

Advances regarding physiological functions and mechanisms of theaflavin-3,3'-digallate (Review)

TENG MA^{1*}, SIWEI ZHANG^{2*}, MIAOMIAO XIAO¹, ZHIJIAN MA³ and JUNHONG GUAN¹

¹Gansu Province Key Laboratory of Environmental Oncology, Cuiying Biomedical Research Center, The Second Hospital and Clinical Medical School of Lanzhou University, Lanzhou, Gansu 730030, P.R. China; ²Department of Digestive Disease, Weinan Central Hospital, Weinan, Shaanxi 714000, P.R. China; ³Department of Experimental Research, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong 510060, P.R. China

Received September 22, 2025; Accepted February 3, 2026

DOI: 10.3892/mmr.2026.13837

Abstract. Theaflavin-3,3'-digallate (TF3) is a major galloylated theaflavin generated during black tea fermentation and has been reported to exhibit a range of biological activities, including antioxidant, anti-inflammatory, antimicrobial, antiviral and anticancer properties. However, due to its chemical instability, low bioavailability and complex biotransformation in the gastrointestinal tract, the *in vivo* effects of TF3 remain inconsistent across studies. The present review summarizes the structural characteristics, degradation behavior and gut microbiota-mediated metabolic processes of TF3, and discusses its pharmacological actions at multiple targets, particularly its regulatory effects on signaling pathways such as the NF- κ B, MAPK and nuclear factor erythroid 2-related factor 2 signaling pathways. Specifically, the present review addresses the issue of whether the biological effects of TF3 are predominantly driven by the parent compound *per se* or are mediated by its metabolites (such as theaflavin, gallic acid). Finally, key directions for future research are proposed, including comparative evaluations of the bioactivities of TF3 and its metabolites, and the integration of pharmacokinetic-pharmacodynamic investigations to facilitate the development of TF3-based therapeutic agents.

Contents

1. Introduction
2. Structure and metabolites of TF3
3. Biological activities of TF3
4. Delivery, dosage and safety research progress of TF3
5. Metabolic mechanisms and clinical translation of TF3
6. Conclusion and future prospects

1. Introduction

Due to their remarkable chemical diversity and biological activity, natural products have long been recognized as a notable source of lead compounds with substantial therapeutic potential. According to published statistics, >70% of drugs approved internationally between 1981 and 2014 were directly derived from natural products, natural product derivatives or synthetic compounds that recapitulate the pharmacological effects of natural products. Collectively, these observations underscore the central role of natural products in the development of modern pharmaceuticals (1,2).

Tea (*Camellia sinensis*; Theaceae), with a history of >5,000 years of consumption and medicinal use in China, is one of the most widely consumed functional beverages worldwide (3). Black tea, the predominant tea product, is widely consumed in Europe and North America, and has been recognized as 'Generally Recognized as Safe' (GRAS) by the U.S. Food and Drug Administration (FDA) (4). During black tea manufacture, catechin polyphenols in tea leaves undergo extensive enzymatic oxidation, yielding polymeric products such as theaflavins and thearubigins (5). Among these, theaflavins are characteristic dimers with a benzotropolone structure (5). In view of their distinctive color and broad bioactivities, theaflavins are often referred to as the 'golden molecules' in black tea and comprise 2-6% of the soluble solids in brewed black tea (6).

At present, four major theaflavin monomers have been identified in black tea, including TF derivatives theaflavin (TF1), theaflavin-3-gallate (TF2A), theaflavin-3'-gallate (TF2B) and theaflavin-3,3'-digallate (TF3) (7) (Fig. 1). Among these, TF3 is not only the most abundant theaflavin in black

Correspondence to: Professor Junhong Guan, Gansu Province Key Laboratory of Environmental Oncology, Cuiying Biomedical Research Center, The Second Hospital and Clinical Medical School of Lanzhou University, 82 CuiYing Men Road, Lanzhou, Gansu 730030, P.R. China
E-mail: ery_guanjh@lzu.edu.cn

Dr Zhijian Ma, Department of Experimental Research, Sun Yat-sen University Cancer Center, 1 Kaiyang 5th Road, Guangzhou, Guangdong 510060, P.R. China
E-mail: mazj@sysucc.org.cn

*Contributed equally

Key words: theaflavin-3,3'-digallate, natural product, biological activity, chronic diseases, mechanism

tea (~1.05%), which is markedly significantly surpassing TF2A (0.34%), TF2B (0.11%) and TF1 (0.08%), but it is also considered one of the most biologically active theaflavin components (8,9). Structurally, TF3 is formed via oxidative dimerization of (-)-epigallocatechin gallate (EGCG) and (-)-epicatechin gallate (ECG), and contains a high number of phenolic hydroxyl groups, thereby conferring strong reducing capacity (9). This structural basis may partially account for its reported antioxidant, anti-inflammatory, antiviral, antimicrobial and anticancer activities (8,10-13).

