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# 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-methylgallic have been found after ingestion of GA-rich foods, this shows the good absorption property of GA [2]. Under acid hydrolysis of hydrolyzable 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].

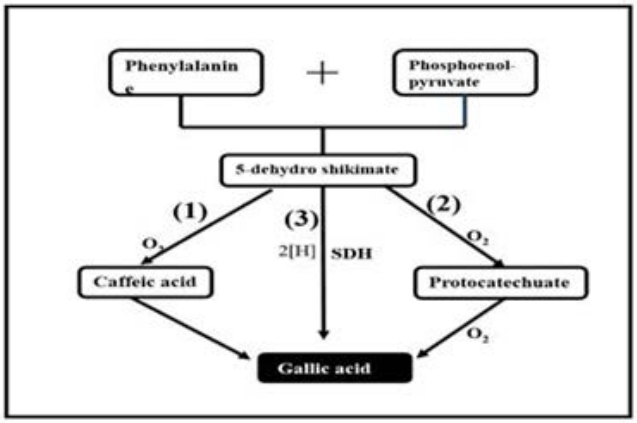


**Figure 1:** Pathways for Gallic acid biosynthesis.

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

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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 antitumor properties, richness in the eating regimen, and their sound impacts in the counteractive action of different oxidative anxiety 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 ester subsidiaries can actuate mitochondrial deterioration. These subsidiaries are specifically cytotoxic 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 disease cell 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 viability. This decrease is mainly due to the limit of GA and 3-O-methylgallic acid to hinder the cell cycle at the G0/G1phase.The limit of these compounds to inactivate translation components NF-kB, 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 GA's 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].

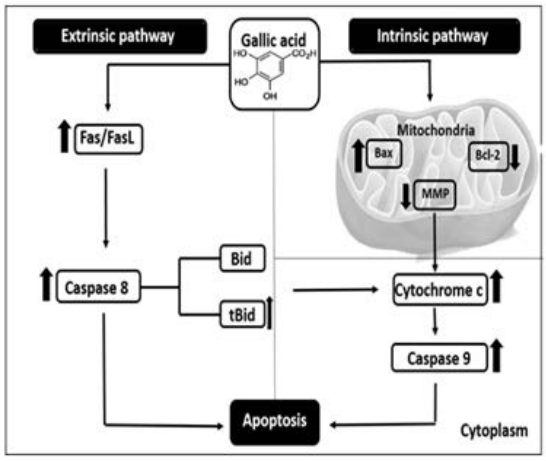


**Figure 2**: Proposed molecular mechanism of cell apoptosis incited by GA in breast cancer MCF-7 cells.

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/EGFR-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 motioning 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-tumorigenic 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].

| Cancer type | Cell lines | Effects produce by GA |
|---|---|---|
| Ovarian cancer | A2780/CP70 and OVCAR-3<br><br>OVCAR3 and SW626 | Tumor cells destruction *via* suppression of VEGF [22,23].<br>Induces autophagy by upregulation of autophagic proteins, LC3B-II and beclin1 [24]. |
| Colon cancer<br><br>Colorectal cancer | HCT-1s5<br><br>Caco-2<br><br>CT-26 and HCT-116 | Cell lysis *via* necrosis or apoptosis [31].<br><br>Arrest cell cycle at Go/G1 phase [32].<br><br>Cell cycle arrest in the G1 stage *via* p53 activation [33]. |
| Breast cancer | MCF-7<br>TNBC MDA-MB-231<br><br>BT474 | Cell apoptosis *via* G2/M phase arrest [35].<br>Inhibition of EGF/EGFR-mediated MMP-9 expression [37].<br>Repression of the PI3K/AKT pathway and regulation of the miR-126 expression [38]. |
| Lung cancer | EGFR mutant NSCLC<br>TKI resistant NSCLC | Reduction in EGFR level [41].<br>Cell apoptosis *via* cell cycle arrest [42]. |

**Table 1:** Action of Gallic acid (GA) on different cancer cell line.

## 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 per-oxidation 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 $Ca^{+2}$ 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 EGCG (Epigallocatechin-3-gallate) has protective role against dichlorodiphenyl Trichloroethane induced dopaminergic SHSY5Y 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 ellagic acid, natural flavonoids, use as antidiabetic agents. Nair et al. evaluated binding of GA and its dimer, ellagic 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 ellagic 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 antioxidant 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-inflammatory 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 coadjutant 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

