

Gallic Acid: A Promising Lead Molecule for Drug Development

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Abstract

Gallic acid and its congeners are commonly present in variety of fruits and number of plants. In addition to its natural origin, large number of synthesized gallic acid derivatives are also available. It has a wide range of industrial uses including its role as standard for determining phenolic content of analytes in pharmaceutical industry, as source material for ink, paints and colour developer. Studies on gallic acid and its derivatives have exhibited its potential for combating oxidative damages, cancer manifestations and microbial infestations. Further, gallic acid extracted from different natural sources has been implicated to possess potency to ameliorate neurodegenerative disorders and aging. Furthermore, large number of research explorations are available to show its ability for the treatment of diabetes, ischemic heart diseases, ulcer and other ailments. In this review, an attempt is made to compile the scattered information on gallic acid and its derivatives for their pharmacological role, isolation and extraction procedures as well as quantification. This might help our research fraternity to explore gallic acid in their future research as a lead compound for new drug development.

Keywords: Gallic acid; Isolation; Pharmacological activities; Quantification

Introduction

Medicinal plants are of great importance to health due to the presence of phytoconstituents. The most important of these constituents are alkaloids, glycosides, tannins, flavonoids, and phenolic compounds [1]. Phenolic acids are diverse group that includes hydroxybenzoic and hydroxycinnamic acids. Various phenolic acids reported from plants are ferulic acid, ellagic acid, synergic acid, caffeic acid etc. They are also of interest in food, cosmetic and pharmaceutical industries as well as substitutes for synthetic antioxidants [2]. One such prominent phenolic acid is gallic acid which is found in a wide variety of vegetables, fruits, tea, coffee and wine. It occurs in plants in the form of free acids, esters, catechin derivatives and hydrolysable tannins. It also occur as methylated gallic acids e.g., syringic acid or galloyl conjugates of catechin derivatives, i.e., flavan-3-ols, or polygalloyl esters of glucose, quinic acid or glycerol [3,4]. Gallic acid has been reported to elicit various biological activities such as antibacterial, anti-fungal, antiviral, anti-inflammatory, antioxidant, anticancer, anti-diabetic etc.

Gallic acid (GA) is a phenolic compound. It is chemically known as 3, 4, 5-trihydroxybenzoic acid. The structure of gallic acid has phenolic groups that are a source of readily available hydrogen atoms so that radicals produced can be delocalized over the phenolic structure [5]. 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 [6,7]. Due to these activities gallic acid could be considered as a promising lead compound for new drug development. Current work is an attempt to compile literature reporting on isolation, quantification and pharmacological activities of gallic acid and its derivatives to provide quick access to research scholars for their research exploration on gallic acid.

Occurrence

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, *Psidium guajava*, *Syzygium cordatum*, *Rhus typhina*, *Tamarix nilotica*, *Vitis vinifera*, *Hamamelis virginiana*, *Toona sinensis* *Oenothera bienni* and *Rubus suavissimus* [8].

Many gallic acid derivatives occur naturally in plant, these include 3-O- β -D-glucopyranoside (3-glucogallic acid) and 3-O-(6-galloylglucoside), 4-O-(6-galloylglucoside) from rhubarb, mudanoside B from *Paeonia suffruticosa*, 3-O-dodecanoyl (3-lauroylgallic acid) with antioxidant and antimicrobial activities from *Satakentia liukuensis*, 3-methyl ether from *Geranium collinum* and *Atraphaxis frutescens*, 3-methyl-5-O-sulfate (as salts) from *Frankenia laevis* and *Tamarix amplexicaulis*, 3-methyl-4-O-[3,4-dihydroxy-5-methoxybenzoyl-(\rightarrow 6)- β -D-glucopyranoside] from *Polygonum bistorta*, 3-methyl-5-O- β -D-glucopyranoside from *Tabernaemontana cymosa*, 3-methyl ether from *Poupartia axillaris* and *Rhus glabra*, 3-ethyl ether from *Phyllanthus emblica*, and 4-ethyl ether from *Mimosa hamata*, *Haematoxylum campechianum*, *Arbutus unedo*, *Eucalyptus gunnii*, *Terminalia chebula* and *Elephantorrhiza elephantina* [8]. A recent study indicated presence of antioxidant gallic acid esters (gallates) in dust from homes and microenvironments [9].

