Pharmacological effects of gallic acid in health and diseases: A mechanistic review

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**Objective(s):** Gallic acid is a natural phenolic compound found in several fruits and medicinal plants. It is reported to have several health-promoting effects. This review aims to summarize the pharmacological and biological activities of gallic acid in vitro and animal models to depict the pharmacological status of this compound for future studies.

**Materials and Methods:** All relevant papers in the English language were collected up to June 2018. The keywords of gallic acid, antioxidant, anticancer, antimicrobial, gastrointestinal-, cardiovascular-, metabolic-, and miscellaneous- diseases were searched in Google Scholar, PubMed, and Scopus.

**Results:** Several beneficial effects are reported for gallic acid, including antioxidant, anti-inflammatory, and antineoplastic properties. This compound has been reported to have therapeutic activities in gastrointestinal, neuropsychological, metabolic, and cardiovascular disorders.

**Conclusion:** Current evidence confirms the pharmacological and therapeutic interventions of gallic acid in multiple health complications; however, available data are limited to just cellular and animal studies. Future investigations are essential to further define the safety and therapeutic efficacy of gallic acid in humans.

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**Introduction**

The term “phytochemical” points to a vast range of biologically active natural compounds with valuable pharmaceutical and nutritional properties. Phenolic compounds are a group of phytochemicals with at least one hydroxylated benzene ring. The members of this large and diverse group of chemical compounds are usually classified based on the number of carbon atoms in their structures. Simple phenolics, phenolic acids, acetophenones, cinnamic acid derivatives, coumarins, chromones, chalcones, aurones, flavonoids, anthocyanins, betacyanins, benzophenones, xanthones, stilbenes, quinones, lignans, lignins, tannins, and phlobaphenes are the main subgroups of natural phenolic compounds (1).

Phenolic acids are an important and abundant subgroup of phenolic compounds with the basic chemical structure of C₆-C₃ (hydroxybenzoic acids) or C₆-C₄ (hydroxycinnamic acids), consisting of a phenolic ring and a carboxyl substituent. The shikimic acid or phenylpropanoid pathway of plant metabolism usually regulate the biosynthesis of phenolic acids. In some cases, phenolic acids are the precursor of other important phytochemicals, such as tannins, coumarins, benzoquinones, and naphthoquinones. Caffeic acid, ferulic acid, p-hydroxybenzoic acid, protocatechuic acid, vanillic acid, salicylic acid, and gallic acid are the most common members of phenolic acids (1, 2).

Today, foodstuffs containing phenolic compounds and their metabolites are of the main interest due to their favorable effects on human health. In this case, the positive effect of red wine polyphenols on cardiac health or the protective role of flavonoids against various types of cancer and age-related diseases are important examples (2).

**Gallic acid and its derivatives: from chemistry to medicine**

Gallic acid or 3,4,5-trihydroxybenzoic acid (CAS No 149-91-7) is one of the most abundant phenolic acids...
in the plant kingdom. It is a colorless or slightly yellow crystalline compound, with extensive application in the food and pharmaceutical industries. Gallic acid has been isolated from different plant species such as *Quercus* spp. and *Punica* spp., via various chromatographical methods; however, from the industrial point of view, gallic acid is produced through the hydrolytic breakdown of tannic acid using a glycoprotein esterase, namely tannase (EC 3.1.1.20) (3).

Gallic acid and its derivatives such as lauryl gallate, propyl gallate, octyl gallate, tetradecyl gallate, and hexadecyl gallate, can inhibit the oxidation and rancidity of oils and fats ascribed to their free radical scavenging and antioxidant nature. Therefore, they can be useful as additives in the food industry (4).

Besides the edible uses of gallic acid and its ester derivatives as flavoring agents and preservatives in the food industry, there are diverse scientific reports on biological and pharmacological activities of these phytochemicals, with emphasis on antioxidant, antimicrobial, anti-inflammatory, anticancer, cardioprotective, gastroprotective, and neuroprotective effects (4). This paper reviews the pertinent biological and pharmacological activities of gallic acid in order to provide a clear view of the therapeutic aspects of this valuable phenolic acid.

**Therapeutic effects of gallic acid and its derivatives**

Figure 1 represents the most relevant pharmacological activities of gallic acid and related compounds.

**Antimicrobial activity**

Structure-activity relationship studies of phenolic acids show that some parameters such as the basic chemical structure, the position, and the number of hydroxyl groups as well as their substituents on the phenolic ring, and the esterification of the carboxyl group, can affect the antimicrobial activity. Generally, hydroxycinnamic acids have higher antibacterial activity compared with hydroxybenzoic acids (5). Hydroxybenzoic acids with a lower degree of hydroxylation in phenol compared with hydroxybenzoic acids (5). Hydroxybenzoic hydroxycinnamic acids have higher antibacterial activity group, can affect the antimicrobial activity. Generally, phenolic ring, and the esterification of the carboxyl hydroxyl groups as well as their substituents on the chemical structure, the position, and the number of parameters such as the basic antioxidant, antimicrobial, anti-inflammatory, anticancer, cardioprotective, gastroprotective, and neuroprotective effects (4). This paper reviews the pertinent biological and pharmacological activities of gallic acid in order to provide a clear view of the therapeutic aspects of this valuable phenolic acid.

