing biomolecules via nucleophilic substitution, leading to the formation of mixed disulfides (S-allylmercapto adducts). This process occurs with low-molecular-weight thiols such as glutathione (GSH) as well as protein thiols, resulting in modulation of enzyme activity, redox homeostasis, and intracellular signaling. These reactions represent a key chemical mechanism underlying the biological effects of allicin. Arrows indicate the direction of changes in biological parameters: ↑—increase; ↓—decrease.

3.6. Polyphenolic Compounds of *Allium* Species

Along with organosulfur compounds, polyphenols—particularly flavonoids and phenolic acids—represent major bioactive constituents of *Allium* species. Flavonoids are mainly present as glycosylated derivatives, with quercetin glucosides accounting for 80–85% of total flavonoids in onion, predominantly quercetin-3,4'-O-diglucoside and quercetin-4'-O-monoglucoside. Major flavonoids include quercetin, kaempferol, myricetin, apigenin, and luteolin, while flavonols (quercetin, isorhamnetin, kaempferol) and anthocyanins (cyanidin, pelargonidin, peonidin—characteristic of red onions) are particularly important. Total flavonol content ranges from 7 to 1917 mg/kg fresh weight, with approximately 52 compounds identified in *Allium* species, the most prevalent being quercetin, kaempferol, and isorhamnetin [61]. The most representative flavonoid structures are shown in Figure 1 (structure 9).

Phenols, as key polyphenolic compounds, contribute to the antioxidant, anti-inflammatory, antimicrobial, cardioprotective, and anticancer effects of *Allium* species. Their composition varies depending on species, plant part, and extraction method. Among them, quercetin is particularly important due to its strong antioxidant activity and ability to modulate cellular signaling pathways. It is a poorly water-soluble flavonoid, more soluble in polar organic solvents, and typically occurs in plants in glycosylated forms (e.g., quercetin-3-O-glucoside and rutin), which improve its stability and bioavailability [61,62]. It has been associated with the reduction in oxidative stress, improvement of insulin resistance, and a decrease in androgen levels in experimental models of polycystic ovary syndrome (PCOS). Quercetin is present at high concentrations in red onions and *Allium ursinum* [62]. Anthocyanins in red onion are mainly cyanidin- and peonidin-derived glycosides, including cyanidin-3-glucoside, cyanidin-3-malonylglucoside, cyanidin-3-arabinoside, and related malonylated derivatives. These compounds are also present in other *Allium* species, such as

A. schoenoprasum, mostly as glucosylated and acylated forms. Structurally, anthocyanins are flavonoid pigments with a flavylum core bound to sugar moieties, often further modified by malonyl groups, which affects their stability and color properties [61]. Phenolic acids, a major group of non-flavonoid polyphenols in *Allium* species, contribute significantly to antioxidant, anti-inflammatory, antimicrobial, and hepatoprotective effects. The most abundant phenolic acids in *Allium* species are illustrated in Figure 1 (structure 10).

Phenolic acids in *Allium* species act as major antioxidants, scavenging free radicals and protecting cell membranes, DNA, and mitochondria from oxidative damage. They occur in free and bound forms (e.g., esters and glycosides), with concentrations depending on species, cultivar, and cultivation and extraction conditions. The most abundant include gallic, ferulic, p-coumaric, caffeic, and sinapic acids, with highest levels typically found in outer bulb layers and leaves. Total phenolic content in *Allium cepa* and *Allium ursinum* ranges from 20–40 mg GAE/g extract [63–65].

The antioxidant activity of polyphenols present in *Allium* species is strongly dependent on their chemical structure, particularly the number and position of hydroxyl groups, the presence of conjugated systems, and their ability to participate in electron or hydrogen transfer reactions. These structural features enable polyphenols to neutralize reactive oxygen species (ROS), stabilize radical intermediates through resonance, and chelate transition metal ions, thereby reducing oxidative stress. The key structural determinants and mechanisms of action of these compounds are summarized in Figure 5.

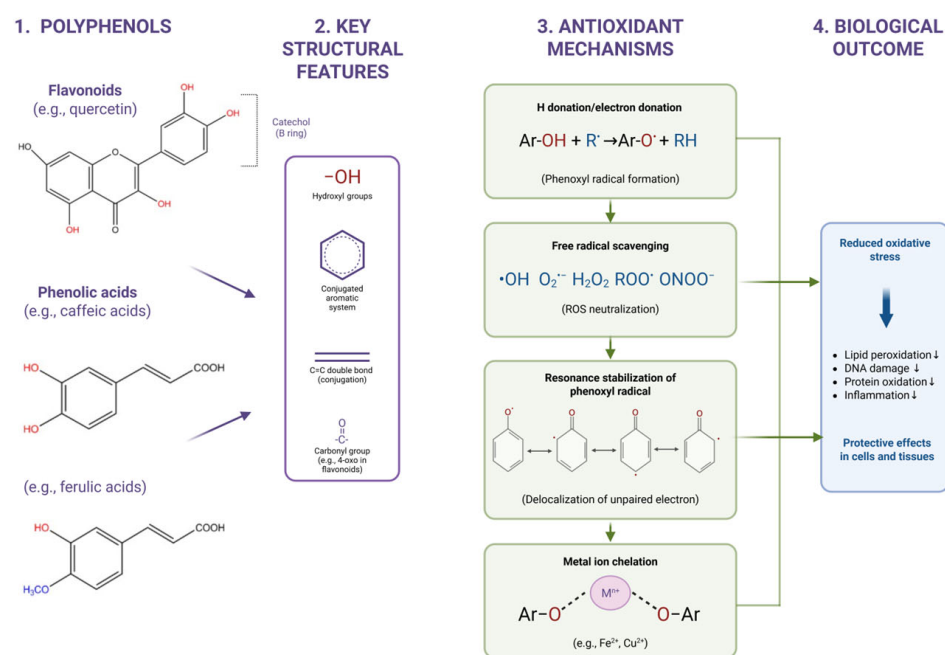


Figure 5. Structural features and antioxidant mechanisms of polyphenols and phenolic acids in *Allium* species. Ar—aromatic ring; R—free radical; ROS—reactive oxygen species; M^{n+} —metal ion. Flavonoids (e.g., quercetin) and phenolic acids (e.g., caffeic and ferulic acids) exhibit biological activity that is closely related to their chemical structure, including the number and position of hydroxyl (–OH) groups, conjugated aromatic systems, and carbonyl functionalities. These features enable hydrogen or electron donation to reactive oxygen species (ROS), resulting in free radical scavenging. The resulting phenoxy radicals are stabilized through resonance delocalization, while additional antioxidant effects arise from the chelation of transition metal ions (e.g., Fe^{2+} , Cu^{2+}), thereby reducing oxidative stress and contributing to cellular protection. Arrows indicate the progression of antioxidant mechanisms and biological effects; ↓ indicates a decrease in oxidative stress-related parameters.

3.7. Terpenoids in *Allium* Species

In *Allium* species, terpenoids represent a significant, yet often underestimated, group of bioactive compounds. Although organosulfur compounds are dominant, numerous studies indicate that terpenoids contribute to their characteristic taste, aroma, and biological activity [66]. Using GC-MS analysis, it was shown that in the water extract of *A. fistulosum*, D-limonene was the most abundant monoterpene among the tested samples. D-limonene has been reported to exhibit antioxidant, anticarcinogenic (along with linalool, farnesol, and caryophyllene, which affect apoptosis and inhibit proliferation), anti-inflammatory, and cardioprotective properties, including reduction in lipid peroxidation and oxidative damage in blood vessels. Through its antioxidant and anti-inflammatory activity, D-limonene may help reduce oxidative damage and low-grade inflammation associated with PCOS. Additionally, its potential beneficial effects on lipid metabolism and cardiovascular health may contribute to the management of metabolic complications frequently observed in PCOS patients [67,68]. Furthermore, Lachowicz et al. determined the carotenoid profile in wild garlic (*Allium ursinum*) using the UPLC-PDA-MS/MS method. The study identified five dominant carotenoids: trans- β -carotene, 9-cis- β -carotene, all-trans-lutein, α -cryptoxanthin, and β -cryptoxanthin. The results showed that the average total carotenoid content was significantly higher in the leaves compared to the stems, flowers, and bulbs. Terpenoids from *Allium* species also exhibit antimicrobial activity, inhibiting the growth of bacteria and fungi such as *Staphylococcus aureus* and *Candida albicans*, and show neuroprotective potential by protecting neurons from oxidative stress, particularly linalool and limonene [69].

Unlike organosulfur compounds and polyphenols, the biological activity of terpenoids is often associated with their physicochemical properties and their ability to influence cellular processes. These compounds can modulate intracellular signaling pathways, thereby contributing to their anti-inflammatory and antioxidant effects. Their activity is frequently mediated through indirect mechanisms, including the regulation of inflammatory mediators and cellular responses rather than direct chemical interaction with reactive species [66,68].

3.8. Phytosterols in *Allium* Species

Another important group of secondary metabolites essential for plant cell membrane function in *Allium* species is phytosterols. Comparative analysis of 70% ethanolic extracts revealed β -sitosterol and campesterol in *A. fistulosum* and *A. ursinum* flowers, while stigmasterol was unique to *A. fistulosum*. The most common phytosterols in *Allium* plants include β -sitosterol (the most abundant), stigmasterol, and campesterol [70–72]. Their biological activities are manifested through several mechanisms: metabolic improvement (competing with cholesterol for intestinal absorption, thereby lowering total cholesterol and LDL-C, and improving insulin sensitivity), anticancer effects (modulation of apoptosis), antioxidant and anti-inflammatory activities, immunomodulatory effects, and the reduction in serum testosterone levels [70,73].

