



A comprehensive review on radioprotective potency and multifaceted biological activities of gallic acid

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ARTICLE INFO

Article Type:

Review

Article History:

Received: 1 Dec. 2024

Revised: 12 May 2025

Accepted: 18 May 2025

published: 1 Jan. 2026

Keywords:

Gallic acid

Neoplasms

Radioprotection

Chemoprotection

Anti-inflammatory effects

Antioxidant effects

ABSTRACT

This review really digs into all the cool ways gallic acid (GA) can help with health, especially its strong powers in fighting off damage from oxygen radicals and stopping cancer from growing. We dive deep into how GA messes with different cancer cells, making them die off in a controlled way. The presentation also discusses how gallium enhances the efficacy of chemotherapeutic drugs, serving as a robust protective barrier against the adverse effects of chemotherapy. Moving on, we look at how GA helps protect the body from harm caused by radiation or other toxic substances, especially in important parts like the liver, kidneys, and brain. But GA's not just about cancer; it's also great at protecting the nerves, keeping blood vessels healthy, and even stopping diseases before they start. By the end, we get a full picture of how GA moves around the body, how it gets broken down, and all the ways it can protect the body, making it a really interesting natural substance for medical use. As no thorough study has yet explored this topic, this review seeks to comprehensively evaluate the most prominent research on the diverse biological activities of GA, including its radioprotective effects.

Implication for health policy/practice/research/medical education:

Gallic acid (GA) possesses well-established properties as an antioxidant, anti-inflammatory, anti-cancer agent, chemoprotective, and radioprotective agent. Proper use of GA can reduce the side effects of radiation and improve treatment output.

Please cite this paper as: Shaghaghi Z, Zamani S, Fathi F, Alvandi M, Kholoosi Taher F, Dehbanpour MR, et al. A comprehensive review on radioprotective potency and multifaceted biological activities of gallic acid. J Herbmmed Pharmacol. 2026;15(1):1-10. doi: 10.34172/jhp.2026.52846.

Introduction

Cancer is a big killer worldwide, caused by lots of different things, such as radiation, which can mess up the DNA in the cells where it hits them (1). Ionizing radiation (IR) is pretty nasty because it can directly damage DNA or make free radicals that break DNA strands, mess up sugar and base parts, leading to cell death, chromosome problems, and mutations. Even though IR helps in finding and treating cancer, there are limits to how safely it can be used for treating tumors. IR is used in things like radiotherapy, making things sterile, and medical check-ups (2), with

X-rays being a big part of medicine. Every year, about 10.9 million people get cancer around the world (3), and half of them get some kind of radiation treatment for it (4). This shows why we need things that can protect us from radiation damage. These protectors need to be easy to give, not too toxic, easy to absorb, cheap, and work at different radiation levels (5). Finding these protectors is super important for doctors who treat cancer with radiation (5). The best radioprotectors we have are things like amino thiols and their friends, including stuff like amifostine (WR-2721). Some of these have helped prevent

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issues in cancer patients getting radiation (6). Research is always going on to find new radioprotective drugs that don't have bad long-term effects, last a long time, and are stable, which are the key things we want in these drugs (5,6). Herbal stuff, which people often use for cancer treatment, has also shown some promise in protecting against radiation's bad effects (5,6). Recent studies have shown that some natural plant chemicals can protect cells in lab tests, looking at things like how much they prevent fat from going bad, DNA damage, free radical cleanup, antioxidant levels, cell survival, and changes in cell structure (7). Gallic acid (GA) is a type of phenolic acid commonly found in various plant-based foods consumed by humans, including blueberries, strawberries (8), mangos (9), grape seeds (10), and carob (11). It is also present in beverages like red wine (12), different types of teas (13-15), and coffee (16). Additionally, GA is believed to contribute to the therapeutic effects of several herbal medicines (17,18) traditionally used for healing purposes. In vitro studies have demonstrated that GA promotes the activity of antioxidant enzymes (19), shields the liver from toxic damage, and inhibits lipid peroxidation caused by radiation exposure. Research has attributed numerous pharmacological properties to GA, such as antioxidant, anti-inflammatory, antineoplastic, antimicrobial, chemoprotective, and radioprotective effects (20-22). This review seeks to provide a comprehensive overview of the studies exploring the diverse biological functions of GA, with a focus on its antioxidant, anti-inflammatory, chemoprotective, and radioprotective roles (22).

