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Gallic Acid: A Review on Its Spectrum of Pharmacological Activities

Sapna Desai, Jhanvi Sethi* and Hardi Shah
Department Of Pharmacology, Pioneer Pharmacy Degree College, Sayayjipura, Vadodara – 390019. Gujarat, India

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***Corresponding Author Email:** jjhanvisethi77@gmail.com

Abstract
The skin is the largest organ of the body and serves as a protective shield against the environmental stress like heat, light, injury and infection. On disclosure of the skin to this kind of variables in complement to chemical contaminants and additional mechanical elements can induce reactive oxygen species and the exhibition of free radicals. These are unstable radicals conjoined with further cellular components which leads to structural and cellular damage, which provoke a deployment in wound healing as well as rev the aging process. A wound is a disruption of normal anatomic structure and function which may result because of the mentioned factors. These wounds can be acute or chronic wounds. The skin has ability to repair such injuries as its essential for the survival but in some situations this potential to heal is disrupted as in cases of high glycemic patients. The healing of injury is a complex process and usually consists of 3 to 4 distinct phases which may be by a primary or a secondary union. Polyphenols, like gallic acid are an eminent category of antioxidants which shows a prominent effect in the series of wound healing. Gallic acid has high oxygen-derived free radical scavenging activity and has also been identified for curative effects like antimutagenicity, antiallergic, anti-inflammatory, anti-diabetic and anticarcinogenic activities. In this review we have focused on the importance of function of gallic acid in wound healing which is not only limited during normal but also hyperglycemic conditions where the healing process is affected.

Keywords
gallic acid, wound healing, antioxidant, anti-inflammatory

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GRAPHICAL ABSTRACT:

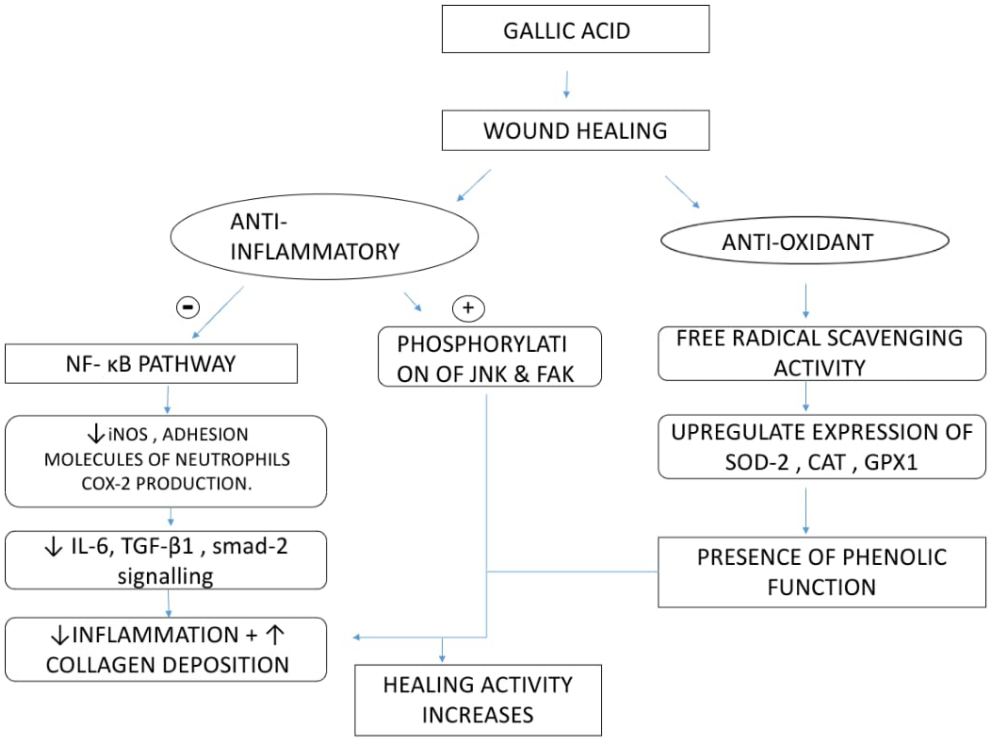

FIGURE I. **Activity of Gallic Acid in Wound Healing**

INTRODUCTION

Skin is the uttermost layer of the human body that is persistently revealed to the surrounding pursuits, like ultra-violate radiation, physical stress, natural or synthetic toxins, heat and is susceptible to instinctive bruising and wounds. Wound healing is a composite procedure carried by a multitude of cellular events that must be tightly coordinated to precisely repair damaged tissue. Abnormalities in wound-linked cellular conducts, as transpires with aging and diabetes, might lead to healing vandalism and the formation of chronic and non-healing wounds.

The body's capability to substitute damaged or dead cells and to rebuild tissues after inflammation is essential to survival. When deleterious agents harm cells and tissues, the host responds by forming in motion a sequence of events that aid to eradicate these agents comprise the impairment, a prepare for surviving cells for replication. The restoration of damaged tissue induced by wounds, surgical resection, and miscellaneous sorts of chronic damage is considerably distinguished into two procedures- healing and regeneration. Healing may reform initial structures but concerns scar formation due to collagen deposition whereas Regeneration results in restitution [1]

Healing of skin wounds is achieved either the two forms- healing by first intention (primary union) and healing by second intention (secondary union). Healing by first intention is proceeded in wounds which have characteristics like clean and uninfected, surgically incised and without much loss of cells and tissues. The events take place immediately after injury, the space between the surfaces of incised wounds is filled with blood which then clots and seals the wounds against dehydration and infection. Next, acute inflammatory responses occur within 24 hours with appearance of polymorphs. The basal cells start proliferating and migrate towards incised space in form of epithelial spurs. By 3rd day the fibroblasts also invade the wound area and by 5th day new collagen fibrils start forming. The scar tissue with exiguous cellular and vascular aspects, an infrequent number of inflammatory cells and the epithelialized surface is formed, during the 4th week.

The secondary intention healing takes place in wounds which are open with large tissue defects, at times infected and having extensive loss of cells and tissues. The initial hemorrhage, inflammatory response and epithelial phases are replica of primary union while changes occur after epithelial changes in which granulation tissue is formed by proliferation of fibroblasts and neovascularization from the adjoining viable elements. This is followed by contraction of wound. The wound starts contracting after 2-3 days and the process is completed by the 14th day. The wound is reduced by approximately 80% of the original size.