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**Antimicrobial activity**

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From the mechanistic point of view, gallic acid can inhibit motility, adherence and biofilm formation of *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus mutans*, *Chromobacterium violaceum*, and *Listeria monocytogenes* (10-12). The compound can also disrupt the integrity of the cell membrane in Gram-positive and Gram-negative bacteria and change the charge, hydrophobicity, and permeability of the membrane surface (13). Gallic acid can interfere with the membrane permeability of *Campylobacter jejuni* and elevate the antibiotic accumulation in the microorganism (14). Moreover, it can disintegrate the outer membrane of Gram-negative bacteria via chelation of divalent cations (15).

In addition to its effects on the bacterial cell membrane, there are some reports on the inhibitory activity of gallic acid against bacterial dihydrofolate reductase and its excitatory activity on topoisomerase IV-mediated DNA cleavage in different bacteria (16). Alkyl gallates can also penetrate the bacterial cell membrane and interfere with the electron transport chain and cellular respiration (17).

Some ester derivatives of gallic acid, i.e., octyl gallate, use the hydrophilic catechol part as a hook to bind to the polar surface of the cell membrane and enter the lipid bilayer using the hydrophobic alkyl part. Subsequently, they act as a nonionic surfactant and interfere with the selective permeability of cell membrane in fungi (17).

Gallic acid can inhibit HIV-1 integrase, HIV-1 transcriptase, HIV-1 protease dimerization (18-22), HCV attachment and penetration, HCV replication, HCV serine protease (23-26), the herpes simplex virus (HSV)-1 and HSV-2 attachment and penetration (22). It also causes disruption in *Haemophilus influenza* A and B particles (27).

In connection with protozoa, gallic acid can bind to the glutamate-gated chloride channels in the nervous system of *Caenorhabditis elegans* and initiates the hyperpolarization of the cell membranes and excitation of muscles. These events finally result in worm paralysis and death (28).

Gallic acid, alkyl gallates and chitosan-based formulations of gallic acid can potentiate the antimicrobial activity of other antibiotics, including erythromycin, gentamicin, norfl Roxacin, ciprofloxacin, ampicillin, penicillin, and oxacillin via synergism (29-34) (Table 1).

![Figure 1](image-url)  
*Figure 1. An overview of the pharmacological activities of gallic acid based on in vitro and in vivo studies*
Anticancer activity

In normal physiological conditions, the cells of a healthy organism are programmed for collaboration and coordination, thereby disruption in cells can evoke different life-threatening diseases, such as cancer. At the cellular level, cancer is defined as an unusual increase of cell division, the resistance of the produced cells to death, and their tendency to invade and metastasize.

The cancerous cells disturb the normal functions of other cells by invasion or metastasis. No matter where the origin of the problem is, the overall quality of life is overshadowed by cancer. According to the official reports of health- and wellness-related organizations, the magnitude of personal and social consequences of cancer is very significant and the investigation of new drugs to control this problem continues (35-38).

Gallic acid can exert its cytotoxic and antitumor effect via modulation of antioxidant/pro-oxidant balance. In some cases, the compound can control the reactive oxygen species (ROS)-induced carcinogenesis through increasing the activity of superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR), and glutathione peroxidase (GPx) and/or by reducing the lipid peroxidation and ROS production. In other cases, gallic acid can induce the cell cycle arrest, autophagy, and apoptosis via activating the caspases pathway and ROS generation. In addition, it can inhibit the invasion and metastasis by decreasing the matrix metalloproteinase expression and activity (39-43).

Moreover, some derivatives of gallic acid, such as isobutyl gallate-3,5-dimethyl ether and methyl gallate-3,5-dimethyl ether, are able to reduce the tumor size and increase the survival rate in in vivo models of cancer (44). Gallic acid regulates the cell-cycle-related proteins such as cyclin A, cyclin D1, and cyclin E, and slow down the cell division by induction of the p27KIP enzyme and inhibition of CDK activity (45). In the case of hepatocellular carcinoma, gallic acid decreased the tumor size and the serum level of tumor marker enzymes such as aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) by inhibiting the proliferation of hepatic cells (46) (Table 1).

Gastrointestinal diseases

Gallic acid protects the mucosal layer of the gastrointestinal tract from ulcer via different mechanisms by reducing the acid secretion, inducing the release of endogenous antioxidant agents and defensive factors (i.e., SOD, CAT, endothelial nitric oxide synthase (e-NOS) and prostaglandin E2 (PGE2)), as well as decreasing oxidative stress and lipid peroxidation. In addition, gallic acid has been associated with several other beneficial pathways including reduction of the expression of pro-inflammatory mediators (i.e., tumor necrosis factor (TNF)-α and inducible nitric oxide synthase (i-NOS)), up-regulation of the pro-angiogenesis factors (i.e., Von Willebrand factor (vWF) VIII, mucosal hepatocyte growth factor (HGF) and vascular endothelial growth factor (VEGF)), promotion of angiogenesis, and inhibition of the expression of apoptosis parameters (i.e., caspase-3 and caspase-9) (47-49) (Table 1).

Gallic acid interferes with various intra-cellular inflammatory pathways that induce ulcerative colitis. The compound inhibits the expression of nuclear transcription factors, such as nuclear factor (NF)-κB and signal transducer and activator of transcription 3 (STAT3), and down-regulates their inflammatory downstream targets (50). It also reduces the expression and/or activity of pro-inflammatory cytokines and inflammatory proteins, including TNF-α, interferon-γ (INF-γ), interleukin (IL)-1β, IL-6, IL-17, IL-21, IL-23, cyclooxygenase (COX)-2, and i-NOS, and decreases the expression and infiltration of neutrophils and CD68+ macrophages into the colon (50-51).

