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Evaluation Of Wound Healing Activity Of Epigallocatechin Gallate Of Green Tea

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Abstract:
Epigallocatechin Gallate was evaluated for antioxidant and wound healing activities. Phytochemicals are the secondary metabolites, synthesized in plants to protect themselves. They include alkaloids, cyanogenic glycosides, terpenes, steroids, saponins, flavonoids, tannins, phenylpropanoids, etc. EGCG inhibits the synthesis of free radicals and also reduces inflammation. Furthermore, EGCG suppresses the expression of the EGF receptor, interrupting the epithelialisation process.
Keywords: Flavonoid, Epigallocatechin gallate;; Antioxidant, Inflammation; angiogenesis, Metallo Proteases

1.INTRODUCTION

Wound healing is a natural physiological process that functions normally but still; it causes discomfort when prone to infection. Some diseases such as diabetes, immune compromised conditions, ischemia, conditions including malnourishment, aging, local infection, and local tissue damage due to burns etc, lead to the delay in healing. Wound healing is a complex and dynamic process. The physiological process of wound repair includes four overlapping phases such as the immediate haemostasis phase, inflammatory phase, proliferative phase and remodelling phase. After the injury, the platelets aggregate at the site of the wound and secrete vaso-constrictive substances and stimulate the intrinsic clotting cascade to form a stable haemostatic plug. The fibrin clot acts as a matrix, which triggers cell interactions to perform phagocytosis and helps in haemostasis. These factors can increase vascular permeability to cause inflammation which is mediated through eicosanoids, prostaglandins, nitric oxide and cytokines. Activated macrophages secrete different cytokines, which up-regulate the expression of Matrix Metallo Proteases (MMP) and down-regulate the synthesis of tissue inhibitors of metalloproteinases (TIMPs). The growth factors secreted by inflammatory cells also stimulate the migration of fibroblasts, epithelial cells and vascular endothelial cells towards the wound. As inflammatory phase prolongs, it causes overproduction of reactive oxygen species and oxidative burst.[1,2]

The factors affecting wound healing include local factors like blood supply, aeration, infection radiation, age, nutrition, and immunity. Injury activates cascades of specific chemo attractants like various growth factors and hormones. Certain drugs adversely affect wound healing and some others promote the process. The presence of free radicals can also seriously delay normal healing process by prolonging the inflammatory phase, disrupting normal clotting mechanism, promoting disordered leucocyte function and delaying angiogenesis. A thorough understanding of these factors and their influence on wound healing is essential for developing better therapeutic options for wound treatment.[3]

Regulation of extracellular matrix degradation is crucial in normal tissue remodeling and in certain pathological states. The major MMPs which regulate the remodelling and turnover of extracellular matrix (ECM) are collagenase and elastase. There is a great interest in the discovery of their inhibitors to treat chronic non-healing wounds.[4]

i) Role of elastase and elastase inhibitors in wound healing

Elastases, a serine proteases that can cleave elastins, has a role in keeping flexibility and elasticity of ECM. The increased elastase activity may cause the degradation of elastins, the local extracellular matrix proteins. An excessive and uncontrolled elastase activity has been implicated in chronic

wounds. Therefore, elastase inhibitors can act as potent therapeutic agent to treat chronic, delayed wound.[5]

ii) Role of collagenase and its inhibitors in wound healing:

Collagenases are zinc-dependent endopeptidases capable of digesting ECM proteins like fibrillar and non-fibrillar collagens. Collagenases also play role in tissue morphogenesis, tissue repair, tissue remodeling, angiogenesis and wound healing. Inhibitors of metalloproteinase can regulate wound contraction and extra cellular matrix remodeling, which may be fundamental to wound resolution. Some plant products which act as matrix metalloproteinase inhibitors (MMPIs) have been used as agents promoting cell migration and wound healing.[6]

2.Wound healing agents:

Some of the modern drugs used in wound healing are antibiotics, corticosteroids and non-steroidal anti-inflammatory drugs like ibuprofen, antiplatelets, anticoagulants, vaso-constrictors, pain relievers, immunosuppressants and colchicines. Antibiotics are overused in the treatment of acute and chronic wounds. Although they are helpful to reduce the risk of infection, it does not improve or promote wound healing.. There are some reports that secondary metabolites from plants like alkaloids, flavanoids, terpenes etc., promote wound healing processes.[7]

Although wound healing is a natural phenomenon, an infection to the injured tissue may prolong the inflammatory phase, disordered leukocyte function, delaying angiogenesis and oxidative damage ultimately can seriously delay the healing process. Anti bacterial, anti inflammatory and antioxidant effects of healing agents are regarded as an important requirement for the proper management of wound.[8]

3.Beneficial Effects of EGCG at Different Healing Stages

The skin wound healing process has four sequential and overlapping stages, includ- ing hemostasis, inflammation, proliferation and tissue remodeling, which involves various types of cells (e.g., leukocytes, fibroblasts and keratinocytes) and several factors, such as cytokines, chemokines, growth factors and enzymes. These cells and factors are differentially featured at each wound healing stage . Hemostasis happens very quickly after injury, which is accompanied by clotting. As injury occurs, platelets stick together to seal the break in vessel, followed by coagulation and the formation of a platelet plug. In addition, platelet activation also leads to the activation of the immune system and the transition to the inflammatory phase through the release of cytokines and growth factors, such as transforming growth factor β (TGF-β), EGF, platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) . Hemostatic hydrogel is developed for halting bleeding quickly, and good adhesiveness, self-recovery capacity and antibacterial properties are desired. A hemostatic hydro- gel was prepared by adding self-assembled keratin–EGCG nanoparticles into cellulose hydrogel, which not only improved the physical properties of pure keratin materials but also exhibited good adhesiveness and hemadsorption . As bleeding is controlled, the inflammatory phase starts, which is characterized by the recruitment of neutrophils, macrophages and lymphocytes. [9,10]

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 .[13,14]
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, de- composing essential metabolites, inhibiting relevant enzyme, inducing ROS stress, chang- ing cell-wall structure, detaching cytoplasm, and so on . It was reported that EGCG inhibited the glucose uptake of Escherichia coli through the interaction with an outer membrane porin protein, which resulted in the growth inhibition of Escherichia coli . Thioredoxin and thioredoxin reductase are crucial to bacterial DNA synthesis and defense against oxidative stress . EGCG showed an inhibitory efficacy towards thioredoxin and thioredoxin reductase in Staphylococcus aureus and Escherichia coli, leading to the sup- pressed growth of these pathogens .[15,16]

4.METHODOLOGY:

Solubility Study

Solubility of epigallocatechin gallate was determined in different solvents using shake flask method in order to meet official standards.[17]

Fourier Transform Infra-Red Spectroscopy (FT-IR)

The FT-IR method is particularly useful for identifying organic and inorganic compounds. It can be used to analyse solids, liquids and gases also quantify some components of an unknown mixture. Fourier Transform Infra-Red Spectroscopy (FT-IR) determination of epigallocatechin gallate individually & epigallocatechin gallate in combination with excipients were carried out using (Shimadzu 8400s Japan). The spectra were produced using KBr pellet technique, and reference standard peaks were compared with obtained ones.[18,19]

Determination of in vitro antioxidant properties:

DPPH (2, 2 diphenyl 2 picryl hydrazyl hydrates) radical scavanging acivity

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 . [20,21]

Evaluation of wound healing activity:

iii) 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 rate of 13 mg/kg b.wt) and ketamin (dose rate 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 (mm2) were measured by using a sq. mm graph paper. Epithelisation period was recorded as the number of days

(mm2) post wounding day and period of epithelialisation in day(s) and the values were expressed as Mean ± SEM.[23-25]