Phytosterols present in *Allium* species, such as β -sitosterol and campesterol, exert their biological effects primarily through modulation of lipid metabolism rather than direct chemical reactivity. Due to their structural similarity to cholesterol, phytosterols competitively inhibit intestinal absorption of dietary cholesterol, leading to reduced plasma cholesterol levels. In addition, they may influence cellular signaling and inflammatory processes, thereby contributing to the regulation of metabolic and cardiovascular functions. These effects contribute to their cardioprotective and metabolic benefits [70,71].

3.9. Vitamins and Minerals in *Allium* Species

Vitamins and minerals in *Allium* species play a dual role: nutritional (as essential micronutrients) and biofunctional, as they support the biosynthesis and activity of phytochemicals responsible for the therapeutic properties of these plants. All species of the genus *Allium* are rich in numerous vitamins and minerals that contribute to their antioxidant, immunomodulatory, and cardioprotective effects. These micronutrients act not only as nutritional components but also as key cofactors in the synthesis and function of bioactive compounds, such as allicin, flavonoids, and saponins, making *Allium* species an important source of natural micronutrients and antioxidants [74]. Furthermore, their antioxidant activity can be enhanced when combined with selenium and flavonoids, resulting in greater cardiovascular and anti-inflammatory benefits. Vitamins—including C, B₁, B₆, B₉ (folate), E, and K—contribute to antioxidant protection, metabolic regulation, and the synthesis of enzymes and hormones. Minerals—such as Ca, Mg, K, P, Fe, Zn, Se, Cu, and Mn—play structural and catalytic roles, participate in electrolyte balance, and are essential for proper muscle and nerve function [75,76].

In addition, several micronutrients, particularly selenium, zinc, and vitamins C and E, contribute to the overall antioxidant capacity of *Allium* species and support cellular redox homeostasis. Together with organosulfur compounds and other phytochemicals, these micronutrients may help protect cells against oxidative stress and complement the biological activity of *Allium*-derived bioactive compounds [75,76].

3.10. Polysaccharides in *Allium* Species

In addition to the previously mentioned bioactive compounds, another important group in *Allium* species is polysaccharides. These compounds play significant pharmacological, biological, and nutritional roles, particularly in enhancing immunity, reducing lipid levels, providing antioxidant protection, and supporting the intestinal microbiota. Polysaccharides in *Allium* species are heteropolysaccharides, primarily composed of fructose as the main monomer, with smaller amounts of glucose, galactose, arabinose, and mannose [77,78]. Polysaccharides act synergistically with sulfur compounds, flavonoids, and vitamins (especially C and E), contributing to cellular protection, immune system enhancement, antioxidant defense, and regulation of lipid and glucose metabolism [79]. Experimental studies in mouse models conducted by Wang et al. and Li et al. demonstrated that polysaccharides from *Allium sativum* exhibit antioxidant and immunomodulatory activities. They enhance the activity of key antioxidant enzymes, including SOD and GSH-Px, while simultaneously reducing MDA levels, thereby decreasing lipid peroxidation and protecting cell membranes. Additionally, these polysaccharides modulate the immune response by lowering pro-inflammatory cytokines and improving the functional status of immune cells. Collectively, these mechanisms result in a synergistic antioxidant and immunoprotective effect under various pathological conditions [80].

In addition, *Allium*-derived polysaccharides, particularly fructans such as inulin-type compounds, may exert their biological effects through prebiotic mechanisms, being fermented by gut microbiota into short-chain fatty acids (SCFAs), which contribute to improved metabolic regulation, anti-inflammatory responses, and maintenance of intestinal barrier function [81].

Table 1 summarizes the major bioactive compounds identified in *Allium* species, their principal biological effects, and their potential relevance to key pathophysiological mechanisms involved in PCOS.

Table 1. Overview of principal phytochemical constituents of *Allium* species and their biological activities relevant to PCOS.

Group of Compounds	Key Bioactive Compounds	Major Sources (<i>Allium</i> Species)	Main Biological Functions	References
Organosulfur compounds	Allicin, ajoene, allyl mercaptan, diallyl sulfide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS), S-allyl cysteine (SAC)	Mostly <i>A. sativum</i> (garlic), also present in <i>A. cepa</i> , <i>A. ursinum</i>	Antioxidant, anti-inflammatory, antiandrogenic, lipid regulation, glycoregulation, anticancer, anticoagulant, antiplatelet, hepatoprotective, nephroprotective	[45–60,67]
Flavonoids	Quercetin, kaempferol, isorhamnetin, myricetin, apigenin, luteolin	<i>A. cepa</i> (especially red onion), <i>A. fistulosum</i> , <i>A. porrum</i> , <i>A. schoenoprasum</i>	Antioxidant, improvement of insulin sensitivity, hypolipidemic effects, vascular protection	[61,62]
Phenolic acids	Ferulic, p-coumaric, caffeic, gallic, sinapic acids	<i>A. cepa</i> , <i>A. porrum</i> , <i>A. schoenoprasum</i> , <i>A. ursinum</i>	Antioxidant, reduction in oxidative stress, lipid peroxidation, anti-inflammatory, hepatoprotective	[63–65]
Terpenoids	Linalool, geraniol, citronellol, α -pinene, β -pinene, limonene, farnesol, nerol, α -terpineol, β -caryophyllene	<i>A. cepa</i> , <i>A. sativum</i> , <i>A. fistulosum</i> , <i>A. ursinum</i>	Antioxidant, anti-inflammatory, antimicrobial, cardioprotective, neuroprotective	[66–69]
Phytosterols	β -sitosterol, stigmasterol, campesterol	<i>A. cepa</i> , <i>A. sativum</i> , <i>A. porrum</i> , <i>A. ursinum</i>	Hypolipidemic (LDL $\downarrow$, HDL $\uparrow$), anti-inflammatory, antioxidant, immunomodulatory, anticancer	[70–72]
Vitamins and minerals	Vitamin C, B1, B6, B9 (folate), E, K; Selenium, Ca, Mg, K, P, Fe, Zn, Mn, Cu	Present in all <i>Allium</i> species, especially <i>A. ursinum</i>	Antioxidant, cofactor in enzymatic reactions, metabolism regulation, immunomodulatory, support of phytochemical activity	[74–76]
Polysaccharides	Fructans (inulin, oligofructose), glucose, galactose, arabinose, mannose	<i>A. sativum</i> , <i>A. cepa</i> , <i>A. porrum</i> , <i>A. ursinum</i>	Prebiotic effect, regulation of intestinal microbiota, improvement of glucose and lipid metabolism, immunomodulatory, antioxidant	[77–81]

3.11. Structure–Activity Relationships (SAR) of *Allium*-Derived Bioactive Compounds and Their Biological Relevance in PCOS

The biological activity of *Allium*-derived organosulfur compounds is strongly influenced by their chemical structure, particularly the number of sulfur atoms, oxidation state, and the presence of reactive functional groups. The thiosulfinate moiety (S(=O)–S), charac-

teristic of allicin, confers high electrophilicity and enables rapid reactions with nucleophilic thiol (-SH) groups in proteins and glutathione, leading to redox modulation and activation of antioxidant pathways such as Nrf2 while inhibiting pro-inflammatory signaling (e.g., NF- κ B). The allyl groups contribute to moderate lipophilicity and membrane permeability, enabling intracellular access to these targets. Although direct evidence specifically linking allicin to PCOS is limited, data from garlic-based studies suggest that it may exert beneficial effects on key pathophysiological features of the syndrome. Allicin has been associated with improvements in metabolic parameters, including reduced fasting glucose, triglycerides, and LDL levels, along with enhanced insulin sensitivity, which may contribute to increased SHBG levels and a consequent reduction in free testosterone. In addition, its anti-inflammatory properties, reflected in decreased CRP and pro-inflammatory cytokines, further support its potential role in modulating the low-grade inflammation characteristic of PCOS, while indirect hormonal effects may help attenuate ovarian androgen production. This high reactivity underlies both its potent biological effects and its marked instability with a short half-life, yet through these interactions allicin can still reduce oxidative stress and inflammation and indirectly improve insulin sensitivity, thereby targeting key features of PCOS [73,74,82].

This underlies its potent biological activity, but also its marked instability and short half-life. Allyl sulfides derived from garlic differ primarily in the number of sulfur atoms linking the two terminal allyl groups, with diallyl sulfide (DAS), diallyl disulfide (DADS), and diallyl trisulfide (DATS) representing the most commonly studied compounds. The most basic member of this series, DAS, is an aliphatic thioether with a single sulfur atom connecting two allyl groups. Compared to higher polysulfides, DAS is less reactive but chemically more stable because of its comparatively simple structure. Its dispersion within biological systems is made easier by the fact that it is a lipophilic, volatile substance with strong membrane permeability. However, because the solitary sulfur atom restricts its redox potential and capacity to interact with proteins that contain thiols, its biological activity is typically less noticeable [36,76].

In contrast, disulfides and trisulfides such as DADS) and DATS exhibit lower electrophilicity but greater chemical stability, allowing more sustained biological effects. With two sulfur atoms, DADS is an intermediate in both structure and biological activity. Because of the disulfide bond (-S-S-), which permits thiol–disulfide exchange interactions with cysteine residues in proteins and low-molecular-weight thiols like glutathione, it belongs to the class of aliphatic disulfides and is more reactive than DAS. Its ability to alter redox-sensitive signaling pathways is based on this reactivity. Compared to more reactive but unstable substances like allicin, DADS has better bioavailability and is a lipophilic, volatile oil that dissolves easily in organic solvents like ethanol and dimethyl sulfoxide. DATS exerts its biological effects largely through the reactivity of its trisulfide chain (-S-S-S-), which can interact with thiol-containing molecules such as cysteine residues and glutathione, leading to modulation of cellular redox balance and increased generation of hydrogen sulfide (H₂S). This redox activity promotes activation of antioxidant pathways (e.g., Nrf2) and suppression of pro-inflammatory signaling (e.g., NF- κ B), processes that are closely involved in the pathophysiology of PCOS [76,83].

