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Green Tea Epigallocatechin Gallate: A Promising Wound Healing Agent

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Abstract: 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 review 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.

Keywords: Epigallocatechin gallate; wound healing; antioxidant; anti-inflammation; angiogenesis;

i) Introduction:

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. Thus, topical application might be an ideal route to fully achieve the functionalities of EGCG, considering the avoidance of gastrointestinal digestion and less adverse effects on other organs. 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[1].

The skin is the first line of defense against external aggressors. The skin's integrity can be damaged by trauma, tears, cuts or contusions, resulting in skin wounds. Full-thickness wounds that extend beyond the two layers of skin (dermis and epidermis) heal through a granulation process and scar formation. Scars are apparently distinguished from the surrounding skin (e.g., darker colour, stretched, depressed or raised), and may also have various symptoms such as inflammation, erythema, pruritus and pain. In some cases, pathological scars (e.g., hypertrophic and keloid scars) inevitably form, adversely impacting sufferers' life quality. In addition, some diseases such as diabetes impede wound healing process through causing long-term inflammation. Wound healing requires suitable environment to promote healing process, e.g., optimal moisture and redox environ- ment . Plant polyphenols as natural antioxidant agents are cost-effective alternatives to current pharmacologic therapeutics, which have been formulated or fabricated in wound dressings to improve the conditions for wound healing[2].

ii) Wound Healing Phases

The contemporary perception of the wound healing process is centred on the myriad of phases and the involvement of the signalling factors. Wound healing is a complex dynamic process that involves four distinct stages: (1) hemostasis, (2) inflammation, (3) proliferation and migration, and (4) remodelling[3,4].

Phase 1: Hemostasis

Hemostasis is the first challenge of cell repair. During this phase, the platelets are activated, aggregate, and adhere to the damaged and defective squamous endothelial to conserve hemostasis via coagulation. As the phenomena are introduced, fibrin from the fibrinogen forms an embolus that acts as an impermanent extracellular matrix (ECM). The activated cells (platelets, neutrophils, and monocytes) release several proteins and growth factors, for example the transforming growth factor β (TGF-β) and platelet-derived growth factor (PDGF). An alteration of the hemostasis phase was observed in diabetes mellitus (DM) patients by reducing the hyper-coagulation and fibrinolysis[5] .

Phase 2: Inflammation

This phase is characterized by neutrophils, mast cells, and macrophages causing the production of inflammatory cytokines (interleukin 1 (IL-1), tumor necrosis factor-alpha (TNF-α), interleukin 6

(IL-6), and interferon-gamma (IFN-γ)) as well as the growth factors of PDGF, TGF-β, insulin-like growth factor 1 (IGF-1), and epidermal growth factor (EGF) as the main essentials in the wound healing process . Xiao et al. reported the presence of a cytokine imbalance in diabetic patients, which could alter the wound healing process. The modified cytokine distribution pattern led to the reduction of their function, causing the wound to be prone to infection[6] .

Phase 3: Proliferation

The migration and proliferation processes begin in this phase, including wound contraction to angiogenesis action. These actions include restoring oxygen supply; the creation of ECM proteins, vitronectin, and collagen; and the proliferation and migration of fibroblasts and keratinocytes, which are essential for integrity recovery and functionality of the tissues . Hyperglycaemic conditions in DM patients alters the ability of the fibroblasts and keratinocytes to migrate and proliferate. Therefore, the abnormal cells cause the stagnation of angiogenesis, which eventually affects the healing process[7] .

