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Micro and nanoformulations of catechins for therapeutic applications: recent advances and challenges

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ABSTRACT

Bioactive metabolites isolated from myriad living organisms, particularly medicinal plants, can synergize the therapeutic activities of conventional drugs. Catechin is a flavan-3-ol related to flavonoids, a bioactive compound causing many therapeutic activities. Micro and nanoformulations of ((-)-epigallocatechin gallate), ((-)-epigallocatechin), ((-)-epicatechin gallate), and ((-)-epicatechin), as the leading catechins derivatives of tea (*Camellia sinensis*) have showed desirable antibacterial, anticancer, antidiabetic, anti-neurodegenerative, activities against Alzheimer, multiple sclerosis, and Parkinson with significant applications in wound healing, tissue engineering, and various prosthetic implants. Different nanosystems produced from zero-, one-, and two-dimensional nanomaterials, such as solid lipid nanoparticles, carbon nanotubes, and nanofilms, have been employed to address the disadvantages of conventional bioactive compounds. In this review, we have attempted to cover these issues, focusing on their benefits and challenges for future studies.

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Introduction

The third most prominent cause of mortality worldwide, specifically in developing countries, is infectious diseases resulting from pathogenic microorganisms [1]. According to World Health Organization (WHO), fighting against these diseases needs new effective strategies to overcome resistant microorganisms, specifically multidrug-resistant (MDR) bacteria [2-4]. Treatment of infectious wounds and removing biofilm formation on the implants caused by MDR bacteria is nearly unyielding. Multidrug resistance of cancer cells to conventional drugs and limitations in treating diabetic and neurodegenerative disease are other complicated issues in the biomedicine [5]. In this respect, nanotechnology has helped various therapeutic and theranostic clinical fields by presenting new organic, inorganic, and semi-organic materials in the nanoscale (1-100 nm) [6]. The nanomaterials such as liposomes, cubosomes, carbon nanotubes, fullerenes, nanofilms, nanoplates, solid lipid nanoparticles, polymeric nanoparticles, metal or metal oxide nanoparticles and nanocomposite, and silica nanoparticles have displayed desirable bio-physicochemical properties to load and delivery of conventional drugs or bioactive compounds [7-10]. Modifying and functionalizing these nanomaterials can lead to higher biocompatibility, bioavailability, and biodegradability inside the body [11].

Therapeutic functions of natural compounds involving primary and secondary metabolites of living organisms, specifically medicinal plants, have been reported by various studies [12, 13]. Catechins, flavan-3-ol, are natural polyphenolic phytochemicals related to the subgroup of flavonoids that exist as secondary metabolites with antioxidant functions in various plants, mainly tea, and legume. In addition, anti-inflammation, protective activity against UV radiation,

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anticancer, antibacterial, anti-allergenic, antiviral, antifungal, vascular protection, and cardiovascular protection have been found for these metabolites [14, 15]. Eight main types of catechins, including GCG ((-)-gallocatechin gallate), CG ((-)-catechin gallate), GC ((-)-gallocatechin), EGCG ((-)-epigallocatechin gallate), EGC ((-)-epigallocatechin), ECG ((-)-epicatechin gallate), EC ((-)-epicatechin), and C ((-)-catechin) have been known to have therapeutic activities [15]. Low stability and low bioavailability are the main disadvantages of catechins for therapeutic applications [16-18]. In recent years, micro and particularly nanoformulations of EGCG, EGC, ECG, and EC as main catechins of tea (*Camellia sinensis*) have had advances and challenges [18, 19], which in this review, we have addressed in the case of antibacterial and anticancer activities.

Antimicrobial activity

Antibiotic resistance of many pathogenic strains of bacteria is a significant problem faced by medical practitioners and scientists worldwide; new options or alternatives are in high demand. Plant secondary metabolites like catechins present a promising strategy to combat antibiotic-resistant bacterial strains by inhibiting the growth of such microbes. Nanoformulation of plant extracts with a rich amount of catechins is a potential candidate for anti-microbial use. Henna (*Lawsonia inermis*) extract containing catechin as the primary, secondary metabolite was made into nanoformulations that showed excellent anti-microbial properties against a group of food-borne pathogens, including bacteria and fungi. Nanoemulsion of the henna extract showed higher antibacterial activity against *B. cereus*, *E. coli*, and *P. aeruginosa* than the henna extract. The antifungal effect of nano henna extract was better than penicillin against *Aspergillus terreus*, *Penicillium digitatum*, and *Saccharomyces cerevisiae* [20]. Treatment of gingivitis and periodontitis is hard owing to the difficulty in removing dental biofilm formation by bacteria (Figure 1). Nanoformulation of chitosan+green tea showed suitable anti-bacterial activity against dental caries-causing organisms, *Lactobacillus casei*, after Er: YAG laser caries removal. This nanoformulation could not prevent the growth of *S. mutans* on dentin. In contrast, EGCG inhibited the *growth of L. casei and S. mutans* at a 1:4 dilution [21].

