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Gallic Acid: A Versatile Molecule with Promising Pharmacological Effect

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Abstract
Gallic acid, also known as 3, 4, 5-trihydroxybenzoic acid, is a naturally occurring secondary metabolite that can help biological cells, tissues, and organs resist oxidative stress. It has significant antioxidant and free radical scavenging characteristics and may be extracted from a range of fruits, plants, and nuts. GA is a phenolic substance present in a variety of fruits and medicinal plants. In a number of plants, it can be present in phytoconstituents like free acids, esters, catechin derivatives, and hydrolysable tannins GA has been reviewed by evaluating information on the Internet (using Google Scholar, CAB Abstracts, Elsevier, Cambridge University Press, JSTOR, Nature Publishing and Science online) and in libraries. Traditional medicinal uses of were recorded in the Ayurveda and Chinese pharmacopeia. The present review study covered chemical constituents and pharmacological properties. This has included GA therapeutic effects of the whole plants and its extracts, fractions and isolated compounds are Antioxidant, Antimicrobial, Anticancer, Antidiabetic Analgesic and Anti-inflammatory, Wound Healing, Hepatoprotective, Cardiovascular, Gastrointestinal, Metabolic, Neuropsychological, Allergic skin disease, Antidepressant, Diuretic, Antifungal, Anthelmintic, Antianxiety activities have all been described and GA's safety and therapeutic efficacy in humans must be further defined through future research.

Keywords: Gallic acid, phytochemistry, pharmacological properties, chemical constituents

Introduction
Gallic acid (GA) (3, 4, 5-trihydroxybenzoic acid) is a naturally occurring low molecular weight triphenolic compound, that can be found in the form of free acids, esters, catechin derivatives, and hydrolysable tannins in most of the plants [1-3]. Natural phenolic compounds can be further devided as, simple Phenolics, phenolic acids, acetophenones, Cinnamic acid derivatives, coumarins, chromones, chalcones, aurones, flavonoids, anthocyanins, betacyanins, benzophenones, xanthones, stilbenes, quinones, lignans, lignins, tannins. The production of phenolic acids is usually regulated by the shikimic acid or phenylpropanoid pathway in plant metabolism. Other essential phytochemicals, such as tannins, coumarins, benzoquinones, and naphthoquinones, are formed from phenolic acids in some situations. Caffeic acid, ferulic acid, p-hydroxybenzoic acid, protocatechuic acid, vanillic aci, salicylic acid, and GA are only a few of the most well-known phenolic acids [4, 5].
GA and its derivatives have reported profound applications in the medicinal, cosmetic, food, printing, and dyeing industries [6, 7]. GA and its derivatives (lauryl gallate, propyl gallate, octyl gallate, tetradecyl gallate, and hexadecyl gallate) found to help prevent the oxidation and rancidity of oils and fats in a variety of foods [9, 10].
GA and its ester derivatives, in addition to their usage as flavouring agents and preservatives found to have other activities such as Antioxidant, Antidepressant, Antimicrobial, Anticancer, Antidiabetic, Anti-inflammatory, Wound Healing, Cardiovascular diseases, Gastrointestinal disease, Metabolic diseases, Neuropsychological diseases and Hepatoprotective (Figure 1) [10-16].

