ISSN 0006-2979, Biochemistry (Moscow), 2026, Vol. 91, No. 3, pp. 432-447 © Pleiades Publishing, Ltd., 2026.

REVIEW

Epigallocatechin Gallate as an Anti-Fibrotic Agent

Yury S. Tarahovsky[1,a]*, Sergey G. Gaidin[2], and Yury A. Kim[2]

[1]*Institute of Theoretical and Experimental Biophysics, Russian Academy of Sciences, 142290 Pushchino, Moscow Region, Russia*

[2]*Institute of Cell Biophysics, Pushchino Scientific Center for Biological Research, Russian Academy of Sciences, 142290 Pushchino, Moscow Region, Russia*

[a]*e-mail: tarahov@rambler.ru*

Received October 21, 2025
Revised February 18, 2026
Accepted February 19, 2026

Abstract—Epigallocatechin gallate (EGCG), a major polyphenolic compound in green tea, exhibits preventive and therapeutic effects in many fibrotic diseases. Tissue fibrosis is characterized by excessive deposition of collagen fibrils in the extracellular matrix, primarily due to dysregulation of cellular signaling pathways. However, we have previously demonstrated that EGCG directly inhibits the formation of collagen fibrils from collagen monomers under *in vitro* experimental conditions that excluded involvement of cellular signaling systems. This review explores the antifibrotic action of EGCG, which may occur through (i) its influence on cellular signaling and (ii) direct binding to collagen monomers, leading to the inhibition of pathological fibrillogenesis, as well as discuss the prospects for targeting the collagen assembly process.

DOI: 10.1134/S0006297925603715

Keywords: collagen, fibrosis, polyphenols, flavonoids, catechin, epigallocatechin gallate

INTRODUCTION

Polyphenolic compounds found in plant-based foods are among the most important functional components of human diet [1, 2]. Special attention has been given to flavonoids – a class of natural polyphenolic compounds abundant in fruits, vegetables, grains, and tea. Flavonoids, widely consumed through everyday foods, exhibit antioxidant, anti-inflammatory, anticancer, antibacterial, and neuroprotective properties, thus reducing the risk of various diseases [3-5]. Some flavonoids possess hepatoprotective properties and have been also investigated as potential treatments for central nervous system disorders, such as the Alzheimer's and Parkinson's diseases, drug addiction, and stroke, as well as for their preventive role in ischemic heart disease [6]. Clinical studies have demonstrated that fruits rich in flavonoids can help prevent cancer by affecting signaling pathways involved in angiogenesis and carcinogenesis [7]. Flavonoids are also clinically effective in preventing type 2 diabetes [8].

In this review, we discuss potential mechanisms underlying the preventive action of epigallocatechin-3-gallate (EGCG), one of the main catechins in tea, in fibrotic diseases of various organs. Using literature data and findings from our own research, we propose a hypothesis for the EGCG action mechanism.

FIBROSIS AND HEALTH

Fibrosis, which accounts for nearly 50% of global mortality, results from uncontrolled inflammatory processes characterized by excessive deposition of the extracellular matrix (ECM), ultimately leading to organ dysfunction [9]. Although the primary causes of fibrosis may vary and are not yet fully understood, these diseases share a common pathological hallmark: the progressive accumulation of fibrous tissue rich in fibrillar proteins (primarily collagen) in affected organs, culminating in organ failure [10-12].

For example, excessive accumulation of collagen fibrils at the site of myocardial injury is known as cardiac fibrosis [13]. Chronic activation of wound healing responses causes fibrosis characterized by

* To whom correspondence should be addressed.

disproportionate ECM formation as a result of sustained inflammation, with activated fibroblasts playing a key role in this process [14, 15]. Initially, fibrosis may serve as a compensatory mechanism in response to prolonged healing, but persistent reparative fibrosis can eventually lead to complications by impairing heart function and increasing tissue rigidity. Thus, the formation and expansion of scar tissue can compromise heart function [16], as damaged cardiomyocytes are replaced by non-contractile fibrous scar tissue, which can lead to heart failure due to the limited ability of the heart muscle to contract [17]. Although replacement of damaged tissues by collagen-rich fibrous scar tissue is a part of body's natural response aimed to expedite the recovery after injury, it often leads to cardiac muscle dysfunction [18, 19]. After myocardial infarction, when coronary artery blockage causes extensive death of heart muscle tissue, this process, known as cardiac remodeling, becomes particularly pronounced.

During cardiac remodeling, necrotic tissue is replaced by the ECM, while the remaining viable cardiomyocytes undergo hypertrophic growth. The ECM is produced primarily by fibroblasts and includes collagen, proteoglycans, fibronectin, tenascin C, laminins, and elastin [15, 20]. The heart contains various types of fibrillar collagen, each with unique physical and chemical properties. Type I collagen, which constitutes ~85% of total cardiac collagen, forms thick fibers that provide strength. In contrast, type III collagen forms flexible, thin fibers that ensure tissue elasticity [21]. Cardiac remodeling, i.e., replacement of damaged tissue with fibrous material, results in the loss of contractile cardiac muscle mass [22].

Chronic liver inflammation is another example of pathology associated with fibrosis. Hepatic fibrogenesis, one of the leading causes of morbidity and mortality worldwide, can be initiated by viral, chemical, or metabolic agents [15]. A key event accelerating liver fibrosis is the activation of collagen-producing hepatic stellate cells (HSCs) [23]. Over time, fibrosis can spread throughout the entire liver, increasing the risk of morbidity and mortality, especially in the context of age-related disorders [24].

Nonalcoholic fatty liver disease is characterized by the inflammation and tissue damage, as well as excessive lipid accumulation that damages hepatocytes and can lead to fibrosis, a pathological process in which normal liver parenchyma is progressively replaced by fibrous connective tissue. This remodeling impairs liver function and eventually progresses to cirrhosis, a condition marked by a significantly reduced liver performance [25, 26]. Activated HSCs are the primary effector cells driving liver fibrogenesis [27] by producing excessive amounts of ECM components [23]. The ECM is a complex network formed by collagens, elastin, glycoproteins, and proteoglycans [28-30]. Since collagen is the main ECM component, it plays a vital role in the development and etiology of chronic liver diseases [31].

THE EFFECT OF EGCG ON FIBROSIS

EGCG is widely recognized for its ability to prevent inflammatory diseases accompanied by tissue fibrosis and damage to many organs. The most promising therapeutic strategies for treating fibrosis have been focused on preserving collagen homeostasis, specifically, by regulating its formation, deposition, and degradation [32]. EGCG has demonstrated significant therapeutic potential against fibrosis in various organs.

Many researchers believe that the modulation of cellular signaling pathways is central to the EGCG's mechanism of action. For example, in liver fibrosis, EGCG exhibits antifibrotic, antioxidant, and anti-inflammatory effects by suppressing the expression of cellular signaling components, such as TNF-α, IL-1β, TGF-β, MMP-2, MMP-9, α-SMA, and COL1A1 [33-36], and by inhibiting pro-inflammatory (IL-5, TNF-α, IFNγ, IL-4, IL-1B, IL-6) and stress (p53, p38, MAPK, XBP1) signaling pathways [37]. EGCG treatment has been associated with reduced levels of the lipid peroxidation marker malondialdehyde, as well as with decreased expression of NF-κB, TNF-α, IL-1β, IL-6, IL-10, TGF-β, and α-SMA [38, 39].

In renal fibrosis, EGCG promotes the transdifferentiation of macrophages into myofibroblasts via the TGF-β/Smad3 and JAK/STAT signaling pathways [40]. In cardiac fibrosis, EGCG reduces atherosclerosis-associated cardiovascular toxicity by suppressing mitochondrial DNA sensitivity regulated by the TBK1/cGAS/STING and NLRP3 signaling pathways [41] and prevents inflammation and cell death by reducing the production of reactive oxygen species (ROS) and Bax expression, while upregulating Bcl-2 expression [42]. Additionally, it has been found that EGCG downregulates collagen expression by inhibiting the TGF-β/Smad3 and LOX signaling pathways [43], activates autophagy, modulates the AMPK/mTOR pathway, suppresses the TGF-β/MMP pathway [44], and reduces the expression of TGF-β, JNK, p-JNK, and TIMP-1, while activating the MMP-9 pathway [45].

In summary, EGCG is one of the most effective agents for preventing inflammation and fibrosis, as evidenced by the reduced levels of pro-inflammatory markers and suppression of oxidative stress, collagen production, and cell apoptosis [23, 46-48].

As illustrated in Fig. 1, EGCG inhibits key components of cellular signaling, including NFκB and STAT transcription factors, as well as the protein kinase

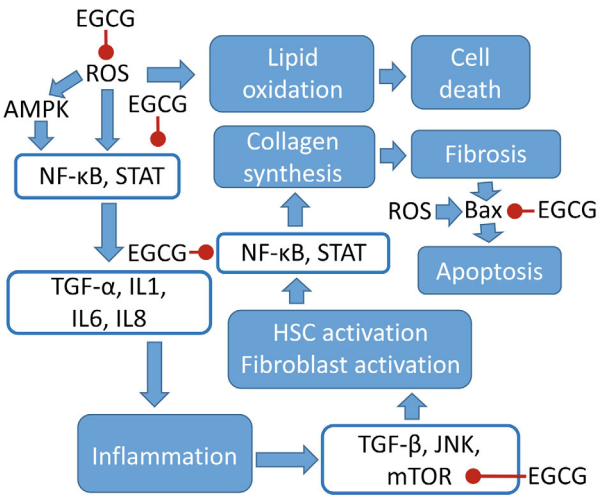

Fig. 1. The effects of EGCG on cell proliferation signaling pathways. The diagram shows molecules frequently mentioned in the studies of EGCG's effects on fibrosis; red circles denote the inhibitory effect of EGCG on the signaling pathway components (see the text for details).

mTOR, particularly in cancer cells [49]; however, this effect in primary cells has been studied insufficiently. Under certain conditions, EGCG acts as an antioxidant and suppresses ROS production, which will be discussed in more detail in the following sections of this review. As an antioxidant, EGCG acts through the NFκB and STAT transcription factors and exerts its anti-inflammatory effect via suppressing the expression of pro-inflammatory cytokines TNF-α, IL-1, IL-6, and IL-8. By acting through the TGF-β, JNK, and mTOR signaling pathways, EGCG suppresses activation of HSCs and fibroblasts, thus downregulating the activity of NFκB and STAT, which inhibits the production of collagen, reduces fibrotic tissue formation, and prevents subsequent cell apoptosis by inhibiting the formation of mitochondrial pores by the Bax protein [50, 51].

ANTI- AND PRO-OXIDANT ACTIVITY OF EGCG

EGCG is widely recognized as a potent antioxidant, whose protective effect is attributed to the ability to upregulate the expression of catalase, superoxide dismutase, and glutathione peroxidase, thus preserving the mitochondrial membrane integrity [52]. However, evidence also suggests that catechins can exhibit the pro-oxidant properties and increase ROS levels. While catechins typically prevent oxidation by scavenging free radicals, they can promote ROS generation and exhibit the pro-oxidant activity [53].