Phase 4: Remodelling

The remodelling phase is in action seven days after the injury and can last up to 6 months. Collagen III is synthesised and replaced with collagen I to restore the ECM. The wound becomes resistant, and the mature scar tissue is formed (granulation tissue). Alteration of the fibroblasts' functionality in diabetics patients causes the deformation of the wound closure. The epithelial wound healing phases are deleterious to the healthy cells' proliferation process, whereby the ROS is crucial for the wound healing activity at the basal level. Various studies have highlighted the significance of a balance in ROS for wound healing because a total suppression of these free radicals and an excessive number of oxidants could impair wound healing. Furthermore, ROS have been implicated as essential cell signalling mediators in wound repair. However, the disproportionate production of these free radicals may be harmful[8,9].

iii) Epigallocatechin Gallate (EGCG)

Camellia sinensis possesses several phenolic compounds consisting of three main groups: flavones, flavanols, and flavonols . Each compound has a unique heterocyclic C-ring, which distinguishes it from its primary structure. The most abundant compound of flavanols in green tea comprises approximately one-third of the dry tea leaf. Flavanols are primarily distributed into four major molecules: epicatechin (EC), epicatechin gallate (ECG), epigallocatechin (EGC), and EGCG.

Chemical Structure of Epigallocatechin Gallate (EGCG)

With a total average of 65% catechin content, EGCG is the main contributor to most of the therapeutic phenomena exerted by green tea . The flavanol catechin EGCG consists of three hydroxyphenyl and hydroxybenzoate moieties with properties of down-regulating inflammatory pathways used in the production of cosmetics and dermatology . In addition, not only is EGCG known for its antioxidant activity, but the green tea catechin is also widely exploited for its anticarcinogenic properties , anti- ageing efficiency in the nutraceutical fields , photo-protection (as a photo carcinogenesis inhibitor), and neuroprotective effect , as it plays an active role against β- amyloid aggregations[10-12].

Structure-activity relationship:

EGCG has three aromatic rings (A, B and D) that are linked together by a pyran ring (C) . The health-promoting function of EGCG is at- tributed to its structure. The antiradical effects of catechins are achieved by oxidation of phenolic groups with atomic or single electron transfer in the B- and D-rings by seniquinone and quinone production. The B- and D-rings are associated with an in- hibition of proteasome activity. This inhibition of proteasome activity is exhibited only by protected analogues. Dehydroxylation of the B- and/or D-ring decreases proteasome-inhibitory activity in vitro. Furthermore, these protected analogues induced apoptotic cell death in a tumour cell-specific man- ner. These data suggest that the B-ring/D-ring peracetate-protected EGCG analogues have great potential to be developed into novel anti-cancer and cancer-preventive agents . The first structure-activity relationships between EGCG and heat-shock protein 90. The re sults obtained suggest that phenolic groups on the A-ring are beneficial for heat-shock protein 90 inhibition, while phenolic substituents on the D-ring are detrimental. Finally, the hydroxyl group at the 5'-position in the B-ring showed 35–104-fold urease inhibition compared with the catechins without the 5'-hydroxyl group and inhibits the growth of Helicobacter pylori in the stomach[13-15] .

Absorption:

In animal experiments, EGCGs show poor bio- availability after oral administration: the absolute bioavailability of EGCG in CF-1 mice and Sprague- Dawley rats was found to be only 26.5 and 1.6%, respectively. Following a single oral administration to Beagle dogs, absorption was rapid with a maximal concentration in plasma at approximately one hour . The low bioavailability of cat- echins may, in part, be caused by first pass effects, which causes drug loss via gastrointestinal metabo- lism and/or extraction by the liver immediately after absorption . The bioavailability for humans is assumed to be in the same range[16] .

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Distribution:

The EGCG levels found in tissues corresponded to 0.0003–0.45% of ingested EGCG . Despite this low absorption, EGCG is rapidly distributed in the body and/or is rapidly converted to metabolites . Indeed, EGCG and its metabolites have been found in serum, plasma, saliva, liver, small intestinal mu- cosa, colon mucosa (faeces), kidneys (urine), pros- tate cells, cancer cells and foetuses and placenta of pregnant rats, they can also penetrate the brain by crossing the blood-brain-barrier[17]

Metabolism:

