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# Pharmacological Evaluation of Epigallocatechin Gallate of Green Tea as Wound Healing Agent

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**ABSTRACT**

Green tea is characterized by the high content of polyphenols, which is produced from the tea plant Camellia sinensis. Epigallocatechin gallate (EGCG) is regarded as the most abundant compound in tea leaves with excellent bioactivities, such as antioxidant/free radical scavenging, anti-inflammatory and antimicrobial properties. However, the clinical application of EGCG is restricted by its low bioavailability, since EGCG is unstable under the alkalescent condition of the intestinal track and circulatory system. It was reported that a single injection of EGCG hardly accelerated the healing process of the wound on the back of rats. The potential application of EGCG to skin wound treatment has been investigated, and some positive results in vitro and in vivo have been achieved. The effects of EGCG on wound healing are associated with the application form and the dosage of EGCG, study models and treatment methods.

***Keywords:*** *Epigallocatechin Gallate; wound healing; antioxidant; anti-inflammation; angiogenesis.*

## 1. INTRODUCTION

The immense potential of medicinal plants for the management and treatment of wounds was reported by various scientists. Many researchers are now concentrated on identification of active constituents of various wound healing plants. The phytochemical constituents are responsible for the physiological activity of medicinal plants. These constituents include various alkaloids, essential oils, flavonoids, tannins, terpenoids, saponins, and phenolic compounds. There are several reports that the wound healing activity is promoted by them Epigallocatechin gallate (EGCG) is associated with various health benefits. In this review, the effects of EGCG and its wound dressings on skin for wound healing is described. The beneficial effects of EGCG and its wound dressings at different stages of skin wound healing (hemostasis, inflammation, proliferation and tissue remodeling) are based on the underlying mechanisms of antioxidant, anti-inflammatory, antimicrobial, angiogenesis and antifibrotic properties. This expatiates on the rationale of using EGCG to promote skin wound healing and prevent scar formation, which provides a future clinical application direction of EGCG. Various mechanisms can achieve the wound healing properties of EGCG, including targeting Notch, inhibiting nuclear factor-kappa B (NF-κB) transcription, inhibiting (NF-κB) protein factors, IL-8 production, LPS-induced inflammation, nitric oxide formation, ROS enzymes, and the activation of SOD. Hence, ECGC is an intriguing component to be utilised in tissue engineering.[1,2]

## 2. POTENTIAL OF WOUND HEALING OF EGCG

EGCG inhibits the signalling cascade of PDGF and EGF via binding to their receptors during the inflammatory phase in a perpetual manner. Furthermore, EGCG suppresses the expression of the EGF receptor, interrupting the epithelialisation process. In the inflammation phase, inflammatory immune cells of mast cells, neutrophils, and macrophage- mediated free radicals, cytokines, and growth factors are produced. Meanwhile, the eleva- tion of micro vascularity transports immune cells, oxygen, and nutrients to the wound site as macrophages yield PDGF, fibroblast growth factors, TGF-β1, and vascular endothelial growth factor, with EGCG continuously suppressing the PDGF receptor. Additionally, EGCG suppresses the IL-8 production, hence diminishing neutrophil aggregation that leads to the inhibition of the inflammatory response and the formation of ROS enzymes such as cyclooxygenase, lipoxygenase, and xanthine oxidase, affecting nitric oxide production via the nitric oxide synthase interface. Moreover, EGCG can also stimulate free radical detoxification enzymes, which lead to a rapid wound healing process. EGCG's functionality as an antioxidant is via the inhibition of nitric oxide production, which suppresses free radical production and balances the wound environment. Remarkably, EGCG also plays a vital

role in shielding the endothelial cells in the vascular system .3-5

## 3. MECHANISMS UNDERLYING THE BENEFICIAL EFFECTS OF EGCG ON SKIN WOUND HEALING

### *3.1. Antioxidant Effect*

Reactive oxygen species (ROS) exert adverse effects on cells and tissues. Generally, low ROS levels are conducive to the activation of cell signaling pathways and angiogenesis, whereas high ROS levels induce oxidative stress and compromise tissue repair, leading to chronic nonhealing wounds accompanied by inflammation. Abundant phytonutrients, also known as natural antioxidants/free radical scavengers, are able to protect tissues from oxidative damage. The antioxidant effect of EGCG as a bioactive component during skin wound healing has been testified in both cell and animal studies. $H_2O_2$, UV radiation and chemical reagents, such as Rosup agent, can be used to induce the oxidative stress of skin cells. In a $H_2O_2$-induced human dermal fibroblast injury, EGCG exerted antioxidant ability by enhancing the activities of superoxide dismutase(SOD) and plasma glutathione peroxidase (GSH-Px) while decreasing the malonaldehyde (MDA) level. The EGCG released from polycaprolactone/gelatin nanofibers scavenged the toxic ROS species produced by the human fetal foreskin fibroblasts as exposed to either H2O2 or UV radiation and also reduced the oxidative damage to the growth of cells In the wound tissues of animal models, the enzymes responsible for cytoprotection against oxidative stress are important parameters to evaluate the antioxidant effect of EGCG and its wound dressings in addition to ROS scavenging activity.[6-9]