Actually, increasing sulfur chain length is generally associated with enhanced lipophilicity and membrane permeability, facilitating intracellular activity. From SAR perspective, biological activity is largely dependent on the quantity of sulfur atoms. Redox activity, electrophilicity, and the ability to produce H₂S—a gaseous signaling molecule involved in metabolic regulation—are all improved by lengthening the sulfur chain. Sulfur content and pharmacological efficacy are clearly correlated, as seen by DATS's highest impacts, DADS's moderate activity, and DAS's limited biological potency. The allyl moieties

($-\text{CH}_2-\text{CH}=\text{CH}_2$) and sulfur-containing linkages are the main functional groups that give DAS and DADS their biological activity. In order to facilitate cellular absorption and tissue distribution, the allyl groups mainly contribute to lipophilicity and membrane permeability. On the other hand, biological interactions such as thiol modification, redox control, and H_2S release directly involve the sulfur atoms, especially the disulfide link in DADS.

These structural characteristics are intimately associated with pertinent biological effects in the setting of polycystic ovarian syndrome (PCOS). By affecting glutathione homeostasis and activating antioxidant pathways like Nrf2, DADS's disulfide functionality can influence oxidative stress while also reducing inflammatory signaling pathways like NF- κ B. Furthermore, better insulin sensitivity and metabolic regulation—two key aspects of PCOS pathophysiology—may result from organosulfur drugs' capacity to increase H_2S bioavailability. DAS, on the other hand, shows somewhat smaller effects on these pathways because of its reduced reactivity and limited redox capacity [84].

Allicin is the source of ajoene, a physiologically active organosulfur molecule with a vinyl disulfide structure that contains both disulfide ($-\text{S}-\text{S}-$) and sulfoxide ($-\text{S}(=\text{O})-$) functional groups. It exists as a mixture of geometric isomers (E- and Z-ajoene). Ajoene is more stable and somewhat lipophilic than allicin, allowing for improved membrane permeability and persistence in biological systems. Thiol-disulfide exchange processes and redox modulation are the main sources of its biological activity, which enables it to affect pathways including Nrf2 and NF- κ B. These characteristics support the antioxidant, anti-inflammatory, and possibly insulin-sensitizing effects of PCOS [85].

Allium species are also the source of S-allyl-L-cysteine (SAC), a water-soluble organosulfur compound with an amino acid backbone that contains amino ($-\text{NH}_2$) and carboxyl ($-\text{COOH}$) functional groups in addition to an allyl thioether group ($-\text{S}-\text{CH}_2-\text{CH}=\text{CH}_2$). SAC has a good bioavailability and safety profile because, in contrast to more reactive polysulfides, it is chemically stable and shows little reactivity toward thiols. Although it promotes high solubility and systemic dispersion, its low lipophilicity ($\log P = -2.1$) restricts passive membrane diffusion. Through indirect mechanisms, such as activation of the Nrf2 pathway and control of oxidative stress, SAC biologically exerts antioxidant and anti-inflammatory actions that may be useful in treating metabolic and inflammatory abnormalities associated with PCOS [86,87].

In addition to organosulfur compounds, flavonoids present in *Allium* species also exhibit structure-dependent biological activity. Their antioxidant potential is largely determined by the number and position of hydroxyl groups, particularly the presence of a catechol moiety in the B ring (3',4'-dihydroxy configuration), which enhances radical-scavenging and metal-chelating properties. Conjugation within the flavonoid structure, especially the presence of a 2,3-double bond in combination with a 4-oxo group, further stabilizes free radicals and contributes to biological activity. Glycosylation, commonly observed in *Allium* flavonoids, improves solubility and stability but may reduce direct antioxidant activity compared to aglycone forms; however, these derivatives may exhibit improved bioavailability and metabolic conversion in vivo. While glycosylation affects solubility and bioavailability, these characteristics also help limit pro-inflammatory signaling (like NF- κ B). *Allium* flavonoids can enhance insulin signaling and reduce oxidative imbalance and inflammation, two important processes that underlie PCOS, through these structure-driven pathways [88].

Overall, the biological effects of *Allium* compounds depend on a balance between chemical reactivity, stability, lipophilicity, and bioavailability. Highly reactive compounds such as allicin act rapidly but transiently, whereas more stable derivatives, including polysulfides, ajoene, and flavonoid glycosides, may exert longer-lasting systemic effects. These structure–activity relationships are summarized in Table 2.

Table 2. Summary of structure–activity relationships, physicochemical properties, and biological effects of major *Allium*-derived bioactive compounds. Arrows indicate the direction of biological effects: ↑—increase/activation; ↓—decrease/inhibition. Symbols (+ to +++) denote qualitative semi-quantitative ranking of relative intensity (from very low to very high) for the indicated physicochemical properties.

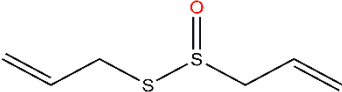
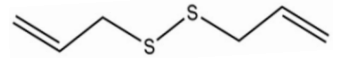
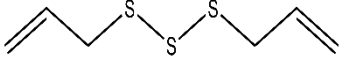
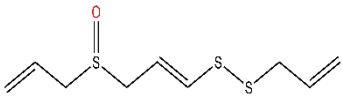
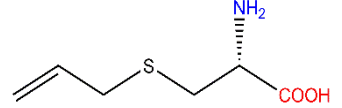
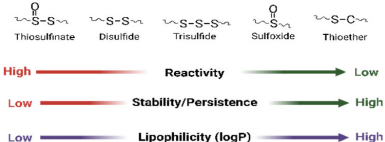
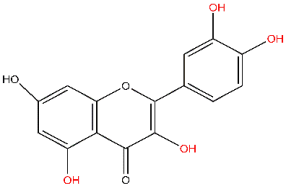
Compound	Chemical Structure (Key Functional Groups)	Key Structural Features	Chemical Properties		Lipophilicity (logP) ^c	Main Biological Activities (Relevant to PCOS)
			Reactivity	Stability		
Allicin (diallyl thiosulfinate)		- Thiosulfinate moiety (S(=O)–S) - Allyl groups with terminal C=C bonds(2) - Strong electrophile	Very high ++++	Very low +	1.3	↑ Antioxidant (↑ Nrf2, ↑ GSH, ↓ ROS) ↓ Inflammation (↓ NF-κB, ↓ cytokines) ↑ Insulin sensitivity ↓ Androgen synthesis ↑ Mitochondrial protection
Diallyl disulfide (DADS)		- Disulfide bond (S–S) - Allyl groups with terminal C=C bonds(2) - Moderate electrophile	Moderate ++	Moderate ++	2.2	↑ Antioxidant ↓ Inflammation ↓ Lipid accumulation ↑ Insulin sensitivity
Diallyl trisulfide (DATS)		- Trisulfide bond (S–S–S) - Allyl groups with terminal C=C bonds (2) - Lower electrophilicity than allicin	Moderate to low +	High ++++	2.6	↑ Antioxidant ↓ Inflammation ↑ Insulin signaling ↓ Oxidative stress
Ajoene (E/Z isomers)		- Sulfoxide (S(=O)) - Vinyldithioether (S–C=C–S) - Conjugated system → greater stability	Moderate ++	High ++++	1.7	↑ Antioxidant ↑ Anti-inflammatory (↓ NF-κB) ↑ Insulin sensitivity ↓ Androgen synthesis
S-allyl-L-cysteine (SAC)		- Thioether (S–C) - Amino acid (zwitterionic) - More stable, less electrophilic	Low +	Very high +++++	−2.1	↑ Antioxidant (indirect ↑ GSH) ↓ Inflammation ↑ Insulin sensitivity ↑ Glucose uptake

Table 2. Cont.

Compound	Chemical Structure (Key Functional Groups)	Key Structural Features	Chemical Properties		Lipophilicity (logP) ^c	Main Biological Activities (Relevant to PCOS)
			Reactivity	Stability		
General SAR trends for organosulfur compounds			SAR of major flavonoids in <i>Allium</i> species			
- Increasing the number of sulfur atoms increases lipophilicity and potential for redox/H₂S-mediated biological effects - Presence of S(=O) increases reactivity but decreases stability (allicin > ajoene > DADS > DATS) - Allyl groups with terminal C=C bonds; groups enhance electrophilicity and biological activity - More lipophilic compounds (DATS, ajoene) show better membrane permeability and longer-lasting effects			Key structural determinants of activity   - Number and position of hydroxyl (–OH) groups: more –OH (especially 3',4'-dihydroxy; catechol in B ring) → stronger antioxidant and metal-chelating activity 2,3-double bond conjugated with 4-oxo group in C ring → better radical stabilization - Glycosylation (R = sugar moiety): ↑ water solubility and stability, but ↓ direct antioxidant activity; may improve bioavailability and metabolic conversion			
			Example: quercetin			

Importantly, the biological effects of *Allium*-derived compounds in PCOS are closely linked to their chemical properties, including electrophilicity, redox activity, and structural features that determine their interaction with molecular targets involved in insulin resistance, inflammation, and steroidogenesis.