The factors influencing the wound healing are divided into two types: the local factors which include infection, poor blood supply, exposure to ionizing radiations, and type, size and location of injury while the systemic factors include age, nutrition, administration of glucocorticoids and uncontrolled diabetes. [2]

Wounds can be categorized in various ways based on the healing time. People are more often to go through from various types of wounds over their entire life span while executing their daily life activities. Based on the cause, depth and place of occurrence, a wound can lead from uncomplicated to critical one. Because of the intrinsic complexity, the categorization of wounds is crucial for the identification, conduction, opting for the right care and restorative counting on the category of the wound. Substantially, burn wounds are classified as a category of wounds in which injury is caused by extreme cold, heat, electrical shock, chemicals, radiation, or erosion. A critical wound is a crevasse of the epidermal layer that emerges spontaneously instead of with time. These wounds may apprehend small or inconsequential cuts with smooth-edged objects such as glass objects or knives, tear in the epidermal layer with rough and uneven edges, blemishes, and wounds after surgery. Acute wounds can occur in whatever place on the body and differ from surface scratches to severe injuries that can impair the blood vessels, muscle tissue, and nerve cells.

In contrary, chronic wounds are wounds that are leisurely cured, cease to function through the normal stages of healing systematically, and results in no consequential improvement leading to recovery within months. These consist of diabetic foot ulcers, arterial ulcers, pressure ulcers, and venous ulcers. These wounds are often persisted in the inflammation stage of the healing process. Patients suffering from chronic wounds in most cases suffers from immobility and dearth in routine functioning, continuous pain, and excessive abnormal stress, along with depression, quarantine, and long-term hospitalization. Points that may influence a wound becoming a chronic consists shock or trauma, strain and wounds with lower severity. Chronic wounds may take a large amount of time to heal or may never heal. These wounds may convict patients through severe sentimental and physical pain and tensity. Therefore, a suitable treatment is necessary. [3]

The most familiar types of chronic wounds are diabetic, pressure ulcers, arterial, and venous.

Arterial ulcers – Usually visual on the legs, they are caused by diminished circulation and might be recognized by pain that shoots after physical stress or at night. They are particularly round-shaped wounds with lain edges, usually influence the full thickness of skin and appear popped up.

Venous ulcers – These wounds often initiate along venous ailments like chronic venous insufficiency (CVI) and varicose veins that progressively get more ominous. These kinds of ulcers, which often originate in the lower leg induce inflammation, pain, and drain laboriously, negatively impacting the quality of life. Venous ulcers can be regarded as about half of chronic ulcers. It is typically agreed that venous depletion is the direct cause of venous hypertension, which eventually leads to the development of venous leg ulcers. [4]

Diabetic ulcers –Numerous diabetic ulcers are neuropathic-related, where unduly dry skin cracks, scales, and form calluses. The calluses can break down and develop ulcers. In different cases, diabetic ulcers tend to be ischemic in origin. In those cases, the ulcer, dull and cool, forms in patients with poor circulation. A common complication in uncontrolled diabetes mellitus, people living with diabetes can develop ulcers on the feet, toes, and heels. They are the result of poor blood circulation, nerve damage, and impaired immune function.

Pressure ulcers –Wounds that are produced by stress, shear, and friction forces are a massive concern for patients and their caretakers and may often result in admission to a healthcare facility. Pressure that is sufficient to either directly necrose tissue or to interrupt blood supply for a duration sufficient to produce necrosis (low pressure, long duration) affects millions of people.

Although pressure/shear/friction is an etiologic aspect for these ulcers, it does not seem to be the explanation for their diligence. Various studies have shown that deduction of pressure from the wound and defense from any redundant concussion might improve multiple pressure ulcers, yet others might fail to heal. [5,6]

There are many factors and conditions that can put the patients at risk while people with chronic conditions such as diabetes and arterial disease are at high risk of developing chronic wounds:

- Diabetes
- patients of an advanced age
- Conditions that affect your vascular system, such as hypertension, heart disease, various veins, and deep venous thrombosis
- Lack of nutrition
- Unhealthy lifestyle habits that include poor hygiene, smoking, and lack of physical activities
- Immobility and prolonged periods of bed rest
- Obesity

- Ailments that compromise one's immune system, including major burn injuries, cancer, AIDS, and high cholesterol
- History of ulcers
- professions that require long periods of sitting [4]

The literature reports many groups of antioxidants, such as flavonoids, phenolic acids, simple phenols, coumarin, tannins, lignin, and tocopherol [7,8]. Phenols and its derivatives are most important antioxidants that can be used against this. Gallic acid, belonging to the group of phenolic acids occurs in variety of plant species.GA is flavonoid compound also named as 3,4,5-trihydroxybenzoic acid. It has a very potential action on acceleration of wound healing process not only in normal but also hyperglycemic conditions mainly by activating focal adhesion kinases (FAK), extracellular signal regulated kinase (Erk), and c-Jun N-terminal kinase (JNK), which might be important for GA mediated wound healing process.[9] On disclosure of the skin to this kind of variables in complement to chemical contaminants and additional mechanical elements can induce reactive oxygen species and the exhibition of free radicals. These are unstable radicals conjoined with further cellular components which leads to structural and cellular damage, which provoke a deployment in wound healing as well as rev the aging process.

STAGES OF WOUND HEALING

To distinguish acute and chronic wounds, it is necessary to understand the stages of healing mechanism. There are four perceptible stages of healing.

Hemostasis:

The endothelium cells of blood vessels that are revealed by the injury triggers platelets to release few factors, which result in vasoconstriction and beginning of the clotting surge. The clot is devised initially at the place of injury to control bleeding. It incorporates mainly of platelets. Many conditions can obstruct the formation of a clot during haemostasias, such as venous insufficiency, diabetes, thrombocytopenia and other blood dyscrasias. Conditions such as these may lead to poor wound healing, therefore careful management of these conditions will be important in the normal process of wound healing. Prostaglandins, Thrombin, growth factors and other cytokines are released at the place of the injury, whose function is to attract inflammatory cells to the area, as well as increase their production and migration.