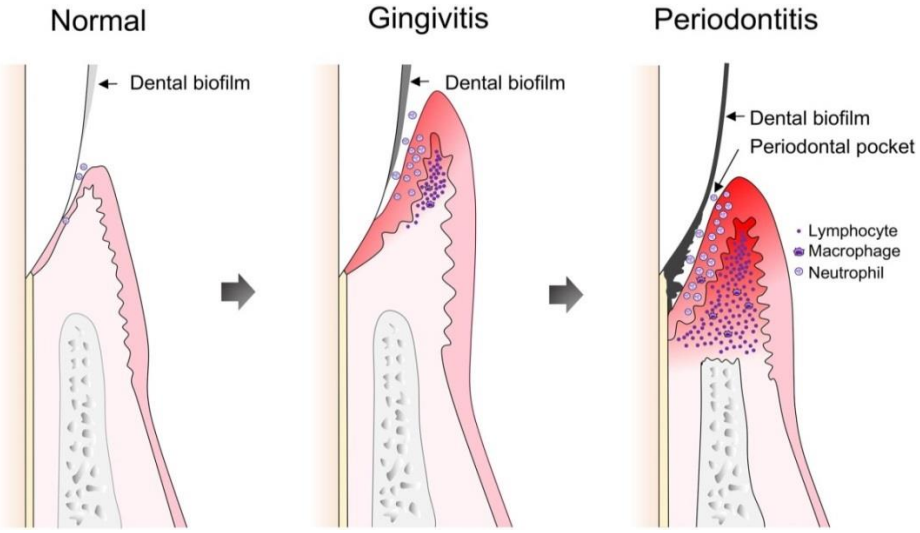


Fig. 1. Dental plaque accumulation causes gingivitis (mild gum infection) and periodontitis (severe gum infection) [22].

Polymerized structures of catechins have shown improved therapeutic properties. The polymeric forms can be made using various techniques like enzymatic polymerization, polycondensation, acid-catalyzed polymerization, etc. But a novel method of polymerization using cross-linking agents was developed by Latos-Brozio et al. The crosslinking agent, glycerol diglycidyl ether, is biocompatible and connects monomeric flavonoids into micro or nanoparticle form. The polymeric form showed a high antibacterial effect against *S. aureus*, which was not

offered by the catechin monomeric form [23]. Bacteria causing urinary tract infections, *E. coli* (MTCC 739), were inhibited by the nanoemulsion formulation of green tea. This nanoformulation in a liquid medium effectively inhibited bacterial adhesion to mammalian cells [24].

Catechins can be antibiotic activity modulated against resistant strains of *S.aureus*, *E.coli*, and *P.aeruginosa*. Catechins have synergetic effects with antibiotics that help to combat resistant strains. Catechins attack the proteins in the bacterial cell, causing their precipitation and resulting in cell wall deformation. Gram-positive bacteria like *S.aureus* are more sensitive to polyphenols. Catechins showed synergistic effects with antibiotics imipenem, tetracycline, and erythromycin against *E.coli*, norfloxacin, and gentamicin against *S. aureus* [25].

One of the significant causes of mortality worldwide is infectious diseases resulting from pathogenic microorganisms [26]. Fighting against microorganisms, especially bacteria, is a global health challenge due to the adverse side effects of conventional drugs and the emerging multiple-drug resistance [5]. Thanks to the synergistic effect, combining antibiotics with bioactive agents may effectively treat MDR bacteria [27]. A combination of EGCG and gentamicin antibiotics was employed against MDR *Escherichia coli* (Gram-negative) and *Staphylococcus aureus* (Gram-positive). The fractional inhibitory concentration index (FICI) of 0.32 was significant for both MDR bacteria. Comparatively; for both bacteria, minimum inhibitory concentrations were 32 and 6.4 µg/mL in alone (gentamicin) and combination (gentamicin + EGCG) formulations, respectively [1].