4. PCOS: Mechanistic and Therapeutic Perspectives

PCOS is the most common endocrine disorder among women of reproductive age worldwide. According to the World Health Organization, PCOS is a complex condition characterized by a hormonal imbalance, specifically elevated levels of androgens (male hormones) and the presence of numerous small follicles on the ovaries that may develop into cysts. Clinical manifestations typically include irregular menstrual cycles, chronic anovulation (lack of ovulation), acne, and hirsutism (excess body hair), making it a leading cause of female infertility globally [89]. It is estimated that PCOS affects between 10% and 13% of reproductive-aged women globally. A significant concern is that up to 70% of women with the syndrome remain undiagnosed. Beyond reproductive challenges, PCOS is a lifelong metabolic condition associated with higher risks of serious long-term health issues, including insulin resistance, type 2 diabetes, obesity, and cardiovascular disease [90,91]. Given that there is currently no definitive cure for PCOS, clinical management is primarily directed toward symptom mitigation and the prevention of long-term sequelae. First-line therapy remains centered on structured lifestyle interventions, specifically targeted dietary modifications and consistent physical activity. Clinical evidence suggests that even modest weight reduction significantly enhances insulin sensitivity and is a primary factor in restoring spontaneous ovulation. When lifestyle changes are insufficient, pharmacological strategies are employed based on the patient's clinical presentation: hormonal contraceptives: combined oral contraceptives are standard for regulating menstrual cycles and managing hyperandrogenic symptoms, such as acne and hirsutism; insulin sensitizers: metformin is frequently utilized to address underlying insulin resistance and metabolic dysfunction, further supporting ovulatory regularity; ovulation induction: in cases where infertility is the primary concern, pharmacological agents such as letrozole or clomifene citrate are administered to facilitate follicular development and ovulation. Conventional pharmacological therapies for PCOS, including clomiphene citrate, spironolactone, and metformin, are frequently associated with a range of adverse effects and limitations, such as gastrointestinal disturbances, hormonal imbalances, and potential long-term risks, which may compromise patient safety and adherence.

Given the chronic nature of PCOS and the need for prolonged treatment, these limitations highlight the importance of exploring alternative strategies, particularly plant-based therapies with improved safety profiles and multitarget therapeutic potential [92]. In response to the potential side effects of long-term conventional pharmacotherapy, there is increasing clinical interest in complementary approaches [93–95]. The use of herbal medicines for the prevention and treatment of various diseases worldwide represents an important component of complementary medicine. Moreover, regarding reproductive issues, a phytotherapeutic approach utilizes medicinal plants and their bioactive compounds to support hormonal balance, reduce inflammation, and improve circulation in the pelvic region. Plants with phytoestrogenic, antiandrogenic, anti-inflammatory, and antioxidant properties are particularly valuable in the management of enhancing female fertility [96,97]. Nevertheless, phytotherapy should be applied as a complementary therapeutic strategy under medical supervision. Phytoestrogens are generally not recommended for women with hormone-dependent tumors, and particular attention should be paid to potential drug–herb interactions, especially with hormonal contraceptives and anticoagulants. Recent evidence suggests beneficial effects of various medicinal plants in the management of PCOS, largely

due to their multitarget activity and the broad spectrum of bioactive compounds they contain (Table 1). In particular, polyphenols have been shown to modulate oxidative stress and low-grade (“silent”) inflammation, which are recognized as key pathophysiological mechanisms underlying PCOS [98]. In addition to polyphenols, sulfur-containing bioactive compounds—predominantly found in species of the genus *Allium*—represent an emerging area of research that has not yet been extensively evaluated as a distinct therapeutic class. Indeed, species such as *Allium sativum* and *Allium cepa* have demonstrated considerable potential in addressing metabolic and hormonal disturbances associated with PCOS. These plants may contribute to the reduction in insulin resistance and hyperandrogenemia, improvement of lipid profiles and oxidative status, and exert anti-inflammatory as well as antimicrobial effects. Furthermore, some studies suggest a possible influence on ovulatory function and estrogenic activity [99,100], highlighting the relevance of such complementary approaches in managing both reproductive and metabolic aspects of PCOS. These effects are largely attributed to the specific chemical composition of *Allium* species and their multitarget mechanisms of action.

5. Overview and Discussion of Clinical and Preclinical Evidence on the Effects of *Allium* Species in PCOS-Related Outcomes

The following section presents the available evidence on the potential role of *Allium* species in PCOS through both a detailed textual analysis and a summarized tabular overview, highlighting the main outcomes reported in clinical and preclinical studies (Tables 3 and 4).

5.1. Evidence from Clinical Studies

5.1.1. Modulation of Glycemic Control and Insulin Resistance

Supplementation with garlic (*Allium sativum*) showed beneficial effects on glycemic parameters in women with PCOS. Zadhouh et al. [101] reported significant reductions in fasting plasma glucose and HOMA-IR, indicating improved glycemic control and insulin sensitivity. A decrease in fasting insulin levels was also observed, while non-significant trends toward improvements in insulin concentration, Free Androgen Index (FAI), and QUICKI suggested potential favorable effects on both metabolic and hormonal parameters that may become evident in studies with larger sample sizes or longer follow-up periods.

Similar results were confirmed in a randomized controlled clinical study by Hesari et al. [82], where the effectiveness of garlic (*Allium sativum*) supplementation on metabolic syndrome components in women with polycystic ovary syndrome was investigated. The study included women with PCOS who at the same time met the criteria for metabolic syndrome, thus examining a population with a marked cardiometabolic risk. After eight weeks of supplementation with a standardized preparation of garlic, significant improvements in metabolic parameters were recorded, primarily in the domain of glycemic control. In the intervention group, there was a significant decrease in fasting glucose, indicating improved insulin sensitivity. These findings are consistent with the known role of insulin resistance in the pathogenesis of PCOS and confirm the potential of garlic as a metabolic modulator in this population.

5.1.2. Effects on Hormonal Homeostasis and Androgen Excess

Garlic supplementation may also influence hormonal dysfunction in PCOS. Zadhouh et al. [101] reported limited changes in hormonal parameters, with no significant modulation of gonadotropins, progesterone, testosterone, or SHBG levels, while only modest improvements in androgen-related indices, including FAI, were observed. These findings suggest that the clinical benefits of garlic in PCOS are primarily mediated through

metabolic rather than direct endocrine effects. Nevertheless, further studies with larger sample sizes and longer follow-up periods are needed to clarify its impact on menstrual function, fertility, and reproductive outcomes.

Although hormonal parameters were not the primary outcome of the study by Hesari et al. [82], a significant increase in the concentration of SHBG was observed in the intervention group. An increase in SHBG may have beneficial endocrine implications, as it leads to a decrease in biologically available androgens, which is relevant in the context of the hyperandrogenism characteristic of PCOS. However, it is important to emphasize that direct changes in androgen or gonadotropin concentrations were not specifically evaluated in this study; therefore, no conclusions regarding the direct effects of garlic supplementation on these hormonal parameters can be drawn.

5.1.3. Impact on Lipid Metabolism and Cardiometabolic Risk Profile

In a randomized controlled study by Zadhoush et al. [102], garlic supplementation in women with PCOS led to significant improvements in lipid profile, including reductions in total cholesterol, LDL-cholesterol, and triglycerides. The mechanism can be explained by the inhibition of HMG-CoA reductase and the modulation of lipoprotein lipase activity by sulfur compounds of garlic. In addition, supplementation led to a reduction in systolic and diastolic blood pressure, indicating a potential improvement in nitric oxide bioavailability and endothelial function. These findings indicate a pronounced cardiometabolic benefit of garlic, which is of particular importance considering the increased risk of dyslipidemia and cardiovascular complications in the PCOS population. However, given that hormonal and reproductive parameters were not examined, direct endocrine effects of this intervention cannot be concluded based on this work.

In a study by Hesari et al., 2025 [82], garlic supplementation led to significant improvements in lipid profile, including reductions in total cholesterol, LDL-cholesterol, and triglycerides. These changes indicate a pronounced antidyslipidemic effect, which has particular clinical significance considering the increased prevalence of dyslipidemia and cardiovascular complications in women with PCOS. The study also showed a reduction in systolic and diastolic blood pressure, which further confirms the beneficial effect of garlic on vascular function and overall cardiometabolic risk. These antihypertensive effects may be related to the improvement of endothelial function, as well as to the antioxidant and anti-inflammatory properties of the bioactive sulfur compounds present in garlic. In the domain of inflammatory parameters, a significant decrease in the concentration of C-reactive protein was recorded, which indicates a reduction in systemic inflammation. Since chronic low-grade inflammation represents an important component of the pathophysiology of PCOS, this finding further supports the role of garlic as a potential immunometabolic modulator.

In a study by Ebrahimi-Mamaghani et al. [103], a high daily intake of raw red onion also had a positive, albeit milder, effect on the lipid profile. The study involved 54 subjects divided into a group with a high onion intake (40–60 g of raw red onion per day) and a group with a lower onion intake (10–15 g per day) over a period of 8 weeks. After this period, a significant decrease in total cholesterol was observed in both groups, with the effect being more pronounced in the group with high onion intake. A significant reduction in LDL cholesterol was also noted in both groups after treatment. These results are based on the unique profile of red onion, which is characterized by the abundant presence of quercetin, flavonoids, and organosulfur compounds, along with the presence of soluble fibers that affect the glycemic response. However, low standardization and greater dependence on individual tolerance and the influence of culinary processing significantly

modulate the results of red onion, and its effects can be considered to be less consistent compared to garlic supplementation.

