INTERNATIONAL JOURNAL OF TECHNOLOGY AND ACADEMIC RESEARCH

ISSN: 2224-6878 | Pakistan Volume 6, No. 10.

IF: 14.91 | 2026 http://waerasia.org/index.php/ijtar

ANTI-INFLAMMATORY EFFECTS OF HIGH PHENOLIC COMPOUNDS ON RAW 264.7 MACROPHAGE CELLS: STRUCTURE, IDENTIFICATION, BIOLOGICAL ACTIVITY AND CYTOKINE REGULATION OF GALLIC, SYRINGIC, VANILLIC, FERULIC AND P-COUMARIC ACIDS, QUERCETIN, EGCG AND ELLAGIC ACID

Akhmadjon Sultonov

[1] Samarkand State University named after Sharof Rashidov, Institute of Biochemistry, Department of Genetics, Samarkand, Uzbekistan

[2] Kyungpook National University, Faculty of Food Science and Biotechnology, Daegu, South Korea

Rakhmat Sultonov, **Mohinur Tolmasova**

Samarkand State University named after Sharof Rashidov, Institute of Biochemistry, Department of Analytical Chemistry, Samarkand, Uzbekistan

*Corresponding authors: Akhmadjon Sultonov, ahmatjon.net@gmail.com; Rakhmat Sultonov, Sultonov.rakhmat@knu.ac.kr

E-mail: Mohinur Tolmasova, tolmasovamohinur11@gmail.com

ORCID, Akhmadjon Sultonov: https://orcid.org/0000-0003-2763-7944

ORCID, Rakhmat Sultonov: https://orcid.org/0009-0004-0880-4991

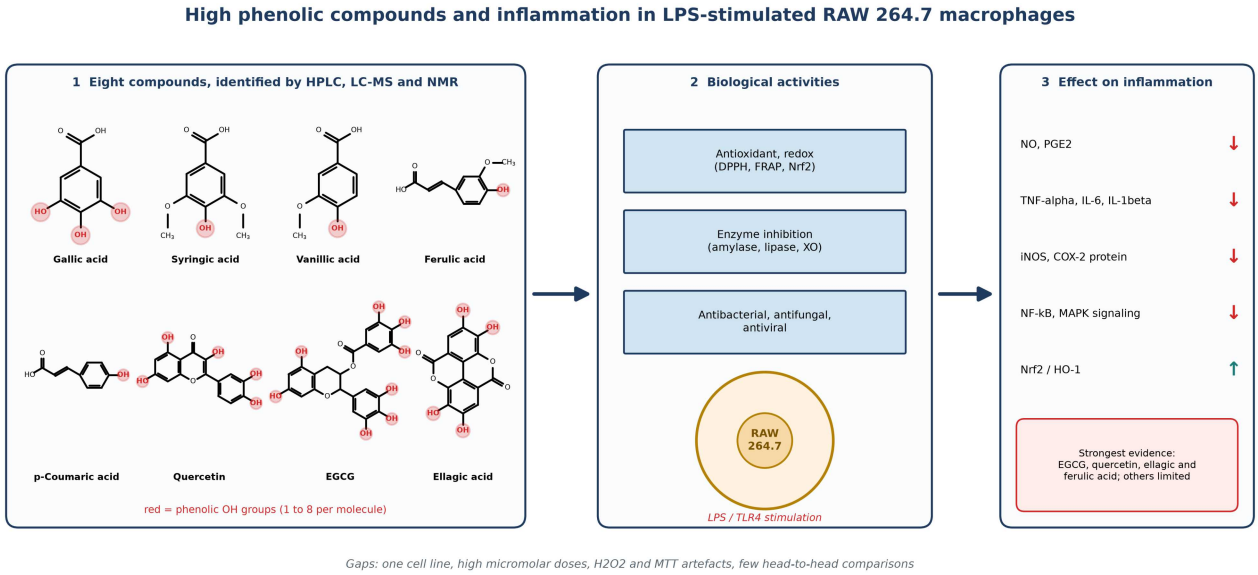
Abstract: High phenolic compounds (HPC) are widely studied as anti-inflammatory agents, but the data on individual compounds in macrophages are scattered. This review focuses on eight HPC: gallic, syringic, vanillic, ferulic and p-coumaric acids, quercetin, epigallocatechin gallate (EGCG) and ellagic acid. We describe their structures and phenolic hydroxyl groups, their natural and synthetic sources, and the methods used for chemical identification (HPLC-DAD, LC-MS/MS, GC-MS and NMR). We then summarize their antioxidant, enzyme-inhibitory and antimicrobial activities and critically evaluate their effects on nitric oxide, prostaglandin E2 and the pro-inflammatory cytokines TNF-α, IL-6 and IL-1β in LPS-stimulated RAW 264.7 macrophages, together with Western blot evidence for iNOS, COX-2, NF-κB, MAPK and Nrf2/HO-1 signaling. The strongest and most consistent evidence in RAW 264.7 cells exists for EGCG, quercetin, ellagic acid and ferulic acid. For gallic, syringic, vanillic and p-coumaric acids the evidence rests largely on derivatives, extracts or other models, and some findings conflict, for example the induction of COX-2 by EGCG. Assay artefacts (H_2O_2 formation in medium, MTT reduction), the use of a single murine cell line and high µM concentrations limit the interpretation. Four tables, four figures and a graphical abstract summarize the evidence, and a standardized workflow is proposed in which identity and purity are verified before all eight compounds are tested under identical conditions.

Keywords: high phenolic compounds; RAW 264.7; macrophages; inflammation; cytokines; NF-κB; gallic acid; quercetin; EGCG; ellagic acid

ISSN: 2224-6878 | Pakistan Volume 6, No. 10.

IF: 14.91 | 2026 http://waerasia.org/index.php/ijtar

Graphical abstract



Graphical abstract. Eight high phenolic compounds (phenolic OH groups in red) are identified chemically, show antioxidant, enzyme-inhibitory and antimicrobial activities, and reduce inflammatory mediators and signaling in LPS-stimulated RAW 264.7 macrophages. The strongest evidence exists for EGCG, quercetin, ellagic acid and ferulic acid.

1. Introduction

Gallic acid, syringic acid, vanillic acid, ferulic acid, p-coumaric acid, quercetin, epigallocatechin gallate (EGCG) and ellagic acid belong to three structural groups of plant phenolics: hydroxybenzoic acids (gallic, syringic and vanillic acid), hydroxycinnamic acids (ferulic and p-coumaric acid), and larger polyphenols (the flavonol quercetin, the flavan-3-ol EGCG and the ellagitannin-derived ellagic acid). They usually occur together in the same plant material. Gallic acid, ellagic acid and quercetin are marker components of *Radix Sanguisorbae* [1], and gallic acid and ellagic acid were isolated from pomegranate, where ellagic acid originates from the hydrolysis of ellagitannins [2-3]. Vanillic, syringic and ferulic acids were quantified in *Dendrobii Herba* [4], ferulic acid is obtained from cereal bran and other grass cell walls [5], and p-coumaric acid was found in adlay testa and in the mushroom *Tremella fuciformis* [6-7]. EGCG is the major catechin of tea [8-9]. Because natural yields are limited, these compounds can also be produced by chemical and biological synthesis, and modified derivatives have been prepared to improve solubility and cell uptake, such as gallic acid-grafted chitosan, lipophilic EGCG esters, and ferulic acid amides and derivatives [10-14].

Correct identification and quantification of these compounds is the first requirement for linking chemistry to bioactivity. Reversed-phase HPLC with photodiode array detection has been used to quantify gallic acid, ellagic acid and quercetin on a C18 column with gradient elution [1] and to measure vanillic, syringic and ferulic acids in a herbal drug [4]. HPLC-DAD of a *Phrynium pubinerve* leaf extract showed 89.19 mg/100 g of syringic acid [15]. Compounds isolated by HPLC were confirmed by mass spectrometry, as for ellagic acid, gallic acid and punicalagin from pomegranate [2], and an untargeted metabolomics approach identified ellagic acid as the active

ISSN: 2224-6878 | Pakistan Volume 6, No. 10.