The biological activity of EGCG largely depends on its concentration, with the antioxidant properties observed only at very low concentrations (0.1-0.01 μM) and the pro-oxidant activity dominating at higher concentrations (1-100 μM), as has been shown in healthy human lymphocytes [54]. A study in hepatocytes reported no detectable toxicity of EGCG at concentrations ≤1 μM, although such toxicity was observed at concentrations ≥10 μM [55]. These findings demonstrated the dual nature of EGCG and its ability to exhibit both anti- and pro-oxidant properties. Remarkably, even at higher concentrations associated with increased ROS production, EGCG can still produce beneficial therapeutic outcomes [56]. For example, EGCG at concentrations of 50-100 μg/mL (1-2 μM) demonstrated antifibrotic, antiangiogenic, and pro-apoptotic effects, contributing to the alleviation of menopausal symptoms and fertility preservation [57]. The pro-oxidant activity of EGCG, when combined with other polyphenols exhibiting antioxidant properties, may have advantages in therapeutic applications [58].

The therapeutic effects of EGCG may arise from its capacity to inhibit the proliferation of rapidly dividing cells, induce cell cycle arrest at the G_0/G_1 phase, initiate cell apoptosis, and suppress cell growth, as has been extensively documented in cancer cells [59]. High ROS levels promote cell death, a phenomenon observed in primary cells and even to a greater extent, in cancer cells, suggesting potential application of EGCG and other flavonoids in anticancer chemotherapy [60, 61]. The strategies enhancing the pro-oxidant action of EGCG can be used in both cancer therapy [61] and treatment of injuries of healthy tissues [62, 63]. One such approach involves generation of increased ROS amounts through the formation of complexes with metal ions (e.g., copper and iron), which induces the production of hydrogen peroxide via the Fenton reaction, thus amplifying the pro-oxidant and cytotoxic effects and ultimately inhibiting cancer cell proliferation. EGCG–Cu^{2+} complexes at the concentrations of 50-300 μM demonstrated a pronounced activity, with EGCG exhibiting the highest potency among tea catechins [64].

It should be emphasized that the action of polyphenol–metal complexes is highly concentration-dependent, a factor that remains investigated rather insufficiently. For example, the EGCG–Zn^{2+} complex reduces ROS production, suppresses inflammatory reactions, and promotes angiogenesis, thereby contributing to a significant therapeutic effect in various diseases [65-67]. Comparative protective effects were observed for the EGCG–Mg^{2+} and EGCG–Cu^{2+} complexes [68, 69]. However, administration of high doses of EGCG may induce significant damage, leading to hepatotoxicity and even lethal outcomes, due to its pro-oxidant action [70].

To illustrate the dual (anti- and pro-oxidant), concentration-dependent role of polyphenolic compounds in modulating cell proliferation, the concept

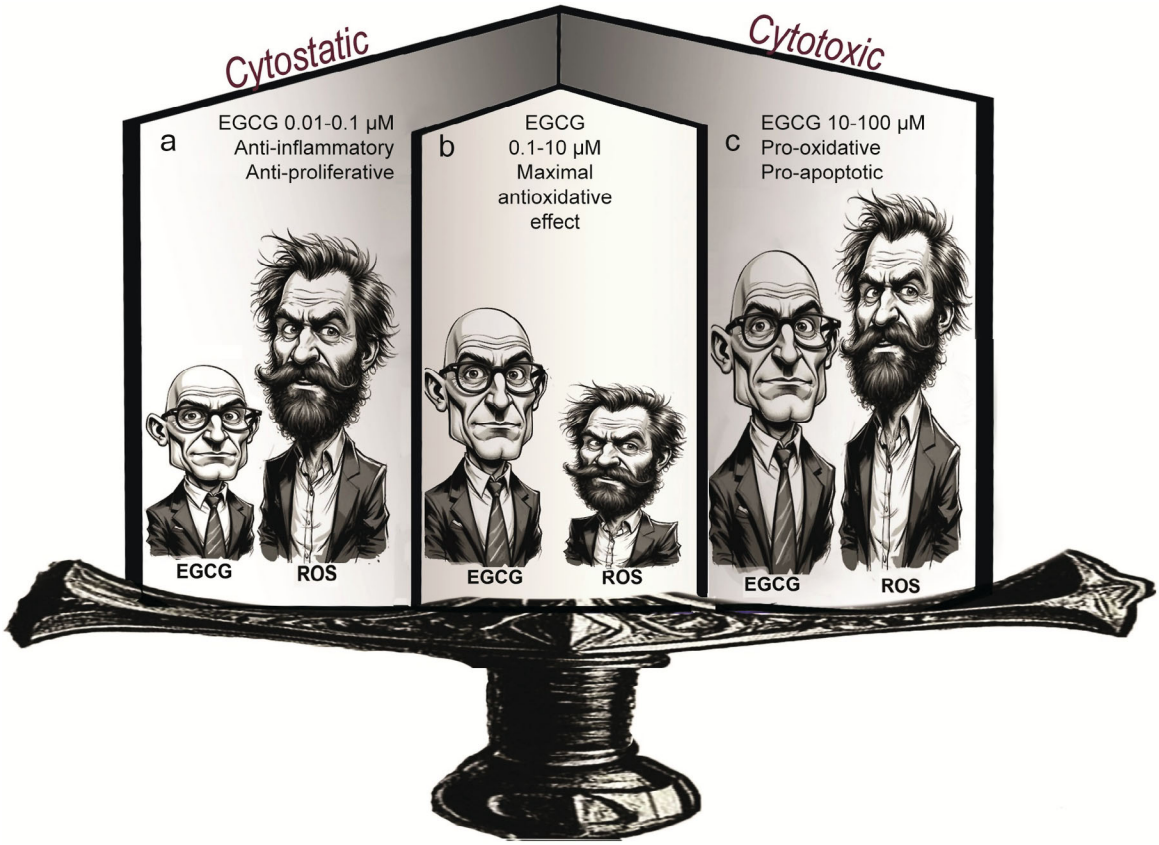

Fig. 2. The "double-edged sword" principle in the antifibrotic action of EGCG in rapidly dividing cells (activated fibroblasts or HSCs) explains the effects of low (a), moderate (b), and high (c) concentrations of EGCG on cell proliferation and viability.

of a "double-edged sword" has been proposed [71-73] (Fig. 2). According to this hypothesis, very low EGCG concentrations (Fig. 2a) are associated with high cytoplasmic ROS levels, resulting in the cytostatic effect. At the same time, EGCG in very high concentrations manifests the pro-oxidant properties, further increasing the content of ROS levels in the cytoplasm and inducing cytotoxicity (Fig. 2c). The lowest ROS levels are observed at moderately high EGCG concentrations (Fig. 2b).

The "double-edged sword" phenomenon has been reported not only for EGCG [74] but also for other natural polyphenolic antioxidants, such as curcumin [75] and resveratrol [59, 76]. To date, this dual action has been documented primarily in the studies of cancer cells. Whether a similar mechanism operates in rapidly proliferating activated fibroblasts and HSCs, i.e., the cells contributing to the collagen production and its fibrotic deposition, remains to be determined.

THE EFFECT OF EGCG ON THE COLLAGEN FIBRIL FORMATION

Collagen molecules, which can self-organize into larger structures called collagen fibrils, are produced by cells from various organs. Collagen fibrils are fundamental components of connective tissue that are responsible for bearing much of the body's mechanical load. They often cluster into higher-order structures, such as intervertebral discs, corneal lamellae, and tendon bundles [77]. Their regenerative potential, mechanical properties, and functions depend on several factors related to the collagen architecture, in particular, alignment of parallel fibers, intermolecular cross-linking, and fibril packing density [78]. The spontaneous assembly of collagen fibrils from collagen monomers can be reproduced *in vitro*. In acidic environments, fibrillar collagen isolated from animal tissues dissociates into individual collagen monomers. When exposed to neutral or weakly alkaline conditions, these molecules reassemble into bundles of fibrils with a characteristic cross-striation that can be observed under an electron microscope (Fig. 3a). As we have previously shown, EGCG inhibits the formation of collagen fibrils from collagen monomers [79]. Thus, in the presence of EGCG, electron microscopy revealed only unstructured material consisting of individual collagen molecules (Fig. 3b).

Turbidimetric analysis further confirmed the EGCG's ability to prevent the formation of collagen fibrillar structures, as evidenced by a significant

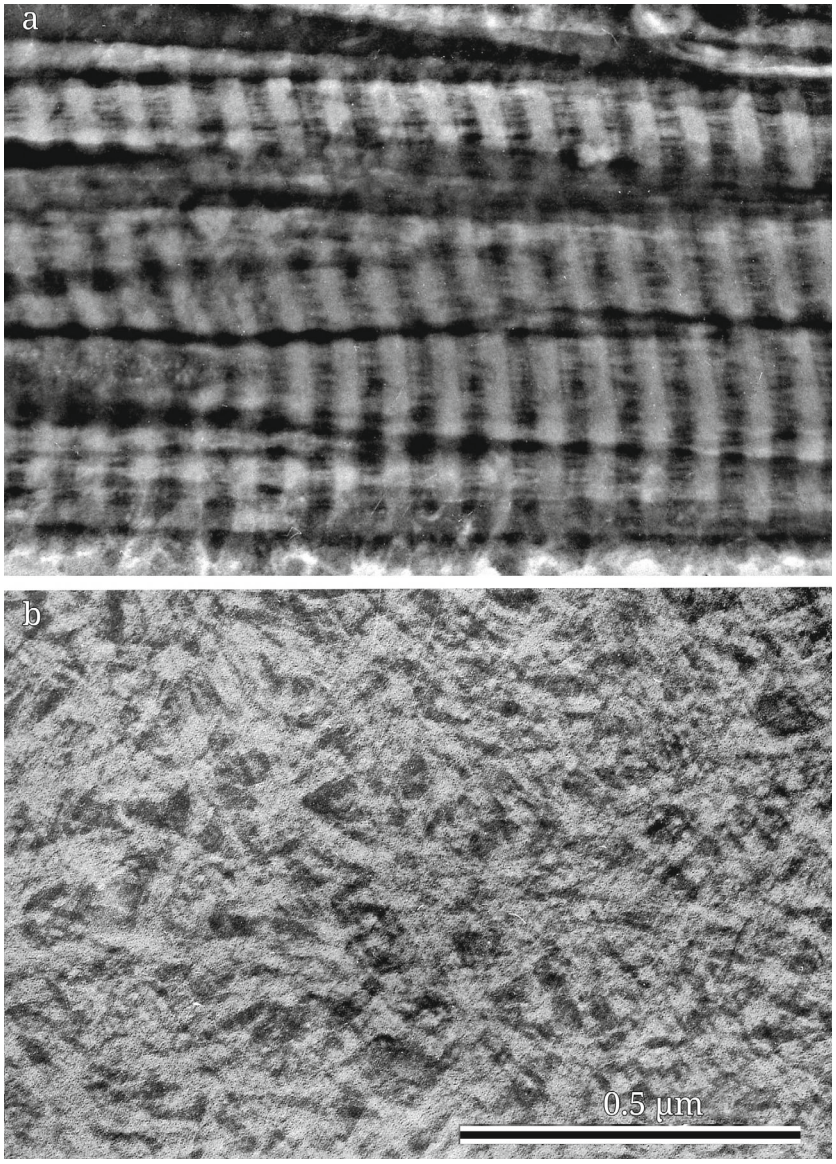

Fig. 3. Transmission electron microscopy of type I collagen fibrils. Cross-striated fibrils (a, control) and disordered collagen monomer molecules in the presence of 1 μM EGCG (b) (see [79] for details).

reduction in the optical density when the collagen solution was transferred from the acidic to neutral environment (Fig. 4). These findings indicate that tea catechins, like some other compounds, significantly affect the formation of collagen fibrils [79-84]. The correlation of the data presented *in vitro* with the *in vivo* experiments is noteworthy. For example, *in vitro* EGCG inhibits fibril assembly, while catechin accelerates this process [79]. Similarly, EGCG prevented the development of nonalcoholic steatohepatitis and, accordingly, inhibited the formation of collagen fibrils and the development of collagenosis in a mouse model, whereas catechin failed to demonstrate this protective effect [85].

