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Review Article

Gallic Acid: Pharmacogical Promising Lead Molecule: A Review

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ABSTRACT
Gallic acid is a naturally occurring polyphenolic compound found in processed beverages such as red wines and green teas. It occurs in plants in the form of free acids, esters, catechin derivatives and hydrolysable tannins. The interest in these compounds is due to its pharmacological activity as radical scavengers. It has been proved to have potential preventive and therapeutic effects in many diseases, where the oxidative stress has been implicated, including cardiovascular diseases, cancer, neurodegenerative disorders and in aging. Thus, it is imperative to promote more credible research on exploring medicinal properties of gallic acid and its congeners. The present review is an attempt to summarize the medicinal and toxicological properties of the gallic acid and its derivatives in various forms for different purpose.

Keywords: Gallic acid, Antioxidants, Antidiabetic, Toxicology, Polyphenols.

INTRODUCTION

Gallic acid (3, 4, 5-trihydroxybenzoic acid) is a naturally occurring polyphenolic compound found in processed beverages such as red wines and green teas. It occurs in plants in the form of free acids, esters, catechin derivatives and hydrolysable tannins[1-2]. The interest in these compounds is due to its pharmacological activity as radical scavengers. It has been proved to have potential preventive and therapeutic effects in many diseases, where the oxidative stress has been implicated, including cardiovascular diseases, cancer, neurodegenerative disorders and in aging[3-5]. Gallic acid has been reported to occur in a number of plants, some of them are *Allan blackia floribunda*, *Garcinia densivenia*, *Bridelia micrantha*, *Caesalpinia sappan*, *Dillenia indica*, *Diospyros cinnabarina*, *Paratecoma peroba*, *Terminalia bellerica*, *etc*. Many gallic acid derivatives occur naturally in plant, these include from *Frankenia laevis* and *Tamarix amplexicaulis*, 3-methyl-4-O-[3,4-dihydroxy-5-methoxybenzoyl-(→6)- β-D-glucopyranoside], *Rhus glabra*, 3-ethyl ether from *Phyllanthus emblica*, and 4-ethyl ether from *Eucalyptus gunnii*, *Terminalia chebula* and *Elephantorrhiza elephantine* [6]. A recent study indicated presence of antioxidant gallic acid esters (gallates) in dust from homes and microenvironments[7]. The purpose of this review summarized the medicinal and toxicological properties of gallic acid, present in active phystoconstitutent in various herbal polyherbal plant preparations.

Physiochemical Profile of Gallic Acid[8]

Chemical formula: $C_7H_6O_5$
Molar mass: 170.12 g/mol
Appearance: White, yellowish-white, or pale fawn-colored crystals
Density: 1.694 g/cm^3 (anhydrous)
Melting point: 260 °C (500 °F; 533 K)

Pharmacological Profile of Gallic Acid

Antidiabetic Activity

Prince *et al* (2011) have reported the antihyperglycaemic, antilipid peroxidative and antioxidant effects of gallic acid on streptozotocin induced diabetic male wister rats. Further, histopathology of pancreas confirmed the protective effects of gallic acid in diabetic rats. *In vitro* study also revealed the potent antioxidant effect of gallic acid[9]. Khanh *et al* (2015) have reported the gallic acid plays its role through the activation of AMP-activated protein kinase (AMPK) and by regulating mitochondrial function via the activation of peroxisome proliferator-activated receptor-alpha coactivator1 alpha (PGC1 alpha). In addition, the administration of GA protected diet-induced body weight gain without a change in food intake[10]. Kyriakis *et al* (2015) have reported the binding of gallic acid and its dimer ellagic acid to glycogen phosphorylase (GP). The authors suggested both compounds are competitive inhibitors with respect to the substrate, glucose-1-phoshate, and non-competitive to the allosteric activator, AMP[11].

Other investigators reported that gallic acid can increase GLUT4 translocation and glucose uptake activity in an Akt-independent but wortmannin-sensitive manner. Further analysis suggested the role of atypical protein kinase Cf/k in gallic acid mediated GLUT4 translocation and glucose uptake[12]. Oliveria *et al* (2016) have reported the effect of gallic acid on the biochemical, histological and oxidative stress parameters in the liver and kidney of diabetic rats. This study indicates that gallic acid can protect against oxidative stress-induced damage in the diabetic state[13]. Huang *et al* (2005) have reported the mechanism of antidiabetic action of gallic acid, which is the active phytoconstituents of *Punica granatum* flower