IF: 14.91 | 2026 http://waerasia.org/index.php/ijtar

component of strawberry fractions [16]. LC-MS and LC-MS/MS with electrospray ionization identify compounds from accurate mass and fragmentation, which is well established for flavonoids such as quercetin [17]. Methods for the separation and detection of phenolic acids and flavonoids [18] and for the determination of gallic acid [19] have been reviewed. NMR spectroscopy (^{1}H, ^{13}C and two-dimensional experiments) confirms structure and purity, which matters for standards used in cell assays [20].

The eight compounds share antioxidant activity, but potency depends on structure. Among 18 phenolic acids, methoxyl and phenolic hydroxyl groups and the -CH=CHCOOH side chain increased DPPH and FRAP activity compared with -COOH [21], in line with the classic structure-activity rules for flavonoids and phenolic acids [22]. Ferulic and p-coumaric acids also showed cellular antioxidant and immunomodulatory activity in splenocytes and macrophages [23]. Adlay and Tremella phenolic fractions combined DPPH or ABTS scavenging and protection against LDL oxidation with NO inhibition in RAW 264.7 cells [6-7]. Enzyme inhibition adds further activity: ellagic acid inhibited xanthine oxidase and NLRP3 inflammasome activation in a hyperuricemia model [24], and dietary polyphenols are known α-glucosidase inhibitors [25]. Phenolic acids are not equivalent in effect; gallic acid, for example, autoxidizes to generate H_2O_2, which altered epithelial redox signaling in a Caco-2/RAW 264.7 co-culture [26].

RAW 264.7 cells stimulated with lipopolysaccharide (LPS) are a standard inflammation model, although the response depends on passage number and culture conditions [27]. LPS signals through Toll-like receptor 4 and induces NO, PGE2, TNF-α, IL-6 and IL-1β [28]. For the present compounds the data are fragmentary. Vanillic, syringic and ferulic acids reduced TNF-α, IL-6 or PGE2 in LPS-stimulated RAW 264.7 cells [4], and ferulic acid lowered MIP-2 production [29] and the mRNA of IL-6, TNF-α and iNOS [30]. Gallic acid and ellagic acid inhibited NO, PGE2 and IL-6 production [2], and ellagic acid was the strongest inhibitor of TNF-α and IL-6 among gallic acid, ellagic acid and quercetin [1]. At 0.3 and 1.0 μM ellagic acid reduced TNF-α, IL-1β and iNOS expression [16]. EGCG decreased NO to 32% of the LPS group and strongly lowered IL-1β, IL-6 and TNF-α expression [8]. Quercetin decreased iNOS mRNA and TNF-α release but not TNF-α mRNA [31], and p-coumaric acid suppressed LPS-induced inflammation in RAW 264.7 cells [32]. Vanillic acid reduced TNF-α, IL-6, PGE2 and NO in mouse peritoneal macrophages [33].

Western blotting links these effects to key enzymes and signaling proteins. iNOS and COX-2 generate NO and PGE2 during inflammation [34-35], and the NF-κB and MAPK pathways control their transcription [36]. Gallic acid, ellagic acid and punicalagin reduced COX-2 protein [2], gallic acid-grafted chitosan decreased iNOS and COX-2 and blocked IκB phosphorylation and MAPK/AP-1 activation [11], and EGCG lowered the P-IκB/IκB ratio by 75% and p-p65/p65 by 50% [8]. Lipophilic EGCG esters suppressed iNOS and COX-2 at protein and mRNA level [12]. Not all findings agree: an early report showed that EGCG itself induced COX-2 and PGE2 through ERK in RAW 264.7 cells [37], and quercetin did not block p50/p65 binding although it inhibited p50/p50 [31]. Later work showed that quercetin inhibits MAPK/AP-1 and IKK/NF-κB signaling [38]. Ellagic acid regulated IκB and MAPKs [16], ferulic acid reduced IKK phosphorylation and modulated the Nrf2 and NF-κB crosstalk [30,39], and p-coumaric acid acted through NF-κB and MAPKs [32]. For syringic acid, iNOS, COX-2 and p65 and IκBα phosphorylation were reduced in LPS-induced lung injury, with effects on RAW 264.7 macrophage polarization [40], and a syringic acid-rich extract downregulated iNOS, COX-2, NF-

ISSN: 2224-6878 | Pakistan Volume 6, No. 10.

IF: 14.91 | 2026 http://waerasia.org/index.php/ijtar

κB, IL-6 and TNF-α in RAW 264.7 cells [15]. Such protein data require proper loading controls and normalization [41].

Despite these studies, the evidence is scattered. Most reports examine one compound or a crude extract, use different LPS doses, concentration ranges and readouts, and some results conflict, as for EGCG and quercetin. To our knowledge, the eight compounds have not been compared side by side with one experimental pipeline. This review therefore compares gallic, syringic, vanillic, ferulic and p-coumaric acids, quercetin, EGCG and ellagic acid in LPS-stimulated RAW 264.7 cells and proposes a unified framework: verification of identity and purity by HPLC, LC-MS and NMR; antioxidant and enzyme assays; cytokine profiling by ELISA and RT-qPCR; and Western blot analysis of iNOS, COX-2, NF-κB and MAPK signaling.

2. Structural characterization and chemical identification

2.1 Structures and classes

The eight compounds (Figure 1) share a phenolic hydroxyl (Ar-OH) pharmacophore but differ in carbon skeleton and substitution. Gallic, syringic and vanillic acids are hydroxybenzoic acids (C6-C1). Gallic acid carries three phenolic OH groups, syringic acid one OH flanked by two methoxy groups, and vanillic acid one OH next to a single methoxy group. Ferulic and p-coumaric acids are hydroxycinnamic acids (C6-C3), in which the acrylic acid side chain is conjugated with the ring and stabilizes the phenoxy radical formed after hydrogen donation [42]. Quercetin is a flavonol with five phenolic OH groups (3, 5, 7, 3' and 4') and a catechol unit in the B ring. EGCG is a flavan-3-ol esterified with gallic acid and carries eight phenolic OH groups, including two pyrogallol units. Ellagic acid, the dilactone of hexahydroxydiphenic acid released from ellagitannins, has four phenolic OH groups on a planar tetracyclic skeleton [3].

The number and arrangement of the phenolic OH groups explain much of the chemistry that is relevant for cell assays. Catechol and pyrogallol arrangements (gallic acid, the B rings of quercetin and EGCG) are strong hydrogen and electron donors but also oxidize readily, which affects their stability in culture medium [43]. Methoxy groups, as in syringic, vanillic and ferulic acids, increase the antioxidant activity of a phenolic acid compared with a single free OH [44]. Solubility and stability are the main practical limitations: quercetin has low solubility and poor bioavailability [45], EGCG has poor physicochemical stability and low oral bioavailability [46], and ellagic acid is poorly absorbed and largely converted by the gut microbiota to urolithins [47].

ISSN: 2224-6878 | Pakistan Volume 6, No. 10.