Table1: Experimental design for excision and incision wound model

Group	Treatment regime
I	Vehicle Control (Excision / Incision Wound) daily for 12 days
II	(Excision / Incision Wound) + Framycetin Sulphate IP daily for 12 days.
III	(Excision / Incision Wound) + epigallocatechin gallate with dose of 100 mg/kg body weight daily for 12 days.
IV	(Excision / Incision Wound) + epigallocatechin gallate with dose 300mg/kg body weight daily for 12 days.
V	(Excision / Incision Wound) + epigallocatechin gallate with dose 900 mg/kg body weight daily for 12 days.

iv) Incision wound model

Animals were divided into a total of five groups for each of the plant containing six in each group. Group I animals was treated with the vehicle control. Group II animals was treated with the 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 rate of 13 mg/kg b.wt) and ketamin (dose rate of 87 mg/kg b.wt) by intraperitoneal route (i/p) prior to the creation of the wounds. The animals were fasted overnight without taking out the water supplement. A longitudinal paravertebral incision, three centimetres in length was made through the skin and cutaneous muscle on the back . Full aseptic measures were not taken and no local or systemic antimicrobials were used throughout the experiment . After the incision, surgical sutures were applied to the parted skin at intervals of one centimetre using nylon surgical threads and a curved needle. The wounds were left undressed to environment. The sutures were removed on the 10^{th} post wound day and the treatment was continued till 12^{th} day. Breaking strength was measured on the last day of the experiment that is on 12^{th} day by the following standard technique.[26,27]

Measurement of healing

The breaking strength, is the force required to open a healing skin wound, indicates the degree of wound healing. It represents how much the healed tissue resists to breaking under tension and may identify the quality of healing tissue. The instrument used for this parameter is called tensiometer and was designed on the same principle as the thread tester used in the textile industry . It consisted of a 6 x 12 inches board with one post of 4 inch long fixed on each side of the longer ends. The board was placed at the end of a table. A pulley with bearing was mounted on the top of one of the posts. An alligator clamp with 1 cm width, was tied on the tip of the post without pulley by a piece of fishing line (20-lb test monofilament) so that the clamp could reach the middle of the board. Another alligator clamp was tied on a piece of fishing line with a 1 – L polyethylene bottle tied on the other end. Before testing, the animals were anaesthetized a combination of xylazine (dose rate of 13 mg/kg b.wt) and ketamin (dose rate of 87 mg/kg b.wt) by intraperitoneal route (i/p). The sutures of the wound were removed with a pair of scissors. The animal was then placed on a stack of paper towels that could be adjusted so that the wound was on the same level of the tips of the posts. The clamps were then carefully clamped on the skin of the opposite sides of the wound at a distance of 0.5 cm away from the wound. The longer piece of fishing line was placed on the pulley and the position of the board was adjusted so that the polyethylene bottle was freely hanging in the air. Water was added to the polyethylene bottle until the wound began to open up. The amount of water in the polyethylene bottle was weighed and considered as the breaking /tensile strength of the wound. The result was recorded in grams of weight added and the values were expressed as Mean ± SEM. [28-30]

v) Dead space wound model:

Animals were divided into a total of five groups for each of the plant containing 6 in each group. Group I animals served as vehicle control and were administered distilled water p.o. Group II animals were treated with Framycetin Sulphate IP the dose rate of 100 mg/kg body weight. Group III, IV and V were administered hydroethanolic extracts of 100, 300, and 900 mg/kg body weight p.o.. Animals were anaesthetized with a combination of xylazine (dose rate of 13 mg/kg b.wt) and ketamin (dose rate of 87 mg/kg b.wt) by intraperitoneal route (i/p) prior to the creation of the wounds. The experiment was kept for 12 days.[31-33]

Table2 : Experimental design for dead space wound model

Group	Treatment regime
I	(Dead Space Wound) + (Distilled water p.o. daily for 12 days).
II	(Dead Space Wound) + Framycetin Sulphate IP (100 mg/kg p.o daily for 12 days).
III	(Dead Space Wound) + epigallocatechin gallate (100 mg/kg p.o. daily for 12 days).
IV	(Dead Space Wound) + epigallocatechin gallate (300 mg/kg p.o. daily for 12 days).
V	(Dead Space Wound) + epigallocatechin gallate (900 mg/kg p.o. daily for 12 days).