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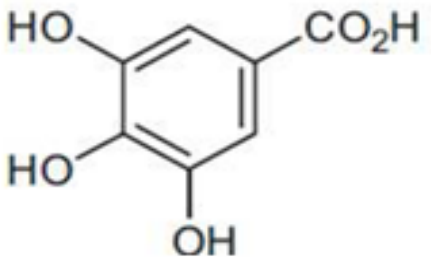
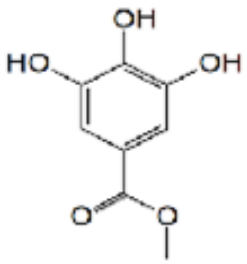
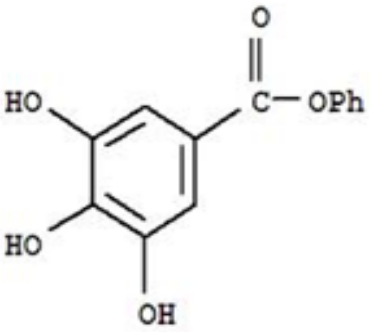


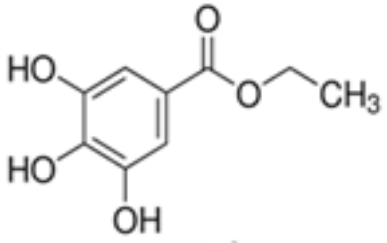
Gallic acid



Methyl gallate



Phenyl gallate



Ethyl gallate

Figure 1: Chemical structure of gallic acid (3, 4, 5-trihydroxybenzoic acid) and some of its D Derivatives

extract (PGF). Authors were concluded that PPAR□ is a molecular target for PGF extract and its prominent component gallic acid, and provide a better understanding of the potential mechanism of the anti-diabetic action of PGF[14].

Neuroprotective Activity

Lu *et al* (2006) have reported the relationship between the structures of gallic acid derivatives, their antioxidant activities, and neuroprotective effects; they examined their free radical scavenging effects in liposome and anti-apoptotic activities in human SH-SY5-Y cell induced by 6-hydrodopamine auto oxidation. The authors reveal that compounds with high antioxidant activity and appropriate hydrophobicity are generally more effective in preventing the injury of oxidative stress in neurodegenerative diseases[15]. Korani *et al* (2014) have reported the neuroprotective role of gallic acid in CNS. They studied the effect of gallic acid (GA; 100 mg/kg, p.o. for 10days) on cognitive deficit and cerebral oxidative stress induced by permanent bilateral common carotid artery occlusion (2VO) as an animal model of vascular dementia (VD). Furthermore, chronic administration of GA significantly restored the spatial memory, totalthiol and GPx contents and also decreased MDA levels in these tissues[16]. Mansouri *et al* (2014) have explored the possible mechanisms involved in the anxiolytic like activity of gallic acid (GA) in the rat elevated plus maze (EPM) test. Authors reported that the treatment with GA markedly produced an increase in the time spent and entries in the open arms of EPM at doses of 30 and 300 mg/kg, respectively. Also this study suggests that the anxiolytic-like activity of GA is primarily mediated by the 5-HT_{1A} but not benzodiazepine receptors[17]. Mansouri *et al* (2012) have investigated the neuroprotective role of gallic acid against cerebral oxidative stress induced by 6-hydroxydopamine in rats. The study results suggest that GA has neuroprotective activity against 6-OHDAinduced oxidative stress *via* enhancement of cerebral antioxidant defense[18].

Gallic acid, founded by investigators to antioxidant properties of polyphenols have been exploited in the inhibition of fibrillar protein deposits that lead to disorders like Alzheimer's and Parkinson's disease[19].

Antioxidant Activity

Chou *et al* (2016) have reported the role of grafting amount of antioxidant gallic acid (GA) on to GN in situ gelling copolymers made of biodegradable gelatin and thermo-responsive poly (N-isopropylacrylamide) for intracameral delivery of pilocarpine in antiglaucoma treatment. Further reported that increasing GA content increased total antioxidant level and decreased nitrite level in the aqueous humor, suggesting a much improved antioxidant status in glaucomatous eyes[20]. Kim (2007) has investigated the melanogenesis inhibitory action of gallic acid (GA). In this current study, the effects of GA on mushroom tyrosinase, tyrosinase inhibitory activity, and melanin content were assessed in B16 melanoma cells (B16 cells). This study suggested that GA exerts antimelanogenic activity coupled with antioxidant properties by suppressing RS generation and maintaining a higher GSH/GSSG ratio[21]. Naksuriya *et al* (2015) have reported the antioxidant power of curcumin in comparison with three important natural antioxidants; gallic acid, ascorbic acid, and xanthone on free radical scavenging action and their combination effects on this activity. Authors have suggest that curcumin-gallic acid combination is the potential antioxidant mixture to be used in place of the individual substance whereas using of curcumin in combination with ascorbic acid or xanthone should be avoid[22]. Bajpai *et al* (2005) have reported that the phenolic contents of medicinal plants responsible for antioxidants activity. Further they have reported *T.bellerica* fruit contain rich source of gallic acid (2290