5.1.4. Effects on Oxidative Stress and Antioxidant Defense Systems

Garlic supplementation improves antioxidant status in women with PCOS. In a clinical randomized, double-blind, placebo-controlled trial, Zadhoush et al. [104] analyzed the effect of garlic (*Allium sativum*) supplementation on markers of oxidative stress in 80 women with PCOS. The participants received 800 mg of garlic supplements or a placebo daily for 8 weeks, while strictly controlling the intake of other supplements and maintaining the usual diet and physical activity. Garlic supplementation led to a significant improvement in serum catalase concentration compared to the placebo group, indicating enhanced activity of endogenous antioxidant enzymes after treatment. A significant increase in glutathione levels, a key antioxidant that plays a role in neutralizing reactive oxygen species, was also noted. However, total antioxidant capacity and levels of MDA, a marker of lipid peroxidation, were not significantly different between the intervention and placebo groups. These findings indicate that garlic supplementation may specifically enhance the activity of certain antioxidant enzymes, but not necessarily increase total antioxidant reserve or reduce all markers of oxidative damage. In addition to the effects on antioxidant markers, garlic supplementation resulted in significant reductions in body weight, body mass index and waist circumference, indicating an improvement in anthropometric factors that are often elevated in women with PCOS. Conversely, changes in hip circumference and waist to hip ratio were not statistically significant.

The analyzed studies [82,101–104] unequivocally show that garlic supplementation acts on several interconnected pathophysiological processes in PCOS: it improves glycemic control and insulin resistance, modulates hormonal dysfunction, improves lipid profile and cardiometabolic parameters, and strengthens antioxidant status, reducing oxidative stress that is crucial for the development of PCOS complications. The effects were achieved with minimal adverse reactions, which highlights the good tolerability and potential application of garlic in an integrated approach to the treatment of PCOS. The effects were achieved with minimal adverse reactions, which confirms the safety and potential application of *Allium* species as adjuvant therapy. However, the limitations of the studies (short duration of the intervention, small samples and variability of natural foods) indicate the need for further research with a larger number of participants, longer follow-up and a wider range of clinical and reproductive parameters in order to accurately assess the long-term impact of supplementation.

5.2. Evidence from Experimental Models of PCOS

The results of the presented experimental and, partly, clinical research indicate that the bioactive components of plants from the genus *Allium* have a multi-layered effect on the key pathophysiological mechanisms of PCOS. Considering that PCOS is a multisystemic disorder, which includes oxidative stress, hormonal imbalance, insulin resistance, chronic inflammation, and ovarian dysfunction, the therapeutic potential of *Allium* species stems precisely from their ability to simultaneously act on multiple pathogenetic levels.

5.2.1. Antioxidant and Redox-Modulating Effects of *Allium* Species

Numerous studies emphasize the importance of *Allium* species in the modulation of oxidative stress in PCOS models [105–107].

The study by Falahatian and colleagues [105] also completes the data on the antioxidant protection of *Allium* species, which indirectly affects the improved hormonal status and reproductive profile of women with PCOS. A significant decrease in malondialdehyde (a marker of oxidative damage) and an increase in the level of glutathione (the main an-

tioxidant) in ovarian tissue were recorded. The researchers noted a statistically significant decrease in MDA levels. MDA is a by-product of lipid peroxidation (fat damage in cells under the influence of free radicals). High levels of MDA in PCOS directly damage egg quality, and the extract successfully suppressed this, which correlates with the results of other studies [106]. The study confirmed an increase in reduced glutathione levels. Since glutathione is the most important internal antioxidant in the body, its increase means that the ovaries have become more resistant to the oxidative stress caused by elevated androgens.

Moreover, the findings reported by Ghasemzadeh A et al. suggest that prolonged treatment with *Allium cepa* seed extract improves antioxidant status in experimental PCOS, as evidenced by elevated total antioxidant capacity after 60 days of administration [107].

5.2.2. Metabolic and Endocrine Regulation in Experimental PCOS Models

Metabolic and endocrine parameters are crucial in the pathogenesis of PCOS, as insulin resistance and dyslipidemia contribute to hyperandrogenism and follicular dysfunction [108,109]. Tedongmo and coworkers investigated the effect of leek (*Allium ampeloprasum* var. *Porrum*) aqueous extract supplementation in Wistar rats with letrozole-induced PCOS [108]. Supplementation led to significant reductions in fasting insulin, HOMA-IR index, total cholesterol, low density lipoprotein and triglycerides levels, as well as body mass and abdominal obesity. In addition to metabolic improvements, the improvement of reproductive parameters through the normalization of the estrous cycle and the histological structure of the ovary was also determined. The mechanism of action of leeks is related to the presence of phenols, flavonoids, terpenoids and anthocyanins, which act on insulin resistance and ovarian function. Through insight into the mechanism of action, as evidence obtained from an animal model, it was shown that *Allium ampeloprasum* can act simultaneously on insulin resistance, dyslipidemia and ovarian function. This highlights the multiple potential of *Allium* species in modulating the metabolic and reproductive aspects of PCOS.

In the study by Lee et al. [109], although metabolic parameters such as insulin and lipid profile were not the primary subjects of analysis, a letrozole-induced PCOS model led to an increase in body weight, which indirectly indicates the presence of metabolic disturbances characteristic of PCOS. Treatment with Welsh onion root extract (*Allium fistulosum*) resulted in a reduction in body weight compared to the PCOS group, which suggests a potential beneficial effect on metabolic homeostasis. Although the mechanisms of this effect have not been directly examined, the authors assume that the bioactive compounds present in *Allium fistulosum* can contribute to the improvement of the body's energy and hormonal balance. Other research on Welsh onion suggests its potential in improving insulin sensitivity through the activation of specific signaling pathways (e.g., AMPK), which is critical for PCOS. Activation of AMPK in the ovaries helps regulate steroidogenesis (hormone production). The findings of this study suggest that the ability of *Allium fistulosum* to enhance AMPK expression is possibly achieved through the inhibition of SGLT2 [110,111].

Table 3. Summary of clinical studies evaluating the effects of *Allium* species in PCOS.

A. spp./ Form/ Dosage	Study Type	Ref.	Aim of Study/ Purpose	Design/ Sample Size/ Duration	Major Findings/ Hormonal Profile	Major Findings/ Anthropometry	Major Findings/ Metabolic Function	Major Findings/ Others
<i>Allium sativum</i> ; Pills; 300 and 500 mg/day	Randomized, double-blind, placebo-controlled clinical trial	[101]	To investigate the effect of garlic supplementation on androgen levels and glycemic-related markers in patients with PCOS	80 women with PCOS Intervention: Garlic tablets 800 mg/day (two divided doses) Duration: 8 weeks	↔ in LH, FSH, testosterone, SHBG, or FAI between groups	↔ in BMI, weight, or waist-to-hip ratio	↓ FPG in the garlic group vs. placebo ↓ HOMA-IR in the garlic group ↓ QUICKI	/
<i>Allium sativum</i> ; Tablets; 800 mg/day	Randomized, double-blind, placebo-controlled	[102]	To evaluate whether garlic supplementation improves lipid parameters and blood pressure in women with PCOS	80 women with PCOS Intervention: Garlic supplement (total 800 mg/day) vs. placebo Duration: 8 weeks	/	/	↓ TC and LDL-C in the garlic group vs. placebo ↔ HDL-C or TG compared with placebo	↓ Systolic BP in the garlic group compared with baseline; between-group difference was not statistically significant ↔ Diastolic BP
<i>Allium sativum</i> ; Tablets; 1000 mg/day	Randomized, double-blind, placebo-controlled	[82]	To evaluate whether garlic supplementation can improve MetS components in women with PCOS who also meet criteria for MetS.	97 women with PCOS and MetS Intervention: Garlic tablets (500 mg, containing 2–3 mg allicin) twice daily (≈1 g/day total) vs. placebo Duration: 8 weeks	↑ SHBG in the garlic group improved QoL & sexual function	↓ body weight, BMI, and waist circumference	↓ fasting blood glucose ↓ TC, LDL-C, and TG; HDL-C slightly increased, but not significantly	↓ in systolic and diastolic BP ↓ CRP
<i>Allium cepa</i> ; raw red onion; High-onion group (100–150 g/day) vs. low-onion (30–40 g/day)	Randomized controlled clinical trial	[103]	To assess whether daily consumption of raw red onion improves metabolic features (lipids, glucose metabolism, anthropometry) in overweight or obese women with PCOS	54 overweight/obese women with PCOS Intervention: High-onion group: 100–150 g/day raw red onion (dose adjusted by BMI) Low-onion group: 30–40 g/day raw red onion Duration: 8 weeks	Slight, non-significant ↑ difference in the occurrence of menstruation in the high-onion group	↔ in weight, BMI, or waist circumference	↓ TC and LDL in the high-onion group ↔ in TG or HDL ↔ in FBG	/

Table 3. Cont.

A. spp./ Form/ Dosage	Study Type	Ref.	Aim of Study/ Purpose	Design/ Sample Size/ Duration	Major Findings/ Hormonal Profile	Major Findings/ Anthropometry	Major Findings/ Metabolic Function	Major Findings/ Others
<i>Allium sativum</i> ; Pills; 800 mg/day	Randomized, double-blind, placebo-controlled clinical trial	[104]	To evaluate the therapeutic effects of garlic (<i>Allium sativum</i>) supplementation on oxidative stress markers and anthropometric indices in women with PCOS	Randomized (<i>n</i> = 80): Intervention (<i>n</i> = 40)—800 mg/day garlic pills Placebo (<i>n</i> = 40) 8 weeks	/	↓ weight ↓ BMI ↓ waist circumference ↔ hip circumference ↔ waist to hip circumference ratio	/	↑ CAT ↑ GSH ↔ TAC ↔ MDA
↓—Decrease; ↑—Increase; ↔—No difference; FPG—fasting plasma glucose; HOMA-IR—homeostatic model assessment for insulin resistance; FAI—free androgen index; QUICKI—quantitative insulin sensitivity check index; SHBG—sex hormone-binding globulin; TC—total cholesterol; PCOS—polycystic ovary syndrome; FSH—follicle-stimulating hormone; LH—luteinizing hormone; MDA—malondialdehyde; SOD—superoxide dismutase; BMI—body mass index; LDL—low-density lipoprotein; HDL—high-density lipoprotein; BP—blood pressure; MetS—metabolic syndrome; QoL—quality of life; FBG—fasting blood glucose; GSH—glutathione; CAT—catalase; TAC—total antioxidant capacity; TG—triglyceride.								