We have previously demonstrated that many polyphenolic compounds, including simple phenols (phenol, pyrocatechol, resorcinol, and pyrogallol) accelerate collagen fibrillogenesis [86]. Among flavonoids, kaempferol and flavone accelerate collagen fibril formation, while quercetin and myricetin suppress it [80, 81], the effect correlating with the number of hydroxyl groups in the B-ring of these molecules [80]. Overall, most polyphenols examined in our studies promoted collagen fibril formation and only a few inhibited it. Although research in this area is far from complete, EGCG likely demonstrates the greatest activity against fibril formation among the agents listed above. It is also well recognized for its antifibrotic action. In recent years, particular attention has been given to EGCG's ability to promote scarless wound healing, which is associated with the downregulation of genes encoding TGF-β1, Col-I,

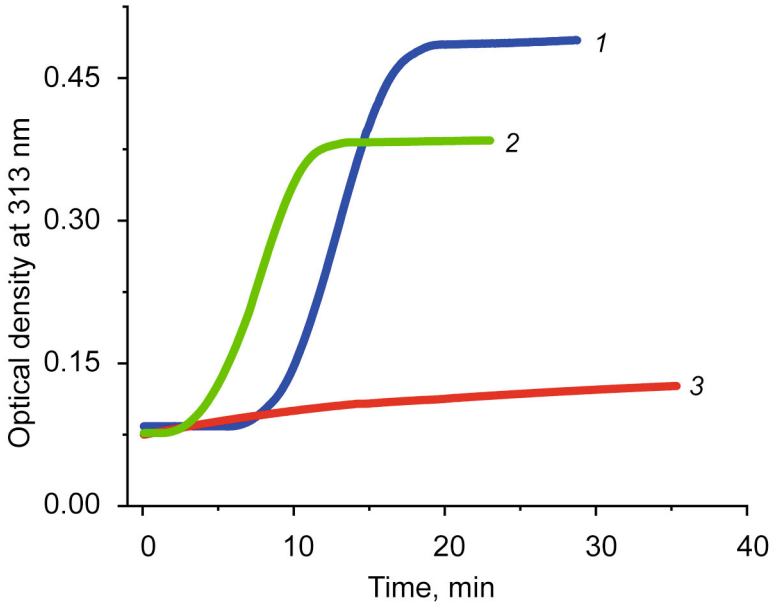

Fig. 4. Effect of green tea catechins on the optical density of collagen monomer solution during collagen fibril formation: control (*1*); in the presence of 1 μM catechin (*2*); in the presence of 1 μM EGCG (*3*) (see [79] for details).

Col-III, α-SMA, and eNOS [87]. The antifibrotic activity that supports scarless wound healing has also been reported for quercetin and myricetin [88, 89], consistent with their capacity to inhibit collagen fibril formation.

THE EFFECT OF EGCG ON PROTEIN–PROTEIN INTERACTIONS

The inhibitory effect of EGCG on collagen fibril formation is not unique and has been observed with other proteins as well. EGCG is known to modify the structure of certain proteins and prevent fibril formation [90]. This activity likely arises from the EGCG's ability to interact with polar and aromatic residues through hydrogen bonds, π–π interactions, and cation–π interactions, due to a greater number of aromatic rings and hydroxyl groups in the EGCG molecule compared to most flavonoids. As a result, EGCG can effectively disrupt intra- and intermolecular interactions in protein aggregates [91].

For example, EGCG prevents the aggregation of various amyloid-forming proteins, which is the cause of amyloidosis [92]. Amyloidoses are a group of more than 40 diseases characterized by the accumulation of protein aggregates in human tissues. Aggregation of amyloid proteins can contribute to neurodegenerative diseases, such as the Huntington's disease, Parkinson's disease, and Alzheimer's disease [93].

Amyloid assembly results from the interaction of protein filaments with the formation of β-sheet-rich fibrillar structures [93]. Small peptides, such as amyloid-beta (Aβ) and islet amyloid polypeptide (IAPP), can form toxic amyloid aggregates via both cross-assembly and self-assembly. Typically, amyloid peptides form stable heterodimers that serve as co-aggregation precursors. By reducing the number of β-sheets in the peptides, EGCG inhibits oligomer formation [94, 95].

EGCG prevents the aggregation of multiple pathogenic proteins, such as huntingtin, Aβ, and α-synuclein. EGCG inhibits the fibrillogenesis of these proteins, reduces amyloid cytotoxicity, and promotes fibril remodeling into non-toxic amorphous structures both *in vitro* and *in vivo* [93]. By blocking the formation of bonds between $A\beta_{40}$ and $A\beta_{42}$, EGCG effectively prevented their co-dimerization, a key process in the pathophysiology of Alzheimer's disease [91]. EGCG binds to $A\beta_{40}$ and $A\beta_{42}$ through hydrogen bonds, π–π interactions, and cation–π interactions with polar and aromatic residues on these peptides. By disrupting long-range interactions, EGCG disaggregates mixed $A\beta_{40}$–$A\beta_{42}$ fibrils [91]. EGCG also inhibited the fibrillogenesis of Aβ and α-synuclein, reducing their cellular toxicity [96]. Additionally, EGCG can suppress the development of pathological processes characteristic of Alzheimer's disease by preventing tau protein aggregation [97, 98].

The effect of EGCG on the NLRP3 inflammasome further demonstrates its ability to modify protein–protein interactions. The NLRP3 inflammasome releases pro-inflammatory cytokines such as IL-1β/IL-18 in response to microbial infection and cell damage. EGCG has a high affinity for the NLRP3 protein, thus preventing inflammasome activation [99].

EGCG INTAKE DOSES AND EGCG BODY CONTENT

The proposed optimal therapeutic dose of EGCG (200 mg/kg body weight) has been shown to significantly reduce the levels of the pro-inflammatory cytokines TNF-α, IL-1β, and IL-18 [100]. Other studies have indicated that the therapeutic effects of EGCG can be observed even at lower doses (20-25 μg/kg body weight) [34, 38, 101]. In cellular models, the effective concentrations of EGCG were 1 μM [102], 0.1 μM, 10 μM [103], and 35 μg/mL [104]. Furthermore, local application of EGCG solutions (10-100 μM) has exhibited the antifibrotic effects and promoted wound healing [34, 105-107].

The bioavailability of EGCG consumed with food is low [108]. Consequently, systemic EGCG concentrations achieved through dietary intake are considerably lower than those used in cell models or local applications. For example, consuming a single cup of tea typically results in the plasma catechin concentration of approximately 0.5 μM [109]. In another study, oral administration of 1.5 mmol of EGCG in volunteers produced the peak blood content of this agent of 1.3 μM within 2-3 h [110-115], followed by a slow elimination at a rate of $t_{1/2\text{-elim}}$ = 5-5.5 h [110]. According to the recommendations of the European Food Safety Authority (EFSA), the daily intake of EGCG for an adult is 90-300 mg (about 4 cups of tea per day) [116]. However, for therapeutic purposes, higher doses can be safely achieved through pharmaceutical formulations, such as capsules or tablets [116]. For example, a clinical study showed that daily intake of 1600 mg of EGCG for 4 weeks, which is equivalent to 16 cups of green tea per day, was well-tolerated in healthy individuals and can be considered safe [117]. Dietary intake of EGCG up to 500 mg/kg per day for 13 weeks in rats and dogs caused no adverse effects and was also determined as safe. However, taking large doses of EGCG on an empty stomach can cause gastrointestinal discomfort and hepatic stress [118]. Very high doses of EGCG (up to 2000 mg/kg) were lethal to rats [119].

EGCG TARGETS IN CELLS AND TISSUES

The data above suggest the existence of multiple potential therapeutic pathways for EGCG, which can act at various stages of fibrotic changes in damaged tissues. EGCG can penetrate into the cytoplasm [120] due to the inherent ability of flavonoids to interact with the phospholipid bilayer of cell membranes [121], a process that can be facilitated by the formation of complexes with transition metals, such as iron [122-124]. Therefore, a few hours after administration of fluorescently labeled EGCG, its presence can be detected in the cytoplasm, cellular compartments, and the nucleus [125], suggesting the EGCG's ability to directly affect various intracellular processes. These include modulation of gene expression through interaction with DNA and RNA [126, 127], modulation of intracellular signaling cascades through acting on lipid rafts in membranes [128-131], and regulation of processes related to the pro- and antioxidant activities of EGCG [120, 132, 133]. Remarkably, the effects of EGCG on cell proliferation can also vary greatly and even be the opposite. For example, in rapidly dividing cells (e.g., tumor cells), EGCG inhibits the activity of signaling cascades responsible for cell division, such as those involving Akt, AMPK, and NF-κB, leading to the cell cycle arrest, increased ROS generation, and apoptosis [134-137], whereas in primary cells, EGCG activates AMPK-involving signaling pathways that promote cell division and reduce ROS production [138-140]. Among tea catechins, EGCG exhibits the strongest capacity to influence intracellular processes, which implies its significant potential for medical applications [141].

Inflammatory processes lead to sustained tissue damage in various organs, accompanied by cell apoptosis and lipid peroxidation capable of triggering the activation of cardiac fibroblasts and HSCs. Once activated, these cells increase the production of proteins involved in the fibrotic deposition, including collagen monomers which assemble in collagen fibrils and contribute to the development of tissue fibrosis as a result of ECM deposition. According to our proposed scheme (Fig. 5), EGCG can intervene at various stages of fibrotic changes. First, it targets cells at the site of inflammation, exerting either cytostatic or cytotoxic effect, depending on the concentration and conditions, thereby inhibiting the activation of fibroblasts or HSCs (Fig. 5a). Second, EGCG can also affect activated fibroblasts and HSCs and suppress collagen monomer synthesis by these cells (Fig. 5b). Finally, we propose a new mechanism for the EGCG's antifibrotic action. According to our findings, EGCG inhibits the formation of collagen fibrils by interacting with collagen monomers (Fig. 5c). This effect increases with the increase in the EGCG concentration [79] and does not weaken or reverse, unlike effects mediated by the anti- and pro-oxidant activities.

It should be noted that the cellular effects of EGCG strongly depend on the mode of application and concentration of this agent. Despite numerous published reports on the ECGC activity, most these studies have not measured its concentration in the blood, nor have they performed continuous monitoring of this parameter. This omission is particularly critical for oral administration, given EGCG's low bioavailability.