IF: 14.91 | 2026 http://waerasia.org/index.php/ijtar

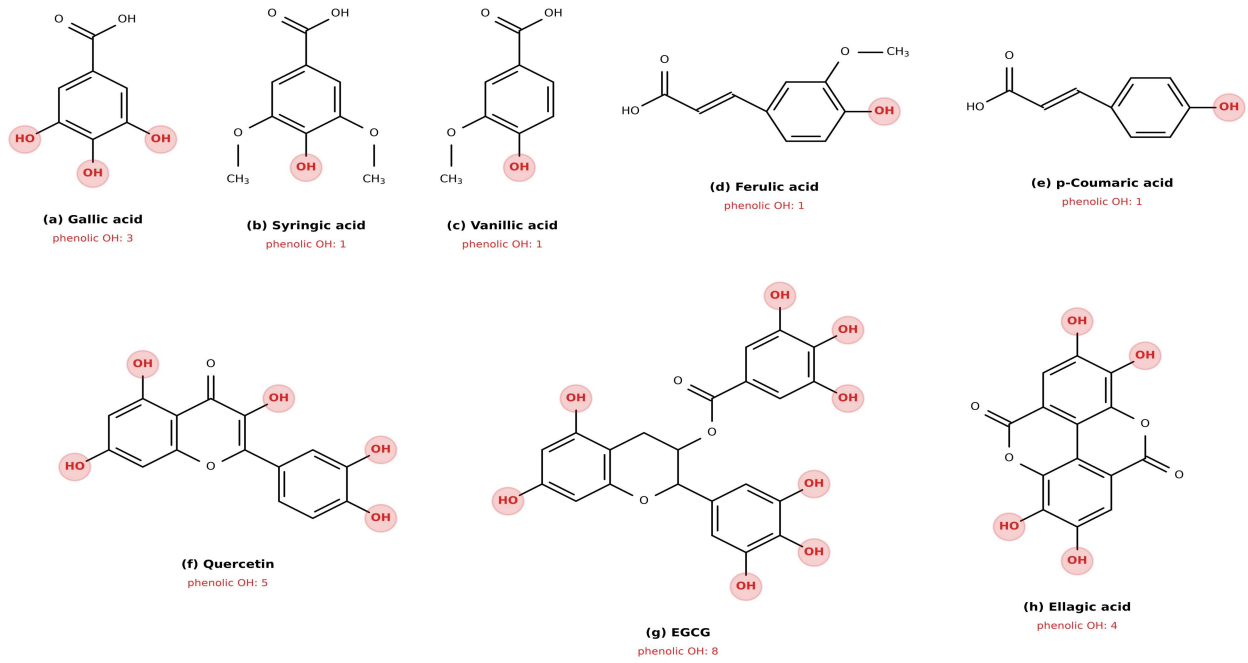


Figure 1. Chemical structures of the eight high phenolic compounds. Phenolic hydroxyl (Ar-OH) groups are marked with red circles and counted below each structure; carboxylic OH, methoxy, lactone and ring oxygens are shown in black. EGCG stereocenters are not drawn.

Table 1. Identity and sources of the eight compounds

Compound	Class	Formula (MW, g/mol)	Phenolic OH	Examples of natural sources and release
Gallic acid	Hydroxybenzoic acid	$C_7H_6O_5$ (170.12)	3	*Saraca asoca* extracts [48]; free form rises during black tea processing [49]; pomegranate [2]
Syringic acid	Hydroxybenzoic acid	$C_9H_{10}O_5$ (198.17)	1	Fruits and vegetables, shikimate pathway [44]; *Dendrobii Herba* [4]
Vanillic acid	Hydroxybenzoic acid	$C_8H_8O_4$ (168.15)	1	*Dendrobii Herba* [4]; wheat gluten (trace) [50]
Ferulic acid	Hydroxycinnamic acid	$C_{10}H_{10}O_4$ (194.18)	1	Bound to cell-wall

ISSN: 2224-6878 | Pakistan Volume 6, No. 10.

IF: 14.91 | 2026 http://waerasia.org/index.php/ijtar

				arabinoxylan in rice bran [51] and wheat gluten [50]; Angelica root [52]
p-Coumaric acid	Hydroxycinnamic acid	$C_9H_8O_3$ (164.16)	1	Rice bran arabinoxylan [51]; adlay testa [6]; *Tremella fuciformis* [7]
Quercetin	Flavonol	$C_{15}H_{10}O_7$ (302.24)	5	*Radix Sanguisorbae* [1]; honey [53]
EGCG	Flavan-3-ol gallate	$C_{22}H_{18}O_{11}$ (458.37)	8	Tea [9]; *Saraca asoca* extracts [48]
Ellagic acid	Ellagitannin-derived dilactone	$C_{14}H_6O_8$ (302.19)	4	Released from ellagitannins of strawberry [54] and raspberry seeds [55]; pomegranate [2]

2.2 Natural sources and extraction

Examples of natural sources and release routes are given in Table 1. Gallic acid and EGCG are co-extracted with other catechins from tea and from medicinal plants. For *Saraca asoca*, recovery of gallic acid, catechins and EGCG depended on the methanol-water ratio and on the plant part, and a validated UPLC-PDA method was used for quantification [48]. During black tea processing the free forms of gallic, p-coumaric and ferulic acids increased, whereas soluble conjugated forms such as p-coumaroylquinic and chlorogenic acids decreased, so the form in which a phenolic acid is present depends on processing [49]. Syringic acid is widely found in fruits and vegetables and is formed through the shikimate pathway [44], and vanillic, syringic and ferulic acids were quantified together in the herbal drug *Dendrobii Herba* [4].

Ferulic and p-coumaric acids occur mostly as esters bound to cell-wall polysaccharides, and their release requires hydrolysis. In rice bran arabinoxylan hydrolysates ferulic acid was the major bound phenolic acid followed by p-coumaric acid [51], and in wheat gluten 50 to 95% of ferulic acid was in the unextractable fraction, with only traces of p-coumaric and vanillic acids [50]. Alkaline hydrolysis, ethanol extraction and hexane extraction were compared for ferulic acid in *Angelica acutiloba* root [52]. Ellagic acid is present mainly as ellagitannins, so total ellagic acid is determined after hydrolysis. Microwave-assisted hydrolysis was developed as a fast alternative to conventional acid hydrolysis in strawberries [54], a citric acid-betaine natural deep eutectic solvent allowed simultaneous hydrolysis and extraction from defatted raspberry seeds [55], and ellagitannin acyl hydrolase can release ellagic acid enzymatically [56]. Overviews of conventional and innovative extraction systems, including enzyme-assisted, pressurized fluid,

ISSN: 2224-6878 | Pakistan Volume 6, No. 10.

IF: 14.91 | 2026 http://waerasia.org/index.php/ijtar

supercritical fluid, ultrasound, microwave and pulsed electric field extraction, are available [57-58].

2.3 Synthetic and semi-synthetic routes

Synthetic work on these compounds aims to improve solubility, lipophilicity, potency or delivery. Electrochemical oxidation converted syringic acid to the stronger antioxidant 3-O-methylgallic acid [59], and syringic acid derivatives were designed as xanthine oxidase inhibitors [60]. O-Alkyl derivatives of ferulic and syringic acids were prepared as lipophilic antioxidants, and the alkyl chain length changed their antioxidant behavior in oil [61]. Amides of vanillic acid and of ferulic acid were obtained by PyBOP or DCC coupling and showed antimicrobial and antifungal activity [62-63], and mitochondria-targeted ferulic acid amides and virtually screened ferulic acid derivatives were evaluated in RAW 264.7 cells [13-14]. Reviews cover the derivatives of ferulic acid [64] and quercetin [45]. For EGCG, lipophilic fatty acid esters [12] and nanoparticles [46] were developed, and ellagic acid was combined with gold nanoparticles against drug-resistant bacteria [65]. Gallic acid was grafted to chitosan [11], and syringic acid was loaded into chitosan nanoparticles [66]. These modified forms are not identical to the parent compounds, and results obtained with them should be reported separately from those of the free compounds.

2.4 Analytical methods for identification and quantification

A recommended workflow from source material to cell assay is shown in Figure 2. Reversed-phase HPLC or UPLC with a diode array detector is the standard method for quantification. Typical conditions are a C18 column and a gradient of acetonitrile with acidified water, for example 0.1% phosphoric acid at pH 2.5, which keeps carboxylic acids protonated; a method of this type was validated according to ICH guidelines for gallic acid, catechins and EGCG [48]. The same approach was used for gallic acid, ellagic acid and quercetin in *Radix Sanguisorbae* [1] and for vanillic, syringic and ferulic acids in *Dendrobii Herba* [4]. Detection wavelengths follow the chromophores (Table 2): about 270 to 280 nm for the benzoic acids and EGCG, about 310 to 320 nm for the cinnamic acids, and 255 and 366 to 370 nm for ellagic acid and quercetin.

Tandem mass spectrometry in negative electrospray mode gives the most selective identification. A UPLC-triple quadrupole method was validated for ten phenolic acids, including free, soluble conjugated and insoluble bound forms [49]. In negative mode, polyphenols fragment by losses of CO, CO_2 and C_3O_2, and high-resolution Orbitrap data allow specific fragmentation pathways to be recognized [67]. Methoxylated flavonoids lose a methyl radical, which separates isomers with the same mass [68]. By analogy, carboxylic acids typically show a loss of 44 (CO_2) and methoxylated phenolic acids a loss of 15 (CH_3), as listed in Table 2. Gas chromatography-mass spectrometry requires silylation with BSTFA, and it was applied to phenolic and benzoic acids in plasma, with an average recovery of 79.3% [69], and to 15 wine phenolics including vanillic, coumaric, gallic and ferulic acids and quercetin [70]. General reviews describe extraction, hydrolysis, HPLC and GC procedures for phenolic acids [18,71] and mass spectrometry of flavonoids [17].