Table 4. Summary of preclinical studies evaluating the effects of *Allium* species in PCOS.

A. spp./ Form/ Dosage	Study Type	Ref.	Aim of Study/ Purpose	Design/ Sample Size/ Duration	Major Findings/ Hormonal Profile and Ovarian Morphology Characteristics	Major Findings/ Anthropometry and Metabolic Function	Major Findings/ Others
<i>Allium ampeloprasum</i> ; Aqueous extract; 192, 384, and 768 mg/kg	Animal experimental study	[108]	To provide scientific evidence of the efficacy of <i>Allium ampeloprasum</i> against female infertility, the effect of the aqueous extract of the said plant (AE) were evaluated in rats with letrozole-induced PCOS	66 female Wistar rats with PCOS induced by letrozole (1 mg/kg orally for 21 days) Treatment: After PCOS induction, rats received aqueous extract (AE) of <i>Allium ampeloprasum</i> var. <i>Porrum</i> (leek) by oral gavage Doses tested: 192, 384, and 768 mg/kg/day for 15 days Comparison/Control groups: Normal control (no PCOS induction); PCOS control (letrozole, no treatment); Positive drug control: clomiphene citrate (1 mg/kg) + metformin (200 mg/kg)	↓ LH ↓ testosterone ↑ number of Graafian follicles and corpora lutea ↓ cystic and atretic follicles restored the estrous cycle; induced uterine epithelial cell hypertrophy	↓ body weight, abdominal fat weight ↓ TC ↓ LDL cholesterol ↓ atherogenic indices ↑ HDL cholesterol	↓ oxidative stress

Table 4. Cont.

A. spp./ Form/ Dosage	Study Type	Ref.	Aim of Study/ Purpose	Design/ Sample Size/ Duration	Major Findings/ Hormonal Profile and Ovarian Morphology Characteristics	Major Findings/ Anthropometry and Metabolic Function	Major Findings/ Others
<i>Allium fistulosum</i> ; Aqueous extract; 500 mg/kg/day	Animal experimental study	[109]	To test whether Welsh onion root extract (from <i>Allium fistulosum</i>) can reverse or ameliorate ovarian dysfunction and hormonal imbalance in a rat model of PCOS induced by letrozole	Female rats were induced with PCOS by letrozole <i>n</i> : total = 27, groups: I control (<i>n</i> = 6), II temporary letrozole removal (<i>n</i> = 5), III letrozole only (PCOS) (<i>n</i> = 6), IV letrozole + AF extract (500 mg/kg/day) (<i>n</i> = 10) 2 weeks	↓ LH (toward normal) ↓ LH/FSH ratio ↑ Estrogen (restored) ↓ Testosterone (partial) ↓ Number of cystic follicles ↑ Graafian follicles & corpora lutea Improved granulosa cell layers Estrous cycle normalization	↔ in body weight ↔ in glucose, triglycerides	↑ <i>Cyp19a1</i> (aromatase) expression ↑ Aromatase protein localization in ovary Normalized <i>Lhr</i> , <i>Pgr</i> , <i>Esr1</i> expression
<i>Allium Sativum</i> ; Aqueous extract, Amicon ultrafiltration system + SDS electrophoresis—R10 fraction; Intraperitoneal injection 20 mg/kg	Animal experimental study	[105]	To evaluate the potential immune-modulatory effects of R10 fraction of garlic in a mouse model of PCOS	Model: NMRI female mice; PCOS induced by a single intramuscular injection of estradiol valerate (40 mg/kg); <i>n</i> = 60 mice divided into 5 groups (normal, PCOS, sham, R10 Treat1, R10 Treat2; <i>n</i> = 12 each)	treatment with R10 fraction both groups: ↓ estradiol, testosterone progesterone R10 Treat 2 group: ↑ number of corpus luteum R10 Treat 2 group: ↓ number of cysts	/	↓ IFN-γ & IL-17, slight ↑ IL-4—R10 Treat1 ↓ IFN-γ & IL-17 significantly, ↑ IL-4 robustly—R10 Treat2 ↑ Gpx3 (near-normal), ↑ Ptx3—R10 Treat2 ↓ MDA; ↑ GSH
<i>Allium cepa</i> seeds ethanol extract oral administration; 0.3 cc/rat/day in sesame oil	Animal experimental study	[107]	To investigate the apoptotic and antioxidant effects of <i>Allium cepa</i> seed ethanolic extract in estradiol valerate-induced experimental PCOS in rats	Female Wistar rats (<i>n</i> = 60). Control groups (saline, extract alone, sesame oil) and experimental PCOS groups induced with single IM injection of estradiol valerate (4 mg/rat). One PCOS group additionally received <i>Allium cepa</i> extract supplementation. Treatment duration: 60 consecutive days	↑ Hyperemia, ovarian cyst number, and granulosa cell apoptosis in PCOS rats and reduced after <i>Allium cepa</i> treatment ↓ Large antral follicles in PCOS groups	/	↑ TAC in extract-treated groups compared with untreated PCOS rats. The extract compensated antioxidant depletion associated with PCOS Oxidative stress markers improved compared with untreated PCOS rats

Table 4. Cont.

A. spp./ Form/ Dosage	Study Type	Ref.	Aim of Study/ Purpose	Design/ Sample Size/ Duration	Major Findings/ Hormonal Profile and Ovarian Morphology Characteristics	Major Findings/ Anthropometry and Metabolic Function	Major Findings/ Others
<i>Allium fistulosum</i> ; Aqueous extract; 500 mg/kg/day	Animal experimental study	[109]	To test whether Welsh onion root extract (from <i>Allium fistulosum</i>) can reverse or ameliorate ovarian dysfunction and hormonal imbalance in a rat model of PCOS induced by letrozole	Female rats were induced with PCOS by letrozole <i>n</i> : total = 27, groups: I control (<i>n</i> = 6), II temporary letrozole removal (<i>n</i> = 5), III letrozole only (PCOS) (<i>n</i> = 6), IV letrozole + AF extract (500 mg/kg/day) (<i>n</i> = 10) 2 weeks	↓ LH (toward normal) ↓ LH/FSH ratio ↑ Estrogen (restored) ↓ Testosterone (partial) ↓ Number of cystic follicles ↑ Graafian follicles & corpora lutea Improved granulosa cell layers Estrous cycle normalization	↔ in body weight ↔ in glucose, triglycerides	↑ <i>Cyp19a1</i> (aromatase) expression ↑ Aromatase protein localization in ovary Normalized <i>Lhr</i> , <i>Pgr</i> , <i>Esr1</i> expression

↓—Decrease; ↑—Increase; ↔—No difference; FPG—fasting plasma glucose; HOMA-IR—homeostatic model assessment for insulin resistance; FAI—free androgen index; QUICKI—quantitative insulin sensitivity check index; SHBG—sex hormone-binding globulin; TC—total cholesterol; PP—pomegranate peel; GP—garlic powder; PCOS—polycystic ovary syndrome; FSH—follicle-stimulating hormone; LH—luteinizing hormone; GSH—glutathione; MDA—malondialdehyde; SOD—superoxide dismutase; PNW4—post-natal week 4; AMH—anti-Müllerian hormone; AST—aspartate aminotransferase; ALT—alanine aminotransferase; TG—triglyceride; LDL-c—Low-density lipoprotein cholesterol; VLDL-c—very-low-density lipoprotein cholesterol; HDL—high-density lipoprotein cholesterol; RBCs—erythrocyte cell counts; WBCs—white blood cells; DEX—dexamethasone; GSH—glutathione; CAT—catalase; IP—Intraperitoneal; Lhr—luteinizing hormone receptor; Pgr—progesterone receptor; Esr1—estrogen receptor 1; IL-17—Interleukin-17; IFN-γ—Interferon-gamma.

5.2.3. Effects on Reproductive Function, Ovarian Morphology and Histopathological Features

In the study by Lee et al. [109], administration of *Allium fistulosum* root extract in letrozole-induced PCOS rats resulted in significant improvements in hormonal, reproductive, and histological parameters, indicating partial restoration of ovarian function. Letrozole, an aromatase inhibitor, induces hyperandrogenism by blocking the conversion of testosterone to estrogen, whereas treatment with the extract reduced serum androgen and LH levels while increasing estradiol, likely through upregulation of aromatase expression (Cyp19a1) and restoration of estrogen feedback mechanisms. These hormonal changes were accompanied by normalization of the estrous cycle and an increase in ovulatory cycles, suggesting recovery of functional ovulation. Histological analysis further confirmed a reduction in cystic and atretic follicles, along with an increase in healthy follicles at different developmental stages and corpora lutea, providing direct evidence of improved ovarian structure and restored ovulatory activity.

A pronounced hormonal imbalance characteristic of PCOS, which was induced in mice, also occurred in the research of Falahatian and colleagues [105]. This 2022 study provides deeper insight into how *Allium* plants work on PCOS, focusing on immune response and fertility genetics. Application of the R10 fraction of garlic (*Allium sativum* L.), residual garlic (*Allium sativum*) extract fraction obtained by ultrafiltration using a 10 kDa membrane, led to a significant reduction in elevated levels of testosterone, estradiol and progesterone, helping to restore hormonal balance in PCOS models. There was also a decrease in the number of cystic follicles and an increase in the number of yellow bodies (corpus luteum), which is a direct indicator of improved ovulation. These results indicate that the R10 fraction acts as a regulator of ovarian endocrine function, potentially through an indirect effect on local inflammation and the immune microenvironment of the ovary.

