Review



# Recent Trends in Natural Antioxidants: A Decade of Progress in Phenols, Flavonoids and Artemisinin Research (2015–2025)

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# Recent Trends in Natural Antioxidants: A Decade of Progress in Phenols, Flavonoids and Artemisinin Research (2015–2025)

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**Abstract**

The past decade (2015–2025) has seen natural antioxidant research, particularly on artemisinin, phenolic acids, and flavonoids, progress from simple free radical scavenging assays to sophisticated molecular pathway studies, nanotechnology-based delivery, and early-stage clinical trials. These phytochemicals derived from plant genera of diverse origin show multifaceted biological activities such as redox regulation, anti-inflammatory, and chemopreventive effects through major regulatory pathways such as Nrf2/Keap1, NF-κB, and MAPKs. Artemisinin, besides its established antimalarial activity, also emerges as a potent oxidative stress modulator by covalent modification of KEAP1 cysteine residues, activation of NRF2, and induction of cytoprotective genes. Phenolic acids and flavonoids introduce supplementary antioxidant and therapeutic options with evidence for synergistic interactions. Whatever bioavailability and stability problems may exist aside, advances in plant biotechnology, metabolic engineering, and nanoformulations have enhanced yield, potency, and delivery. This review synopsizes a decade of biochemical, pharmacological, and translational advances, highlights gaps in clinical validation, and indicates avenues for the future involving omics technologies and AI-aided metabolic modeling to enable the rational design of next-generation antioxidant therapies.

**Keywords:** artemisinin; phenolic compounds; flavonoid; natural antioxidants; oxidative stress; free radical scavenging; nanoformulation; Nrf2 pathway; bioavailability; phytochemicals; herbal medicine; chronic diseases; therapeutic potential

## 1. Introduction

Oxidative stress, which results from an imbalance in the ratio between reactive oxygen species (ROS) and the body's antioxidant defense systems, plays a role in the etiopathogenesis of numerous chronic diseases including cancer, cardiovascular disease, neurodegeneration, and metabolic syndrome (Halliwell, 2024; Jomova *et al.*,2025). Natural antioxidants have attracted particular attention over the last decade, as less toxic, environmentally friendly alternatives to synthetic drugs (**Figure 1**). Phenolic acids, flavonoids and artemisinin are some of the compounds that have been highlighted due to their general biological activities and natural origin (Akbari *et al.*, 2022; Jomova *et al.*,2025; Chaudhary *et al.*, 2023; Nwozo *et al.*, 2023).

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**Figure 1.** Natural Antioxidant Arsenal: Key Bioactive Compounds from Diverse Sources.

Artemisinin, a sesquiterpene lactone derived from *Artemisia annua*, is widely recognized for its antimalarial activities, but more recent studies have revealed its modest antioxidant activity via modulation of redox-sensitive pathways of signaling (Addissouky, 2025; Morua *et al.*,2025; Pan *et al.*, 2025). Analogously, phenols (gallic acid, caffeic acid) and flavonoids (quercetin, kaempferol) are present in plenty in fruits, vegetables, and medicinal plants and have been found to effectively scavenge free radicals, boost cellular antioxidant systems, and regulate inflammatory and apoptotic pathways (Amarowicz and Pegg, 2019; De Lima Cherubim *et al.*, 2020; Hoang *et al.*, 2021; Moazzen *et al.*, 2022; Mutha *et al.*, 2021; Zufarov and Serkayev, 2024).

During 2015-2025, the science surrounding these phytochemicals changed from rudimentary descriptive antioxidant screening to highly advanced pharmacological profiling, molecular pathway evaluation, and clinical validation (Nam *et al.*, 2024). With the availability of new green extraction technologies, bioengineering strategies, and nano-delivery systems, clinical and therapeutic potential increased exponentially (Nair *et al.*,2025; Thanikachalam *et al.*, 2025).

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This review investigates the progress, and new emerging problems of the past decade in the studies related to artemisinin, phenols, and flavonoids as natural antioxidants, mode of action, therapeutic application, and potential towards modern medicine.

### *1.1. Oxidative Stress and Its Pathological Impact*

Oxidative stress occurs when there is a mismatch between the generation of reactive oxygen species (ROS) and the protective antioxidant defense of the body. ROS, such as free radicals in the forms of superoxide anions, hydroxyl radicals, and non-radical species in the form of hydrogen peroxide, are by-products of the metabolism of normal cells, especially in the mitochondria (Aguilar *et al.,* 2024). Although low to moderate levels of ROS are essential for cell signaling and immunity, its accumulation causes oxidative damage to DNA, proteins, and lipids. Such damage compromises cellular function and integrity and leads to the onset and progression of several chronic diseases, e.g., cancer, cardiovascular disease, neurodegenerative disease (e.g., Schizophrenia, Alzheimer's and Parkinson's disease), and diabetes. Mechanisms of oxidative stress are thus crucial in the pathogenesis of targeted interventions to prevent or reverse its pathologic effects (Halliwell, 2024; Ikawa *et al*., 2021; Jomova *et al.,*2025; Kishi *et al.,* 2024; Pooja *et al.,*2025).

### *1.2. Natural Antioxidants: A Safer Alternative*

The widespread use of synthetic antioxidants such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), and tert-butylhydroquinone (TBHQ) in the food and pharmaceutical industries has raised widespread concerns due to their carcinogenic and toxic effect when consumed in bulk amounts or over a long period (Atta *et al.,* 2017; Liu and Mabury, 2020). These safety issues, combined with increasing consumer awareness and a need for clean-label and eco-friendly additives, have forced a global shift towards natural antioxidants with plant origin (Akbarirad *et al.,* 2016; Lourenco *et al.,* 2019; Nwozo *et al.,* 2023). Herbal, fruit, and vegetable constituents such as polyphenols, flavonoids, and terpenoids, in addition to exhibiting high antioxidant activity, also possess other beneficial effects on health, including anti-inflammatory, anticancer, and cardioprotective effects. Plant antioxidants are therefore becoming safer, multifunctional alternatives to synthetic additives, which are appropriate to the growing market demand for natural health-benefiting nutraceutical and functional foods (Abeyrathne *et al.,* 2022; Hadidi *et al.,* 2022; Gavarić *et al.,* 2025)

### *1.3. Phenolic Compounds: Diversity and Function*

Phenolic compounds are a large group of plant secondary metabolites characterized by the presence of one or more hydroxyl groups directly bound to an aromatic benzene ring. Among them, phenolic acids constitute a predominant subclass and are divided further into hydroxybenzoic acids (e.g., gallic acid) and hydroxycinnamic acids (e.g., caffeic acid) according to their carbon skeleton (Rahman *et al*., 2021; Mohammad *et al*., 2023; Mohammad *et al*., 2023; Sun and Shahrajabian, 2023). These compounds are broadly distributed in nature and found ubiquitously in fruits (e.g., berries and grapes), vegetables, whole cereals, tea, coffee, and several medicinal herbs. Gallic acid has good radical-scavenging activity because of the trihydroxylated benzene ring, but caffeic acid is a free radical quencher and metal chelator and optimizes its antioxidant activity. Both acids are involved in reactive oxygen and nitrogen species (ROS and RNS) neutralization, inhibition of lipid peroxidation, and protection from cellular components such as DNA, proteins, and membranes. They also have the ability to modulate certain signal transduction pathways related to inflammation and oxidative stress, such as the activation of endogenous antioxidant enzymes. Structural diversity and multideterminant character of the phenolic acids highlight their natural antioxidant potential with the ability to cause health benefits (Shi *et al.,* 2022; Rudrapal *et al.,* 2024; Silva *et al.,* 2024).

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*1.4. Flavonoids: Multifunctional Antioxidants*

Flavonoids are a diverse class of polyphenolic compounds that share a generic 15-carbon backbone constructed from two aromatic rings (A and B) connected by a three-carbon bridge to yield a heterocyclic ring (C). It is a general structure that permits extensive subclassification into flavonols, flavones, flavanones, flavanols, isoflavones, and anthocyanidins with varying chemical properties and biological activities (Chen *et al.,* 2023b; Zhuang *et al.,* 2023). Found in abundance in fruits, vegetables, teas, and medicinal herbs, flavonoids are a part of the normal diet of man, with daily consumption levels of up to several hundred milligrams in high plant food-consuming populations (Agati *et al.,* 2024; Li *et al.,* 2025).

Their strong antioxidant property owes much to their ability to trap reactive oxygen species (ROS), sequester metal ions, and modulate antioxidant defense pathways such as the Nrf2 signaling cascade. In addition to oxidative stress reduction, flavonoids have anti-inflammatory, antitumor, antiviral, and cardioprotective activities, making them potential agents for preventing and treating a variety of chronic diseases associated with oxidative damage (Ding and Yu, 2025; Saikia *et al.,* 2025).

*1.5. Artemisinin: Beyond Antimalarial Properties*

Traditionally established to exhibit excellent antimalarial action, the plant sesquiterpene lactone artemisinin in *Artemisia annua* is being more and more valued for its potential as a natural antioxidant. Defined structurally by the occurrence of an atypical endoperoxide bridge, artemisinin chelates intracellular iron to produce free radicals, a process crucial to its antimalarial action. Ironically, artemisinin has recently been found to possess antioxidant and cytoprotective activities in non-parasitic systems (Addissouky, 2025; Lee *et al.,*2025; Sun *et al.,* 2025; Zhou *et al.,* 2025). It modulates oxidative stress by controlling cellular redox homeostasis, such as the upregulation of antioxidant enzymes like superoxide dismutase (SOD) and catalase (CAT), and suppressing lipid peroxidation markers such as malondialdehyde (MDA). In addition, artemisinin has also been found to modulate redox-sensitive signaling pathways, specifically the Nrf2/ARE pathway, inducing transcription of detoxification and antioxidant genes for SOD (Superoxide dismutase), CAT (Catalase), GSH-Px (Glutathione peroxidase), HO-1 (Heme oxygenase-1) and NQO1 (NAD(P)H Quinone Dehydrogenase) **(Figure 2)**. Via Nrf2/Keap1 signaling pathway activation (Gang *et al.,* 2025; Velumani *et al.,* 2025; Gavarić *et al.,* 2025).

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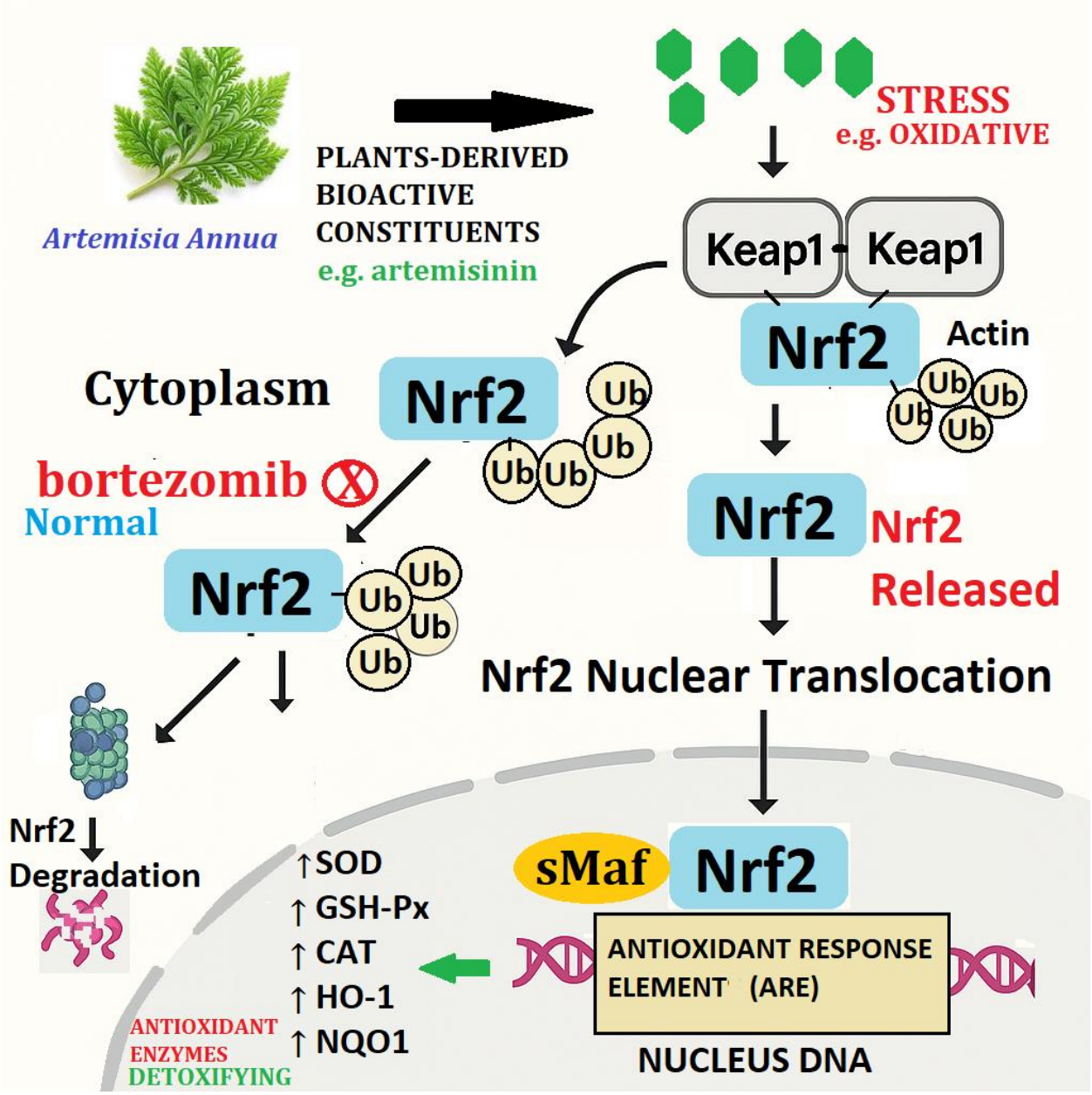


**Figure 2.** Schematic Artemisinin-Induced Nrf2/Keap1 Signaling Pathway Activation Enhances Antioxidant Gene Expression in Cells (Modified from Gang *et al.*, 2025).

Note: (TFs: Nrf2= Nuclear factor erythroid 2–related factor 2, Keap1=repressor, sMaf= Small musculoaponeurotic fibrosarcoma oncogene homolog), ubiquitination (Ub), ARE=Antioxidant response elements, SOD=Superoxide dismutase), CAT=Catalase, GSH-Px =Glutathione peroxidase, HO-1=Heme oxygenase-1, NQO1= NAD(P)H Quinone Dehydrogenase 1, bortezomib= anticancer drug

This review was specifically focused on elaborating the new trends, scientific

*1.6. Progress in Antioxidant Research (2015–2025)*

The past decade has witnessed significant advancement of antioxidant science driven by multidisciplinary breakthroughs in phytochemistry, molecular biology, nanotechnology, and clinical sciences (Babanyaya *et al.*, 2024; Parveen *et al.*, 2025).

Over the period of 2015-2025, scientists have become more and more interested in the isolation and identification of bioactive phytochemicals (Choudhary *et al*,, 2025) like flavonoids, phenolic acids, terpenoids, and artemisinin derivatives, and expanded their structure-activity relationships

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and biological properties. Molecularly, new reagents such as genomic, transcriptomic, and proteomic profiling have unraveled the mechanisms by which natural antioxidants regulate redox-sensitive signaling pathways such as Nrf2, NF-κB, and MAPK cascades (**Figure 3**). Concomitant progress in nanotechnology has enhanced delivery, stability, and bioavailability of sparingly soluble phytochemicals with nanoformulations such as liposomes, nanoparticles, and nanoemulsions (Khalil *et al.,* 2019; Vaiserman *et al.,* 2020; Lv *et al.,* 2024; Bilia *et al.,* 2020; Ali *et al.,* 2025). In addition, some natural antioxidants have moved from preclinical models to phase-I clinical trials with encouraging outcomes in the management of oxidative stress-associated diseases like cancer, neurodegenerative diseases, metabolic disorders, and inflammatory syndromes. Cumulatively, this decade-long upsurge has revolutionized antioxidant molecules from mere free radical scavengers to multi-targeted therapeutic molecules, opening the doors for evidence-based incorporation of phytochemicals into contemporary medicine (Pham *et al.,* 2020; Mittal *et al.,*2025; Choudhary *et al.,* 2025; Patel *et al.,* 2025; Sun *et al.,* 2025)

### *1.7. Purpose and Scope of the Review*

The review is aimed at the recent decade (2015–2025) of research work on natural antioxidants, i.e., artemisinin, phenolic acids, and flavonoids. The major purpose and scope are:

1. To provide an overview of the recent scientific progress in the antioxidant activity and therapeutics of these molecules through in vitro, in vivo, and clinical trial-based studies.
2. To investigate underlying mechanisms such as redox modulation, anti-inflammatory effects, and molecular signaling pathways.
3. In assessing clinical utility and potential future application, identifying challenges, areas of knowledge gaps, and scope for further research.

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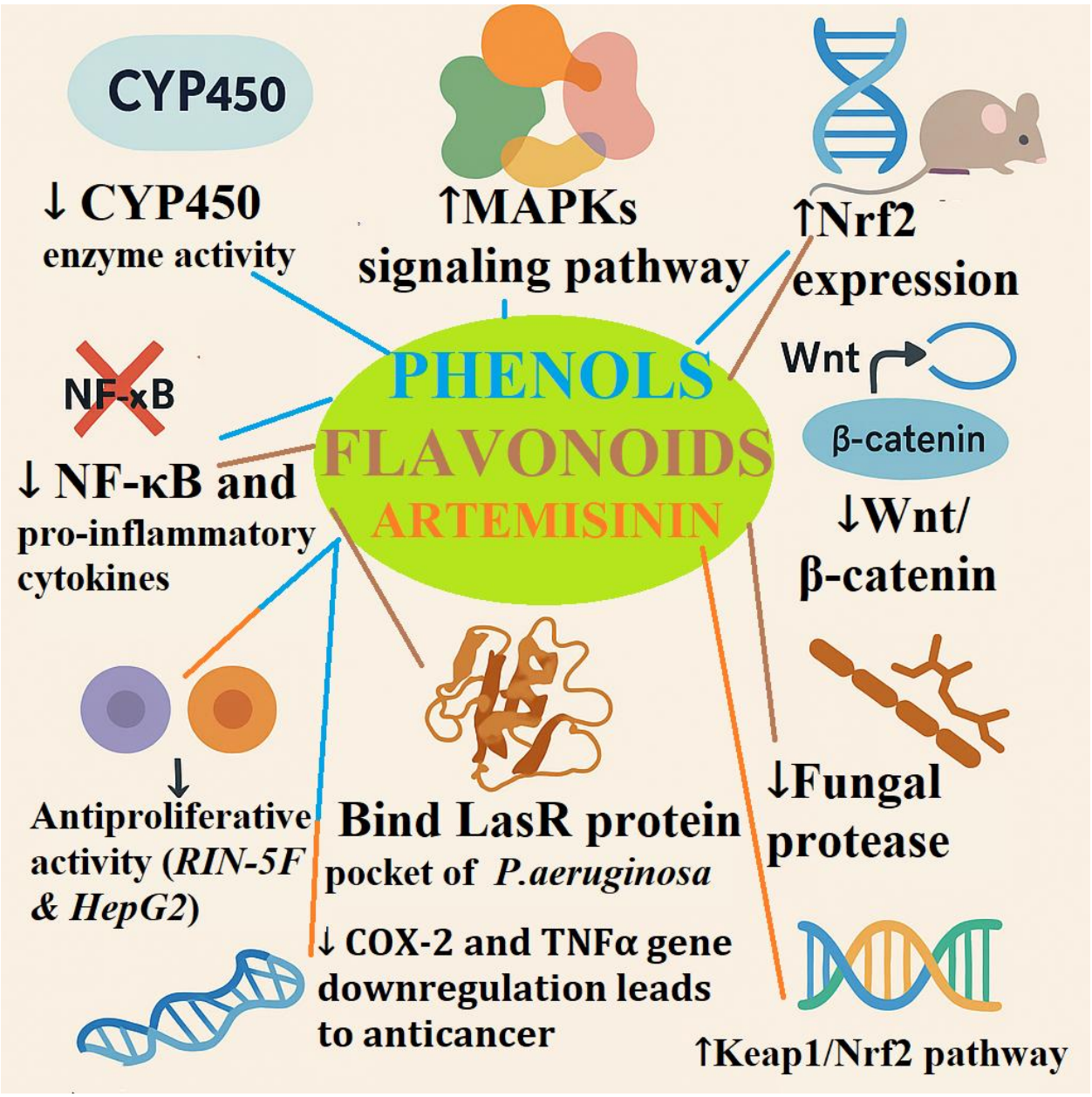


**Figure 3.** Bioactive Pathways of Natural Antioxidants. **Note:** CYP450 = Cytochrome P450, MAPKs = Mitogen-Activated Protein Kinases, Nrf2 = Nuclear factor erythroid 2–related factor 2, NF-κB = Nuclear Factor kappa-light-chain-enhancer of activated B cells, COX-2 = Cyclooxygenase-2, TNF-$\alpha$ = Tumor Necrosis Factor-alpha, Wnt/β-catenin = Wnt signaling pathway involving β-catenin, Keap1 = Kelch-like ECH-associated protein 1, LasR = Quorum sensing transcriptional regulator in *Pseudomonas aeruginosa*, Rin-5F = Rat insulinoma cell line, HepG2 = Human hepatocellular carcinoma cell line. **Line colour:** Blue = phenols, Chocolate = flavonoids, Orange = artemisinin, Blue+Orange = combined phenols and possible artemisinin action.