For dead space wound model all the animals were inflicted by implanting two sterilized cotton pellets (50 mg), one on either side in the pectoral region of each rat by the technique and kept for 12 days. On the 12th post-wounding day, the granulation tissue formed on the implanted cotton pellet was carefully removed under anesthesia. The wet weight of the granulation tissue was noted. These granulation tissues were dried at 60°C for 12 hours, and weighed, and the dry weight were recorded. To the dried tissue were added 5 ml 6 N HCl and kept at 110°C for 24 hours. The neutralized acid hydrolysate of the dry tissue was used for the determination of hydroxyproline. The results were recorded as wet weight (mg) of granulation tissue, dry weight (mg) of granulation tissue. [34-38]

Estimation of hydroxyproline:

Ten mg of dried tissue was placed in an ampoule. Two ml of 6N HCl was added and it was incubated at 110^{o}C for 18 hours. The ampoule was broken and a pinch of activated charcoal was added. After 30 minutes, it was filtered and neutralized with sodium carbonate solution (pH 6.5 – 7.0). One ml of neutralized solution was then taken in a test tube along with blank and two ml isopropyl alcohol was added to all the test tubes and mixed well. One ml of Chloramin T (7%) and two ml of Ehrlich's reagent was added to all the test tubes. The sample was then incubated at 60^{o}C in hot water bath for 25 minutes and then allowed to cool. The optical density was measured at 560 nm in spectrophotometer and the amount of hydroxyproline was determined. The quantity of hydroxyproline was expressed in mg/g of dry tissue.[39,40]

3. RESULTS:

Melting point determination

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.

Table3: Solubility of EGCG in various solvents (mg/ml)

Solvent	EGCG Solubility (mg/mL)
Water	1.2
Ethanol	20.0
Methanol	12.5

Acetone	3.5
DMSO	50.0
Propylene Glycol	8.0

FTIR analysis of pure drugs

The FTIR spectrum of Epigallocatechin Gallate (EGCG) exhibits several key peaks that provide insights into its molecular structure. A broad peak at 3400 cm^{-1} is indicative of the numerous hydroxyl groups present in EGCG, showing extensive hydrogen bonding. Peaks around 3050 cm^{-1} confirm the presence of aromatic rings, which are typical for catechins like EGCG. The aliphatic C-H bonds, are reflected in the peaks at 2950 cm^{-1}. Stretching vibrations of the aromatic rings are evident from the peaks at 1650 cm^{-1} and 1500 cm^{-1}, confirming the polyphenolic structure of EGCG. Additionally, the peak at 800 cm^{-1} is indicative of out-of-plane bending vibrations in aromatic C-H bonds, providing further evidence of the presence of aromatic rings .

