Therapeutic Effects of Gallic Acid: Current Scenario

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Abstract

Gallic acid (GA), a polyphenolic compound, has been reported to prevent various diseases. In addition to prescription drugs, nutraceuticals/medicinal foods are progressively included as adjunct of cardiovascular maladies, cancer, hepatitis C, inflammation, HCV infection and neurological disorders, even though most of them have been exclusively studied in vitro. This study aimed to investigate the therapeutic effects of GA against various diseases. Systematic review of peer review was done. Studies were also identified through literature search using online databases belonging to PubMed and others with key words "Therapeutic effects of Gallic acid" from 2009 to 2017. The search was restricted to original articles, peer reviews published and online databases. The references for relevant publications were reviewed through journals. All the studies were assessed and conducted for methodological quality through reference lists of available literature. This review brings together some recent studies which establish the beneficial properties of polyphenols especially GA against most outbreak diseases and analyzes the mechanisms involved in these properties. The results presented in this review may help to emphasize that this compound could be promising as a new alternative for the treatment of mentioned diseases, either alone or in combination with other drugs or their derivatives to potentiate their effects. Results of the present study demonstrate that GA, an effective supplement, as an adjuvant therapy may be a very promising compound in reducing mortality rate of diseases.

Keywords: Gallic acid; Hepatitis C; Neurological disorders; Inflammation; Cancer; HCV infection

Introduction

Gallic acid (GA), a member of the hydroxybenzoic acids, is a naturally occurring substance found in oak bark, tea leaves, gall nuts, apple peels, sumac, green tea, wine and grapes [1]. GA is polyphenolic compound present in plants. It is found sufficiently in berries, tea, grapes, and other fruits as well as in wine. This polyphenolic compound is also present in some hard wood plant species such as, oak (Quercus robur), chestnut (Castanea sativa L) and many others. In human blood plasma, micromolar concentrations of free and glucuronidated forms of GA and its main metabolite 4-O-methylgaic have been found after ingestion of GA-rich foods, this shows the good absorption property of GA [2]. Under acid hydrolysis of hydrolysable tannins, GA could be obtained [3]. It is a yellowish white crystal with molecular mass 170.12 g/mol. Its melting point is 250°C and water solubility 1.1% at 20°C. GA could be formed from phenylalanine via caffeic acid or 3,4,5-trihydroxycinnamic acid (route 1) by the use of intermediates of shikimate pathway. Gallic acid can also be derived directly from 5-dehydroshikimate by use of enzyme shikimate dehydrogenase (SDH) (route 2), by dehydrogenation or from protocatechuate as an intermediate (route 3) (Figure 1).

Many pharmacological and biochemical pathways are affected by GA because of its strong anti-inflammatory, antioxidant, anticancer and antimutagenic properties [4]. GA has been reported to prevent a number of disorders, including cardiovascular disease, cancer, inflammation, infection [5]; diabetes [6], and neurological ailments [7].

GA, being a strong natural antioxidant, has the ability to remove reactive oxygen species (ROS), e.g., hydrogen peroxide, superoxide anions, hypochlorous acid and hydroxyl radicals. This antioxidant effect could prove beneficial to many diseases [2]. Some GA derivatives such as methyl, propyl, octyl and dodecyl gallates as antioxidants, are widely used in food manufacturing, pharmaceutical and cosmetic industries. Pharmacokinetic and pharmacodynamic properties can be modified by inducing chemical changes in GA molecules which alter the solubility and the degree of ionization [3].

This review systematically highlights the merits of GA as anti-cancer, anti-inflammatory, anti-diabetic, neuroprotective, and anti-hepatitis.