Studies have indicated that the biological effects of TF3 are not confined to a single disease entity or signaling pathway; rather, they span multiple systemic disease domains. Accumulating evidence suggests that TF3 may exert protective or interventional effects in tumorigenesis and progression, viral and bacterial infections, diabetes and its complications, non-alcoholic and alcoholic liver diseases, osteoporosis and arthritis, atherosclerosis, and neurodegenerative disorders such as Alzheimer's disease (14-22). These effects are typically mediated by the modulation of multiple mechanisms, including cell cycle regulation, apoptosis, oxidative stress responses, inflammatory signaling, angiogenesis and metabolic homeostasis, supporting the multitarget and network-regulatory properties of TF3 (19-22).

To the best of our knowledge, despite the increasing number of studies on TF3, a comprehensive review integrating its structural characteristics, biotransformation, mechanisms of action and disease-related biological effects remains unavailable. In particular, the understanding of the translational trajectory of TF3 from a dietary bioactive constituent to applications in functional foods and nutraceuticals is still fragmented. Therefore, the present review aims to provide a systematic review focusing on the chemical structure and metabolic characteristics of TF3, its principal pharmacological activities and molecular mechanisms, as well as key issues such as delivery strategies, safety and the feasibility of human intake, thereby providing a theoretical basis for further mechanistic research and translational development of TF3.

2. Structure and metabolites of TF3

Structure and origin of TF3. As one of the most popular functional beverages globally, black tea has attracted widespread attention due to its unique flavor and putative health benefits in humans (23,24). Numerous epidemiological studies have suggested that tea-derived polyphenols are associated with a reduced risk of various chronic diseases (25). The main phenolic components of black tea are theaflavins and thearubigins, which are primarily formed during the processing of tea leaves through enzymatic oxidation and subsequent non-enzymatic oxidation reactions of catechins (5).

Theaflavins are a class of dimeric polyphenols with a characteristic benzotropolone skeleton, comprising a central tricyclic structure and two phenolic side-chain rings (5). Biological and pharmacological study have generally focused on the four major tea catechins, namely ECG, EGCG, (-)-epicatechin (EC) and (-)-epigallocatechin (EGC) (26). During black tea fermentation/manufacture, these catechins undergo oxidative polymerization, catalyzed by polyphenol oxidase or peroxidase, leading to the formation of different

structural types of theaflavin monomers through pathways such as C2-C2' or C4-C8 coupling (5,27). EC and EGC combine to form TF1, EC and EGCG combine to form TF2A, ECG and EGC combine to form TF2B, and ECG and EGCG combine to form TF3 (9) (Fig. 2). Accordingly, structural differences among these theaflavins are considered to contribute to variation in biological potency and functional specificity (5).

TF3 is the most abundant (~1.05%) and is widely regarded as one of the most biologically active theaflavin constituents in black tea (28). TF3 is formed through the enzyme-catalyzed oxidative dimerization of EGCG and ECG, and its molecular structure is rich in eight phenolic hydroxyl groups and multiple ester bonds, thereby conferring strong free radical-scavenging capacity. Collectively, these structural features provide a physicochemical basis for its antioxidant, anti-inflammatory and anticancer effects (10,18,29).

Stability and degradation mechanisms of TF3. Although TF3 exhibits strong biological activity, its intrinsic structural lability contributes to rapid degradation in complex environments, thereby limiting its further application in food and medical contexts (30). The abundant phenolic hydroxyl groups in TF3 are prone to redox reactions, and its stability is influenced by multiple factors, including solution pH, temperature, oxygen exposure, light and the presence of metal ions (31-33).