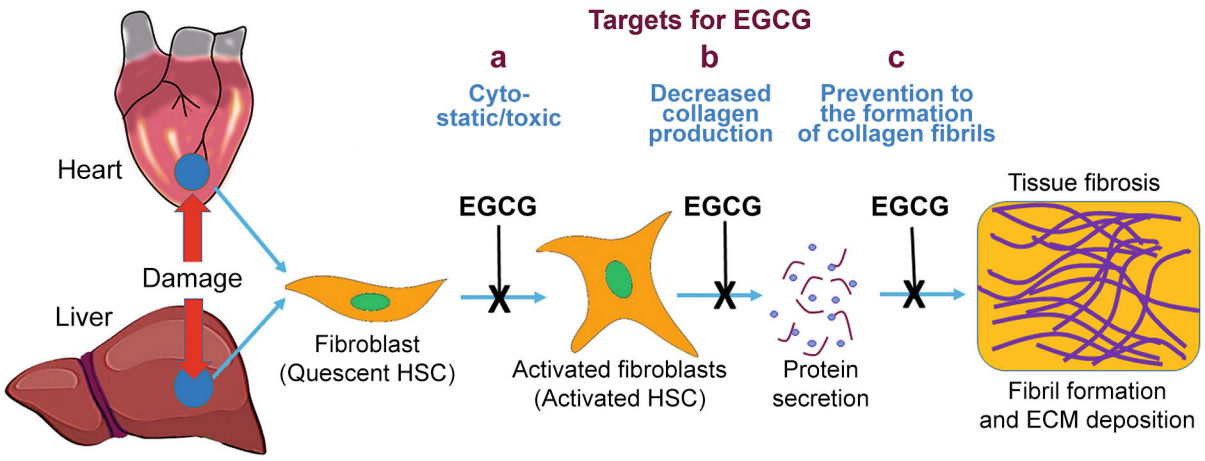

Fig. 5. Possible EGCG targets in the treatment of tissue fibrosis in cardiac muscle and liver. EGCG prevents the activation of fibroblasts and HSCs (a), inhibits the secretion of proteins (mostly, collagen) by cells (b), and suppresses collagen fibril formation and ECM deposition (c).

PROSPECTS FOR THE USE OF EGCG IN PREVENTING FIBROTIC DISEASES

Many polyphenolic compounds, including EGCG, have low solubility and bioavailability, which significantly limits their therapeutic applications. Moreover, the concentrations of these substances required to achieve a therapeutic effect can sometimes have adverse effects on healthy organs. Therefore, approaches are being developed to locally increase the concentration of polyphenolic compounds directly at the site of therapeutic intervention.

One of the most notable examples of the use of the EGCG's antifibrotic activity is the development of new EGCG-enriched materials designed to prevent keloid scar formation [62, 106, 142]. Even a simple local injection of the preparation into the damaged area produced significant anti-scar effect due to the increased local EGCG concentration [87, 106]. In an experimental scar formation model (healing of rabbit ears after injury), injection of 1 mg of EGCG has a markedly greater healing and anti-scar effect compared to injection of 0.5 mg of EGCG under the same conditions, indicating a clear dose-dependent relationship [87].

Currently, several strategies have been developed to sustain elevated levels of EGCG in the damaged area. These include encapsulation of Cu^{2+}–EGCG complexes in a hydrogel to promote the healing of severe burn wounds without scarring. This approach exemplifies successful exploitation of EGCG's pro-oxidant properties when complexed with metal ions [62, 63]. Another example is creation of nanosized coacervates containing fibroblast growth factor and attached EGCG–polylysine complex, which effectively prevented scar formation by achieving high local EGCG concentrations in the damaged area [143].

In these and similar studies, the observed therapeutic effects of EGCG have been mostly attributed to the EGCG's ability to scavenge ROS from tissues or to modulate cell signaling, thereby suppressing inflammation and activating angiogenesis during wound healing [62, 143-145]. We propose that the EGCG's ability to prevent fibrosis and promote scarless wound healing may result not only from its effect on cellular signaling but also from the direct interaction with collagen monomers, which blocks collagen fibril formation. Our research indicates (Fig. 4) that screening for potent inhibitors of collagen fibrillogenesis among polyphenol-based compounds or their derivatives can be carried out *in vitro* by analyzing the dynamics of light scattering in collagen solutions during fibril formation [79]. This approach can substantially reduce research time and costs and facilitate the development of new drugs.

CONCLUSION

It is well established that EGCG can directly interact with amyloid proteins and inhibit amyloid fibril formation, thereby mitigating development of neurological disorders, such as the Alzheimer's disease. In contrast, most studies on the effect of EGCG on the formation of collagen fibrils involved in fibrosis development have been focused on its antioxidant properties and ability to influence intracellular signaling. The EGCG's potential to directly influence collagen fibrillogenesis, however, has often been overlooked.

Our previous experiments have demonstrated that EGCG can effectively inhibit collagen fibril formation *in vitro*, which excludes the involvement

of cellular signaling systems and suggests the possibility of direct inhibitory effect of EGCG on the formation of collagen fibrils *in vivo*. Understanding the mechanisms by which EGCG modulates collagen fibrillogenesis may open new prospects in the development of drugs for the treatment of fibrotic diseases.

Abbreviations

Aβ	amyloid-beta
EGCG	epigallocatechin-3-gallate
ECM	extracellular matrix
HSC	hepatic stellate cell
ROS	reactive oxygen species

Contributions

Yu.S.T. developed the concept and wrote the text of the article; S.G.G. participated in the described experiments and edited the manuscript; Yu.A.K. developed the concept, supervised the study, and edited the manuscript.

Funding

This study was supported by the Ministry of Science and Higher Education of the Russian Federation as a part of the State Assignment for the Institute of Cell Biophysics, Russian Academy of Sciences (no. 075-00612-26-00) and the State Assignment for the Institute of Theoretical and Experimental Biophysics, Russian Academy of Sciences (no. 075-00224-26-00).

Ethics approval and consent to participate

This work does not contain studies involving human or animal subjects.

Conflict of interest

The authors of this work declare that they have no conflicts of interest.

REFERENCES

1. Rana, A., Samtiya, M., Dhewa, T., Mishra, V., and Aluko, R. E. (2022) Health benefits of polyphenols: a concise review, *J. Food Biochem.*, **46**, e14264, https://doi.org/10.1111/jfbc.14264.
2. Di Lorenzo, C., Colombo, F., Biella, S., Stockley, C., and Restani, P. (2021) Polyphenols and human health: the role of bioavailability, *Nutrients*, **13**, 273, https://doi.org/10.3390/nu13010273.
3. Shen, N., Wang, T., Gan, Q., Liu, S., Wang, L., and Jin, B. (2022) Plant flavonoids: Classification, distribution, biosynthesis, and antioxidant activity, *Food Chem.*, **383**, 132531, https://doi.org/10.1016/j.foodchem.2022.132531.
4. Al-Khayri, J. M., Sahana, G. R., Nagella, P., Joseph, B. V., Alessa, F. M., and Al-Mssallem, M. Q. (2022) Flavonoids as potential anti-inflammatory molecules: a review, *Molecules*, **27**, 2901, https://doi.org/10.3390/molecules27092901.
5. Chagas, M. D. S. S., Behrens, M. D., Moragas-Tellis, C. J., Penedo, G. X. M., Silva, A. R., and Gonçalves-de-Albuquerque, C. F. (2022) Flavonols and flavones as potential anti-inflammatory, antioxidant, and antibacterial compounds, *Oxid. Med. Cell. Longev.*, **2022**, 9966750, https://doi.org/10.1155/2022/9966750.
6. Nicolucci, C., Padovani, M., Rodrigues, F. d. C., Fritsch, L. N., Santos, A. C., Priolli, D. G., and Sciani, J. M. (2024) Flavonoids: the use in mental health and related diseases, *Nat. Prod. Res.*, **38**, 4223-4233, https://doi.org/10.1080/14786419.2023.2275275.
7. Pyo, Y., Kwon, K. H., and Jung, Y. J. (2024) Anticancer potential of flavonoids: their role in cancer prevention and health benefits, *Foods*, **13**, 2253, https://doi.org/10.3390/foods13142253.
8. Bouyahya, A., Balahbib, A., Khalid, A., Makeen, H. A., Alhazmi, H. A., Albratty, M., Hermansyah, A., Ming, L. C., Goh, K. W., and El Omari, N. (2024) Clinical applications and mechanism insights of natural flavonoids against type 2 diabetes mellitus, *Heliyon*, **10**, e29718, https://doi.org/10.1016/j.heliyon.2024.e29718.
9. Stone, R. C., Chen, V., Burgess, J., Pannu, S., and Tomic-Canic, M. (2020) Genomics of human fibrotic diseases: disordered wound healing response, *Int. J. Mol. Sci.*, **21**, 8590, https://doi.org/10.3390/ijms21228590.
10. Ye, X., Li, J., Liu, Z., Sun, X., Wei, D., Song, L., and Wu, C. (2023) Peptide mediated therapy in fibrosis: Mechanisms, advances and prospects, *Biomed. Pharmacother.*, **157**, 113978, https://doi.org/10.1016/j.biopha.2022.113978.
11. Walraven, M., and Hinz, B. (2018) Therapeutic approaches to control tissue repair and fibrosis: extracellular matrix as a game changer, *Matrix Biol.*, **71-72**, 205-224, https://doi.org/10.1016/j.matbio.2018.02.020.
12. Rosenbloom, J., Macarak, E., Piera-Velazquez, S., and Jimenez, S. A. (2017) Human fibrotic diseases: current challenges in fibrosis research, *Methods Mol. Biol.*, **1627**, 1-23, https://doi.org/10.1007/978-1-4939-7113-8_1.
13. Boer, R. A. d., Keulenaer, G. d., Bauersachs, J., Brutsaert, D., Cleland, J. G., Diez, J., Du, X.-J., Ford, P., Heinzel, F. R., Lipson, K. E., McDonagh, T., Lopez-Andres, N., Lunde, I. G., Lyon, A. R., Pollesello, P., Prasad, S. K., Tocchetti, C. G., Mayr, M., Sluijter, J. P. G., Thum, T., Tschöpe, C., Zannad, F., Zimmermann, W.-H., Ruschitzka, F., Filippatos, G., Lindsey, M. L., Maack, C., and Heymans, S. (2019) Towards better definition, quantification and treatment of fibrosis in heart failure. A scientific roadmap by the Committee of Translational Research of the Heart Failure