Catechins are enzymatically metabolised in the human body into many biologically active sub- stances. Methylation, glucuronidation, sulfation and ring-fission biotransformation represent the main metabolic pathways for tea catechins. Methylation. Catechol-O-methyltransferase (COMT) is one human enzyme involved in the catabolism of various catecholic compounds and substances with catechol-like structures. The gen- eral function of the COMT metabolic system is to eliminate potentially active or toxic endogenous and/or exogenous catechol compounds such as di- etary phytochemicals. The following methylated catechin products have been observed in rat liver homogenates: 3'- and 4'-O-methyl-EC, 4'-O-methyl EGC, 4"-O-methyl ECG and EGCG and 4',4"-di-O- methyl-EGCG . Glucuronidation. UGT-catalysed glucuronida- tion is metabolic pathway which increases water- solubility and reduces the toxicity of endogenous and endogenous substances, and, in this way, sup- ports their excretion from the body through urine or faeces. The major product of EGCG glucuronidation is EGCG-4"-O-glucuronide . Sulfation. Sulfation is the transfer of a sulfate group to a amine or alcohol substrate. The reaction is catalysed by sulfotransferase enzymes (SULT) . LC/MS analysis has been used to characterise the EC, EGC and EGCG sulfates in rodent and human samples). Glucosidation. Glucosidation in positions 7 of the A-ring and 4' of the B-ring generates a new EGCG metabolite, 7-O-beta-D-glucopyranosyl-EGCG-4"-O-beta-D-glucupyranoside, which was detected with the analytical LC/ESI–MS2 method . Thiol conjugation. Mono-, bi-, and triglu- tathione conjugates of a (+)-catechin dimer are formed by glutathione from quinone derivatives. Microbial metabolism. The gut microbiota catalyses the metabolic conversion of most poly- phenols into the bioactive compounds which are responsible for the protective effects of tea drinking[18,19].

iv) Mechanisms Underlying the Beneficial Effects of EGCG on Skin Wound Healing

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 in- flammation 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[20] .

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[21] .

Along with their known antioxidant activity, accumulating evidence has shown the antimicrobial potential of EGCG towards Gram-negative bacteria (*E. coli*, *Pseudomonas*, *Salmonella*) and Gram-positive bacteria (*Staphylococcus aureus*, *Bacillus*) with 95% zone in- hibition. This is a crucial discovery as EGCG can be utilised as the gold standard to enhance healing recovery for the management of DFU as chronic wounds mainly face stalled inflammatory phase caused by the overproduction of ROS and biofilm microbial infection. A study conducted by Hassan et al. showed a prevalence of 77.3% monomicro- bial and 22.7% polymicrobial infections, respectively, in diabetic foot ulcers identified as *A. baumanni*, *S. aureus*, *K. pneumonia*, and *S. aureus* . Furthermore, an in vivo study on chronic plantar showed a significant result as the wound healed drastically (>84% ulcer reduction in 10 days) with the application of topical EGCG[22].

Studies that exploit the effectiveness of EGCG towards DFU patients and diabetic induced in vivo models have discovered enhanced neovascularisation, increased collagen, granulation tissue thickness, a rise of capillary density, enhanced angiogenesis, and cellular reorganisation . Hence, the antibacterial and free radical scavenging ability of EGCG suggests effective therapeutic modality for dermal wound management[23].

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 in- jury, 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 H_2O_2 or UV radiation and also reduced the oxidative damage to the growth of cells[24] .

In the wound tissues of animal models, the enzymes responsible for cryoprotection against oxidative stress are important parameters to evaluate the antioxidant effect of EGCG and its wound dressings in addition to ROS scavenging activity. The application of EGCG, α-lipoic acid and gold nanoparticles mixture (AuEA) to the wound area of BALB/c mice significantly elevated the protein level of SOD in the wound tissue, compared with the vehicle control group . Heme oxygenase 1 (HO-1) is a cytoprotective enzyme responding to cellular stress , the induction of which is associated with the efficient wound closure and neovascularization. EGCG significantly elevated the HO-1 protein level compared with the placebo, which showed the great potential for scar therapy applications [25].

Oxidative Stress in Chronic Wounds

The intricate equilibrium of ROS and their pro-oxidants are crucial in wound heal- ing 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[26].

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 pro-inflammatory status. Redox imbalance occurs when the levels of ROS exceed the capacity of endogenous antioxidants to scavenge them, which dysregulates the healing process[27] .