1. Aoki C, Hartati S, Santi MR, Lydwina, Firdaus ,et al. (2014) Isolation and identification of substances with anti-hepatitis c virus activities from kalanchoe pinnata. Int J Pharm Pharm Sci 6: 211-215.
2. American Diabetes Association, Standards of medical care in diabetes-2012 Diabetes care, 35(Supplement 1) S11-S63.
3. Bahorun T, Luximon RA, Neergheen BVS, Gunness TK, Googoolye K, et al. (2012) The effect of black tea on risk factors of cardiovascular disease in a normal population. Pre Med 54: S98-S102.
4. Banerjee N, Kim H, Krenek K, Talcott ST, Mertens-Talcott SU (2015) Mango polyphenolics suppressed tumor growth in breast cancer xenografts in mice: Role of the PI3K/AKT pathway and associated microRNAs. Nutr Res 35: 744-751.
5. Boghossian S, Hawash A (2012) Chemoprevention in colorectal cancer-where we stand and what we have learned from twenty years experience. The Surgeon 10: 43-52.
6. Bray F, Ren JS, Masuyer E, Ferlay J (2013) Global estimates of cancer prevalence for 27 sites in the adult population in 2008. Int J cancer 132: 1133-1145.
7. Camilleri A, Vassallo N (2014) NThe centrality of mitochondria in the pathogenesis and treatment of Parkinson's disease. CNS neurosci Ther 20: 591-602.
8. ChenYJ, Lee YC, Huang CH, Chang LS (2016) Gallic acid-capped gold nanoparticles inhibit EGF-induced MMP-9 expression through suppression of p300 stabilization and NFκB/c-Jun activation in breast cancer MDA-MB-231 cells. Toxicol Appl pharmacol 310: 98-107.
9. Cho YS, Kim SK, Ahn CB, Je JY (2011) Inhibition of acetylcholinesterase by gallic acid-grafted-chitosans. Carbohydrate Polymers 84: 690-693.
10. Choi HJ, Song HJ, Park KS, Baek SH (2010) In vitro anti-enterovirus 71 activity of gallic acid from Woodfordia fruticosa flowers. Lett Appl microbiol 50: 438-440.
11. Dadzuang J, Palasap A, Daduang S, Boonsiri P, Suwannalert P (2015) Gallic acid enhancement of gold nanoparticle anticancer activity in cervical cancer cells. Asian Pac J Cancer Prev16: 169-174.
12. Daglia M, Lorenzo Di A, Nabavi S F, Talas Z S, Nabavi S M (2014) Polyphenols: Well beyond the antioxidant capacity: Gallic acid and related compounds as neuroprotective agents: you are what you eat! Curr Pharm Biotechnol 15: 362-372.
13. Dai J, Mumper R J (2010) Plant phenolics: Extraction, analysis and their antioxidant and anticancer properties. Molecules 15: 7313-7352.
14. Danaei G, Finucane MM, LuY, Singh GM, Cowan MJ, et al. (2011) National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2• 7 million participants. The Lancet 378: 31-40.
15. De A, De A, Papasian C, Hentges S, Banerjee S, et al. (2013) Emblica officinalis extract induces autophagy and inhibits human ovarian cancer cell proliferation, angiogenesis, growth of mouse xenograft tumors. PLoS One 8: e72748.
16. de Mejia E , Ramirez-Mares M V, Puangpraphant S (2009) Bioactive components of tea: cancer, inflammation and behavior. Brain, behavior, and immunity 23: 721-731.
17. de Oliveira LS, Thomé GR, Lopes TF, Reichert KP, de Oliveira JS, et al. (2016) Effects of gallic acid on delta-aminolevulinic dehydratase activity and in the biochemical, histological and oxidative stress parameters in the liver and kidney of diabetic rats. Biomed Pharmacother 84: 1291-1299.
18. Dragicevic N, Smith A, Lin X ,Yuan F, Copes N, et al. (2011) Green tea epigallocatechin-3-gallate (EGCG) and other flavonoids reduce Alzheimer's amyloid-induced mitochondrial dysfunction. J Alzheimers Dis 26: 507-521.
19. Engelender S, Isacson O (2017) The threshold theory for Parkinson's disease. Trends Neurosci 40: 4-14.
20. Fabiani, Roberto, Rosignoli, Patrizia, De Bartolomeo, et al. (2011) The production of hydrogen peroxide is not a common mechanism by which olive oil phenols induce apoptosis on HL60 cells. Food Chem 125: 1249-1255.
21. Ferlay J, Shin H, Bray F, Forman D, Mathers C, et al. (2010) Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 127: 2893-2917.
22. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, et al. (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012 Int J Cancer 136: E359-386.
23. Forester SC, Choy YY, Waterhouse AL, Oteiza PI (2014) The anthocyanin metabolites gallic acid, 3-O-methylgallic acid, and 2, 4, 6-trihydroxybenzaldehyde decrease human colon cancer cell viability by regulating pro-oncogenic signals Mol Carcinog 53: 432-439.
24. Gallaher D, Trudo S, (2013) Nutrition and colon cancer. Nutri Prevent Treat Dis 3: 697-715.
25. Ghanemi FZ, Belarbi M, Fluckiger A, Nani A, Dumont A, et al. (2017) Carob leaf polyphenols trigger intrinsic apoptotic pathway and induce cell cycle arrest in colon cancer cells. J Funct Foods 33: 112-121.
26. Gil-Longo J, González-Vázquez C (2010) Vascular pro-oxidant effects secondary to the autoxidation of gallic acid in rat aorta. J Nutr Biochem 21: 304-309.
27. Govea SM, Rivas EAM, Rodríguez HR, Lozano SSA, Aguilar GCN, et al. (2016) Gallic acid decreases hepatitis C virus expression through its antioxidant capacity. Ther Med 11: 619-624.
28. He Z, Chen AY, Rojanasakul Y, Rankin GO, ChenYC (2016) Gallic acid, a phenolic compound, exerts anti-angiogenic effects via the PTEN/AKT/HIF-1α/VEGF signaling pathway in ovarian cancer cells. Oncol Rep 35: 291-297.
29. He Z, Li B, Rankin GO, Rojanasakul Y, ChenYC (2015) Selecting bioactive phenolic compounds as potential agents to inhibit proliferation and VEGF expression in human ovarian cancer cells. Oncol Lett 9: 1444-1450.
30. Ho HH, Chang CS, HoWC, Liao SY, Wu CH, et al. (2010) Anti-metastasis effects of gallic acid on gastric cancer cells involves inhibition of NF-κB activity and down regulation of PI3K/AKT/small GTPase signals. Food ChemToxicol 48: 2508-2516.