Gallic acid inhibits the lipid peroxidation and malondialdehyde production by inducing transcription factors (i.e., NR12) and its cytoprotective downstream targets including NAD(P)H quinone dehydrogenase 1 (NQO1) and UDP-glucuronosyltransferase (UDT-GT) (50-51).

Beside the gastroprotective activity, gallic acid ameliorates the hepatotoxic effects of xenobiotic agents by acting as an antioxidant compound that scavenges free radicals, such as ROS, and improves the capacity of antioxidant defense systems including SOD, GST, GPx, CAT, GSH, and cytochrome P450-dependent detoxifying enzymes (52-57) (Table 1).

Cardiovascular diseases

Myocardial ischemia is defined as a condition that is caused by an imbalance between oxygen supply and demand of the myocardium, of which coronary artery atherosclerosis is known to be the main cause. To decrease the risk of myocardial infarction, the ischemia can be treated using different surgical methods and/or pharmacological agents.

Gallic acid pretreatment decreases the harmful oxidative consequences of myocardial infarction in the context of its antioxidant potency (58), either by increasing the activity of antioxidant enzymes, such as SOD, CAT, GST, and GPx (58) and/or by elevation of the level of non-enzymatic antioxidant agents, such as GSH, vitamin C, and vitamin E (58). All of these activities can inhibit the detrimental effects of free radicals on the integrity and function of myocytes membranes, and consequently, the concentration of serum cardiac biomarkers, including cardiac troponin T (cTnT) and creatine kinase-MB (CK-MB) decreases after infarction (35, 58) (Table 1).

Metabolic diseases

Obesity, diabetes mellitus, and hyperlipidemia are the most prevalent metabolic disorders among adults.

The ability to store the excess energy in adipocytes and release it in the future is vital for survival. However, genetic susceptibility, excessive energy intake and sedentary lifestyle may provoke increased adipose storage and further cause metabolic disorders.

In metabolic disorders, gallic acid inhibits diet-induced hyperglycemia and hypertriglyceridemia, reduces the size of adipocytes, and protects pancreatic β-cells by inducing the expression of peroxisome proliferator-activated receptor-γ (PPAR-γ), a nuclear transcription factor that induces differentiation and insulin sensitivity in adipocytes (59). Gallic acid also increases the cellular glucose uptake via stimulation...
of the phosphatidylinositol 3-kinase (PI3K)/p-Akt signaling pathway and translocation of insulin-stimulated glucose transporters, such as GLUT4, GLUT2, and GLUT1 (59). The compound prevents the diet-induced oxidative stress by stimulating various enzymatic and non-enzymatic antioxidant defenses (60). Gallic acid can up-regulate the hepatic glycolysis enzymes, such as hexokinase, aldolase, and phosphofructokinase, and down-regulate the hepatic gluconeogenesis enzyme, named fructose-1,6-bisphosphatase, in rodents fed a high fructose diet (59-63) (Table 1).

**Neuropsychological diseases**

Alzheimer's disease is a cognitive neurodegenerative problem (35), which commonly results in dementia in elderly individuals. Insidious memory loss and progressive dementia over the years are the major clinical presentations of patients. In this disease, the atrophy of the brain starts from the temporal lobe and spreads to the parietal and frontal lobes. In the microscopic scale, plaques of amyloid-β (Aβ) molecules and fibrillary tangles of hyperphosphorylated tau filaments are visible in the nervous system (35).

The protective effect of gallic acid on nerve cells is a controversial issue. On the one hand, gallic acid decreases the Aβ-induced toxicity in cultured cortical neurons of rats via inhibiting Ca2+ release from the endoplasmic reticulum into the cytoplasm or Ca2+ influx, inhibiting ROS generation and apoptosis (64). The compound restores the streptozotocin (STZ)-induced cerebellar oxidative stress and cognitive impairment in rats by scavenging free radical molecules such as ROS, inhibiting lipid peroxidation, and stimulating the activity of endogenous antioxidant agents, such as SOD, CAT, and GPx (65). Gallic acid is also able to reverse the scopolamine-induced amnesia in mice, probably through inhibiting oxidative stress and decreasing acetylcholinesterase (AChE) enzyme activity in the brain (66).

On the other hand, gallic acid decreases the viability of PC-12 rat pheochromocytoma cells in the H2O2-induced toxicity model (67). In this manner, gallic acid increases the rate of apoptosis via stimulation of the c-Jun N-terminal kinase (JNK) protein, down-regulation of Bcl-2 protein, inducing poly (ADP-ribose) polymerase cleavage, or even increasing intracellular Ca2+ and ROS generation (67) (Table 1).

**Miscellaneous diseases**

As shown in Figure 2, gallic acid can extinguish the flames of inflammation via different mechanisms. It decreases the expression and release of pro-inflammatory and inflammatory mediators, such as bradykinin, substance P, COX-2, NF-κB, IL-2, IL-4, IL-5, IFN-γ, and TNF-α. The compound also inhibits the phagocyte- or polymorphonuclear (PMN)-mediated inflammatory responses by scavenging ROS and decreasing the myeloperoxidase (MPO) activity (69-73).

