Brainwave: A Multidisciplinary Journal (ISSN: 2582-659X), Vol. 3, No. 4, December 2022, pp. 267-275

GALLIC ACID AND ITS ESTER DERIVATIVES IN HEALTH AND DISEASES: A REVIEW

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Received on: November 07, 2022 | Accepted on: December 21, 2022 | Published on: December 28, 2022

Abstract

There are numerous uses for gallic acid and its derivatives in many different scientific disciplines. These substances are widely dispersed in medicinal plants and fruits in nature, and as a result, the human population uses them directly or indirectly as food ingredients, preservatives, etc. They have also been successfully used as antioxidant, anticancer, antimicrobial, gastrointestinal, cardiovascular, metabolic, neuropsychological agents, and for several other diseases, etc. In many reports derivatives of gallic acid prove to be more efficient as compared to gallic acid alone. This review would certainly create a great interest of the scientific community towards the developments and uses of gallic acid and its derivatives in future.

Keywords: *Gallic acid, gallic acid esters, ethyl gallate, methyl gallate, propyl gallate, health, diseases*

1. Introduction

Gallic acid (GA), which belongs to the phenolic chemical class and is often referred to as 3,4,5-trihydroxybenzoic acid, is a naturally occurring secondary metabolite that can be found in a variety of plants, vegetables, nuts, and fruits[1]. Gallic acid and its derivatives are present in nearly every part of the plant, such as bark, wood, leaf, fruit, root and seed. They are present in different concentrations in common foodstuffs such as blueberry, blackberry, strawberry, plums, grapes, mango, cashew nut, hazelnut, walnut, tea, wine. Gallic acid esters have much greater health benefits e.g., when we drink tea , Gallic acid **esters** pass on to blood imparting their health benefits. Gallic acid itself as such does not have much health benefits. It is the esters of Gallic acid which are responsible for health benefits, for example when we drink tea, the esters of gallic acid goes in the blood which have many health benefits and from here it goes to liver in the ester form .Multiple physiological and pathological processes respond defensively to environmental stimuli and tissue damage by exerting protective mechanisms known as inflammatory responses. There are numerous inflammatory pathways, including IL-6/JAK/STAT3, PI3K, and p38 MAPK. Major inflammatory modulators as FoxO1/3, TNF, IL-6, COX2, HIF-1, AP-1, JAK, and STAT are also included. All of the aforementioned modulators have been shown to be inhibited by gallic acid. Therefore, gallic acid can prevent many diseases by reducing inflammatory signals[2].Currently non-steroidal anti-inflammatory drugs are known to protect from inflammatory disease progression; however, it comes with a lot of side effects. Therefore, development of a naturally available anti-inflammatory compounds and its derivatives are highly required. The molecular mass of gallic acid, which is a yellowish-white crystal with a melting point of 250 °C and a water solubility of 1.1% at

20 °C, is 170.12 g/mol. It can be produced from phenylalanine using trihydroxycinnamic acid or caffeic acid. It can also be produced directly from a shikimate pathway intermediary, such as protocatechuate or 5-dehydroshikimate[3]. It is well known for its natural and strong anti-oxidative, pro-oxidant, anti-mutagenic, anti-carcinogenic, anti-allergic, anti-inflammatory, anti-viral, anti-bacterial, anti-arteriosclerosis activities[4]. Consuming gallic acid in the right amounts can have positive benefits on the prevention of conditions including diabetes, obesity, Parkinson's, Alzheimer's, and other illnesses. They can also be employed as natural colours, prebiotic components, hydrogels, nanocomplexes, and to enhance the physicochemical properties of starch. These substances also hold promise for advancement in a wide range of technological sectors, such as organic fine chemistry, fundamental materials chemistry, medicines, food chemistry, and chemical engineering[5].