Inflammation:

When wounds are blocked in the inflammatory phase, proper management of exudate is an important step in assisting wounds with moving on to the proliferative phase. Neutrophils produce inflammatory mediators that activate and recruit fibroblasts and epithelial cells to the injury site. When neutrophils are depleted, they are replaced by macrophages, which help to produce elastase and collagenase and get rid the wound of devitalized tissue. Macrophages also prompt beginning of the proliferative phase of wound healing and an ending of the inflammatory phase and the neutrophils also attach themselves to the endothelial cell walls of the damaged vasculature and travel to the point of injury and, within hours of clot formation. These neutrophils phagocytize dead tissue, bacteria, and any foreign material present and hence provide protection against infection. Unfortunately, inflammatory mediators may sometimes prolong the inflammatory phase of healing and can cause tissue damage. Therefore, any process which leads to prolongation of the inflammatory phase is due to increase number of neutrophils (and thus forms inflammatory mediators).

Proliferation:

During the proliferation phase, protection of newly growing tissues and maintenance of a moist wound environment is crucial. Any condition that obstructs with any of these may lead to prolongation of the proliferation phase. Granulation tissue is composed of immature collagen fibroblasts, an extracellular matrix, blood vessels and macrophages. In duration of this phase of healing the wound fills with new connective tissue (epithelialization, contraction and granulation) and decreases in size. As other cells, including keratinocytes, fibroblasts and endothelial cells, begin to produce and release growth factors and continue to multiply, macrophages begin to decrease in number. The growth of granulation tissue results in narrowing of wound margins and filling of the wound. Ultimately, the wound forms a scar and closes off. As granulation tissue grows, it forms the new scaffolding by promoting the migration of endothelial cells and fibroblasts into the wound as it stimulates collagen production and fibroblasts.

Remodeling:

Remodeling occurs in the early inflammatory phase in which the fibrin clot is replaced by the granulation tissue that is abundant with collagen III and blood vessels during the proliferative phase. Consequently, it is reintegrated with much less mature blood vessels by a collagenous scar rich in type I collagen. In this stage, Collagen proliferates, remodels and matures; this procedure can take many months. The main key features of wound repairing mechanism are the growth factors which as attract new cells to the

wound as well as trigger cellular proliferation and are polypeptides released at the wound site by several activated cells.

GALLIC ACID:

The use of natural products from plants for treatment of wounds has been practiced since ancient times. Due to the fact that plant-extracted treatments are easily accessible and relatively safe, there is a steadily growing interest in using natural compounds to prevent and combat skin pathologies. Moreover, polyphenols have been widely used in traditional medicines to treat several chronic skin diseases, such as psoriasis and vitiligo, and they are also known to be therapeutically beneficial in wound healing and show anti-inflammatory effects when applied topically [10,11]. Despite the fact that GA exhibits several beneficial properties including antioxidant, anti-inflammatory, and anti-tumor activities, there is only little evidence on the role of GA in skin and skin pathology. Here, we studied the effect of GA on would healing in human keratinocytes.[12]. In addition, GA has shown strong protective effects on disease progression in type 1- and type 2-diabetes animal models [13]. In the current study, we reviewed that GA has antioxidant properties, as well as cell migration effects in both normal and high glucose conditions, suggesting that GA has a curative potential for chronic wounds in DM.

Gallic acid also referred to as 3,4,5-trihydroxy benzoic acid, a triphenolic compound usually transpiring low molecular weight, generated by reactive species often confronted in biological methods including, hydroxyl, and the non-radicals, hypochlorous acid, and hydrogen peroxide superoxide and peroxyl, implements an effective shield against oxidative impairment and has been advised to maintain potent antioxidant actions in many considerations. [14–19] Besides, GA has been exhibited as the principal antioxidant element accountable for the effective antiradical and anticancer qualities of several plant essences. [20–25] Likewise, gallic acid derivatives (GADs) have also been observed in many phytomedicines with distinct biological and pharmacological pursuits, intervening with the cell signaling pathways, such as apoptosis of cancer cells and ROS scavenging. [26–29] This recent attribute i.e., initiation of apoptosis, is principally linked with its prooxidant, preferably than antioxidant response. GA can thus show both prooxidants as well as antioxidant characteristics, [30] displaying a dual-edge knife function. There is a distinct category of bioactive natural molecules occupying the GA moiety, conferring numerous pharmacological and industrial purposes such as being used as a requisite building block for multiple pharmaceutical elements, including podophyllotoxin, combretastatin A-4, and colchicine. [31] A few of its ester derivatives (octyl gallate, propyl gallate, and lauryl gallate) are broadly used in processed food, cosmetics, and food packing supplies to counteract oxidative rancidity and deterioration.

BIOSYNTHESIS OF GALLIC ACID:

Three pathways have been proposed for the biosynthesis of gallic acid which have been depicted in the figure II:

(a) β-oxidation of the side chain of 3,4,5-trihydroxycinnmaic acid
(b) Dehydrogenation of shikimic acid, presumably with 3-dehydrshikimic acid as an intermediate
(c) Hydroxylation of protocatechuic acid [32]