NMR spectroscopy (^1H, ^{13}C and two-dimensional experiments) confirms structure and purity of isolated compounds and of commercial standards [20]. Diagnostic signals are the AA'BB' or ABX aromatic patterns, the methoxy singlet near 3.8 ppm, and, for hydroxycinnamic acids, two olefinic doublets with a coupling constant of about 16 Hz that prove the trans configuration (Table 2). Purity matters for cell work, because trace contamination with a more potent

ISSN: 2224-6878 | Pakistan Volume 6, No. 10.

IF: 14.91 | 2026 http://waerasia.org/index.php/ijtar

compound, or degradation during storage, can change a biological result. Identity and purity should be confirmed before each series of cell experiments, and the batch, supplier and solvent should be reported.

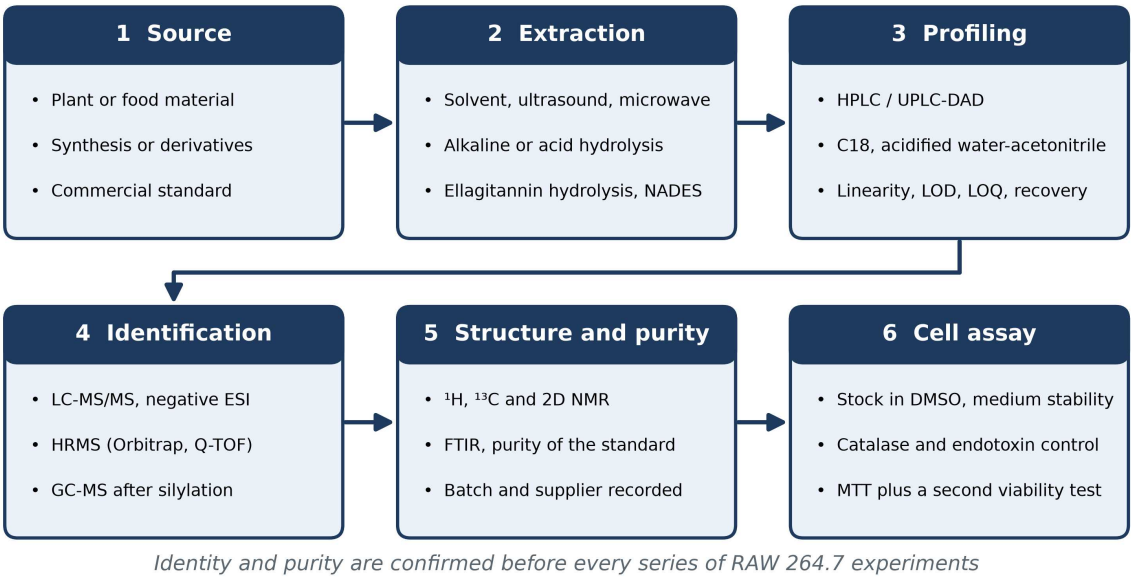


Figure 2. Recommended workflow from source material to cell assay: extraction or synthesis, chromatographic profiling, mass spectrometric and NMR identification, purity check, and preparation of stock solutions for RAW 264.7 experiments.

Table 2. Typical analytical data for identification (values depend on solvent, instrument and ionization conditions and should be confirmed with authentic standards)

Compound	$[M-H]^-$ (m/z)	Typical MS/MS fragments (m/z)	UV maxima (nm)	Diagnostic ^1H NMR signals (DMSO-d6, ppm)
Gallic acid	169.014	125 ($-CO_2$)	about 271	6.9 to 7.0 (s, 2H)
Syringic acid	197.046	182 ($-CH_3$), 153 ($-CO_2$)	about 275	7.2 to 7.3 (s, 2H); 3.8 (s, 6H)
Vanillic acid	167.035	152 ($-CH_3$), 123 ($-CO_2$)	about 260 and 290	7.4 to 7.5 (m, 2H); 6.8 to 6.9 (d, 1H); 3.8 (s, 3H)
Ferulic acid	193.051	178 ($-CH_3$), 149 ($-CO_2$), 134	about 320	7.5 and 6.4 (d, J about 16 Hz); 3.8 (s, OCH_3)
p-Coumaric acid	163.040	119 ($-CO_2$)	about 310	7.5 and 6.3 (d, J about 16 Hz); AA'BB' 7.5 and

ISSN: 2224-6878 | Pakistan Volume 6, No. 10.

IF: 14.91 | 2026 http://waerasia.org/index.php/ijtar

				6.8
Quercetin	301.035	179, 151, 121	about 255 and 370	6.2 and 6.4 (d, J about 2 Hz, H-6 and H-8); B ring 7.7, 7.5, 6.9
EGCG	457.078	305, 169, 125	about 275	5.0 (H-2) and 5.5 (H-3); galloyl and B ring singlets 6.5 to 6.9
Ellagic acid	301.001	257, 229, 185	about 254 and 366	7.5 (s, 2H)

3. Biological activity of High Phenolic Compounds (HPC)

3.1 Antioxidant activities

The antioxidant activity of the eight compounds is based on donation of hydrogen atoms or electrons from the phenolic OH groups and on stabilization of the resulting radical. In ferulic acid the phenoxy radical is stabilized by resonance with the ring and the conjugated side chain [42], and ferulic acid scavenged hydroxyl radicals, nitric oxide and superoxide in electron spin resonance experiments and reduced NO production by LPS-stimulated RAW 264.7 cells [72]; its applications as an antioxidant were reviewed [73]. Quantum chemical descriptors were used to explain the radical scavenging of gallic acid [74]. In quercetin, oxidation proceeds stepwise, with the catechol moiety as the first redox-active site [75]. Ellagic acid and its metabolites, the urolithins, are potent antioxidants *in vitro*, but urolithins reach tissues better than ellagic acid [76]. The classical structure-antioxidant rules for phenolic acids and flavonoids [21-22] therefore apply to all eight compounds.

Cellular and *in vivo* studies show that antioxidant action is not limited to direct scavenging. Syringic acid protected retinal ganglion cells from H_2O_2-induced apoptosis through PI3K/Akt activation and lowered ROS and malondialdehyde [77]. Quercetin induced the Nrf2/GCL/GSH antioxidant pathway in a hepatotoxicity model [78]. Vanillic acid and vanillin restored glutathione, superoxide dismutase and catalase activities in Fe2+-treated brain tissue [79], and vanillic acid also protected plasma proteins from peroxynitrite and reduced the oxidative burst of human neutrophils [80].

The same chemistry causes artefacts. Quercetin, EGCG and catechin generate H_2O_2 within minutes after addition to common culture media [43]. Autoxidation of EGCG produces superoxide and H_2O_2 in medium, and this may not occur in tissues, where the oxygen pressure is lower [81]. Gallic acid was degraded rapidly in medium and also produced H_2O_2, which changed the growth-inhibitory effect of the compound until catalase was added [82]. Gallic acid autoxidation also altered redox signaling in an epithelial and macrophage co-culture [26]. Experiments with these compounds should therefore include catalase controls and should report the medium composition.

ISSN: 2224-6878 | Pakistan Volume 6, No. 10.

IF: 14.91 | 2026 http://waerasia.org/index.php/ijtar

3.2 Enzyme activities and inhibitions

Enzyme inhibition by the eight compounds has been studied mainly for carbohydrate-digesting enzymes, lipase, xanthine oxidase, tyrosinase and cholinesterases. Quercetin inhibited the human intestinal α-glucosidases sucrase, maltase and isomaltase in Caco-2/TC7 extracts, and its potency was compared with acarbose and EGCG [83]. Among five polyphenols, EGCG was the strongest inhibitor of porcine pancreatic α-amylase [84]. Gallic acid, epigallocatechin and EGCG were the most active pancreatic lipase inhibitors in a flavonoid and non-flavonoid panel, with IC50 values between 237 and 391 μM, and the galloyl moiety appeared to be important [85].