2. Various applications of gallic acid and its derivatives

Gallic acid: Allergy-related dermatitis, rhinitis, asthma, purpura, and anaphylactic shock are examples of Allergic inflammatory diseases that can have a negative impact on a patient's everyday life or potentially be life-threatening. Fortunately, GA has been demonstrated to influence allergy and inflammatory illnesses via controlling the intracellular MAPK and NF-B pathways. By controlling intracellular cyclic adenosine monophosphate (cAMP) and Ca2+ levels, GA prevented the release of histamine. Additionally, it attenuated the activation of NF-B and p38 MAPK, which reduced the expression of the inflammatory cytokines TNF- and IL-6[6]. Recent studies have demonstrated that tumor-like Fibroblast-like stem cells can migrate to bone and cartilage, where they can speed up the release of pro-inflammatory cytokines, chemokines, and matrix metalloproteinases (MMPs), leading to the development of pannus. Surprisingly, it was demonstrated that GA might cause FLSs to undergo apoptosis by increasing the expression of proteins that promote apoptosis, such as Caspase-3, Bax, and p53, while suppressing the expression of proteins that prevent it, such as Bcl-2 and p-AKT,thereby preventing rheumatoid arthritis[7]. Inflammatory bowel disease and ulcerative colitis may be treated with GA by inhibiting the NF-B signalling pathway, which lowers the levels of the pro-inflammatory factors COX-2 and iNOS[8]. Pneumonia caused by (COPD) may result in a minor airway blockage, deterioration of the parenchyma and (chronic bronchitis) (emphysema). GA effectively reduced the emphysema and lung inflammation in rats with COPD, in part by blocking the IB/NF-B signalling pathway[9]. It is generally recognised that obesity can contribute to chronic inflammation, which in turn can result in metabolic illnesses like insulin resistance, type 2 diabetes, cardiovascular diseases, and a variety of cancers. Adipocyte hypertrophy and the paracrine interaction of adipocytes and invading macrophages resulted in adipose tissue inflammation. GA had a crucial function in reducing body obesity by limiting the activation of macrophages brought on by adipocyte hypertrophy and down-regulating the expression of inflammatory mediators[10]. In the animal model of Alzheimer's disease, GA, a histone acetyltransferase inhibitor, could prevent amyloid-induced neurotoxicity by selectively reducing NF-B activation[11]. Furthermore, Liu et al. reported that in LPS-simulated Parkinson's disease, GA may lower levels of IL-1, NO, and iNOS by regressing -nucleoprotein, GFAP, and ED-1 proteins[12]. By blocking the activity of the IB/NF-B and PI3K/AKT signalling pathways, GA prevents gastric cancer cells from secreting MMP-2/9 and migrating [13]. By chance, blocking p300/CBP-mediated p65 acetylation and subsequent activation of the IB/NF-B signal, A549 lung cancer cells may express fewer inflammatory mediators.

Additionally, it reduced the expression of genes involved in cell survival and antiapoptosis, including XIAP, Bcl-2, cyclin D1, and c-Myc [14]. According to the aforementioned investigations, Garca-Rivera demonstrated that GA could control IK/IB/NF-B, MAPK, and In MDA-MB231 breast cancer, MEK1/p90RSK/MSK signalling pathways are involve [15]. Target genes for metastasis, apoptosis prevention, and inflammation include IL-6/8, COX2, CXCR4, XIAP, and Bcl-2 [15]. In addition to being employed in illnesses, it is also used in dyes, photographic film, and printing inks [16]. Its anti-oxidant properties make it suitable for use as food additives in a variety of eatable products, including baked goods, confectionery, and chewing gums, as they reduce the rancidity and spoiling of fats and oils [17]. Since it shields cells from UV-B or ionising radiation, it can be applied to cosmetics [18]. Gallic acid can be used as an addition in cosmetics to reduce pigmentation because a study on B16F10 melanocyte cells revealed that it suppressed melanogenesis [19].It has been reported that gallic acid displayed anti-bacterial property against a wide range of pathogens including *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Klebsiella pneumonia* [20]. Gallic acid is also known to contribute to the astringent sensory quality of red wine.[21]

Natural materials like cheukbaek leaves that contain gallic acid can be utilised to make liquid toothpaste, mouthwashes, mouth sprays, ointments, or oral varnish for use in treating and preventing oral disorders [21]. An anti-aging cosmetic product with isoflavones and gold nanoparticles treated with gallic and protocatechuic acids was also reported [22].

Gallic acid esters: One of the primary phenolic components of both black and green tea is gallic acid, along with its catechin derivatives. Gallic acid esters are used in a wide variety of industrial applications, including as antioxidants in food, cosmetics, and the pharmaceutical sector. Gallic acid is also used as a source of raw materials for paints, colourants, and inks[23]. Propyl gallate, inhibited the growth of bacteria that can cause food poisoning, aquatic bacteria, and microorganisms that can cause foul flavours. The hydrolysis of the ester bond between gallic acid and the polyols hydrolyzed following the ripening of many edible fruits seems to be responsible for their antibacterial capabilities. In the food, pharmaceutical, and cosmetic industries, methyl, propyl, octyl, and dodecyl gallates and their derivatives are frequently used as antioxidants. Previous research has demonstrated that these substances have strong antitumoral, antibacterial, and antiviral effects, as well as being strong antioxidants and reactive oxygen species scavengers. [24]. Regardless of the type of cell, the cytotoxicity of GA, methyl, and propyl gallate is mediated by the production of ROS. Subsequent biochemical studies revealed that intracellular Ca2+ and ROS production significantly influence the modulation of the early signalling pathway of apoptosis induced by GA. The anti-proliferative potential of derivatives like lauryl and octyl gallate against tumour cells is higher than that of gallic acid, though [25]. An improved method for treating acne vulgaris that inhibits or kills the microorganism *Proprionibacterium* without utilizing antibiotics.is using Gallic acid ester, preferably propyl gallate to inhibit acne by reducing follicular reactivity inflammation[26].Propyl gallate encapsulated liposomes were used for intranasal administration and for targeting several brain diseases[27].