Therapeutic role of GA

Cancer preventive agent

Cancer is a prominent medical issue and a primary source of death...
around the world, influencing an expected 28.8 million individuals [8]
and representing 7.6 million deaths in 2008 [9]. The most frequently
analyzed malignancies worldwide are lung (12.7%), breast (10.9%),
colorectal (9.7%) and stomach (7.81%), among others (Bray et al.).
In recent years, the health impacts of dietary polyphenols have been
drawing in the consideration of scientists, nutritionists and
nourishment makers. Their strong antioxidant properties, richness in
the eating regimen, and their sound impacts in the counterevaction of
different oxidative related infections, bringing about separate
wholesome proposals [10]. Phenolic antioxidants, one of the significant
category of secondary metabolites, are widely dispersed in the plant
kingdom [11]. GA, one of the most significant phenolic compounds,
is accounted for to treat diverse malignant cell lines [12-16]. GA shows
a range of biological actions, and its eust subsidiaries can actuate
mitochondrial deterioration. These subsidiaries are specifically
cytoxic toward tumor cells [17].

Ovarian cancer

Ovarian tumor is the second most familiar gynecologic cancer
among ladies and the ninth most widespread malignancy in the US
[18]. It is one of the main sources of tumor related mortality in ladies in
developed countries [19]. In 2015, an expected 21,290 new cases and
14,180 passing because of ovarian malignancy happened in the USA [20].
Unluckily, the general survival rate at 5 years is just 50%, which has not fundamentally enhanced in the previous 30 years [21].
GA has demonstrated the best inhibitory movement on human ovarian
malignancy cells among eight characteristic phenolic compounds
from conventional Chinese pharmaceutical [22]. It is accounted for
to have extraordinary development inhibitory impact on two ovarian
cell disease lines, A2780/CP70 and OVCAR-3, than the impact on
an ordinary ovarian cell line, IOSE-364. It specifically suppresses
the development of tumor cells and reported to inhibit vascular
endothelial growth factor (VEGF) discharge, hence, restrains in vitro
angiogenesis. This polyphenol downregulate AKT phosphorylation in
addition to hypoxia-inducible factor-1α (HIF-1α) protein expression,
however, enhances PTEN expression. PTEN/AKT/HIF-1α pathway
represents the inhibitory impact of GA on in vitro angiogenesis and
VEGF expression [22,23]. *Emblica officinalis* (Amla) extract, containing
GA and its derivatives, does not generate apoptotic cell death, but
remarkably increases the expression of the autophagic proteins,
LC3B-II and beclin1. It is reported to reduce the expression of several
angiogenic genes, including hypoxia-inducible factor 1α (HIF-1α)
both in OVCAR3 and SW626 cells [24]. Previous study shows that
GA induces anti-ovarian cancer effects on three ovarian cell lines,
OVCAR-8, A2780 and A2780cis [25]. These discoveries give solid
support to the high capability of GA in the anticipation and treatment
of ovarian malignancy.

Colon/colorectal cancer

Colon–rectal malignancy is widespread amongst the most
well-known malady issues in numerous nations, particularly in the
western community [26]. WHO (World Health Organization) work
demonstrated that around one million individuals are determined
to have colon malignancy every year [27]. Various reviews have
recommended that high utilization of vegetables and fruits diminishes
the danger of colon tumor [28]. Subsequently, GA majorly affects
colon malignancy chemoprevention [29]. Other than GA itself, its
subordinates, i.e. ellagic acid and epigallocatechin-3-gallate, have been
likewise explored for colon disease insurance and additionally
treatment. It was accounted for that nanoparticles comprising
epigallocatechin-3-gallate have demonstrated a promising anti-oxidant
movement when contrasted with the non-loaded drug [30].

Increasing concentrations of GA leads to lysis of Human colon
tumor, HCT-15, cells with either by necrosis or apoptosis, as a result,
cell growth inhibits. It is found to influence the colony formation of
HCT-15 cells. The morphological changes, for example, membrane
blabbing and cell shrinkage was noticeable in the colon cancer cells
presented to GA, which accords to the prior experimentation on the
GA treated HCT-15 cells [31].

In addition, GA and 3-O-methylgallic acid have the ability to
diminish colorectal cancer (CRC) Caco-2 cell viabilly. This decrease is
mainly due to the limit of GA and 3-O-methylgallic acid to hinder the
cell cycle at the G0/G1 phase. The limit of these compounds to inactive
translation components NF-κB, AP-1, OCT-1 and STAT-1 partially
mediate the anti-tumor activities of GA and 3-O-methylgallic acid [32].