Available evidence indicates that TF3 is highly susceptible to degradation under near-neutral or alkaline conditions. *In vitro* experiments using high-performance liquid chromatography (HPLC) have demonstrated that after incubation for 35 min at 37°C in 50 mM Tris-HCl buffer, TF3 content decreased by >50% (12). Furthermore, TF3 exhibits pronounced thermal instability, as it is prone to hydrolysis and/or degradation under high-temperature tea brewing or pasteurization conditions (6). Oxygen is also a key determinant of stability. Oxygen-rich environments can promote rapid oxidation, resulting in the formation of pigmented byproducts (30). In addition, within food matrices, TF3 may undergo non-enzymatic binding or complexation with proteins, polysaccharides or minerals, further compromising bioactivity retention and oral bioavailability (34). Accordingly, in the development of tea-based functional foods, parameters such as storage-related pH fluctuations, thermal processing conditions, oxygen control and interactions with other food components should be systematically considered to improve TF3 stability in complex matrices.

Bioavailability, metabolites and conversion of TF3. The oral bioavailability of TF3 under physiological conditions is generally low, primarily due to its high polarity, large molecular weight (~868.7 Da), low lipophilicity and intrinsic structural lability (35). An animal study showed that after continuous consumption of black tea containing TF3 (50 mg/g diet) for 2 weeks, TF3 concentrations in mice remained markedly low (~1 nmol/g) (36). In a human study, volunteers who ingested 700 mg of a pure theaflavin mixture (equivalent to drinking ~30 cups of black tea) had a maximum plasma concentration of TF3 of 1 ng/ml, with a urinary concentration of 4.2 ng/ml (37). Collectively, these findings indicate that the *in vivo* absorption efficiency of TF3 is low, with bioavailability constrained by gastrointestinal instability (such as pH-induced degradation), limited transmembrane transport and substantial first-pass

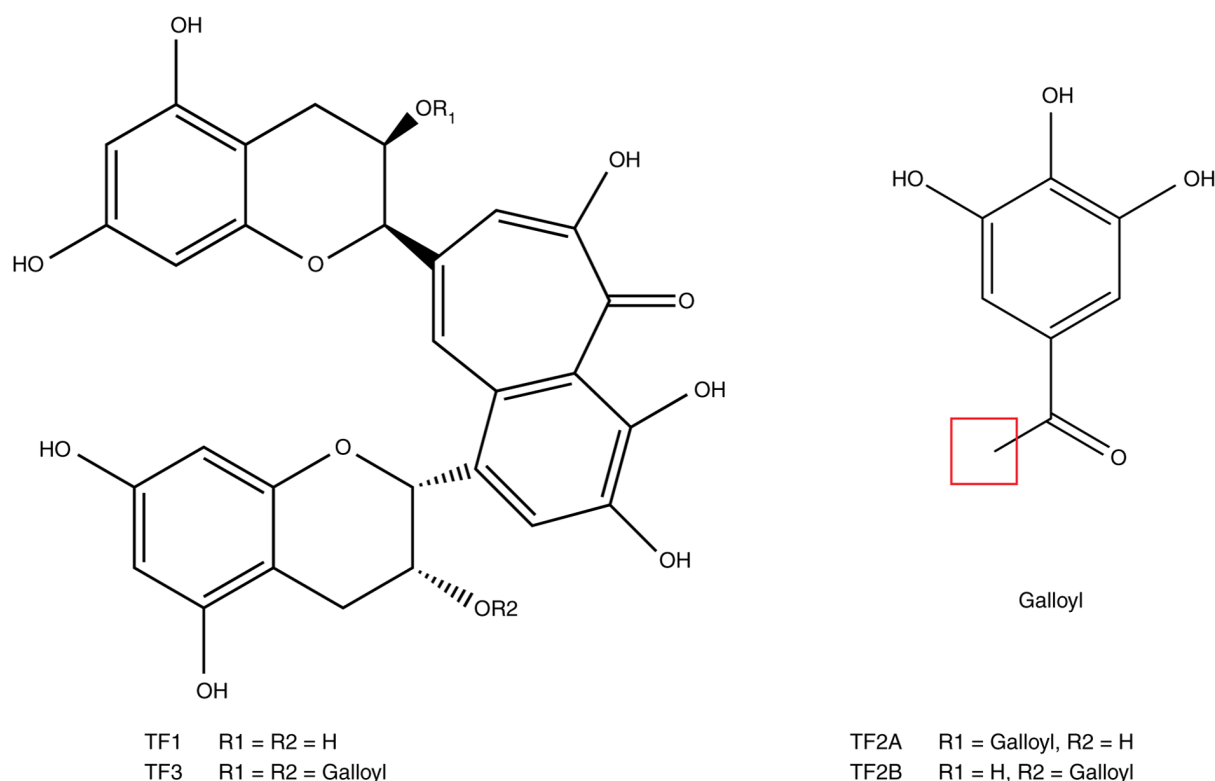


Figure 1. Structural diversity of theaflavins. TF1, theaflavin; TF2A, theaflavin-3-gallate; TF2B, theaflavin-3'-gallate; TF3, theaflavin-3,3'-digallate.

