

Review Article

Phenolic Compounds in Plants: Sources, Biosynthesis, and Medical Applications

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Article History

Received: 28.07.2026

Accepted: 22.09.2026

Published: 24.09.2026

Journal homepage:

<https://www.easpublisher.com>

Quick Response Code



Abstract: Phenolic compounds are one of the most structurally diverse and biologically important groups of plant secondary metabolites with over 10,000 structures identified so far. Such aromatic compounds are a common feature of all plants and play an important role in plant defense, pigmentation, UV-radiation screening and inter-specific communication. Over the past 20 years, researchers have thoroughly investigated their remarkable health benefits. This comprehensive review of the literature combines 47 peer-reviewed papers published between 2010 and 2027 that cover classification, sources, biosynthesis and therapeutic uses of phenolic compounds. The review categorizes phenolics into their major structural classes phenolic acids (hydroxybenzoic and hydroxycinnamic acids), flavonoids (flavones, flavanol's, flavanones, flavanols, isoflavones, anthocyanins), tannins, stilbenes, lignans, and coumarins and traces their biosynthetic origin through the shikimate and phenylpropanoid pathways. This cites important fruits and vegetables. Highlighted will be certain classed medicinal herbs, trees, and agro-industrial residue. The entire documented medical functions will be considered. The main categories will be, but not restricted to, antioxidants, and/or anti-inflammatory, and/or antimicrobial, and/or anticancer, and/or cardioprotective, and/or neuroprotective, and/or antidiabetic, and/or other medicinal properties. It will describe the molecular mechanisms and include and/or the responsible signaling pathways. Benchmark compounds, quercetin, curcumin, resveratrol, kaempferol, and/or epigallocatechin gallate (EGCG) will be studied. The challenges and future research of bioavailability will be shown.

Keywords: Phenolic Compounds, Polyphenols, Flavonoids, Plant Secondary Metabolites, Antioxidants and Anti-Inflammatories Anticancer and Medicinal Plants, Biosynthesis, and Bioavailability.

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1. INTRODUCTION

Plants have taken millennia to adapt and develop secondary metabolites. While these chemicals are not necessary for primary growth, they aid plants in surviving and thriving in their ecosystems. Many, if not most, of these secondary metabolites are phytochemicals and are classified by their numbers and variety of their structures. They can be found in three major groups in the plant kingdom: terpenoids, alkaloids, and phenolic compounds. Existing in the greatest numbers and in extensive structural diversity, phenolic compounds are estimated to be greater than 10,000 in number [1, 2]. Phenolic compounds are characterized by the presence of at least one aromatic ring with one or more -OH (hydroxyl) groups. The structural diversity of phenolic compounds spans from simple single-ringed molecules,

such as gallic acid, to highly polymerized structures, such as condensed tannins [3].

A surge of interest in plant phenolic compounds began in the 1990s, following the discovery of the link between the regular consumption of fruits and vegetables, especially with a high tannin (phenolic) content, and the reduced incidence of chronic diseases, such as hyperlipidemia, type 2 diabetes, and other degenerative diseases including some cancers [4, 5]. Many ascribe some of the health benefits of the Mediterranean diet to the large consumption of phenolic-rich foods such as olive oil, wine, legumes, and vegetables. The multifaceted, multi-target therapeutic potential of phenolic compounds of plants incited several mechanistic studies. [6].

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The plant-derived phenolics market is developing quickly in several areas: pharmacology, nutraceuticals, functional foods, cosmetics, and agriculture. Phenolic compounds influence several molecular targets like transcription factors (NF- κ B, Nrf-2), inflammatory enzymes (COX-2, LOX), apoptotic enzymes (Bax, caspase-3), and antioxidant enzymes (SOD, CAT, GPx) which have made such compounds good candidates in drug development and in preventive nutrition.

The aim of this literature review is to construct a critical, coherent and comprehensive summary of plant phenolic compounds, to describe their morphological, structural and categorical plant sources, their biosynthetic pathways, and to review as many documented therapeutic uses as possible. Phenolic compounds will be analyzed and compared, with a focus on the most researched clinically effective compounds like quercetin, curcumin, resveratrol, egcg, and kaempferol. This review will also highlight the gaps and shortcomings in the research (including bioavailability) and future research recommendations.

2. Classification of Phenolic Compounds

Phenolics are classified based on the number of phenolic rings and other structural elements that link the phenolic rings together [8]. The key classes are outlined below and summarised in Table 1.

2.1 Simple Phenolic Acids

Phenolic acids are an important and well-defined category of phenolic compounds existing in the plant kingdom [9]. Fundamentally, these compounds are phenolic compounds that are characterized by a carboxylic acid group, and can be categorized into two general groups:

- **Hydroxybenzoic acids (C6-C1 skeleton):** Some examples are gallic acid, syringic acid, protocatechuic acid, p-hydroxybenzoic acid, vanillic acid, gentisic acid, and salicylic acid. These acids are usually bound to some smaller organic acids, glycosyl units, or cellular structural components [10].
- **Hydroxycinnamic acids (C6-C3 skeleton):** This group contains, Caffeic acid, p-coumaric acid, ferulic acid and sinapic acid. These acids are often esterified with Quinic acid (for example, Chlorogenic acid) or glucose and are widely distributed in cereal grains, coffee and a number of fruits [9, 10].