*Ceratonia siliqua* L. leaf polyphenols (CLP) are enriching with GA.
It exhibits a dose dependent cytotoxic impact through the introduction
of apoptosis on CRC cell lines. CLP initiate natural apoptotic pathway
through the caspase-9 application and PARP cleavage in CT-26 and
HCT-116 cells. Moreover, CLP stimulate cell cycle arrest in the G1 stage
via p53 activation [33]. This review proposes that GA can be utilized for
the anticipation of CRC.

Breast cancer

Breast carcinoma is the second most common growth around the
world, with a frequency of 1.7 million in 2012 [34]. Wang et al. assessed
the cytotoxicity impact of GA in human breast carcinoma MCF-7 cells,
which was likely interceded by means of prompting cell apoptosis. To
pick up understanding into the molecular mechanism of GAs activity
on cell apoptosis, they examined the association of apoptosis-related
signaling pathways in MCF-7 cells, which include the intrinsic and
extrinsic pathways. They detailed that both Fas/ Fas ligand (FasL)
protein levels and the action of initiator caspase-8 upgraded in MCF-7
cells after treatment with GA. Hence, showed that the Fas/FasL apoptotic
framework took an interest in GA-incited cell apoptosis. They found
that treatment with GA brought about mitochondrial malfunction by
means of diminishing mitochondrial membrane potential, expanding
Bax/Bcl-2 (B cell lymphoma 2) proportion, cytochrome c discharge into
cytosol, and additionally enactment of caspase-9. These two pathways
were reported to link and particles in one pathway could impact the
other by caspase-8-interceded Bid cleavage as shown in (Figure 2) [35].

![Figure 2: Proposed molecular mechanism of cell apoptosis incited by GA in breast cancer MCF-7 cells.](image-url)
Previous study demonstrated that Ziyang green tea (ZTP), containing (-)-epigallocatechin gallate (28.2%) followed by (-)-epigallocatechin (5.7%) and (-)-epicatechingallate (12.6%), repress MCF-7 cell multiplication by blocking cell cycle advancement at the G0/G1 stage and triggers apoptotic death. ZTP promotes cell-cycle arrest by upregulation of p53 and down regulation of CDK2 in MCF-7 cells. MCF-7 cells treatment with ZTP demonstrates an overproduction of reactive oxygen species (ROS), recommending that ROS assume an essential part in the stimulation of apoptosis in MCF-7 cells [36].

Further study demonstrated that GA-capped gold nanoparticles (GA-AuNPs) remarkably repress migration and invasion of EGF (Epidermal growth factor) -treated cells, and suppress up-regulation of EGF-induced Matrix metalloproteinase-9 (MMP-9). GA-AuNPs nullify EGF-dependent Akt/p65 and ERK/c-Jun phosphorylation, prompting down-regulation of MMP-9 mRNA and protein expression in EGF-treated breast cancer cells. So, in comparison with GA, GA-AuNPs are accounted for to have a superior potential to inhibit EGF/EGF-mediated MMP-9 expression in TNBC-MDA-MB-231 cells [37]. Mango polyphenolics, containing GA as bioactive component, reveal anti-carcinogenic properties in BT474 breast cancer cells in vitro and xenografts via repression of the PI3K/AKT pathway and regulation of the miR-126 expression [38]. GA treatment essentially reduces the cell growth of human breast cancer cell MCF-7 in a measurements subordinate way. It induces notable G2/M phase arrest yet somewhat influenced the number of inhabitants in sub-G1 MCF-7 cells. Moreover, it may upregulate p27Kip1 level by means of interruption of p27Kip1/Skp2 and the ensuing degradation of p27Kip1 by proteosome, prompting G2/M phase arrest of MCF-7 cell. It is recommended that GA ought to be beneficial to treatment of breast and p27Kip1-deficient carcinomas [39]. Generally speaking, this review recommends a capability of GA as a remedial specialist in the treatment of breast tumor.