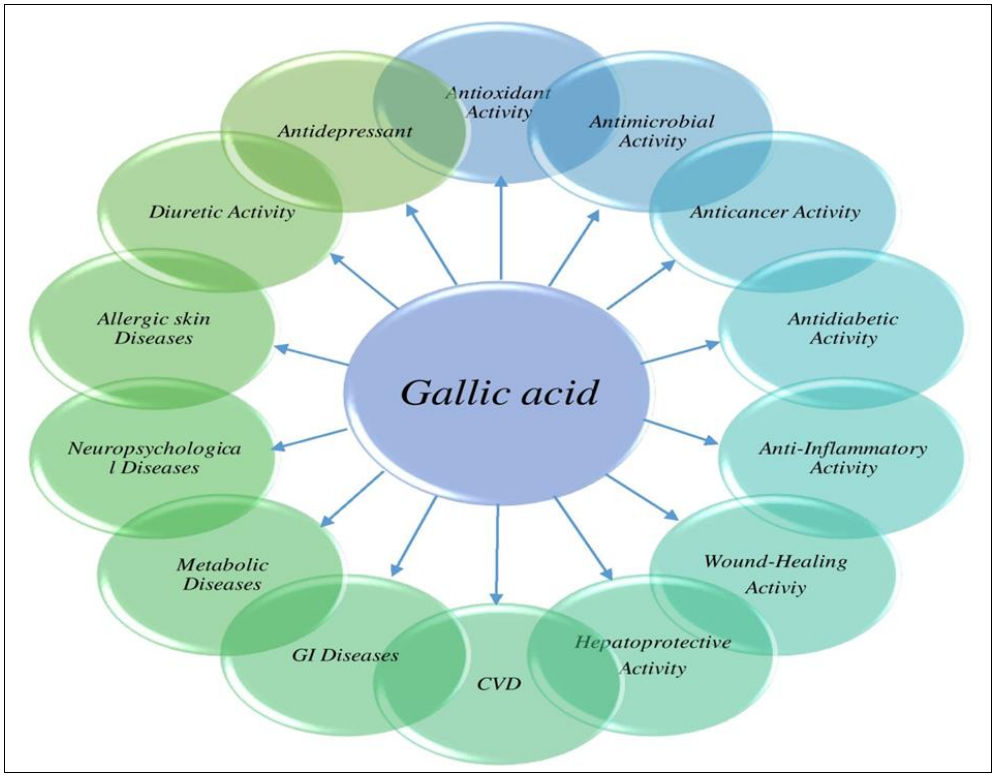

Fig 1: Pharmacological activities of Gallic acid

Pharmacological activities

Antioxidant Activity

Liwen Hea *et al*. (2019) reported that during ensiling, the antioxidant activities of GA (GA) in Moringa oleifera leaves silage progressively grew within a modest value, which was combination of curcumin and GA. Kang *et al*. 2017 studied GA and chitosan combination in hydrogel system and found that GA-modified hydrogels with a longer chitosan backbone had higher antioxidant activity than those with a shorter chitosan moiety. [19] Alves *et al*. 2016 assessed the antioxidant activity of GA and nanoparticles containing GA using a colorimetric radical cation measurement. In all concentrations studied, ABTS•+ GA had higher scavenger activity, with a reduction in activity only after 48 hours in the lowest concentration.[20]

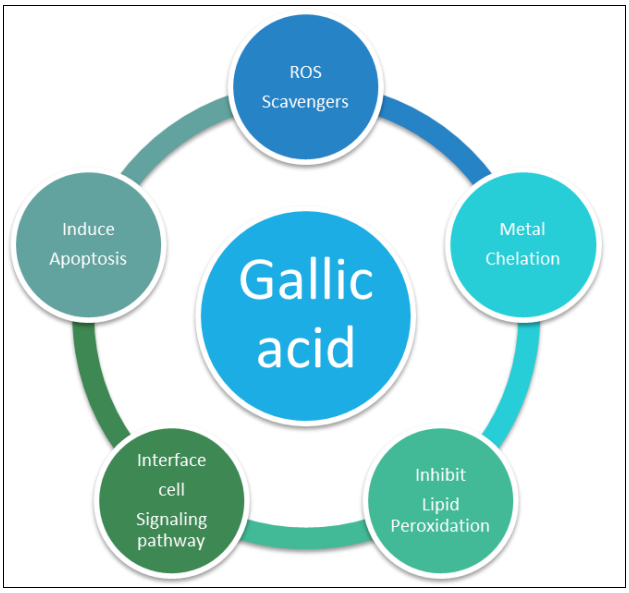

Fig 2: Antioxidant activity of Gallic acid

Antimicrobial activity

Microorganisms such as Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus mutans, and others have been discovered to be inhibited in motility, adhesion, and biofilm formation by GA [21-23]. GA alters cell membrane integrity and changes the charge, hydrophobicity, and permeability of the membrane surface, as well as destroying Gram-negative bacteria's outer membrane by chelating divalent cations.[24,25] GA has been shown to have MICs of 250 g/mL against M. haemolytica and 500 g/mL against P. multocida. At a concentration of 3.91 g/mL, GA inhibited the growth of bacteria by 8% [26].

Sarjit *et al*. 2015 reported the action of pH (H+) on bacterial cells is responsible for GA's antibacterial properties [27]. All examined strains had minimum inhibitory concentrations (MIC) of 2.5 mg/mL of GA, with the exception of P. fluorescens DSMZ 50090T, which had a MIC of 5 mg/mL of GA. For all strains, the Minimum Bactericidal Concentration (MBC) was 10 mg/mL. The examination of kinetic parameters revealed that survival decreased as GA concentrations increased from 2.5 to 10 mg/mL, with P. fluorescens proving to be the most resistant strain. [28] GA was shown to have a broad spectrum of antifungal activity, with MICs ranging from 43.75 and 83.33 g/mL for all of the dermatophyte strains examined. Three Candida strains were likewise active against GA, with MICs ranging from 12.5 and 100.0 µg/mL. Candida albicans was the most sensitive Candida species (MIC = 12.5 µg/mL), whereas Trichophyton rubrum was the most sensitive filamentous species (MIC = 43.75 µg/mL) [29, 30].