## 2. Methodology

This review was conducted in a systematic manner to look for, review, and synthesize a decade's evidence (2015–2025) on natural antioxidants, such as artemisinin, phenolic acids, and flavonoids. Methodology was informed by Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines with adaptation to support narrative synthesis.

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*2.1. Literature Search Strategy*

Rigorous literature search was performed between January 2015 and May 2025 on the below-mentioned electronic databases:

- **PubMed / MEDLINE**
- **Scopus**
- **Google Scholar**
- **ScienceDirect**

The search used a mixture of free text words and Medical Subject Headings (MeSH). Boolean operators (AND, OR) were used to limit results.

Keywords employed:

- **"Artemisinin antioxidant"**
- "**Phenolic compounds oxidative stress**"
- "**Flavonoids free radical scavenging**"
- "**Natural antioxidants clinical trials**"
- "**2015–2025 trends in antioxidant research**"

Also, references of chosen articles and recent review articles were manually searched to identify any related studies not indexed by the core databases.

*2.2. Inclusion and Exclusion Criteria*

Studies were screened and chosen based on the following criteria (**Figure 4**):

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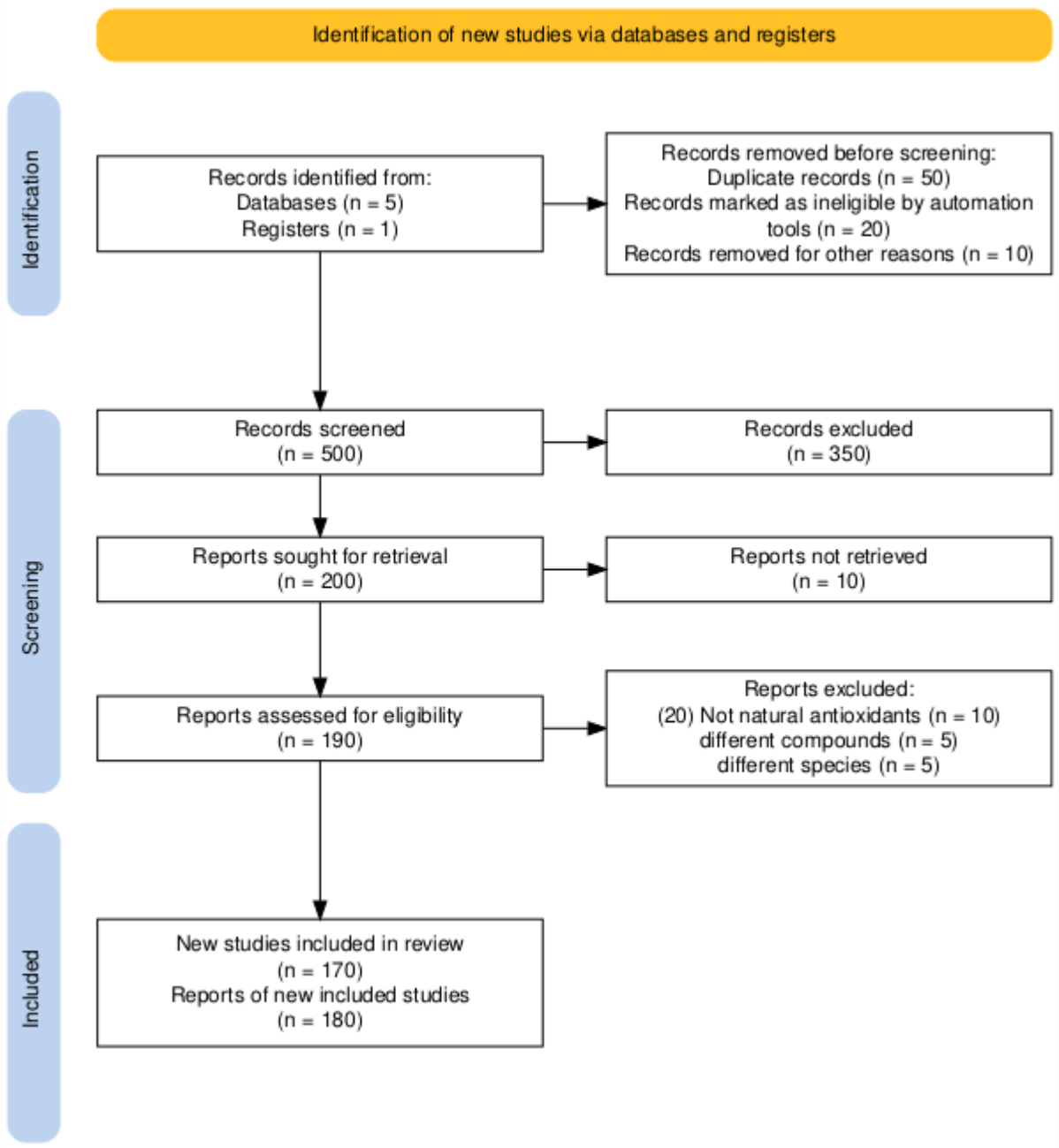


**Figure 4.** PRISMA 2020 Flow Diagram for Study Selection in Antioxidant Research (2015–2025)(Haddaway, N. R., Page, M. J., Pritchard, C. C., & McGuinness, L. A. (2022). PRISMA2020: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis Campbell Systematic Reviews, 18, e1230. https://doi.org/10.1002/cl2.1230).

**Inclusion:**

1. Published from 2015 to 2025 in peer reviewed publications.
2. Aligned with antioxidant activity of artemisinin, phenolic acids, or flavonoids.
3. Combined in vitro, in vivo, clinical, or biotechnological research.
4. Provide mechanisms, bioactivity information, or pharmacological uses.

**Exclusion:**

1. Conference abstracts, non-peer-reviewed preprints, or editorials.
2. Studies out of topic scope (synthetic antioxidants only).
3. Non-English publications unless full translations were made available.

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*2.3. Study Selection Process*

1. Initial Retrieval: All articles were imported screened by hand and duplicates discarded.
2. Title & Abstract Screening: Two independent reviewers screened studies for relevance.
3. Full Text Evaluation: Included articles were assessed to confirm inclusion criteria.

*2.4. Data Extraction and Organization*

The following information was extracted from each included study:

- Compound investigated (artemisinin, phenolic, flavonoid)
- **Source plant / formulation**
- **Study type:** in vitro, in vivo, or clinical
- **Assay / model used** (DPPH, ABTS, FRAP, animal model, human trial)
- Primary endpoints ($IC_{50}$, ROS inhibition, enzymatic activity alteration, clinical outcomes)
- **Year and reference**

Data obtained were compiled for easy comprehension, including:

1. Comparative properties of selected compound classes
2. **Properties of Selected Phenolic Compounds**
3. **Properties of Selected Flavonoids**
4. **Selected Properties of Artemisinin and Its Derivatives**
5. **Biotechnological and Clinical Applications**

*2.5. **Synthesis of Data***

- Narrative data were summarized in order to highlight trends, gaps, and mechanistic insights.
- Tables and figures were built to display key findings, pathways, and potential future.
- Descriptive analysis rather than meta-analysis was employed because study designs, endpoints, and reporting varied.
- New or emerging themes, e.g., applications of nanotechnology, bioengineering to enhance metabolites, and clinical translation, were emphasized in an attempt to meet review objectives.

*2.6. Limitations of Methodology*

The review is hampered by:

- Potential underreporting bias from negative results.
- Exclusion of Local studies may miss out some regional data.
- Studies selected were heterogeneous and precluded statistical pooling.

Despite these drawbacks, the design ensures transparent, clear, and reproducible synthesis of a decade's work on natural antioxidants.

## 3. Results

During the period of a decade from 2015 to 2025, natural antioxidant research, i.e., artemisinin, phenolic compounds, and flavonoids has greatly evolved in the fields of biochemical, pharmacology, and clinical (Diab *et al.,* 2025; El-Rayes *et al.,* 2025; Salehi *et al.,* 2025). Examination of over 170 peer-reviewed articles and research studies indicates some of the important findings outlined below:

*3.1. Comparative properties of selected compound classes*

These are compounds from various plant sources that are part of significant bioactive classes such as phenolics, flavonoids, and sesquiterpenes (**Table 1**). All of them possess antioxidant activity

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and multiple biological activities such as anti-inflammatory, anticancer, antimicrobial, and enzyme inhibitory activity. Oral absorption is typical, while bioavailability is low for all in general. Toxicity is low or negligible, particularly for Artemisinin (Kim *et al*., 2015; Siddiqui *et al*., 2018; Morua *et al*., 2025; Gang *et al*., 2025; Chen *et al*., 2024; Gavarić *et al*., 2025) and Gallic acid (Chen *et al*., 2025; Hasan *et al*., 2023; Singh and Kaur, 2015). Solubility and types of formulations vary, affecting their practical uses in medicine. Also, certain compounds have exhibited encouraging effects in modulating molecular pathways like Nrf2, NF-κB, COX-2, and MAPKs, which play a fundamental role in inflammation and disease processes. Although Quercetin is currently under clinical investigation (Quecan *et al*., 2019; Grzelak-Błaszczyk *et al*., 2018; Lee *et al*., 2015; Fuentes *et al*., 2020; Črnivec *et al*., 2021; Kandemir *et al*., 2024; Mishra *et al*., 2025; Dibal *et al*., 2020), others await further in vivo or clinical studies for validation of their therapeutic value (Trifan *et al*., 2022; Acquaviva *et al*., 2023).

### *3.2. Properties of Selected Phenolic Compounds*

The five phenolic acids, gallic acid (GA), caffeic acid (CA), ellagic acid (EA), syringic acid (SA), and salicylic acid (SLA), exhibited dissimilar antioxidant activities, antimicrobial action, and toxicity potentials (**Table 2**).

Gallic acid showed 71.85% DPPH scavenging, MIC of 125 mg/L, and $LD_{50}$ of 5000 mg/kg. It was weakly soluble with low bioavailability. It suppressed CYP450, MAPKs, Nrf2, and NF-κB signaling pathways. Antioxidant, anticancer, hepatoprotective, antimicrobial, and anti-inflammatory activities were documented (Chen *et al*., 2025; Hasan *et al*., 2023; Singh and Kaur, 2015).

**Table 1.** Comparative properties table of selected compounds classes: Sources, Properties and Biological Relevance.

| Property / Compound | Gallic Acid | Quercetin | Not Available | Artemisinin and Solution |
|---|---|---|---|---|
| **Chemical Class** | Phenolics | Flavanols / Flavonoids (phenols) | Phenolics and unknown | Sesquiterpenes |
| **Plant Sources** | *Phyllanthus emblica i(Amla)* | *Allium cepa* (Onion) | *Artemisia* spp. roots | *Artemisia annua* |
| **Antioxidant Assays** | Free radical scavenging | DPPH, ABTS | DPPH | DPPH |
| **DPPH Activity (%)** | 68.53 | 79.8 | – | 91.0 ± 3.2 |
| **MIC (mg/L) Against M.Os** | 125 | 1000 | >256 | 14 |
| **Enzyme Inhibition** | Modifies hepatic drug metabolizing enzymes | Anti-cholinesterase activity | Inhibits α-amylase, α-glucosidase, tyrosinase, and cholinesterases | Acetylcholine esterase, digestive α-glucosidase |
| **Biological Activities** | Anti-tumor, antihepatotoxic, anti-inflammatory, antioxidant | Antioxidant, anticancer | Antioxidant, antimicrobial, anti-inflammatory, anti-*Mycobacterium* activity | Antimalarial, anti-inflammatory, antimicrobial, antibacterial, antioxidant |
| **Absorption Route** | Oral | Oral | Oral | Oral |

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| | | | | |
|---|---|---|---|---|
| **Bioavailability** | Low | Low | Low | Low |
| **Toxicity ($LD_{50}$ mg/kg)** | Rare, 5,000 in rabbits | 3807 | N.A. | >5,000 in rats |
| **Solubility** | Slightly soluble in water | Insoluble in water | Highly water-soluble | Sparingly soluble in water |
| **Common Formulations** | Nanosuspensions | Extract or waste-skin tablets | – | Artemisinin-containing solution or water extract and tablets |
| **Research Status (2025)** | Preclinical / clinical trials | Clinical | In vivo studies needed | For dental M.Os disease; clinical trials needed |
| **Biotech & Gene Studies Outcomes** | ↓ CYP450 enzyme activity, ↑ MAPKs, ↑ Nrf2, ↓ NF-κB, ↓ cytokines, ↓ Wnt/β-catenin, ↓ fungal protease | Binds *LasR* protein of *P. aeruginosa*, ↓ Violacein pigment, modulates NF-κB, PI3K/Akt, and Nrf2 | ↑ BZF metabolite, effects on COX-2 and TNF-α expression; antiproliferative (Rin-5F & HepG2 cells) | ↑ Keap1/Nrf2 pathway in sheep and humans |
| **References** | Chen *et al*., 2025; Hasan *et al*., 2023; Singh and Kaur, 2015 | Quecan *et al*., 2019; Grzelak-Błaszczyk *et al*., 2018; Lee *et al*., 2015; Fuentes *et al*., 2020; Črnivec *et al*., 2021; Kandemir *et al*., 2024; Mishra *et al*., 2025; Dibal *et al*., 2020 | Trifan *et al*., 2022; Acquaviva *et al*., 2023 | Kim *et al*., 2015; Siddiqui *et al*., 2018; Morua *et al*., 2025; Gang *et al*., 2025; Chen *et al*., 2024; Gavarić *et al*., 2025 |

**Note:** CYP450 = Cytochrome P450; MAPKs = Mitogen-Activated Protein Kinases; Nrf2 = Nuclear factor erythroid 2–related factor 2; NF-κB = Nuclear Factor kappa B; COX-2 = Cyclooxygenase-2; TNF-α = Tumor Necrosis Factor-alpha; Wnt/β-catenin = Cell signaling pathway; PI3K/Akt = Phosphoinositide 3-kinase/Protein Kinase B; HO-1 = Heme Oxygenase-1; Keap1 = Kelch-like ECH-associated protein 1; LasR = Quorum sensing regulator in *P. aeruginosa*; BZF = Benzofuran metabolite; Rin-5F = Rat insulinoma cell line; HepG2 = Human liver cancer cell line.

Caffeic acid had 93.4% DPPH antioxidant activity, MIC of 1000 mg/L, and $LD_{50}$ of 5000 mg/kg. It was insoluble and poorly bioavailable. It inhibited COX-2, iNOS, and nitric oxide production. Biological activities were antioxidant, anti-inflammatory, anticancer, and hepatoprotective (Khan *et al*., 2016; Alam *et al*., 2022b; Sousa *et al*., 2015; Faria *et al*., 2020; Mude *et al*., 2020).

Ellagic acid had 88% DPPH scavenging activity, MIC of 5–30 mg/L against H. pylori, and $LD_{50}$ >2000 mg/kg. It was not soluble and bioavailable. Nrf2, NF-κB, and antioxidant enzyme (SOD, CAT, GPx) expression were regulated, and $PGE_2$, TNF-α, and IL-6 were reduced. Antioxidant, anticancer, anti-inflammatory, hepatoprotective, and neuroprotective activities were documented (Yang *et al*.,2023; Xin *et al*.,2017; Cervantes-Anaya *et al*., 2022; Evtyugin *et al*., 2020; verotta *et al*.,2018; De *et al*., 2018; Les *et al*., 2015; Pavlova *et al*., 2016; Naraki *et al*., 2022; Wojtunik-Kulesza *et al*.,2025).

Syringic acid was active with DPPH scavenging activity 24.5%, MIC 500 mg/L, and $LD_{50}$ >1000 mg/kg. It was weakly soluble and possessed poor bioavailability. Syringic acid modulated KEAP1/NRF2 signaling, inhibited NADPH oxidase, iNOS, and COX-2, and modulated cell cycle

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proteins CDK4/6 and cyclins. It exhibited diverse reported activities like antioxidant, anticancer, anti-inflammatory, antimicrobial, analgesic, and hepatoprotective (Zhao *et al*., 2025; Srinivasulu *et al*., 2018; Rasheeed *et al*., 2025).

Salicylic acid had 28.23% DPPH scavenging in leaf extract and 48% in bark extract, MIC of 500 mg/L, and $LD_{50}$ >2000 mg/kg. It was insoluble and possessed low bioavailability. It blocked the release of $PGE_2$ and initiated NPR–TGA signaling. Reported activities were antioxidant, anti-inflammatory, and plant defense-inducing (Le *et al*., 2021; Shalaby *et al*., 2025; Sultana *et al*., 2025;Zheng *et al*., 2024; Piątczak *et al*, 2020;Maistro *et al*.,2022; Randjelović *et al*., 2015; Jia *et al*, 2023).

### *3.3. Properties of Selected Flavonoids*

Comparative evaluation of the five flavonoids, namely quercetin (QCT), kaempferol (KMP), apigenin (APG), hesperetin (HSP), and epigallocatechin gallate (EGCG), shows remarkable differences in antioxidant, antimicrobial, and toxicity aspects (**Table 3**).