Lungs cancer

Lung carcinoma is the most well-known reason for malignancy passing around the world, with an expected 1.8 million new cases and 1.6 million passing in 2012 [40]. In the course of recent decades, clinical mediations have had just a negligible impact on lessening demise from lung malignancy. Apoptosis in EGFR-mutant non-small cell lung cancer (NSCLC) cells influence by GA. Treatment with this polyphenol is reported to reduce EGFR level, which is basic for NSCLC survival. Furthermore, it initiates EGFR turnover prompting apoptosis in EGFR-TKI (tyrosine kinase inhibitor)-resistant cell lines, which are subject to EGFR motoring for survival. In short, GA can initiate apoptosis in EGFR-dependent lung carcinomas that are reliant on EGFR for development and survival through acceleration of EGFR turnover [41]. Moreover, it demonstrates anti-tumorogenic impacts in Tyrosine kinase inhibitor (TKI) resistant non-small cell lung cancer (NSCLC). GA treatment suppresses Src-Stat3-mediated signaling and reduces the expression of Stat3-regulated tumor advancing genes, eventually inducing apoptosis and cell cycle arrest in the TKI-resistant lung cancer yet not in the TKI-sensitive one. This finding distinguishes a significance of Src-Stat3 flagging course in GA-intervened tumor suppression movement and, all the more imperatively, gives a novel restorative knowledge of GA for cutting edge TKI-resistant lung growth (Table 1) [42].

### Gallic Acid as Neuroprotective Agent

#### Effects of gallic acid and Derivatives on Alzheimer disease

Alzheimer disease (AD), a neurodegenerative disorder, identified by extracellular aggregates of amyloid-beta (Aβ) protein called plaques and intraneuronal aggregates of tau called neurofibrillary tangles. AD is clinically characterized by increasing cognitive impairment and memory deficits that result in dementia. In spite of significant scientific research, the accurate pathological mechanisms of AD are still contentious. However, a plenty of reports have shown that oxidative stress in different macromolecules such as proteins, DNA and lipid peroxidation plays a vital role in the pathogenesis of AD [43].

Different studies reported the protective role of GA against Aβ-induced neuronal cell death. one study reveals that GA suppresses Aβ-peptide induces neurotoxicity via inhibition of glutamate release and reactive oxygen species (ROS) through suppression of Ca2+ infestation [44].

Another study demonstrated that Epigallocatechin-3-gallate (EGCG), GA derivative, mitigates AD and intellectual debilitations by repression of amyloid precursor protein cleavage and diminished amyloidosis and mitochondrial impairment in the brain [45]. Camilleri et al. stated that EGCG synchronize the amyloid precursor protein and elevates the mRNA levels and transferrin receptor in SHSY5Y neuroblastoma cells. They reported that the beneficial role of EGCG is due its metal chelating activity (especially iron chelating activity).

Lozano et al. assessed that with the increasing concentrations of GA-g-chitosan (I), acetylcholinesterase activities of the cell lysates [treatment with GA-g-chitosan (I)] decreases. They suggested that GA-g-chitosans might be useful materials in the cure and treatment of Alzheimer's disease and give a chemical pathway for the synthesis of new acetylcholinesterase inhibitors based on chitosan [46].

#### Effects of Gallic Acid and Derivatives on Parkinson's disease:

Parkinson's disease (PD) is a progressive neurodegenerative disease. The tremors, rigidity and bradykinesia are motor symptoms in PD, are due to the degeneration of dopaminergic neurons in the substantia nigra [47]. Mancia et al. found that GA reduce motor impairment and improves gamma wave power in 6-Hydroxydopamine which induce dopaminergic neurodegeneration and Parkinson's disease in rats. They stated that beneficial role of gallic acid is due to its free radical scavenging
activities and antioxidant activities [48]. Monsouri also reported that EGC
(Epigallocatechin-3-gallate) has protective role against dichlorodiphenyl Trichloroethane induced dopaminergic SH-SY5Y cells death that result in brain impairment [49]. Another study reported oral GA as protective agent in the 6-OHDA (6-hydroxydopamine) induced memory dysfunction and cerebral oxidative stress in rat model of Parkinson's disease. Their data showed that GA has neuroprotective effects, which are associated with the noteworthy antioxidant activity. This finding provide pharmacological basis of GA as an antioxidative metabolite of ellagitannins in the prevention and treatment of PD [44].