Phenolic acids

The word "phytochemical" covers a whole bunch of natural stuff that's good for us, with lots of health and nutrition benefits. Among all these, phenolic compounds are a big deal, having at least one ring of benzene with oxygen stuck to it. This huge group of chemicals is sorted by how many carbon atoms they have, like simple phenolics, phenolic acids, and a bunch of others like acetophenones, cinnamic acid stuff, coumarins, and so on (8).

Phenolic acids are a group of compounds defined by the presence of a benzene ring, a carboxylic acid group, and one or more hydroxyl and/or methoxyl groups (Figure 1). They are among the most widespread non-flavonoid phenolic compounds found in plants and can exist in free form, as soluble conjugates, or bound to plant cell walls in an insoluble form. Structurally, phenolic acids are derived from either benzoic acid or cinnamic acid, both of which feature a carboxyl group attached to a benzene ring. Examples of hydroxybenzoic acids include GA, protocatechuic acid, vanillic acid, and syringic acid, while hydroxycinnamic acids include caffeic, ferulic, sinapic, and coumaric acids (8-22).

Phenolic acids are pretty important and common, with a simple structure of a ring with either a short (C6-C1) or

a bit longer (C6-C3) chain attached. They are made up of a ring with a carboxyl group hanging off. Some common ones are caffeic acid, ferulic acid, p-hydroxybenzoic acid, protocatechuic acid, vanillic acid, salicylic acid, and GA (23). Right now, people are really into foods that have these phenolic compounds because they are good for us (23). Polyphenols are probably the most common type of these compounds in nature (24). A lot of research has shown they do all sorts of cool things for our health (25). GA, or 3,4,5-trihydroxybenzoic acid (CAS No 149-91-7), is super common in plants (23).

Gallic acid

GA, or gallate, is a big deal because it is a type of benzoic acid that helps make up galatotanins, which are a kind of tannin you can break down that has sugar and different phenol acids in it. This stuff, known as 3,4,5-trihydroxybenzoic acid (Figure 2), has both a phenol and a carboxylic acid vibe, with just one benzene ring. Its formula is $C_7H_6O_5$, which means it weighs about 170.12 grams. GA looks like a white or light yellow powder that melts at 235 to 240 °C, but then it breaks down. If you heat it up to 100-120 °C, it loses its water and gets unstable (26). It is made by breaking down tannic acid with sulfuric acid at 110 to 120 °C (26). You can find it in lots of foods like strawberries, blueberries, tea, blackberries, grapes, mangoes, walnuts, cashews, hazelnuts, wine, plums, and more (26). It is also in plants like bearberry leaves, pomegranate bark, sumac, witch hazel, oak bark, and tea leaves, either by itself or as part of tannins (27). Red wine has a lot of it, but green tea has even more, and cocoa has the most of all (27). GA can fight inflammation and oxidation (27) in lab tests and in living things (28). It has three OH groups that help it fight off harmful radicals (27). It is good at stopping fungi, bacteria, viruses, allergies, swelling, skin darkening,

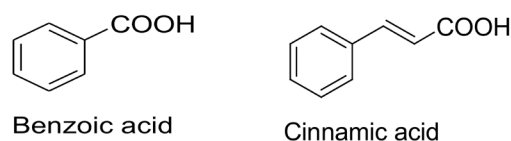
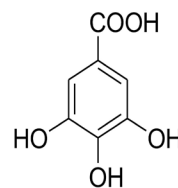


Figure 1. Structures of benzoic acid and cinnamic acid, the backbones of phenolic acids.



Gallic acid (3,4,5-trihydroxy-benzoic acid)

Figure 2. The chemical structure of gallic acid.

tuberculosis, mutations, stomach ulcers, high cholesterol, and weight gain (26-28). It is also protective for the brain, heart, liver, and kidneys (26-29). It fights colds (30-32), high blood pressure (33), and aging (34). Because it is great at cleaning up oxygen radicals. It kills germs like *E. coli*, Staph, Pseudomonas, and Klebsiella. It is tough on cancer cells but leaves normal cells alone, messes with bacterial enzymes, and affects how bacteria cut DNA (35-40). It also stops HIV from doing its thing (35,36), messes with hepatitis C (37,38), and stops herpes from sticking and entering cells. However, it is not perfect; it doesn't get absorbed well, doesn't stick around long in the body, and gets cleared out fast (39,40) (Figure 3).