2.2 Flavonoids

- Flavonoids constitute the most extensive and heterogeneous category of phenolic compounds, characterized by a C6-C3-C6 backbone comprising two aromatic rings (designated A and B) linked via a three-carbon

bridge that forms a heterocyclic structure (C) [11]. This group is further categorized into six principal subclasses:

- Flavones (e.g., luteolin, apigenin) found in parsley, thyme, and chamomile
- Flavonols (e.g., quercetin, kaempferol, myricetin) the most abundant flavonoids; found in onions, kale, apples
- Flavanones (e.g., naringenin, hesperidin) characteristic of citrus fruits
- Flavanols / Catechins (e.g., catechin, epicatechin, EGCG) abundant in green tea, cocoa, and grapes
- Isoflavones (e.g., genistein, daidzein) found primarily in legumes and soybeans
- Anthocyanins (e.g., cyanidin, delphinidin) responsible for red, blue, and purple pigmentation in berries and flowers

2.3 Tannins

Tannins comprise high-molecular weight polyphenols with protein-precipitating abilities. The two major types of tannins are hydrolyzable tannins and condensed tannins. Gallotannins and ellagitannins are examples of hydrolyzable tannins and can be released through hydrolysis as gallic or ellagic acids. Proanthocyanidins are classified as condensed tannins as these are composed of a polymerization of flavan-3-ols. Significant sources of tannins are found in black tea as well as of oak bark, pomegranate, and grape seeds [12].

2.4 Stilbenes

Stilbenes are a class of polyketides and are classified as phytoalexins that possess antifungal and/or antibacterial property and are synthesized in response to various plant stresses. One of the well-known stilbenes is resveratrol (3,5,4'-trihydroxy-trans-stilbene), which is found in grape skins, berries, and peanuts. Other stilbenes include pterostilbene, piceatannol, and gnetol [13, 14].

2.5 Lignans

Lignans are dimeric molecules synthesized from two phenylpropanoid units that are covalently linked at the beta carbon of their respective side chains. Exemplary lignans encompass pinoresinol, secoisolariciresinol, and enterolactone. These compounds are prevalent in sources such as flaxseeds, sesame seeds, and whole grains, and are distinguished by their phytoestrogenic characteristics [11].

2.6 Coumarins and Other Phenolics

Coumarins are a subclass of benzopyranones that are known for their antifungal, anti-inflammatory, and anticoagulant properties. Coumarins, along with xanthenes, and quinones, are Structurally Unique Phenolic Classes with large pharmacological potential (for example curcumin, a curcuminoid from *Curcuma longa*) [6].

Table 1: The classification of the primary classes' phenolic compounds along with their structure and representative samples

Class	Skeleton	Sub-classes	Examples	Key Plant Sources
Phenolic Acids	C6-C1 / C6-C3	Hydroxybenzoic, Hydroxycinnamic	Gallic, caffeic, ferulic, chlorogenic	Coffee, wheat, green tea, berries
Flavonoids	C6-C3-C6	Flavones, Flavonols, Catechins, Anthocyanins, Flavanones, Isoflavones	Quercetin, EGCG, Cyanidin, Luteolin, Genistein	Onions, green tea, berries, citrus, soybean
Tannins	Polymeric	Hydrolyzable, Condensed	Galloylglucose, Proanthocyanidin	Oak bark, pomegranate, grape seeds, tea
Stilbenes	C6-C2-C6	Trans-stilbenes, Pterostilbenes	Resveratrol, Pterostilbene, Piceatannol	Grape, peanut, blueberry, mulberry
Lignans	C6-C3-C3-C6	Furofuranoid, Arylnaphthalene	Pinoresinol, Secoisolariciresinol, Enterolactone	Flaxseed, sesame, rye, broccoli
Coumarins / Coumarinoids	C6-C3-lactone	Benzopyranones, Diarylheptanoids	Umbelliferone, Curcumin, Bisdemethoxycurcumin	Celery, carrot, Curcuma longa (turmeric)

Source: Compiled from Sun *et al.* (2023) [6], Tsimogiannis *et al.* (2019) [8], and da Silva *et al.* (2023) [9].

3. Plant Sources of Phenolic Compounds

Phenolic compounds are present in all plants, but identity, quantity and structural diversity can be traced back to the needs of the particular plant species, organ, stage of differentiation and growing conditions [3-15]. The main sources of phenolic compounds are presented in Table 2.

3.1 Fruits

Fruits are rich sources of phenolic compounds. Berries such as blueberries, raspberries, strawberries, blackcurrants and cranberries display extremely high concentrations of anthocyanins, ellagitannins and flavonols [16]. Blackberries and black raspberries are particularly noted for their high levels of cyanidin-3-glucoside and ellagic acid. Grapes (*Vitis vinifera*) are a complex phenolic network that includes over 183 compounds identified in the vegetation parts, including stilbenes, flavonols, flavan-3-ols and anthocyanins [5]. Flavanones (hesperidin and naringenin) and hydroxycinnamic acids are the main phenolic compounds found in citrus fruits. Pomegranate, apple, and cherry are well known for their ellagitannins and quercetin glycosides, respectively [16, 17].