As mentioned earlier, gallic acid can partially neutralize the substance-induced toxicity in the liver and neural system. The beneficial and protective effects of gallic acid on substance- or radiation-induced toxicity in connective tissue, especially bone marrow, renal, reproductive, and respiratory systems have been proven. Almost all of the above-mentioned effects are linked to the antioxidant activity of gallic acid (74-82).

Topical application of gallic acid prevents the UV-B induced hyperpigmentation and photoaging of mice skin via down-regulating the melanogenic genes such as tyrosinase, increasing the skin hydration and transforming growth factor (TGF)-β1 induced production of procollagen type I and elastin, and decreasing ROS activation, wrinkle formation, and epidermal thickening (83, 84) (Table 1).

**Conclusion**

Studies presented here showed that the most important pharmacological properties of gallic acid are attributed to its antioxidant and anti-inflammatory potentials. In addition, gallic acid is involved in various signaling pathways that regulate the wide range of biological functions including pro- and inflammatory pathways, NO signaling pathway, intrinsic and extrinsic pathways of apoptosis, and NF-κB signaling pathway. Gallic acid and its derivatives demonstrated a broad range of beneficial effects in prevention and/or management of several disorders, also their acceptable safety and stability profiles, make them significant options to be introduced as dietary supplements.

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**Conflicts of Interest**

All authors declare no potential conflicts of interest.
### Table 1. Pharmacological activities of gallic acid and its derivatives in different diseases

| Disease category | Compound name | Model | Effects | References |
|------------------|---------------|-------|---------|------------|
| **Anti-inflammatory** | Gallic acid | In vitro: LPS-induced inflammation in A549 lung cancer cells | In vitro: JHAT, iNOS & COX-2 inhibition, p38 & JNK mediated iNOS dephosphorylation | (107) |
| | Gallic acid | In vivo: LPS-induced inflammation in mice | In vivo: interleukin-1β, IL-1β & IL-6 production, IL-6 & TNF-α, IL-6 & IL-8 expression | (71) |
| | Gallic acid ethyl ester | Acetic acid-induced abdominal constriction, formalin-induced nociception, rat paw hyperalgesia induced by substance-P, bradykinin, PGE2 or carrageenan | Acetic acid-induced abdominal constriction, formalin-induced nociception, | (70) |
| | Bergeonin (C-glycoside of 4-O-methylgallic acid) | Mycobacterium tuberculosis-induced inflammatory arthritis in mice | Inflammatory arthritis, IL-2, IFN-γ, TNF-α, IL-4 & IL-5 | (69) |
| | Gallic acid | In vitro: AEGs-treated rabbit chondrocytes | In vitro: iNOS, collagen II & aggrecan degradation, NO, i-NOS, COX-2, PGE2, TGFβ, SOD | (73) |
| | | | In vivo: collagen-induced knee osteoarthritis in rabbit | | |
| | | | In vivo: 50% Mankin’s score | | |
| | Gallic acid | ISO-induced myocardial infarction in rats | Myocardial infarction, ITC, TG, LDL-C, HDL-C, MDA, TBA, L-C, CAT & GSH, TNFα, TNFβ, β2M, IL-6 | (85) |
| | Gallic acid | ISO-induced cardiotoxicity in rats | LCK-MB & LDH, βlysosomal membrane damage, LPO, TSH | (86) |
| | Gallic acid | Lindane-induced cardiotoxicity | LCK, LDH & LPO, 5HT, SOD, GSH & GST, TNFα, TNFβ, β2M, IL-6, TSH | (87) |
| | Gallic acid | Evaluation of antioxidant enzymes in the heart of male Sprague-Dawley rats | Cardiac SOD, GSH, CoQ10, CAT, SHH, GSH/GSSG ratio, heart oxygenase-I & Nrf2 | (88) |
| | Gallic acid | AEGs-induced cardiac remodeling in rats | Cardiac fibrosis, LTNF-α, TGF-β, MMP-2 & MMP-9 | (89) |
| | Gallic acid | STZ-induced myocardial dysfunction in diabetic rats | LCK-MB, LIDH, LPO, LDL-C & VLDL-C, JMBP, SEBP & bradycardia, collagen content, | (90) |
| | Gallic acid | Isoproterenol-induced myocardial infarction in rats | LCK-MB, TCO, CAT, GSH, HDL, GSH, Fc & E, iNOS, TNFα, TSH | (58) |
| | Gallic acid | Fructose-enriched-diet-induced cardiac fibrosis | LIP, HOMA-IR, INAPDH oxidase subunits gp91 phox & p22 phox, icotilase I & iNOS | (91) |
| | Gallic acid | AL(OH)3-induced myocardial injury | LLDH, CPK, CK-MB, TG, LDL, TNF-α & MDA, THBD, GSH, SOD & CAT | (92) |
| | Gallic acid | Allsace-induced diabetes & endothelial dysfunction | LMDA, TTAC & histamine vasodilatory response of mesenteric vascular bed | (93) |
| | Gallic acid | L-NAME-induced hypertension | LSRP, LV wall thickness & cardiac fibrosis, hypotrophy markers, | (94) |
| | Gallic acid | Cyclophosphamide-induced cardiac dysfunction | LMDA & H2O2, TCGT, GST, GSH & GSH | (95) |
| | | | | |
| **Cardiovascular** | Gallic acid | Cyclophosphamide-induced hypertension | Cyclophosphamide-induced hypertension | (53) |
| | Gallic acid | CCL4-induced hepatotoxicity in Charles Foster rats & Swiss albino mice | Sleep time & paralysis time, ILPO, Thapatic amyloidoprotein-N-Demythlated, | (57) |
| | Gallic acid | Hepatic ischemia & repension injury in rats | ALT, AST & LDH activities, TCA & GPs, IMDA | (86) |
| | Gallic acid | n-propyl gallate | L moreover, p53, Bax & Bak, LPO | (96) |
| | Gallic acid | Brush border disaccharidases inhibition in rat, LACA/L mice, 3 d induces & rabbit | Sicerase, malate, trehalase & lactate activity | (97) |
| | Gallic acid | Primary HSC & hepatocytes | Cytotoxicity to HCS but not hepatocytes, | (98) |
| | Gallic acid | Ethanol-induced neuroprotection in rats | Citrulline α-Cα & p-coumaric acid | (99) |
| | Gallic acid | Ethanol-induced liver damage in rats | JNK, TAK1, LCK-MB, LPO, LDL-C & VLDL-C, JMBP, SEBP & bradycardia, | (54) |
| | Gallic acid | Gastric mucosal lesions caused by ischemia-reperfusion injury in rats | Total area of gastric lesions, iNOS-2 & i-NOS | (47) |
| | Gallic acid | In vitro: rat gastric epithelial cells | In vitro: iNOS & CYP2J2 expression, iNOS & CYP2J2 expression | (48) |
| | Tryptamine-gallic acid | In vivo: indomethacin & diclofenac-induced gastropathy | In vivo: iNOS activity, iNOS, COX-2, p55NF-kB & IL-6/p-STAT3/705 activation | (108) |
| | | In vitro: rat gastric epithelial cells | In vivo: iNOS activity, iNOS, COX-2, p55NF-kB & IL-6/p-STAT3/705 activation | (50) |
| | Gallic acid | DSS-induced experimental colitis in mice | JDAI & colon shortening, IL-11, IL-23, MDA, TCO, GSH, CAT, GSH, GSH, GSH | (51) |
Table 1, Continued