Significance of Antioxidants in Chronic Wound Healing

The oxygen molecule is made up of two electrons with identical spin quantum num- bers, from which ROS are derived. These ROS are chemicals that contain oxygen that is highly reactive compared to the ground state oxygen . Hydroxyl radicals (OH) or superoxide anion radicals (O_2) are ROS species that are generated through the oxygen to water conversion in human cells. When there is an imbalance in the number of free radicals and antioxidants, oxidative stress-related diseases will emerge, leading to complications such as chronic wound healing . Therefore, this imbalance needs to be overcome with radical scavenging molecules.

Antioxidants are molecules that avert oxidative occurrence. These compounds detox- ify ROS to obviate damage effects via the multi-mechanism of free radical scavengers and the inhibition of lipid peroxidation. These mechanisms aid in potentiating the immune mechanism during a particular septic state or even ageing. Antioxidants preserve and stimulate the function of immune cells against homeostatic disturbances . ROS and its corresponding pro-inflammatory cell signalling hold a vital role in wound healing . Exogenic antioxidants are emitted as soon as the overflow of oxidative stress coerces the endogenic antioxidants, permitting inhibition of the inflammatory pathway that leads to the acceleration of wound healing due to the ROS balance . ROS play a vital role in the body's physiological process. However, they bring more harm than good as they are responsible for hastening ageing in organisms and deteriorating food intake. Various studies have shown that these free radicals not only cause ageing and impairment, but are also one of the primary sources of degenerative disease . The most common representation of ROS damage can be seen in chronic wound healing. The free radicals are highly reactive, which help initiate the signalling pathway of the immune response to stimulate redox-mediated intracellular oxidation and bacterial resistance . However, in a substantial amount, the ROS will lead to oxidative stress towards nucleic acids, proteins, and lipids. Oxidative stress may lead to cell apoptosis and systemic injury, which then cause wound-healing impairment. On the other hand, antioxidants have been proven to efficiently restore metabolic and enzymatic repair for cell

recovery. Therefore, antioxidant incorporated biomaterials are in great demand in the tissue engineering field, as the development of high-efficiency novel bioscaffolds with outstanding biocompatibility and capability to sustain intracellular redox balance is anticipated to overcome metabolic disorder induced by stress[28]

Anti-Inflammatory Effect

Inflammation plays an important role in fighting pathogens and skin wound healing. The anti-inflammatory effects of EGCG and its wound dressings. Different cell lines are used to establish inflammatory models, including keratinocytes, macrophages, endothelial cells and muscle cells, which are stimulated by lipopolysac- charides (LPS) or TNFα . Clearly, EGCG in the native form or in wound dressings exerted inhibition on the generation of certain pro-inflammatory cytokines released to the supernatants of cells, such as TNFα, IL-1β and IL-8 , or downregulated the corresponding gene expressions in cells . The anti-inflammatory effect of EGCG was also verified in the animal studies, with reduced levels of IL-1β, TNFα and IL-6 in the wound tissues. In addition, the combinational effects of EGCG and other phytonutrients on the anti-inflammatory activity during skin wound healing were also reported . The pres- ence of EGCG in the mixture of ginkgo biloba leaves exerted cumulative downregulating effect on the secretion of IL-8 in the culture supernatants of normal human keratinocytes stimulated with TNFα .

The nuclear factor kappa B (NF-κB) pathway plays a crucial role in inflammation . NF-κB can be activated under oxidative stress and translocated to the nucleus, inducing the transcription of the downstream genes such as TNFA, CXCL8 and iNOS. The upregulated gene expressions of TNFA, CXCL8 and iNOS lead to increased levels of TNFα, IL-8 and NO, respectively. The pro-inflammatory 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 . The Notch signaling path- way regulates the cell-fate determination during development . EGCG inhibited the LPS-induced inflammation response in mouse macrophages through targeting the Notch signaling pathway . In addition to the verified NF-κB and Notch signal pathways in the skin cells or the wound tissues of animal studies, the roles of inflammation-related signal pathways in skin wound healing, such as mitogen-activated protein kinase (MAPK) and nuclear factor erythroid 2-related factor 2 (Nrf2) , are also worthy of investigations. Different from pro-inflammatory cytokines, IL-4 and IL-10 are the anti-inflammatory cytokines known to suppress pro-inflammatory cytokine production . of IL-4 and IL-10 than those of the undressed and Tegaderm film treated groups .