Ghasemzadeh A et al. [107] reported that administration of *Allium cepa* seed extract for 60 days markedly reduced the number of cystic follicles in rats with estradiol valerate-induced PCOS. These findings indicate a beneficial effect of *Allium cepa* on ovarian morphology and suggest its potential role in alleviating follicular abnormalities associated with experimental PCOS. The beneficial effect of *Allium cepa* on ovarian histology has also been demonstrated in other studies investigating experimental PCOS models. These findings further support the potential protective and restorative role of *Allium cepa* in improving ovarian morphology and follicular development under PCOS conditions. Moreover, there is evidence that *Allium cepa* can alter the endocrine system, which supports physiological hormonal activity, apart of PCOS [112]. Furthermore, regarding follicular development, Mannani and Modaresi described the histological changes of the ovaries after the administration of red onion extract, confirming the preservation of follicular development and the slowing down of degenerative changes, with a dose-dependent stimulation of follicles [113]. Although the focus was on histology, the authors link these changes to a potential increase in LH and folliclestimulating hormone (FSH), which directly stimulate follicular growth. A study showed that red onion extract (especially at a dose of 400 mg/kg) led to an increase in ovarian weight. This is usually interpreted as a sign of increased follicular activity and tissue growth. Histological analysis confirmed a significant increase in the number of: primordial follicles, primary and secondary follicles, Graafian (mature) follicles. The results suggest that onion extract acts as a stimulator of oogenesis (egg cell formation). The authors attribute this to the high concentration of antioxidants such as quercetin and sulfur compounds, which protect ovarian germ cells from apoptosis (programmed cell death). It was noted that the effect of the strengthening effect showed dose dependence. The best results on ovarian tissue were observed at moderate concentrations, while extremely high doses did not necessarily achieve a proportionally greater benefit. This indicates the importance of a balanced intake of active substances. The results highlight the mechanistic

basis of red onion application in models of reproductive disorders such as PCOS. This is especially related to the preservation of follicular development and the reduction in degenerative changes in the ovaries.

Considering the potential use of *Allium cepa* extracts as supportive therapy in PCOS, it is particularly important to evaluate their safety in females of reproductive age, especially in the context of conception and pregnancy. Therefore, the assessment of possible transgenerational effects and the safety profile represents an important aspect of preclinical research on *Allium cepa* supplementation. In that context, Suri et al. provides key evidence of the long-term safety and efficacy of red onion (*Allium cepa*) extract on reproduction, following effects across two generations of rats, an extremely rare and important type of research for natural supplements. They investigated the effect of onion extract through two generations of rats, recording a significant improvement in fertility, number of fertilized eggs and offspring, regulation of reproductive hormones (LH, FSH, estradiol) and improvement in the histological structure of the ovaries [114]. The most important result is that the diet enriched with red onion extract did not negatively affect the reproductive abilities of the parental generation (F0) or their offspring (F1). The offspring developed normally, reached sexual maturity and successfully reproduced on their own (F2 generation). Rats given onion extract had increased levels of FSH and LH compared to the control group, indicating more active ovarian stimulation. Elevated levels of estrogen and progesterone were also recorded, which is directly related to healthier menstrual cycles and preparation of the uterus for pregnancy. The extract significantly increased the weight of the ovaries, fallopian tubes and uterus, which is in line with the findings of the study by Mannani and coworkers and indicates an increased metabolic and reproductive activity of the organs. This is a key study for application in human nutrition. The authors conclude that onion extract does not cause any toxicity or adverse effects on the reproductive system or general health of animals even with long-term, daily consumption. These results complement previous research by Falahatian et al., highlighting the multifaceted potential of *Allium* species in preserving functional ovarian tissue and histological follicle integrity. Taken together, current findings suggest that *Allium cepa* may represent a valuable adjunctive strategy in PCOS management due to its favorable effects on ovarian morphology, oxidative balance, and reproductive function.

5.2.4. Immunomodulatory and Anti-Inflammatory Mechanisms in PCOS

The mentioned effects of *Allium fistulosum* extract (significant decrease in serum concentration of androgens and LH, and increase in estradiol levels) related to an improved hormonal profile can be described in more detail through the modulation of the immune system and the expression of certain genes [109]. The stimulation of aromatase production was achieved thanks to the ability of Welsh onions to increase the expression of the Cyp19a1 gene. In this study, researchers used the RT-qPCR method to precisely measure mRNA levels in ovarian tissue. The results showed that the root extract of the Welsh onion (*Allium fistulosum*) directly affects the increase in the expression of kit ligand and bone morphogenetic proteins. Also, the impact on hormone receptors and their restoration after the application of the extract was demonstrated: estrogen receptor 1 and progesterone receptor. The study emphasizes that the increase in expression of aromatase gene is actually the “trigger” for all other changes. When aromatase levels increase, androstenedione is converted to estradiol, which starts a chain reaction that activates kit ligand and bone morphogenetic proteins and receptors, leading to successful ovulation. These findings confirm that chives do not only act superficially on hormones, but carry out reprogramming at the gene level in ovarian tissue.

Allium species also show the ability to modulate the immune response and reduce inflammation, which is crucial for PCOS. Falahatian and coworkers demonstrated that the R10 fraction of garlic redirects the T cell response towards an anti-inflammatory phenotype, increasing IL-4 and decreasing IL-17 and IFN- γ , which reduces cysts and supports the ovulation process [105]. PCOS is now considered a chronic inflammatory condition. This study found that fraction R10 (specific extract) balanced the ratio of Th1/Th2 and Th17/Treg cells. The R10 fraction acted by increasing IL-4 (anti-inflammatory Th2 response) and decreasing IFN- γ and IL-17 (pro-inflammatory Th1 and Th17 responses). A significant increase in the expression of Gpx3 and Ptx3 genes, which are usually downregulated in PCOS, was observed, indicating an improvement in reproductive potential. These effects fit the concept of chronic inflammation in ovarian granulosa and theca cells, where inflammation can cause ovulatory dysfunction and reproductive deficits [115]. On the other hand, PCOS is known as a risk factor for tumor development [116], anti-inflammatory and immunomodulatory effects may have an additional role in the prevention of tumor progression [47,61]. Limitations of the study include the animal model and the specificity of using the isolated R10 fraction. In commercial supplements or raw garlic, the concentration of this specific fraction varies. Without precise pharmaceutical standardization, the results cannot be directly transferred to the consumption of ordinary garlic or available preparations on the market. The study does not provide answers about the long-term safety of a high dose of the R10 fraction, nor about whether the symptoms and hormonal imbalance would return after stopping the intake (the so-called rebound effect). Although the study looked deeply into immunity and hormones, the metabolic aspects of PCOS (such as insulin resistance, glucose levels and lipid profile) were not the primary focus. Given that insulin resistance is a key driver of PCOS in most women, the lack of these data limits understanding of the full therapeutic potential of the R10 fraction. Also, the researchers focused on the genes Gpx3 and Ptx3. Although they are important, fertility and follicle development are controlled by hundreds of genes. The study did not use broader methods like RNA sequencing to get a broader picture of the effect on the ovarian genome. Another important limiting factor relates to the use of a fixed dose of 50 mg/kg. The lack of a dose–response analysis (where lower and higher doses would be tested) makes it difficult to determine the lowest effective or toxic dose, which is necessary for future clinical research. Nevertheless, the results suggest that bioactive fractions of *Allium sativum* may have multifaceted therapeutic potential, including hormonal regulation, modulation of the inflammatory response, and support for genetic regulation of reproductive function in PCOS.

On a molecular level (Figure 6), the biological effects of *Allium*-derived organosulfur compounds can be explained through their interaction with key intracellular signaling pathways involved in oxidative stress, inflammation, and metabolic regulation. A central mechanism is the activation of the nuclear factor erythroid 2–related factor 2 (Nrf2) pathway, which regulates the expression of antioxidant response element (ARE)-dependent genes. Activation of Nrf2 leads to upregulation of endogenous antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), thereby enhancing cellular defense against reactive oxygen species (ROS) and reducing oxidative stress, which is a major contributor to PCOS pathophysiology.