Xanthine oxidase, a target in hyperuricemia, was inhibited by ellagic acid isolated from *Lagerstroemia speciosa* leaves [86], and ellagic acid also inhibited xanthine oxidase and NLRP3 inflammasome activation in a hyperuricemia model [24]. Syringic acid derivatives were synthesized and analyzed computationally as xanthine oxidase inhibitors [60]. For tyrosinase the results conflict: green tea components inhibited the mushroom enzyme [87], but EGCG and epigallocatechin are oxidized by tyrosinase-generated o-quinones, and the apparent inhibition may result from reduction of dopaquinone [88]. The ethyl ester of p-coumaric acid inhibited tyrosinase noncompetitively with an IC50 of 4.89 μg/mL, but this is the ester and not the free acid [89]. Vanillic acid inhibited acetylcholinesterase and butyrylcholinesterase in brain tissue [79]. Enzyme data for syringic, vanillic and p-coumaric acids as free compounds are limited.

3.3 Microbiological activities

Phenolic acids inhibit commensal, probiotic and pathogenic bacteria to different extents [90], and ferulic and gallic acids are active against pathogenic bacteria through a defined mode of action [91]. p-Coumaric acid kills bacteria through dual damage mechanisms [92]. Syringic acid had an MIC of 5 mg/mL against *Cronobacter sakazakii* and changed membrane potential, membrane integrity and cell morphology [93], and syringic acid and vanillin inhibited biofilms of methicillin-resistant *Staphylococcus epidermidis* [94]. Vanillic acid had an MIC of 1.0 mg/mL against *Vibrio alginolyticus* and damaged the cell membrane [95], and it acted on the membrane and biofilm of carbapenem-resistant *Enterobacter hormaechei* [96]. These MIC values are high compared with antibiotics and indicate a modest, mainly membrane-directed activity.

Gallic acid reduced capsular polysaccharide biosynthesis in hypervirulent *Klebsiella pneumoniae* [97] and had broad antifungal activity *in vitro* and *in vivo* [98], and ellagic acid showed a comparable antifungal spectrum [99]. Combinations are often more promising than single compounds: ferulic acid potentiated quinolones against *Acinetobacter baumannii* by increasing redox imbalance [100], gallic acid potentiated tulathromycin against two bovine respiratory pathogens [101], and ellagic acid potentiated fluconazole against *Candida albicans* [102]. Quercetin damages membranes, inhibits nucleic acid and protein synthesis and reduces virulence and biofilm formation [103], inhibits quorum-sensing-dependent biofilm formation in *Pseudomonas aeruginosa* [104], and blocked the entry of influenza A virus through the HA2 subunit with IC50 values of 2.7 to 7.8 μg/mL [105]. Galloylated catechins such as EGCG show the highest antibacterial activity among green tea catechins, through virulence inhibition, membrane damage, enzyme inhibition, oxidative stress, DNA damage and iron chelation [106]. The MIC of EGCG was 4 to 64 times higher in complex media than in a protein-free defined medium, so growth medium must be reported [107]. General reviews cover flavonoids [108] and the antiviral potential of ferulic acid [109], and ferulic acid esters and ferulic acid-chitosan

ISSN: 2224-6878 | Pakistan Volume 6, No. 10.

IF: 14.91 | 2026 http://waerasia.org/index.php/ijtar

nanoparticles were active against bacteria and Candida biofilms [110-111]. Dietary polyphenols also shape the gut microbiota, which in turn metabolizes them [112].

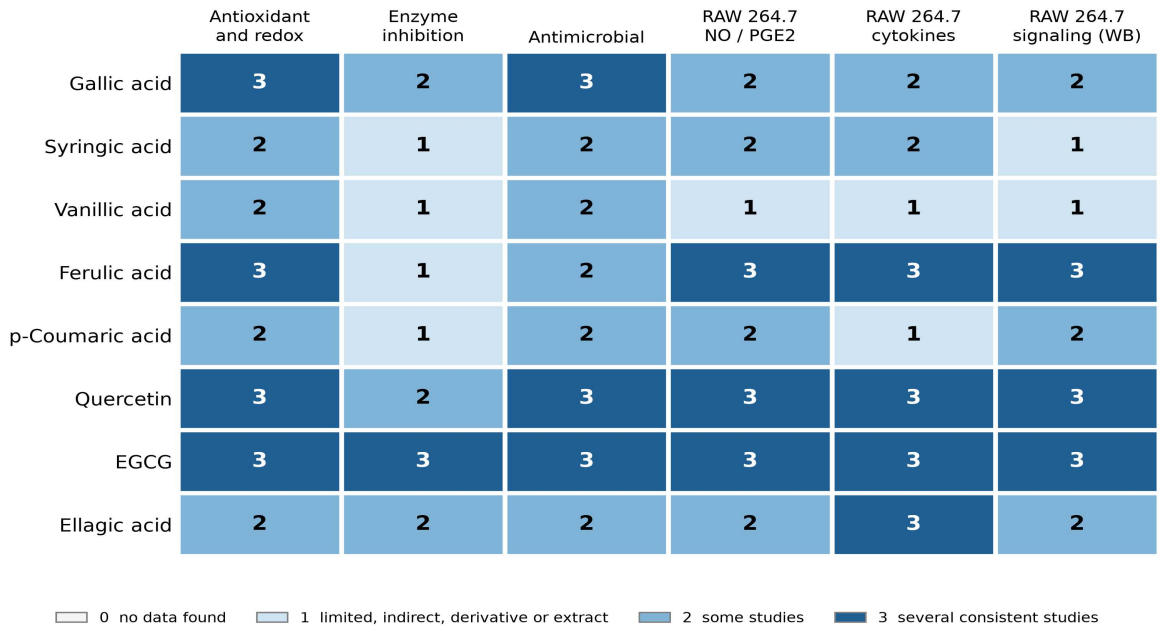


Figure 3. Qualitative evidence matrix for the eight compounds across biological activities and RAW 264.7 endpoints. Scores (0 to 3) are the authors' interpretation of the studies cited in Chapters 3 and 4: 3, several consistent studies on the pure compound; 2, some studies; 1, limited, indirect or derivative/extract data; 0, no data found.

Table 3. Summary of biological activities of the eight compounds

Compound	Antioxidant and redox	Enzyme inhibition	Antimicrobial
Gallic acid	Radical scavenger [74]; autoxidation, H_2O_2 in medium [26,82]	Pancreatic lipase [85]	Antifungal [98]; *K. pneumoniae* capsule [97]; synergy with tulathromycin [101]
Syringic acid	Methoxy groups enhance activity [44]; PI3K/Akt-mediated protection [77]	Xanthine oxidase (derivatives) [60]	MIC 5 mg/mL, *C. sakazakii* [93]; *S. epidermidis* biofilm [94]
Vanillic acid	Restores GSH, SOD, catalase [79]; peroxynitrite scavenging [80]	Cholinesterases [79]	MIC 1.0 mg/mL, *V. alginolyticus* [95]; *E. hormaechei* [96]
Ferulic acid	Stable phenoxy radical [42]; scavenges OH, NO, O2 [72]	Limited data	Potentiates quinolones [100]; antiviral potential [109]

ISSN: 2224-6878 | Pakistan Volume 6, No. 10.

IF: 14.91 | 2026 http://waerasia.org/index.php/ijtar

p-Coumaric acid	Cellular antioxidant in macrophages [23]	Tyrosinase (ethyl ester) [89]	Dual damage mechanisms [92]
Quercetin	Catechol oxidized first [75]; Nrf2/GCL/GSH [78]	Intestinal α-glucosidases [83]	Membrane damage, biofilm [103-104]; influenza A entry [105]
EGCG	Pro-oxidant H_2O_2 in medium [43,81]	α-amylase [84]; lipase [85]; tyrosinase disputed [88]	Galloyl-dependent activity [106]; medium-dependent MIC [107]
Ellagic acid	Antioxidant, low bioavailability [76]	Xanthine oxidase [24,86]	Antifungal [99]; synergy with fluconazole [102]

The evidence for each compound is summarized in Table 3 and, as a qualitative score, in Figure 3. The three activity groups are connected to inflammation in macrophages. Oxidative stress and ROS amplify NF-κB and MAPK signaling, enzyme targets such as xanthine oxidase and lipoxygenases produce inflammatory mediators, and microbial products such as LPS are the usual stimulus in the cell model used in the next chapter.