Anticancer Activity

GA has been shown to have anticancer properties in a range of cancer cells. GA's cytotoxic and antitumor effects are mediated through changes in the antioxidant/pro-oxidant balance. The chemical can decrease ROS-induced

carcinogenesis in some situations by increasing the activities of superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR), and glutathione peroxidase (GPx), as well as lowering lipid peroxidation and ROS production. GA, via activating the caspases pathway and creating reactive oxygen species (ROS), can also induce cell cycle arrest, autophagy, and death. It can also reduce matrix metalloproteinase expression and activity, limiting invasion and metastasis. In addition, various GA derivatives, such as isobutyl gallate-3, 5-dimethyl ether and methyl gallate 3, 5-dimethyl ether, have been shown to inhibit tumour development and improve survival rates *in vivo* cancer models [31-35].

Gu *et al*. (2018) examined GA's activity in acute myeloid leukaemia is thought to be mediated through Akt/mammalian target of rapamycin (mTOR)-dependent suppression of mitochondrial respiration (AML). GA, through a caspase-dependent mechanism, dramatically promotes apoptosis in AML cell lines, primary mononuclear cells (MNC), and CD34 stem/progenitors isolated from AML patients. GA suppresses mitochondrial respiration in a dose- and time-dependent manner, resulting in reduced ATP generation and oxidative stress [36, 37].

Anti-inflammatory Activity

Pandurangan AK *et al*. 2015 stated that reduction in activation of p65-NF-B and IL-6/p-STAT3Y705 is thought to be the mechanism through which GA exerts potentially therapeutically beneficial anti-inflammatory effects.[38] GA's ability to scavenge superoxide anions, limit myeloperoxidase release and activity, and interfere with NADPH-oxidase activity have all been proposed as possible anti-inflammatory mechanisms [39].

The MAPK and NF-B signalling pathways were primarily engaged in GA's anti-inflammatory actions. As a result, it reduces the production of inflammatory cytokines, chemokines, adhesion molecules, and cell infiltration, weakening the inflammatory response. GA is predicted to be a viable option for the treatment of several inflammation-related disorders due to its outstanding pharmacological properties. GA not only has less adverse effects than regularly used anti-inflammatory medicines in clinical practise, but it also considerably increases the body's immunologic function. Furthermore, it offers the obvious benefits of multi-action targets [40]. GA may reduce the inflammatory process by scavenging superoxide anions, inhibiting the release and activity of myeloperoxidase, and perhaps interfering with the assembly of active NADPH-oxidase. GA's o-dihydroxy group is critical for its inhibitory effect, according to a structure-activity relationship [41].

Wound Healing Activity

Yang *et al*. (2016) have studied GA's impact on wound healing in human keratinocytes and fibroblasts in normal and hyperglucidic circumstances to mimic diabetes GA treatment stimulates wound-healing factors such focal adhesion kinases (FAK), c-Jun N-terminal kinases (JNK), and extracellular signal-regulated kinases (Erk), meaning that GA promotes wound healing [42]. Kokane *et al*. (2009) have evaluated the wound-healing properties of Mimosa pudica root extract and the phenol components responsible for it, such as GA In animals, the methanolic extract of the plant has a wound-healing effect [43].

Kaparekar *et al*. 2020 confirmed the GACSNPs nanocomposite scaffold for wound healing has healing and therapeutic activities because dermal fibroblasts are the first line of defence against injuries, and fibroblast proliferation in the wound bed is critical for wound repair. [44] The antibacterial treatment containing CS-Cu-GA NCs promoted the healing of S. aureus-infected wounds while causing minimal injury to normal tissues. [45] Fruit ethanolic extract and GA wound healing activity in diabetic animals has been established. Yet, the wound healing effect was increasingly reported with GA [46].

Hepatoprotective Activity

Tung *et al*. (2009) have reported GA has hepatoprotective properties against carbon tetrachloride (CCl4)-induced hepatotoxicity. GA has also been reported to protect the liver against sodium fluoride-induced oxidative damage [47].