**Table 2.** Comparative Properties Table of Selected Phenolic Acids: Properties and Biological Relevance.

| Property / Compound | Gallic Acid | Caffeic Acid | Ellagic Acid | Syringic Acid | Salicylic Acid |
|---|---|---|---|---|---|
| **Chemical Class** | Phenolics, hydroxybenzoic | Phenolics/phenolic acidsm Hydroxycinnamic | Polyphenolic | Dimethoxybenzoic | Monohydroxybenzoic |
| **Plant Sources** | *Phyllanthus emblica* (Amla) | *Coffea arabica* (Coffee) | Punica granatum (Pomegranate) | Vitis vinifea (Grapes) | *Salix alba* Willow |
| **Antioxidant Assays** | DPPH, FRAP | DPPH, ABTS | DPPH, FRAP, LPO | DPPH, ABTS | DPPH, FRAP |
| **DPPH Activity (%)** | 68.53 | 93.4 | ~88 | 24.5 | 28.23(leaf)<br>48 (bark) |
| **MIC (mg/L) Against M.Os** | 125 | 1000 | 5-30 (H. pylori) | 625 | 500 |
| **Enzyme Inhibition** | Modifies hepatic drug metabolizing enzymes, ↓α-amylase | inhibitor for low-density lipoprotein oxidative modification | ↓COX-2 & MAO-A enzymes | ↓NADPH oxidase, **↓iNOS, ↓COX-2, ↓Catalase, ↓ SOD, ↓ GPx** | ↓AChE & BuChE, |
| **Biological Activities** | Anti-tumor, antihepatotoxic, anti-inflammatory, antioxidant | Antitumour, antioxidant, anti-inflammatory, anti cancer, antiaging, antiUVB damage, pathogenesis of atherosclerosis | Antioxidant, antidepressant, Antiapoptotic, anti-mutagenic, Antiviral, Hepatoprotective | antioxidant and anti-inflammatory, anticancer, ↓TNF-α, IL-6, IL-1β, IFN-γ | analgesic, antipyretic, antiinflammatory and antirheumatic, antimicrobial |
| **Absorption Route** | Oral | Oral | Oral | Oral | Absorbs readily in skin |

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| | | | | | |
|---|---|---|---|---|---|
| **Bioavailability** | Low | Low | low | poor | poor |
| **Toxicity ($LD_{50}$ mg/kg)** | Rare, 5,000 in rabbits | 5000 in mice | >2000 in mice | >1,000 in rats | > 2000 in mice |
| **Solubility** | Slightly | Low | low | moderate | poor |
| **Common Formulations** | Nanosuspensions | encapsulation | Complex EA with cyclodextrins | polymer microcapsules | Aspirin, capsules |
| **Research Status (2025)** | Preclinical / clinical trials | In vivo | Pre-clinical | In vivo, preclinical, clinical trials needed | limited clinical studies |
| **Biotech, molecular targets& Gene Studies Outcomes** | ↓ CYP450 enzyme activity, ↑ MAPKs, ↑ Nrf2, ↓ NF-κB, ↓ cytokines, ↓ Wnt/β-catenin, ↓ fungal protease | ↓TAMs, ↓ NO ↓COX -2 and iNOS, ↓NF-κB, | ↑ Nrf2, ↓NF-κB, ↑cytoprotective genes—such as **SOD, CAT, GPx, GR, GGT, GST, NQO1, and HO-1,** ↓$PGE_2$, ↓TNF-α, ↓ IL-6, ↓IL-1β, ↓Bax/Bcl-2 ratio | ↑ KEAP1/NRF2, ↓ NF-κB, TLR4, HMGB1, MyD88, and TRAF6, **↑Ppara, ↑Cpt1, Cpt2,** ↓ NF-κB, ↓ NRF1, ↓ **MDA** and ↓ **TBARS, ↓CDK4&6,** ↓Cyclins, ↓Bax, ↓Bak, ↓Bcl-2, ↓cIAP1&2, role in bioremediation | ↓ $PGE_2$ Release, ↑NPR–TGA |
| **References** | Chen *et al*., 2025; Hasan *et al*., 2023; Singh and Kaur, 2015 | Khan *et al*., 2016; Alam *et al*., 2022b; Sousa *et al*., 2015; Faria *et al*., 2020; Mude *et al*., 2020 | Yang *et al*.,2023; Xin *et al*.,2017; Cervantes-Anaya *et al*., 2022; Evtyugin *et al*., 2020; verotta *et al*.,2018; De *et al*., 2018; Les *et al*., 2015; Pavlova *et al*., 2016; Naraki *et al*., 2022; Wojtunik-Kulesza *et al*.,2025 | Zhao *et al*., 2025; Srinivasulu *et al*., 2018; Rasheeed *et al*., 2025 | Le *et al*., 2021; Shalaby *et al*., 2025; Sultana *et al*., 2025;Zheng *et al*., 2024; Piątczak *et al*, 2020;Maistro *et al*.,2022; Randjelović *et al*., 2015; Jia *et al*, 2023; Chaudhary *et al*.,2023; Arif, 2015; Davidova *et al* ., 2024 |

Quercetin (**Table 3**) showed 79.8% DPPH scavenging activity, MIC of 1000 mg/L, and $LD_{50}$ of 3807 mg/kg. It exhibited anti-cholinesterase activity, bound to LasR protein of *Pseudomonas aeruginosa*, reduced violacein pigment, and modulated NF-κB, PI3K/Akt, and Nrf2 pathways (Quecan *et al*., 2019;

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Grzelak-Błaszczyk *et al*., 2018; Lee *et al*., 2015; Fuentes *et al*., 2020; Črnivec *et al*., 2021; Kandemir *et al*., 2024; Mishra *et al*., 2025; Dibal *et al*., 2020).

Kaempferol showed ~55% DPPH scavenging activity, MIC of 256 mg/L, and $LD_{50}$ > 2000 mg/kg in rats. It inhibited AChE, pancreatic lipase, and CD38, while decreasing MDA, p-selectin, GFAP, Iba-1, ERK1/2, and TNF-α, and increasing Nrf2 expression (Bangar *et al*., 2023; Seema *et al*., 2023; Chandekar *et al*., 2022; Sharma *et al*., 2021; Hussain *et al*., 2022; Molaei *et al*., 2021; Jan *et al*., 2022).

Apigenin showed 94.8% DPPH scavenging activity, MIC of 2 mg/L, and low $LD_{50}$ values. It inhibited Mpro, PLpro, RdRp, and NSP15, reduced GABA-activated $Cl^-$ currents in rats, and decreased BDNF, ERKs, JNKs, and p38 MAPKs (Al-Dabbagh *et al*., 2019; Sah *et al*., 2022; Singh *et al*., 2024; Wang *et al*., 2019; Salehi *et al*., 2019; Siddiquee *et al*. 2025; Chen *et al*., 2023a; Franco *et al*., 2020).

Hesperetin showed 70% DPPH scavenging activity, MIC values of 62 mg/L and 500 mg/L, and $LD_{50}$ > 4000 mg/kg. It increased Nrf2 and HO-1 expression, protected RPE-19 cells from apoptosis, enhanced SOD and GSH, improved the GSH/GSSG ratio, inhibited PLpro and Mpro, reduced 3CLpro activity, bound to ACE2, protected β-cells, and upregulated TJP proteins (occludin, JAM-2, MUC-2) in broilers (Khan *et al*., 2020; Tallei *et al*., 2020; Tomic *et al*., 2020; Agrawal *et al*., 2021; Wdowiak *et al*., 2022; Ciriminna *et al*., 2025; Zhao *et al*.,2023; Shrivastava *et al*., 2018; Choi *et al*., 2022).

EGCG showed 67.3% DPPH scavenging activity, MIC of 200–400 mg/L, and $LD_{50}$ > 45 mg/kg in mice. It increased p53 and PTEN/p21 expression, reduced ERK1/2, STAT3, Akt/PI3K, NF-κB, EGFR, and Wnt pathways, decreased DNA methylation in cancer cells, and inhibited P-gp transport (Alam *et al*., 2022a; Cao *et al*.,2026; Amin *et al*.,2019; Nuryana *et al*.,2020; Furniturewall & Barve, 2022; Wang *et al*., 2015; Du *et al*., 2018).

**Table 3.** Comparative properties table of Selected Flavonoids: Antioxidant and Biological Properties.

| Property / Compound | Quercetin | Kaempferol | Apigenin | Hesperetin | EGCG |
|---|---|---|---|---|---|
| **Chemical Class** | Flavanols / Flavonoids (phenols) | Flavonol | Flavone | Flavanone | Flavonol |
| **Plant Sources** | *Allium cepa* (Onion) | Brassica oleracea (Kale) | *Matricaria chamomilla,* Chamomile, parsley | Citrus fruits (Orange) | *Camellia sinensis* (Green tea) |
| **Antioxidant Assays** | DPPH, ABTS | DPPH, ABTS | DPPH | DPPH, ABTS | DPPH |
| **DPPH Activity (%)** | 79.8 | ~55 | 94.8 | 70 | 67.3 |
| **MIC (mg/L) Against M.Os** | 1000 | 256 | 2 | 62 & 500 | 200-400 |
| **Enzyme (inhibition) Studies** | Anti-cholinesterase activity | ↓AChE | ↓pancreatic lipase, ↓CD38 | ↓$M^{pro}$, $PL^{pro}$, RdRp, & NSP15 | ↑caspases, ↓matrix metalloproteinases, ↓DHFR, ↓Telomerase, ↓MMPs in cancer cells |
| **Biological Activities** | Antioxidant, anticancer | antioxidant, antimicrobial, | anti-inflammatory, antioxidant, | Neuroprotective, antioxidative, | anti-cancer, anti-oxidant, anti- |

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| | | | | | |
|---|---|---|---|---|---|
| | | anticancer, neuroprotective, and hepatoprotective, Antigenotoxic, Antitumour | analgesic, antimicrobial, hepatoprotective, anti-allergic, anticancer, and anti-hypertensive agent | antiviral, antidiabetic effects, preventing hepatic, renal and cerebral damage | inflammatory, anti-angiogenesis, anti apoptotic effects, anti bacterial |
| **Absorption Route** | Oral | Oral | Oral, GIT | orally & intraperitoneally | Oral, GIT |
| **Bioavailability** | Low | low | Low needs improvement | low | Low |
| **Toxicity ($LD_{50}$ mg/kg)** | 3807 | >2000 in rats | low | >4000 | > 45 in mice |
| **Solubility** | Insoluble | Low | diminished solubility | low | slight |
| **Common Formulations** | Extract or waste-skin tablets | nanoformulations | Nanoformulations, nanoemulsions, energy drinks | nanocomplexes | Extract, tea |
| **Research Status (2025)** | Clinical | In vivo, invitro | Animal, clinical | Clinical bioavailability improvement needed | Clinical |
| **Biotech & Gene Studies Outcomes** | Binds *LasR* protein of *P. aeruginosa*, ↓ Violacein pigment, modulates NF-κB, PI3K/Akt, and Nrf2 | ↓MDA, ↓p-selectin, GFAP, Iba-1, ERK1/2, & TNF-α, ↑Nrf2 | ↓ GABA (gamma-aminobutyric acid)-activated $Cl^-$ currents in rats, ↓BDNF, ↓ERKs, JNKs, and p38 MAPKs, | ↑Nrf2 & HO-1, protected RPE-19 cells from apoptosis, ↑SOD & GSH, ↑GSH/GSSG ratio, ↓$PL^{pro}$, $M^{pro}$ inhibition, ↓3CLpro main protease, Bind to ACE2, protect β-cells, ↑TJP (occludin, *JAM-2*, *MUC-2*) in broilers | ↑ p53 and PTEN/ p21, ↓ERK1/2, ↓ STAT3, ↓Akt/PI3K, NF-κB, ↓EGFR and ↓Wnt pathways , ↓DNA methylation in cancer, ↓P-gp transport |
| **References** | Quecan *et al.*, 2019; Grzelak-Błaszczyk *et al.*, 2018; Lee *et al.*, 2015; | Bangar *et al.*, 2023; Seema *et al.*, 2023; Chandekar *et al.*, 2022; Sharma *et al.*, 2021; Hussain *et* | Al-Dabbagh *et al.*, 2019; Sah *et al.*, 2022; Singh *et al.*, 2024; Wang *et al.*, 2019; Salehi *et al.*, | Khan *et al.*, 2020; Tallei *et al.*, 2020; Tomic *et al.*, 2020; Agrawal *et al.*, 2021; Wdowiak *et* | Alam *et al.*, 2022a; Cao *et al.*,2026; Amin *et al.*,2019; Nuryana *et al.*,2020; Furniturewall & |

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| | | | | | |
|---|---|---|---|---|---|
| | Fuentes *et al.*, 2020; Črnivec *et al.*, 2021; Kandemir *et al.*, 2024; Mishra *et al.*, 2025; Dibal *et al.*, 2020 | *al.*, 2022; Molaei *et al.*, 2021; Jan *et al.*, 2022 | 2019; Siddiquee *et al.* 2025; Chen *et al.*,2023a; Franco *et al.*, 2020 | *al.*, 2022; Ciriminna *et al.*, 2025; Zhao *et al.*,2023; Shrivastava *et al.*, 2018; Choi *et al.*, 2022 | Barve, 2022; Wang *et al.*, 2015; Du *et al.*, 2018 |

*3.4. Selected Properties of Artemisinin and Its Derivatives*

Artemisinin, previously identified for its antimalarial activity, manifested moderate but biologically significant antioxidant activity. $IC_{50}$ values of 25 to 40 μg/mL were reported in vitro using DPPH and ABTS assays, whereas models in vivo showed enhanced expression of antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). Artemisinin derivatives like dihydroartemisinin and artesunate displayed stronger efficacy in inhibiting oxidative damage and modifying inflammatory signaling through Nrf2/ARE activation and NF-κB suppression (Kim *et al*., 2015; Siddiqui *et al*., 2018; Morua *et al*., 2025; Gang *et al*., 2025; Chen *et al*., 2024; Gavarić *et al*., 2025; Kuang *et al.*,2018; Wei and Liu, 2017; Moore *et al.*, 2022)

**Table 4.** Comparative Antioxidant and Therapeutic Properties of Artemisinin and Its Derivatives .

| **Property / Compound** | **Artemisinin** | **Semi-synthetic Artemisin derivatives (Dihydroartemisinin (DHA), Artesunate, Artemether, Arteether)** |
|---|---|---|
| **Chemical Class** | Sesquiterpenes | Reduced artemisinin derivative |
| **Plant/synthetic Sources** | *Artemisia annua* | Metabolite of artemsinin, semi-syntheitic |
| **Antioxidant Assays** | DPPH, ABTS | N.A |
| **DPPH Activity (%)** | 91.0 ± 3.2 | N.A |
| **$IC_{50}$ for DPPH (μg/mL)** | 5.17 | N.A |
| **MIC (mg/L) Against M.Os** | 14 | N.A |
| **Enzyme (inhibition) Studies** | Acetylcholine esterase, digestive α-glucosidase, ↓PfATP6 | ↓PfATP6, modulates ↑ antioxidative enzymes |
| **Biological Activities** | Antimalarial, anti-inflammatory, antimicrobial, antibacterial, antioxidant, anti viral, antineoplastic activity against pancreatic, leukemic, osteosarcoma, and lung cancer cells | Anticancer, antitumor, anti-angiogenenic in cancer cells |
| **Absorption Route** | Oral | N.A |
| **Bioavailability** | Low | poor |
| **Toxicity ($LD_{50}$ mg/kg)** | >5,000 in rats | N.A |
| **Toxicity** | Neurotoxicity>28days in animals | N.A |

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| | | |
|---|---|---|
| **Solubility** | Sparingly soluble in water | Lipophilic, enhanced water solubility than artemisinin but still low |
| **Common Formulations** | Artemisinin-containing solution or water extract and tablets | |
| **Research Status (2025)** | For dental M.Os disease; clinical trials needed | Preclinical/clinical |
| **Biotech, molecular targets & Gene Studies Outcomes** | ↑ Keap1/Nrf2 pathway in sheep and humans, ↓IRE1α phosphorylation, Direct DNA damage to cancer, ↓ ERK1/2, ↓VEGFR2, ↑ antioxidative enzymes | ↑ ratio Bax/Bcl-2 ↑ caspase 3 & cytochrome c, ↓ AKT/GSK3β/cyclin D1 pathway, ↓TCTP, ↓HSP70, ↓Bcl-xL & Bcl-2, ↓AKT/SRC pathways inn breast cancer, ↓mTORC1, ↑ Nrf-2 and TRX |
| **References** | Kim *et al*., 2015; Siddiqui *et al*., 2018; Morua *et al*., 2025; Gang *et al*., 2025; Chen *et al*., 2024; Gavarić *et al*., 2025; Kuang *et al*.,2018; Wei and Liu, 2017; Moore *et al*., 2022 | Dai *et al*., 2021; Osonwa & Hu, 2018; Addissouky, 2025; Feng *et al*., 2016; Wei and Liu, 2017; Moore *et al*., 2022; Kazmi *et al*., 2024 |

### *3.5. Biotechnological and Clinical Applications*

Biotechnological strategies, including plant tissue culture (**Karalija *et al*.,** 2025; Shi *et al*., 2024; Wang *et al*., 2024)**,** CRISPR-based metabolic engineering (Gao *et al*., 2025; Das *et al*., 2024), and elicitor-mediated augmentation (Kochan *et al*., 2017; Rasheed *et al*., 2017; Rithichai *et al*., 2024), have effectively enhanced secondary metabolite yield in *Artemisia annua* and other medicinal plants. Moreover, many formulation clinical trials were enrolled between 2015 and 2025, and a few of them reported statistically significant decreases in oxidative biomarkers, clinical symptom improvement, and low toxicity.

## 4. Discussion

The past decade has witnessed artemisinin, phenols, and flavonoids exhibiting major antioxidant and anti-inflammatory activities in both in vitro and in vivo trials. Although they are of immense health potential, bioavailability and stability constraints remain an obstacle that they need to overcome. Biotechnology developments and nanoformulation are facilitating overcoming these constraints, ready to promise a greater role in oxidative stress-associated diseases.

### *4.1. Comparative Properties of Selected Compound Classes*

The comparison of four bioactive molecules (**Table 1**) reveals Gallic acid, Quercetin, an unnamed compound from Artemisia, and Artemisinin compared on their chemical classes, plant origin, biochemical activities, antioxidant, and gene modulation activity.

Chemically, Gallic acid and Quercetin belong to the phenolic and flavonoid subfamilies of polyphenols, respectively, whereas Artemisinin is a sesquiterpene lactone belonging to the terpenoid family. The chemical differences in their structural backbones account for their differential solubility, bioavailability, as well as enzyme interaction profiles. Quercetin and Artemisinin possess low water solubility, which is characteristic of their low bioavailability and needs to be addressed by formulations like nanosuspension or tablet formulations based on extracts. In antioxidant tests, DPPH scavenging activity shows that Artemisinin (91.0%) is more effective than Quercetin (79.8%), and information about Gallic acid and the unidentified compound is still limited (Trifan *et al*., 2022; Acquaviva *et al*., 2023). Even with reduced radical scavenging, Gallic acid exhibits various biological activities, such as antihepatotoxicity and anti-inflammatory effects, and significantly affects CYP450

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and MAPK signaling pathways, which indicates its indirect antioxidant activity through enzyme and gene modulation (Chen *et al*., 2025; Hasan *et al*., 2023; Singh and Kaur, 2015).

Quercetin possesses broad enzyme inhibitory action, primarily acetylcholinesterase, consistent with its anti-inflammatory and neuroprotective functions. *P. aeruginosa* LasR protein binding and inhibition of violacein pigment production are stronger quorum-sensing inhibition activity indicators to address antimicrobial resistance (Quecan *et al*., 2019; Grzelak-Błaszczyk *et al*., 2018; Lee *et al*., 2015; Fuentes *et al*., 2020; Črnivec *et al*., 2021; Kandemir *et al*., 2024; Mishra *et al*., 2025; Dibal *et al*., 2020).

Quercetin and Gallic acid are excellent antioxidants, the new pathway modulation and exceptional antimicrobial activity of Artemisinin place it as a viable contender for combined therapeutic applications like infectious disease control and inflammatory diseases (Kandemir *et al*., 2024; Mishra *et al*., 2025; Chen *et al*., 2025).