4. Pro-inflammatory cytokine activities of HPC

4.1 The RAW 264.7 model and its limitations

RAW 264.7 is a murine macrophage line that responds strongly to LPS through TLR4. The classical M1-like response includes NO, PGE2, TNF-α, IL-6 and IL-1β [28], but macrophage activation covers a spectrum rather than two states [113], and nomenclature and reporting guidelines have been proposed [114]. The response of RAW 264.7 cells changes with passage number [27]. Human THP-1 cells are a widely used alternative model for immune modulation [115], and primary bone marrow-derived macrophages avoid the drawbacks of a transformed line; in these cells several flavonoids, including quercetin, reduced macrophage proliferation and some inhibited TNF-α production [116]. Because most of the evidence for the eight compounds comes from RAW 264.7 cells, studies in other cells are marked in this chapter.

Two technical points affect interpretation. First, antioxidants and plant extracts can reduce MTT in the absence of cells, which overestimates viability [117], so an additional viability method should be used. Second, H_2O_2 formed in medium by EGCG, quercetin and gallic acid can mimic or mask a biological effect [43,82]. NO is usually measured by the Griess assay and cytokines by ELISA, and mRNA by RT-qPCR; the results may differ between levels, as seen for quercetin, which lowered TNF-α release but not TNF-α mRNA [31].

4.2 Effects on NO, PGE2 and cytokines

Representative RAW 264.7 data are collected in Table 4. Gallic acid and ellagic acid, isolated from pomegranate, inhibited LPS-induced NO, PGE2 and IL-6 production in RAW 264.7 cells [2]. Among gallic acid, ellagic acid and quercetin from *Radix Sanguisorbae*, all three lowered PGE2, and ellagic acid was the most potent inhibitor of TNF-α and IL-6 [1]. Ellagic acid at 0.3 and 1.0 μM reduced TNF-α, IL-1β and iNOS expression and acted on IκB and MAPKs [16].

ISSN: 2224-6878 | Pakistan Volume 6, No. 10.

IF: 14.91 | 2026 http://waerasia.org/index.php/ijtar

Gallic acid grafted to chitosan reduced NO, PGE2, iNOS, COX-2, and TNF-α, IL-1β and IL-6 at protein and mRNA level [11], but this is a derivative.

For syringic, vanillic and ferulic acids, a study with four marker compounds from *Dendrobii Herba* showed that 4-hydroxybenzoic, vanillic and syringic acids reduced TNF-α, that 4-hydroxybenzoic, syringic and ferulic acids reduced IL-6, and that all four reduced PGE2 [4]. A syringic acid-rich leaf extract reduced NO and ROS/RNS and the expression of iNOS, COX-2, NF-κB, IL-6 and TNF-α [15]. Syringic acid itself reduced iNOS, COX-2 and the phosphorylation of p65 and IκBα in LPS-induced lung injury and shifted macrophage polarization [40]. Vanillic acid lowered TNF-α, IL-6, COX-2, PGE2 and NO in mouse peritoneal macrophages [33], and *in vivo* it reduced inflammatory pain, oxidative stress, cytokines and NF-κB activation [118].

Ferulic acid reduced MIP-2 and, less strongly than dexamethasone, TNF-α [29], and lowered NO and the mRNA of IL-6, TNF-α and iNOS [30]. The picture is not uniform: ferulic acid alone did not inhibit iNOS and COX-2 expression in RAW 264.7 and BV2 cells under conditions in which a caffeic acid-ferulic acid hybrid did [119], and, unlike caffeic acid, ferulic acid did not block macrophage pyroptosis [120]. p-Coumaric acid suppressed LPS-induced inflammation in RAW 264.7 cells [32]. In a panel of mushroom phenolic acids, p-coumaric acid derivatives, especially the carboxyl-methylated derivative, inhibited NO production similarly to dexamethasone [121].

Quercetin at 0.1 to 0.2 mM reduced iNOS mRNA and NO release [31], quercetin was among the flavonoids that inhibited NO at 10 to 100 μM [122], and it lowered the transcript levels of IL-1α, IL-1β, IL-10, MCP-1 and COX-2 in LPS-stimulated RAW 264.7 cells [123]. Quercetin also reduced the M1 markers IL-6, TNF-α and IL-1β, iNOS and COX-2 in macrophages and microglia [124], and it inhibited STAT-1 and NF-κB activation and iNOS expression [125]. EGCG decreased LPS-induced TNF-α production by 50% at 100 μM, together with TNF-α mRNA and NF-κB binding [126], lowered NO to 32% of the LPS group, and suppressed IL-1β, IL-6, TNF-α and iNOS [8]. A honey extract rich in ellagic, gallic and ferulic acids inhibited NO production in stimulated macrophages [53].

Table 4. Representative RAW 264.7 data for the eight compounds (derivatives, extracts and other macrophage models are marked)

Compound	System and form	Main findings	Concentration stated
Gallic acid	RAW 264.7, isolated from pomegranate [2]	Reduced NO, PGE2, IL-6; COX-2 by Western blot	Not stated in abstract
Gallic acid	RAW 264.7, gallic acid-g-chitosan (derivative) [11]	Reduced NO, PGE2, iNOS, COX-2, TNF-α, IL-1β, IL-6 (protein and mRNA); less IκB phosphorylation, AP-1 and MAPK activation	Not stated in abstract
Syringic acid	RAW 264.7, marker compound [4]	Reduced TNF-α, IL-6, PGE2	Not stated in abstract
Syringic acid	RAW 264.7, syringic acid-rich extract [15]	Reduced NO, iNOS, COX-2, NF-κB, IL-6, TNF-α	IC50 28.2 μg/mL (NO, extract)

ISSN: 2224-6878 | Pakistan Volume 6, No. 10.

IF: 14.91 | 2026 http://waerasia.org/index.php/ijtar

Vanillic acid	RAW 264.7, marker compound [4]	Reduced TNF-α and PGE2	Not stated in abstract
Vanillic acid	Mouse peritoneal macrophages [33]	Reduced TNF-α, IL-6, COX-2, PGE2, NO; less NF-κB and caspase-1 activation	Not stated in abstract
Ferulic acid	RAW 264.7 [30,39]	Reduced NO, IL-6, TNF-α, iNOS mRNA; less p-IKK; NF-κB and Nrf2 modulated	Not stated in abstract
Ferulic acid	RAW 264.7 and BV2 [119]	No inhibition of iNOS and COX-2 by ferulic acid alone (hybrid active)	Not stated in abstract
p-Coumaric acid	RAW 264.7 [32]	Suppressed LPS-induced inflammation; NF-κB and MAPK involved	Not stated in abstract
p-Coumaric acid	RAW 264.7, derivatives [121]	Methylated derivative inhibited NO similar to dexamethasone	EC50 values in µg/mL for extracts
Quercetin	RAW 264.7 [31]	Reduced iNOS mRNA, NO and TNF-α release; no effect on TNF-α mRNA	0.1 to 0.2 mM
Quercetin	RAW 264.7 [38]	Inhibited MAPK/AP-1 and IKK/NF-κB-dependent mediator production	Not stated in abstract
EGCG	RAW 264.7 [126]	Reduced TNF-α, TNF-α mRNA, NF-κB binding	50% inhibition at 100 µM
EGCG	RAW 264.7 [8]	NO 32% of LPS group; lower IL-1β, IL-6, TNF-α, iNOS; p-IκB/IκB down 75%, p-p65/p65 down 50%	Not stated in abstract
EGCG	RAW 264.7 [37]	Induced COX-2 and PGE2 through ERK (opposite effect)	Not stated in abstract
Ellagic acid	RAW 264.7, strawberry fraction [16]	Reduced TNF-α, IL-1β, iNOS; acted on IκB and MAPKs	0.3 and 1.0 µM
Ellagic acid	RAW 264.7, *Radix Sanguisorbae* [1]	Reduced PGE2, TNF-α, IL-6 (most potent of three)	Not stated in abstract

ISSN: 2224-6878 | Pakistan Volume 6, No. 10.