3.2 Vegetables and Leafy Plants

Dietary quercetin is found in the highest amount in *Allium cepa* and predominantly as glycosides. Phenolics of Brassica vegetables (kale, broccoli) are derived from kaempferol, quercetin and glucosinolates. Tomato phenolics are derived from chlorogenic and caffeic acids. Caffeic acid derivatives and cynarin are found in artichokes. Apigenin and luteolin are abundant in parsley (*Petroselinum crispum*), while spinach contributes significantly to the flavone glycosides [6-11].

3.3 Medicinal Herbs and Spices

Turmeric (*Curcuma longa*) provides 2–5% of the dried rhizome in curcuminoids, where curcumin is the main one. Green tea (*Camellia sinensis*) is the primary source of catechins, including EGCG. Rosemary

(*Rosmarinus officinalis*) and sage (*Salvia officinalis*) contain large amounts of rosmarinic acid and carnosic acid. Ginger (*Zingiber officinale*) contributes more gingerol and shogaol. También, medicinal Chinese plants give relatively high concentrations of flavonoids and phenolic acids, that have demonstrated significant levels of bioactivity, including *Scutellaria baicalensis* Rhizoma, *Rheum officinale*, and *Sophora japonica* [18].

3.4 Cereals, Legumes, and Seeds

Whole grains like wheat, rye, oats, and maize, are rich in phenolic acids, especially in ferulic acid, which bind mostly to the cell wall polysaccharides. Flaxseeds are the richest source of the lignan, secoisolariciresinol diglucoside (SDG), among the food sources. Among the legumes, soybeans are exceptional, due to the presence of isoflavones like, genistein and daidzein, which are the most popular phytoestrogens with potential cardioprotective role. Proanthocyanidins, especially the oligomeric procyanidins are abundant in grape seeds. Cocoa and chocolate are also rich in flavan-3-ol content [4-11].

3.5 Trees and Woody Plants

Scots pine (*Pinus sylvestris*) and Norway spruce (*Picea abies*) hold high concentrations of stilbenes (pinosylvin and resveratrol), flavonoids (taxifolin, quercetin, and kaempferol), and phenolic acids in their bark, wood, and needle constituents. These products of the forest are largely unused resources of bioactive phenolics. The leaves and wood of the olive tree (*Olea europaea*) contain compounds such as hydroxytyrosol, phenolic tyrosol, and oleuropein, which are cardinal components in the cardioprotective aspects of the Mediterranean diet [19, 20].

3.6 Agricultural By-products

Recent research focuses on valorizing food processing waste for their phenolic content. Waste generated after processing grapes, olives, fruit peels, and seed hulls is rich in phenolics, yet most is discarded. The

phenolic profile of these residual plant materials is typically characterized by plant part. For instance, luteolin is found in greater concentrations in leaves and

stalks, hydroxycinnamic acids are concentrated in peels and husks, and seeds contain tannins and stilbenes [15-21].

Table 2: Major plant sources of phenolic compounds with predominant compounds and documented biological activities

Plant / Source	Major phenolic Compounds	Plant part	Documented Activities
Green tea (<i>Camellia sinensis</i>)	EGCG, Catechin, Epicatechin	Leaves	Antioxidant, anticancer, anti-inflammatory, antidiabetic
Turmeric (<i>Curcuma longa</i>)	Curcumin, Bisdemethoxycurcumin	Rhizome	Anti-inflammatory, anticancer, antimicrobial, antidiabetic
Grapes (<i>Vitis vinifera</i>)	Resveratrol, Quercetin, Anthocyanins, OPCs	Skin, Seeds, Leaves	Cardioprotective, anticancer, antioxidant
Onion (<i>Allium cepa</i>)	Quercetin, Isorhamnetin	Bulb, outer skin	Antioxidant, anti-inflammatory, antimicrobial
Blueberry (<i>Vaccinium spp.</i>)	Anthocyanins, Chlorogenic acid	Fruit	Antioxidant, neuroprotective, anti-aging
Pomegranate (<i>Punica granatum</i>)	Ellagic acid, Punicalagin, Anthocyanins	Peel, Seeds, Fruit	Anticancer, antimicrobial, anti-inflammatory
Olive (<i>Olea europaea</i>)	Hydroxytyrosol, Oleuropein, Tyrosol	Fruit, Leaves, Oil	Cardioprotective, anti-inflammatory, antioxidant
Flaxseed (<i>Linum usitatissimum</i>)	Secoisolariciresinol, Matairesinol	Seeds	Phytoestrogenic, antioxidant, anticancer
Citrus spp.	Hesperidin, Naringenin, Diosmetin	Peel, Fruit	Antimicrobial, anticancer, anti-inflammatory
Soybean (<i>Glycine max</i>)	Genistein, Daidzein, Formononetin	Seeds	Phytoestrogenic, cardioprotective, antidiabetic
Scots pine (<i>Pinus sylvestris</i>)	Pinosylvlin, Taxifolin, Kaempferol	Bark, Wood, Needles	Antimicrobial, antioxidant, anti-inflammatory
Rosemary (<i>Rosmarinus officinalis</i>)	Rosmarinic acid, Carnosic acid	Leaves	Antioxidant, antimicrobial, neuroprotective
Cocoa / Chocolate	Epicatechin, Procyanidin B2	Seeds	Cardioprotective, antioxidant, antidiabetic
Wheat / Rye / Oats	Ferulic acid, p-Coumaric acid	Bran, Germ	Antioxidant, anticancer, anti-inflammatory

Sources: Goufo *et al.*, (2020) [5], Sun *et al.*, (2023) [6], Golovinskaia & Wang (2021) [16], Metsämuuronen & Sipponen (2019) [19].