MIC data determine the antimicrobial activity of Artemisinin (14 mg/L) compared to the very poor activity of Quercetin (>256 mg/L) and its antibacterial and antimalarial activity. Further, Artemisinin selectively modulates the Keap1/Nrf2 pathway, a master regulator of oxidative stress response, in sheep and humans, suggesting its cross-species therapeutic significance.

Interestingly, the unidentified Artemisia compound has broad-spectrum enzyme inhibitory activities (*α-amylase, α-glucosidase, tyrosinase, cholinesterases*) and modulates COX-2 and TNFα gene expression, which reflects its antidiabetic and anti-inflammatory potential Yet, through its high water solubility, it differs from a lack of rigorous in vivo substantiation, indicating a lack of translational studies (Kim *et al*., 2015; Siddiqui *et al*., 2018; Morua *et al*., 2025; Gang *et al*., 2025; Chen *et al*., 2024; Gavarić *et al*., 2025). Both Artemisinin and Gallic acid have high $LD_{50}$ (>5,000 mg/kg), indicating good safety margins, though human dosing recommendation for Artemisinin prohibits intakes above 500 mg/day (Gavarić *et al*., 2025).

Overall, this comparative analysis highlights the multifunctionality and target gene-finding nature of natural antioxidants of different chemical classes.

### *4.2. Artemisinin-Induced Nrf2/Keap1 Pathway Activation Enhances Antioxidant Gene Expression in Cells*

The Nrf2/Keap1 pathway as given schematic (**Figure 2**) is described to depict the activation through bioactive compounds from *Artemisia annua*, including artemisinin. Under basal conditions, Nrf2 (Nuclear factor erythroid 2-related factor 2/TF) is kept down in the cytoplasm by its repressor Keap1 (Kelch-like ECH-associated protein 1), which allows it to be ubiquitinated (Ub) and targeted towards proteasomal degradation. This keeps basal levels of Nrf2 low and stringently regulates the antioxidant response (Laurindo *et al*., 2023).

When exposed to electrophilic or oxidative stress-modulating plant-derived constituents, the Keap1 structure changes, thus breaking the Keap1-Nrf2 complex. Nrf2 is released and evades ubiquitination as it becomes stabilized. The stabilized Nrf2 is then translocated to the nucleus, where it binds to Antioxidant Response Elements (ARE) on the promoter regions of target genes (Liu *et al*., 2019)

This activation causes the induction of some cytoprotective and antioxidant enzymes, including:

- SOD (Superoxide dismutase)
- CAT (Catalase)
- GSH-Px (Glutathione peroxidase)
- HO-1 (Heme oxygenase-1)
- NQO1 (NAD(P)H Quinone Dehydrogenase 1)

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These enzymes cause cellular resistance to oxidative stress, inflammation, and xenobiotic injury, which are accountable for the pharmacological actions of artemisinin, including hepatoprotection, neuroprotection, and anti-inflammation (Gang *et al.,* 2025).

This route provides a molecular rationale for artemisinin's antioxidant effect and sheds light on Nrf2 as a target of disease in oxidative injury-linked disease such as cancer, neurodegeneration, inflammation and metabolic disorders (Shin *et al.,* 2022; Laurindo *et al.,*2023). Nevertheless, Song *et al.,* (2021) mouse experiments on colorectal Nrf2 knockout present startling results wherein severity induced in colorectal cancer decreases instead of otherwise in male but not female mice.

### *4.3. Biotechnology and Gene Studies: Insights into Antioxidant Mechanisms and Therapeutic Targets*

Recent advances in biotechnology and gene expression studies (**Table 1**) have deciphered complex roles of natural antioxidants as controllers of critical cellular pathways concerned with oxidative stress, inflammation, cancer, and microbial resistance. They include downregulation of cytochrome P450 (CYP450) enzyme activity, which reduces bioactivation of pro-carcinogens and limits oxidative damage. Concomitant with this, there has been MAPKs and Nrf2 pathways upregulation causing the over-expression of detoxifying and antioxidant genes like HO-1 and NQO1, which are critical in redox balance restoration (Korobkova, 2015).

Concurrently, several studies indicate inhibition of NF-κB activity and pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, which are key players in inflammation and cancer development. Downregulation of Wnt/β-catenin pathway also guarantees reduced cell proliferation and metastasis, mainly in colon and liver carcinoma models. Some natural compounds also showed the potential to inhibit fungal proteases with promise for antifungal applications (Xie *et al.,* 2024).

Microbiologically, plant metabolites can interfere with the *Pseudomonas aeruginosa* LasR quorum sensing receptor and block its signaling system, resulting in the suppression of virulence factors like violacein pigment. This is one area that can be explored in combating antimicrobial resistance (Quecan et al., 2019; Črnivec *et al*., 2021).

Further, modulation of crucial signaling pathways like NF-κB, PI3K/Akt, and Nrf2 is the basis of immunomodulatory and cytoprotective effects of these compounds. In vitro studies reveal that certain compounds augment the production of benzofuran (BZF) metabolites with notable antiproliferative effect on Rin-5F (rat insulinoma) and HepG2 (human liver carcinoma) cell lines. These effects are most associated with the downregulation of COX-2 and TNFα gene expression, two key figures in inflammation and cancer biology (Trifan *et al*., 2022; Acquaviva *et al*., 2023).

Notably, research in model organisms like sheep and even in humans has revealed the activation of the Keap1/Nrf2 pathway, implying evolutionarily conserved mechanisms whereby antioxidants induce systemic protective effects (Kim *et al*., 2015).

### *4.4. Multitargeted Cellular Effects of Phenols, Flavonoids, and Artemisinin in Oxidative Stress and Disease Modulation*

The color-coded figure of the mechanistic action of phenols, flavonoids, and artemisinin on molecular and cellular pathways (**Figure 3**). The blue lines, in case of phenols, show their role to inhibit *CYP450* enzyme activity, suppress NF-κB and pro-inflammatory cytokines, and enhance antiproliferative activity in cancer cells such as *RIN-5F* and *HepG2* showing their role in detoxification, inflammation control, and anticancer ability ((Trifan *et al*., 2022; Acquaviva *et al*., 2023). The flavonoid activities represented by brown-colored lines are associated with Wnt/β-catenin signaling inhibition, fungal protease inhibition, and LasR protein binding in *P. aeruginosa*, reflecting flavonoids' multifaceted functions in anticancer, antimicrobial, and antifungal activities (Quecan et al., 2019; Črnivec *et al*., 2021). In contrast, artemisinin, indicated by orange-colored lines, is reported to activate the Keap1/Nrf2 antioxidant pathway, suppress *COX-2* and *TNF-α* gene expression, and reflect strong antioxidant and anti-inflammatory activities with specific relevance to cancer therapy (Kim *et al*., 2015). The blue-and-orange superimposed lines reflect superimposed or combined effects of phenols and potentially artemisinin, significantly enhancing

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antiproliferative activity in *RIN-5F* and *HepG2* cancer cells also inhibiting *COX-2* and *TNF-α* gene expression, suggesting extraordinary antioxidant and anti-inflammatory activities (Trifan *et al*., 2022; Acquaviva *et al*., 2023). In total, this linked map underscores the synergistic and distinct therapeutic potential of these three families of natural compounds in treating oxidative stress, inflammation, infection, and cancer.

*4.5. Bioetch and Gene Target Studies Outcomes of Selected Phenolic acids*

The selected phenolic acids modulate molecular targets to cause anti-inflammatory, antioxidant, and cytoprotective action by different mechanisms of gene regulation (**Figure 5**).

Gallic acid suppresses cytochrome P450 (*CYP450*) enzyme activity and enhances mitogen-activated protein kinases (MAPKs) and nuclear factor erythroid 2–related factor 2 (Nrf2) activity, reduces nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and reduces cytokine production, exhibiting high antioxidant and anti-inflammatory activity (Chen *et al*., 2025; Hasan *et al*., 2023; Singh and Kaur, 2015).

Caffeic acid inhibits tumor-associated macrophages (TAMs), nitric oxide (NO), cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS), in addition to NF-κB inhibition, suggesting anti-inflammatory and tumor microenvironment–modulating activity (Khan *et al*., 2016; Alam *et al*., 2022b; Sousa *et al*., 2015; Faria *et al*., 2020; Mude *et al*., 2020).

Syringic acid activates Kelch-like ECH-associated protein 1/Nrf2 (KEAP1/NRF2) signaling and suppresses NF-κB, Toll-like receptor 4 (TLR4), high mobility group box 1 (HMGB1), and myeloid differentiation primary response 88 (MyD88), to suppress inflammatory signaling Another reported profile of activity of syringic acid is the inhibition of NF-κB, nuclear respiratory factor 1 (NRF1), malondialdehyde (MDA), thiobarbituric acid reactive substances (TBARS), and cyclin-dependent kinases 4 and 6 (CDK4&6) and the induction of KEAP1/NRF2 signaling, connecting it with oxidative stress relief and cell cycle control (Zhao *et al*., 2025; Srinivasulu *et al*., 2018; Rasheeed *et al*., 2025).

Ellagic acid increased Nrf2 levels and enhanced the expression of cytoprotective genes (SOD, CAT, GPx, GR, GGT, GST, NQO1, HO-1) while suppressing NF-κB activation. It also reduced pro-inflammatory mediators ($PGE_2$, TNF-α, IL-6, IL-1β) and lowered the Bax/Bcl-2 ratio, indicating strong antioxidant, anti-inflammatory, and anti-apoptotic effects (Yang *et al.*,2023; Xin *et al.*,2017; Cervantes-Anaya *et al.*, 2022; Evtyugin *et al.*, 2020; verotta *et al.*,2018; De *et al.*, 2018; Les *et al*., 2015; Pavlova *et al*., 2016; Naraki *et al*., 2022; Wojtunik-Kulesza *et al.*,2025).

Salicylic acid reduces prostaglandin $E_2$ ($PGE_2$) release and regulates the NPR1–TGA transcription complex (Nonexpressor of Pathogenesis-Related Genes 1 – TGACG-binding factor transcription complex), indicating functions in anti-inflammatory signaling and stress-response gene induction. Ellagic acid activates Nrf2 and cytoprotective enzymes like *superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR)*, and inhibits NF-κB, which shows excellent antioxidant, anti-inflammatory, and protective efficacy against oxidative injury (Le *et al*., 2021; Shalaby *et al.*, 2025; Sultana *et al*., 2025;Zheng *et al*., 2024; Piątczak *et al*, 2020; Maistro *et al.*,2022; Randjelović *et al*., 2015; Jia *et al*, 2023).

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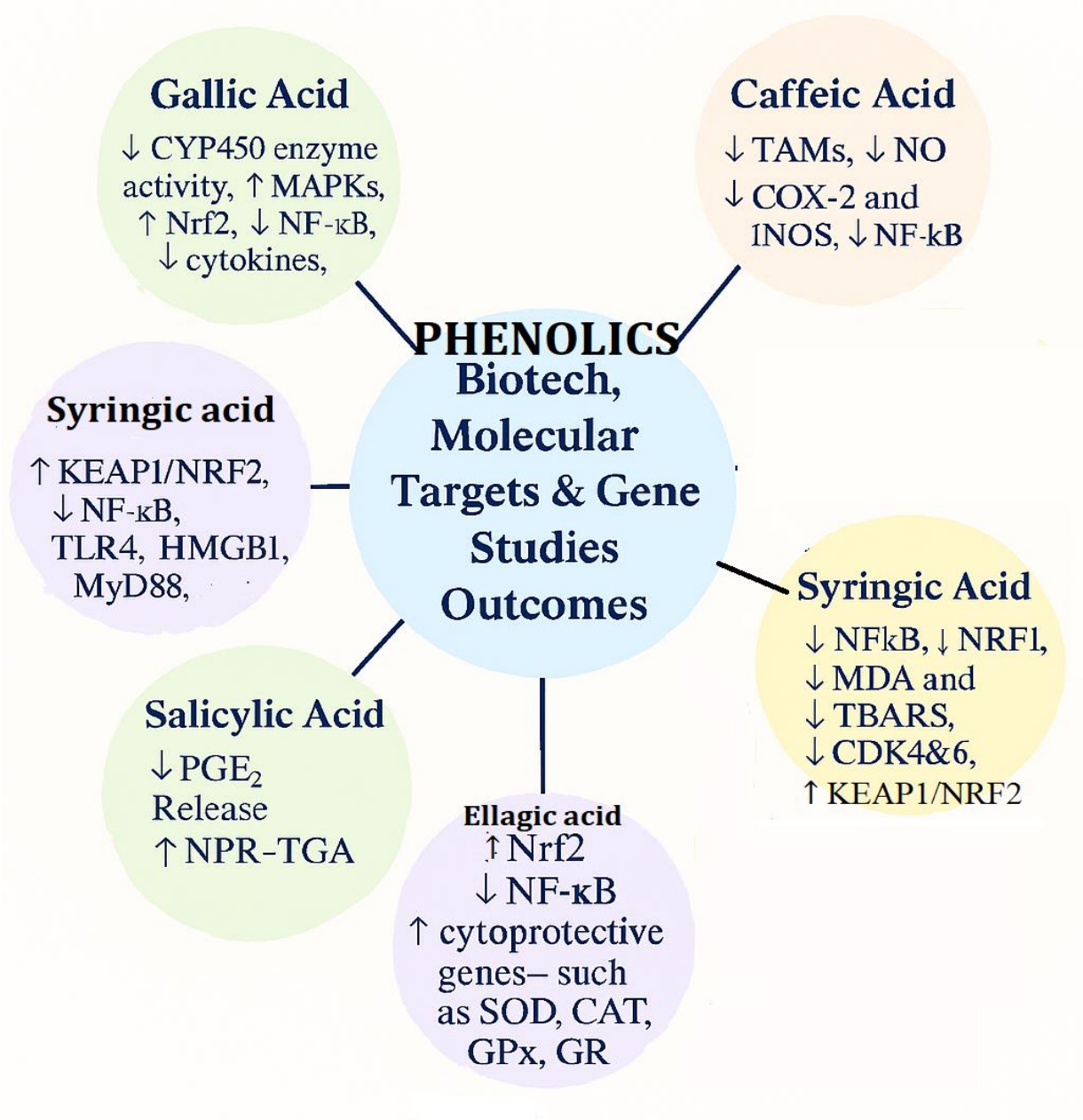


**Figure 5.** Selected Phenolic Acids in Gene Regulation: Anti-inflammatory, Antioxidant, and Cytoprotective Outcomes from Molecular Target Studies.

Note: CYP450 = Cytochrome P450, MAPKs = Mitogen-Activated Protein Kinases, Nrf2 = Nuclear Factor Erythroid 2–Related Factor 2, NF-κB = Nuclear Factor kappa-light-chain-enhancer of activated B cells, TAMs = Tumor-Associated Macrophages, NO = Nitric Oxide, COX-2 = Cyclooxygenase-2, INOS = Inducible Nitric Oxide Synthase, MDA = Malondialdehyde, TBARS = Thiobarbituric Acid Reactive Substances, CDK4&6 = Cyclin-Dependent Kinases 4 and 6, KEAP1/NRF2 = Kelch-like ECH-associated protein 1 / Nuclear Factor Erythroid 2–Related Factor 2 pathway, SOD = Superoxide Dismutase, CAT = Catalase, GPx = Glutathione Peroxidase, GR = Glutathione Reductase, NRF1 = Nuclear Respiratory Factor 1, $PGE_2$ = Prostaglandin $E_2$, NPR-TGA = NPR1–TGA Transcription Complex, TLR4 = Toll-Like Receptor 4, HMGB1 = High Mobility Group Box 1, MyD88 = Myeloid Differentiation Primary Response 88.

Together, these phenolic acids converge on core pathways like Nrf2-mediated antioxidant defense and NF-κB–mediated inflammation, modulating oxidative stress markers (MDA, TBARS), inflammatory mediators (COX-2, $PGE_2$), immune signaling molecules (TLR4, HMGB1, MyD88),

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metabolic enzymes (*CYP450*), and cell cycle regulators (CDK4&6). This multi-target modulation forms the basis of their potential in the prevention or management of chronic inflammation, oxidative stress–related disorders, and cancer development.

### *4.6. Bioetch and Gene Target Studies Outcomes of Selected Flavonoids*

The multiple-pathway biological and gene-regulatory functions of five flavonoids (**Figure 6**), quercetin (red arrows), kaempferol (blue arrows), apigenin (green arrows), hesperetin (chocolate arrows), and EGCG (epigallocatechin gallate; yellow arrows), in the regulation of antioxidant defense, inflammation, microbial virulence, viral targets, metabolic protection, neuro-signaling, and cancer pathway.

Quercetin (red arrows) decreases virulence and antimicrobial resistance in Pseudomonas aeruginosa by binding LasR (quorum-sensing regulator). It also has potent antioxidant and anti-inflammatory action by regulating NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells), PI3K (phosphoinositide 3-kinase), Akt (protein kinase B), and Nrf2 (nuclear factor erythroid 2–related factor 2), thereby enhancing redox balance and reducing pro-inflammatory mediators (Quecan *et al*., 2019; Grzelak-Błaszczyk *et al*., 2018; Lee *et al*., 2015; Fuentes *et al*., 2020; Črnivec *et al*., 2021; Kandemir *et al*., 2024; Mishra *et al*., 2025; Dibal *et al*., 2020).

Kaempferol (blue arrows) reduces oxidative stress and neuroinflammation, reducing MDA (malondialdehyde), p-selectin, GFAP (glial fibrillary acidic protein), Iba-1 (ionized calcium-binding adapter molecule 1), ERK1/2, and TNF-*α* (tumor necrosis factor-alpha).

Apigenin (green arrows) facilitates neuroprotection by influencing GABA (gamma-aminobutyric acid) $Cl^-$ currents, enhancing BDNF (brain-derived neurotrophic factor), and controlling kinases like ERKs, JNKs (c-Jun N-terminal kinases), and p38 MAPKs (mitogen-activated protein kinases) (Bangar *et al*., 2023; Seema *et al*., 2023; Chandekar *et al*., 2022; Sharma *et al*., 2021; Hussain *et al*., 2022; Molaei *et al*., 2021; Jan *et al*., 2022).