Antioxidant effects of gallic acid

GA is really good at fighting off damage from oxygen radicals in lab tests (41). Its special parts, the hydroxyl groups, catch these harmful oxygen bits and stop them from causing more trouble. This helps protect fats, DNA, proteins, and enzymes from getting messed up by these radicals (7). Scientists have done all sorts of calculations to see how well it fights different radicals like OH and OOH (42,43). It is great at shielding the cells from damage by stuff like hydroxyl, superoxide, and peroxy radicals, plus non-radicals like hydrogen peroxide and hypochlorous acid. This makes it super important in stopping cancer and other damage from plant extracts (22). GA tweaks the balance between good and bad oxygen in the body, affecting enzymes like SOD, CAT, GR, and GPx, and it helps cut down on fat damage and controls the production of harmful oxygen (44-47). It also helps protect our liver from poisons by catching free radicals and boosting the body's antioxidant defenses (48-50). One GA can take out up to six DPPH radicals (51). Sometimes, it can make things worse by helping make more harmful radicals when it hooks up with iron, especially when there's not much GA or the pH is low (52). In tests, it is better at catching radicals than stuff like vitamin C, Trolox, caffeic acid, sinapic acid, and vitamin E (53). It has also been shown to help with hardening of the arteries by messing with an enzyme called alkaline phosphatase (54). When mixed with metals like copper, zinc, chromium, or selenium, it is even more effective in lab tests (55). Together with other stuff, it has helped calm down overactive airways in guinea pigs caused by allergies (56). Being overweight makes our body's antioxidant defenses weaker, but in rats, eating too much fat, GA helped boost these defenses, reducing weight gain, and easing problems like fat damage, bad cholesterol levels, and fatty liver (57). With brain cells, GA is a bit of a hero, reducing damage from Alzheimer's-like protein in rat brain cells, stopping calcium from leaking out, and cutting down on cell death (58). It is also really good at protecting nerves, hearts, and livers (7). In some cases, it can harm rat nerve cells when there is too much hydrogen peroxide around (59). It has also protected

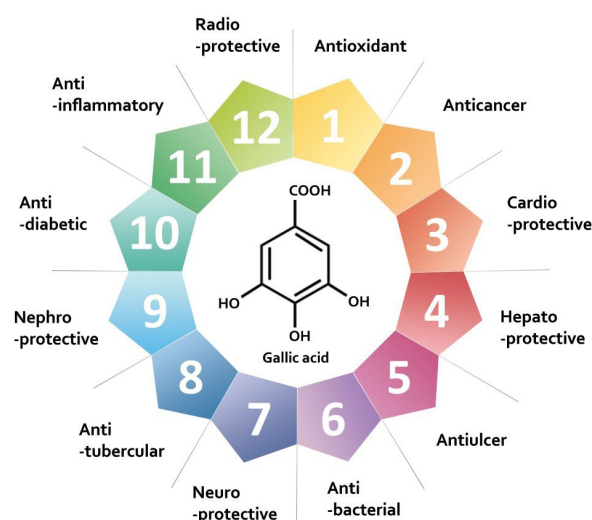


Figure 3. Functions and biological activities of gallic acid.

mouse livers from damage by paracetamol by stopping fat damage, reducing inflammation, and bringing back the body's antioxidant balance (60). GA from Daylily flowers made rats' blood and liver better at fighting radicals (61). It has even helped mice remember better by fighting off brain damage and messing with an enzyme that breaks down a memory-related chemical (62). A recent study showed it could help with stomach ulcers in rats by being an antioxidant (63). GA fights off the bad protein clumps in diseases like Alzheimer's and Parkinson's disease (64). It is good at saving kidneys from damage when blood flow is cut off and then restored (65). It works through some body signals to stop fat damage and harmful stuff like malondialdehyde (66,67). It has also prevented heart damage from a drug in rats (68) and helped clean up damage from aluminum in rats' hearts (69). It was effective against long-term liver damage from a drug in rats (70) and saved kidneys from another drug's harm by boosting antioxidant enzymes (71). In a human study, drinking water with GA reduced damage from oxygen radicals and improved some antioxidant levels without changing the overall antioxidant power (22).