| Gallic acid | Pharmacological effects of gallic acid and human health |
|-------------|-------------------------------------------------------|
| Paracetamol-induced liver damage in mice | lALT, AST, ALP, & JTNF-α, TSD, CAT, GSH, GPs & GST (101) |
| CCl4-induced liver damage in rats | lVacuole formation, inflammation & necrosis, JAST, ALT, TG, TC, LPO & JTNF-α, TSD, CAT & GSH (102) |
| Aspirin + pycnogenol-induced gastric ulcer in rats | lUlcer index, gastric juice volume, free & total acidity, total protein, carboxydrates concentration, TSD, CAT, GSH, GPs, GR & glucose-6-phosphate dehydrogenase (103) |
| Bromobenzene-induced liver injury in rat | lHistidine hydrolase & AMMD activity, ILPO, Tepoxide hydrolase activity (52) |
| CCL4-induced liver fibrosis in mice | lLiver fibrosis, NA, MDA, ALT, AST & GSH (104) |
| Beryllium-induced hepatoprotective dysfunction in rats | lBilirubin, Cr, LDH, GGT, LPO, AST, ALT, ALP, TSHG, SOD & CAT (105) |
| Lead-induced toxicity in blood, liver & kidney of rats | lLPO & carbonyl, prevention of body weight loss, TALA-D activity, TSD, CAT & GSH (56) |
| CCl4-induced chronic liver injury in rats | lALT, AST & MDA, TSD, CAT, GSH, GR, GPs & GSH/GIST (107) |
| Lindane-induced hepatoprotective toxicity in rats | lALT, AST, ALP, LPO, creatinine & urea, TSHG, CAT, SOD, GPs & GGT (108) |
| Beryllium-induced hepatoprotective toxicity | lALT, ALP, LPO, AMMD, TSHG, CAT, SOD, GPs & GST, ICR & urea (109) |
| Cyclophosphamide-induced hepatotoxicity in rats | lACT, ALT, MDA, TSHG, CAT, SOD & GST (55) |
| Indomethacin-induced gastric ulcer in Swiss albino mice | ↑Ulcer healing, JPE2 synthesis, 1e-NOS/i-NOS ratio (49) |
| Diet-induced obesity in mice | lITAG & FBS, adipocyte size in the epidymidal white adipose tissue, TPAAR + expression, 1Akt signaling pathway activity, glucose tolerance & lipid metabolism (59) |
| High-fat-diet- & STZ-induced type 2 diabetes in rats | lBody weight gain, PBS & FPI, adipose tissue insulin sensitivity, Cytoprotective action on pancreatic β-cell, TPAAR expression in treated tissue, liver & skeletal muscle, Tissulin-dependent glucose transport, Interactions with the GLUT4, GLUT1, PTK & P-Akt, Lipoxygenase (60) |
| High-fat-diet-induced dyslipidemia, hepatosteatosis & oxidative stress in rats | lObesity, liver weight, percental & epididymidal adipose tissue weights, Insulin TAG, phospholipid, TC, LDL-C, insulin & leptin, lipid droplets size, iNOS/TAG & cholestrol, loadisive stress & GES, TSHG, GPs, GR & GST (61) |
| High-fructose-diet-induced diabetes | ↑Glucose uptake, JALDOG, M & HOMA-IR, 1C-peptide, fructosamine & cardiovascular risk index, TH, IR-1, PTK, Akt/protein kinase B & GLUT-2, JF-1, J-6, JBP, Thomsokinin, PFK & aldolase (62) |
| STZ-induced diabetic rats | l1αCet, GSH, ILPO, Three radical scavenging property, Fe2+, chelating ability & Fe3+ reducing property, TCAT, GST, 3-aminolevulinic acid dehydratase & LDL, ippotremic enzymes (56) |
| STZ-induced diabetic Wistar rats | l1BSF, regeneration of β-cells, JTC, TAG, LDH-C, urea, uric acid, creatinine, TPFI, C-peptide & glucose tolerance restored the total protein, albumin & body weight (110) |
| Fructose-induced metabolic syndrome & cardiac fibrosis in rats | ↓Insulin resistance, ROS & NADPH overproduction, collagen I & osteopontins (98) |
| In vitro: porcine pancreatic lipase kit | In vitro: lipase activity (111) |
| In vivo: high-fat-diet-induced obesity in mice | ↑Glucose uptake, JALDOG, M & HOMA-IR, 1C-peptide, fructosamine & cardiovascular risk index, TH, IR-1, PTK, Akt/protein kinase B & GLUT-2, JF-1, J-6, JBP, Thomsokinin, PFK & aldolase (62) |
| STZ-induced diabetes in rats | TPPI, hepatic hexokinase activity, CAT, SOD, GPs, lFBF, HBA1C, Gelβp & fructose-1, 6-biophosphatase, LPO (112) |
| STZ-induced diabetes in rats | lFBF, HBA1C, LPO, TPPI, Vit C, SOD, CAT, GSH, GR, GST, GPs, HMG-Coa reductase activity (113) |
| Alloxan-induced diabetes in rats | lFBF, TPPI, GSH, GPs, CAT, SOD & osmotic fragility of RBCs (114) |
| STZ-induced diabetes in rats | lFBF, brain LPO, SOD, CAT, GR, GST, GPs, brain lipids (37) |
| Chromium-induced thyroid dysfunction | lSOD & GST up-regulation, JNO, i-NOS, TNF-α, IL-6 & COX-2 (115) |
| In vitro: high glucose toxicity in NBE 52E rat proximal tubular epithelial cells | In vitro: FP38 MAPK, NF-κB activation (116) |
| In vivo: high fat diet/STZ-induced diabetes in rats | In vivo: weight gain, Triceps neutral fat (117) |
| STZ-induced diabetes in rats | TPPI, hepatic hexokinase activity, CAT, SOD, GPs, lFBF, HBA1C, Gelβp & fructose-1, 6-biophosphatase, LPO (112) |
| 6-Hydroxydopamine induced oxidative stress in rats | ↑Passive avoidance memory, TTM, GPs, lMDA (165) |
| STZ-induced memory deficits & oxidative stress in rats | ↑Passive avoidance & spatial memory, performance, TTM, SOD, GPs & CAT, lMDA (118) |
| EPM in rats | ↑Time spent & entries in the open arms of EPM, locomotor activity, involvement of 5-HT1A receptors, ILPO, TSDO & GSH (119) |
| Sodium-fluoride-induced oxidative stress in rat brain | ↑Body weight & body weight, Cr, Cr clearance, BUN, IL-1β, IL-6, TNF-α & iMDA, Irenal p38 MAPK, NF-κB activation, TGF-β, fibroectin, TSHG, GIST, GST/GSH/GST ratio, GR, CAT, SOD & GPs (117) |
| STZ-induced oxidative damage in rat brain | ↑R05 & lipid peroxidation, TSDO & 6-ALA-D, CAT, GSH & vit C (117) |
| Spinal cord injury-induced oxidative stress in rat | ↑Passive avoidance memory, TTM, GPs, lMDA (165) |
| Neuropsychological | ↑Time spent & entries in the open arms of EPM, locomotor activity, involvement of 5-HT1A receptors, ILPO, TSDO & GSH (119) |
| EPM in rats | ↑Passive avoidance memory, TTM, GPs, lMDA (118) |
| Sodium-fluoride-induced oxidative stress in rat brain | ↑Time spent & entries in the open arms of EPM, locomotor activity, involvement of 5-HT1A receptors, ILPO, TSDO & GSH (119) |
| STZ-induced oxidative damage in rat brain | ↑Body weight & body weight, Cr, Cr clearance, BUN, IL-1β, IL-6, TNF-α & iMDA, Irenal p38 MAPK, NF-κB activation, TGF-β, fibroectin, TSHG, GIST, GST/GSH/GST ratio, GR, CAT, SOD & GPs (117) |
| Spinal cord injury-induced oxidative stress in rat | ↑Passive avoidance memory, TTM, GPs, lMDA (165) |
| Gallic acid (as chitosan nanoparticles) | ↑Transfer latency in the EPM test, Spatial learning & memory in MWM, LACHe activity, (66) |
| 6-Hydroxydopamine induced oxidative stress in rat brain | ↑Time spent & entries in the open arms of EPM, locomotor activity, involvement of 5-HT1A receptors, ILPO, TSDO & GSH (119) |
| STZ-induced oxidative damage in rat brain | ↑Body weight & body weight, Cr, Cr clearance, BUN, IL-1β, IL-6, TNF-α & iMDA, Irenal p38 MAPK, NF-κB activation, TGF-β, fibroectin, TSHG, GIST, GST/GSH/GST ratio, GR, CAT, SOD & GPs (117) |
| Spinal cord injury-induced oxidative stress in rat | ↑Passive avoidance memory, TTM, GPs, lMDA (165) |
| Gallic acid (as chitosan nanoparticles) | ↑Transfer latency in the EPM test, Spatial learning & memory in MWM, LACHe activity, (66) |