µg/g plant material dry weight)[23]. Gaulejac *et al* (1999) have reported antioxidant activity of polyphenol. Plyphenol compounds were found to be efficient free radical scavengers even for the weak concentrations in wines. Their activity in grapes or wines was much stronger than that of other commercially available natural antioxidants (such as ascorbic acid and gallic acid)[24]. Traditional use of gallic acid as an anti-oxidant agent[25]. Gallic acid has high oxygen derived free radical scavenging activity due to the presence of polyphenolic functionality[26].

It prevents the rancidity and spoilage of fats and oils due to its antioxidant nature facilitating its application as food additives in various eatable materials like baked goods, candy and chewing gums[27]. It can be used as an antioxidant to protect human cells against oxidative damage, to treat albuminuria and diabetes and as a remote astringent in case of internal hemorrhage[28]. Another investigators have been reported the different vascular protective effects of gallic acid, like- gallic acid non-enzymatically oxidized in physiological solutions by generating superoxide anions, the low level of H2O2 levels and the cyclooxygenase activation, endothelium-independent relaxation with respect to levels of H2O2 and the activation of smooth muscle K+ channels; an irreversible, slow-developing endothelium-independent relaxation due to high H2O2 levels and quinines, which cause cellular damage[29].

Anti-inflammatory Activity

Pandurangan *et al* (2015) have reported the effects of a naturally occurring polyphenol, gallic acid (GA), in an experimental murine model of UC. A significant blunting of weight loss and clinical symptoms was observed in dextran sodiumsulfate (DSS)-exposed, GA-treated mice compared with control mice. Investigators suggest that GA exerts potentially clinically useful anti-inflammatory effects mediated through the suppression of p65-NF-κB and IL-6/p-STAT3^{Y705} activation[30]. Piana *et al* (2016) have reported the extract from *S. corymbiflorum* leaves the crotonoil-induced ear edema and myeloperoxidase (MPO) activity with maximum inhibition of 87±3% and 45±7%, respectively in the dose of 1 mg/ear. Authors have been reported their activity at least in part, the presence of polyphenols (195.28 mg GAE/g) and flavonoids, as chlorogenicacid (59.27 mg/g), rutin (12.72 mg/g), rosmarinic acid, caffeic acid and gallic acid found by high performance liquid chromatography (HPLC) analysis[31]. Abarikwu *et al* (2014) have reported the effects of administration of gallic acid (Gal) with or without curcumin (Cur) on the sperm output, steroid level and antioxidant defenses in rat testis *in vivo* and the expression of inflammatory responsive genes in *vitro*. Further, they have been reported that the level of testosterone and the activities of the steroidogenic enzymes were significantly increased after treatment with Cur alone. Malondialdehyde concentration was unchanged following Gal treatment, while a significant decrease in malondialdehyde level was observed following treatment with Cur alone or in combination with Gal[32]. Saygin *et al* (2016) have reported the effects of methotrexate (MTX) on the lung via inflammatory and apoptotic pathway biomarkers and the role of gallic acid (GA). GA significantly reduced the comet score and IMA levels in the blood, TOS and OSI values in the lung tissue in MTX+GA group compared with MTX group ($p < 0.05$)[33].

Couto *et al* (2013) have reported the anti-inflammatory and antiallodynic effects of spray dried powders starting from leaves, stems, roots, the mixture of leaves and stems, as well as the whole plant aqueous solutions of *Phyllanthus niruri* L., Phyllanthaceae. Gallic acid, used as chemical marker, was quantified by HPLC in the spray dried powders. Investigators revealed the direct relationship of anti-inflammatory and antiallodynic effects with the gallic acid content especially in the spray dried powders of leaves, they have been used of spray dried powders of leaves plus stems showed to be more effective, further they suggesting a synergic effect between their constituents[34].