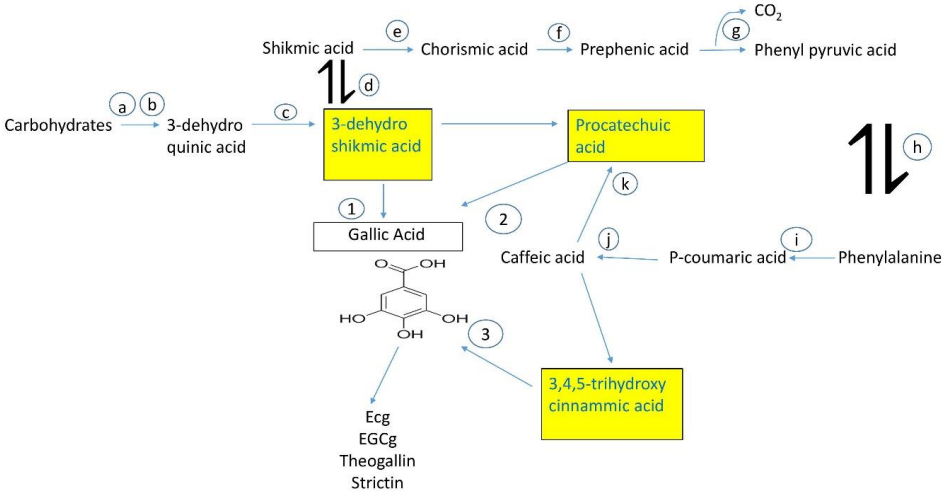

Figure II. Biosynthesis Of Gallic Acid

a	3-Deoxy-7-phosphoheptulosonate synthase (EC 2.5.1.54)
b	3-Dehydroquinate synthase (EC 4.2.3.4)
c	3-Dehydroquinate dehydratase (EC 4.2.1.10)
d	Shikimate dehydrogenase (EC 1.1.1.25)
e	Chorismate synthase (EC 4.2.3.5)
f	Mutase (EC 5.4.99.5)
g	Prephenate dehydratase (EC 4.2.1.51)
h	Tyrosine transaminase (EC 2.6.1.5)
i	Trans-cinnamate 4-monooxygenase (EC 1.14.13.11)
j	p-coumarate 3-dehydrogenase
k	β-oxidation of caffeic acid
1	3-dehydro-shikimaate dehydrogenase
2	Hydroxylation of protocatechuic acid
3	β-oxidation of 3,4,5 trihydroxy cinnamic acid

Table I. Enzymes in Biosynthetic Pathway of Gallic Acid Shown In Figure II

BIOAVAILABILITY OF GALLIC ACID:

Gallic acid is largely found in free form or as a derivative in several food origins such as nuts, tea, grapes, and sumac (Rhus coriaria L.) and exists in the plant kingdom. [33–35] Other origins include different berries, gallnuts, oak bark, honey, mango, pomegranate, and beverages and other fruits, vegetables. [36–41] Gallic acid is detected in plant tissues in several esters with sugars glycosides, polyols and phenols and ester form and have been reported. [42] Aside from the plant species included the quantity of GA in plant tissues may also get altered due to some surface inducements such as chemical stressors, UV radiation, and microbial infections. In related words, the phenolic formation in grape juices and wines gets influenced by constituents such as grape species, storage, and processing practices. [42] In distinct, red wine has a great content of this phenolic acid. Burns et al. examined some red wines and observed the cumulative phenolic content as 1100 to 3165 mg L1, out of which 120 to 360 mg L1 and 35 to 70 mg L1 are earmarked to the epicatechin gallate and GA derivatives, respectively. [41]

GA content is more eminent in green tea. [41] but the inclusive gallate content of cocoa is determined to be even more eminent than that of green tea or red wine.

Owing to its extensive array of applicability, it is widely used in chemical research and medicine and other industries including cosmetic pharmaceutical, and food industries [43]. Due to the presence of polyphenolic functionality, Gallic acid has high oxygen-derived free radical scavenging activity [44]. By Folin–Ciocalteau assay is also used as a standard for delimiting the phenolic content. Besides this, it is also used in dyes, printing inks, and photography [45]. It inhibits the deterioration and rancidity of fats and oils due to its antioxidant nature. Research on B16F10 melanocyte cells explained that gallic acid repressed melanogenesis, which could make it an additive in cosmetics to subdue pigmentation [46]. It has been proclaimed that gallic acid exhibited antibacterial attributes abreast an extensive assortment of pathogens including Escherichia coli, Klebsiella pneumonia, Staphylococcus aureus, and Pseudomonas aeruginosa, [47]. It is also identified for some curative effects like antimutagenic, antiallergic, anti-inflammatory, and anticarcinogenic [48,49,50]. It can be utilized as an antioxidant to guard human cells against oxidative injury, treat diabetes and albuminuria, and as a remote astringent in states of internal hemorrhage [51]. It was observed to show cytotoxic impacts without wrecking normal cells against cancer cell [52]. Gallic acid therapy was found to modify the metabolism to its natural state in a mice model with nonalcoholic fatty liver disease (NAFLD) [53]. Obesity has been identified to decrease the antioxidant capability by lowering the level of antioxidant enzymes. Research had been done in rats served with high-fat diets (HFD) and gallic acid, to examine the antiobesity outcomes of Gallic acid. It was discerned that level of antioxidant enzymes was extended along with a reduction in weight gain besides the decrease of complexities like dyslipidemia, oxidative stress, and hepatosteatosis [54].

Novel research in rats by Sen et al. revealed that gallic acid occupied antioxidant and antiulcer action. This shielding role against ulcers was associated with the enhanced generation of phlegm that carried glycoproteins which serve to guard the gastric lining [55]. Along with other composites, gallic acid was found to significantly diminish allergen and platelet-activating factor (PAF) effected bronchial hyper-reactivity in guinea pigs [56]. The antioxidant characteristics of polyphenols have been exploited in the interference of fibrillar protein heaps that lead to ailments like Parkinson's disease and Alzheimer's [57]. Gallic acid was affirmed to guard the animal model of Parkinson's disease against neural

impairment due to oxidative tension caused by 6-hydroxydopamine [58].

GALLIC ACID AS ANTI – DIABETIC AGENT

Diabetes mellitus (DM) is one of the dominant public wellness problems and is deemed a chronic metabolic ailment that concerns about 347 million people globally [57]. It is principally delineated by hyperglycemia which emerges from defects in the operation or secretion of insulin. The described traits of DM are polyuria, polydipsia, polyphagia, weight loss, loss of vision, and fatigue. These signs can be moderate or even be absent. [58]. De Oliveira et al. study explains the influence of GA on biochemical and histological parameters and biomarkers of oxidative stress in the kidney and liver of streptozotocin (STZ)- aided diabetic rats. GA introduces a variation in the lipid profile of the handled creatures since it decreases levels of TG, TC, and LDL. In extension to reductions in free radical levels and lipid peroxidation, it increments enzymatic and non-enzymatic cancer inhibition agent protection in these tissues. Their conclusions show that GA might be estimable for the treatment of hepatic and renal complications associated to DM and raise the probability of another application as an analogous approach associated with hypoglycemic medications [25]. Research insinuates that GA and ellagic acid, natural flavonoids, are used as antidiabetic agents. Nair et al. assessed the binding of GA and its dimer, ellagic acid, to glycogen phosphorylase (GP) enzyme, a principal applicant of glucose homeostasis. This dimer is described as a potent inhibitor as correlated to GA. Both these bioactive composites function as competing inhibitors for glucose-1-phosphate and non-competitive for allosteric activator, AMP. For this purpose, ellagic acid is conceivably used as an antihyperglycemic agent [59].