Improvement of prosthesis quality

A missing body part can be replaced by a prosthesis or prosthetic implants as an artificial device [28]. Recently, micro and nano aspects of various prosthetic implants, such as dental prostheses and bone prostheses, have been improved by biotechnology and nanotechnology. Different bone implants are made of metal such as titanium and applied as devices for procedures including bone augmentation, partial and total joint replacement, and fracture fixation [29]. Coating of medical implants by nano-thin of decaffeinated green tea extract showed increased antibacterial compared to raw green tea extract coated-implant [30]. The application of titanium-based implants is common for hard tissue repair and replacement. Limitations of titanium-based implants are emerging bacterial infections and tissue reactions to corrosion implants. EGCG can coat these implants)/Zn by a one-step hydrothermal method due to improving antibacterial activities, corrosion resistance, osteogenic properties, and the ability of the biomimetic mineralization [31]. Coating the surface of titanium dental implant by EGCG and polyethyleneglycol (PEG) attenuated non-specific adhesion, bacterial attachment, and bacterial biofilm formation [32]. Titanium-based implants are joint implants for orthopedic and dental clinics. However, this type of metal implant has no suitable osseointegration (direct connection between bone and the surface of an artificial implant) at the bone–implant interface field [33].

Applying the metal-polyphenol network can be another effective strategy to improve osseointegration of the bone implant. In this regard, the EGCG-Mg^{2+}-coated titanium implant displayed increased mRNA expression of osteogenic markers, alkaline phosphatase activity, the mineralization of human adipose-derived stem cells, prominently enhancing the calcium content (22.2 µg) than cells grown on bare titanium (13.5 µg) [34]. It is worth noting that augmenting the activity of alkaline phosphatase results in the presence of osteoblast cells and the bone formation [35]. EGCG can be used between polyanionic polyethyleneimine (PEI)-tempol as a weak cross-linker for the formation of nanogels and the multifunctional coating on the implants owing to their abundant phenolic hydroxyl groups. Moreover, EGCG has anti-inflammatory properties and can protect the endothelial cell function and inhibit the proliferation of smooth muscle cells suitable for coating blood-contacting implants [36].