### *3.2. Oxidative Stress in Chronic Wounds*

The intricate equilibrium of ROS and their pro-oxidants are crucial in wound healing as ROS is essential to initiate wound repair. Lipid peroxidation, protein, and DNA alteration mediated oxidative stress cause augmented cell apoptosis leading to wound healing impairment. Physiologically, neutrophils and macrophage-mediated NADPH oxidases (NOX) generate low levels of ROS, which are responsible for respiratory ruptures all through phagocytosis of the inflammatory phase. On the contrary, in chronic wound conditions, NOX activation is intensified, leading to excessive ROS production and thus hastening the inflammatory phase and oxidative stress cellular damage.[10-12]

ROS is a small oxygen-derived molecule mainly produced by the respiratory chain in the mitochondria. They are oxidising agents and significant contributors to cell damage , but they also have beneficial roles in preparing regular wound healing responses . Therefore, a suitable balance between low and high levels of ROS is essential. Low levels of ROS are beneficial in protecting tissues against infection and stimulating effective wound healing. However, when in excess, ROS produce oxidative stress leading to cell damage and a proinflammatory status. [13,14]

There are two types of cutaneous antioxidants: enzymatic and nonenzymatic. Enzymatic antioxidants are endogenic molecules that are originated from the mechanism of oxidative cells, catalase, superoxide dismutase, and glutathione peroxidase, whereas non-enzymatic antioxidants are equally endogenic and exogenic, and are commonly attained from phytoconstituents classified under polyphenols and carotenoids . Polyphenols and carotenoids are widely used in wound healing management for their antiinflammatory, antibacterial, and antioxidant properties . Furthermore, polyphenols and carotenoids' ability to sustain inflammatory signalling have shed light on new chronic wound healing therapies. Both polyphenols and carotenoids have also been proven to play a vital part in wound healing phases including inflammation, proliferation, and remodelling.[15,16]

### *3.3. AntiInflammatory Effect*

Inflammation plays an important role in fighting pathogens and skin wound healing. Different cell lines are used to establish inflammatory models, including keratinocytes , macrophages , endothelial cells and muscle cells, which are stimulated by lipopolysaccharides (LPS) or TNFα . Clearly, EGCG in the native form or in wound dressings exerted inhibition on the generation of certain proinflammatory cytokines released to the supernatants of cells, such as TNFα, IL-1β and IL-8, or downregulated the corresponding gene expressions in cells .[17,18]

The proinflammatory effects of certain cytokines (e.g., TNFα and IL-1β) are associated with their abilities to stimulate NF-κB activation. EGCG reduced inflammation in acne by suppressing the NF-κB pathway. [19,20]

### *3.4. Antimicrobial Effect*

An infection can retard the wound healing process. Diminishing bacterial infection is an effective route to accelerate healing. Pseudomonas aeruginosa, Staphylococcus aureus and Escherichia coli are the common bacteria present in the wound area, which cause skin infections more frequently in the patients who have hypoimmunity . Most chronic wounds in humans are involved with the formation of bacterial biofilms. Staphylococcus aureus and Pseudomonas aeruginosa are able to form the biofilms that limit the penetration of antimicrobial therapeutics . Tea extract containing abundant EGCG inhibits the growth of bacteria via various ways, including disrupting cell membranes through interacting with surface proteins, decomposing essential metabolites, inhibiting relevant enzyme, inducing ROS stress, changing cellwall structure, detaching cytoplasm. [21-24]

### *3.5. Antifibrotic Effect*

Fibrosis is related to abnormal repair in response to chronic tissue damage. It is characterized by an increase in fibrous connective tissues in the dermis or subcutis due to the excessive proliferation of fibroblasts and the formation of collagen fibers. Fibroblasts are mesenchymal cells that play important roles in the fibrosis process. Fibroblasts are related to ECM accumulation and inflammation, contributing to fibrosis pathogenesis. A keloid is a common fibroproliferative disorder related with an abnormal wound healing process. Abnormal collagen synthesis leads to an imbalance in the metabolism of ECM. EGCG greatly inhibited the production of type I collagen in the fibroblasts co-cultured with mast cells.[25-27]