4. Biosynthesis of Phenolic Compounds

The biosynthetic processes underlying the formation of phenolic compounds in flora occur via two primary interrelated pathways: the shikimate pathway and the phenylpropanoid pathway. Comprehending these metabolic routes is essential for both the manipulation of phenolic content in plants through selective breeding and genetic engineering, as well as for elucidating the abiotic factors that influence the accumulation of phenolics [22, 23].

4.1 The Shikimate Pathway

The presence of the shikimate pathway in plants, fungi and bacteria but not in animals, makes the pathway and its enzymes desirable drug targets. The pathway commences with the condensation of phosphoenolpyruvate (PEP) which derived from glycolysis, and erythrose-4-phosphate (which is generated from the pentose phosphate pathway). The condensation product is 3-deoxy-D-arabino-heptulosonic acid 7-phosphate (DAHP). DAHP

undergoes a total of seven steps to be converted to the branch-point metabolite chorismate [23].

Once the shikimate pathway is complete, the subsequent pathway that leads to either phenylalanine, tyrosine and/or tryptophan. Through the phenylalanine pathway, phenylalanine is converted to the phenylpropanoid metabolism. The first step of this deamination pathway is catalyzed by the enzyme Phenylalanine Ammonia-Lyase (PAL) where L-phenylalanine is converted to trans-cinnamic acid [22].

4.2 The Phenylpropanoid Pathway

The overarching phenylpropanoid metabolic pathway generates a variety of C6-C3 (hydroxycinnamic acid) intermediates that function as precursors for all principal classes of phenolic compounds. Significant enzymatic steps encompass:

PAL: L-Phenylalanine → trans-Cinnamic acid (this step is rate-limiting and is profoundly upregulated in response to stress)

C4H (Cinnamate 4-hydroxylase): Cinnamic acid → **p-Coumaric acid** **4CL (4-Coumaroyl-CoA ligase):** p-Coumaric acid → **p-Coumaroyl-CoA** (serving as a central node for metabolic branching)

From p-Coumaroyl-CoA, several divergent pathways emerge leading to the predominant classes of phenolic compounds. The flavonoid biosynthetic pathway commences with chalcone synthase (CHS), the initiating enzyme responsible for the production of naringenin chalcone, which acts as the universal precursor for flavonoids. The synthesis of stilbenes diverges at this juncture through the action of stilbene synthase (STS), which competes with CHS for the same substrate molecules. Lignin biosynthesis proceeds from monolignols (p-coumaryl, coniferyl, and sinapyl alcohols) produced by progressive hydroxylation and methylation of the phenylpropanoid backbone [22-24].

4.3 Regulation of Phenolic Biosynthesis

Phenolic biosynthesis is under complex transcriptional regulation by MYB, bHLH (basic helix-loop-helix), and WD40 transcription factor complexes that govern tissue-specific and stress-responsive expression of pathway genes [15]. Abiotic stresses UV-B radiation, drought, temperature extremes, heavy metals, and salinity strongly upregulate phenylpropanoid metabolism through activation of PAL and downstream enzymes. This results in enhanced accumulation of flavonoids, anthocyanins, and other phenolics that serve protective roles including ROS scavenging, UV screening, and osmotic adjustment [25].

Biotic stresses (pathogen attack, herbivory) trigger jasmonate and salicylate signaling, which also induce phenolic biosynthesis. Phytoalexins such as resveratrol in grapes and pinosylvin in pines exemplify this defense response [19-25].