Kroes *et al* (1992) have investigated the anti-inflammatory activity of gallic acid. Gallic acid was found to possess anti-inflammatory activity towards zymosan-induced acute food pad swelling in mice. Structure-activity relationship analysis showed that the o-dihydroxy group of gallic acid is important for the inhibitory activity *in vitro*[35]. Anti-inflammatory activity has been evaluated by various inflammatory induced animal models likely- zymosan induced acute food pad swelling in mice, carrageeenan-induced paw edema, acetic acid induced writhing response and formalin induced pain by investigators. Also they have reported possible anti-inflammatory mechanism of gallic acid due to its scavenging of superoxide anions, inhibition of myeloperoxidase release and activity as well as interference with activity of NADPH-oxidase[36].

Wound Healing Activity

Yang *et al* (2016) have reported the effects of gallic acid (GA, 3, 4, 5-trihydroxybenzoic acid, a plant-derived polyphenolic compound) on wound healing in normal and hyperglucidic conditions, to mimic diabetes, in human keratinocytes and fibroblasts. The study reveals that GA is a potential antioxidant that directly up regulates the expression of antioxidant genes. Further, GA treatment activated factors known to be hallmarks of wound healing, such as focal adhesion kinases (FAK), c-Jun N-terminal kinases (JNK), and extracellular signal-regulated kinases (Erk), underpinning the beneficial role of GA in wound repair[37]. Nhat *et al* (2012) have reported that the gallic acid is a main phytoconstitutents of plant in ethnopharmacological survey on the traditional use of *Ximenia Americana* among healers in Mali. Gallic acid, gallotannins and flavonoids were identified in the genus *Ximenia*. Healers interviewed reported the use against throat infections, amenorrhea, as tonic, for wound healing and against pain[38]. Kokane *et al* (2009) have evaluated the wound healing activity of *Mimosa pudica* root extract and they have concluded the phenol constituents such as gallic acid responsible for it. The methanolic extract of plant has effective in wound healing effect in animals[39].

Hepatoprotective Activity

Tung *et al* (2009) have reported the hepatoprotective effects of *A. confuse* bark extract (ACBE) and its active constituent gallic acid was evaluated against carbon tetrachloride (CCl_4)-induced hepatotoxicity in rats. Liver

histopathology also showed that ACBE, gallic acid or silymarin could significantly reduce the incidence of liver lesions induced by CCl_4[40]. The hepatoprotective activities of T.bellerica extract and gallic acid in alleviating CCl4 induced liver damaged in rats have been reported[41]. Gallic acid also showed protective effect in liver damage by sodium fluoride-induced oxidative stress[42].

Anticancer Activity

Hsun *et al* (2010) have investigate the effect of phenolic acids found abundantly in vegetables, i.e. gallic acid (GA), caffeic acid (CA) and protocatechuic acid (PCA), on the inhibition of gastric adenocarcinoma (AGS) cell metastasis. GA had potent inhibitory effects on AGS cell migration. Investigators have concluded that, GA may have the potential to be an effective agent for prevention and treatment of gastric cancer metastasis[43]. Chen *et al* (2009) have investigated the role of gallic acid present in active constituents in leaf extract of *Toona sinensis,* gallic acid is identified as the major anti-cancer compound in *T. sinensis* leaf extracts. In addition, gallic acid has a synergistic effect with doxorubicin in suppressing the growth of DU145 cells. Through this study, investigators suggest that gallic acid has the potential to be developed into an anti-prostate cancer drug and is worthy of further studies[44].

It has been reported antimutagenicity induced by N nitroso-compounds in mouse as well as obviating mouse lung adenomas by amines or ureas plus nitrate and by nitroso compounds[45]. Gallic acid has been reported to suppress cell viability, proliferation, invasion and angiogenesis in human glioma cells, inhibits the growth of HeLa cervical cancer cells via apoptosis and necrosis, induces apoptosis in tumoral cells lines and inhibits lymphocyte proliferation[46]. It has also inhibits ribonucleotide reductase and cyclooxygenases in human HL-60 promyelocytic leukemias cells, causes inactivating phosphorylation via ATM-ChK2 activation, leading to cell cycle arrest[47-49].

Miscellaneous Pharmacological Activity

The other reported pharmacological activities of gallic acid are anti depressant[50], antiparkinson[51], antimalarial[52], diuretic[53], Cardioprotective[54], anti-viral[55], antifungal[56], wound healing[57], anthelmintic[58] and anxiolytic[59].