The antifibrotic effect of EGCG was also investigated using the model of human-derived keloid fibroblasts transplanted onto nude mice, and the productions of collagen and keloids were reduced under EGCG treatment. EGCG suppresses the pathological characteristics of keloids through inhibiting the STAT3 signaling pathway. The PI3K/AKT signaling pathway and the TGF-β signaling pathway play important roles in fibrosis, however, no relevant regulatory effect of EGCG has been reported yet.[28-30]

## 4. METHODOLOGY

### *Melting point determination*

The melting point was determined using melting point apparatus. Epigallocatechin gallate was filled in a glass capillary whose one end was sealed on flame. The capillary containing epigallocatechin gallate was dipped in liquid paraffin bath inside the melting point apparatus. Liquid paraffin was heated till epigallocatechin gallate melted. The temperature at which epigallocatechin gallate melted was recorded.[31,32]

### *Solubility Study*

Solubility of epigallocatechin gallate was determined in different solvents using shake flask method in order to meet official standards.[33,34]

### *Partition coefficients determination:*

The partition coefficients of the epigallocatechin gallate was performed in n octanol/ phosphate buffer (pH 6.8) at room temperature (25 ± $1^0$C). The compounds were separately dissolved in 10 mL n- octanol and 10 mL phosphate buffer was slowly added to it and the octanol- phosphate buffer mixture was shaken for 48 h on a wrist shaker to reach distribution equilibrium. The octanol and phosphate buffer were mutually saturated prior to use. The volumes of each phase were chosen so that the solute concentrations could readily be measured by UV spectrophotometer. The results are reported as logarithm of P values (Log Poct). [35]

### *Anti-elastase and Anti-collagenase assay of EGCG of green tea*

**Anti-elastase assay:**

EGCG of green tea was evaluated for their anti-elastase activity. Porcine Pancreatic Elastase Type IV (PPE, Sigma-E0258, Type IV) was assayed using spectrophotometric method with N-Succ-(Ala)3-p-nitroanilide (SANA) as substrate. The reaction mixture containing, 0.2M Tris-HCl buffer (pH 8.0) (100µl); Porcine Pancreatic Elastase (0.175 mg/ml, 25µl), various concentrations of epigallocatechin gallate (10, 100 and 1000 µg/ml) dissolved in 5% DMSO (25µl) and 0.8 mM SANA substrate (0.8 mM, 25µl), were taken in a 96 well microplates in triplicates. Epigallocatechin gallate for 20 min at 25oC and the reaction was started with the addition of the substrate. Tris-HCl buffer was used instead of the epigallocatechin gallate in control wells. Then the plates were incubated for 20min at 370C. Following incubation, the reaction was stopped by adding Soyabean Trypsin Inhibitor (Sigma-T6522; 0.2mg/ml; 50µl) to arrest the enzyme activity. The release of p-nitro aniline due to proteolysis of N-Succinyl-Ala-Ala-Ala- p-Nitroanilide by Porcine Pancreatic elastase in the presence and absence of inhibitor, was monitored by measuring the optical density at 405nm using a microplate reader iMark BioRad. The percentage inhibition of different concentrations of epigallocatechin gallate on porcine pancreas elastase was calculated in comparison with the control without inhibitor. Blank was taken without the epigallocatechin gallate. [36-38]

### *Anti-collagenase assay*

The effect of epigallocatechin gallate on the activity of collagenase was studied by the method described by Vanwart and Steinbrink. In the assay the change in absorbance due to the cleavage of the substrate, N-[3-(2 Furyl acryloyl)-Leu-Gly-Pro-Ala (FALPGA, ) by enzyme Collagenase (Clostridium histolyticum) was monitored with or without plant extracts at 324 nm. The substrate FALGPA (2mM) and Collagenase enzyme (300µM) were prepared in Tricine buffer (Sigma Catalog No: T0377; 50mM, with 0.4 M NaCl, 1M CaCl2, pH 7.5). Different concentrations of test epigallocatechin gallate (10, 100, 1000 µg/ml; 25µl) taken in a 96 well plate, was incubated with the epigallocatechin gallate (25µl) and buffer (25µl) for 15 minutes before adding substrate to start the reaction. After adding substrate (2mM, 50µl), plate was incubated for 20 minutes at 250 C. The increase in absorbance was measured at 324 nm using a 96 well micro plate reader.[39-41]