Association (HFA) of the European Society of Cardiology, *Eur. J. Heart Fail.*, **21**, 272-285, https://doi.org/10.1002/ejhf.1406.
14. Wei, W., Li, T., Chen, J., Fan, Z., Gao, F., Yu, Z., and Jiang, Y. (2024) SIRT3/6: an amazing challenge and opportunity in the fight against fibrosis and aging, *Cell. Mol. Life Sci.*, **81**, 69, https://doi.org/10.1007/s00018-023-05093-z.
15. Burke, R. M., Burgos Villar, K. N., and Small, E. M. (2021) Fibroblast contributions to ischemic cardiac remodeling, *Cell. Signal.*, **77**, 109824, https://doi.org/10.1016/j.cellsig.2020.109824.
16. Segura, A. M., Frazier, O. H., and Buja, L. M. (2014) Fibrosis and heart failure, *Heart Fail. Rev.*, **19**, 173-185, https://doi.org/10.1007/s10741-012-9365-4.
17. Mei, X., and Cheng, K. (2020) Recent development in therapeutic cardiac patches, *Front. Cardiovasc. Med.*, **7**, 610364, https://doi.org/10.3389/fcvm.2020.610364.
18. Xie, Y., van Handel, B., Qian, L., and Ardehali, R. (2023) Recent advances and future prospects in direct cardiac reprogramming, *Nat. Cardiovasc. Res.*, **2**, 1148-1158, https://doi.org/10.1038/s44161-023-00377-w.
19. Hashimoto, H., Olson, E. N., and Bassel-Duby, R. (2018) Therapeutic approaches for cardiac regeneration and repair, *Nat. Rev. Cardiol.*, **15**, 585-600, https://doi.org/10.1038/s41569-018-0036-6.
20. Yang, B., Qiao, Y., Yan, D., and Meng, Q. (2024) Targeting interactions between fibroblasts and macrophages to treat cardiac fibrosis, *Cells*, **13**, 764, https://doi.org/10.3390/cells13090764.
21. Ravassa, S., López, B., Treibel, T. A., San José, G., Losada-Fuentenebro, B., Tapia, L., Bayés-Genís, A., Díez, J., and González, A. (2023) Cardiac fibrosis in heart failure: focus on non-invasive diagnosis and emerging therapeutic strategies, *Mol. Aspects Med.*, **93**, 101194, https://doi.org/10.1016/j.mam.2023.101194.
22. Kretschmar, C., Hernández-Cáceres, M. P., Reyes, M., Peña-Oyarzún, D., García-Navarrete, C., Troncoso, R., Díaz-Castro, F., Budini, M., Morselli, E., Riquelme, J. A., Hill, J. A., Lavandero, S., and Criollo, A. (2023) Methods for studying primary cilia in heart tissue after ischemia-reperfusion injury, *Methods Cell Biol.*, **176**, 85-101, https://doi.org/10.1016/bs.mcb.2022.12.013.
23. Zhang, Y., Ren, L., Tian, Y., Guo, X., Wei, F., and Zhang, Y. (2024) Signaling pathways that activate hepatic stellate cells during liver fibrosis, *Front. Med. (Lausanne)*, **11**, 1454980, https://doi.org/10.3389/fmed.2024.1454980.
24. Thaiss, W. M., Sannwald, L., Kloth, C., Ekert, K., Hepp, T., Boesmueller, H., Klag, T., Nikolaou, K., Horger, M., and Kaufmann, S. (2019) Quantification of hemodynamic changes in chronic liver disease: correlation of perfusion-CT data with histopathologic staging of fibrosis, *Acad. Radiol.*, **26**, 1174-1180, https://doi.org/10.1016/j.acra.2018.11.009.
25. Barbarroja, N., Ruiz-Ponce, M., Cuesta-López, L., Pérez-Sánchez, C., López-Pedrera, C., La Arias-de Rosa, I., and Collantes-Estévez, E. (2022) Nonalcoholic fatty liver disease in inflammatory arthritis: relationship with cardiovascular risk, *Front. Immunol.*, **13**, 997270, https://doi.org/10.3389/fimmu.2022.997270.
26. Lucantoni, F., Martínez-Cerezuela, A., Gruevska, A., Moragrega, Á. B., Víctor, V. M., Esplugues, J. V., Blas-García, A., and Apostolova, N. (2021) Understanding the implication of autophagy in the activation of hepatic stellate cells in liver fibrosis: are we there yet? *J. Pathol.*, **254**, 216-228, https://doi.org/10.1002/path.5678.
27. Akkız, H., Gieseler, R. K., and Canbay, A. (2024) Liver fibrosis: from basic science towards clinical progress, focusing on the central role of hepatic stellate cells, *Int. J. Mol. Sci.*, **25**, 7873, https://doi.org/10.3390/ijms25147873.
28. Bülow, R. D., and Boor, P. (2019) Extracellular matrix in kidney fibrosis: more than just a scaffold, *J. Histochem. Cytochem.*, **67**, 643-661, https://doi.org/10.1369/0022155419849388.
29. Theocharis, A. D., Manou, D., and Karamanos, N. K. (2019) The extracellular matrix as a multitasking player in disease, *FEBS J.*, **286**, 2830-2869, https://doi.org/10.1111/febs.14818.
30. Csapo, R., Gumpenberger, M., and Wessner, B. (2020) Skeletal muscle extracellular matrix – What do we know about its composition, regulation, and physiological roles? A narrative review, *Front. Physiol.*, **11**, 253, https://doi.org/10.3389/fphys.2020.00253.
31. Onursal, C., Dick, E., Angelidis, I., Schiller, H. B., and Staab-Weijnitz, C. A. (2021) Collagen biosynthesis, processing, and maturation in lung ageing, *Front. Med. (Lausanne)*, **8**, 593874, https://doi.org/10.3389/fmed.2021.593874.
32. Luangmonkong, T., Parichatikanond, W., and Olinga, P. (2023) Targeting collagen homeostasis for the treatment of liver fibrosis: opportunities and challenges, *Biochem. Pharmacol.*, **215**, 115740, https://doi.org/10.1016/j.bcp.2023.115740.
33. Yang, L., Chen, F., Li, X., Sun, X., Li, H., Shi, H., and Zhao, G. (2026) EGCG inhibits hepatic stellate cell activity and liver fibrosis by targeting the MDM2/MUC5AC-mediated TGF-β1/Smad signaling pathway, *Pathol. Res. Pract.*, **277**, 156298, https://doi.org/10.1016/j.prp.2025.156298.
34. Yu, D.-K., Zhang, C.-X., Zhao, S.-S., Zhang, S.-H., Zhang, H., Cai, S.-Y., Shao, R.-G., and He, H.-W. (2015) The anti-fibrotic effects of epigallocatechin-3-gallate in bile duct-ligated cholestatic rats and human hepatic stellate LX-2 cells are mediated by the PI3K/Akt/Smad pathway, *Acta Pharmacol. Sin.*, **36**, 473-482, https://doi.org/10.1038/aps.2014.155.

35. Mostafa-Hedeab, G., Ewaiss Hassan, M., Halawa, T. F., and Ahmed Wani, F. (2022) Epigallocatechin gallate ameliorates tetrahydrochloride-induced liver toxicity in rats via inhibition of TGFβ/p-ERK/p-Smad1/2 signaling, antioxidant, anti-inflammatory activity, *Saudi Pharm. J.*, **30**, 1293-1300, https://doi.org/10.1016/j.jsps.2022.06.021.
36. Burgy, O., and Königshoff, M. (2024) Teatime: epigallocatechin gallate targets fibroblast-epithelial cell crosstalk to combat lung fibrosis, *J. Clin. Invest.*, **134**, e183970, https://doi.org/10.1172/JCI183970.
37. Cohen, M. L., Brumwell, A. N., Ho, T. C., Garakani, K., Montas, G., Leong, D., Ding, V. W., Golden, J. A., Trinh, B. N., Jablons, D. M., Matthay, M. A., Jones, K. D., Wolters, P. J., Wei, Y., Chapman, H. A., and Le Saux, C. J. (2024) A fibroblast-dependent TGF-β1/sFRP2 noncanonical Wnt signaling axis promotes epithelial metaplasia in idiopathic pulmonary fibrosis, *J. Clin. Invest.*, **134**, e174598, https://doi.org/10.1172/JCI174598.
38. Adamcakova, J., Balentova, S., Barosova, R., Hanusrichterova, J., Mikolka, P., Prso, K., Mokry, J., Tatarkova, Z., Kalenska, D., and Mokra, D. (2023) Effects of green tea polyphenol epigallocatechin-3-gallate on markers of inflammation and fibrosis in a rat model of pulmonary silicosis, *Int. J. Mol. Sci.*, **24**, 1857, https://doi.org/10.3390/ijms24031857.
39. Mohan, T., Velusamy, P., Chakrapani, L. N., Srinivasan, A. K., Singh, A., Johnson, T., and Periandavan, K. (2017) Impact of EGCG supplementation on the progression of diabetic nephropathy in rats: an insight into fibrosis and apoptosis, *J. Agric. Food Chem.*, **65**, 8028-8036, https://doi.org/10.1021/acs.jafc.7b03301.
40. Li, G., Yang, H., Zhang, D., Zhang, Y., Liu, B., Wang, Y., Zhou, H., Xu, Z.-X., and Wang, Y. (2024) The role of macrophages in fibrosis of chronic kidney disease, *Biomed. Pharmacother.*, **177**, 117079, https://doi.org/10.1016/j.biopha.2024.117079.
41. Li, F., Zhou, Y., Liu, B., Du, Z., and Huang, W. (2025) Epigallocatechin gallate-mediated inhibition of mitochondrial DNA sensing regulated by TBK1/cGAS/STING and NLRP3 alleviates cardiovascular toxicity in atherosclerosis, *Int. Immunopharmacol.*, **164**, 115375, https://doi.org/10.1016/j.intimp.2025.115375.
42. Wang, L., Li, L., Zhao, D., Yuan, H., Zhang, H., Chen, J., Pang, D., Lu, Y., and Ouyang, H. (2024) MYH7 R453C induced cardiac remodelling via activating TGF-β/Smad2/3, ERK1/2 and Nox4/ROS/NF-κB signalling pathways, *Open Biol.*, **14**, 230427, https://doi.org/10.1098/rsob.230427.
43. Li, T., Tong, Q., Wang, Z., Yang, Z., Sun, Y., Cai, J., Xu, Q., Lu, Y., Liu, X., Lin, K., and Qian, Y. (2024) Epigallocatechin-3-gallate inhibits atrial fibrosis and reduces the occurrence and maintenance of atrial fibrillation and its possible mechanisms, *Cardiovasc. Drugs Ther.*, **38**, 895-916, https://doi.org/10.1007/s10557-023-07447-y.
44. Jia, Q., Yang, R., Mehmood, S., and Li, Y. (2022) Epigallocatechin-3-gallate attenuates myocardial fibrosis in diabetic rats by activating autophagy, *Exp. Biol. Med. (Maywood)*, **247**, 1591-1600, https://doi.org/10.1177/15353702221110646.
45. Gui, L., Wang, F., Hu, X., Liu, X., Yang, H., Cai, Z., Qi, M., and Dai, C. (2022) Epigallocatechin gallate protects diabetes mellitus rats complicated with cardiomyopathy through TGF-β1/JNK signaling pathway, *Curr. Pharm. Des.*, **28**, 2758-2770, https://doi.org/10.2174/1381612828666220902115437.
46. Ren, L. L., Li, X. J., Duan, T. T., Li, Z. H., Yang, J. Z., Zhang, Y. M., Zou, L., Miao, H., and Zhao, Y. Y. (2023) Transforming growth factor-β signaling: from tissue fibrosis to therapeutic opportunities, *Chem. Biol. Interact.*, **369**, 110289, https://doi.org/10.1016/j.cbi.2022.110289.
47. He, C., Wang, D., Wang, R., Huang, Y., Huang, X., Shen, S., Lv, J., and Wu, M. (2022) Epigallocatechin gallate induces the demethylation of actinin alpha 4 to inhibit diabetic nephropathy renal fibrosis via the NF-κB signaling pathway *in vitro*, *Dose Response*, **20**, 15593258221105704, https://doi.org/10.1177/15593258221105704.
48. Zhang, Y., Li, J., Wang, Z., Chen, J., Zhao, M., Guo, C., Wang, T., Li, R., Zhang, H., Ma, X., Wen, Y., Zeng, J., and Efferth, T. (2025) Preclinical evidence construction for epigallocatechin-3-gallate against non-alcoholic fatty liver disease: a meta-analysis and machine learning study, *Phytomedicine*, **142**, 156651, https://doi.org/10.1016/j.phymed.2025.156651.
49. Li, D., Cao, D., Sun, Y., Cui, Y., Zhang, Y., Jiang, J., and Cao, X. (2024) The roles of epigallocatechin gallate in the tumor microenvironment, metabolic reprogramming, and immunotherapy, *Front. Immunol.*, **15**, 1331641, https://doi.org/10.3389/fimmu.2024.1331641.
50. Neuzil, J., Wang, X.-F., Dong, L.-F., Low, P., and Ralph, S. J. (2006) Molecular mechanism of 'mitocan'-induced apoptosis in cancer cells epitomizes the multiple roles of reactive oxygen species and Bcl-2 family proteins, *FEBS Lett.*, **580**, 5125-5129, https://doi.org/10.1016/j.febslet.2006.05.072.
51. Vostrikova, S. M., Grinev, A. B., and Gogvadze, V. G. (2020) Reactive oxygen species and antioxidants in carcinogenesis and tumor therapy, *Biochemistry (Moscow)*, **85**, 1254-1266, https://doi.org/10.1134/S0006297920100132.
52. Meng, Q., Velalar, C. N., and Ruan, R. (2008) Effects of epigallocatechin-3-gallate on mitochondrial integrity and antioxidative enzyme activity in the aging process of human fibroblast, *Free Radic. Biol. Med.*, **44**, 1032-1041, https://doi.org/10.1016/j.freeradbiomed.2007.11.023.