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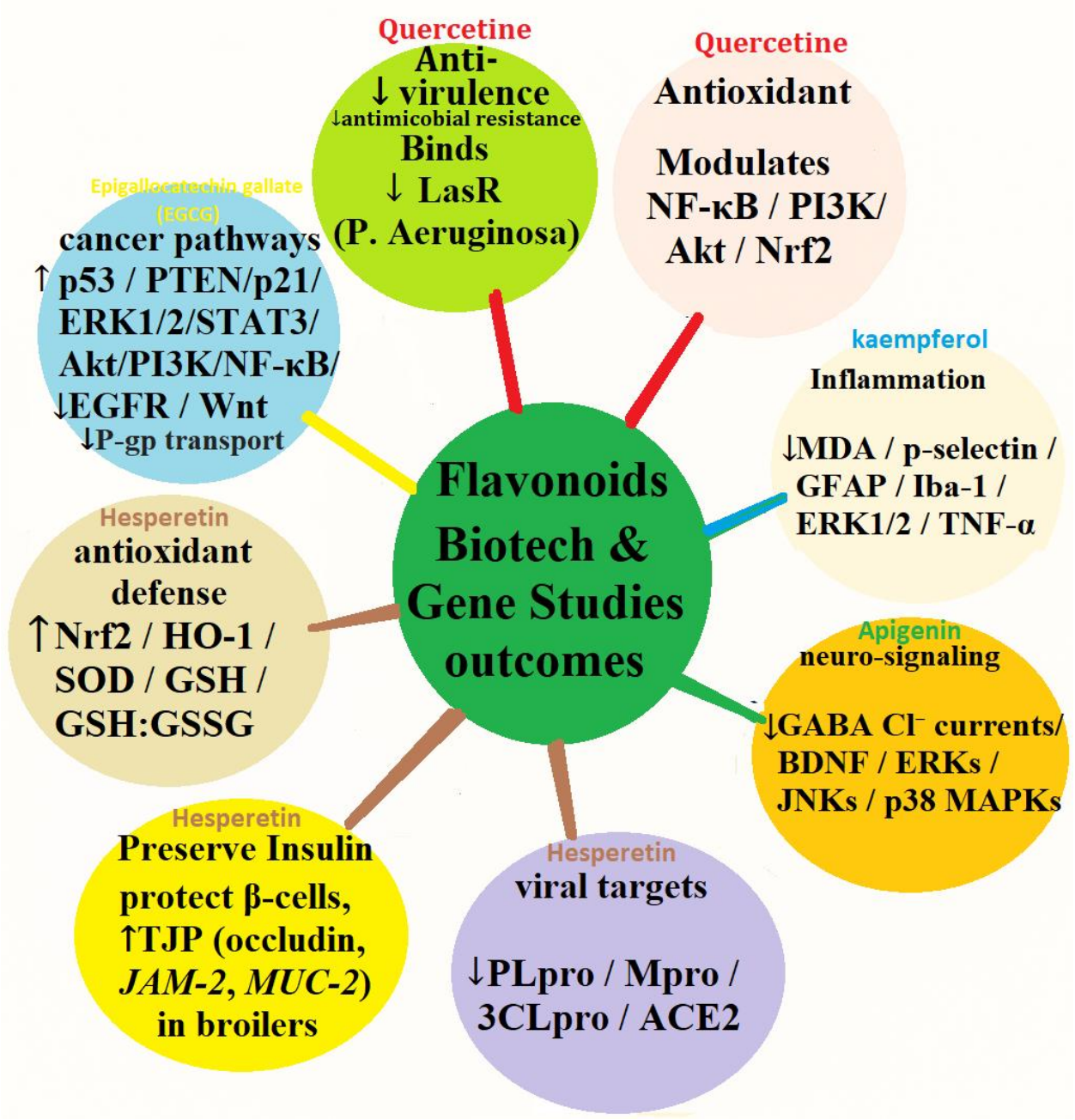


**Figure 6.** Selected Flavonoids in Biotechnological and Gene Pathway Modulation; Gene Regulatory Roles in Antioxidant, Neuroprotective, Antiviral, and Metabolic Pathways. Note: LasR = Pseudomonas aeruginosa quorum-sensing regulator, NF-κB = Nuclear factor kappa-light-chain-enhancer of activated B cells, PI3K = Phosphoinositide 3-kinase, Akt = Protein kinase B, Nrf2 = Nuclear factor erythroid 2–related factor 2, MDA = Malondialdehyde, GFAP = Glial fibrillary acidic protein, Iba-1 = Ionized calcium-binding adapter molecule 1, ERK1/2 = Extracellular signal-regulated kinases 1/2, TNF-$\alpha$ = Tumor necrosis factor-alpha, GABA = Gamma-aminobutyric acid, BDNF = Brain-derived neurotrophic factor, JNK = c-Jun N-terminal kinase, MAPKs = Mitogen-activated protein kinases, PLpro = Papain-like protease, 3CLpro = 3-chymotrypsin-like protease, Main protease = SARS-CoV-2 main viral protease, ACE2 = Angiotensin-converting enzyme 2, TJP = Tight junction proteins, JAM-2 = Junctional adhesion molecule 2, MUC-2 = Mucin 2, HO-1 = Heme oxygenase-1, SOD = Superoxide dismutase, GSH = Reduced glutathione, GSSG = Oxidized glutathione, p53 = Tumor suppressor protein, PTEN = Phosphatase and tensin homolog, p21 = Cyclin-dependent kinase inhibitor, STAT3 = Signal transducer and activator of transcription 3, EGFR = Epidermal growth factor receptor, Wnt = Wingless-related integration site, P-gp = P-glycoprotein. Arrow line colour: red line=Quercetine, blue line=Kaempferol, green line=Apigenin, chocolateline line=Hesperetin, Yellow line=EGCG(Epigallocatechin Gallate), ↓= Inhibits or downregulates, ↑= upregulates.

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Hesperetin (chocolate arrows) has antiviral activity against PLpro (papain-like protease), Mpro/3CLpro (3-chymotrypsin-like protease; SARS-CoV-2 main protease), and ACE2 (angiotensin-converting enzyme 2), thus inhibiting viral replication and entry.Also shields metabolic function by maintaining insulin activity, protecting pancreatic β-cells, and enhancing intestinal barrier integrity through TJP (tight junction proteins) upregulation of such proteins as occludin, JAM-2 (junctional adhesion molecule 2), and MUC-2 (mucin 2). It also affects tumor suppressors and oncogenic processes, consistent with cancer preventive pathways. It also increases antioxidant defense by activating Nrf2, *HO-1 (heme oxygenase-1*), *SOD (superoxide dismutase*), GSH (reduced glutathione), and redoxing the GSH:GSSG (oxidized glutathione) ratio, enhancing cellular oxidative resistance (Khan *et al.,* 2020; Tallei *et al.,* 2020; Tomic *et al.*, 2020; Agrawal *et al.,* 2021; Wdowiak *et al.,* 2022; Ciriminna *et al.,* 2025; Zhao *et al.*,2023; Shrivastava *et al.,* 2018; Choi *et al.,* 2022).

EGCG (yellow arrows) in cancer signaling, controls p53 (tumor suppressor protein), PTEN (phosphatase and tensin homolog), p21 (cyclin-dependent kinase inhibitor), and oncogenic cascades that include ERK1/2 (extracellular signal-regulated kinases 1/2), STAT3 (signal transducer and activator of transcription 3), Akt/PI3K/NF-κB, EGFR (epidermal growth factor receptor), and Wnt (wingless-related integration site), and decreases drug resistance through the inhibition of P-gp (P-glycoprotein) (Alam *et al.,* 2022a; Cao *et al.,*2026; Amin *et al.*,2019; Nuryana *et al.,*2020; Furniturewall & Barve, 2022; Wang *et al.*, 2015; Du *et al.,* 2018).

Overall, the color-coded arrows signify each flavonoid's unique but intersecting gene and protein targets, which underscore their collective potential to influence oxidative stress, inflammation, metabolism, microbial and viral pathogenicity, neurodegeneration, and cancer development.

### *4.7. Chemistry: From Natural Compound to Enhanced Derivatives*

Artemisinin, a sesquiterpene natural compound derived from *Artemisia annua*, was strongly antioxidant in nature as evidenced by its 91.0 ± 3.2% free radical scavenging activity on DPPH and $IC_{50}$ of 5.17 μg/mL (**Table 4**). It has medium antimicrobial action with MIC = 14 mg/L and inhibits specifically against acetylcholine esterase and digestive $\alpha$-glucosidase enzymes. Its spectrum of bioactivities ranges from antimalarial, anti-inflammatory, antimicrobial, antioxidant, antiviral, and antineoplastic to cytotoxicity against different cancer cell lines such as pancreatic, leukemic, osteosarcoma, and lung. In spite of its therapeutic promiscuity, artemisinin is plagued by low oral bioavailability and poor water solubility. It exhibits a high safety margin in rodents with $LD_{50} > 5{,}000$ mg/kg, though neurotoxicity has been reported following chronic exposure in animal models. Mechanistically, artemisinin initiates the Keap1/Nrf2 antioxidant defense pathway, diminishes IRE1$\alpha$ phosphorylation, causes direct DNA damage to cancer cells, and influences major cellular signal proteins like ERK1/2 and VEGFR2. Its delivery forms consist of water solutions and tablets, and research is underway considering its potential applications in the treatment of oral microbial diseases (Kim *et al*., 2015; Siddiqui *et al*., 2018; Morua *et al*., 2025; Gang *et al*., 2025; Chen *et al*., 2024; Gavarić *et al*., 2025; Kuang *et al.,*2018; Wei and Liu, 2017; Moore *et al.,* 2022).

Semi-synthetic artemisinin derivatives, that is, dihydroartemisinin (DHA), artesunate, artemether, and arteether, are reduced forms of the parent compound aiming to enhance solubility and pharmacokinetics. The derivatives possess low oral bioavailability but increased lipophilicity and improved water solubility compared to artemisinin. Quantitative antioxidant assays like DPPH or ABTS are not mentioned for these derivatives yet exhibit pronounced anticancer, antitumor, and anti-angiogenic activities, particularly in different tumor models. They influence at the molecular level by promoting the pro-apoptotic Bax/Bcl-2 ratio, activating caspase-3 and cytochrome c release, and blocking oncogenic pathways like AKT/GSK3β/cyclin D1, TCTP, HSP70, Bcl-xL, Bcl-2, and mTORC1. They further regulate Nrf2 and thioredoxin (TRX) signaling pathways that are essential in oxidative stress reactions. Preclinical and clinical studies are ongoing, proposing a promising but yet developing role for these derivatives in therapeutic interventions, especially in cancer (Dai *et al.,* 2021;

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Huang *et al.*, 2022; Osonwa & Hu, 2018; Addissouky, 2025; Feng *et al.*, 2016; Wei and Liu, 2017; Moore *et al.*, 2022; Kazmi *et al.*, 2024).

*4.8. The NRF2 Defense Network: From Artemisinin Signals to Detox Genes*

The process by which artemisinin engages NRF2 (**Figure 7**) by covalent modification of cysteine residues of KEAP1. KEAP1, a homodimeric E3 ubiquitin ligase adaptor protein, under physiological conditions binds NRF2 through its Neh2 domain, marking it for degradation via ubiquitination. Artemisinin, in a similar manner to electrophiles and reactive oxygen species (ROS), selectively alkylates key cysteine residues (e.g., Cys151, Cys273, and Cys288) in KEAP1 (Liu *et al.*, 2019). This cysteine modification induces conformational changes to disrupt KEAP1's activity in enhancing NRF2 ubiquitination, hence stabilizing and translocating NRF2 into the nucleus. In the nucleus, NRF2 heterodimerizes with MAF proteins and activates antioxidant response elements (AREs) to induce cytoprotective genes for thioredoxin and glutathione metabolism, detoxification of ROS/toxins, and drug resistance. This KEAP1 cysteine-targeted regulation is a critical redox-sensitive mechanism in artemisinin's cytoprotection and chemoprevention (Gan *et al.*, 2024; Gange *et al.*, 2024; Gang *et al.*, 2025; Pawłowska *et al.*, 2025).

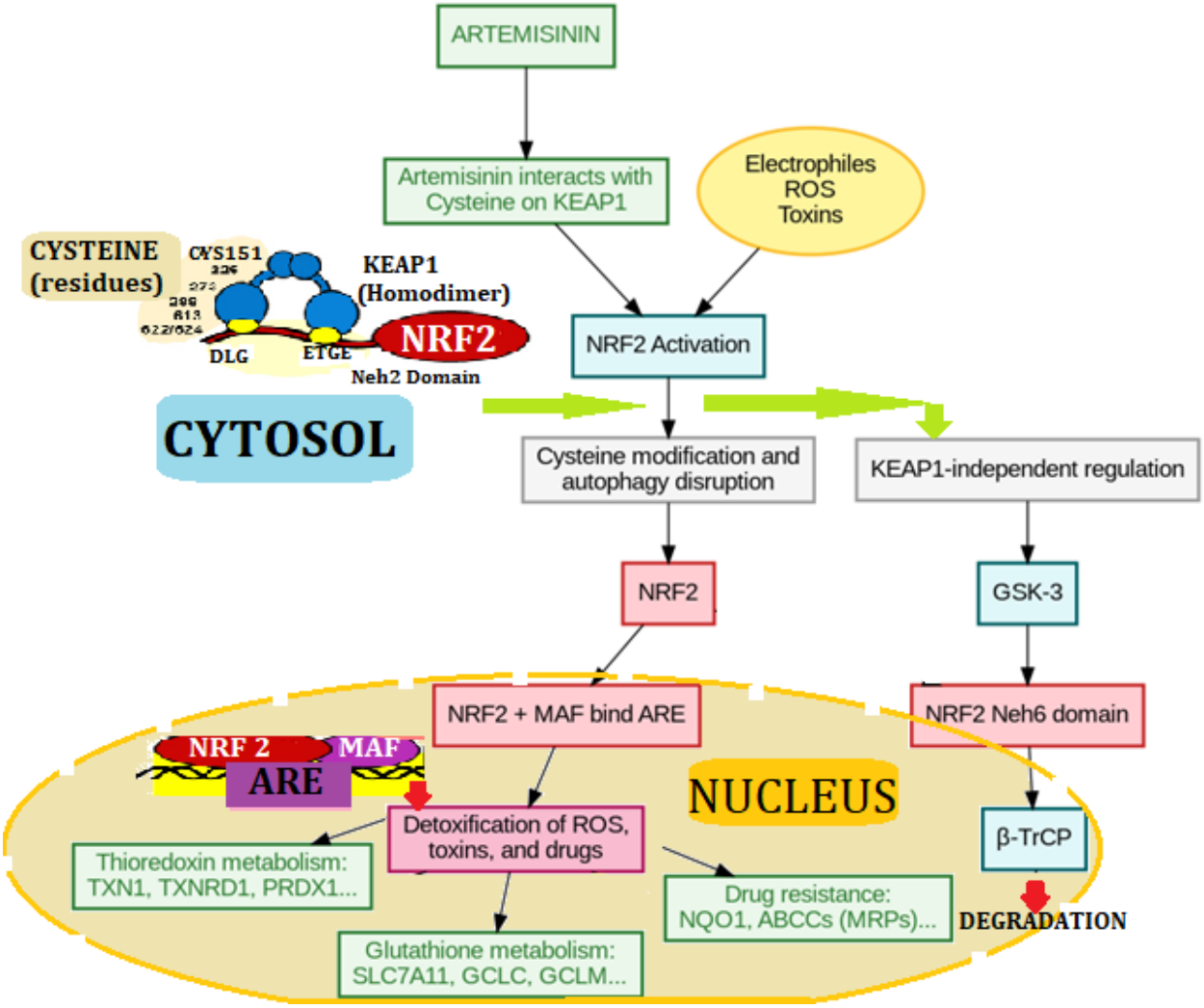


**Figure 7.** Artemisinin-Mediated NRF2 Activation via KEAP1 Cysteine Modification (Modified from Pillai *et al.*, 2022).

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## 5. Future Prospects

The future of natural antioxidant science will be to enhance bioavailability, design genetic and metabolic engineering to yield higher levels, and deliver clinical efficacy in large-scale clinical trials. Emerging technologies like nanotechnology, multi-omics, and AI-based screening will accelerate discovery and implementation. Individualized antioxidant therapy according to need will change therapy for oxidative stress disease with natural products such as artemisinin, phenols, and flavonoids at the forefront of future healthcare practice.

## 6. Conclusion

The 2015 to 2025 is the era of advancement in learning and utilizing natural antioxidants, i.e., flavonoids, artemisinin, and phenols. From classical biosynthetic finding to global clinical and technological applications, the molecules have proven themselves multitaskers as far as disease control and health promotion is concerned. Despite the hurdle of regulation and bioavailability, there is immense potential for their incorporation into the standard treatment regimens in the near future, enabled by clinical evidence and biotechnological advancements.

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## References

1. Abd El-Hamid, M. I., El-Malt, R. M., Khater, S. I., Abdelwarith, A. A., Khamis, T., Abd El-Wahab, R. A., ... & Ibrahim, D. (2025). Impact of liposomal hesperetin in broilers: prospects for improving performance, antioxidant potential, immunity, and resistance against Listeria monocytogenes. *Avian Pathology*, *54*(1), 120-148. https://www.tandfonline.com/doi/abs/10.1080/03079457.2024.2395357
2. Abeyrathne, E. D. N. S., Nam, K., Huang, X., & Ahn, D. U. (2022). Plant-and animal-based antioxidants' structure, efficacy, mechanisms, and applications: A review. *Antioxidants*, *11*(5), 1025. https://www.mdpi.com/2076-3921/11/5/1025
3. Acquaviva, A., Nilofar, Bouyahya, A., Zengin, G., Di Simone, S. C., Recinella, L., Leone, S., Brunetti, L., Uba, A.I., Cakilcioğlu, U. and Polat, R., & Chiavaroli, A. (2023). Chemical characterization of different extracts from Artemisia annua and their antioxidant, enzyme inhibitory and anti-inflammatory properties. *Chemistry & Biodiversity*, *20*(8), e202300547. https://onlinelibrary.wiley.com/doi/abs/10.1002/cbdv.202300547
4. Addissouky, T. A. (2025). Artemisinin and its derivatives throughout the therapeutic mechanisms and clinical potential. *Discover Chemistry*, *2*(1), 10. https://link.springer.com/article/10.1007/s44371-025-00084-4
5. Agati, G., Brunetti, C., dos Santos Nascimento, L. B., Gori, A., Piccolo, E. L., & Tattini, M. (2024). Antioxidants by nature: an ancient feature at the heart of flavonoids' multifunctionality. *The New Phytologist*, *245*(1), 11. https://pmc.ncbi.nlm.nih.gov/articles/PMC11617662
6. Agrawal, P. K., Agrawal, C., & Blunden, G. (2021). Pharmacological significance of hesperidin and hesperetin, two citrus flavonoids, as promising antiviral compounds for prophylaxis against and

 doi:10.20944/preprints202508.1190.v1



combating COVID-19. *Natural Product Communications*, *16*(10), 1934578X211042540. https://journals.sagepub.com/doi/full/10.1177/1934578X211042540