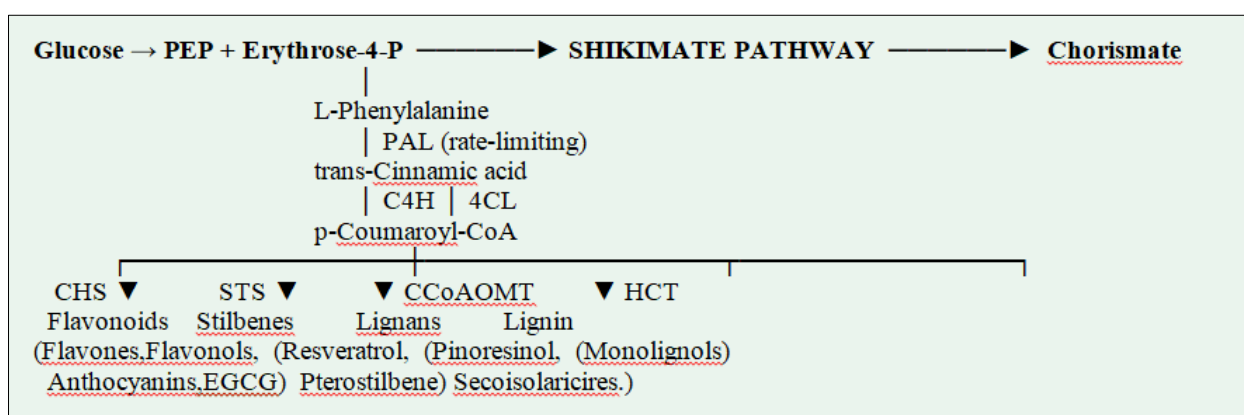


Figure 1: Simplified schematic of the shikimate and phenylpropanoid pathways leading to major phenolic compound classes

Abbreviations: PEP = phosphoenolpyruvate; PAL = phenylalanine ammonia-lyase; C4H = cinnamate 4-hydroxylase; 4CL = 4-coumaroyl-CoA ligase; CHS = chalcone synthase; STS = stilbene synthase; CCoAOMT = caffeoyl-CoA O-methyltransferase; HCT = hydroxycinnamoyl transferase.

5. Medical and Therapeutic Applications

The therapeutic potential of plant phenolic compounds has been the subject of thousands of peer-reviewed studies. Their actions span multiple disease

categories through diverse mechanisms, often targeting the same molecular pathways simultaneously a property known as pleiotropy. Table 3 provides a summary of major therapeutic categories and key compounds.

Table 3: Summary of therapeutic applications of plant phenolic compounds with documented activities and mechanisms

Therapeutic Category	Key phenolic Compounds	Molecular Targets/ Mechanisms	Key References
Antioxidant	Quercetin, EGCG, Resveratrol, Curcumin, Hydroxytyrosol	ROS scavenging, Nrf-2 activation, SOD/CAT/GPx upregulation, NADPH oxidase inhibition	Li <i>et al.</i> , (2014), Xia <i>et al.</i> , (2017), Zagorskina <i>et al.</i> , (2023)
Anti-inflammatory	Curcumin, Resveratrol, Luteolin, Quercetin, Oleuropein	NF-κB inhibition, COX-2/LOX suppression, pro-inflammatory cytokine reduction (TNF-α, IL-6)	Rahman <i>et al.</i> , (2021), Bucciantini <i>et al.</i> , (2021)
Antimicrobial	Quercetin, Kaempferol, Catechin, Gallic acid	Cell membrane disruption, biofilm inhibition, virulence factor targeting, antibiotic synergism	Górniak <i>et al.</i> , (2018), Zhang <i>et al.</i> , (2011)

Anticancer	Curcumin, Quercetin, Resveratrol, EGCG, Kaempferol	Apoptosis induction (Bax/Bcl-2, caspases), cell cycle arrest, PI3K/Akt/mTOR inhibition, anti-angiogenesis	Giordano <i>et al.</i> , (2019), Patel <i>et al.</i> , (2020), Salehi <i>et al.</i> , (2018)
Cardioprotective	Resveratrol, Quercetin, Anthocyanins, Hydroxytyrosol, Grape OPCs	ACE inhibition, platelet aggregation inhibition, lipid profile improvement, endothelial function	Rasines-Perea <i>et al.</i> , (2017), Xia <i>et al.</i> , (2017)
Neuroprotective	Resveratrol, EGCG, Curcumin, Rutin	AChE inhibition, A β aggregation reduction, SIRT1 activation, neuroinflammation suppression	Malaguarnera (2019), Shahidi & Ambigaipalan (2018)
Antidiabetic	Chlorogenic acid, Quercetin, Berberine, Resveratrol	α -amylase/ α -glucosidase inhibition, insulin sensitization, AMPK activation, gut microbiome modulation	Lin <i>et al.</i> , (2016), Martiniaková <i>et al.</i> , (2025)

5.1 Antioxidant Activity

The antioxidant capacity of phenolic compounds is their most widely studied property and forms the mechanistic foundation for many of their biological activities. There are many ways that phenolic compounds can act as antioxidants. For example, they can directly interact with ROS and RNS species. They can also inhibit certain types of pro-oxidant enzymes. They can also increase levels of the body's own endogenous antioxidants that are normally upregulated via the Nrf-2/ARE signaling pathway. Also, they can intercept certain transition metal ions in order to stop the catalization of ROS [4-26].

It is apparent that Li *et al.*, (2014) show evidence of a high resistance to oxidative damage and free radical scavenger availability in the presence of polyphenols in plants through the inhibition of the enzymes that create ROS. Resveratrol, in particular, is known to inhibit the production of ROS via NADPH oxidase and inhibit the production of a superoxide species at the mitochondria. It is also known to inhibit eNOS and thereby promote its coupling through the stimulation of GTP cyclohydrolase I [27].

5.2 Anti-inflammatory Activity

Most chronic, non-communicable diseases, like cardiovascular disease, type 2 diabetes, neurodegenerative diseases, and cancers, share a common factor: chronic inflammation. Phenolic compounds from plants have anti-inflammatory properties through several synergistic mechanisms. The most notable include inhibition of the NF- κ B transcription factor and the COX-2 and 5-LOX enzymes. COX-2 and 5-LOX enzymes catalyze the synthesis of leukotrienes and prostaglandins [7].