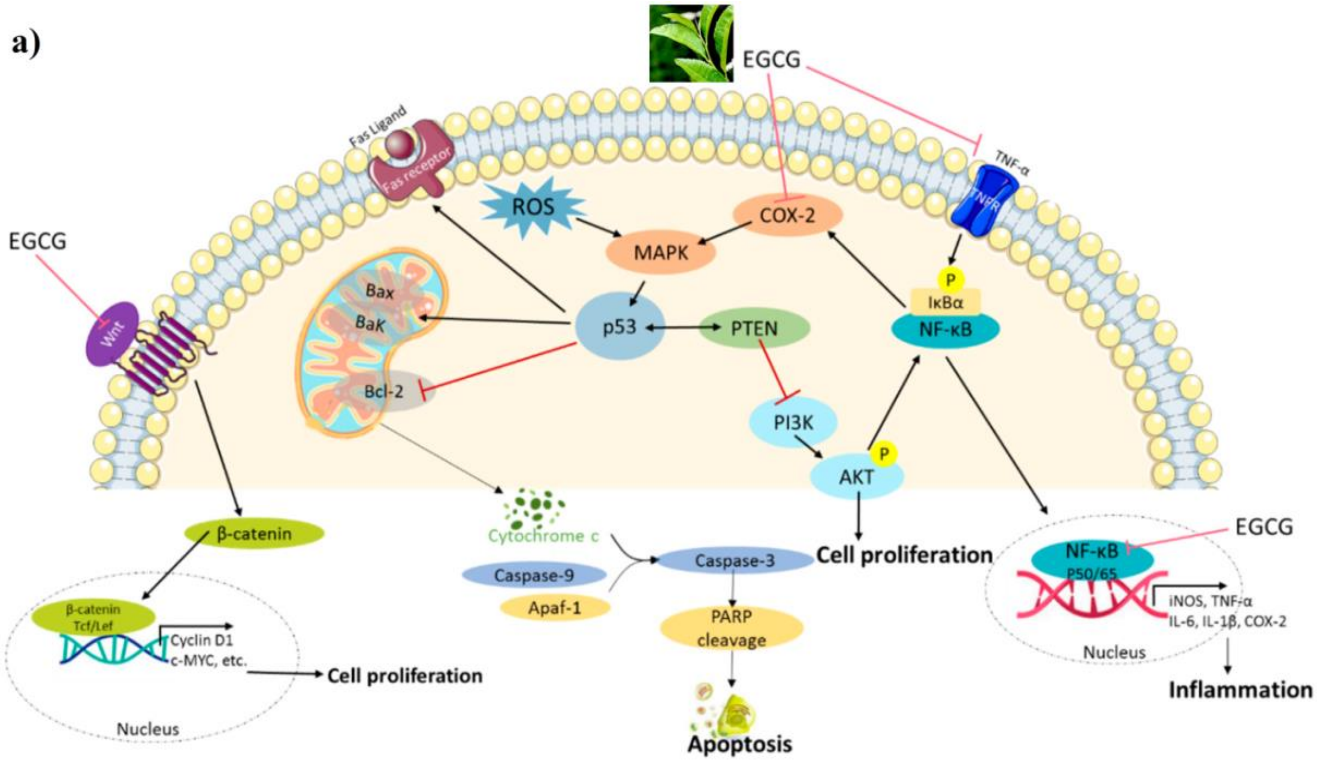
Tissue engineering

In tissue engineering, stem cells, materials or biomaterials, and growth factors are applied to improve or replace tissues such as bone, cartilage, skin, blood vessels, and muscle [37]. Bone defects can cause infection (osteomyelitis), trauma, and tumor, which may be treated by various strategies, including growth factors, bioactive materials, three-dimensional (3D) printing, and autogenous bone [38, 39]. EGCG reduced

stress-induced premature senescence (SIPS) in the formulation of lipopolysaccharide (LPS) sustained-release gelatin sponge (LS-G-EGCG), which caused increased bone regeneration. This ability results from the anti-inflammatory and antioxidant properties of EGCG for suppressing cellular senescence [40]. Production of reactive oxygen species (ROS) at a surplus level during cell transplantation and biomaterial implantation is a complicated issue leading to reduced therapeutic effects' efficiency. Coating polycaprolactone (PCL) film surface by cation metals and EGCG increased anti-oxidative enzyme expression and hydrophilicity properties and reduced apoptotic gene expression [41]. EGCG has chondrogenesis (the earliest phase of skeletal development) properties and can be formulated in various scaffolds to stimulate cartilage regeneration. Loaded EGCG in albumin nanoparticles (spherical shape by sizes in the range of 110 nm–210 nm) was incorporated into interlinked porous PCL scaffolds and exhibited a sustained release of EGCG. An increase in glycosaminoglycan (cell adhesion, cell growth, and proliferation regulator) deposition was observed under the influence of EGCG after 21 days of treatment [42]. In a similar study, EGCG was integrated into gelatin sponges, which attenuated the expression of 4-hydroxynonenal (4-HNE, a marker of oxidation), matrix metalloproteinase-2, and matrix metalloproteinase-9. Implantation of this formulation increased osteogenesis or bone tissue regeneration in male Sprague-Dawley rats compared to EGCG-free gelatin sponge as the control group [43].

Antineoplastic activity

Anti-inflammatory and apoptosis induction mechanisms of the EGCG are presented in Figure 2a [44]. Non-small cell lung cancer (NSCLC), with 80–85% accounts, and small cell lung cancer (SCLC) are the two main types of lung cancer. Adenosine monophosphate-activated protein kinase (AMPK) limits cancer growth by mediating the tumor suppressor, the liver kinase B1 (LKB1). Nanoemulsion formulation of EGCG and EGCG alone blocked the development of H1299 lung cancer cells via the activation of the AMPK signaling pathway at half-maximal inhibitory concentrations (IC_{50}) of 4.71 µM and 36.03 and, respectively, [45]. EGCG can inhibit metastasis and angiogenesis by several molecular mechanisms (Figure 2b).