Anand *et al*. confirmed that GA contains hepatoprotective properties. Serum transaminases, and bilirubin levels were the key measures investigated. Lipid peroxidation, drug metabolising enzymes, glucose-6-phosphatase, and triglycerides were among the hepatic indicators examined [48]. Bhattacharyya *et al*. 2013 In comparison to the CCl4-induced group, the complex of GA–phospholipid dramatically lowered hepatic marker enzymes and restored antioxidant enzyme levels ($P \leq 0.05$ and $P \leq 0.01$). GA's pharmacokinetics were also enhanced by the complex, which increased relative bioavailability and elimination half-life.[49] The significantly increased level of (92%), AST (106%) and ALP (72.5%) in serum were significantly altered on treatment with GA [50].

Cardiovascular diseases

GA pretreatment lowers the harmful oxidative consequences of myocardial infarction by increasing the activity of antioxidant enzymes such as SOD, CAT, GST, and GPx, as well as non-enzymatic antioxidant agents such as GSH, vitamin C, and vitamin E [51]. Serum cardiac biomarkers like cardiac troponin T (cTnT) and creatine kinase-MB (CK-MB) decrease after a myocardial infarction, reducing the negative effects of free radicals on the integrity and function of myocyte membranes. [52] GA has a possible cardioprotective effect, and it has been hypothesized that it can be used to treat the underlying causes of CVDS [53].

GA inhibits the expression of collagen type I and connective tissue growth factor, as indicated by Trichrome II Blue staining. GA also suppresses fibrosis-related genes and collagen type I deposition in TGF-1-treated cardiac fibroblasts, suggesting that GA might be used to treat cardiac dysfunction and fibrosis in chronic heart failure patients [54]. GA extracted from Spirogyra sp. offers a variety of therapeutic properties and might be used to treat cardiovascular disease.[55] Ngamukote *et al*. [11] reported that GA binds to bile acids and reduces the solubility of cholesterol in micelles, inhibiting pancreatic cholesterol esterase [56].

Gastrointestinal diseases

GA protects the mucosal layer of the gastrointestinal tract from ulcers through a variety of mechanisms, including lowering acid secretion, inducing the release of endogenous antioxidants and defensive factors (i.e. SOD, CAT, endothelial nitric oxide synthase (e-NOS), and prostaglandin E2 (PGE2)), and lowering oxidative stress and lipid peroxidation. GA acts as an antioxidant, scavenging free

radicals like ROS and boosting antioxidant defence systems including SOD, GST, GPx, CAT, GSH, and cytochrome P450-dependent detoxifying enzymes, which helps to attenuate the hepatotoxic effects of xenobiotics [57]. Gomez *et al* 2013 reported GA's antibacterial impact on Helicobacter pylori cultures was measured using a 600 nm absorbance of liquid culture media, an agar-well diffusion method, and a colony forming unit scoring system. On two strains of H. pylori, polyphenol had a significant growth inhibitory impact (26695 and ATCC 43504). Dose, contact duration, and polyphenol type all influenced antibacterial effects [58].

Asokkumar *et al*. 2014 reported that GA and famotidine, in various combinations, were tested to see if they might prevent an ulcer caused by aspirin and pyloric ligation. Combination therapies have a synergistic protective effect against peptic ulcer, which has been linked to the gastroprotective, antisecratory, and antioxidant activities of the therapies. GA combined with an antiulcer medication will be more effective in preventing and treating peptic ulcers [59]. Zhou *et al*.2020. Stated that GA's mechanism Ethanol-induced gastric ulcers may be implicated in the Nrf2/HO-1 anti-oxidative pathway, and hence perform an anti-apoptotic function via regulating Bax, Bcl-2, and Caspase-3 [60].

Metabolic diseases

The most common metabolic diseases in adults are obesity, diabetes, and hyperlipidemia. GA, by promoting the synthesis of PPAR-, a nuclear transcription factor that promotes differentiation and insulin sensitivity in adipocytes, inhibits diet-induced hyperglycemia and hypertriglyceridemia, shrinks adipocytes, and protects pancreatic -cells in metabolic disorders. GA also increases cellular glucose absorption via stimulating the phosphatidylinositol 3-kinase (PI3K)/p-Akt signalling pathway and the translocation of insulin-stimulated glucose transporters including GLUT4, GLUT2, and GLUT1 [61].