IF: 14.91 | 2026 http://waerasia.org/index.php/ijtar

4.3 Signaling pathways and Western blot evidence

iNOS and COX-2 produce NO and PGE2 in activated macrophages and are controlled mainly by NF-κB and MAPK signaling [34-36,127]. The protein-level evidence for the eight compounds is summarized in Figure 4. EGCG lowered the p-IκB/IκB ratio by 75% and p-p65/p65 by 50% and reduced TLR4 protein [8], ferulic acid reduced IKK phosphorylation and nuclear translocation of NF-κB and Nrf2 [30], and ellagic acid acted on IκB and MAPKs [16]. Quercetin disrupted the association of PI3K and MyD88 and inhibited MAPK/AP-1 and IKK/NF-κB signaling [38], and quercetin suppressed proinflammatory cytokine production through MAP kinases and NF-κB in LPS-stimulated macrophages in earlier work [128]. The effect on NF-κB is not always inhibitory at the level of DNA binding: quercetin did not block p50/p65 binding in one study but inhibited p50/p50 [31]. Gallic acid-g-chitosan prevented IκB phosphorylation and MAPK/AP-1 activation [11], p-coumaric acid involved NF-κB and MAPKs [32], and a p-coumaric acid-containing fraction of *Adenostemma lavenia* reduced iNOS, COX-2, p-IκBa and MAPK phosphorylation and activated AMPK, Nrf2 and HO-1 [129]. Ellagic acid suppressed p38 phosphorylation in RAW 264.7 cells during RANKL-induced osteoclast differentiation at 1 μM [130].

Nrf2 and NF-κB are linked. Nrf2 blocks transcription of proinflammatory cytokine genes in macrophages [131], and the molecular cross-talk between the two pathways is complex [132]. Ferulic acid illustrates this: in LPS-stimulated RAW 264.7 cells it modulated both pathways, acting like an IKK inhibitor and reducing Nrf2 activity [39]. Polyphenols and flavonoids also regulate inflammasome activation [133-134], but RAW 264.7 data for the eight compounds on NLRP3 are very limited, and the best-described effect is the inhibition of NLRP3 activation by ellagic acid in a hyperuricemia model [24].

ISSN: 2224-6878 | Pakistan Volume 6, No. 10.

IF: 14.91 | 2026 http://waerasia.org/index.php/ijtar

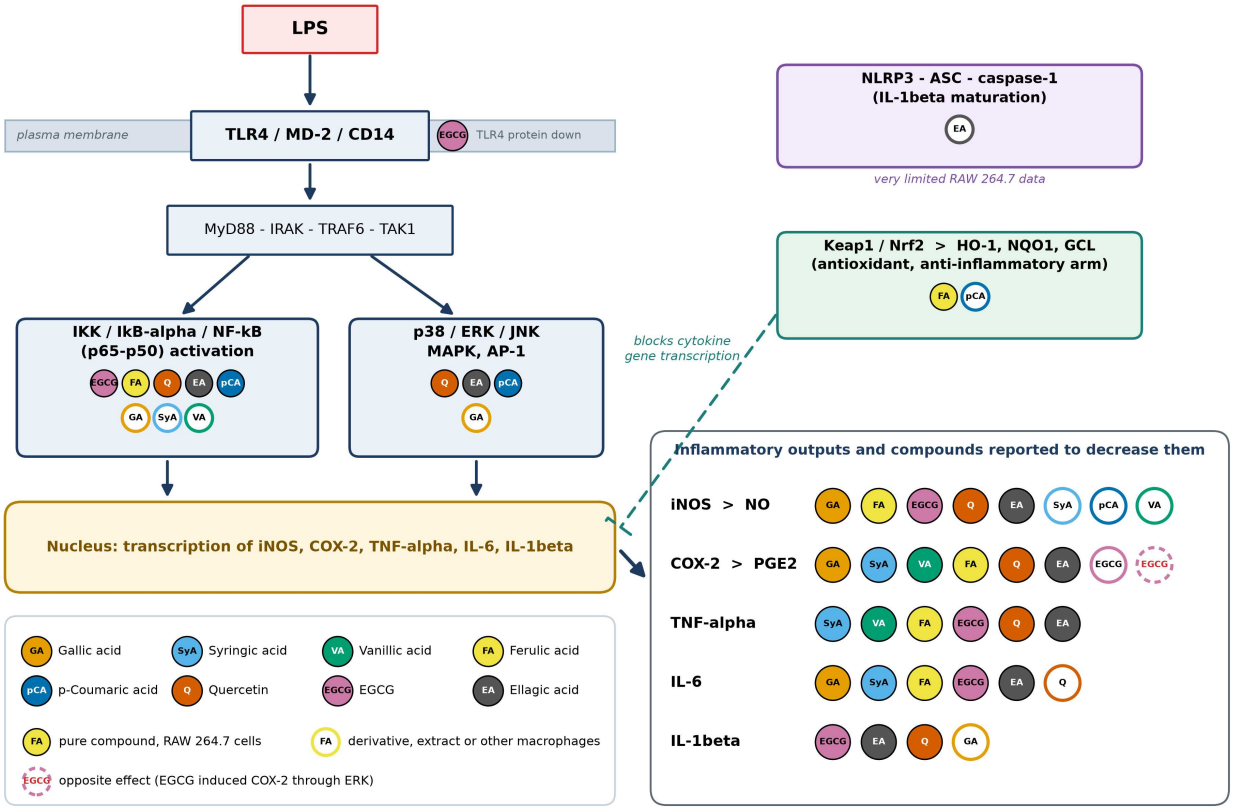


Figure 4. Pro-inflammatory cytokine pathway in LPS-stimulated RAW 264.7 macrophages and the nodes at which the eight compounds were reported to act. Filled chips mark studies on the pure compound in RAW 264.7 cells; open chips mark derivatives, extracts or other macrophage models. The dashed chip indicates an opposite effect (EGCG induced COX-2).

4.4 Structure-activity trends, polarization and translation

For flavonoids in RAW 264.7 cells, the flavones apigenin, wogonin and luteolin were the strongest NO inhibitors, quercetin was less active, flavanones and flavonoid glycosides were inactive up to 100 µM, and a C2-C3 double bond appeared to be important [122]. Synthetic flavones were most active with 5,7-dihydroxy A rings and 3',4'-dihydroxy B rings and reduced iNOS induction without directly inhibiting the enzyme [135]. For phenolic acids, conjugation by methylation or glucuronidation changed the activity but did not remove it [121], which matters because circulating forms differ from the compounds added to cells. The galloyl group of EGCG and gallic acid is linked to the strongest enzyme and antibacterial effects (Chapter 3), but in cells it may also increase autoxidation. The structural comparison remains tentative because the eight compounds have rarely been tested together under identical conditions.

Polarization offers a second readout. Quercetin reduced M1 markers [124], syringic acid favored the shift from M1 to M2 macrophages [40], ferulic acid influenced microglia and macrophage polarization through the ROS/NF-κB axis in retinal neovascularization [136], and natural products in general modulate M2 polarization [137]. These data are mostly from other models than RAW 264.7. Translation to humans is limited by exposure: polyphenol bioavailability is low and governed by absorption and metabolism [138-139], gut microbiota convert ellagic acid and

ISSN: 2224-6878 | Pakistan Volume 6, No. 10.

IF: 14.91 | 2026 http://waerasia.org/index.php/ijtar

others [47], and the concentrations used in cell studies are often above plasma levels. Gallic acid [10], syringic acid [140], ferulic acid [64] and vanillic acid [118] also reduced inflammation in animal models, which supports the cell data but does not replace it.

5. Conclusions

Gallic, syringic, vanillic, ferulic and p-coumaric acids, quercetin, EGCG and ellagic acid form a structurally graded set of phenolics, from one to eight phenolic OH groups, that can be identified reliably by HPLC-DAD, LC-MS/MS and NMR. Their antioxidant, enzyme-inhibitory and antimicrobial activities are well documented for gallic acid, quercetin, EGCG and ellagic acid, but data for syringic, vanillic and p-coumaric acids as free compounds are limited. In LPS-stimulated RAW 264.7 cells the strongest and most consistent evidence is for EGCG, quercetin, ellagic acid and ferulic acid, which reduce NO, PGE2, TNF-α, IL-6 and IL-1β, in most cases by inhibiting NF-κB and MAPK signaling, with Nrf2/HO-1 as a second arm. Evidence for gallic, syringic, vanillic and p-coumaric acids rests largely on derivatives, extracts or other models, and some findings conflict, for example the induction of COX-2 by EGCG and the lack of effect of ferulic acid alone in one study.