There are two phenotypes of macrophages: M1 macrophages (classically activated) and M2 macrophages (alternatively activated). M1 macrophages contribute to inflamma- tion, while M2 macrophages promote collagen synthesis. Macrophage cells simulated with LPS, Arginase-1 (ARG-1), CD163 and CD206, as a functional marker of the M2 phenotype , were transcriptionally upregulated upon EACPA hydrogel treatment. CD68, as an M1 phenotype marker , was downregulated at the protein level in the wound tissue of diabetes mellitus mice treated with AuEA compared to the vehicle control group . Moreover, EGCG or EGCG-containing wound dressing sup- pressed the responses of immune cells such as monocytes and macrophages in an in vivo mouse skin full defect model[29].

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 . the antimicrobial mechanism of EGCG in the skin wound healing process, including the antimicrobial effect on bacteria and the inhibitory effect on the formation of biofilms[30].

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 . The antibacterial activity of EGCG-containing gold nanoparticles (AuNPs) against *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli* was reported, which was attributed to the morphological deformations of bacteria due to the surface interaction with AuNPs . A sandwiched dressing con- taining gelatin/chitosan/EGCG nanoparticles showed the antimicrobial property against *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* [31] .

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Angiogenesis Effect

Angiogenesis is the process of new branching network formation, which is mediated by various pro- and antiangiogenic factors. VEGF, as an important proangiogenic factor, can be produced by inflammatory cells . The inflammatory reaction stimulated by TNFα regulates the expression of VEGF . Conversely, VEGF is also involved in the regulation of inflammation, reinforcing the interrelation between inflammation and angiogenesis. The topical treatments with EGCG-containing cream impacted the expression of VEGF, which is conducive to the prevention of telangiectasias. The receptor of advanced glycation end products (RAGE) was related to oxidative stress and abnormal angiogenesis in wound healing. The topical treatment with AuEA accelerated skin repair in diabetic mice through decreasing the transcription of RAGE and Angiopoietin-2 while increasing the gene expression of VEGF . In the wound tissue of a human study, VEGFA and CD31 were reduced at both the transcriptional and protein levels under zonal priming and direct topical treatment with EGCG in first 1–2 weeks of recovery compared to the placebo control group . The antiangiogenic effects of EGCG was involved in the inhibition of PI3K/AKT and MEK/ERK pathways[32,33] .

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 . 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[34,35].

In a recent study the antioxidative and ROS scavenging properties of EGCG-coated biomaterials designed for tissue engineering. They found that EGCG- coated polycaprolactone (PCL) film increases cell attachment, viability, and proliferation of human adipose-derived stem cells

(hADSCs) against H_2O_2 exposure while regulating cell signalling that diminishes apoptotic genes, thus augmenting the expression of the anti-oxidative enzyme. The amalgamated EGCG-coated PLLA fibre spheroids showed better cell viability and anti-oxidative activities in response to H_2O_2 induced oxidative stress compared to the control.

v. Conclusions and Perspective

Tea has been known for its various health benefits, such as antioxidant, anti-inflammatory and antimicrobial effects due to the high amounts of catechin compounds, especially EGCG. However, the oral administration application is extremely restricted by the low bioavailability of EGCG. This intrigues the research interest in the potential application of EGCG as a topical treatment. This review summarizes the beneficial effects of EGCG at different skin wound healing stages. In addition to the application of EGCG in its native form, EGCG is also carried by different types of wound dressings to achieve better adhesive and infiltrative properties.

EGCG has shown promising antioxidant and free radical scavenging properties, which are proven through various studies. 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. Currently, the immediate treatment of cutaneous injuries is a realistic approach to improve the rate of healing and minimise the risk of complications.

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