31. Hsu JD, Kao SH, Ou TT, ChenYJ, Li YJ, et al. (2011) Gallic acid induces G2/M phase arrest of breast cancer cell MCF-7 through stabilization of p27Kip1 attributed to disruption of p27Kip1/Skp2 complex. J Agric Food Chem 59: 1996-2003.

32. Hsu WC, Chang SP, Lin LC, Li CL, Richardson CD, et al. (2015) Limonium sinense and gallic acid suppress hepatitis C virus infection by blocking early viral entry. Antiviral Res 118: 139-147.

33. Jara JA, Castro CV, Saavedra OJ, Peredo L, Pavanni M, et al. (2014) Antiproliferative and uncoupling effects of delocalized, lipophilic, cationic gallic acid derivatives on cancer cell lines. Validation in vivo in singenic mice. J Med Chem 57: 2440-2454.

34. Jemal A, Bray F, Center MM, FerlayJ, Ward E, et al. (2011) Global cancer statistics. CA: Cancer J Clin 61: 69-90.

35. Johnson AOR, Richardson A, Li WW (2015) Cytotoxic effects of stem bark extracts and pure compounds from Margaritaria discoidea on human ovarian cancer cell lines. Phytomedicine 22: 1-4.

36. Kang N, Lee JH, Lee W, Ko JY, Kim EA, et al. (2015) Gallic acid isolated from Spirogyra sp. improves cardiovascular disease through a vasorelaxant and antihypertensive effect. Environ Toxicol Pharmacol 39: 764-772.