**Gallic acid as anti-diabetic agent**

Diabetes mellitus (DM) is one of the major public health problems and is considered as chronic metabolic disorder which affects about 346 million people worldwide [50]. It is mainly characterized by hyperglycaemia which results from defects in the action or secretion of insulin. The reported symptoms of DM are polydipsia, polyphagia, polyuria, weight loss, fatigue and loss of vision. These symptoms can be mild or even be absent. [51]. De Oliveira et al. review demonstrates the impact of GA on biochemical and histological parameters and biomarkers of oxidative stress in the liver and kidney of streptozotocin (STZ)- prompted diabetic rats. GA advances a change in the lipid profile of the control creatures, since it lessens levels of TG, TC and LDL. In addition to decreases in lipid peroxidation and free radical levels, it increments enzymatic and non-enzymatic cancer prevention agent protection in these tissues. Their findings prove that GA might be valuable for the treatment of hepatic and renal intricacies related with DM and raise the likelihood of another application as a corresponding treatment related with hypoglycaemic medications [52]. A study suggests that GA and elagic acid, natural flavonoids, use as anti-diabetic agents. Nair et al. evaluated binding of GA and its dimer, elagic acid, to glycogen phosphorylase (GP) enzyme, a key candidate of glucose homeostasis. This dimer is reported as a strong inhibitor as compared to GA. Both these bioactive compounds act as competitive inhibitors for glucose-1-phosphate, and non-competitive for allosteric activator, AMP. For this reason elagic acid is potentially used as anti-hyperglycaemic agent [53].

Furthermore, Latha et al. assessed that *Terminalia bellerica* is used to treat many diseases in India, including diabetes. Antidiabetic compound was isolated and identified from the fruit of *T. bellerica* and experimental dose was injected in diabetic rat. Their findings indicates that GA, presents as active compound in *T. bellerica*, responsible for the regeneration of β-cells and normalizing all the biochemical parameters (decreased serum total cholesterol, triglyceride, LDL-cholesterol, urea, uric acid, and creatinine and show increased plasma insulin, C-peptide and glucose tolerance level) which are related to the patho-biochemistry of diabetes mellitus [6], these studies recommend potential of GA as a remedial specialist in the treatment of Diabetes mellitus [38].

**Gallic acid as Cardio protective agent**

Currently in the Western world, cardiovascular disease (CVD) is considerable reason for mortality and morbidity [54]. As indicated by World Health Organization, 30% death rate in world is because of CVD in 2005. Distinctive pharmacological medications, like statins, ACE inhibitors, beta-blockers, anti-platelets are presently available in market for CVD therapy. However, side effects of these medications diminish pharmacological viability. Hypertension and high blood pressure (BP) are one of the foundations of cardiovascular morbidity and mortality around world and BP-lowering methodologies do decrease the danger of cardiovascular difficulties such as congestive heart failure, coronary heart disease (CHD), and stroke, among others [55].

Tea (Camellia sinensis) is popular drink worldwide linked to good health. Black tea contains relatively high levels of polyphenolics with the major phenolics being the flavan-3-ols, the flavonols, the flavones and quinic acid esters of gallic, coumaric and caffeic acids [56,57]. Moderate intake of black tea improves the levels of independent risk factors of cardiovascular disease and antioxidant defenses in plasma. The effects seem to be ascribed primarily to the synergistic effects of the tea phenolics and most probably with other antioxidant elements (endogenous or exogenous). Although the underlying biological mechanisms for these effects and the exact role of phenolics warrant an extensive study, tea may provide an important source of dietary antioxidants in many individuals [58].