GALLIC ACID AS ANTIOXIDANT AGENT

It is observed that the oxidative damage of biomolecules, incorporated under severe and chronic oxidative stress, is implicated in the pathogenesis of extensive diseases, such as degenerative diseases, cancer, cardiovascular diseases, and metabolic diseases. Hence, it is necessary to know the role of medicines, gallic acid in this shows action in the inhibition of oxidative stress and handling of oxidative damage diseases. Gallic acid has been described to exert both pro-oxidant and antioxidant activities [58]. Interestingly, a phenolic compound like GA was latterly correlated with cell death caused by oxidative stress derived from ROS and mitochondrial dysfunction [25]. The intracellular ROS formation was evaluated using a particular probe and GA enhanced ROS after only 30 minutes of expression in lung cancer cells [59]. These aspects were also proclaimed in two well-established lung carcinoma cell lines A549 and Calu-6 [59]. The levels of a well-known ROS were reduced in the presence of GA from 100 µM to 400 µM like for superoxide ions. [59]. Nevertheless, concentrations up to 50 µM slightly reduced the formation of such ions. Authors advised that GA usually plays a role as a pro-oxidant, but its impact is dependent on the concentration used in the assays, period of incubation, and cell types. As shown in figure Gallic acid played its role by upregulating the expression of antioxidant genes like superoxide dismutase-2(SOD-2), catalase (CAT), and glutathione peroxidase-1(Gpx-1) in dermal cells. This signified that GA shows its antioxidant activity by upregulating the anti-oxidant genes.

GALLIC ACID AS ANTI – INFLAMMATORY AGENT

Inflammation is the preeminent problem of many chronic health ailments, immune-inflammatory impact is a shielding mechanism to prevent the incipience of contagions induced by a wound or microbial intrusion. Phenolic compounds are the front-line protection of plants like subsequent metabolites. The mechanisms of anti-inflammatory impacts of the phenolic compounds are commonly estimated to derive from their ability to restore antioxidant enzyme activities, eliminate free radicals, and in regulating cytokine-induced inflammation [60]. Gallic Acid, a naturally transpiring polyphenol, uses conceivably medically beneficial anti-inflammatory effects reconciled through the abolition of p65-NF-κB and IL-6/p-STAT3Y705 activation. In gallic acid anti-inflammatory response, one of the potentials given mechanisms includes a decrease of the neutrophilic infiltration in the colon followed by a decreased appearance of CD68+. Also, the pro-inflammatory proteins iNOS and COX-2 expression lessened by inhibiting the expressions of p-STAT3Y705 and restraining the p65-NF-κB-mediated transcriptional activation [61]. The acetylation of p65 regulates the biological behavior of NF-κB, including the activation of the transcription, DNA binding activity, and IκBα assembly. It has been advised that GA hindered the activation of NF-κB-dependent p65 acetylation and the production of inflammatory markers. The low acetylation rate of p65 occurred in a total loss of function of NF-κB, intimating that its acetylation is crucial for the signaling pathway mediated by NF-κB. Therefore, researchers advised that restraint in the scrupulous acetylation of p65 with small molecules

as GA might be considered as a novel class of anti-inflammatory drugs. The low acetylation rate of p65 occurred in a total loss of function of NF-κB, intimating that its acetylation is crucial for the signaling pathway mediated by NF-κB. Gallic acid was reported to inhibit and prevent inflammation, NF-KB and other changes linked to pathology.[24,27,31] As mentioned in figure, it also decreases iNOS, neutrophil's adhesion molecules and production of cyclooxygenase.[27,38] Rong et al noted that gallic acid reduced TGF B1 smad-2-signalling and Interleukin-6 which reduced inflammation in vivo.[39] The inflammation lessened and deposition of collagen increased with enhanced fibroblast cell count and activity promotes the healing process. Thus, gallic acid decreased the inflammatory cell infiltration and cell count in vivo. [40,41]

GALLIC ACID IN WOUND HEALING:

Many constituents available from plant show advantageous effects on physiology of skin via regulating the redox homeostasis. to figure out in what way gallic acid plays its role in wound healing Kirfel G.et al observed its effect on human keratinocytes by growing HaCaT cells which were wounded by scratching and then incubated in the presence of epidermal growth factor. It came into notice that in the presence of GA the wound sites gradually closed and also the extent of wound closure in human keratinocytes decreased.[62] This process of healing involves cell proliferation and migration and the regulation of such cellular processes is done by focal adhesion kinase (FAK) which is a cytoplasmic protein tyrosine kinase.[63] In Drosophila wing and abdomen wound models, c-Jun N-terminal kinase(JNK) is predominantly phosphorylated in the cells adjoining the wound, intimating JNK signaling is claimed for epithelial cells at the wound margin close to the wound.[63,64] The mitogen-activated protein kinase (MAPK) signaling pathway also executes a function in the control of cell migration and wound healing. All this indicated that GA activates FAK, Erk, and JNK, which may be important for GA-mediated wound healing process. It can be elucidated that GA has a role in wound healing which might be the resultant of its anti-oxidant and anti-inflammatory mechanisms. Gallic acid blocks NF-kB, prevent inflammation by upregulating major pro-inflammatory cytokines like IL-6 and TNF-α and blockage of this pathway results in inhibition of inflammation [8,24,27,28]. In addition to the anti-inflammatory effect, gallic acid also enhances collagen I and extracellular matrix synthesis and osteoblast proliferation [41]. The decrease in inflammation and increase in collagen deposition with increased fibroblast cell counts and activity accelerate the healing process, and gallic acid was reported to reduce inflammatory cell infiltration and cell counts in vivo [31,33]. Reduction in inflammation, along with increased fibroblast activity, is the most critical effect of gallic acid contributing to wound healing which is also reported after gallic acid administration in skin wounds in rats [31]. Improved wound healing results in shorter healing period and faster epithelization as Tsala et al. and Upadhyay et al. reported by shortened healing time with increased epithelization rate, fibroblast proliferation, and decreased inflammatory cell infiltration [33,66].