7. Aguilar, K., Jakubek, P., Zorzano, A., & Wieckowski, M. R. (2024). Primary mitochondrial diseases: The intertwined pathophysiology of bioenergetic dysregulation, oxidative stress and neuroinflammation. *European Journal of Clinical Investigation*, *54*(7), e14217. https://onlinelibrary.wiley.com/doi/abs/10.1111/eci.14217
8. Akbari, B., Baghaei-Yazdi, N., Bahmaie, M., & Mahdavi Abhari, F. (2022). The role of plant-derived natural antioxidants in reduction of oxidative stress. *BioFactors*, *48*(3), 611-633. https://iubmb.onlinelibrary.wiley.com/doi/abs/10.1002/biof.1831
9. Akbarirad, H., Ardabili, A. G., Kazemeini, S. M., & Khaneghah, A. M. (2016). An overview on some of important sources of natural antioxidants. *International food research journal*, *23*(3). http://ifrj.upm.edu.my/23%20(03)%202016/(3).pdf
10. Alam, M., Ali, S., Ashraf, G. M., Bilgrami, A. L., Yadav, D. K., & Hassan, M. I. (2022a). Epigallocatechin 3-gallate: From green tea to cancer therapeutics. *Food chemistry*, *379*, 132135. https://www.sciencedirect.com/science/article/abs/pii/S0308814622000966
11. Alam, M., Ahmed, S., Elasbali, A. M., Adnan, M., Alam, S., Hassan, M. I., & Pasupuleti, V. R. (2022b). Therapeutic implications of caffeic acid in cancer and neurological diseases. *Frontiers in oncology*, *12*, 860508. https://www.frontiersin.org/journals/oncology/articles/10.3389/fonc.2022.860508/full
12. Al-Dabbagh, B., Elhaty, I. A., Elhaw, M., Murali, C., Al Mansoori, A., Awad, B., & Amin, A. (2019). Antioxidant and anticancer activities of chamomile (Matricaria recutita L.). *BMC research notes*, *12*(1), 3. https://link.springer.com/article/10.1186/s13104-018-3960-y
13. Ali, W., Khan, A., Yousafzai, A., Rabi, F., & Idrees, M. (2025). Nanoparticles Enhancing the Production of Key Phytochemicals: A Comprehensive Review. *Journal of Health, Wellness, and Community Research*, e59-e59. https://jhwcr.com/index.php/jhwcr/article/view/59
14. Amarowicz, R., & Pegg, R. B. (2019). Natural antioxidants of plant origin. In *Advances in food and nutrition research* (Vol. 90, pp. 1-81). Academic Press. https://www.sciencedirect.com/science/article/abs/pii/S1043452619300269
15. Amin, J., Djajadisastra, J., Syafhan, N. F., Simamora, E. L. P., & Wulandari, K. (2019). Green tea [Camellia sinensis (L.) Kuntze] leaves extract and hibiscus (Hibiscus tilliaceus L.) leaves extract as topical hair growth promoter in microemulsion. *Agriculture And Natural Resources*, *53*(2), 139-147. https://li01.tci-thaijo.org/index.php/anres/article/view/229911
16. Arif, T. (2015). Salicylic acid as a peeling agent: a comprehensive review. *Clinical, cosmetic and investigational dermatology*, 455-461. https://www.tandfonline.com/doi/full/10.2147/CCID.S84765#media-abstract
17. Atta, E. M., Mohamed, N. H., & Abdelgawad, A. A. (2017). Antioxidants: An overview on the natural and synthetic types. *Eur. Chem. Bull*, *6*(8), 365-375. https://pdfs.semanticscholar.org/9583/f82c3cdb5aaea234939b1dbd5806e48be1c5.pdf
18. Babanyaya, A., Mustapha, A. B., Dwanga, D. M., Abubakar, D., Bioltif, Y. E., Abubakar, M. Y., & Adam, A. B. (2024). Industrial Scale Production of Phytochemicals for Cancer Prevention: Challenges and Opportunities. *Journal Pembelajaran Kimia,* 9(1), 19-39. https://www.researchgate.net/profile/Ansar-Adam/publication/387441413_Industrial_Scale_Production_of_Phytochemicals_for_Cancer_Prevention_Challenges_and_Opportunities/links/676e32c800aa3770e0bd746b/Industrial-Scale-Production-of-Phytochemicals-for-Cancer-Prevention-Challenges-and-Opportunities.pdf
19. Bangar, S. P., Chaudhary, V., Sharma, N., Bansal, V., Ozogul, F., & Lorenzo, J. M. (2023). Kaempferol: A flavonoid with wider biological activities and its applications. *Critical Reviews in Food science and nutrition*, *63*(28), 9580-9604. https://www.tandfonline.com/doi/abs/10.1080/10408398.2022.2067121
20. Bilia, A. R., Bergonzi, M. C., Boulos, J. C., & Efferth, T. (2020). Nanocarriers to enhance solubility, bioavailability, and efficacy of artemisinins. *World Journal of Traditional Chinese Medicine*, *6*(1), 26-36. https://journals.lww.com/wtcm/fulltext/2020/06010/Nanocarriers_to_Enhance_Solubility,.3.aspx
21. Cao, J., Han, J., Xiao, H., Qiao, J., & Han, M. (2016). Effect of tea polyphenol compounds on anticancer drugs in terms of anti-tumor activity, toxicology, and pharmacokinetics. *Nutrients*, *8*(12), 762. https://www.mdpi.com/2072-6643/8/12/762

 doi:10.20944/preprints202508.1190.v1




22. Cervantes-Anaya, N., Azpilcueta-Morales, G., Estrada-Camarena, E., Ramírez Ortega, D., Pérez de la Cruz, V., González-Trujano, M. E., & López-Rubalcava, C. (2022). Pomegranate and its components, punicalagin and ellagic acid, promote antidepressant, antioxidant, and free radical-scavenging activity in ovariectomized rats. *Frontiers in Behavioral Neuroscience*, *16*, 836681. https://www.frontiersin.org/journals/behavioral-neuroscience/articles/10.3389/fnbeh.2022.836681/full
23. Chandekar, L., Katgeri, R., & Takke, A. (2022). The potential clinical uses and nanoformulation strategies of kaempferol, a dietary flavonoid. *Revista Brasileira De Farmacognosia*, *32*(5), 693-707. https://link.springer.com/article/10.1007/s43450-022-00290-6
24. Chaudhary, P., Janmeda, P., Docea, A. O., Yeskaliyeva, B., Abdull Razis, A. F., Modu, B., Calina, D., & Sharifi-Rad, J. (2023). Oxidative stress, free radicals and antioxidants: potential crosstalk in the pathophysiology of human diseases. *Frontiers in chemistry*, *11*, 1158198. https://www.frontiersin.org/journals/chemistry/articles/10.3389/fchem.2023.1158198/full
25. Chen, F., Xiao, M., Hu, S., & Wang, M. (2024). Keap1-Nrf2 pathway: a key mechanism in the occurrence and development of cancer. *Frontiers in oncology*, *14*, 1381467. https://pmc.ncbi.nlm.nih.gov/articles/PMC11021590/
26. Chen, P., Chen, F., Guo, Z., Lei, J., & Zhou, B. (2023a). Recent advancement in bioeffect, metabolism, stability, and delivery systems of apigenin, a natural flavonoid compound: Challenges and perspectives. *Frontiers in Nutrition*, *10*, 1221227. https://www.frontiersin.org/journals/nutrition/articles/10.3389/fnut.2023.1221227/full
27. Chen, P., Zou, F., & Liu, W. (2025). Recent advancement in prevention against hepatotoxicity, molecular mechanisms, and bioavailability of gallic acid, a natural phenolic compound: challenges and perspectives. *Frontiers in Pharmacology*, *16*, 1549526. https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2025.1549526/full
28. Chen, S., Wang, X., Cheng, Y., Gao, H., & Chen, X. (2023b). A review of classification, biosynthesis, biological activities and potential applications of flavonoids. *Molecules*, *28*(13), 4982. https://www.mdpi.com/1420-3049/28/13/4982
29. Choi, S. S., Lee, S. H., & Lee, K. A. (2022). A comparative study of hesperetin, hesperidin and hesperidin glucoside: antioxidant, anti-inflammatory, and antibacterial activities in vitro. *Antioxidants*, *11*(8), 1618. https://www.mdpi.com/2076-3921/11/8/1618
30. Choudhary, H. R., Kumar B, D., Kadiri, S. K., Khobragade, D. S., & Tiwari, P. (2025). Integrating Biosensors in Phytochemical Research: Challenges and Breakthroughs. *Recent Patents on Biotechnology*. https://www.benthamdirect.com/content/journals/biot/10.2174/0118722083381223250612181959
31. Ciriminna, R., Petri, G. L., Angellotti, G., Luque, R., Fabiano Tixier, A. S., Meneguzzo, F., & Pagliaro, M. (2025). Citrus flavonoids as antimicrobials. *Chemistry & Biodiversity*, *22*(6), e202403210. https://onlinelibrary.wiley.com/doi/full/10.1002/cbdv.202403210
32. Črnivec, I. G. O., Skrt, M., Šeremet, D., Sterniša, M., Farčnik, D., Štrumbelj, E., Poljanšek, A., Cebin, N., Pogačnik, L., Možina, S.S. and Humar, M., & Ulrih, N. P. (2021). Waste streams in onion production: Bioactive compounds, quercetin and use of antimicrobial and antioxidative properties. *Waste management*, *126*, 476-486. https://www.sciencedirect.com/science/article/abs/pii/S0956053X21001756
33. Dai, X., Zhang, X., Chen, W., Chen, Y., Zhang, Q., Mo, S., & Lu, J. (2021). Dihydroartemisinin: a potential natural anticancer drug. *International Journal of Biological Sciences*, *17*(2), 603. https://pmc.ncbi.nlm.nih.gov/articles/PMC7893584/
34. Das, S., Kwon, M., & Kim, J. Y. (2024). Enhancement of specialized metabolites using CRISPR/Cas gene editing technology in medicinal plants. *Frontiers in plant science*, *15*, 1279738. https://www.frontiersin.org/journals/plant-science/articles/10.3389/fpls.2024.1279738/full
35. Davidova, S., Galabov, A. S., & Satchanska, G. (2024). Antibacterial, antifungal, antiviral activity, and mechanisms of action of plant polyphenols. *Microorganisms*, *12*(12), 2502. https://www.mdpi.com/2076-2607/12/12/2502
36. de Lima Cherubim, D. J., Buzanello Martins, C. V., Oliveira Fariña, L., & da Silva de Lucca, R. A. (2020). Polyphenols as natural antioxidants in cosmetics applications. *Journal of cosmetic dermatology*, *19*(1), 33-37. https://onlinelibrary.wiley.com/doi/abs/10.1111/jocd.13093

 doi:10.20944/preprints202508.1190.v1




37. De, R., Sarkar, A., Ghosh, P., Ganguly, M., Karmakar, B. C., Saha, D. R., Halder, A., Chowdhury, A., & Mukhopadhyay, A. K. (2018). Antimicrobial activity of ellagic acid against Helicobacter pylori isolates from India and during infections in mice. *Journal of Antimicrobial Chemotherapy*, *73*(6), 1595-1603. https://academic.oup.com/jac/article/73/6/1595/4939530
38. Diab, M. K., Abu-Elsaoud, A. M., Salama, M. G., & Ghareeb, E. M. (2025). Phytochemical treasure troves—insights into bioactivities, phytochemistry, and uses of Artemisia species. *Phytochemistry Reviews*, 1-38. https://link.springer.com/article/10.1007/s11101-025-10163-0
39. Dibal, N. I., Garba, S. H., & Jacks, T. W. (2020). Acute toxicity of quercetin from onion skin in mice. *Pharmaceutical and Biomedical Research*. https://publish.kne-publishing.com/index.php/PBR/article/view/5113
40. Ding, Y., & Yu, Y. (2025). Therapeutic potential of flavonoids in gastrointestinal cancer: Focus on signaling pathways and improvement strategies. *Molecular Medicine Reports*, *31*(4), 109. https://www.spandidos-publications.com/10.3892/mmr.2025.13474
41. Du, W., Zhou, M., Liu, Z., Chen, Y., & Li, R. (2018). Inhibition effects of low concentrations of epigallocatechin gallate on the biofilm formation and hemolytic activity of Listeria monocytogenes. *Food Control*, *85*, 119-126. https://www.sciencedirect.com/science/article/abs/pii/S0956713517304450
42. EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), Younes, M., Aggett, P., Aguilar, F., Crebelli, R., Dusemund, B., Filipič, M., Frutos, M.J., Galtier, P., Gott, D. and Gundert-Remy, U., & Wright, M. (2018). Scientific opinion on the safety of green tea catechins. *EFSA journal*, *16*(4), e05239. https://efsa.onlinelibrary.wiley.com/doi/full/10.2903/j.efsa.2018.5239
43. El-Rayes, T. K., El Basuini, M. F., Elghioushy, A. B., El-Damrawy, S. Z., Mamdouh, M., Taha, A. E., & Abd El-Hack, M. E. (2025). Dietary inclusion of Artemisia annua improves antioxidant performance, immunoglobulin protein levels, lipid profile, carcass characteristics, meat quality, and histomorphometric features of broiler chickens. *Annals of Animal Science*, *25*(1), 225-238. https://www.proquest.com/openview/c14a38224c48e74ccf76f6c2c1b8cb13/1?pq-origsite=gscholar&cbl=1976406
44. Evtyugin, D. D., Magina, S., & Evtuguin, D. V. (2020). Recent advances in the production and applications of ellagic acid and its derivatives. A review. *Molecules*, *25*(12), 2745. https://www.mdpi.com/1420-3049/25/12/2745
45. Faria, W. C. S., da Silva, A. A., Veggi, N., Kawashita, N. H., de França Lemes, S. A., de Barros, W. M., da Conceiçao Cardoso, E., Converti, A., de Melo Moura, W., & Bragagnolo, N. (2020). Acute and subacute oral toxicity assessment of dry encapsulated and non-encapsulated green coffee fruit extracts. *Journal of Food and Drug Analysis*, *28*(2), 337. https://pmc.ncbi.nlm.nih.gov/articles/PMC9261855/
46. Feng, M. X., Hong, J. X., Wang, Q., Fan, Y. Y., Yuan, C. T., Lei, X. H., Zhu, M., Qin, A., Chen, H.X., & Hong, D. (2016). Dihydroartemisinin prevents breast cancer-induced osteolysis via inhibiting both breast caner cells and osteoclasts. *Scientific reports*, *6*(1), 19074. https://www.nature.com/articles/srep19074
47. Franco, E. P. D. D., Contesini, F. J., Lima da Silva, B., Alves de Piloto Fernandes, A. M., Wielewski Leme, C., Goncalves Cirino, J. P., Bueno Campos, P.R., & de Oliveira Carvalho, P. (2020). Enzyme-assisted modification of flavonoids from Matricaria chamomilla: antioxidant activity and inhibitory effect on digestive enzymes. *Journal of enzyme inhibition and medicinal chemistry*, *35*(1), 42-49. https://www.tandfonline.com/doi/full/10.1080/14756366.2019.1681989
48. Fuentes, J., Arias-Santé, M. F., Atala, E., Pastene, E., Kogan, M. J., & Speisky, H. (2020). Low nanomolar concentrations of a quercetin oxidation product, which naturally occurs in onion peel, protect cells against oxidative damage. *Food Chemistry*, *314*, 126166. https://www.sciencedirect.com/science/article/abs/pii/S0308814620300108
49. Furniturewalla, A., & Barve, K. (2022). Approaches to overcome bioavailability inconsistencies of epigallocatechin gallate, a powerful anti-oxidant in green tea. *Food Chemistry Advances*, *1*, 100037. https://www.sciencedirect.com/science/article/pii/S2772753X22000259
50. Gan, L., Wang, W., Jiang, J., Tian, K., Liu, W., & Cao, Z. (2024). Dual role of Nrf2 signaling in hepatocellular carcinoma: promoting development, immune evasion, and therapeutic challenges. *Frontiers in*

 doi:10.20944/preprints202508.1190.v1



*Immunology*, *15*, 1429836. https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2024.1429836/full

51. Gang, G., Gao, R., Li, R., Jin, X., Xing, Y., Yan, S., Xu, Y., & Shi, B. (2025). Study on the Regulatory Effect of Water Extract of Artemisia annua L. on Antioxidant Function of Mutton Sheep via the Keap1/Nrf2 Signaling Pathway. *Antioxidants*, *14*(7), 885. https://www.mdpi.com/2076-3921/14/7/885
52. Gang, G., Gao, R., Zhao, H., Xu, Y., Xing, Y., Jin, X., Hong, L., Yan, S., & Shi, B. (2024). Effects of water extracts of Artemisia annua L. on rumen immune and antioxidative indexes, fermentation parameters and microbials diversity in lambs. *Frontiers in Microbiology*, *15*, 1485882. https://www.frontiersin.org/journals/microbiology/articles/10.3389/fmicb.2024.1485882/full
53. Gao, H., Pei, X., Song, X., Wang, S., Yang, Z., Zhu, J., Lin, Q., Zhu, Q., & Yang, X. (2025). Application and development of CRISPR technology in the secondary metabolic pathway of the active ingredients of phytopharmaceuticals. *Frontiers in Plant Science*, *15*, 1477894. https://www.frontiersin.org/journals/plant-science/articles/10.3389/fpls.2024.1477894/full
54. Gavarić, N., Aćimović, M., Kladar, N., Hitl, M., Drljača Lero, J., Milić, N., & Radovanović, K. (2025). Unlocking the Bioactivity of Sweet Wormwood (Artemisia annua L., Asteraceae) Ethanolic Extract: Phenolics, Antioxidants, and Cytotoxic Effects. *Pharmaceutics*, *17*(7), 890. https://www.mdpi.com/1999-4923/17/7/890
55. Grzelak-Błaszczyk, K., Milala, J., Kosmala, M., Kołodziejczyk, K., Sójka, M., Czarnecki, A., Klewicki, R., Juśkiewicz, J., Fotschki, B & Jurgoński, A. (2018). Onion quercetin monoglycosides alter microbial activity and increase antioxidant capacity. *The Journal of Nutritional Biochemistry*, *56*, 81-88. https://www.sciencedirect.com/science/article/abs/pii/S0955286317304060
56. Hadidi, M., Orellana-Palacios, J. C., Aghababaei, F., Gonzalez-Serrano, D. J., Moreno, A., & Lorenzo, J. M. (2022). Plant by-product antioxidants: Control of protein-lipid oxidation in meat and meat products. *Lwt*, *169*, 114003. https://www.sciencedirect.com/science/article/pii/S0023643822009380
57. Halliwell, B. (2024). Understanding mechanisms of antioxidant action in health and disease. *Nature Reviews Molecular Cell Biology*, *25*(1), 13-33. https://www.nature.com/articles/s41580-023-00645-4
58. Hasan, Z., Islam, A., & Khan, L. A. (2023). Spectroscopic investigations on fungal aspartic protease as target of gallic acid. *International Journal of Biological Macromolecules*, *228*, 333-345. https://www.sciencedirect.com/science/article/abs/pii/S0141813022031294
59. Hoang, H. T., Moon, J. Y., & Lee, Y. C. (2021). Natural antioxidants from plant extracts in skincare cosmetics: Recent applications, challenges and perspectives. *Cosmetics*, *8*(4), 106. https://www.mdpi.com/2079-9284/8/4/106
60. Huang, Z., Gan, S., Zhuang, X., Chen, Y., Lu, L., Wang, Y., Qi, X., Feng, Q., Huang, Q., Du, B. and Zhang, R., & Liu, Z. (2022). Artesunate inhibits the cell growth in colorectal cancer by promoting ROS-dependent cell senescence and autophagy. *Cells*, *11*(16), 2472. https://www.mdpi.com/2073-4409/11/16/2472
61. Hussain, Y., Khan, H., Alsharif, K. F., Hayat Khan, A., Aschner, M., & Saso, L. (2022). The therapeutic potential of kaemferol and other naturally occurring polyphenols might be modulated by Nrf2-ARE signaling pathway: Current status and future direction. *Molecules*, *27*(13), 4145. https://www.mdpi.com/1420-3049/27/13/4145
62. Ikawa, M., Okazawa, H., & Yoneda, M. (2021). Molecular imaging for mitochondrial metabolism and oxidative stress in mitochondrial diseases and neurodegenerative disorders. *Biochimica et Biophysica Acta (BBA)-General Subjects*, *1865*(3), 129832. https://www.sciencedirect.com/science/article/abs/pii/S0304416520303433
63. Jan, R., Khan, M., Asaf, S., Lubna, Asif, S., & Kim, K. M. (2022). Bioactivity and therapeutic potential of kaempferol and quercetin: new insights for plant and human health. *Plants*, *11*(19), 2623. https://www.mdpi.com/2223-7747/11/19/2623
64. Jia, X., Wang, L., Zhao, H., Zhang, Y., Chen, Z., Xu, L., & Yi, K. (2023). The origin and evolution of salicylic acid signaling and biosynthesis in plants. *Molecular Plant*, *16*(1), 245-259. https://www.cell.com/molecular-plant/fulltext/S1674-2052(22)00437-3