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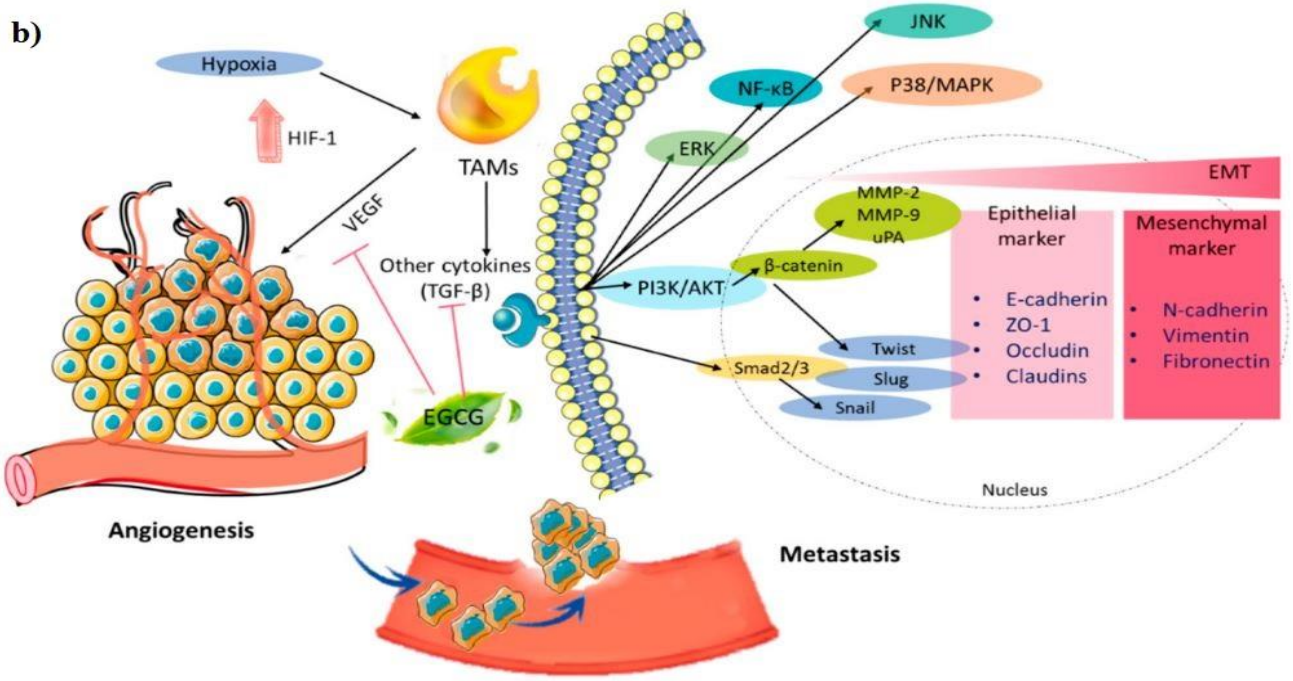

Fig. 2. Schematic image pressing anti-inflammatory and apoptosis induction mechanisms (a) as well as anti-angiogenic and anti-metastatic mechanisms (b) of the EGCG (adapted and modified from [44]) under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

Alzheimer

Alzheimer's disease (AD), a type of dementia, results from the accumulation of the abnormal proteins amyloid and tau proteins around and in brain cells [46]. Butyryl-cholinesterase (BuChE) and acetylcholinesterase (AChE) are therapeutic targets in treating AD. A mixture of catechin, EGCG, EC, and EGC in a 1:1:1:1 ratio at a concentration of 1.25 mg/mL showed synergism effect as inhibition of AChE and BuChE by values of 99.22% and 56.02%, respectively [47]. EGCG can protect against AD through anti-amyloid effects and decrease the risk of age-related cognitive reduction [48]. *Tieguanyin* oolong tea extract with EGCG at a range of 77.42-105.21 mg/g reduced the expression of iNOS, COX-2, interleukin 6 (IL-6), NF-κB p65, IL-1β, and TNF-α with improving cognitive ability resulted from the reduction of inflammation [49].

Multiple sclerosis (MS)

Multiple sclerosis (MS) is a progressive neurodegenerative disease with demyelinating of nerve cells in the central nervous system, causing the inability of parts of the nervous system to transmit signals [50]. Pro-inflammatory cytokines such as IL-6 are high in patients with MS. Combination therapy in a clinical trial with coconut oil, and EGCG caused a decrease in IL-6 level [51]. MS is mediated by the activation of myelin-specific T helper 17 (TH17) and T helper 1 (TH1) cells that promote a chronic inflammatory response. The generation of TH17 cytokines, including IL-23R and IL-17 expression is affected by the RORC2 gene. Anti-inflammatory and immunomodulatory effects have been reported for EGCG. EGCG significantly reduced RORC2 gene expression with no effect on hypoxia-inducible factor 1-alpha (HIF-1α) [52].

Anti-obesity

Caffeine and EGCG are the main effective metabolites of weight loss in *C. sinensis*. The combination of these two bioactive metabolites in low doses compared to each metabolite alone can synergize anti-obesity by regulating bile acid metabolism and gut microbiota. *Bifidobacterium* and Firmicutes were increased and reduced under caffeine + EGCG treatment. This treatment exhibited increased fecal acetic acid, total short-chain fatty acids, and propionic acid with reduced G-protein coupled receptor 43 (GPR43) expression. Moreover, microbial bile salt hydrolase in the gut was increased concomitantly with fecal bile acid loss and production of unconjugated bile acids [53].