Phenolic compounds have the potential to inhibit COX and other inflammatory mediators, perhaps, through the inhibition of the NF- κ B, and the activation of the Nrf-2 transcription factor, which modulates the antioxidant response. Of the naturally occurring COX-2 inhibitory compounds, curcumin is perhaps the most powerful. Of the naturally occurring compounds in the luteolin and quercetin, up to 80% results in the inhibition

of IL-6 and TNF- α production in mpMacs [18]. The polyphenols of the olive fruit have been shown to inhibit NF- κ B and the production of prostaglandin E2 and other inflammatory mediators, and they co-do not have the side effects of other NSAIDs [20].

5.3 Antimicrobial Activity

Plant phenolics have potential as natural antimicrobials, and their significance is greatly amplified in today's world, where antibiotics have lost their effectiveness due to resistance. The in vitro examination of the microbial inhibitory activity of flavonoids revealed a broad inhibitory activity toward pathogenic microorganisms, with the mechanisms of cell membrane, nucleic acid, and energy metabolism disruption, as well as disruption of the biofilm [28].

An all-inclusive review of the antimicrobial effects of flavonoids by Górniak *et al.*, (2018), noted that flavonoids are synthesized by the plants they inhabit when their microbial antagonists attack, and these particular flavonoids not only preferentially target bacterial cells and inhibit their virulence factors, but also reverse antibiotic resistance, making them good candidates for the development of drugs against multi-drug resistant microorganisms. With regards to phenolic acids, both gallic acid and caffeic acid inhibited Gram positive, Gram negative bacteria, as well as Candida and Aspergillus (fungi) [29].

Zhang *et al.*, (2011) found that several traditional Chinese medicine plants, including *Scutellaria baicalensis*, *Taxillus chinensis*, and *Sophora japonica*, showed inhibitory activity of NO and TNF- α production and demonstrated a strong anti-inflammatory activity with a strong activity and inactivation of both NO and TNF- α production occurring in macrophages. This activity can be strongly correlated with both the total flavonoids and total phenolics present.

5.4 Anticancer Activity

One of the most thoroughly studied fields of phytochemistry is the anticancer efficacy of the phenolic compounds. These compounds are known to act on all the stages of carcinogenesis. They can prevent the

initiation stage of carcinogenesis by preventing DNA damages; the promotion stage of carcinogenesis by suppressing the proliferation of cells; and the progression stage of carcinogenesis by inhibiting invasion, metastasis, and angiogenesis [30, 31].

Among the natural anticancer agents, the most powerful and highly active agents are the curcumin compounds. Giordano & Darzynkiewicz (2019) described the many aspects of anticancer activity of curcumin compounds by their ability to modulate the activity of a number of growth factors, enzymes, transcription factors, and kinases, both inflammatory and proapoptotic and antiapoptotic cytokines. It is known to upregulate and increase the activity of Bax and decrease that of Bcl-2, thereby activating all three caspases, namely, 3, 8 and 9; and in addition to all these activities, curcumin can also inhibit NF- κ B, and the canonical signaling pathways of both STAT3 and Wnt/ β -catenin. Clinical studies have seen curcumin tested at up to 12 g/day and seen as completely safe in these trials, and of longstanding anticancer activity of curcumin, the poor bioavailability still remains its greatest drawback [32, 33].

To have effects on all three stages of carcinogenesis, Resveratrol was shown to inhibit the initiation, promotion, and progression phases of carcinogenesis; she has effects on breast, colon, prostate, lung, liver, and pancreatic cancers. It is known to act through inhibition of PI3K/Akt combined with the synthesis of tumor suppressor SIRT1 and modulation of suppressor p53 [13-34]. Apoptosis is also induced by kaempferol and quercetin which are shown to induce G2/M cell cycle arrest in various types of cancers. Quercetin is also known to have the ability to inhibit the angiogenesis and invasiveness of the tumors specifically by acting on the extracellular matrix MMPs and activity of the green tea EGCG [31-35].

5.5 Cardioprotective Effects

Worldwide, cardiovascular disease (CVD) is the numeral one fatal disease, and there is an abundance of evidence of the that many dietary phenolics help prevent CVD. The ways in which these dietary phenolics prevent CVD is vast. They include, improvement of endothelial function, anti-thrombotic effects, and an alteration of these lipids that would create a more healthy lipids profile, as well as the reduction of LDL oxidation and hypertensive effects through ACE inhibition [7-36].

James *et al.*, (2023) state that well-balanced dietary patterns that include various phenolics and polyphenolics from grapes, have been found to have protective properties from CVD and to be beneficial in the prevention of CVD (677). Rasines-Perea & Teissedre (2017) even report that grape polyphenols and a grape polyphenol-rich diet, not only help to lower the risk and incidence of hypertension, but also help increase the overall health of the vascular system, stating specifically

that the two principal cardiovascular protective phenolics, as well as polyphenolics, would be anthocyanins and resveratrol. Resveratrol oxidation's antioxidant effects to the cardiovascular system have been linked to the Nrf-2 and the SIRT1, the inhibition of the NADPH oxidase and the prevention of the eNOS uncoupling [27]. Hydroxytyrosol and olive polyphenols also have been proven to lower the prevalence of and the severity of cardiovascular risk factors during the live population-centered clinical trials of the PREDIMED research [20].