Anti-inflammatory effects of gallic acid

When the body gets hurt or attacked by something from outside, it fights back with inflammation, which involves sending out signals like IL-1 β , TNF- α , NO, and PGE2 (72). GA is pretty good at calming this down in different ways. It turns down the volume on a bunch of these signals, like bradykinin, COX-2, substance P, NF- κ B, a whole bunch of interleukins, IFN- γ , and TNF- α . It also stops our immune cells from going overboard by cleaning up harmful oxygen bits, reducing MPO activity, and keeping certain cells from rushing into our gut. GA messes with the control centers of our cells, too, like STAT3

(56,66,67,73,74). It helps by lowering the production of things that make inflammation worse, like i-NOS, and by boosting stuff that helps heal, like vWF, HGF, and VEGF, encouraging new blood vessel growth and stopping cell death (74). It has been shown to protect brain cells from damage by reducing inflammation (75). GA also interacts with the body's pathways to control allergies and inflammation, stopping histamine from coming out and reducing reactions (76). It is even involved in turning off a protein that messes with healing, helping with eye issues by calming inflammation (77). It stops certain pathways in cells that would otherwise make inflammation worse, helping with fat-related inflammation and obesity (78). It is good at stopping new blood vessels from forming where they shouldn't, which is important for healing and preventing scars (79).

Anticancer effects of gallic acid

Cancer cells are weird; they grow, move, and react to treatments differently from normal cells. Each cancer type needs its own special treatment, often involving cutting it out, poisoning it with chemo, or zapping it with radiation (80). Polyphenols, which are natural antioxidants, are great at fighting cancer in lots of ways. They can be the main fighters or help make other treatments work better and reduce their side effects (81). GA is especially good at making cancer cells die in a bunch of different cancers, like leukemia, prostate, lung, stomach, colon, breast, cervical, and liver cancers (82). It can make cancer cells produce more harmful oxygen, which helps kill them off, but this depends on stuff like how much oxygen is around, the pH, and metal levels in the cells (83,84). It messes with cancer cell survival by blocking certain pathways (85). Researchers have seen GA make prostate cancer cells die by cutting up important proteins (22,86). It has been shown to stop cancer cells from growing, moving, and dying in a controlled way, while leaving normal cells alone (87). GA can make cancer cells commit suicide through different pathways, including messing with their energy factories, the mitochondria (88). It can also stop cancer cells from fixing their DNA or growing new blood vessels, which they need to survive (88). It has been shown to reduce cancer cell movement and growth in different cancers by messing with their signal pathways (89,90). In some studies, GA has made cancer cells less able to spread or hide, showing promise for treatments for brain cancer (91-94). It has also been used with other drugs to make them work better against cancer, like in breast cancer (85,95-97). GA makes cancer cells grow less and die more, even in cancers that are hard to treat. It stops cancer from growing new blood vessels or spreading. In some experiments, GA has shrunk tumors and helped animals live longer. Even extracts from plants rich in GA have shown that they can slow down cancer growth. In leukemia, GA has shown that it can really mess with the

cancer cells' ability to survive (98,99).

Chemoprotective effects of gallic acid

Chemo is a go-to for treating cancer, but it sucks that 90% of folks hit a wall with it because the cancer fights back, making the treatment fail (100). Scientists have been mixing chemo drugs with natural stuff like GA, tannic acid, quercetin, myrecitin, and serotonin to make them work better together and cut down on the bad side effects. These natural compounds are safe and can fight cancer on their own, so they are great to use with chemo, either alone or with other treatments (101). When GA is mixed with chemotherapy drugs, it has been shown to work better than just using one, especially with lung cancer (102). GA and curcumin together may stop triple-negative breast cancer before it even starts in lab tests (103). Giving GA before doxorubicin chemo can help by tweaking, easing, or even undoing the harm doxorubicin does. Before getting doxorubicin, taking GA has helped with liver damage and stress from the treatment, acting like a shield for the liver during cancer fights (104). GA has also been good at protecting against the bad stuff from cyclophosphamide, which can mess with the brain and liver, and the ability to have kids (49,105,106). In mice, it has helped keep blood pressure down, stop the heart from changing shape, and reduce scarring when they had high blood pressure from a drug (107). GA has been shown to fight back against brain damage, calming down some of the body's stress signals (108).