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| Gallic acid | Tyrosin hydroxylase Gal/THAS-X | in vivo: locomotor activity, protection of dopaminergic neurons, Tâle span & climbing abilities | (123) |
| --- | --- | --- | --- |
| Gallic acid | BDNF, Drosophila melanogaster model of Parkinson’s disease Neurotoxicity in rats | Neurotoxicity, cerebellar & cerebral MDA & nitrite, TAT, GST & SOD | (55) |
| Gallic acid | Reserpine-induced vacuous chewing movements in rats | Various chewing movements | (124) |
| Gallic acid | Lead-induced locomotor damage & brain oxidative stress in rats | Locomotor & exploratory activities by attenuating crossing & rearing time, brain levels of PB, TSD & TGH | (125) |
| Gallic acid | Sodium nitroprusside oxidative stress-induced mitochondrial impairment | ↓NO level, mitochondrial protein tyrosine nitrification, ILP0, ↓protein carbonyl, TSGH & iMP7 | (126) |
| Gallic acid | In vitro: medium hydroxyltate-induced mitochondrial dysfunctions in SH-SYST cells | In vitro: protects against cytotoxicity of SH-SYST cells, mitochondrial dysfunction, level of mitochondrial ROS by \( {\text{HCHO}} \)-fluorescence intensity, intracellular DCF fluorescence intensity, intracellular MDA, by modulating mitochondrial dysfunctions by \( {\text{Co}} \) oxygen consumption | (127) |
| Gallic acid (as chitosan nanoparticles) | Oral health | In vivo: total infant volume | |
| Gallic acid | Aβ-induced toxicity in cultured rat cortical neurons | Immunobility in FST & TST, JMAO-A activity & MDA, TSHG & CAT | (64) |
| Gallic acid | In vitro: cerebral ischemia/reperfusion induced by middle cerebral artery occlusion | Increased serum retinol binding protein, increased serum vitamin E, increased serum vitamin C | |
| Gallic acid | H2O2-induced apoptosis in rat pheochromocyta PC12 cells | Methyl gallate: T cell viability; mitochondrial depolarization, caspase-9 activation & DNA degradation | (68) |
| Gallic acid | Immobilization-induced Swiss male albino mice | iPLasma nitrite in both unstressed & stressed mice, iplasma corticosterone, In-90S activity, lastancy in behavioral tests | (129) |
| Gallic acid | Global ischemia/reperfusion in Wistar rats | TGlut performance, serinotomor disorders, & hypoglyesia | (130) |
| Gallic acid | Experimental sciatic nerve crush in rats | Improved motor coordination & SMOY sciatic nerve conduction velocity, Tailayed foot lifting | (131) |
| Gallic acid | Aβ-induced AD in rats | Improved LTP amplitude & area under the curve, TPS Amp, LTP plaque | (132) |
| Gallic acid | H2O2-induced apoptosis in rat pheochromocyta PC12 cells | iCell viability, TPARP cleavage, TTNK phosphorylation, Tβc-2 | (67) |
| Gallic acid | STZ-induced cerebral oxidative stress in rats | Weight loss, ↓hyperglycemia, HbA1C, LPO, ACHE & purinergic enzymes, Tradiical scavenging & P2+ chelating ability, Vit C, GSH, CAT, GST, cerebral LDH & Na+K+ATFase activity | (133) |
| Gallic acid | In vitro: Aβ-induced neurotoxicity in murine microglial BV-2 cells & neuroblastoma Neuro-2A cells | In vitro: ↓MDA acylation & cytokine production, cell death, ↓viability of Neuro-2A, inmemory deficits in Ab peptide-induced mice | (134) |
| Gallic acid | In vivo: Aβ-induced AD in ICR mice | In vivo: Lysyten production, neuronal cell death, nuclear NF-xB & IL-1β | (135) |
| Gallic acid | Chronic cerebral hypoperfusion-induced cognitive deficit & brain oxidative damage in rats | ↓Neurotoxicity, TSGH, iGSSG, Lelievan in (Cat) αJ | (136) |
| Gallic acid & its derivatives | 6-OHD-induced toxicity in human SH-SYST neuroblastoma cells | Reminalization of enamel caries lesions, residual first molar enamel volume & mineral density values, liewerity of molar enamel caries | (137) |
| Oral health | Streptococcus sobrinus 6715- induced enamel caries in rats | Rate of DNA repair process in peripheral blood leucocytes, bone marrow cells, & splenocytes, TGx, GSH, inmotability, weight loss & LPO | (82) |
| Radiation-induced toxicity | Whole body γ-radiation exposure in mice | ↑Survival (IGDE>MGDE), NK cells cytotoxicity & in vivo Radiosensitization | |
| Gallic acid | In vitro: rat liver microsomes & placid pBR322 DNA exposed to γ-irradiation | In vivo: ILPO in rat liver microsomes, ↓DNA damage in plasmid | (81) |
| Respiratory | In vitro: whole body γ-irradiation in mice | In vivo: ↓DNA damage in leucocytes | |
| Gallic acid | Blonycin-induced pulmonary fibrosis in rats | ↓Lesions & fibrosis, collagen content, hydroxyproline accumulation, LPO, JTNF-α & IL-1β, TGF activity & TTM | (80) |
| Gallic acid | Desorubcint-induced chronic kidney disease in rats | TAlbumin, JAST, IALT, JTG, cholesterol, ILPO, IBUN | (79) |
| Gallic acid | Glyoxal-induced renal fibrosis in rats | ↓Renal fibrosis, IBUN, ALP, collagen I & III, MMP-2 & -9, Nox & ROS, TSD | (78) |
| Gallic acid | Ferric nitrolic acid-induced renal toxicity in rats | ↑Renal toxicity & cell proliferation, BUN, H2O2, renal microsomal LPO & quinone reductase, TAT, xantine oxidase, GPx, GSH & G6PD | (77) |
| Gallic acid | Cisplatin-induced nephrotoxicity in rats | ↓ILPO, ROS, Cu, ura, uric acid, arginine, TAT, TSD, CAT, GSH & GPs | (75) |
| Gallic acid | Experimental renal ischemia-reperfusion in rats | TAlbumin, Cr, MDA | (74) |
| Urogenital | Cyclophosphamide-induced toxicity in tests & epididymis of rats | ↓Reproductive toxicity, nitrite, H2O2, & MDA TSD, FSH, LH & testosterone | (55) |
| Gallic acid | Cyclophosphamide-induced toxicity in tests & epididymis of rats | ↓MDMA, NO, H2O2, TSHG, GPS, SOD, CAT & testosterone | (76) |
| Gallic acid | STZ-induced oxidative stress in tests of rats | ↑SOD & CAT, ↓MDA, TSD, FSH, LH & testosterone | (138) |
| Dermal | In vitro: normal human dermal fibroblasts exposed to UVB | In vitro: transcription factor activation protein 1 activity | (84) |
### Table 1, Continued