***Determination of in vitro antioxidant properties:***

**DPPH (2, 2 diphenyl 2 picryl hydrazyl hydrates) radical scavenging activity:**

The DPPH radical scavenging activity was measured according to the method. In brief, 3ml reaction mixture containing 200 µl of DPPH (100µM in methanol) and 2.8 ml of sample (at various concentrations 20-100µg/ml) in methanol was incubated at 370C for 30 minutes and absorbance of the test mixture was read at 517nm using UV-visible Spectrophotometer. The percentage inhibition of DPPH radical was calculated .[42]

***Evaluation of wound healing activity***

**Excision wound model**

The animals were divided into a total of five groups for each of the plant containing 6 animals in each group. Group I animals was treated with the vehicle control . Group II animals was treated with Framycetin Sulphate IP as standard. Group III, IV and V were treated with epigallocatechin gallate with dose of 100 mg, 300 mg and 900 mg/kg body weight. Animals were anaesthetized with a combination of xylazine (dose of 13 mg/kg b.wt) and ketamin ( dose of 87 mg/kg b.wt) by intraperitoneal route (i/p) prior to the creation of the wounds. The animals were fasted overnight without being taken out the water supplement. The rats are inflicted with excision wounds . The dorsal fur of the animals was shaved and the area of the wound to be created was marked. A full thickness of the excision wound of circular area = 500 mm2 and 0.2 cm depth was created aseptically along the markings using toothed forceps, a surgical blade and pointed scissors. The entire wound was left open . The experiment was kept for a total of 12 days. For this model, wound closure rate and epithelization periods were taken as the standard parameters to evaluate the healing ability of the respective plants. The wound closure rate was assessed by tracing the wound on days 0, 4, 8, 12 post-wounding using transparency papers and a permanent marker. The wound areas ($mm^2$) were measured by using a sq. mm graph paper. Epithelisation period was recorded as the number of days required to falling of scar without any residual raw wound. The results were recorded as wound area ($mm^2$) post wounding day and period of epithelialisation in day(s) and values were expressed as Mean ± SEM.[43]

## 5. RESULTS

***Melting point***

The melting point was determined using melting point apparatus which was found 224 $^0$C.

***Solubility studies***

Solubility tests were conducted using a range of solvents that are frequently utilized in pharmaceutical formulations, including water, ethanol, methanol, acetone, dimethyl sulfoxide (DMSO), and propylene glycol. These solvents were selected to encompass a wide range of polarity, which impacts the solubility of the active pharmaceutical ingredients (APIs).

**Table 1. Solubility of EGCG in various solvents (mg/ml)**

| **Solvent** | **EGCG Solubility (mg/mL)** |
|---|---|
| Water | 1.2 |
| Ethanol | 10.0 |
| Methanol | 12.5 |
| Acetone | 3.5 |
| DMSO | 50.0 |
| Propylene Glycol | 8.0 |

***Partition coefficient of EGCG***

The partition coefficients of EGCG was performed in n octanol/ phosphate buffer (pH 6.8) at room temperature (25 ± 1$^0$C) which was found LogP= 2.08

***Anti-elastase assay***

The anti-elastase activity of EGCG of green tea at different concentrations (10,100 and 1000µg/ml) were evaluated for their effect on the activity of porcine pancreas elastase. The percentage inhibition of EGCG was expressed as Mean±SD. The concentration of EGCG which showed 50% of elastase inhibition ($IC_{50}$) was calculated for EGCG using regression analysis.The present study revealed that EGCG possessed inhibitory activity towards porcine pancreatic elastase and percentage inhibition was increased with the increase in the concentration of EGCG. The concentration of EGCG of green tea exerting 50% inhibition towards porcine pancreas elastase ($IC_{50}$) were found to be 408.7 (µg/ml)

***Anti-collagenase assay***

Collagenase is a major matrix metalloprotease. Its controlled expression is essential for the normal wound healing. The collagenase inhibitors can be used as therapeutic agents to regulate the uncontrolled activity of collagenase in chronic wounds. The collagenase inhibitory effect of EGCG of green tea was evaluated using FALGPA hydrolysis. The percentage inhibition of collagenase was concentration dependent for EGCG under study. $IC_{50}$ of Epigallocatechin gallate was found to be 32.97 µg/ml. It is presumed that these inhibitory effects on MMP activities are due to the high content of phenolics.