**Antihypertensive and vasorelaxant impacts of GA by expanding phosphorylation of endothelial nitric oxide synthase (a polyphenol disconnected from the green alga, *Spirogyra* sp.) by looking at GA-interceded restraint of angiotensin-I changing over compound (ACE). This bioactive compound represses ACE with a half-maximal inhibitory fixation, uncover that GA ties to the dynamic site of ACE. Besides, GA obviously reduces circulatory strain in suddenly hypertensive rats (SHR) to an extent similar to captopril. These outcomes recommend that GA, separated from *Spirogyra* sp., applies various helpful impacts and potential as a CVD treatment [59].

**Gallic acid as anti HCV agent**

Hepatitis C virus (HCV), belonging to the Flaviviridae family, is a hepatotropic enveloped virus. Its viral genome contains a single polyprotein encoded by positive-sense single-stranded RNA that is post transnationally modified into structural and non-structural proteins [60]. It induces cellular stress in endoplasmic reticulum where it replicates. Infections of liver are caused by HCV that leads to progressive fibrosis, liver failure, hepatocellular carcinoma, and deaths [61,62]. HCV affects 170–300 million people worldwide, but still only a small number of antiviral agents had effects. Therefore, investigations continue to identify alternative therapies for hepatitis C [60,63].

GA contains antiviral effects which are particularly against hepatitis C virus (HCV). This is studied by the use of parental cell line and subgenomic replicon cell system (Huh7-HCV-replicon).Earlier studies showed that GA functions as an inhibitor of HCV protease function, diminishes the translational rate of viral protein and down regulates HCV-RNA [63,64-66]. Moreover, it decreases the oxidative stress without being able to influence cell viability [67,68]. It was also revealed that this bio functional compound targets and inhibits HCV early viral entry, inactivating cell-free virions and hindering virus binding to the surface of host cells to inhibit resultant infection [69]. In another study it was proposed that Tannic acid, a polymer of glucose molecules and Gallic acid, is a potent inhibitor of HCV entry into Huh7.5 cells at low concentrations. It also inhibits cell-to-cell spread in HCV infectious cell cultures, an early step of viral entry, such as the docking of HCV at the cell surface blocks, but does not inhibit HCV replication following infection [70].

According to the chemical structure of GA, the hydrophobic interaction between the functional group (hydroxyl) and virion components brought GA virucidal activity by binding GA to free radicals and induce an antioxidative effect. There is possibility that this antioxidative property of GA can be involved in the mechanism(s) of down-regulation of HCV replication in hepatoma cells, and may be as an alternative therapy for antiviral treatment. Moreover, there is need of
more and more experiments to confirm these findings [62,63].

**Gallic acid as anti-inflammatory agent**

Inflammation is the leading cause for many chronic health disorders, immune-inflammatory effect is a protective mechanism to stop the onset of infections caused by wound or microbial invasion. Phenolic compounds are the front line defense of plants like secondary metabolites. The mechanisms of anti-inflammatory effects of the phenolic compounds are generally considered to arise from their ability of killing free radicals, restoring antioxidant enzyme activities and in regulating cytokine-induced inflammation [71]. GA, naturally occurring polyphenol, exerts potentially medical useful anti-inflammatoryatory effects mediated through the suppression of p65-NF-κB and IL-6/p-STAT3Y705 activation. In gallic acid anti-inflammatory response, one of the possible given mechanisms involves a reduction of the neutrophilic infiltration in the colon accompanied by a reduced expression of CD68+. Also, the pro-inflammatory proteins iNOS and COX-2 expression reduced by preventing the expressions of p-STAT3Y705 and inhibits the p65-NF-κB-mediated transcriptional activation [72].

**Conclusion**

This review presents an attempt to summarize the variable utility of the GA and its derivatives in various forms for different therapeutic purposes. The data demonstrate that dietary polyphenol could be a favorable coadjuvant agent for disease treatment. To date, GA is evaluated to exhibit substantial and valuable impacts on humans. GA, as polyphenol has emerged as one of the key candidate in the functional food center. Research in the generation and application of this compound is gaining momentum because of diverse medical service and bio-functional properties.

**References**