| Gallic acid | In vitro: murine melanoma B16F10 cells | In vitro: melanin production & tyrosinase activity, melanogenesis regulatory genes, activation of ERK pathway, involvement of AKT/GSK3β & PKA/CREB signaling | (83) |
| Malignancy | Gallic acid | DMM-induced colon carcinogenesis in male Wistar rats | TSD, GSH, GR, GPs, & CAT activity, LPO modification | (39) |
| Gallic acid | DMH-induced colon carcinogenesis in mice | Activity of phase I enzymes (cyt. P450 & cyt. b5), lacticity of phase II enzymes (GST, DTT & GGT) | (139) |
| Gallic acid | in vitro: EAT & LLC1 cells | in vitro: no significant cytotoxic effects | (44) |
| Gallic acid | in vitro: EAT cells /BALB/c mice & LLC1 cells (J57/6) mice | in vitro: EAT cells Survival (IGDE>MGDE), NK cells cytotoxicity | (140) |
| Gallic acid | in vivo: IL-6 human promyelocytic leukemia | in vivo: Tumor progression | (46) |
| Gallic acid | in vivo: human NCSLC NCI-H648 cells | in vivo: viability | (141) |
| Gallic acid | in vivo: mouse NCI-H648 xenograft model | in vivo: tumor size | (142) |
| Gallic acid | in vivo: LL-2 lung cancer cells | in vivo: tumor size, Tumor or apoptotic cells in tumor, synergistic effects in combination with cisplatin | (143) |
| Gallic acid & methyl gallate | in vivo: two-stage skin carcinogenesis in ICR mice | in vitro: induction of G2/M phase cell cycle arrest, 11nuclearar Ca++, CDK1 activity, caspase-3, caspase-8 & caspase-9 activation, IAP | (40) |
| Gallic acid | in vitro: cell-free kinases, primary HUVECs, primary human dermal LECs, human HT29 colon carcinoma cells & MT-450 rat mammary carcinoma cells | in vitro: slight inhibition of RTKs, LVEGF-induced autophosphorylation of VEGFR-2 in H9T2 cells, iproliferation & Taperogenesis in all cell lines | (45) |
| Pyrogallol | in vivo: MT-450 tumor-bearing rats | in vitro: induction of S phase cell cycle arrest | (43) |
| Pyrogallol | in vivo: xenograft mouse model of MCF10DICS.com cells | in vitro: induction of S phase cell cycle arrest | (46) |