53. Lambert, J. D., and Elias, R. J. (2010) The antioxidant and pro-oxidant activities of green tea polyphenols: a role in cancer prevention, *Arch. Biochem. Biophys.*, **501**, 65-72, https://doi.org/10.1016/j.abb.2010.06.013.
54. Kanadzu, M., Lu, Y., and Morimoto, K. (2006) Dual function of (–)-epigallocatechin gallate (EGCG) in healthy human lymphocytes, *Cancer Lett.*, **241**, 250-255, https://doi.org/10.1016/j.canlet.2005.10.021.
55. Collins, Q. F., Liu, H.-Y., Pi, J., Liu, Z., Quon, M. J., and Cao, W. (2007) Epigallocatechin-3-gallate (EGCG), a green tea polyphenol, suppresses hepatic gluconeogenesis through 5′-AMP-activated protein kinase, *J. Biol. Chem.*, **282**, 30143-30149, https://doi.org/10.1074/jbc.M702390200.
56. Helvacıoğlu, S., Hamitoğlu, M., Yıldırım, E., Vural Korkut, Ş., Yaba, A., and Aydın, A. (2025) Protective effects of rosmarinic acid and epigallocatechin gallate against doxorubicin-induced cytotoxicity and genotoxicity in CHO-K1 cells, *Turk. J. Pharm. Sci.*, **21**, 536-543, https://doi.org/10.4274/tjps.galenos.2024.80552.
57. Hazimeh, D., Massoud, G., Parish, M., Singh, B., Segars, J., and Islam, M. S. (2023) Green tea and benign gynecologic disorders: a new trick for an old beverage? *Nutrients*, **15**, 1439, https://doi.org/10.3390/nu15061439.
58. Yang, L., Jia, L., Li, X., Zhang, K., Wang, X., He, Y., Hao, M., Rayman, M. P., and Zhang, J. (2022) Prooxidant activity-based guideline for a beneficial combination of (–)-epigallocatechin-3-gallate and chlorogenic acid, *Food Chem.*, **386**, 132812, https://doi.org/10.1016/j.foodchem.2022.132812.
59. Vladu, A. F., Ficai, D., Ene, A. G., and Ficai, A. (2022) Combination therapy using polyphenols: An efficient way to improve antitumor activity and reduce resistance, *Int. J. Mol. Sci.*, **23**, 10244, https://doi.org/10.3390/ijms231810244.
60. Lee, Y., Lee, J., and Lim, C. (2021) Anticancer activity of flavonoids accompanied by redox state modulation and the potential for a chemotherapeutic strategy, *Food Sci. Biotechnol.*, **30**, 321-340, https://doi.org/10.1007/s10068-021-00899-8.
61. Nakagawa, H., Hasumi, K., Woo, J.-T., Nagai, K., and Wachi, M. (2004) Generation of hydrogen peroxide primarily contributes to the induction of Fe(II)-dependent apoptosis in Jurkat cells by (–)-epigallocatechin gallate, *Carcinogenesis*, **25**, 1567-1574, https://doi.org/10.1093/carcin/bgh168.
62. Chen, S., Xiong, Y., Yang, F., Hu, Y., Feng, J., Zhou, F., Liu, Z., Liu, H., Liu, X., Zhao, J., Zhang, Z., and Chen, L. (2024) Approaches to scarless burn wound healing: application of 3D printed skin substitutes with dual properties of anti-infection and balancing wound hydration levels, *EBioMedicine*, **106**, 105258, https://doi.org/10.1016/j.ebiom.2024.105258.
63. Hu, Y., Xiong, Y., Zhu, Y., Zhou, F., Liu, X., Chen, S., Li, Z., Qi, S., and Chen, L. (2023) Copper-epigallocatechin gallate enhances therapeutic effects of 3D-printed dermal scaffolds in mitigating diabetic wound scarring, *ACS Appl. Mater. Interfaces*, **15**, 38230-38246, https://doi.org/10.1021/acsami.3c04733.
64. Farhan, M., Khan, H. Y., Oves, M., Al-Harrasi, A., Rehmani, N., Arif, H., Hadi, S. M., and Ahmad, A. (2016) Cancer therapy by catechins involves redox cycling of copper ions and generation of reactive oxygen species, *Toxins (Basel)*, **8**, 37, https://doi.org/10.3390/toxins8020037.
65. Chen, Z., Duan, J., Diao, Y., Chen, Y., Liang, X., Li, H., Miao, Y., Gao, Q., Gui, L., Wang, X., Yang, J., and Li, Y. (2021) ROS-responsive capsules engineered from EGCG-zinc networks improve therapeutic angiogenesis in mouse limb ischemia, *Bioact. Mater.*, **6**, 1-11, https://doi.org/10.1016/j.bioactmat.2020.07.013.
66. Tang, C., Wang, H., Guo, L., Cui, Y., Zou, C., Hu, J., Zhang, H., Yang, G., and Zhou, W. (2025) Multifunctional nanomedicine for targeted atherosclerosis therapy: activating plaque clearance cascade and suppressing inflammation, *ACS Nano*, **19**, 3339-3361, https://doi.org/10.1021/acsnano.4c12131.
67. Wang, J., Zhang, R., Xie, H., Yang, Y., Chen, H., and Lin, Q. (2025) Metal-phenolic epigallocatechin gallate-zinc antioxidant nanoparticles for cataract treatment, *J. Control. Release*, **383**, 113798, https://doi.org/10.1016/j.jconrel.2025.113798.
68. Wei, H., Qin, J., Huang, Q., Jin, Z., Zheng, L., Zhao, J., and Qin, Z. (2023) Epigallocatechin-3-gallate (EGCG) based metal-polyphenol nanoformulations alleviates chondrocytes inflammation by modulating synovial macrophages polarization, *Biomed. Pharmacother.*, **161**, 114366, https://doi.org/10.1016/j.biopha.2023.114366.
69. Wang, Z., Shi, R., Niu, M., Liu, Y., Tang, C., Li, S., Lv, Y., Liu, Z., and Zhao, X. (2025) A metal-phenolic functionalized bacterial cellulose hydrogel: a novel strategy for near infrared triggered multistage regulation of infected wound healing, *Int. J. Biol. Macromol.*, **331**, 148452, https://doi.org/10.1016/j.ijbiomac.2025.148452.
70. Ouyang, J., Zhu, K., Liu, Z., and Huang, J. (2020) Prooxidant effects of epigallocatechin-3-gallate in health benefits and potential adverse effect, *Oxid. Med. Cell. Longev.*, **2020**, 9723686, https://doi.org/10.1155/2020/9723686.
71. Martin, K. R., and Barrett, J. C. (2002) Reactive oxygen species as double-edged swords in cellular processes: Low-dose cell signaling versus high-dose toxicity, *Hum. Exp. Toxicol.*, **21**, 71-75, https://doi.org/10.1191/0960327102ht213oa.

72. Seifried, H. E., Anderson, D. E., Fisher, E. I., and Milner, J. A. (2007) A review of the interaction among dietary antioxidants and reactive oxygen species, *J. Nutr. Biochem.*, **18**, 567-579, https://doi.org/10.1016/j.jnutbio.2006.10.007.
73. Raza, M. H., Siraj, S., Arshad, A., Waheed, U., Aldakheel, F., Alduraywish, S., and Arshad, M. (2017) ROS-modulated therapeutic approaches in cancer treatment, *J. Cancer Res. Clin. Oncol.*, **143**, 1789-1809, https://doi.org/10.1007/s00432-017-2464-9.
74. Fernández-Iglesias, A., Quesada, H., Díaz, S., Pajuelo, D., Bladé, C., Arola, L., Josepa Salvadó, M., and Mulero, M. (2013) DHA sensitizes FaO cells to tert-BHP-induced oxidative effects. Protective role of EGCG, *Food Chem. Toxicol.*, **62**, 750-757, https://doi.org/10.1016/j.fct.2013.10.013.
75. Kumar, A., and Bora, U. (2013) Interactions of curcumin and its derivatives with nucleic acids and their implications, *Mini Rev. Med. Chem.*, **13**, 256-264, https://doi.org/10.2174/1389557511313020007.
76. Salehi, B., Mishra, A. P., Nigam, M., Sener, B., Kilic, M., Sharifi-Rad, M., Fokou, P. V. T., Martins, N., and Sharifi-Rad, J. (2018) Resveratrol: a double-edged sword in health benefits, *Biomedicines*, **6**, 91, https://doi.org/10.3390/biomedicines6030091.
77. Siadat, S. M., and Ruberti, J. W. (2023) Mechanochemistry of collagen, *Acta Biomater.*, **163**, 50-62, https://doi.org/10.1016/j.actbio.2023.01.025.
78. Wohlgemuth, R. P., Brashear, S. E., and Smith, L. R. (2023) Alignment, cross linking, and beyond: a collagen architect's guide to the skeletal muscle extracellular matrix, *Am. J. Physiol. Cell Physiol.*, **325**, C1017-C1030, https://doi.org/10.1152/ajpcell.00287.2023.
79. Tarahovsky, Y. S., Gaidin, S. G., and Kim, Y. A. (2024) Effects of catechins on the formation of collagen fibrils *in vitro* [in Russian], *Biofizika*, **69**, 707-714, https://doi.org/10.31857/S0006302924040038.
80. Kim, Y. A., Tarahovsky, Y. S., Gaidin, S. G., Yagolnik, E. A., and Muzafarov, E. N. (2017) Flavonoids determine the rate of fibrillogenesis and structure of collagen type I fibrils *in vitro*, *Int. J. Biol. Macromol.*, **104**, 631-637, https://doi.org/10.1016/j.ijbiomac.2017.06.070.
81. Tarahovsky, Y. S., Selezneva, I. I., Vasilieva, N. A., Egorochkin, M. A., and Kim, Y. A. (2007) Acceleration of fibril formation and thermal stabilization of collagen fibrils in the presence of taxifolin (dihydroquercetin), *Bull. Exp. Biol. Med.*, **144**, 791-794, https://doi.org/10.1007/s10517-007-0433-z.
82. Williams, B. R., Gelman, R. A., Poppke, D. C., and Piez, K. A. (1978) Collagen fibril formation. Optimal *in vitro* conditions and preliminary kinetic results, *J. Biol. Chem.*, **253**, 6578-6585, https://doi.org/10.1016/S0021-9258(19)46970-6.
83. Ferrer, E. G., Salinas, M. V., Correa, M. J., Naso, L., Barrio, D. A., Etcheverry, S. B., Lezama, L., Rojo, T., and Williams, P. A. M. (2006) Synthesis, characterization, antitumoral and osteogenic activities of quercetin vanadyl(IV) complexes, *J. Biol. Inorg. Chem.*, **11**, 791-801, https://doi.org/10.1007/s00775-006-0122-9.
84. Bozec, L., van der Heijden, G., and Horton, M. (2007) Collagen fibrils: Nanoscale ropes, *Biophys. J.*, **92**, 70-75, https://doi.org/10.1529/biophysj.106.085704.
85. Dey, P., Olmstead, B. D., Sasaki, G. Y., Vodovotz, Y., Yu, Z., and Bruno, R. S. (2020) Epigallocatechin gallate but not catechin prevents nonalcoholic steatohepatitis in mice similar to green tea extract while differentially affecting the gut microbiota, *J. Nutr. Biochem.*, **84**, 108455, https://doi.org/10.1016/j.jnutbio.2020.108455.
86. Kim, Y. A., Gaidin, S. G., and Tarahovsky, Y. S. (2018) The influence of simple phenols on collagen type I fibrillogenesis *in vitro*, *Biophysics*, **63**, 162-168, https://doi.org/10.1134/S0006350918020148.
87. Song, Y., Wang, T., Yang, L., Wu, J., Chen, L., Fan, X., Zhang, Z., Yang, Q., Yu, Z., and Song, B. (2023) EGCG inhibits hypertrophic scar formation in a rabbit ear model, *J. Cosmet. Dermatol.*, **22**, 1382-1391, https://doi.org/10.1111/jocd.15587.
88. Fan, Z., Xia, G., Zhu, F., Yang, N., Ma, A., Shi, Y., Jiang, Z., Zhou, X., and Hou, Z. (2025) Ruthenium-quercetin coordinated nanotherapeutics with macrophage polarization regulation to rapidly promote bacterial-infected wound healing, *Mater. Today Bio*, **33**, 101983, https://doi.org/10.1016/j.mtbio.2025.101983.
89. McKay, T. B., Emmitte, K. A., German, C., and Karamichos, D. (2023) Quercetin and related analogs as therapeutics to promote tissue repair, *Bioengineering (Basel)*, **10**, 1127, https://doi.org/10.3390/bioengineering10101127.
90. Zhang, N., Yan, C., Yin, C., Hu, X., Guan, P., and Cheng, Y. (2022) Structural remodeling mechanism of the toxic amyloid fibrillary mediated by epigallocatechin-3-gallate, *ACS Omega*, **7**, 48047-48058, https://doi.org/10.1021/acsomega.2c05995.
91. Li, X., Zhang, Y., Wang, Y., Zhang, S., and Zhang, L. (2024) Molecular insights into the inhibition and disaggregation effects of EGCG on Aβ40 and Aβ42 cofibrillation, *J. Phys. Chem. B*, **128**, 1843-1853, https://doi.org/10.1021/acs.jpcb.3c07232.
92. Ziaunys, M., Mikalauskaite, K., Sakalauskas, A., and Smirnovas, V. (2021) Interplay between epigallocatechin-3-gallate and ionic strength during amyloid aggregation, *PeerJ*, **9**, e12381, https://doi.org/10.7717/peerj.12381.