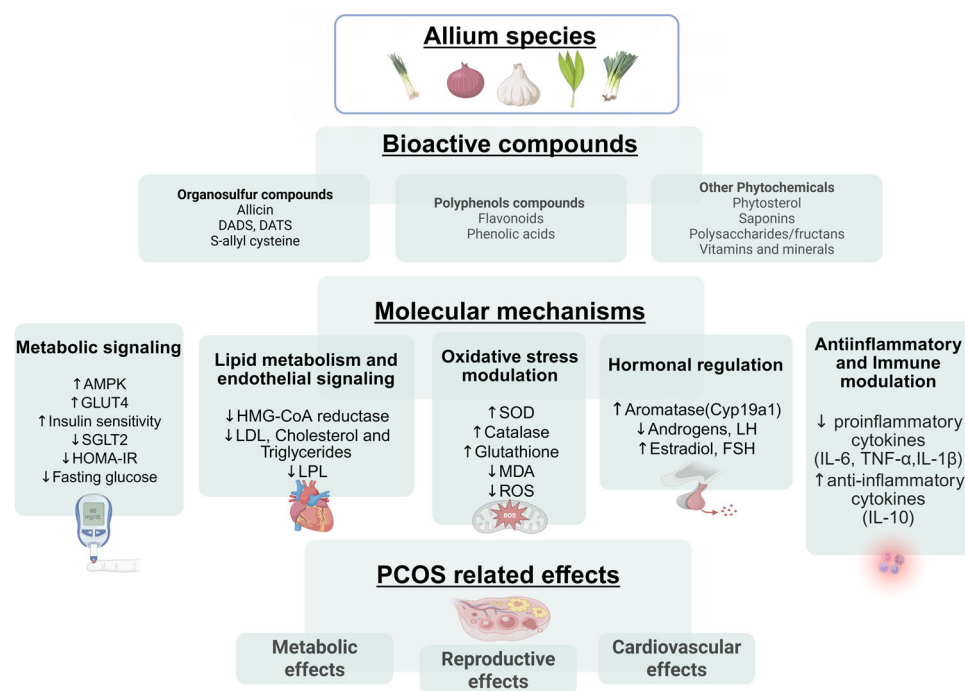


Figure 6. Translational relevance of bioactive compounds derived from *Allium* species in PCOS management regarding reproductive, metabolic and cardiovascular features. ↓—Decrease; ↑—Increase; DADS—diallyl disulfide, DATS—diallyl trisulfide; AMPK—adenosine monophosphate activated protein kinase; GLUT4—glucose transporter type 4; SGLT—sodium-glucose co-transporter; HOMA-IR—homeostatic model assessment for insulin resistance; HMG-CoA—hydroxymethylglutaryl coenzyme A; LDL—low density lipoprotein; LPL—lipoprotein lipase; SOD—superoxide dismutase; MDA—malondialdehyde; ROS—reactive oxygen species; FSH—follicle-stimulating hormone; LH—luteinizing hormone; IL-6—Interleukin-6; IL-10—Interleukin-10; IL-1 β —Interleukin-1 β ; TNF- α —Tumor necrosis factor alpha; PCOS—polycystic ovary syndrome.

In parallel, *Allium* bioactive compounds have been shown to suppress pro-inflammatory signaling, primarily through inhibition of the nuclear factor kappa B (NF- κ B) pathway. This results in decreased expression of pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6, as well as reduced activity of inflammatory mediators including cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS). Beyond their antioxidant and anti-inflammatory effects, emerging evidence suggests that these compounds may also modulate insulin signaling pathways. In particular, activation of the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) pathway contributes to improved glucose uptake and insulin sensitivity, which are frequently impaired in PCOS.

Additionally, organosulfur compounds may influence stress-related signaling cascades, such as mitogen-activated protein kinase (MAPK) pathways (e.g., JNK, p38, and ERK), leading to attenuation of cellular stress responses and inflammation. Modulation of ovarian steroidogenesis represents another important mechanism, where these compounds may affect the activity of key steroidogenic enzymes, including cytochrome P450 enzymes such as CYP17A1 and aromatase (CYP19A1), thereby contributing to the regulation of androgen synthesis and hormonal balance in PCOS. Collectively, these interconnected molecular mechanisms support the multitarget therapeutic potential of *Allium* species in the management of PCOS.

5.3. Translational Relevance of *Allium* Species in PCOS Management

The translational relevance of *Allium* species in the management of PCOS lies in their ability to simultaneously target multiple key pathophysiological mechanisms underlying

the disorder. Evidence from experimental and clinical studies indicates that bioactive compounds derived from *Allium* species, including organosulfur compounds and polyphenols, exert pleiotropic effects on insulin resistance, oxidative stress, chronic low-grade inflammation, and hormonal imbalance, all of which are central features of PCOS. This multitarget mode of action is particularly relevant given the heterogeneous and multisystem nature of the syndrome.

From a clinical perspective, *Allium*-based interventions may represent a valuable adjunct to lifestyle modification and conventional pharmacotherapy, especially in patients with predominant metabolic phenotypes of PCOS. Improvements in glycemic control, lipid metabolism, antioxidant status, and inflammatory markers observed in clinical and pre-clinical studies suggest potential benefits in reducing cardiometabolic risk and improving overall metabolic health. Moreover, emerging experimental evidence indicates that certain *Allium* constituents may influence androgen signaling pathways and ovarian morphology, highlighting their possible role in addressing reproductive dysfunction.

Importantly, the long history of dietary use of *Allium* species, together with their favorable safety profile and widespread availability, supports their feasibility for long-term use as functional foods or phytotherapeutic agents. However, despite promising preclinical findings, the translation of these effects into routine clinical practice remains limited by the scarcity of well-designed, large-scale randomized controlled trials in women with PCOS. Standardization of extracts, identification of optimal doses, and clarification of bioavailability and pharmacokinetics are essential steps toward clinical implementation.

Overall, *Allium* species represent a promising translational bridge between nutritional interventions and targeted phytotherapy in PCOS management. Future research integrating mechanistic insights with robust clinical evidence is warranted to define their precise role within personalized and multidisciplinary treatment strategies for PCOS.

5.4. Toxicity and Safety Profile

While *Allium* species are recognized as generally safe for dietary use and have a long history of medicinal value, excessive consumption can occasionally lead to systemic effects. Beyond mild gastrointestinal discomfort, high intake may result in symptoms such as dizziness, tachycardia, or orthostatic hypotension [117].

From a clinical perspective, the safety profile and tolerability of *Allium*-derived preparations should be considered particularly relevant for women with PCOS, who frequently require long-term pharmacological and lifestyle-based management. In humans, the most commonly reported adverse effects of *Allium* preparations, especially garlic-derived products, include gastrointestinal discomfort, bloating, nausea, heartburn, and characteristic breath or body odor, which may negatively affect patient adherence during prolonged use. Since metformin and combined oral contraceptives are among the most commonly used pharmacological approaches in PCOS management, potential herb–drug interactions with these therapies should also be considered. Although direct clinical evidence regarding herb–drug interactions involving *Allium ursinum* is scarce, caution is warranted when considering its concomitant use with therapies commonly prescribed in PCOS. In relation to metformin, clinically relevant CYP-mediated pharmacokinetic interactions are unlikely, since metformin is not significantly metabolized and is primarily eliminated unchanged through renal excretion involving organic cation and multidrug and toxin extrusion transporters. However, a pharmacodynamic interaction cannot be excluded, as garlic supplementation has been reported to exert additive glucose- and lipid-lowering effects when combined with metformin in patients with type 2 diabetes, suggesting a potential enhancement of metabolic effects rather than a classical metabolic drug interaction [118,119]. Regarding combined oral contraceptives, no direct clinical evidence currently demonstrates that *Allium*-derived

preparations reduce contraceptive efficacy. Nevertheless, because ethinyl estradiol and several progestins are partly metabolized through CYP3A-dependent pathways, and because garlic preparations have shown variable effects on CYP3A4 and P-glycoprotein activity, including reduced exposure to selected CYP3A4/P-glycoprotein substrates, a theoretical interaction cannot be completely excluded, particularly with concentrated supplements or high-dose extracts [120–122]. Therefore, future clinical studies evaluating *A. ursinum* preparations, especially in women with PCOS receiving metformin and/or oral contraceptives, should carefully document gastrointestinal tolerability, odor-related acceptability, adherence, concomitant medication use, and potential pharmacodynamic and pharmacokinetic interactions.

Overall, available preclinical and clinical evidence indicates that species of the genus *Allium* are generally safe for use and may exert beneficial effects on both metabolic and reproductive parameters in women with PCOS. Accordingly, when administered within defined and clinically relevant dosage ranges (Table 3), these plants can be considered safe; however, their use should be regarded as complementary and implemented under appropriate medical supervision.

6. Limitations and Future Implications

Most of these studies have been performed in animal models, which limits direct translation to the human population. Specific bioactive fractions, such as R10 garlic, vary in concentration in natural supplements and cannot be directly compared to standard consumption of *Allium* species. In addition, metabolic, hormonal, or immunological effects have not been fully evaluated in some studies, and the lack of dose–response analysis makes it difficult to determine the optimal therapeutic dose. Nevertheless, the synthesis of all studies shows the multifaceted action of *Allium* species—antioxidant, metabolic-endocrine, reproductive-histological, and immunomodulatory-anti-inflammatory—which makes them a promising adjuvant therapy in PCOS. Future human clinical research should focus on standardization of doses, duration of interventions, combination with other antioxidant agents, and monitoring of transgenerational effects.

7. Conclusions

PCOS requires a holistic and individualized therapeutic approach that, in addition to conventional therapy, includes modification of lifestyle and diet. Bioactive components of plants from the genus *Allium* represent a promising addition in the modulation of hormonal imbalance, insulin resistance and oxidative stress in PCOS. Clinical studies in women with PCOS show that garlic supplementation contributes to the improvement of lipid profile, glycemic control and hormonal status, while simultaneously reducing oxidative stress and strengthening antioxidant defenses. Findings from animal models additionally confirm these effects, indicating improvement of reproductive and metabolic parameters, hormonal regulation, antioxidant and immunomodulatory action. Collectively, these results confirm the multifaceted mechanism of action of *Allium* species in modulating key pathophysiological aspects of PCOS. Although there are methodological limitations, including the short duration of the interventions, the small number of participants, and the heterogeneity of the *Allium* species and doses used, the available data consistently point to their therapeutic potential in PCOS. A comprehensive review of studies suggests that *Allium* species may represent a useful adjunct to standard therapy, contributing to the improvement of metabolic, hormonal and reproductive parameters, with the need for further, more extensive and standardized clinical research.

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Abbreviations

The following abbreviations are used in this manuscript:

PCOS	Polycystic ovary syndrome
DAS	Diallyl sulfide
DADS	Diallyl disulfide
DATS	Diallyl tri-sulfide
SAC	S-allyl cysteine
ROS	Reactive oxygen species
SOD	Superoxide dismutase
GSH-Px	Glutathione peroxidase
MDA	Malondialdehyde
SHBG	Sex hormone-binding globulin
DTS	Diallyl tetrasulfide
FPG	Fasting plasma glucose
FAI	Free androgen index
CAT	Catalase
LH	Luteinizing hormone
FSH	Follicle-stimulating hormone
SAR	Structure-activity relationship

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