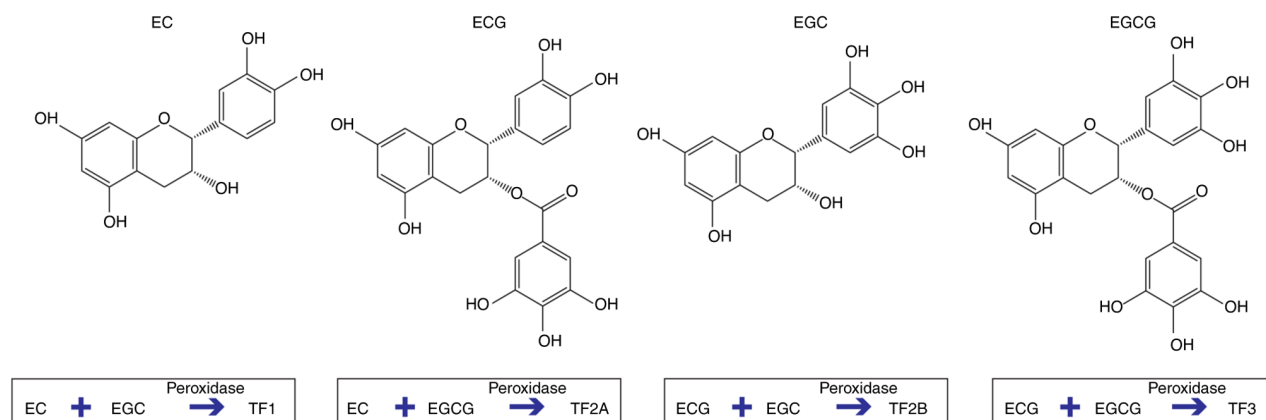


Figure 2. Tea polyphenols are oxidized to form theaflavins. ECGG, (-)-epigallocatechin gallate; ECG, (-)-epicatechin gallate; EC, (-)-epicatechin; EGC, (-)-epigallocatechin; TF1, theaflavin; TF2A, theaflavin-3-gallate; TF2B, theaflavin-3'-gallate; TF3, theaflavin-3,3'-digallate.

metabolism (38). During digestion, unabsorbed TF3 can enter the colon and undergo gradual transformation into a series of small-molecule metabolites under the action of the gut microbiota, including theaflavin, TF2A, TF2B, gallic acid (GA) and protocatechuic acid (PG) (39) (Fig. 3). Probiotic strains such as *Lactobacillus plantarum* 299v and *Bacillus subtilis* have been reported to participate in the metabolic transformation of TF3, suggesting that the gut microbiota may serve a notable role in shaping TF3-associated pharmacological effects (40,41).

Although the parent compound of TF3 appears to exert limited biological effects *in vivo*, studies have increasingly suggested that its metabolites possess pharmacological activities and may synergistically contribute to the overall *in vivo* activity attributed to TF3. The partially de-esterified dimers,

TF2A and TF2B, retain antioxidant and antimicrobial activities, and may continue to exert effects as colon-delivered active forms (41-43). GA, a degradation product of TF3, has been reported to inhibit NF- κ B signaling and reduce inflammatory cytokine expression in multiple disease models, indicating anti-inflammatory and anticancer potential (44,45). Similarly, PG has been reported to induce apoptosis in A549 lung cancer cells, inhibit tumor growth *in vivo* and exhibit antioxidant activity (46-48).