Antidiabetic activity

The major disadvantages of EGCG are high hydrophobicity, fast oxidation, low stability, and bioavailability in physiological conditions, wherein 90% of this metabolite can be lost in sodium phosphate buffer (pH 7.4) after 3 h. The high hydrophobicity of EGCG leads to difficulty in its passive diffusion through the phospholipid bilayer of the cell membranes. An esterification reaction between EGCG and palmitoyl chloride prepared the EGCG palmitate. It is noteworthy that α-glucosidase and α-amylase hydrolyze the disaccharides and polysaccharides and cause postprandial hyperglycemia in diabetic patients. IC_{50} values of acarbose, PEGCG, and EGCG were 0.15, 0.22, and 11.50 μM against α-glucosidase. Additionally, in the case of α-amylase, IC_{50} amounts for acarbose, PEGCG, and EGCG were 1.10, 1.64, and 7.44 μM, respectively [54].

Wound healing

The scavenging of ROS is a vital antioxidant mechanism of EGCG. EGCG was introduced to silk fibroin at mild basic pH by the nucleophilic addition reaction between EGCG quinone and lysine residues in silk proteins. Tyramine-substituted SF obtained co-cross linkage of EGCG-silk fibroin (SF) to prepare tyramine-substituted SF-EGCG-SF- hydrogel. This wound dressing displayed accelerated wound healing by reducing oxidative tissue damage via scavenging ROS such as hydroxyl radical (•OH) and superoxide anion radical ($O_2^{\bullet -}$) [55]. A metal–organic framework (MOF) is a coordination network by organic ligands consisting of metal ions or clusters in three-, two-, or one-dimensional structures [56]. MOF $Zn(BTC)_4$ was loaded by EGCG as EGCG@MOF $Zn(BTC)_4$ to provide a sustained release of EGCG and decrease the degradation rate of EGCG. By this formulation, the collagen accumulation and re-epithelialization levels in mice with diabetic wounds were prominently more than control group (Figure 3). The main limitations of MOF are low bioavailability, biodegradability, and biocompatibility in the body [57].

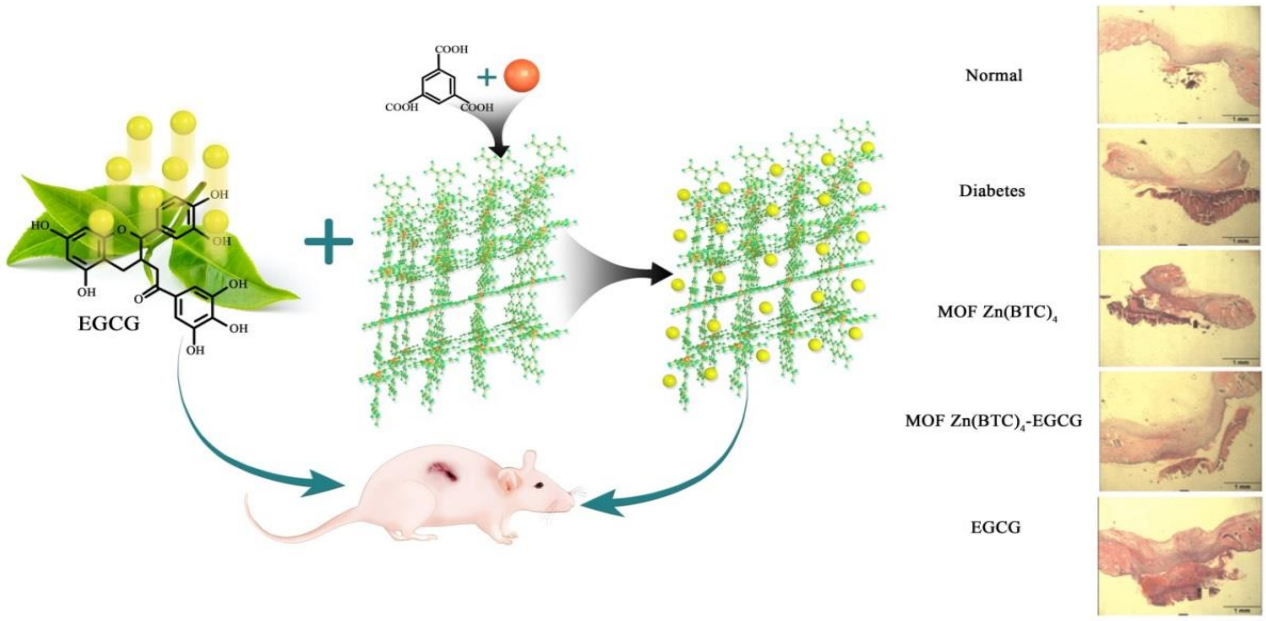

Fig 3. histological change of skin wound healing in diabetic mice under the effect of EGCG@MOF $Zn(BTC)_4$ (adapted and modified from [57] under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/)).