37. Kyriakis E, Stravodimos GA, Kantsadi AL, Chatzileontiadou DS, Skamnaki VT, et al. (2015) Natural flavonoids as antidiabetic agents. The binding of gallic and ellagic acids to glycogen phosphorylase b. FEBS Lett 589: 1787-1794.

38. Latha RCR, Daisy P (2011) Insulin-secretagogue, antihyperlipidemic and other protective effects of gallic acid isolated from Terminalia bellerica Roxb. in streptozotocin-induced diabetic rats. Chem Biol Interact 189: 112-118.

39. Lee JC, Chen WC, Wu SF, TsengCk, Chiou CY, et al. (2011) Anti-hepatitis C virus activity of Acacia confusa extract via suppressing cyclooxygenase-2. Antiviral Res 89: 35-42.

40. Li D, Liu Z, Zhao W, Xi Y, Niu F (2011) A straightforward method to determine the cytocidal and cytopathic effects of the functional groups of gallic acid. Process Biochem 46: 2210-2214.

41. Li W, He N, Tian L, Shi X, Yang X (2016) Inhibitory effects of polyphenol-enriched extract from Ziyang tea against human breast cancer MCF-7 cells through reactive oxygen species-dependent mitochondria molecular mechanism. J Food Drug Anal 24: 527-538.

42. Lindenbach BD, Rice CM (2013) The ins and outs of hepatitis C virus entry and assembly. Nat Rev Microbiol 11: 688-700.

43. Liu S, Chen R, Hagedorn C H (2015) Tannic acid inhibits hepatitis C virus entry into Huh7. 5 cells. PloS one10: e0131358.

44. Liu X, Zhao M, Wu K, Chai X, Yu H, et al. (2012) Immunomodulatory and anticancer activities of phenolics from emblica fruit (Phyllanthus emblica L.). Food Chem 131: 685-690.

45. Locatelli C, Filippin MFB, Creczynski PTB (2013) Alkyl esters of gallic acid as anticancer agents: A review. Eur J Med Chem 60: 233-239.

46. Lozano SSA, Bryan MOL, Cordova FC, Gutierrez RMC, Rivas EAM (2015. Oxidative stress modulation in hepatitis C virus infected cells. World J hepatol 7: 2880-2889.

47. Luo W, Zhao M, Yang B, Ren J, Shen G, et al. (2011) Antioxidant and antiproliferative capacities of phenolics purified from Phyllanthus emblica L. fruit. Food Chem 126: 277-282.

48. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, et al. (2014) 2013 ESH/ESC Practice Guidelines for the Management of Arterial Hypertension. Blood Press 23: 3-16.

49. Mansouri MT, FarboodY, Sameri MJ, Sarkaki A, Naghizadeh B, et al. (2013) Neuroprotective effects of oral gallic acid against oxidative stress induced by 6-hydroxydopamine in rats. Food Chem 138: 1028-1033.

50. Manvar D, Mishra M, Kumar S, Pandey VN (2012) Identification and evaluation of anti hepatitis C virus phytochemicals from Eclipta alba. J Ethnopharmacol 144: 545-554.

51. Mehrab MM, Sendi H, Steuerwald N, Ghosh S, Schrum LW, et al. (2011) Legalon-SIL downregulates HCV core and NS5A in human hepatocytes expressing full-length HCV. World J Gastroenterol 17: 1694-1700.

52. Micha R, Kalantarian S, Wirojratana P, Byers T, Danaei G, et al. (2012) Estimating the global and regional burden of suboptimal nutrition on chronic disease: Methods and inputs to the analysis. Eur J Clin Nutr 66: 119-129.

53. Nair HB, Sung B, Yadav VR, Kannappan R, Chaturvedi MM, et al. (2010) Delivery of antiinflammatory nutraceuticals by nanoparticles for the prevention and treatment of cancer. Biochem Pharmacol 80: 1833-1843.

54. Nam B, Rho JK, Shin DM, Son J (2016) Gallic acid induces apoptosis in EGFR-mutant non-small cell lung cancers by accelerating EGFR turnover. Bioorganic Med Chem Lett 26: 4571-4575.