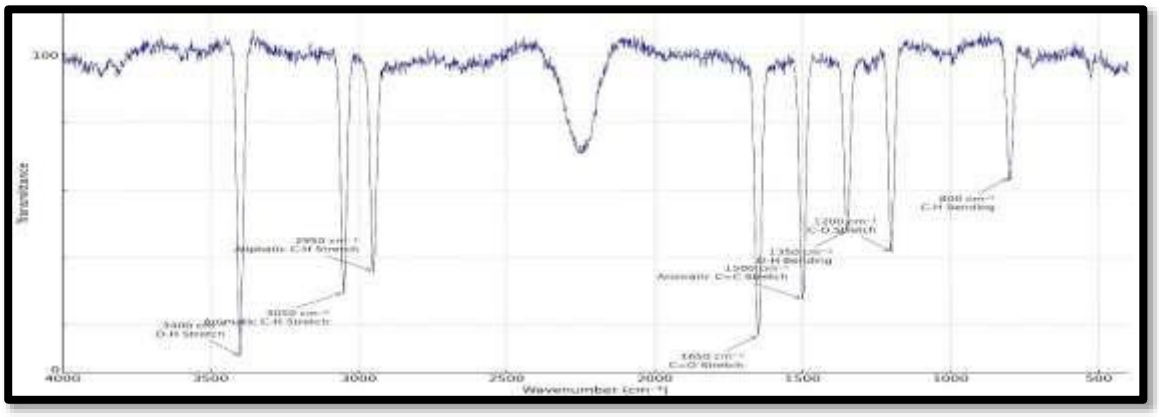

Figure1: Characterization of EGCG by Fourier Transform Infrared (FTIR)

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 ability of compounds as free radical scavengers by hydrogen donors and to evaluate the antioxidant activity.

Table4: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	81.97±2.61

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

Wound healing activity:

vi) Excision wound model

Table 5: Effect of epigallocatechin gallate on wound healing

Groups	Contracted wound area (mm^2)				Epithelialization periods
	0 Day	4th Day	8th Day	12th Day	
(Control)	384.50±1.73	377.20±2.80	359.50±3.02	354.50±2.94	29.67±1.41
Framycetin Sulphate IP	385.00±1.27	316.80±2.89	166.50±7.14	67.67±1.48	17.83±1.82
(100 mg/kgp.o.)	381.30±1.02	356.80±1.78	265.20±3.37	117.20±2.59	22.33±1.89
(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
(900mg/kgp.o.)	385.70±1.36	330.00±1.65	183.30±2.08	105.50±1.61	17.17±0.60

vii) Incision wound model

Table6: Effect of epigallocatechin gallate on breaking strength

Groups	Breaking strength (gm)
(Control)	233.80±1.70
Framycetin Sulphate IP	518.20±2.70
(100 mg/kgp.o.)	321.70±1.84
(300 mg/kg p.o.)	417.30±2.17
(900 mg/kg p.o.)	517.70±1.89

viii) Dead space wound model

Table 7:Effect of Epigallocatechin gallate on wet and dry weight of tissue

Groups	Granulation tissue	
	Wet weight (mg)	Dry weight (mg)
(Control)	350.80 ±1.62	130.20±1.11
Framycetin Sulphate IP	443.30±1.40	211.70±2.01
(100 mg/kgp.o.)	377.80±2.06	143.20±2.65
(300 mg/kg p.o.)	400.50±3.66	171.30±1.86
(900 mg/kg p.o.)	441.20±2.63	209.00±2.03

Effect of Epigallocatechin gallate on hydroxyprolein content of tissue

Table8: Effect of Epigallocatechin gallate on Hydroxyprolein content

Groups	Hydroxyprolein content (mg/g tissue)
(Control)	42.00±1.46
Framycetin Sulphate IP(100mg/kgp.o.)	94.78±1.89
(100 mg/kgp.o.)	62.83±1.64
(300 mg/kg p.o.)	77.83±1.30
(900 mg/kg p.o.)	92.50±0.72

CONCLUSION :

Wound healing is a complex and dynamic process. The physiological process of wound repair includes four overlapping phases such as the immediate haemostasis phase, inflammatory phase, proliferative phase and remodelling phase. After the injury, the platelets aggregate at the site of the wound and secrete vaso-constrictive substances and stimulate the intrinsic clotting cascade to form a stable haemostatic plug. The fibrin clot acts as a matrix, which triggers cell interactions to perform phagocytosis and helps in haemostasis. Green tea is better natural source to improve wound healing on the basis of activities against wound because it leads to improve wound contraction , epithelialization time and breaking strength for wound healing.

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