PG treatment inhibited the growth of lung cancer cells, especially Calu-6 cells via caspase-dependent apoptosis as well as G1 phase arrest of the cell cycle [28].Inclusion complexes with cyclodextrin and propyl gallate were used as water soluble antioxidants in food industry because it showed improved solubility and radical scavenging capacity[29]. Theaflavin-3'-gallate (TF2b) and other gallate derivatives could successfully stop the replication of the influenza

viruses H1N1-UI182, H1N1-PR8, H3N2, and H5N1, and other most substantial antiviral activity in vivo, according to the Cytopathic Effect (CPE) Reduction Assay[30]. From a mechanistic perspective, it was discovered that propyl gallate: (a) protected hepatocytes from the cascade of oxyradicals produced by xanthine oxidase-hypoxanthine; (b) protected hepatocytes from the superoxide radicals generated specifically by menadione; (c) protected the functionally significant hepatic vascular endothelial cells and reduced the amount of oxyradical damage.[31]. Nonyl gallate were reported to exhibit fungicidal effects on *Saccharomyces cerevisiae* [32]. Gallic acid ester containing drugs were reported to be effective in treating enteric bacterial infections [33]. With its anti-virus, anti-tumor, anti-mutation, and oxidation-resistant properties, a composition of 70-95% calcium gallic acid chelate, 0-8% zinc gallic acid chelate, 0-2% magnesium gallic acid chelate, 0-2% strontium gallic acid chelate, and 5-18% inulin can be used to treat and prevent acralcerosis or cholasma. [33]. Through Inhibition of ROS and the NF-k B Pathway, propyl gallate inhibits the migration of malignant glioma cells that have been treated with temozolomide[34]. Propyl gallate reduces the development of hepatocellular carcinoma cells via causing ROS and activating autophagy[35]. By reducing the buildup of intracellular lipid droplets, Propyl gallate may prevent adipogenic development in human adipose tissue-derived mesenchymal stem cells (hAMSCs). Adipocyte-specific indicators such as the peroxisome proliferator-activated receptor (PPAR), CCAAT enhancer binding protein (C/EBP), lipoprotein lipase (LPL), and adipocyte fatty acid-binding protein 2 were also considerably downregulated by PG (aP2)[36]. Epigallocatechin gallate, EGCG has been known to inhibit obesity and obesity related hormones in women[37]. Methyl gallate (MG), a phenolic molecule obtained from plants, is well known for having a notable anti-inflammatory impact in a variety of experimental animals, including arthritis caused by zymosan, colitis, paw oedema, and pleurisy[38]. The efficacy of the antibiotic orbifloxacin (ORB) against *E. coli* increased by combining it with a phenolic component, propyl gallate (PG)[39]. In the early stages of diabetic nephropathy, propyl gallate inhibits angiogenesis and glomerular endothelial cell growth, providing nephroprotective effects[40]. In vitro antifungal imidazole action against Candida albicans is enhanced by propyl gallate[41]. Two experimental animal models, the acetic acid-induced permeability model in mice and the air pouch model in rats, were used to demonstrate the anti-inflammatory effect of n-propyl gallate. In the lipopolysaccharide (LPS)-stimulated RAW264.7 macrophage cells, it inhibited nitric oxide synthesis and the generation of inducible nitric oxide synthase and cyclooxygenase-2. Reactive oxygen species levels that had increased in LPS-stimulated RAW264.7 macrophage cells may be reduced by it. Additionally, it reduced matrix metalloproteinase-9's gelatinolytic activity, which was increased in LPS-stimulated RAW264.7 macrophage cells. In the activated macrophage cells, it increased NF-B promoter activity and reduced inhibitory B- degradation. In the activated macrophage cells, it was able to prevent c-Jun NH(2)-terminal kinase 1/2 (JNK1/2) phosphorylation and activation of c-Jun promoter activity. By inhibiting NF-kB and JNK, n-propyl gallate has anti-inflammatory properties[42].Therefore by effecting multitude inflammatory pathways it gallic acid esters can inhibit a lot of inflammatory markers and inflammatory diseases. In a patent, Vyavahare et al. demonstrated how to maintain connective tissues(arteries,aorta) by combining tannic acid, pentagalloylglucose, nobotanin, epigallocatechin gallate, gallotannins, ellagic acid, and procyanidins with a particular carrier [43]. Along with ellagitannin, hydrolysable tannin (gallic acid derivative or ellagic acid derivative) attached to a hydroxyl group in glucose via an ester bond was used to treat diabetes and fatty liver caused by the