Prince *et al*. (2011) have reported that GA is an antioxidant with antihyperglycemic, antilipid peroxidative, and antihyperglycemic effects. The preventive effects of GA in diabetic rats were also confirmed by pancreatic histopathology. GA can improve GLUT4 translocation and glucose uptake activity in a wortmannin-independent but wortmannin-sensitive manner because it is a competitive inhibitor of the substrate glucose-1-phoshate but not of the allosteric activator AMP. The atypical protein kinase Cf/k may be involved in GLUT4 translocation and GA-mediated glucose absorption [62]. Oliveria *et al*. (2016) have reported Gallic protect diabetics against the harmful effects of oxidative stress [63]. GA had a strong anti-diabetic effect, which might be due to changes in TNF- and adipocytokine secretions, as well as increased PPAR mRNA expression [64]. GA enhanced insulin sensitivity via activating the Akt signalling route rather than the AMPK signalling system, whereas E. officinalis fruit juice demonstrated combined activation of Akt and AMPK [65]. Wong *et al*. 2019 reported a combination therapy, 2:1 combination of GA and andrographolide showed synergistic hypoglycaemic action with favourable dosage reduction as compared to a single drug treatment [66].

Alzheimer's diseases

Mansouri *et al*. 2013 reported GA lowers induced toxicity in cortical neurons by reducing Ca2+ release from the endoplasmic reticulum into the cytoplasm, as well as ROS production and death. By scavenging free radical molecules like ROS, lowering lipid peroxidation, and increasing the activity of endogenous antioxidant agents like SOD, CAT, and GPx, the medication counteracts the effects of streptozotocin (STZ) on cerebellar oxidative stress and cognitive impairment in rats [67]. GA elevates α- and reduces β-secretase activity, In a pre-clinical animal model of Alzheimer's disease, suppresses neuroinflammation and stabilises brain oxidative stress. Further GA promotes ADAM10 via increasing the quantity of the ADAM10 proprotein convertase furin, inhibits BACE1 activity directly, but has no effect on Adam10 or Bace1 transcription [68].

Ogunlade *et al*. 2020 stated that After GA treatment, there was a substantial drop in antioxidant enzymes (CAT, GSH, and SOD), serum electrolyte (except K), and neurotransmitter levels (except norepinephrine), as well as a corresponding rise in stress indicators (MDA, H2O2, and NO) [69]. GA decreases neuronal damage and amyloid neuropathology in the brain, as well as improving cognitive performance, by scavenging free radicals and preventing Aβ oligomerization [70].

Antidepressant

R Chhillar *et al*. 2012 reported that in unstressed animals, GA increased MAO-A activity, malondialdehyde levels, and catalase activity, and dramatically inhibited stress-induced glutathione and catalase activity. Stress lowered MAO-A activity, malondialdehyde levels, plasma nitrite levels, and corticosterone levels considerably. GA's antioxidant qualities and reduction of MAO-A activity, as well as a drop in plasma nitrite levels, likely contributed to its antidepressant-like effects. GA had antidepressant-like effects in stressed mice, which was probably due to a drop in plasma corticosterone levels [71]. GA appears to have a dual mode of action, boosting both serotonin and catecholamine levels in central nervous system synaptic clefts. This antidepressant-like effect also appears to include alpha adrenergic, 5-HT2A/2C and 5-HT3 serotonergic, and D1, D2, and D3 dopaminergic receptors [72].

GA had antidepressant-like effect in both unstressed and stressed rats, most likely due to its antioxidant action and suppression of MAO-A activity, as well as a reduction in plasma nitrite levels. GA also had antidepressant-like effects in stressed mice, most likely due to a drop in plasma corticosterone levels [73]. GA has been shown to have antidepressant-like properties, which may be due to CNS effects such as increased glutathione levels, catalase activity, and decreased malonaldehyde levels in the brain [74].

Conclusions

To conclude, GA is a prospective lead molecule for novel drug development because it is obvious that it plays a key function in imparting medicinal characteristics to the plant. GA is a potent antioxidant and anti-inflammatory. It can be found in a variety of plants and is utilised in a variety of polyherbal formulas. As a result, it's critical to encourage more reputable research into GA's and its congeners' therapeutic effects. Due to the presence of many phytoconstituents such as free acids, esters, catechin derivatives, and hydrolysable tannins etc. It is used as

Antioxidant, Antidepressant, Antimicrobial, Anticancer, Antidiabetic, and Anti-inflammatory, also used in Wound Healing, Cardiovascular diseases, gastrointestinal disease, metabolic diseases, Neuropsychological diseases and as a Hepatoprotective.

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