5.6 Neuroprotective Effects

"Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis represent a class of diseases with neuroinflammation, oxidative stress, and neuronal loss caused by apoptosis. Phenolic compounds can target all three pathological components [7-37].

Neuroprotection of Resveratrol has been shown through the following mechanisms. Resveratrol has an impact on the SIRT1-mediated deacetylation mechanism of p53 and NF- κ B, and also has the ability to slow the aggregation process of amyloid- β (A β), suppress neuroinflammation by microglia, and activate autophagic activity, which also has the ability to remove highly toxic protein aggregates [34]. Some research has shown that Curcumin can prevent the formation of A β and remove them from the brain, and also has the ability to inhibit tau phosphorylation. EGCG has been shown to affect the activity of the β -secretase (one of the critical enzymes in the formation of A β), as well as chelate metals such as Fe²⁺, Cu²⁺ which are more neurotoxic than others and are also involved in the process of oxidative neurodegeneration. Similarly, Quercetin has the ability to inhibit acetylcholinesterase (AChE), which is the target enzyme that also works with drug treatment in Alzheimer's involving donepezil and rivastigmine [7], and also works mainly through the inhibition of microglia which are the brain's innate immune cells who are actively inflamed (neuroinflammation)."

5.7 Antidiabetic Activity

Diabetes mellitus type-2 is a long-term condition that is marked by chronic high blood glucose (hyperglycemia) levels and the slow loss of the insulin-secreting beta-cell function. Specific types of phenanthrenes remove the enzymes (α -amylase and α -glucosidase) that degrade carbohydrates. This helps lower the glycemia levels that increase after eating. Some of them positively alter insulin sensitivity, and enhance insulin production by the pancreas beta-cells. These types of compounds also reduce the inflammation and oxidative damage that causes beta-cells to lose their function [38, 39].

Lin *et al.*, (2016) presented a preliminary discussion of the role of phenolics from plants in the control of diabetes and reported that berries and some other fruits are good candidates for the management of

glycemia in the early phases of hyperglycemia due to their ability to inhibit glycosidase. Martiniaková *et al.*, (2025) analyzed how some polyphenols (like quercetin, kaempferol, and rutin) and also epicatechin, resveratrol, and chlorogenic acid) reduce hyperglycemia, increase insulin sensitivity, reduce the inflammation, scavenge

free radical oxidative species, and positively alter gut microflora in T2DM. Additionally, the combination of polyphenols and some of the traditional antidiabetic medications (like metformin and glipizide) also provides a promising approach for diabetes management [38].

Cancer	CVD	Diabetes	Neurodegeneration	Infection
PI3K/Akt/mTOR NF-κB Bcl-2/Bax Caspase-3/9 Wnt/β-catenin	ACE inhibition NADPH oxidase LDL oxidation Platelet aggreg. NO production	α-Amylase/Glucosidase AMPK activation Insulin sensitivity Glut-4 expression β-cell protection	AChE inhibition Aβ aggregation SIRT1 activation Tau phosphorylation Microglial activation	Cell membrane Biofilm formation DNA gyrase Virulence factors Antibiotic synergy

Figure 2: Overview of molecular targets of phenolic compounds in major disease categories

Sources: Compiled from Rahman *et al.*, (2021) [7], Giordano & Darzynkiewicz (2019) [32], Lin *et al.*, (2016) [38], Górniak *et al.*, (2018) [28].

6. Bioavailability and Challenges

Despite their remarkable in vitro and in vivo activities, a critical translational challenge for phenolic compounds is their limited bioavailability in the human body. Bioavailability is governed by multiple factors: aqueous solubility, stability in the gastrointestinal environment, intestinal absorption, first-pass hepatic metabolism, and systemic distribution [40].

Curcumin is a prime example: despite potent in vitro anticancer activity at micromolar concentrations, oral curcumin achieves very low plasma concentrations due to poor solubility, rapid intestinal degradation, and extensive conjugation in intestinal and hepatic cells. Clinical studies have confirmed that standard oral doses of 12 g/day of pure curcumin yield peak plasma concentrations of only 0.05–2 μM. Co-administration with piperine (from black pepper), which inhibits CYP450 and UGT conjugating enzymes, increases curcumin bioavailability by 2,000% [33].

For resveratrol, the fast processes of conjugation (glucuronidation and sulfation) restrict the

levels of free resveratrol in the plasma. Methods to improve bioavailability involve a variety of polymeric nanoparticles and lipid nanocarriers, liposomes, cyclodextrin inclusion complexes, and phospholipid complexes. Yıldırım *et al.*, (2023) provided a summary on studies showing that the bioavailability of polymeric nanoparticles flies higher than other free compounds when addressing cancer, when these nanoparticles are a carrier of phytochemicals [41].