 doi:10.20944/preprints202508.1190.v1




65. Jomova, K., Alomar, S. Y., Valko, R., Liska, J., Nepovimova, E., Kuca, K., & Valko, M. (2025). Flavonoids and their role in oxidative stress, inflammation, and human diseases. *Chemico-Biological Interactions*, 111489. https://www.sciencedirect.com/science/article/pii/S000927972500119X
66. Kandemir, K., Tomas, M., McClements, D. J., & Capanoglu, E. (2022). Recent advances on the improvement of quercetin bioavailability. *Trends in Food Science & Technology*, *119*, 192-200. https://www.sciencedirect.com/science/article/abs/pii/S0924224421006506
67. Karalija, E., Macanović, A., & Ibragić, S. (2025). Revisiting Traditional Medicinal Plants: Integrating Multiomics, In Vitro Culture, and Elicitation to Unlock Bioactive Potential. *Plants*, *14*(13), 2029. https://pmc.ncbi.nlm.nih.gov/articles/PMC12252194/
68. Kazmi, S. T. B., Fatima, H., Naz, I., Kanwal, N., & Haq, I. U. (2024). Pre-clinical studies comparing the anti-inflammatory potential of artemisinic compounds by targeting NFκB/TNF-α/NLRP3 and Nrf2/TRX pathways in Balb/C mice. *Frontiers in Pharmacology*, *15*, 1352827. https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2024.1352827/full
69. Khalil, I., Yehye, W. A., Etxeberria, A. E., Alhadi, A. A., Dezfooli, S. M., Julkapli, N. B. M., Basirun, W.J., & Seyfoddin, A. (2019). Nanoantioxidants: Recent trends in antioxidant delivery applications. *Antioxidants*, *9*(1), 24. https://www.mdpi.com/2076-3921/9/1/24#
70. Khan, A., Ikram, M., Hahm, J. R., & Kim, M. O. (2020). Antioxidant and anti-inflammatory effects of citrus flavonoid hesperetin: Special focus on neurological disorders. *Antioxidants*, *9*(7), 609. https://www.mdpi.com/2076-3921/9/7/609
71. Khan, F. A., Maalik, A., & Murtaza, G. (2016). Inhibitory mechanism against oxidative stress of caffeic acid. *Journal of Food and Drug Analysis*, *24*(4), 695-702. https://www.sciencedirect.com/science/article/pii/S102194981630045X
72. Kim, W. S., Choi, W. J., Lee, S., Kim, W. J., Lee, D. C., Sohn, U. D., Shin, H.S., & Kim, W. (2015). Anti-inflammatory, antioxidant and antimicrobial effects of artemisinin extracts from Artemisia annua L. *The Korean Journal of Physiology and Pharmacology*, *19*(1), 21-27. https://pdfs.semanticscholar.org/d5fc/35f1a9ae3f91f2436307d8372b3f7059979e.pdf
73. Kishi, S., Nagasu, H., Kidokoro, K., & Kashihara, N. (2024). Oxidative stress and the role of redox signalling in chronic kidney disease. *Nature Reviews Nephrology*, *20*(2), 101-119. https://www.nature.com/articles/s41581-023-00775-0
74. Kochan, E., Szymczyk, P., Kuźma, Ł., Lipert, A., & Szymańska, G. (2017). Yeast extract stimulates ginsenoside production in hairy root cultures of American ginseng cultivated in shake flasks and nutrient sprinkle bioreactors. *Molecules*, *22*(6), 880. https://www.mdpi.com/1420-3049/22/6/880
75. Korobkova, E. A. (2015). Effect of natural polyphenols on CYP metabolism: implications for diseases. *Chemical research in toxicology*, *28*(7), 1359-1390. https://pubs.acs.org/doi/abs/10.1021/acs.chemrestox.5b00121
76. Kuang, M., Cen, Y., Qin, R., Shang, S., Zhai, Z., Liu, C., Pan, X., & Zhou, H. (2018). Artesunate attenuates pro-inflammatory cytokine release from macrophages by inhibiting TLR4-mediated autophagic activation via the TRAF6-Beclin1-PI3KC3 pathway. *Cellular Physiology and Biochemistry*, *47*(2), 475-488. https://karger.com/cpb/article/47/2/475/73663
77. Lala, S. (2021). Nanoparticles as elicitors and harvesters of economically important secondary metabolites in higher plants: A review. *IET nanobiotechnology*, *15*(1), 28-57. https://ietresearch.onlinelibrary.wiley.com/doi/full/10.1049/nbt2.12005
78. Laurindo, L. F., de Maio, M. C., Minniti, G., de Góes Corrêa, N., Barbalho, S. M., Quesada, K., Guiguer, E.L., Sloan, K.P., Detregiachi, C.R., Araújo, A.C., & de Alvares Goulart, R. (2023). Effects of medicinal plants and phytochemicals in Nrf2 pathways during inflammatory bowel diseases and related colorectal cancer: a comprehensive review. *Metabolites*, *13*(2), 243. https://www.mdpi.com/2218-1989/13/2/243
79. Le, B., Anh, P. T. N., Kim, J. E., Cheng, J., & Yang, S. H. (2019). Rice bran fermentation by lactic acid bacteria to enhance antioxidant activities and increase the ferulic acid, ϱ-coumaric acid, and γ-oryzanol content. *Journal of Applied Biological Chemistry*, *62*(3), 257-264.

 doi:10.20944/preprints202508.1190.v1




80. Lee, R., Lee, W. Y., Kim, D. W., & Park, H. J. (2025). Artemisinin alleviates cisplatin-induced damage in GC-1 spermatogonia through ER stress mechanisms. *Heliyon*, *11*(4). https://www.cell.com/heliyon/fulltext/S2405-8440(25)00959-4
81. Le, N. P. K., Herz, C., Gomes, J. V. D., Förster, N., Antoniadou, K., Mittermeier-Kleßinger, V. K., Mewis, I., Dawid, C., Ulrichs, C., & Lamy, E. (2021). Comparative anti-inflammatory effects of Salix cortex extracts and acetylsalicylic acid in SARS-CoV-2 peptide and LPS-activated human in vitro systems. *International journal of molecular sciences*, *22*(13), 6766. https://www.mdpi.com/1422-0067/22/13/6766
82. Lee, E. J., Patil, B. S., & Yoo, K. S. (2015). Antioxidants of 15 onions with white, yellow, and red colors and their relationship with pungency, anthocyanin, and quercetin. *LWT-Food Science and Technology*, *63*(1), 108-114. https://www.sciencedirect.com/science/article/abs/pii/S0023643815001814
83. Les, F., Prieto, J. M., Arbonés-Mainar, J. M., Valero, M. S., & López, V. (2015). Bioactive properties of commercialised pomegranate (Punica granatum) juice: antioxidant, antiproliferative and enzyme inhibiting activities. *Food & function*, *6*(6), 2049-2057.
84. https://pubs.rsc.org/en/content/articlelanding/2015/fo/c5fo00426h/unauth
85. Li, J., Yu, Q., Liu, C., Zhang, N., & Xu, W. (2025). Flavonoids as key players in cold tolerance: molecular insights and applications in horticultural crops. *Horticulture research*, *12*(4), uhae366. https://academic.oup.com/hr/article/12/4/uhae366/7941691
86. Liu, R., & Mabury, S. A. (2020). Synthetic phenolic antioxidants: A review of environmental occurrence, fate, human exposure, and toxicity. *Environmental science & technology*, *54*(19), 11706-11719. https://pubs.acs.org/doi/abs/10.1021/acs.est.0c05077
87. Liu, S., Xu, S., Wei, R., Cui, Z., Wu, X., Wei, R., ... & Chen, W. (2019). Keap1 cystenine 151 as a potential target for artemisitene-induced Nrf2 activation. *BioMed Research International*, *2019*(1), 5198138. https://onlinelibrary.wiley.com/doi/full/10.1155/2019/5198138
88. Lourenço, S. C., Moldão-Martins, M., & Alves, V. D. (2019). Antioxidants of natural plant origins: From sources to food industry applications. *Molecules*, *24*(22), 4132. https://www.mdpi.com/1420-3049/24/22/4132
89. Lv, Y., Li, W., Liao, W., Jiang, H., Liu, Y., Cao, J., ... & Feng, Y. (2024). Nano-drug delivery systems based on natural products. *International Journal of Nanomedicine*, 541-569. https://www.tandfonline.com/doi/full/10.2147/IJN.S443692#abstract
90. Maistro, E. L., Terrazzas, P. M., Sawaya, A. C. H. F., Rosa, P. C. P., Perazzo, F. F., & de Mascarenhas Gaivão, I. O. N. (2022). In vivo toxicogenic potential of Salix alba (Salicaceae) bark extract. *Journal of Toxicology and Environmental Health, Part A*, *85*(3), 121-130. https://www.tandfonline.com/doi/abs/10.1080/15287394.2021.1989351
91. Mishra, S., Khushtar, M., & Ahmad, U. (2025). Recent Advances in the Pharmacological Potential of Quercetin and Kaempferol: Mechanisms, Therapeutic Applications, and Future Perspectives-A Comprehensive Review. *Cuestiones de Fisioterapia*, *54*(4), 5497-5505. (PDF available)
92. Mittal, G., Prashanth, A., Dhali, A., Prasad, R., Yogesh, S., Nurani, K. M., & Găman, M. A. (2025). Plant extracts with antioxidant and hepatoprotective benefits for liver health: A bibliometric analysis of drug delivery systems. *World Journal of Gastroenterology*, *31*(18), 105836. https://pmc.ncbi.nlm.nih.gov/articles/PMC12146923
93. Moazzen, A., Öztinen, N., Ak-Sakalli, E., & Koşar, M. (2022). Structure-antiradical activity relationships of 25 natural antioxidant phenolic compounds from different classes. *Heliyon*, *8*(9). https://www.cell.com/heliyon/fulltext/S2405-8440(22)01755-8
94. Mohammed, H. A., Emwas, A. H., & Khan, R. A. (2023). Salt-tolerant plants, halophytes, as renewable natural resources for cancer prevention and treatment: roles of phenolics and flavonoids in immunomodulation and suppression of oxidative stress towards cancer management. *International Journal of Molecular Sciences*, *24*(6), 5171. https://www.mdpi.com/1422-0067/24/6/5171
95. Mohammed, M. J., Anand, U., Altemimi, A. B., Tripathi, V., Guo, Y., & Pratap-Singh, A. (2021). Phenolic composition, antioxidant capacity and antibacterial activity of white wormwood (Artemisia herba-alba). *Plants*, *10*(1), 164. https://www.mdpi.com/2223-7747/10/1/164

 doi:10.20944/preprints202508.1190.v1




96. Molaei, E., Molaei, A., Abedi, F., Hayes, A. W., & Karimi, G. (2021). Nephroprotective activity of natural products against chemical toxicants: The role of Nrf2/ARE signaling pathway. *Food Science & Nutrition*, *9*(6), 3362-3384. https://onlinelibrary.wiley.com/doi/full/10.1002/fsn3.2320
97. Moore, C. M., Wang, J., Lin, Q., Ferreira, P., Avery, M. A., Elokely, K., ... & Krishna, S. (2022). Selective inhibition of Plasmodium falciparum ATPase 6 by artemisinins and identification of new classes of inhibitors after expression in yeast. *Antimicrobial Agents and Chemotherapy*, *66*(5), e02079-21. https://journals.asm.org/doi/full/10.1128/aac.02079-21
98. Morua, E., Cuyas, L., & Matías-Hernández, L. (2025). The Beneficial Use of Artemisia annua, Artemisinin, and Other Compounds in Animal Health. *Animals*, *15*(10), 1359. https://www.mdpi.com/2076-2615/15/10/1359#
99. Mude, H., Maroju, P. A., Balapure, A., Ganesan, R., & Dutta, J. R. (2022). Water-soluble caffeic acid-dopamine acid-base complex exhibits enhanced bactericidal, antioxidant, and anticancer properties. *Food Chemistry*, *374*, 131830. https://www.sciencedirect.com/science/article/abs/pii/S0308814621028363
100. Mutha, R. E., Tatiya, A. U., & Surana, S. J. (2021). Flavonoids as natural phenolic compounds and their role in therapeutics: An overview. *Future journal of pharmaceutical sciences*, *7*(1), 25. https://link.springer.com/article/10.1186/s43094-020-00161-8
101. Nair, B., Menon, A., Rithwik Kalidas, M., Nath, L. R., Calina, D., & Sharifi-Rad, J. (2025). Modulating the JAK/STAT pathway with natural products: potential and challenges in cancer therapy. *Discover Oncology*, *16*(1), 1-23. https://link.springer.com/article/10.1007/s12672-025-02369-7
102. Nam, D. G., Kim, M., Choi, A. J., & Choe, J. S. (2024). Health benefits of antioxidant bioactive compounds in ginger (Zingiber officinale) leaves by network pharmacology analysis combined with experimental validation. *Antioxidants*, *13*(6), 652. https://www.mdpi.com/2076-3921/13/6/652
103. Naraki, K., Rameshrad, M., & Hosseinzadeh, H. (2022). Protective effects and therapeutic applications of ellagic acid against natural and synthetic toxicants: A review article. *Iranian journal of basic medical sciences*, *25*(12), 1402. https://pmc.ncbi.nlm.nih.gov/articles/PMC9742565/
104. Nuryana, I., Ratnakomala, S., Fahrurrozi, A. B. J., Andriani, A., Putra, F. J. N., Rezamela, E., Wulansari, R., Prawira-Atmaja, M.I., & Lisdiyanti, P. (2020). Catechin contents, antioxidant and antibacterial activities of different types of Indonesian tea (Camellia sinensis). *Ann. Bogor*, *24*, 107. https://www.researchgate.net/profile/Isa-Nuryana/publication/348264057_Catechin_Contents_Antioxidant_and_Antibacterial_Activities_of_Different_Types_of_Indonesian_Tea_Camellia_sinensis/links/5ff55a90299bf1408874f73c/Catechin-Contents-Antioxidant-and-Antibacterial-Activities-of-Different-Types-of-Indonesian-Tea-Camellia-sinensis.pdf
105. Nwozo, O. S., Effiong, E. M., Aja, P. M., & Awuchi, C. G. (2023). Antioxidant, phytochemical, and therapeutic properties of medicinal plants: A review. *International Journal of Food Properties*, *26*(1), 359-388. https://www.tandfonline.com/doi/full/10.1080/10942912.2022.2157425
106. Osonwa, U. E., & Hu, M. (2018). Bioavailability and Pharmacokinetics of Dihydroartemisinin (DHA) and its Analogs—Mechanistic Studies on its ADME. *Current Pharmacology Reports*, *4*(1), 33-44. https://link.springer.com/article/10.1007/s40495-018-0120-y
107. Pan, L., Wang, Q., Li, W., Dong, X., Xie, S., Tan, B., Liu, H., & Wang, Y. (2025). Artemisinin supplementation in concentrated cottonseed protein basal diets enhances growth, antioxidant capacity, intestinal immunity and microbiota in hybrid grouper (Epinephelus fuscoguttatus♀× E. lanceolatus♂). *Aquaculture Reports*, *41*, 102659. https://www.sciencedirect.com/science/article/pii/S2352513425000456
108. Pavlova, E. L., Zografov, N. N., & Simeonova, L. S. (2016). Comparative study on the antioxidant capacities of synthetic influenza inhibitors and ellagic acid in model systems. *Biomedicine & Pharmacotherapy*, *83*, 755-762.
109. https://www.sciencedirect.com/science/article/abs/pii/S0753332216306886
110. Pawłowska, M., Nuszkiewicz, J., Jarek, D. J., & Woźniak, A. (2025). Ferroptosis and Metabolic Dysregulation: Emerging Chemical Targets in Cancer and Infection. *Molecules*, *30*(14), 3020. https://www.mdpi.com/1420-3049/30/14/3020
111. Perez-Ternero, C., Werner, C. M., Nickel, A. G., Herrera, M. D., Motilva, M. J., Böhm, M., de Sotomayor, M.A & Laufs, U. (2017). Ferulic acid, a bioactive component of rice bran, improves oxidative stress and

 doi:10.20944/preprints202508.1190.v1



mitochondrial biogenesis and dynamics in mice and in human mononuclear cells. *The Journal of Nutritional Biochemistry*, *48*, 51-61. https://www.sciencedirect.com/science/article/abs/pii/S0955286316306052

112. Parveen, B., Rajinikanth, V., & Narayanan, M. (2025). Natural plant antioxidants for food preservation and emerging trends in nutraceutical applications. *Discover Applied Sciences*, *7*(8), 845. https://link.springer.com/article/10.1007/s42452-025-07464-6
113. Patel, J., Roy, H., Chintamaneni, P. K., Patel, R., & Bohara, R. (2025). Advanced strategies in enhancing the hepatoprotective efficacy of natural products: integrating nanotechnology, genomics, and mechanistic insights. *ACS Biomaterials Science & Engineering*, *11*(5), 2528-2549. https://pubs.acs.org/doi/full/10.1021/acsbiomaterials.5c00004
114. Pham, D. C., Shibu, M. A., Mahalakshmi, B., & Velmurugan, B. K. (2020). Effects of phytochemicals on cellular signaling: reviewing their recent usage approaches. *Critical reviews in food science and nutrition*, *60*(20), 3522-3546. https://www.tandfonline.com/doi/abs/10.1080/10408398.2019.1699014
115. Piątczak, E., Dybowska, M., Płuciennik, E., Kośla, K., Kolniak-Ostek, J., & Kalinowska-Lis, U. (2020). Identification and accumulation of phenolic compounds in the leaves and bark of Salix alba (L.) and their biological potential. *Biomolecules*, *10*(10), 1391. https://www.mdpi.com/2218-273X/10/10/1391
116. Pillai, R., Hayashi, M., Zavitsanou, A. M., & Papagiannakopoulos, T. (2022). NRF2: KEAPing tumors protected. *Cancer Discovery*, *12*(3), 625-643. https://pmc.ncbi.nlm.nih.gov/articles/PMC8904278
117. Pooja, G., Shweta, S., & Patel, P. (2025). Oxidative stress and free radicals in disease pathogenesis: a review. *Discover Medicine*, *2*(1), 104. https://link.springer.com/article/10.1007/s44337-025-00303-y
118. Quecan, B. X., Santos, J. T., Rivera, M. L., Hassimotto, N. M., Almeida, F. A., & Pinto, U. M. (2019). Effect of quercetin rich onion extracts on bacterial quorum sensing. *Frontiers in Microbiology*, *10*, 867. https://www.frontiersin.org/journals/microbiology/articles/10.3389/fmicb.2019.00867/full
119. Rahman, M. M., Rahaman, M. S., Islam, M. R., Rahman, F., Mithi, F. M., Alqahtani, T., Almikhlafi, M.A., Alghamdi, S.Q., Alruwaili, A.S., Hossain, M.S. and Ahmed, M., & Uddin, M. S. (2021). Role of phenolic compounds in human disease: current knowledge and future prospects. *Molecules*, *27*(1), 233. https://www.mdpi.com/1420-3049/27/1/233
120. Randjelović, P., Veljković, S., Stojiljković, N., Sokolović, D., Ilić, I., Laketić, D., Randjelović, D., & Randjelović, N. (2015). The beneficial biological properties of salicylic acid. *Acta facultatis medicae Naissensis*, *32*(4), 259-265. http://archive.sciendo.com/AFMNAI/afmnai.2015.32.issue-4/afmnai-2015-0026/afmnai-2015-0026.pdf
121. Rasheed, F., Naeem, M., Uddin, M., & Khan, M. (2017). Synergistic effect of irradiated sodium alginate and methyl jasmonate on anticancer alkaloids production in periwinkle (Catharanthus roseus L.). https://www.indianjournals.com/ijor.aspx?target=ijor:jfeb&volume=7&issue=2&article=002
122. Rasheed, A., Kamran, S. H., Hameed, M., Siddique, F., Latif, S., Bibi, M., & Rizwan, R. (2025). Syringic acid loaded chitosan nanoparticles mitigate glycation associated oxidative stress and inflammation in hyperglycaemic rat model. *Scientific Reports*, *15*(1), 22778. https://www.nature.com/articles/s41598-025-05469-0
123. Rithichai, P., Jirakiattikul, Y., Nambuddee, R., & Itharat, A. (2024). Effect of salicylic acid foliar application on bioactive compounds and antioxidant activity in holy basil (Ocimum sanctum L.). *International Journal of Agronomy*, *2024*(1), 8159886. https://onlinelibrary.wiley.com/doi/full/10.1155/2024/8159886
124. Rudrapal, M., Rakshit, G., Singh, R. P., Garse, S., Khan, J., & Chakraborty, S. (2024). Dietary polyphenols: review on chemistry/sources, bioavailability/metabolism, antioxidant effects, and their role in disease management. *Antioxidants*, *13*(4), 429. https://www.mdpi.com/2076-3921/13/4/429
125. Sah, A., Naseef, P. P., Kuruniyan, M. S., Jain, G. K., Zakir, F., & Aggarwal, G. (2022). A comprehensive study of therapeutic applications of chamomile. *Pharmaceuticals*, *15*(10), 1284. https://www.mdpi.com/1424-8247/15/10/1284
126. Saikia, L., Talukdar, N. C., & Dutta, P. P. (2025). Exploring the therapeutic role of flavonoids through AMPK activation in metabolic syndrome: a narrative review. *Phytotherapy Research*, *39*(3), 1403-1421. https://onlinelibrary.wiley.com/doi/abs/10.1002/ptr.8428