GALLIC ACID IN WOUND HEALING IN HYPERGLUCIDIC CONDITION:

GA also has a positive effect on wound repair in hyperglycemic condition in fibroblasts, the wound healing effect of GA in fibroblasts in either low glycemic or high glycemic conditions was examined. [65] Hyperglycemia inhibited wound repair as it should have, and treatment with GA significantly improved wound healing similar to that of EGF. The wound repair was significantly elevated in mitomycin C-treated cells in a hyperglycemic condition as well, indicating that the improved wound healing by GA in HG condition might not be due to cell proliferation but rather due to accelerated cell migration. These results highly indicate that GA significantly improves wound healing not only in keratinocytes but also in fibroblasts.

The effect of gallic acid was evident even in diabetic conditions [41]. Thanikachalam et al. revealed that gallic acid increased cell migration from wound borders and promoted wound healing both in vitro and in vivo [43]. Furthermore, Pellenz et al. showed decreased apoptosis in the keratinocyte and fibroblast cells after gallic acid treatment [44]. In terms of matrix degradation, Wang et al. reported that gallic acid down-regulated MMP-1 and -3 expressions while upregulating tissue inhibitors with the inhibition of AKT and ERK1/2 signaling [45]. Increased angiogenesis, collagen deposition, and regeneration were also reported after gallic acid administration [48]. Luo et al. also reported faster wound contraction, epithelialization, increased hydroxyproline content, high tensile strength, collagen deposition, and vascularization with decreased IL-6, NO, and TNF-α levels [42].

GA accelerated cell migration of keratinocytes and fibroblasts in both normal and hyperglycemic conditions. 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. Therefore, this demonstrate that GA might be a viable wound healing agent and a potential intervention to treat wounds resulting from metabolic complications.

CONCLUSION:

The literature survey represented that Gallic acid belonging to the group of phenolic acids which are most important antioxidants. Gallic acid which is a flavonoid is an important agent which has diverse pharmacological spectrum. Its activity has been reported for various properties like antioxidant, anti-inflammatory, anti-diabetic, anti-tumor, anti-infection along with its prominent role in wound healing. The findings of its activity are in line with its antioxidant and anti-inflammatory property. Gallic acid activates FAk, Erk and JNK which is essential for GA-mediated wound healing process. The importance lies in the fact that it not only promotes healing in normal conditions but also in hyper-glycemic conditions.

REFERENCES:

1. Vinay Kumar, Abul Abbas, Nelson Fausto, Robins and Cotran Pathologic Basis of Disease,7thEdn, Saunders an imprint of Elsevier, 88-89, (2004)
2. Harsh Mohan, Textbook of Pathology ,5thEdn, Jaypee Brothers medical publishers Ltd, 171-176, (2015)
3. Han G., Ceilley R., Chronic Wound Healing: A Review of Current Management and Treatments. Advances in therapy, 34 (3):599-610, (2017)
4. S. Percival, K. Cutting, Microbiology of wounds, CRC Press, 220-225, (2010)
5. Ochs R.F., Horn S.D., van Rijswijk L., Pietsch C., Smout R.J., Comparison of air-fluidized therapy with other support surfaces used to treat pressure ulcers in nursing home residents. Ostomy/wound management, 51 (2):38-68, (2005)
6. McInnes E., Jammali-Blasi A., Bell-Syer S.E., Dumville J.C., Middleton V., Cullum N., Support surfaces for pressure ulcer prevention. The Cochrane database of systematic reviews, (9):CD001735, (2015)
7. Giftson J.S., Jayanthi S., Nalini N., Chemopreventive efficacy of gallic acid, an antioxidant and anticarcinogenic polyphenol, against 1,2-dimethyl hydrazine induced rat colon carcinogenesis. Investigational new drugs, 28 (3):251-259, (2010)
8. Ravikanth V, Singh R.P, Zhengjie L, Thompson J.A, Agarwal, Agarwal C, Fractionation of grape seed extract and identification of gallic acid as one of the major active constituents causing growth inhibition and apoptotic death of DU145 human prostate carcinoma cells. Carcinogenesis, 27(7):1445-1453, (2006)
9. BhadoriyaU, Sharma P, Solanki S.S, In Vitro Free Radical Scavenging Activity of Gallic Acid Isolated from Caesalpinia Decapetala Wood, Asian Pacific Journal of Tropical Disease,2 (2): S833-S836, (2012)
10. Tse, W.P., Cheng, C.H., Che, C.T., Zhao, M., Lin, Z.X., Induction of apoptosis underlies the Radix Rubiae-mediated anti-proliferative action on human epidermal keratinocytes: implications for psoriasis treatment, Int J Mol Med, 20(5):663-672, (2007)
11. Korkina, L.G., Mikhal'chik, E., Suprun, M.V., Pastore, S., Dal Toso, R., Molecular mechanisms underlying wound healing and anti-inflammatory properties of naturally occurring biotechnologically produced phenylpropanoid glycosides, Cell Mol Biol (Noisy-le-grand), 53(5):84-91, (2007)
12. Doan, K.V., Ko, C.M., Kinyua, A.W., Yang, D.J., Choi, Y.H., Oh, I.Y., Nguyen, N.M., Ko, A., Choi, J.W., Jeong, Y., Jung, M.H., Cho, W.G., Xu, S., Park, K.S., Park, W.J., Choi, S.Y., Kim, H.S., Moh, S.H., Kim, K.W., Gallic acid regulates body weight and glucose homeostasis through AMPK activation, Endocrinology, 156(1):157-168, (2015)
13. Latha, R.C., Daisy, P., Insulin-secretagogue, antihyperlipidemic and other protective effects of gallic acid isolated from Terminalia bellericaRoxb. in streptozotocin-induced diabetic rats, Chem Biol Interact, 189(1-2):112-118, (2011)
14. Khan N. S, Ahmad A, Hadi S.M, Antioxidant, pro-oxidant properties of tannic acid and its binding to DNA.Chemico-Biological Interactions,125 (3):177-189, (2000)
15. Kim D.O., Lee K.W., Lee H.J., Lee C.Y., Vitamin C equivalent antioxidant capacity (VCEAC) of phenolic phytochemicals. Journal of agricultural and food chemistry, 50 (13):3713-3717, (2002)
16. Abdelwahed, A., Bouhlel, I., Skandrani, I., Valenti, K., Kadri, M., Guiraud.P, Study of antimutagenic and antioxidant activities of gallic acid and 1,2,3,4,6-pentagalloylglucose from Pistacia lentiscus. Confirmation by microarray expression profiling, Chem Biol Interact, 165(1):1-13, (2007)
17. Kim Y.J., Antimelanogenic and antioxidant properties of gallic acid. Biological & pharmaceutical bulletin, 30 (6):1052-1055, (2007)
18. Priscilla D.H., Prince P.S., Cardioprotective effect of gallic acid on cardiac troponin-T, cardiac marker enzymes, lipid peroxidation
19. products and antioxidants in experimentally induced myocardial infarction in Wistar rats. Chemico-biological interactions, 179 (2-3):118-124, (2009)
20. Giftson J.S., Jayanthi S., Nalini N., Chemopreventive efficacy of gallic acid, an antioxidant and anticarcinogenic polyphenol, against 1,2-dimethyl hydrazine induced rat colon carcinogenesis. Investigational new drugs, 28 (3):251-259, (2010)
21. Ravikanth V, Singh R.P, Zhengjie L, Thompson J.A, AgarwalR, Agarwal C, Fractionation of grape seed extract and identification of gallic acid as one of the major active constituents causing growth inhibition and apoptotic death of DU145 human prostate carcinoma cells. Carcinogenesis, 27(7):1445-1453, (2006)
22. Chia Y.C., Rajbanshi R., Calhoun C., Chiu R.H., Anti-neoplastic effects of gallic acid, a major component of