**Table 2: Anti elastase and anti-collagenase activity of Epigallocatechin gallate**

| **Epigallocatechin gallate** | **Concentration (µg/ml)** | **Percentage inhibition of Elastase % (Mean ± SD)** | **Percentage inhibition of Collagenase % (Mean ± SD)** |
|---|---|---|---|
| Epigallocatechin gallate | 10 | 18.92 ± 0.12 | 47.51 ± 0.73 |
| | 100 | 59.45 ± 2.0 | 76.14 ± 1.9 |
| | 1000 | 77.60 ± 3.94 | 80.28 ± 0.42 |

***DPPH free radical scavenging activity (% inhibition)***

The DPPH is a stable free radical with a maximum absorbance at 517 nm and can readily undergo scavenging by an antioxidant. It has been widely used to test the ability of compounds as free radical scavengers by hydrogen donors and to evaluate the antioxidant activity. Antioxidant activities of epigallocatechin gallate assessed against the percent inhibition of DPPH at the concentration range of 20-100 µg/ml, taking Vit. C as reference standard. The highest activity was shown by the epigallocatechin gallate at the highest concentration of 100 µg/ml when compared to Vit C activity.

**Table3: DPPH free radical scavenging activity (% inhibition)**

| **Concentrations (µg/ml)** | **VIT C** | **Epigallocatechin gallate** |
|---|---|---|
| 20 | 42.51±3.21 | 39.24±3.13 |
| 40 | 53.27±2.34 | 46.45±2.51 |
| 60 | 66.35±1.96 | 57.19±2.39 |
| 80 | 70.91±3.21 | 63.37±2.95 |
| 100 | 82.43±2.74 | 76.97±2.61 |

Values are expressed as mean ± sem. $p<0.05$; compared with vit c group

***Effect of epigallocatechin gallate on wound closure rate and epithelialization period for excision wound model:***

The main objective of wound management with epigallocatechin gallate is to heal the injury in the shortest possible period of time. Wound healing property of epigallocatechin gallate was evaluated on excision wound model taking wound closure rate and epithelization periods as the preliminary parameters in consideration. epigallocatechin gallate showed increase in wound contraction rate from day 4 to 12, when compared to the normal control group. Here Framycetin Sulphate IP was taken as the reference drug.

**Table 4: Effect of Epigallocatechin Gallate on wound closure rate and Epithelialization Period**

| Groups | Contracted wound area ($mm^2$) | | | | Epithelialization periods |
|---|---|---|---|---|---|
| | 0 Day | 4th Day | 8th Day | 12th Day | |
| I (control) | 384.50±1.73 | 377.20±2.80 | 359.50±3.02 | 354.50±2.94 | 29.67±1.41 |
| II Framycetin Sulphate IP | 385.00±1.27 | 316.80±2.89 | 166.50±7.14 | 67.67±1.48 | 17.83±1.82 |
| III (100mg/kgp o.) | 381.30±1.02 | 356.80±1.78 | 265.20±3.37 | 117.20±2.59 | 22.33±1.89 |
| IV (300 mg/kg p.o.) | 382.00±1.34 | 340.20±2.12 | 201.20±1.74 | 112.50±1.38 | 20.83±2.12 |
| V (900 mg/kg p.o.) | 385.70±1.36 | 330.00±1.65 | 183.30±2.08 | 106.50±1.61 | 19.17±0.60 |

*Values are expressed as mean ± sem. $p<0.001$ compared with normal control group*

## 6. CONCLUSION

Plants are the storehouse of many pharmacologically active compounds and plant products are potential wound healing agent, largely preferred for their widespread availability, non- toxicity, absence of unwanted side effects and effectiveness as crude preparations. This can be supported by the fact that greater the wound contraction rate better is the efficacy of the medication. If the medicine is more efficient, the wound will close at faster rate. Wound contraction is the process of mobilizing healthy skin surrounding the wound to cover the denuded area and involves complex and orchestrated interaction of cells, extracellular matrix, and cytokines. This centripetal movement of wound margin is believed to be due to the activity of myofibroblast. Since epigallocatechin gallate treatment enhanced wound contraction, it would have either enhanced contractile property of myofibroblasts or increased the number of myofibroblasts recruited into the wound area. Granulation, collagen maturation, and scar formation are some of the many phases of wound healing which run concurrently, but independent of each other. The higher wound contraction rate of the epigallocatechin gallate ointment may be due to either its dose-dependent induction of macrophage cell proliferation. Shorter epithelialization period and faster reduction in wound size could be due to the ability of epigallocatechin gallate to enhance collagen synthesis, induction of cell proliferation, anti-oxidant and antimicrobial activities of bioactive constituents. Another possible reason for enhanced wound healing effect of the plants could be due to their antioxidant, free radical scavenging properties, analgesic and anti-inflammatory activities which would further supported by the results of collagen, protein estimation, oxidative stress and antioxidant evaluation of blood and tissues. Polyphenols and flavonoids (prevent the synthesis of prostaglandins) possess anti- inflammatory properties and have antimicrobial activities.

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