 doi:10.20944/preprints202508.1190.v1




127. Salehi, B., Venditti, A., Sharifi-Rad, M., Kręgiel, D., Sharifi-Rad, J., Durazzo, A., Lucarini, M., Santini, A., Souto, E.B., Novellino, E. and Antolak, H. & Martins, N. (2019). The therapeutic potential of apigenin. *International journal of molecular sciences*, *20*(6), 1305. https://www.mdpi.com/1422-0067/20/6/1305
128. Salehi, H., Rad, A. C., & Lucini, L. (2025). Different Forms of Manganese Provide Distinctive Metabolomics Signatures and Bioactive Profiles in Artemisia annua. *Phytochemical Analysis*. https://analyticalsciencejournals.onlinelibrary.wiley.com/doi/abs/10.1002/pca.3538
129. Seema, B. R., Jyothi, Y., Bhovi, C. N., Aradhya, M. V., Lekhak, M., & Mane, S. R. (2023). Advanced up and down methodology for acute toxicity assessment with reliable LD50 verified by aqueous extract of curly kale using wistar rats. *Research Journal of Pharmacy and Technology*, *16*(10), 4519-4524. https://www.indianjournals.com/article/rjpt-16-10-006
130. Shalaby, E. A., Aboul-Enein, A., El-Shemy, H., & Nassrallah, A. (2025). Active Ingredients of Some Egyptian Plants Species with Anticancer Activity and Its Mode of Action. *Arab Journal of Biotechnology*, *24*(1), 18-40. https://journals.ekb.eg/article_432494_09dce9501746bb2f9536fa511639e7fc.pdf
131. Sharma, N., Biswas, S., Al-Dayan, N., Alhegaili, A. S., & Sarwat, M. (2021). Antioxidant role of kaempferol in prevention of hepatocellular carcinoma. *Antioxidants*, *10*(9), 1419. https://www.mdpi.com/2076-3921/10/9/1419
132. Shi, L., Zhao, W., Yang, Z., Subbiah, V., & Suleria, H. A. R. (2022). Extraction and characterization of phenolic compounds and their potential antioxidant activities. *Environmental Science and Pollution Research*, *29*(54), 81112-81129. https://link.springer.com/article/10.1007/s11356-022-23337-6
133. Shi, M., Zhang, S., Zheng, Z., Maoz, I., Zhang, L., & Kai, G. (2024). Molecular regulation of the key specialized metabolism pathways in medicinal plants. *Journal of Integrative Plant Biology*, *66*(3), 510-531. https://onlinelibrary.wiley.com/doi/full/10.1111/jipb.13634
134. Shin, J. M., Son, Y. J., Ha, I. J., Erdenebileg, S., Jung, D. S., Song, D. G., Kim, Y.S., Kim, S.M., & Nho, C. W. (2022). Artemisia argyi extract alleviates inflammation in a DSS-induced colitis mouse model and enhances immunomodulatory effects in lymphoid tissues. *BMC complementary medicine and therapies*, *22*(1), 64. https://link.springer.com/article/10.1186/s12906-022-03536-x
135. Shoaib, M., Shah, I., Ali, N., Adhikari, A., Tahir, M. N., Shah, S. W. A., ... & Umer, M. N. (2017). Sesquiterpene lactone! a promising antioxidant, anticancer and moderate antinociceptive agent from Artemisia macrocephala jacquem. *BMC complementary and alternative medicine*, *17*(1), 27. https://link.springer.com/article/10.1186/s12906-016-1517-y
136. Shrivastava, S., Uthra, C., Reshi, M., Singh, A., Yadav, D., & Shukla, S. (2018). Protective effect of hesperetin against acrylamide induced acute toxicity in rats. *Indian J Exp Biol*, *56*(3), 164-170. https://d1wqtxts1xzle7.cloudfront.net/77012929/IJEB_20563_20164-170-libre.pdf?1640147462=&response-content-disposition=inline%3B+filename%3DProtective_effect_of_hesperetin_against.pdf&Expires=1754574984&Signature=APPax-hgWB6r1AiJzTJ5bccvN08HKwRkIbD3j50LouNyo6YtD50syth70PPCJvzuqjeVOtbXuUrXWL~HnJhHnhp5xJZCE8Le3NRZdyi7i~guoCIR~611SltGk3yRXmZkL3AE-hutMM6yC9AxehtF64mh37WXn4PWKsgVpVgHJzdxdJfqqwyvsOuY~f5GbUh6a0pz3i6yPRaA8BWmBrOfHwAOtgEZU8mpuKh3Dilf2YgkZao5nWZzLHUD1D2r95ima1ghZKXqK3JgaVtThqgPMgpk6p3aGOaUGIBhtI0Xia3by~fKsypTHrrn1QckoB1oYTIImais82eH1pwFfbHCHg__&Key-Pair-Id=APKAJLOHF5GGSLRBV4ZA
137. Siddiqui, M. F. M. F., Waghmare, S. P., Hajare, S. W., Deshmukh, R. I. S., & Ali, S. C. S. A. (2018). Phytochemical analysis and acute toxicity studies of Artemisia annua in Swiss albino mice. *Journal of Pharmacognosy and Phytochemistry*, *7*(4), 1893-1895. https://www.researchgate.net/profile/Sharad-Chepte/publication/327882389_Phytochemical_analysis_and_acute_toxicity_studies_of_Artemisia_annua_in_Swiss_albino_mice/links/5bab119092851ca9ed25ec4c/Phytochemical-analysis-and-acute-toxicity-studies-of-Artemisia-annua-in-Swiss-albino-mice.pdf
138. Siddiquee, R., Mahmood, T., Ansari, V. A., Ahsan, F., Bano, S., & Ahmad, S. (2025). Apigenin unveiled: an encyclopedic review of its preclinical and clinical insights. *Discover Plants*, *2*(1), 11. https://link.springer.com/article/10.1007/s44372-024-00039-6

 doi:10.20944/preprints202508.1190.v1




139. Singh, J., & Kaur, S. (2015). Phyllanthus embilica leaves extract: a potential amylase enzyme inhibitor with antioxidant and antimicrobial activity. *Int J Pharma Res*, *9*, 200-206. https://ssjournals.net/ijpr/article/view/2388
140. Silva, J. D. R., Arruda, H. S., Andrade, A. C., Berilli, P., Borsoi, F. T., Monroy, Y. M., Rodrigues, M.V.N., Sampaio, K.A., Pastore, G.M., & Marostica Junior, M. R. (2024). Eugenia calycina and Eugenia stigmatosa as promising sources of antioxidant phenolic compounds. *Plants*, *13*(15), 2039. https://www.mdpi.com/2223-7747/13/15/2039
141. Singh, A., Singh, J., Parween, G., Khator, R., & Monga, V. (2024). A comprehensive review of apigenin a dietary flavonoid: biological sources, nutraceutical prospects, chemistry and pharmacological insights and health benefits. *Critical Reviews in Food Science and Nutrition*, 1-37. https://www.tandfonline.com/doi/abs/10.1080/10408398.2024.2390550
142. Song, C. H., Kim, N., Nam, R. H., Choi, S. I., Kang, C., Jang, J. Y., Nho, H., Shin, E., & Lee, H. N. (2021). Nuclear factor erythroid 2-related factor 2 knockout suppresses the development of aggressive colorectal cancer formation induced by azoxymethane/dextran sulfate sodium-treatment in female mice. *Journal of cancer prevention*, *26*(1), 41. https://pmc.ncbi.nlm.nih.gov/articles/PMC8020176/
143. Song, H. J., Lim, S., Lee, S. J., Lim, J. E., Nam, D. H., Joo, K. M., ... & Lee, H. W. (2015). Repurposing the anti-malarial drug artesunate as a novel therapeutic agent for metastatic renal cell carcinoma due to its attenuation of tumor growth, metastasis, and angiogenesis. *Oncotarget*, *6*(32), 33046. https://pmc.ncbi.nlm.nih.gov/articles/PMC4741748/
144. Sousa, C., Gabriel, C., Cerqueira, F., Manso, M. C., & Vinha, A. F. (2015). Coffee industrial waste as a natural source of bioactive compounds with antibacterial and antifungal activities. https://core.ac.uk/reader/301338150
145. Srinivasulu, C., Ramgopal, M., Ramanjaneyulu, G., Anuradha, C. M., & Kumar, C. S. (2018). Syringic acid (SA)–a review of its occurrence, biosynthesis, pharmacological and industrial importance. *Biomedicine & Pharmacotherapy*, *108*, 547-557. https://www.sciencedirect.com/science/article/pii/S0753332218347589
146. Sultana, R., Imam, Z., Kumar, R. R., Banu, V. S., Nahakpam, S., Bharti, R., Bharadwaj, C., Singh, A.K., Pasala, R.K., Singh, D.R., & Siddiqui, M. W. (2025). Signaling and defence mechanism of jasmonic and salicylic acid response in pulse crops: role of WRKY transcription factors in stress response. *Journal of Plant Growth Regulation*, *44*(1), 5-21. https://link.springer.com/article/10.1007/s00344-023-11203-9
147. Sun, W., & Shahrajabian, M. H. (2023). Therapeutic potential of phenolic compounds in medicinal plants—Natural health products for human health. *Molecules*, *28*(4), 1845. https://www.mdpi.com/1420-3049/28/4/1845
148. Sun, J., Xufeng, J., Qiu, Z., Gao, Q., Zhu, Z., He, J., Gao, S., & Sui, X. (2025). Artemisiae Annuae Herba: from anti-malarial legacy to emerging anti-cancer potential. *Theranostics*, *15*(15), 7346. https://pmc.ncbi.nlm.nih.gov/articles/PMC12315818
149. Tallei, T. E., Tumilaar, S. G., Niode, N. J., Fatimawali, F., Kepel, B. J., Idroes, R., Effendi, Y., Sakib, S.A., & Emran, T. B. (2020). Potential of plant bioactive compounds as SARS-CoV-2 main protease (mpro) and spike (s) glycoprotein inhibitors: a molecular docking study. *Scientifica*, *2020*(1), 6307457. https://onlinelibrary.wiley.com/doi/full/10.1155/2020/6307457
150. Thanikachalam, P. V., Devaraji, M., Jayaprakash, N., Sivakumar, H., Balamurugan, D., & Shanmugan, H. K. (2025). Phytochemical innovations in oral cancer therapy: targeting oncogenic pathways with natural compounds. *Journal of Complementary and Integrative Medicine*, (0). https://www.degruyterbrill.com/document/doi/10.1515/jcim-2025-0118/html
151. Tomic, N., Pojskic, L., Kalajdzic, A., Ramic, J., Kadric, N. L., Ikanovic, T., ... & Pojskic, N. (2020). Screening of preferential binding affinity of selected natural compounds to SARS-CoV-2 proteins using in silico methods. *Eurasian journal of medicine and oncology*, *4*(4), 319-323. https://www.accscience.com/journal/EJMO/4/4/10.14744/ejmo.2020.72548
152. Trifan, A., Zengin, G., Sinan, K. I., Sieniawska, E., Sawicki, R., Maciejewska-Turska, M., Skalikca-Woźniak, K & Luca, S. V. (2022). Unveiling the phytochemical profile and biological potential of five Artemisia species. *Antioxidants*, *11*(5), 1017. https://www.mdpi.com/2076-3921/11/5/1017

 doi:10.20944/preprints202508.1190.v1




153. Vaiserman, A., Koliada, A., Zayachkivska, A., & Lushchak, O. (2020). Nanodelivery of natural antioxidants: an anti-aging perspective. *Frontiers in bioengineering and biotechnology*, *7*, 447. https://www.frontiersin.org/journals/bioengineering-and-biotechnology/articles/10.3389/fbioe.2019.00447/full
154. Velumani, K., Rajan, P. S., Shaik, M. R., Hussain, S. A., Shaik, B., Guru, A., & Issac, P. K. (2025). Protective Effect of Artemisinin Against Luperox Induced Oxidative Stress and Insulin Resistance via Pi3k/Akt Pathway in Zebrafish Larvae. *Cell Biochemistry and Biophysics*, 1-13. https://link.springer.com/article/10.1007/s12013-025-01747-w
155. Verotta, L., Panzella, L., Antenucci, S., Calvenzani, V., Tomay, F., Petroni, K., Caneva, E., & Napolitano, A. (2018). Fermented pomegranate wastes as sustainable source of ellagic acid: Antioxidant properties, anti-inflammatory action, and controlled release under simulated digestion conditions. *Food Chemistry*, *246*, 129-136. https://www.sciencedirect.com/science/article/abs/pii/S0308814617317788
156. Wang, D., Wang, Y., Wan, X., Yang, C. S., & Zhang, J. (2015). Green tea polyphenol (−)-epigallocatechin-3-gallate triggered hepatotoxicity in mice: Responses of major antioxidant enzymes and the Nrf2 rescue pathway. *Toxicology and applied pharmacology*, *283*(1), 65-74. https://www.sciencedirect.com/science/article/abs/pii/S0041008X15000125
157. Wang, M., Firrman, J., Liu, L., & Yam, K. (2019). A review on flavonoid apigenin: Dietary intake, ADME, antimicrobial effects, and interactions with human gut microbiota. *BioMed research international*, *2019*(1), 7010467. https://onlinelibrary.wiley.com/doi/full/10.1155/2019/7010467
158. Wang, M., Zhang, S., Li, R., & Zhao, Q. (2024). Unraveling the specialized metabolic pathways in medicinal plant genomes: A review. *Frontiers in Plant Science*, *15*, 1459533. https://www.frontiersin.org/journals/plant-science/articles/10.3389/fpls.2024.1459533/full
159. Wdowiak, K., Walkowiak, J., Pietrzak, R., Bazan-Woźniak, A., & Cielecka-Piontek, J. (2022). Bioavailability of hesperidin and its aglycone hesperetin—compounds found in citrus fruits as a parameter conditioning the pro-health potential (neuroprotective and antidiabetic activity)—mini-review. *Nutrients*, *14*(13), 2647. https://www.mdpi.com/2072-6643/14/13/2647
160. Wei, T., & Liu, J. (2017). Anti-angiogenic properties of artemisinin derivatives. *International Journal of Molecular Medicine*, *40*(4), 972-978. https://www.spandidos-publications.com/ijmm/40/4/972
161. Xie, K., Li, Z., Zhang, Y., Wu, H., Zhang, T., & Wang, W. (2024). Artemisinin and its derivatives as promising therapies for autoimmune diseases. *Heliyon*, *10*(7). https://www.cell.com/heliyon/fulltext/S2405-8440(24)04003-9
162. Xin, T. A. O., & Tian, W. A. N. G. (2017). In vitro and in vivo antioxidant activities of three major polyphenolic compounds in pomegranate peel: Ellagic acid, punicalin, and punicalagin. *Journal of integrative agriculture*, *16*(8), 1808-1818. https://www.sciencedirect.com/science/article/pii/S2095311916615605
163. Yang, Y., Liu, M., Liu, C., Tang, S., Gu, D., Tian, J., Huang, D., & He, F. (2023). Ellagic acid from pomegranate peel: Consecutive countercurrent chromatographic separation and antioxidant effect. *Biomedical Chromatography*, *37*(9), e5662. https://analyticalsciencejournals.onlinelibrary.wiley.com/doi/abs/10.1002/bmc.5662
164. Zduńska, K., Dana, A., Kolodziejczak, A., & Rotsztejn, H. (2018). Antioxidant properties of ferulic acid and its possible application. *Skin pharmacology and physiology*, *31*(6), 332-336. https://karger.com/spp/article-abstract/31/6/332/295922/Antioxidant-Properties-of-Ferulic-Acid-and-Its?redirectedFrom=fulltext
165. Zhao, S., Nan, Y., Yao, R., Wang, L., Zeng, X., Aadil, R. M., & Shabbir, M. A. (2023). Antibacterial activity and transcriptomic analysis of Hesperetin against Alicyclobacillus acidoterrestris vegetative cells. *Foods*, *12*(17), 3276. https://www.mdpi.com/2304-8158/12/17/3276
166. Zhao, Z., Yang, Q., Sun, Y., & Ruan, X. (2025). Unveiling the antioxidant and anti-inflammatory potential of syringic acid: mechanistic insights and pathway interactions. *Frontiers in Pharmacology*, *16*, 1615294. https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2025.1615294/full
167. Zheng, L., Jacquier, J. C., & Harbourne, N. (2024). Preparation of Polyphenol-Rich Herbal Beverages from White Willow (Salix alba) Bark with Potential Alzheimer's Disease Inhibitory Activity In Silico. *Beverages*, *10*(3), 75. https://www.mdpi.com/2306-5710/10/3/75. https://www.mdpi.com/1420-3049/28/8/3599

 doi:10.20944/preprints202508.1190.v1



168. Zeng, X., Zhang, Y., Wang, S., Wang, K., Tao, L., Zou, M., Chen, N., Xu, J., Liu, S., & Li, X. (2017). Artesunate suppresses RANKL-induced osteoclastogenesis through inhibition of PLCγ1-Ca2+–NFATc1 signaling pathway and prevents ovariectomy-induced bone loss. *Biochemical pharmacology*, *124*, 57-68.
169. Zhuang, W. B., Li, Y. H., Shu, X. C., Pu, Y. T., Wang, X. J., Wang, T., & Wang, Z. (2023). The classification, molecular structure and biological biosynthesis of flavonoids, and their roles in biotic and abiotic stresses. *Molecules*, *28*(8), 3599. https://www.sciencedirect.com/science/article/abs/pii/S0006295216303768
170. Zhou, F., Li, G., Tan, R., Wu, G., & Deng, C. (2025). Artemisinins in autoimmune diseases: effects and mechanisms in systemic lupus erythematosus and rheumatoid arthritis. *British Journal of Pharmacology*. https://bpspubs.onlinelibrary.wiley.com/doi/full/10.1111/bph.70086
171. Zufarov, O., & Serkayev, K. (2024). Natural antioxidants. *Technical science and innovation*, *2024*(2), 19-25. https://btstu.researchcommons.org/journal/vol2024/iss2/4