Toona sinensis leaf extract, on oral squamous carcinoma cells. Molecules (Basel, Switzerland), 15 (11):8377-8389, (2010)
23. BhadoriyaU, Sharma P, Solanki S.S, In Vitro Free Radical Scavenging Activity of Gallic Acid Isolated from Caesalpinia Decapetala Wood, Asian Pacific Journal of Tropical Disease,2 (2): S833-S836, (2012)
24. Palafox-Carlos, H., Gil-Chávez, J., Sotelo-Mundo, R.R., Namiesnik, J., Gorinstein, S. and González-Aguilar, G.A. Antioxidant Interactions between Major Phenolic Compounds Found in "Ataulfo" Mango Pulp: Chlorogenic, Gallic, Protocatechuic and Vanillic Acids. Molecules, 17:12657-12664. (2012)
25. Avila, J & Rodrigo-Garcia, Joaquin & Aguilar, Gustavo & De la Rosa, Laura, The Antidiabetic Mechanisms of Polyphenols Related to Increased Glucagon-Like Peptide-1 (GLP1) and Insulin Signalling. Molecules, 22:903, (2017)
26. Inoue M, Sakaguchi N, Isuzugawa K, Tani H, Ogihara Y, Role of Reactive Oxygen Species in Gallic Acid-Induced Apoptosis. Biological and Pharmaceutical Bulletin, 23 (10):1153-1157, (2000)
27. Sohi, K. K., Mittal, N., Hundal, M. K., and Khanduja, K. L., Gallic acid, an antioxidant, exhibits antiapoptotic potential in normal human lymphocytes: A Bcl-2 independent mechanism. J. Nutr. Sci. Vitaminol., 49:221-227 (2003)
28. Saeki K, Yuo A, Isemura M, Abe II, Seki T and Noguchi H, Apoptosis inducing activity of lipid derivatives of gallic acid. Biol Pharm Bull 23: 1391-1394, (2000)
29. Strlic M., Radovic T., Kolar J., Pihlar B., Anti- and prooxidativeproperties of gallic acid in fenton-type systems. Journal of agricultural and food chemistry, 50 (22):6313-6317, (2002)
30. Saxena H.O., Faridi U., Srivastava S., Kumar J.K., Darokar M.P., Luqman S., et al, Gallic acid-based indanone derivatives as anticancer agents. Bioorganic & medicinal chemistry letters, 18 (14):3914-3918, (2008)
31. Damiani E, Bacchetti T, Padella L, Tiano L, Carloni P, Antioxidant activity of different white teas: Comparison of hot and cold tea infusions. Journal of Food Composition and Analysis,33: 59-66 (2014)
32. Zhao J., Khan I.A., Fronczek F.R., Gallic Acid. Acta crystallographic. Section E, Structure reports online, 67 (Pt 2): o316-7, (2011)
33. Saijo R, Pathway of gallic acid biosynthesis and Its esterification with catechins in young Tea shoots. Agricultural and Biological Chemistry, 47(3): 455-460, (1983)
34. Samanidou, V., Tsagiannidis, A. and Sarakatsianos, I., Simultaneous determination of polyphenols and major purine alkaloids in Greek *Sideritis* species, herbal extracts, green tea, black tea, and coffee by high-performance liquid chromatography-diode array detection. J. Sep. Science, 35: 608-615, (2012)
35. Schmitzer V., Slatnar A., Veberic R., Stampar F., Solar A., Roasting affects phenolic composition and antioxidative activity of hazelnuts (Corylus avellana L.). Journal of food science, 76 (1): S14-9, (2011)
36. Shahrzad S., Aoyagi K., Winter A., Koyama A., Bitsch I., Pharmacokinetics of gallic acid and its relative bioavailability from tea in healthy humans. The Journal of nutrition, 131 (4):1207-1210, (2001)
37. Agbagwa O. E., Otokunefor K., Therapeutic Potential of Commercial Honey: Antioxidant Activity. American Journal of Microbiological Research, 6(3):88-93, (2018)
38. Ma J., Luo X.D., Protiva P., Yang H., Ma C., Basile M.J., et al, Bioactive novel polyphenols from the fruit of Manilkara zapota (Sapodilla). Journal of natural products, 66 (7):983-986, (2003)
39. Tako E., Beebe S.E., Reed S., Hart J.J., Glahn R.P., Polyphenolic compounds appear to limit the nutritional benefit of biofortified higher iron black bean (Phaseolus vulgaris L.). Nutrition journal, 13:28, (2014)
40. Yuan Y, Song Y, Jing W, Wang Y, Yang X and Liua D, Simultaneous determination of caffeine, gallic acid, theanine, (-) epigallocatechin and (-) epigallocatechin-3-gallate in green tea using quantitative ^{1}H-NMR spectroscopy. Analytical Methods ,6 (3): 907-914, (2014)
41. Li J., He X., Li M., Zhao W., Liu L., Kong X., Chemical fingerprint and quantitative analysis for quality control of polyphenols extracted from pomegranate peel by HPLC. Food chemistry, 176:7-11, (2015)
42. Bharti Badhani, Neha Sharma and Rita Kakkar*, Gallic acid: A versatile antioxidant with promising therapeutic and industrial applications. Royal Society of Chemistry Advances**.**, 5:27540-27557, (2015)
43. Ough C.S, Amerine M.A, Methods for analysis of musts and wines. A Wiley-Interscience publication, 1999
44. Brewer, M., Natural Antioxidants: Sources, Compounds, Mechanisms of Action, and Potential Applications. Comprehensive Reviews in Food Science and Food Safety, 10: 221-247, (2011)
45. Locatelli C., Filippin-Monteiro F.B., Creczynski-Pasa T.B., Alkyl esters of gallic acid as anticancer agents: a review. European journal of medicinal chemistry, 60:233-239, (2013)
46. Saeed, N., Khan, M.R. & Shabbir, M. Antioxidant activity, total phenolic and total flavonoid contents of whole plant extracts *Torilisleptophylla* L. *BMC Complement Altern Med* 12**,** 221 (2012).
47. Su T.R., Lin J.J., Tsai C.C., Huang T.K., Yang Z.Y., Wu M.O., et al, Inhibition of melanogenesis by gallic acid: possible involvement of the PI3K/Akt, MEK/ERK and Wnt/β-catenin signalling pathways in B16F10 cells. International journal of molecular sciences, 14 (10):20443-20458, (2013)
48. Vaquero MJ, Alberto MR, de Nadra MC, Antibacterial effect of phenolic compounds from different wines. Food Control 18(2):93–101 (2007)
49. Singleton V.L., Naturally occurring food toxicants: phenolic substances of plant origin common in foods. Advances in food research, 27:149-242, (1981)
50. Gali H.U., Perchellet E.M., Perchellet J.P., Inhibition of tumor promoter-induced ornithine decarboxylase activity by tannic acid and other polyphenols in mouse epidermis in vivo. Cancer research, 51 (11):2820-2825, (1991)