93. Fernandes, L., Cardim-Pires, T. R., Foguel, D., and Palhano, F. L. (2021) Green tea polyphenol epigallocatechin-gallate in amyloid aggregation and neurodegenerative diseases, *Front. Neurosci.*, **15**, 718188, https://doi.org/10.3389/fnins.2021.718188.
94. Srivastava, A., Al Adem, K., Shanti, A., Lee, S., Abedrabbo, S., and Homouz, D. (2024) Inhibition of the early-stage cross-amyloid aggregation of amyloid-β and IAPP via EGCG: Insights from molecular dynamics simulations, *ACS Omega*, **9**, 30256-30269, https://doi.org/10.1021/acsomega.4c00500.
95. Al Adem, K., Shanti, A., Srivastava, A., Homouz, D., Thomas, S. A., Khair, M., Stefanini, C., Chan, V., Kim, T.-Y., and Lee, S. (2022) Linking Alzheimer's disease and type 2 diabetes: characterization and inhibition of cytotoxic Aβ and IAPP hetero-aggregates, *Front. Mol. Biosci.*, **9**, 842582, https://doi.org/10.3390/fmolb.2022.842582.
96. Bieschke, J., Russ, J., Friedrich, R. P., Ehrnhoefer, D. E., Wobst, H., Neugebauer, K., and Wanker, E. E. (2010) EGCG remodels mature α-synuclein and amyloid-β fibrils and reduces cellular toxicity, *Proc. Natl. Acad. Sci. USA*, **107**, 7710-7715, https://doi.org/10.1073/pnas.0910723107.
97. Sonawane, S. K., Chidambaram, H., Boral, D., Gorantla, N. V., Balmik, A. A., Dangi, A., Ramasamy, S., Marelli, U. K., and Chinnathambi, S. (2020) EGCG impedes human Tau aggregation and interacts with Tau, *Sci. Rep.*, **10**, 12579, https://doi.org/10.1038/s41598-020-69429-6.
98. Valverde-Salazar, V., Ruiz-Gabarre, D., and García-Escudero, V. (2023) Alzheimer's disease and green tea: epigallocatechin-3-gallate as a modulator of inflammation and oxidative stress, *Antioxidants (Basel)*, **12**, 1460, https://doi.org/10.3390/antiox12071460.
99. Jena, A. B., Dash, U. C., and Duttaroy, A. K. (2022) An *in silico* investigation on the interactions of curcumin and epigallocatechin-3-gallate with NLRP3 inflammasome complex, *Biomed. Pharmacother.*, **156**, 113890, https://doi.org/10.1016/j.biopha.2022.113890.
100. Fan, Q., Zhou, X.-H., Wang, T.-F., Zeng, F.-J., Liu, X., Gu, Y., Chen, B., Yang, J., Pang, Z.-Y., Liu, J.-G., and Bai, G.-H. (2023) Effects of epigallocatechin-3-gallate on oxidative stress, inflammation, and bone loss in a rat periodontitis model, *J. Dent. Sci.*, **18**, 1567-1575, https://doi.org/10.1016/j.jds.2023.02.019.
101. Yasuda, Y., Shimizu, M., Sakai, H., Iwasa, J., Kubota, M., Adachi, S., Osawa, Y., Tsurumi, H., Hara, Y., and Moriwaki, H. (2009) (–)-Epigallocatechin gallate prevents carbon tetrachloride-induced rat hepatic fibrosis by inhibiting the expression of the PDGFRβ and IGF-1R, *Chem. Biol. Interact.*, **182**, 159-164, https://doi.org/10.1016/j.cbi.2009.07.015.
102. Wei, Y., Dong, W., Jackson, J., Ho, T.-C., Le Saux, C. J., Brumwell, A., Li, X., Klesney-Tait, J., Cohen, M. L., Wolters, P. J., and Chapman, H. A. (2021) Blocking LOXL2 and TGFβ1 signalling induces collagen I turnover in precision-cut lung slices derived from patients with idiopathic pulmonary fibrosis, *Thorax*, **76**, 729-732, https://doi.org/10.1136/thoraxjnl-2020-215745.
103. Pan, M., Li, H., and Shi, X. (2024) A new target for hepatic fibrosis prevention and treatment: the Warburg effect, *Front. Biosci. (Landmark Ed)*, **29**, 321, https://doi.org/10.31083/j.fbl2909321.
104. Li, Y., Zhu, M., Huo, Y., Zhang, X., and Liao, M. (2018) Anti-fibrosis activity of combination therapy with epigallocatechin gallate, taurine and genistein by regulating glycolysis, gluconeogenesis, and ribosomal and lysosomal signaling pathways in HSC-T6 cells, *Exp. Ther. Med.*, **16**, 4329-4338, https://doi.org/10.3892/etm.2018.6743.
105. Won, H.-R., Lee, P., Oh, S.-R., and Kim, Y.-M. (2021) Epigallocatechin-3-gallate suppresses the expression of TNF-α-induced MMP-1 via MAPK/ERK signaling pathways in human dermal fibroblasts, *Biol. Pharm. Bull.*, **44**, 18-24, https://doi.org/10.1248/bpb.b20-00304.
106. Huang, Y., Liu, R., Meng, T., Zhang, B., Ma, J., and Liu, X. (2024) The TGFβ1/SMADs/Snail1 signaling axis mediates pericyte-derived fibrous scar formation after spinal cord injury, *Int. Immunopharmacol.*, **128**, 111482, https://doi.org/10.1016/j.intimp.2023.111482.
107. Park, G., Yoon, B. S., Moon, J.-H., Kim, B., Jun, E. K., Oh, S., Kim, H., Song, H. J., Noh, J. Y., Oh, C., and You, S. (2008) Green tea polyphenol epigallocatechin-3-gallate suppresses collagen production and proliferation in keloid fibroblasts via inhibition of the STAT3-signaling pathway, *J. Invest. Dermatol.*, **128**, 2429-2441, https://doi.org/10.1038/jid.2008.103.
108. Lam, W. H., Kazi, A., Kuhn, D. J., Chow, L. M. C., Chan, A. S. C., Dou, Q. P., and Chan, T. H. (2004) A potential prodrug for a green tea polyphenol proteasome inhibitor: Evaluation of the peracetate ester of (–)-epigallocatechin gallate (–)-EGCG, *Bioorg. Med. Chem.*, **12**, 5587-5593, https://doi.org/10.1016/j.bmc.2004.08.002.
109. Reddy, V. C., Vidya, S. G. V., Sreeramulu, D., Venu, L., and Raghunath, M. (2005) Addition of milk does not alter the antioxidant activity of black tea, *Ann. Nutr. Metab.*, **49**, 189-195, https://doi.org/10.1159/000087071.
110. Van Amelsvoort, J. M., van Hof, K. H., Mathot, J. N., Mulder, T. P., Wiersma, A., and Tijburg, L. B. (2001) Plasma concentrations of individual tea catechins after a single oral dose in humans, *Xenobiotica*, **31**, 891-901, https://doi.org/10.1080/00498250110079149.