Radioprotective effects of gallic acid

Radiotherapy (RT) is another big hitter in cancer treatment, often teaming up with surgery and chemotherapy. However, it is a mixed bag; some people get better, while others' cancers get tougher and spread (1,109,110). GA has been mentioned for helping with the damage caused by drugs and radiation, especially in the liver and brain. Its good deeds spread to other parts too, like bones, kidneys, reproductive bits, and lungs (65,111). When GA is put in silver nanoparticles, it has changed the cancer cells' reaction to radiation in lab tests (112). GA has helped protect human blood cells from getting their DNA trashed by radiation, stopping them from dying off, too (113). This makes a strong case for using GA, this safe stuff, as a way to protect against radiation, maybe even in food or drugs (114). In mice zapped with radiation, GA has cut down on damage to their DNA, stopped their bone marrow from freezing in time, and kept their bone marrow cells from dying off, showing it is pretty good at protecting against radiation (115).

Discussion

GA has really caught people's eyes because it is so good at fighting off damage from oxygen radicals and stopping cancer (116). However, getting the most out of phenolic

acids like GA can be tricky because they don't always stick around long, they're not always easily absorbed, and they can be hard for the body to use (117). GA is a well-known herbal bioactive compound found in many herbs and foods like tea, wine, cashew nuts, hazelnuts, walnuts, plums, grapes, mangoes, blackberries, blueberries, and strawberries. GA has been reported for several pharmacological activities, such as antioxidant, anti-inflammatory, antineoplastic, antimicrobial, antifungal, antibacterial, antiviral, antiallergic, antimelanogenic, antitubercular, antimutagenic, antiulcer, anticholesterol, antiobesity, and immunomodulatory effects. It also shows protective effects on the nervous system, heart, liver, and kidneys. Beyond its therapeutic properties, GA and its esters are also used in various industrial applications, such as food additives and cosmetic products (118). Despite its impressive health benefits, GA is limited by its low permeability and poor bioavailability, which hinder its therapeutic potential (119). However, innovative drug delivery systems have been developed to address these limitations (120). Among these, GA-loaded nanoparticles have shown promise. Nanocarrier systems enhance the physical and chemical stability of GA by encapsulating it within lipid or polymer-based structures. Several types of nanocarriers have been explored for delivering GA, including liposomes, transfersomes, niosomes, dendrimers, phytosomes, micelles, nanoemulsions, metallic nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, and polymer conjugates (34,121,122). These systems offer improved reactivity, effectiveness, and bioavailability compared to traditional delivery methods, though their clinical use still faces hurdles (123). While nanoparticles offer advantages such as enhanced efficacy and bioavailability, their integration into clinical practice remains challenging. Major concerns include biocompatibility and the risk of triggering immune responses (123). Regulatory agencies like the USFDA and EMA have set strict guidelines to evaluate the toxicity, safety, quality, and efficacy of nanoparticle-based therapies. One issue is that nanoparticles can activate the immune system's complement pathway, potentially causing hypersensitivity reactions. Another concern is the production of free radicals by nanoparticles, which may lead to oxidative stress and damage to lipids, proteins, DNA, and other cellular components. Additionally, the complex and costly manufacturing processes for nanoparticles can limit their accessibility (124). Therefore, further research is essential to improve their safety, understand their interaction with the human body, and streamline regulatory approval.

Acknowledgments

The authors would like to thank the Clinical Research Development Unit of Farshchian Heart Hospital,

Hamadan University of Medical Sciences, Hamadan, Iran, for their assistance throughout the period of study. The manuscript contains details and investigations extracted from previously published literature.

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Conflict of interests

Not to declare.

Declaration of AI-assisted tools in the writing procedure

The English language of the article was improved with ChatGPT. Upon generating draft language, the author reviewed, edited, and revised the language to their own liking and takes ultimate responsibility for the content of this publication.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication, etc) have been completely observed by the authors.

Funding/Support

None.

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