**Malignancy**

Gallic acid: Pyrogallol

**i-NOS:** nitric oxide synthase; IL-2: interleukin-2; IFN-γ: interferon-γ; TNF-α: tumour necrosis factor-α; IL-4: interleukin-4; IL-5: interleukin-5; IL-1β: interleukin-1β; COX-2: cyclooxygenase-2; IL-6: interleukin-6, NO: nitric oxide; SOD: superoxide dismutase; GPx: glutathione peroxidase; UVB: ultraviolet B; TAC: total antioxidant capacity; L-NAME: NG-nitro-L-argininemethyl ester; MB: malignant melanoma; UMR-106: murine osteosarcoma cell line; HUVECs: human umbilical vein endothelial cells; H9T2: human small intestine carcinoma cell line; L-arginine: nitrogen donor and substrate of NO synthesis; AEGs: advanced glycation end products; AMPK: AMP-activated protein kinase; AKT/GSK3β & P38 pathway: AKT/GSK3β & P38 MAPK signaling; VEGF: vascular endothelial growth factor; HSCs: hepatic stellate cells; UVB: ultraviolet B; TAC: total antioxidant capacity; L-NAME: NG-nitro-L-argininemethyl ester; SBP: systolic blood pressure; LV: left ventricle; HDAC: histone deacetylase; VEGF: vascular endothelial growth factor
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