111. Yang, C. S., Chen, L., Lee, M. J., Balentine, D., Kuo, M. C., and Schantz, S. P. (1998) Blood and urine levels of tea catechins after ingestion of different amounts of green tea by human volunteers, *Cancer Epidemiol. Biomarkers Prev.*, **7**, 351-354.
112. Lee, M.-J., Maliakal, P., Chen, L., Meng, X., Bondoc, F. Y., Prabhu, S., Lambert, G., Mohr, S., and Yang, C. S. (2002) Pharmacokinetics of tea catechins after ingestion of green tea and (−)-epigallocatechin-3-gallate by humans: formation of different metabolites and individual variability, *Cancer Epidemiol. Biomarkers Prev.*, **11**, 1025-1032.
113. Janle, E. M., Morré, D. M., Morré, D. J., Zhou, Q., and Zhu, Y. (2008) Pharmacokinetics of green tea catechins in extract and sustained-release preparations, *J. Diet. Suppl.*, **5**, 248-263, https://doi.org/10.1080/19390210802414279.
114. Chow, H. H., Cai, Y., Alberts, D. S., Hakim, I., Dorr, R., Shahi, F., Crowell, J. A., Yang, C. S., and Hara, Y. (2001) Phase I pharmacokinetic study of tea polyphenols following single-dose administration of epigallocatechin gallate and polyphenon E, *Cancer Epidemiol. Biomarkers Prev.*, **10**, 53-58.
115. Clifford, M. N., van der Hooft, J. J. J., and Crozier, A. (2013) Human studies on the absorption, distribution, metabolism, and excretion of tea polyphenols, *Am. J. Clin. Nutr.*, **98**, 1619S-1630S, https://doi.org/10.3945/ajcn.113.058958.
116. Rovaldi, E., Di Donato, V., Paolino, G., Bruno, M., Medei, A., Nisticò, S. P., Pellacani, G., Kiss, N., Azzella, G., Banvolgyi, A., and Cantisani, C. (2025) Epigallocatechin-gallate (EGCG): An essential molecule for human health and well-being, *Int. J. Mol. Sci.*, **26**, 9253, https://doi.org/10.3390/ijms26189253.
117. Chow, H.-H. S., Cai, Y., Hakim, I. A., Crowell, J. A., Shahi, F., Brooks, C. A., Dorr, R. T., Hara, Y., and Alberts, D. S. (2003) Pharmacokinetics and safety of green tea polyphenols after multiple-dose administration of epigallocatechin gallate and polyphenon E in healthy individuals, *Clin. Cancer Res.*, **9**, 3312-3319.
118. Chow, H. H., Hakim, I. A., Vining, D. J., Crowell, J. A., Ranger-Moore, J., Chew, W. M., Celaya, C. A., Rodney, S. R., Hara, Y., and Alberts, D. S. (2005) Effects of dosing condition on the oral bioavailability of green tea catechins after single-dose administration of Polyphenon E in healthy individuals, *Clin. Cancer Res.*, **11**, 4627-4633, https://doi.org/10.1158/1078-0432.CCR-04-2549.
119. Isbrucker, R. A., Edwards, J. A., Wolz, E., Davidovich, A., and Bausch, J. (2006) Safety studies on epigallocatechin gallate (EGCG) preparations. Part 2: Dermal, acute and short-term toxicity studies, *Food Chem. Toxicol.*, **44**, 636-650, https://doi.org/10.1016/j.fct.2005.11.003.
120. Lorenz, M. (2013) Cellular targets for the beneficial actions of tea polyphenols, *Am. J. Clin. Nutr.*, **98**, 1642S-1650S, https://doi.org/10.3945/ajcn.113.058230.
121. Uekusa, Y., Kamihira-Ishijima, M., Sugimoto, O., Ishii, T., Kumazawa, S., Nakamura, K., Tanji, K.-i., Naito, A., and Nakayama, T. (2011) Interaction of epicatechin gallate with phospholipid membranes as revealed by solid-state NMR spectroscopy, *Biochim. Biophys. Acta*, **1808**, 1654-1660, https://doi.org/10.1016/j.bbamem.2011.02.014.
122. Tarahovsky, Y. S. (2022) Hitchhiking into a cell: flavonoids may produce complexes with transition metals for transmembrane translocation, *Biometals*, **35**, 1299-1306, https://doi.org/10.1007/s10534-022-00445-x.
123. Kim, Y. A., Tarahovsky, Y. S., Yagolnik, E. A., Kuznetsova, S. M., and Muzafarov, E. N. (2015) Integration of quercetin-iron complexes into phosphatidylcholine or phosphatidylethanolamine liposomes, *Appl. Biochem. Biotechnol.*, **176**, 1904-1913, https://doi.org/10.1007/s12010-015-1686-z.
124. Kim, Y. A., Tarahovsky, Y. S., Yagolnik, E. A., Kuznetsova, S. M., and Muzafarov, E. N. (2013) Lipophilicity of flavonoid complexes with iron(II) and their interaction with liposomes, *Biochem. Biophys. Res. Commun.*, **431**, 680-685, https://doi.org/10.1016/j.bbrc.2013.01.060.
125. Han, D. W., Matsumura, K., Kim, B., and Hyon, S. H. (2008) Time-dependent intracellular trafficking of FITC-conjugated epigallocatechin-3-O-gallate in L-929 cells, *Bioorg. Med. Chem.*, **16**, 9652-9659, https://doi.org/10.1016/j.bmc.2008.10.009.
126. Kuzuhara, T., Tanabe, A., Sei, Y., Yamaguchi, K., Suganuma, M., and Fujiki, H. (2007) Synergistic effects of multiple treatments, and both DNA and RNA direct bindings on, green tea catechins, *Mol. Carcinog.*, **46**, 640-645, https://doi.org/10.1002/mc.20332.
127. Kuzuhara, T., Sei, Y., Yamaguchi, K., Suganuma, M., and Fujiki, H. (2006) DNA and RNA as new binding targets of green tea catechins, *J. Biol. Chem.*, **281**, 17446-17456, https://doi.org/10.1074/jbc.M601196200.
128. Tarahovsky, Y. S., Kim, Y. A., Yagolnik, E. A., and Muzafarov, E. N. (2014) Flavonoid-membrane interactions: involvement of flavonoid-metal complexes in raft signaling, *Biochim. Biophys. Acta*, **1838**, 1235-1246, https://doi.org/10.1016/j.bbamem.2014.01.021.
129. Tarahovsky, Y. S., Muzafarov, E. N., and Kim, Y. A. (2008) Rafts making and rafts braking: How plant flavonoids may control membrane heterogeneity, *Mol. Cell. Biochem.*, **314**, 65-71, https://doi.org/10.1007/s11010-008-9766-9.

130. Patra, S. K., Rizzi, F., Silva, A., Rugina, D. O., and Bettuzzi, S. (2008) Molecular targets of (–)-epigallocatechin-3-gallate (EGCG): specificity and interaction with membrane lipid rafts, *J. Physiol. Pharmacol.*, **59**, 217-235.
131. Zhu, W., Deng, X., Peng, J., Zou, B., and Li, C. (2017) A-type ECG and EGCG dimers inhibit 3T3-L1 differentiation by binding to cholesterol in lipid rafts, *J. Nutr. Biochem.*, **48**, 62-73, https://doi.org/10.1016/j.jnutbio.2017.06.012.
132. Koonyosying, P., Tharanon, W., Pairojthanachai, K., Samakarn, Y., Meejak, K., Paradee, N., Kerdto, O., Yubo, S., Zhong, Y., and Srichairatanakool, S. (2025) Green tea catechins mitigate hepatocyte ferroptosis through attenuation of oxidative stress and improvement of antioxidant systems, *Antioxidants (Basel)*, **14**, 1483, https://doi.org/10.3390/antiox14121483.
133. Prananda, A. T., Nugraha, S. E., Situmorang, P. C., and Syahputra, R. A. (2025) Comparative effectiveness of plant-derived compounds in keloid management: a review, *Front. Pharmacol.*, **16**, 1576851, https://doi.org/10.3389/fphar.2025.1576851.
134. Li, W., Mei, X., and Tu, Y. Y. (2012) Effects of tea polyphenols and their polymers on MAPK signaling pathways in cancer research, *Mini Rev. Med. Chem.*, **12**, 120-126, https://doi.org/10.2174/138955712798995011.
135. Van Aller, G. S., Carson, J. D., Tang, W., Peng, H., Zhao, L., Copeland, R. A., Tummino, P. J., and Luo, L. (2011) Epigallocatechin gallate (EGCG), a major component of green tea, is a dual phosphoinositide-3-kinase/mTOR inhibitor, *Biochem. Biophys. Res. Commun.*, **406**, 194-199, https://doi.org/10.1016/j.bbrc.2011.02.010.
136. Halder, B., Das Gupta, S., and Gomes, A. (2012) Black tea polyphenols induce human leukemic cell cycle arrest by inhibiting Akt signaling: possible involvement of Hsp90, Wnt/β-catenin signaling and FOXO1, *FEBS J.*, **279**, 2876-2891, https://doi.org/10.1111/j.1742-4658.2012.08668.x.
137. Lee, M. H., Han, D.-W., Hyon, S.-H., and Park, J.-C. (2011) Apoptosis of human fibrosarcoma HT-1080 cells by epigallocatechin-3-O-gallate via induction of p53 and caspases as well as suppression of Bcl-2 and phosphorylated nuclear factor-κB, *Apoptosis*, **16**, 75-85, https://doi.org/10.1007/s10495-010-0548-y.
138. Pullikotil, P., Chen, H., Muniyappa, R., Greenberg, C. C., Yang, S., Reiter, C. E. N., Lee, J.-W., Chung, J. H., and Quon, M. J. (2012) Epigallocatechin gallate induces expression of heme oxygenase-1 in endothelial cells via p38 MAPK and Nrf-2 that suppresses proinflammatory actions of TNF-α, *J. Nutr. Biochem.*, **23**, 1134-1145, https://doi.org/10.1016/j.jnutbio.2011.06.007.
139. Lorenz, M., Wessler, S., Follmann, E., Michaelis, W., Düsterhöft, T., Baumann, G., Stangl, K., and Stangl, V. (2004) A constituent of green tea, epigallocatechin-3-gallate, activates endothelial nitric oxide synthase by a phosphatidylinositol-3-OH-kinase-, cAMP-dependent protein kinase-, and Akt-dependent pathway and leads to endothelial-dependent vasorelaxation, *J. Biol. Chem.*, **279**, 6190-6195, https://doi.org/10.1074/jbc.M309114200.
140. Ohishi, T., Hayakawa, S., and Miyoshi, N. (2023) Involvement of microRNA modifications in anticancer effects of major polyphenols from green tea, coffee, wine, and curry, *Crit. Rev. Food Sci. Nutr.*, **63**, 7148-7179, https://doi.org/10.1080/10408398.2022.2038540.
141. Nagle, D. G., Ferreira, D., and Zhou, Y.-D. (2006) Epigallocatechin-3-gallate (EGCG): chemical and biomedical perspectives, *Phytochemistry*, **67**, 1849-1855, https://doi.org/10.1016/j.phytochem.2006.06.020.
142. Tong, M.-Q., Lu, C.-T., Huang, L.-T., Yang, J.-J., Yang, S.-T., Chen, H.-B., Xue, P.-P., Luo, L.-Z., Yao, Q., Xu, H.-L., and Zhao, Y.-Z. (2023) Polyphenol-driven facile assembly of a nanosized acid fibroblast growth factor-containing coacervate accelerates the healing of diabetic wounds, *Acta Biomater.*, **157**, 467-486, https://doi.org/10.1016/j.actbio.2022.11.054.
143. Cao, X., Deng, Y., Xu, Z., Wang, T., Tang, B., Han, J., Guo, R., and Yin, R. (2024) A versatile natural gelatin-based hydrogel for emergency wound treatment through hemostasis, antibacterial, and anti-inflammation, *Biofabrication*, **17**, 015017, https://doi.org/10.1088/1758-5090/ad89ff.
144. Xu, F.-W., Lv, Y.-L., Zhong, Y.-F., Xue, Y.-N., Wang, Y., Zhang, L.-Y., Hu, X., and Tan, W.-Q. (2021) Beneficial effects of green tea EGCG on skin wound healing: a comprehensive review, *Molecules*, **26**, 6123, https://doi.org/10.3390/molecules26206123.
145. He, X., Gao, Y., Wang, X., Zhang, C., Xia, Z., Xu, W., Yang, H., Tao, G., Cai, R., Chen, J., and He, Y. (2025) Dual-network hydrogel loaded with antler stem cells conditioned medium and EGCG promotes diabetic wound healing through antibacterial, antioxidant, anti-inflammatory, and angiogenesis, *Mater. Today Bio*, **31**, 101612, https://doi.org/10.1016/j.mtbio.2025.101612.