The gut microbiome is important both positively and negatively to the bioavailability of phenolics. Several phenolics, and in particular the flavonoid glycosides and tannins, are usually poorly absorbed in the small intestine and end up in the colon, where the microbiota ferment these compounds to smaller, bioavailable molecules such as urolithins (derived from ellagitannins) and enterolactone (derived from some lignans). These microbial metabolites also may have some biological activity of significance. Additionally, phenolics may influence the composition of the gut microbiome, and in this case also represent the beneficial side of these two interactive processes [42].

Table 4: Challenges of bioavailability and their enhancement for some phenolic compounds

Compound	Class	Key challenges	Enhancement Strategies	References
Curcumin	Curcuminoid	Poor solubility, rapid conjugation, low plasma levels	Piperine co-administration, liposomes, nanoparticles	Patel <i>et al.</i> , (2020)
Resveratrol	Stilbene	Fast glucuronidation/sulfation, short half-life	Nano-encapsulation, methylated analogues (pterostilbene)	Navarro <i>et al.</i> , (2018)
Quercetin	Flavonol	Glycoside hydrolysis needed; efflux transporters	Glycoside form, nanoformulations, food matrix effects	Mutha <i>et al.</i> , (2021)
EGCG	Catechin	Oxidative degradation, low pH stability	Encapsulation, prodrug derivatives	Singh <i>et al.</i> , (2024)
Ellagic acid	Polyphenol	Low intestinal absorption; converted to urolithins	Consumed as tannins (punicalagin); rely on gut microbiome	Tischer <i>et al.</i> , (2023)

7. Research Gaps and Future Perspectives

7.1 Methodological Gaps

There are many thousands of *in vitro* studies reported in the literature that show the biological effects of phenolic compounds but very few of these studies result in any clinically relevant translation. In most studies, the uses of supraphysiological doses that are virtually impossible to replicate in humans using diet and/or supplementation. Protocols for standardized assays and bioavailability data, and more rigorously designed randomized controlled clinical trials are needed [6, 7].

7.2 Population and Context Gaps

The preponderance of clinical studies has focused on Western populations, and the impacts of various genetic polymorphisms that affect metabolism (including CYP1A2 and UGT1A1) and gut microbiota on phenolic efficacy have not been well-studied. Moreover, the potential of selective phenolics phenolic combinations of phenolics found in particular foods is still largely unexplored. Phenolics, still in its infancy, should focus on foodomics and metabolomics for developing appropriate methodologies to tackle the issue [3-15].

7.3 Conceptual Gaps

The exact molecular targets and dose-response characteristics for the majority of phenolics are still inadequate. The possible risks of taking such supplementation at high doses (e.g., pro-oxidant behavior, drug-phenolic interactions) are still not systematically studied and should be properly assessed. The interaction between phenolics and the gut microbiome, as well as the individual differences, is an emerging and very interesting research area. The use of metabolic engineering and synthetic biology for increasing phenolic production in plants and microbial systems is another area of interest [22-25].

7.4 Future Directions

- Development of novel nanocarrier and encapsulation systems to enhance bioavailability of poorly absorbed phenolics
- Large-scale multi-center clinical trials with standardized phenolic extracts for metabolic syndrome, cancer prevention, and neurodegeneration
- Microbiome-phenolic interactome studies across diverse populations using multi-omics approaches
- CRISPR-based and metabolic engineering approaches to enhance phenolic content in crop plants
- Structure-activity relationship (SAR) studies to design semi-synthetic phenolic derivatives with improved pharmacokinetics
- Investigation of phenolic compounds as adjuncts to conventional cancer chemotherapy to overcome resistance

8. CONCLUSION

Phenolic compounds derived from plants serve as a biologically active defense system that enhances human health. Phenolic compounds can be found in almost every type of plant. Besides their complex distribution, they are also of great significance in both nutrition and pharmacology, because of their wide range of biosingular characteristics. These characteristics include antioxidant, anti-inflammatory, anti infective, anti tumor, cardioprotective, neuroprotective and antidiabetic.

From the shikimate and phenylpropanoid biosynthetic pathways, their origins along the stress pathways and molecular mechanisms of their health promoting properties, we have enhanced our knowledge in the last 10 years. Hundreds of clinical trials have been conducted to study the effects of the benchmark compounds like EGCG, Resveratrol, Curcumin, and quercetin. This has demonstrated their health advantages and biological functions, however, all of them suffer the problem of bioavailability.

Advancement of this area of study relies on the combination of systems biology and clinical trial integration along with technology that can deliver and design. These will focus on bioanalytic approaches and will bridge the schism that is evident among both *in-vitro* and animal study evidence that remain untapped to realize the health benefits of these compounds for human beings.

The phenolic compound field thus sits at an exciting intersection of traditional phytomedicine, modern molecular pharmacology, and nutritional science with enormous potential to contribute to global health.

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Cite This Article: Salman, N. A., Mahdi, E. I., & Hamzah, S. S. (2026). Phenolic Compounds in Plants: Sources, Biosynthesis, and Medical Applications. *EAS J Pharm Pharmacol*, 8(5), 87-97. <https://doi.org/10.36349/easjpp.2026.v08i05.002>