It also reported gallic acid, when combine with other natural product such as, calycosin, reported to synergistically attenuate neutrophil infiltration and subsequent injury in isoproterenol-induced myocardial infarction[60]. It has been reported that gallic acid has anti-microbial activity against methicillin-resistant *Staphylococcus aureus* and *Helicobacter pylori*[61-62]. Gallic acid was found to significantly reduce allergen and platelet activating factor induced bronchial hyper-reactivity in guinea pigs[63]. Gallic acid inhibits pancreatic cholesterol esterase by binding to bile acids and reducing the solubility of cholesterol in micelles[64]. Authors have investigated the role of gallic acid and linoleic acid as antihyperlipidemic action in C57BL/6 mice fed a high-fat diet[65]. Gallic acid having cardioprotecting role in isoproterenol-induced myocardial infarction in rats[66].

Toxicological Study of Gallic Acid

Many investigations have been attempted to explore the toxicity profile of gallic acid. Some are discussing here, Oral administration of gallic acid in mice at a dose as high as 500 mg/kg did not produce any signs of toxicity or mortality. Gallic acid at a dose of 1000 mg/kg body weight did not significantly alter the hematological parameters. Further, no appreciable change was noted in the various biochemical parameters such as AST or ALT, as well as many serum constituents such as protein, cholesterol, urea, and bilirubin. Therefore, from this study, it may be concluded that gallic acid is non-toxic up to a level of 5000 mg/kg body weight, when given orally. In addition, the subacute study indicated the absence of cumulative toxicity, as reflected by the non significant alterations in the parameters investigated. The no-observed-adverse-effect-level (NOAEL) was 5000 mg/kg body weight, the highest dose tested. As gallic acid is non-toxic at an acute dose of 5000 mg/kg body weight, this is considered the NOAEL for gallic acid in mice. A subacute administration of 1000 mg/kg body weight also confirmed its safety at this level[67].

Subchronic toxicity of gallic acid was investigated in F344 rats by feeding diets containing 0, 0.2, 0.6, 1.7 and 5% gallic acid for 13 weeks. Each group consisted of 10 rats of each sex; and 0.2% was determined to be the NOAEL in rats. This level was translated into 119 and 128 mg/kg/day, respectively, for male and female rats[68]. Joint FAO/WHAO committee 1962, 1965, 1974 and 1976, have been found the acute oral toxicity of propyl gallate in mice, rats, hamsters and rabbits varies from 2000 to 3800 mg/kg body weight[69-72].

In guinea-pigs, propyl gallate showed sensitizing properties which were more powerful after intradermal application than after epicutaneous treatment. Sensitization did not occur when there were oral pre-exposure[73]. Recently a 4-week feeding study in rats was performed by investigators, in this study; a dose level of 25,000 mg/kg feed of gallic acid produced growth retardation, anaemia, hyperplasia in the tubuli of the outer kidney medulla and increased activity of several microsomal and cytoplasmic hepatic drug-metabolizing enzymes. The increased liver enzyme activities were also found at 5000 mg/kg. And also no toxicities effects were found at 1000 mg/kg dose of gallic acid[74]. Investigators have been observed an inhibitory effect by propyl gallate on the intragastric formation of an N-nitrosamine. The inhibition was complete at an oral dose level of 225 mg/kg body weight but was absent at 25 mg/kg[75]. The teratogenecity study of propyl gallate has been shown in rats. The dose levels of 4000, 10,000 and 25,000 mg/kg diet, maternal toxicity and slight retardation of foetal development occurred at the highest dose level, but teratogenic effects were not observed[76].

Conclusion and future perspectives

To conclude, it is evident that gallic acid play a pivotal role in imparting medicinal properties of the plant and therefore it is considered as promising lead molecule for new drug development. Gallic acid is a very important common antioxidant. It is found naturally in various plants and used in several polyherbal formulations. Thus, it is imperative

to promote more credible research on exploring medicinal properties of gallic acid and its congeners. The present review is an attempt to summarize the medicinal and toxicological properties of the gallic acid and its derivatives in various forms for different purpose. The information gathered herein is particularly drawn from scientific investigations worldwide which would be beneficial to scientific community in various sectors. Further research involving natural or synthetic may provide the exploration and development of newer properties or biological potential of these compounds. Gallic acid is well known for its role in drug development. However, information on clinical research is scanty, which is essential for its ultimate application in treating and preventing various deadly diseases.

Even though, in the last few years there has been an increase in the numbers of publications on gallic acid, it might be more appropriate to carry out such research on human subjects following established system of standardization.

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