body's inability to absorb fructose as a result of obesity. [44]. For the purpose of preventing or treating gingivitis or periodontitis, Brading et al. created an oral care composition with an alkyl ester of gallic acid and a source of citrate ions[45]. Epigallocatechin- 3-gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG), epicatechin (EC), and jaborandi extract were all used in an oral care composition that was utilised to treat xerostomia [46]. Applying fruit or vegetable polyphenolic chemicals (gallic acid, catechin, epicatechin, gallocatechin, epigallocatechin, catechin) to keratinous materials was described by L'Oreal[47]. A synergistic blend of a polygallate molecule and a gallic acid ester in an effective amount, together with an appropriate vehicle, with or without other skin benefit agents, was developed by Rao et al. as a skin care agent and cosmetic and/or dermopharmaceutical compositions [48].

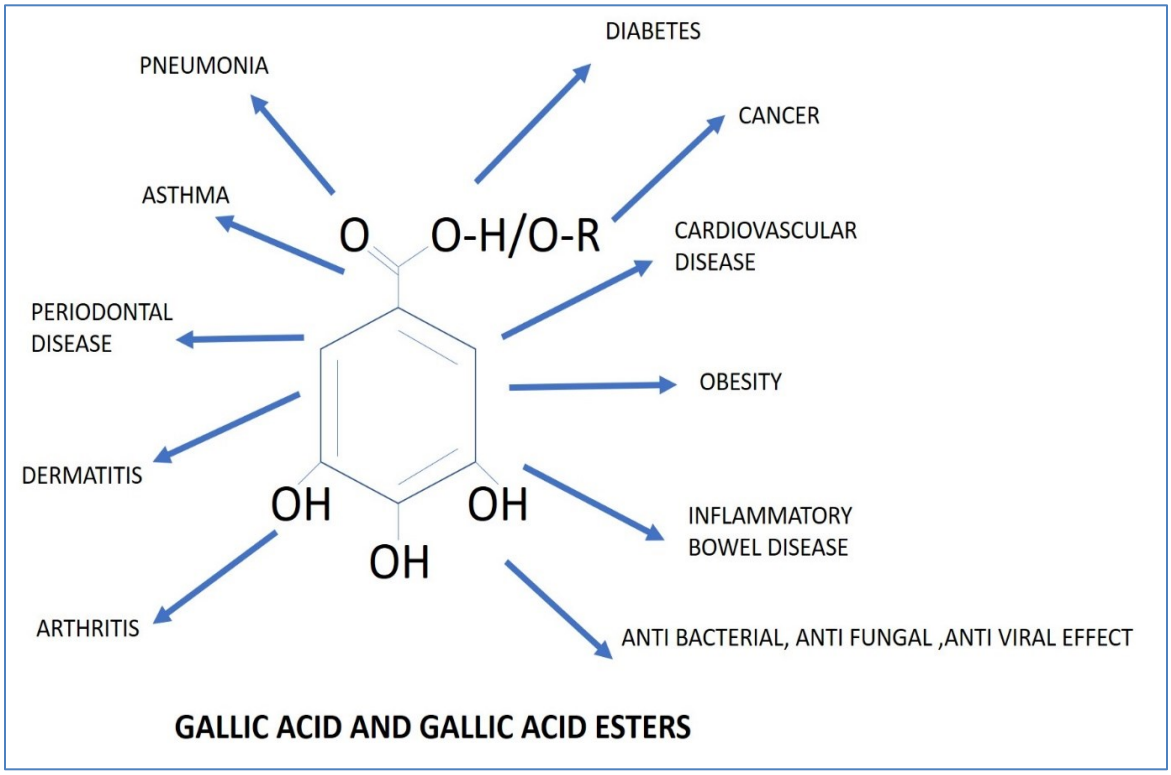

Figure 1 This figure shows the effect of gallic acid and gallic acid esters on various diseases.

3. Conclusion

This review focuses on gallic acid and gallic acid derivatives in maintaining health and alleviating various diseases like cancer, diabetes, cardiovascular disease, obesity, oral infection, allergy, arthritis, inflammatory bowel disorders, preventing ageing and a lot of other diseases as well.

4. Future Perspectives

The goal of this review is to provide a concise summary of the numerous applications of gallic acid and its ester derivatives in diverse forms. The data obtained here is primarily taken from global papers and patents, and it will be useful to the scientific community across a variety of fields. The fact that there are so many publications on the use of gallic acid and its derivatives for treating diseases, preventing illnesses, and other conditions shows how popular these natural compounds are because they are safe and easy to obtain. Although gallic acid is known for its biological effects and drug designing, further studies are required in the field of clinical research so that gallic acid and its derivatives can be applicable for human health and diseases in a true sense.

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