The main weaknesses are the use of one murine cell line and one stimulus, the high µM concentrations, assay artefacts caused by H_2O_2 formation and MTT reduction, and the lack of head-to-head comparisons. Future work should (1) test all eight compounds under identical conditions with confirmed purity, (2) include catalase and alternative viability controls, (3) validate results in primary and human macrophages, (4) use transcriptomics, proteomics and docking to define targets, (5) evaluate metabolites, combinations and delivery systems at realistic concentrations, and (6) report LPS dose, endotoxin level, passage number and medium. The take-home message is that structure alone does not predict the anti-inflammatory ranking of these phenolics in macrophages, and only standardized comparisons will show which of them is most useful.

Abbreviations

COX-2, cyclooxygenase-2; DAD, diode array detector; EGCG, epigallocatechin gallate; HO-1, heme oxygenase-1; IL, interleukin; iNOS, inducible nitric oxide synthase; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa B; NMR, nuclear magnetic resonance; NO, nitric oxide; Nrf2, nuclear factor erythroid 2-related factor 2; PGE2, prostaglandin E2; TLR4, Toll-like receptor 4; TNF, tumor necrosis factor; XO, xanthine oxidase.

Author Contributions

A.S. and R.S. contributed equally to this work and are the corresponding authors. They developed the concept and the methodology, carried out the literature analysis and wrote the manuscript. M.T. assisted with editing and with the preparation of the figures.

Funding

This review received no external funding. The authors funded the work themselves.

ISSN: 2224-6878 | Pakistan Volume 6, No. 10.

IF: 14.91 | 2026 http://waerasia.org/index.php/ijtar

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Shin HK, Seo CS, Jeong SJ, Yoo SR, Lee NR. Quantitative Analysis and In vitro Anti-inflammatory effects of gallic acid, ellagic acid, and quercetin from radix sanguisorbae. Pharmacognosy Magazine. 2016;12(46):104. doi:10.4103/0973-1296.177908
2. BenSaad LA, Kim KH, Quah CC, Kim WR, Shahimi M. Anti-inflammatory potential of ellagic acid, gallic acid and punicalagin A&B isolated from *Punica granatum*. BMC Complementary and Alternative Medicine. 2017;17(1):47. doi:10.1186/s12906-017-1555-0
3. Landete JM. Ellagitannins, ellagic acid and their derived metabolites: A review about source, metabolism, functions and health. Food Research International. 2011;44(5):1150-1160. doi:10.1016/j.foodres.2011.04.027
4. Yoo SR, Jeong SJ, Lee NR, Shin HK, Seo CS. Simultaneous determination and anti-inflammatory effects of four phenolic compounds in *Dendrobii Herba*. Natural Product Research. 2017;31(24):2923-2926. doi:10.1080/14786419.2017.1300798
5. Kumar N, Pruthi V. Potential applications of ferulic acid from natural sources. Biotechnology Reports. 2014;4:86-93. doi:10.1016/j.btre.2014.09.002
6. Huang DW, Kuo YH, Lin FY, Lin YL, Chiang W. Effect of Adlay (Coix lachryma-jobi L. var. ma-yuen Stapf) Testa and Its Phenolic Components on Cu 2+ -Treated Low-Density Lipoprotein (LDL) Oxidation and Lipopolysaccharide (LPS)-Induced Inflammation in RAW 264.7 Macrophages. Journal of Agricultural and Food Chemistry. 2009;57(6):2259-2266. doi:10.1021/jf803255p
7. Li H, Lee H, Kim S, Moon B, Lee C. Antioxidant and Anti-inflammatory Activities of Methanol Extracts of *Tremella fuciformis* and Its Major Phenolic Acids. Journal of Food Science. 2014;79(4). doi:10.1111/1750-3841.12393
8. Hossen I, Kaiqi Z, Hua W, Junsong X, Mingquan H, Yanping C. Epigallocatechin gallate (EGCG) inhibits lipopolysaccharide-induced inflammation in RAW 264.7 macrophage cells via modulating nuclear factor kappa-light-chain enhancer of activated B cells (NF- κ B) signaling pathway. Food Science & Nutrition. 2023;11(8):4634-4650. doi:10.1002/fsn3.3427
9. Singh BN, Shankar S, Srivastava RK. Green tea catechin, epigallocatechin-3-gallate (EGCG): Mechanisms, perspectives and clinical applications. Biochemical Pharmacology. 2011;82(12):1807-1821. doi:10.1016/j.bcp.2011.07.093
10. Bai J, Zhang Y, Tang C, Hou Y, Ai X, Chen X, et al. Gallic acid: Pharmacological activities and molecular mechanisms involved in inflammation-related diseases. Biomedicine & Pharmacotherapy. 2021;133:110985. doi:10.1016/j.biopha.2020.110985
11. Ahn CB, Jung WK, Park SJ, Kim YT, Kim WS, Je JY. Gallic Acid-g-Chitosan Modulates Inflammatory Responses in LPS-Stimulated RAW264.7 Cells Via NF-κB, AP-1, and MAPK Pathways. Inflammation. 2016;39(1):366-374. doi:10.1007/s10753-015-0258-2
12. Zhong Y, Chiou YS, Pan MH, Shahidi F. Anti-inflammatory activity of lipophilic epigallocatechin gallate (EGCG) derivatives in LPS-stimulated murine macrophages. Food Chemistry. 2012;134(2):742-748. doi:10.1016/j.foodchem.2012.02.172

ISSN: 2224-6878 | Pakistan Volume 6, No. 10.

IF: 14.91 | 2026 http://waerasia.org/index.php/ijtar

13. Xie Y, Liu Y, Sun J, Zheng L. Synthesis of mitochondria-targeted ferulic acid amide derivatives with antioxidant, anti-inflammatory activities and inducing mitophagy. Bioorganic Chemistry. 2022;127:106037. doi:10.1016/j.bioorg.2022.106037
14. Shi Y, Chen X, Qiang S, Su J, Li J. Anti-Oxidation and Anti-Inflammatory Potency Evaluation of Ferulic Acid Derivatives Obtained through Virtual Screening. International Journal of Molecular Sciences. 2021;22(21):11305. doi:10.3390/ijms222111305
15. Islam MA, Huq Atanu MS, Siraj MA, Acharyya RN, Ahmed KS, Dev S, et al. Supplementation of syringic acid-rich *Phrynium pubinerve* leaves imparts protection against allergic inflammatory responses by downregulating iNOS, COX-2, and NF-κB expressions. Heliyon. 2023;9(2):e13343. doi:10.1016/j.heliyon.2023.e13343
16. Lee J, Kim S, Namgung H, Jo YH, Bao C, Choi HK, et al. Ellagic Acid Identified through Metabolomic Analysis Is an Active Metabolite in Strawberry ('Seolhyang') Regulating Lipopolysaccharide-Induced Inflammation. Journal of Agricultural and Food Chemistry. 2014;62(18):3954-3962. doi:10.1021/jf4038503
17. Cuyckens F, Claeys M. Mass spectrometry in the structural analysis of flavonoids. Journal of Mass Spectrometry. 2004;39(1):1-15. doi:10.1002/jms.585
18. Stalikas CD. Extraction, separation, and detection methods for phenolic acids and flavonoids. Journal of Separation Science. 2007;30(18):3268-3295. doi:10.1002/jssc.200700261
19. Fernandes FHA, Salgado HRN. Gallic Acid: Review of the Methods of Determination and Quantification. Critical Reviews in Analytical Chemistry. 2016;46(3):257-265. doi:10.1080/10408347.2015.1095064
20. Kim HK, Choi YH, Verpoorte R. NMR-based metabolomic analysis of plants. Nature Protocols. 2010;5(3):536-549. doi:10.1038/nprot.2009.237