55. Pandurangan AK, Mohebali N, Esa NM, Looi CY, Ismail S, Saadatdoust Z (2015) Gallic acid suppresses inflammation in dextran sodium sulfate-induced colitis in mice: Possible mechanisms. Int Immunopharmacol 28: 1034-1043.

56. Phan AN, Hua TN, Kim MK, Vo VT, Choi JW, et al. (2016) Gallic acid inhibition of Src-Stat3 signaling overcomes acquired resistance to EGF receptor tyrosine kinase inhibitors in advanced non-small cell lung cancer. Oncotarget 7: 54702-54713.

57. Ravikumar Y, Ray U, Nandhitha M, Perween A, Naika HR, et al. (2011) Inhibition of hepatitis C virus replication by herbal extract: Phyllanthus amarus as potent natural source. Virus Res 158: 89-97.

58. Reddy BU, Mullick R, Kumar A, Sudha G, Srinivasan N, et al. (2014) Small molecule inhibitors of HCV replication from pomegranate. Scientific reports 4: 5411.

59. Roleira FM, Tavares-da-Silva EJ, Varela CL, Costa SC, Silva T, et al. (2015) Plant derived and dietary phenolic antioxidants: Anticancer properties. Food Chem 183: 235-258.

60. Rouanet JM, Décordé K, Rio DD, Auger C, Borges G, et al. (2010) Berry juices, teas, antioxidants and the prevention of atherosclerosis in hamsters. Food Chem 118: 266-271.

61. Senapathy JG, Jayanthi S, Viswanathan P, Umadevi P, Nalini N (2011) Effect of gallic acid on xenobiotic metabolizing enzymes in 1, 2-dimethyl hydrazine induced colon carcinogenesis in Wistar rats-A chemopreventive approach. Food and Chem Toxicol 49: 887-892.

62. Sharma M, Li L, Celver J, Killian C, Kovoor A, et al. (2010) Effects of fruit ellagitannin extracts, ellagic acid, and their colonic metabolite, urolithin A, on Wnt signaling. J Agric Food Chem 58: 3965.

63. Siegel R, Naishadham D, Jemal A (2013) Cancer statistics 2013. CA: Cancer J Clin, 63: 11-30.

64. Stewart B, Wild CP (2014) World cancer report, International Agency for Research on Cancer (IARC). WHO Press, France.

65. Subramanian AP, Jaganathan S K, Mandal M, Supriyanto E, Muhamad II (2016) Gallic acid induced apoptotic events in HCT-15 colon cancer cells. World J of Gastroenterol 22: 3952-3961.

66. Vargas HVM, Moreno EMA, Acosta-AG, Vargas AVM (2014) Management of recurrent epithelial ovarian cancer. Gland Surg 3: 198.

67. Verma S, Singh A, Mishra A (2013) Gallic acid: Molecular rival of cancer. Environ Toxicol Pharmacol 35: 473-485.

68. Wang K, Zhu X, Zhang K, Zhu L, Zhou F (2014) Investigation of gallic acid induced anticancer effect in human breast carcinoma MCF-7 cells. J Biochem Mol Toxicol 28: 387-393.

69. Yoon CH, Chung SJ, Lee SW, Park YB, Lee SK, et al. (2013) Gallic acid, a natural polyphenolic acid, induces apoptosis and inhibits proinflammatory gene expressions in rheumatoid arthritis fibroblast-like synoviocytes. Joint Bone Spine, 80: 274-279.

70. Zhang H, Tsao R (2016) Dietary polyphenols, oxidative stress and antioxidant and anti-inflammatory effects. Curr Opin Food Sci 8: 33-42.

71. Zhang Q, Yang H, Wang J, Li A, Zhang W, et al. (2013) Effect of green tea on reward learning in healthy individuals: A randomized, double-blind, placebo-controlled pilot study. Nutr J, 12: 84.

72. ZhaoY, Raichle ME, Wen J, BenzingernTL, Fagan AM, et al. (2017) In vivo detection of microstructural correlates of brain pathology in preclinical and early Alzheimer Disease with magnetic resonance imaging. Neuroimage, 148: 296-304.