Synthetic Derivatives

Gallic acid derivatives have been synthesized and reported to possess number of biological and pharmacological activities. The alkyl esters of gallic acid have been reported to possess anticancer, antioxidant ability and neuroprotective effect [10], scavenging free radicals [11], inducing apoptosis of cancer cells [12], inhibiting squalene epoxidase [13], interfering the signal pathways involving

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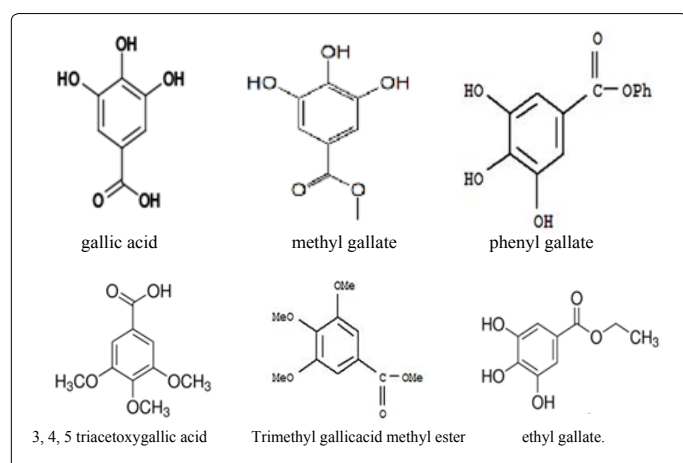
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Ca²⁺ and oxygen free radicals [14]. The schiff bases of gallic acid were synthesized and reported for analgesic, anti-inflammatory and anticonvulsant activities [15]. Gallic acid-based indanone derivatives have been prepared and reported to possess anticancer activity [16]. A series of 2-(3,4,5-trihydroxy phenyl)-5-aryl-1,3,4-oxadiazole were synthesized and evaluated for their anti-tubercular activity [17]. A series of gallic hydrazones containing an indole moiety were evaluated for cytotoxic and antioxidant activities [18]. Derivatives such as 5-{6-(substituted phenyl)-5,6-dihydro-(1,2,4) triazolo(3,4-b)(1,3,4) thiadiazol-3-yl}benzene-1,2,3-triol were synthesized and screened for antimicrobial and anti-inflammatory effects [19]. A series of 33 gallic acid derivatives were synthesized and evaluated for antibacterial and antifungal activities [20]. Other derivatives of gallic acid such as 3,4-methylenedioxyphenyl 3,4,5-trihydroxybenzoate (GD-1) and S-(3,4-methylenedioxyphenyl)-3,4,5-trihydroxy-thiobenzoate (GD-3) were evaluated for cell death-inducing activity in cancer cell lines [21]. A series azo gallic acid complexes were prepared and evaluated for their antimicrobial activity [22].

Isolation

Gallic acid (GA) has been isolated from a number of plants. It has been extracted from rind, seed, stem, fruit, leaves, bark, wood etc. The solvents generally used are water, ethanol and methanol. Some of the plant extract from which GA has been isolated are methanolic extract of whole plant of *Bergia suffruticosa*, aqueous ethanolic extract of leaves of *Ceratonia siliqua*, methanolic extract of the leaves of *Tectona grandis* as well as methanolic extracts of bark, wood, leaf and fruits of *Casuarina equisetifolia* [23-25]. A bioassay guided isolation and identification of gallic acid derivatives epicatechin-(2 β \rightarrow O \rightarrow 7, 4 β \rightarrow 8)-catechin (proanthocyanidin A1) and epicatechin-(β \rightarrow 2 O \rightarrow 7, 4 β \rightarrow 8)-epicatechin (proanthocyanidin A2) were reported from peanut skin [26].