Wound healing is delayed due to excessive or insufficient activity of fibroblast and myofibroblast [58]. Catechins are the major flavonoids that contribute to the cell migration and proliferation of human fibroblasts, thus promoting wound healing. Many plant extracts, especially *Dioscorea bulbifera*, rich in catechins, have displayed excellent wound-healing properties [59]. Catechin can form nanoconjugate with silver and help in the scarless regeneration of chronic wounds caused due to burns. Here catechin acts as an envelope/cage for silver NPs. Catechin-silver nanocomposite tethered

collagen scaffold had antibacterial activity against *P. aeruginosa* with angiogenic properties accelerating healing of diabetic chronic infected wounds. Additionally, catechins help hair follicle and sweat gland growth by re-epithelization effect [60]. Since lowering the inflammation levels help in faster healing of wounds, catechin fastens the healing mechanism due to its anti-inflammatory agent. Catechins and quercetin showed anti-inflammatory action by blocking the mitogen-activated protein kinase signaling pathway [61]. Catechins, when encapsulated in nanoparticles, can retain their activity for many weeks. The anti-inflammatory action of catechins, tea catechins, remained stable when encapsulated with gelatin by the self-assembling process as catechin/gelatin NPs with a size of ~ 200 nm and negative charge. The activity was retained for more than 3 weeks. Thus nanoformulations of flavonoids like catechins help control the activity of these phytochemicals, which help in efficient wound healing function [62]. Flavonoids exert scar-free wound healing by regulating the genes for scar formation and reducing the abnormal deposition of collagen fibers. Combining catechins with biomaterials will form an alternative option for scarless wound healing (Figure 4) [63].

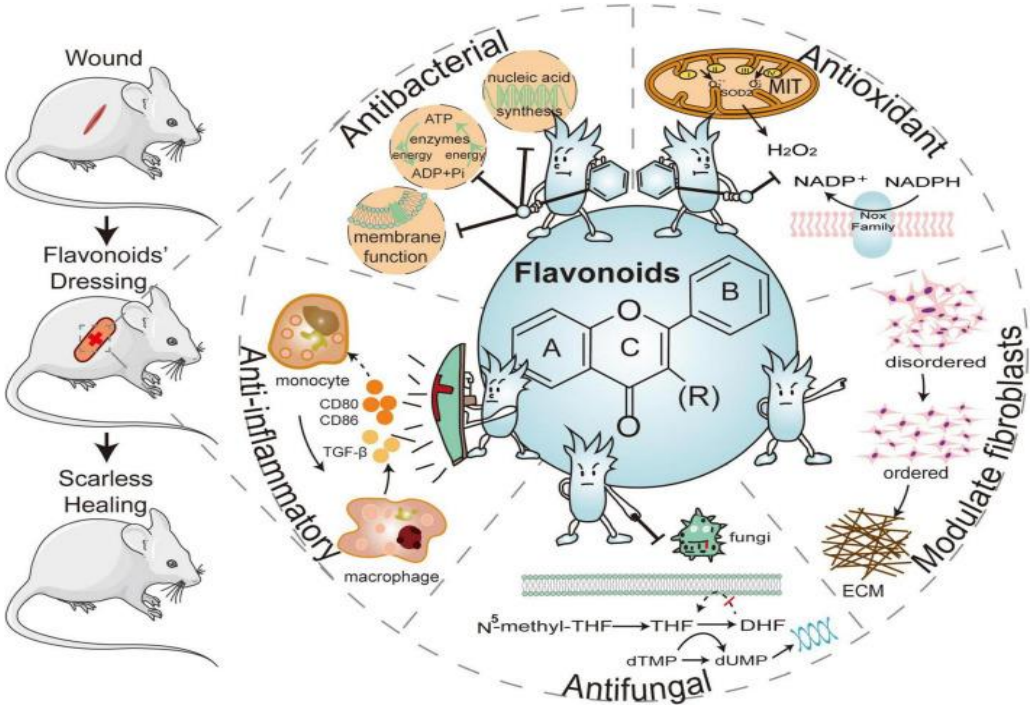

Fig. 4. Schematic Diagram showing Flavonoids' effects on scarless wound healing, including catechin. Reproduced from [63]. ATP, adenosine triphosphate; ADP, adenosine diphosphate; CD80, cluster of differentiation 80; CD86, cluster of differentiation 86; TGF-β1, transforming growth factor-β1; THF, tetrahydrofolate; DHF, dihydrofolate; dTMP, deoxythymidine phosphate; dUMP, deoxyuridine phosphate; ECM, extracellular matrix; NADPH, nicotinamide adenine dinucleotide phosphate.