51. Gali H.U., Perchellet E.M., Klish D.S., Johnson J.M., Perchellet J.P., Hydrolysable tannins: potent inhibitors of hydroperoxide production and tumour promotion in mouse skin treated with 12-O-tetradecanoylphorbol-13-acetate in vivo. International journal of cancer, 51 (3):425-432, (1992)
52. Abbasi S, Daneshfar A, Hamdghadareh S, Farmany A. Quantification of sub-nanomolar levels of gallic acid by adsorptive stripping voltammetry. International journal of electrochemical science ,6(10): 4843–4852 (2011)
53. Choubey S., Varughese L.R., Kumar V., Beniwal V., Medicinal importance of gallic acid and its ester derivatives: a patent review. Pharmaceutical patent analyst, 4 (4):305-315, (2015)
54. Chao J., Huo T.I., Cheng H.Y., Tsai J.C., Liao J.W., Lee M.S., et al, Gallic acid ameliorated impaired glucose and lipid homeostasis in high fat diet induced NAFLD mice. PloS one, 9 (2): e96969, (2014)
55. Hsu C.L., Yen G.C., Effect of gallic acid on high fat diet-induced dyslipidaemia, hepatosteatosis and oxidative stress in rats. The British journal of nutrition, 98 (4):727-735, (2007)
56. Sen S., Asokkumar K., Umamaheswari M., Sivashanmugam A.T., Subhadradevi V., Antiulcerogenic effect of gallic Acid in rats and its effect on oxidant and antioxidant parameters in stomach tissue. Indian journal of pharmaceutical sciences, 75 (2):149-155, (2013)
57. Dorsch W., Bittinger M., Kaas A., Müller A., Kreher B., Wagner H., Antiasthmatic effects of Galphimia glauca, gallic acid, and related compounds prevent allergen- and platelet-activating factor-induced bronchial obstruction as well as bronchial hyperreactivity in guinea pigs. International archives of allergy and immunology, 97 (1):1-7, (1992)
58. Porat Y., Abramowitz A., Gazit E., Inhibition of amyloid fibril formation by polyphenols: structural similarity and aromatic interactions as a common inhibition mechanism. Chemical biology & drug design, 67 (1):27-37, (2006)
59. Mansouri M.T., Farbood Y., Sameri M.J., Sarkaki A., Naghizadeh B., Rafeirad M., Neuroprotective effects of oral gallic acid against oxidative stress induced by 6-hydroxydopamine in rats. Food chemistry, 138 (2-3):1028-1033, (2013)
60. You B.R., Park W.H., Gallic acid-induced lung cancer cell death is related to glutathione depletion as well as reactive oxygen species increase. Toxicology in vitro: an international journal published in association with BIBRA, 24 (5):1356-1362, (2010)
61. Zhang Q., Yang H., Wang J., Li A., Zhang W., Cui X., et al, Effect of green tea on reward learning in healthy individuals: a randomized, double-blind, placebo-controlled pilot study. Nutrition journal, 12:84, (2013)
62. Zhao Y., Raichle M.E., Wen J., Benzinger T.L., Fagan A.M., Hassenstab J., et al, In vivo detection of microstructural correlates of brain pathology in preclinical and early Alzheimer Disease with magnetic resonance imaging. NeuroImage, 148:296-304, (2017)
63. Kirfel G., Herzog V., Migration of epidermal keratinocytes: mechanisms, regulation, and biological significance. Protoplasm, 223 (2-4):67-78, (2004)
64. Mitra S.K., Hanson D.A., Schlaepfer D.D., Focal adhesion kinase: in command and control of cell motility. Nature reviews. Molecular cell biology, 6 (1):56-68, (2005)
65. Bosch M., Serras F., Martín-Blanco E., Baguñà J., JNK signalling pathway required for wound healing in regenerating Drosophila wing imaginal discs. Developmental biology, 280 (1):73-86, (2005)
66. Yang D.J., Moh S.H., Son D.H., You S., Kinyua A.W., Ko C.M., et al, Gallic Acid Promotes Wound Healing in Normal and Hyperglycaemic Conditions. Molecules (Basel, Switzerland), 21 (7): E899, (2016)
67. Sawa T., Nakao M., Akaike T., Ono K., Maeda H., Alkyl peroxyl radical-scavenging activity of various flavonoids and other phenolic compounds: implications for the anti-tumour-promoter effect of vegetables. Journal of agricultural and food chemistry, 47 (2):397-402, (1999)