Structures of Gallic Acid and Some of its Derivatives



Quantification

Various methods have been reported for the quantification of GA in herbal raw materials and formulations which include TLC, HPLC, HPTLC, RP-HPLC etc. Gallic acid has been quantified from the flower buds of *Syzygium aromaticum* by TLC [27]. Further, HPLC technique is used for quantification of gallic acid in *Ocimum sanctum* [28]. Furthermore, UHPLC method was used for quantifying gallic acid in methanolic, ethanolic and hydroalcoholic extract of the seed of *Cornus officinalis* [29]. Gallic acid was quantified in hydroalcoholic

extract of dried flowers of *Nymphaea stellata* and *Eucalyptus hybrida* by HPTLC [30]. Another study showed use of RP-HPLC method for quantification of GA in *Symplocos racemose* [31].

Pharmacology

There are several reports for the pharmacological activities of gallic acid and its derivatives. Review of literature reveals hepatoprotective potential of gallic acid in alleviating paracetamol-induced liver damage in mice, hepatic ischemia reperfusion injury in rats, CCl₄-induced acute liver injury in rats, sodium fluoride-induced oxidative stress, acute liver damage induced by CCl₄ [32,33], N nitroso-compounds-induced mutagenicity as well as obviating mouse lung adenomas by amines or ureas plus nitrite and by nitroso compounds [34]. GA 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 cell lines and inhibit lymphocyte proliferation, inhibits ribonucleotide reductase and cyclooxygenases in human HL-60 promyelocytic leukemia cells, causes inactivating phosphorylation via ATM-Chk2 activation, leading to cell cycle arrest [35-38]. It is also reported to possess anti-oxidant activity [39].

It has been reported that GA has anti-microbial activity against methicillin-resistant *Staphylococcus aureus* and *Helicobacter pylori* [40,41]. Anti-inflammatory activity has been evaluated by zymosan-induced acute food pad swelling in mice, carrageenan-induced paw edema, acetic acid-induced writhing responses and formalin-induced pain in animal models as reported in numerous publications and the suggested mechanisms were scavenging of superoxide anions, inhibition of myeloperoxidase release and activity as well as interference with activity of NADPH-oxidase [42-44]. The other reported activities are anti depressant [45], antiparkinson [46], anti diabetic [47], anti malarial [48], diuretic [49], cardioprotective [50], anti-viral [51], anti-fungal [52], wound healing [53], anthelmintic [54] and anxiolytic [55]. Gallic acid, when combine with other natural products such as, calycosin, reported to synergistically attenuate neutrophil infiltration and subsequent injury in isoproterenol-induced myocardial infarction [56].

Other Uses of Gallic Acid

As described above, gallic acid is routinely employed in pharmaceutical industry as standard for establishing phenolic content of analyte. One of the recent report indicated estimation of phenolic content in the extract of stinging nettle (*Urtica dioica*, L) was done in comparison with gallic acid equivalent/g [57]. Another research exploration on different drying treatments for green tea also evaluated total phenolic content based on gallic acid equivalent [58]. Further, Rosmarinic Acid, a New Polyphenol from *Baccaurea ramiflora* Lour. leaf was also subjected for estimating total phenolic content based on gallic acid equivalent [59].

Conclusion

To conclude, it is evident that gallic acid and its derivatives play a pivotal role in imparting medicinal properties of the plant and therefore it is considered as promising lead molecule for new drug development. Thus, it is imperative to promote more credible research on exploring medicinal properties of gallic acid and its congeners. Eventhough, in the the last few years there has been an increase in the number of publications on gallic acid, it might be more appropriate to carryout such research on human subjects following established system of standardization.

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