Cardioprotective effect

Two main hindrances to chemotherapy for cancer disease are emerging drug resistance and severe side effects on healthy cells. In the case of cervical cancer and urinary bladder cancer, cisplatin is prescribed for patients. This anticancer drug can lead to cardiotoxicity, nephrotoxicity, and renal damage. Administration of green tea extract plus cisplatin increased antioxidant enzymes and improved histological features, hearth weight, and hearth index compared to albino mice treated with cisplatin alone. The hearth index value for oral co-administration of green tea extract and cisplatin and cisplatin alone were 2.86 and 2.66 g, respectively [64].

Conclusions

EGCG can significantly stimulate apoptosis and limit cell division in several cancers. Furthermore, this

bioactive compound in nanoemulsion alone can inhibit the activation of the AMPK signaling pathway in NSCLC. In the case of anti-obesity activity, a synergistic effect has been found for a combination of EGCG and caffeine in low doses than each metabolite alone via regulation of bile acid metabolism and gut microbiota as increased microbial bile salt hydrolase. For wound healing, scavenging ROS is the main antioxidant mechanism of EGCG, which can be improved by incorporating EGCG into micro and nanostructures such as hydrogels and MOF-forming wound dressings. In the MOF formulation of EGCG, the collagen accumulation and re-epithelialization levels in diabetic wounds were prominently higher compared to the control group. The main limitations of using EGCG are low stability, fast oxidation, and low bioavailability in physiological conditions. Modifications of EGCG, such as EGCG palmitate, can be synthesized to improve its metabolic stability and bioavailability. In the case of metal implant, formulation of metal-EGCG network such as Mg^{2+}-EGCG-coated titanium can improve osseointegration of the bone implant via the metal ion delivery as the osteoinductive agent with the synergistic effects of EGCG.

Study Highlights

- EGCG stimulates apoptosis and limit cell division in several cancers.
- EGCG in nanoemulsion alone can inhibit the activation of the AMPK signaling pathway in NSCLC.
- A synergistic effect has been found for a combination of EGCG and caffeine in low doses than each metabolite alone via regulation of bile acid metabolism and gut microbiota as increased microbial bile salt hydrolase.
- In the MOF formulation of EGCG, the collagen accumulation and re-epithelialization levels in diabetic wounds were prominently higher compared to the control group.
- The main limitations of using EGCG are low stability, fast oxidation, and low bioavailability in physiological conditions.
- Formulation of metal-EGCG network such as Mg^{2+}-EGCG-coated titanium can improve osseointegration of the bone implant.

Abbreviations

ADP: Adenosine diphosphate
AMPK: Adenosine monophosphate-activated protein kinase
ATP: Adenosine triphosphate
CD80: Cluster of differentiation 80
CD86: Cluster of differentiation 86
CG: (-)-catechin gallate
DHF: Dihydrofolate
dTMP: Deoxythymidine phosphate
dUMP: Deoxyuridine phosphate
EC: (-)-epicatechin)
ECG: (-)-epicatechin gallate
ECM: Extracellular matrix
EGC: (-)-epigallocatechin
EGCG: Epigallocatechin gallate
GC: (-)-gallocatechin
GCG: (-)-gallocatechin gallate
IC_{50}: Half-maximal inhibitory concentrations
LKB1: Liver kinase B1
MDR: Multidrug-resistant
MOF: Metal-organic framework
MS: Multiple sclerosis
NADPH: Nicotinamide adenine dinucleotide phosphate
NSCLC: Non-small cell lung cancer
ROS: Reactive oxygen species
SCLC: Small cell lung cancer
SF: Silk fibroin
TGF-β1: Transforming growth factor-β1
THF: Tetrahydrofolate
WHO: World Health Organization
FICI: Fractional inhibitory concentration index
PEG: Polyethyleneglycol
3D: Three-dimensional
PCL: Polycaprolactone
PEI: Polyethyleneimine
SIPS: Stress-induced premature senescence
LPS: Lipopolysaccharide
BuChE: Butyryl-cholinesterase
TH17: T helper 17
TH1: T helper 1
HIF-1α: Hypoxia-inducible factor 1-alpha
GPR43: G-protein coupled receptor 43

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with animals or human participants performed by any of the authors.

Author Contributions

MA: conceptualization and preparing the first draft; RY, MS, and ST: writing and editing.

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