The microbiota-driven conversion of TF3 into GA and PG may shift the bioactivity profile of TF3 toward enhanced anticancer and anti-inflammatory effects (49); however, to the best of our knowledge, the extent to which this metabolic process contributes to specific disease outcomes remains

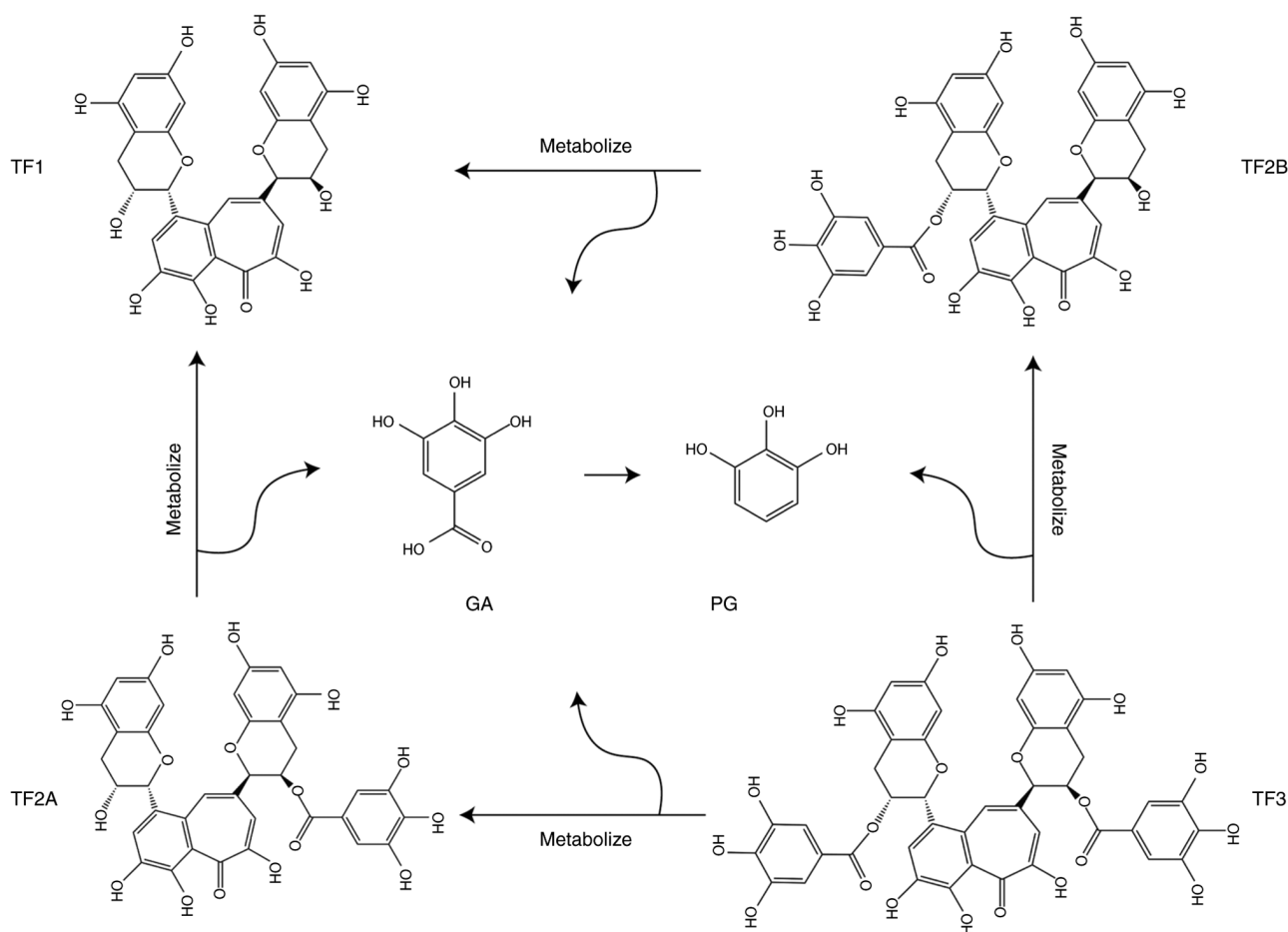


Figure 3. Major metabolites and possible biotransformation pathways of TF3 in mice or the human gut. TF1, theaflavin; TF2A, theaflavin-3-gallate; TF2B, theaflavin-3'-gallate; TF3, theaflavin-3,3'-digallate; GA, gallic acid; PG, protocatechuic acid.

unclear. Addressing this gap will require integrated pharmacokinetic-pharmacodynamic investigations that compare TF3 and its metabolites within the same disease models to delineate metabolite contributions to overall efficacy. In this context, TF3 may function as a precursor or prodrug, which could broaden its application as a functional food ingredient or dietary supplement. Overall, these observations suggest that TF3-related biological effects may not be solely dependent on the parent structure but may instead reflect the combined actions of metabolites such as GA, PG, TF2A and TF2B. Therefore, elucidating the mechanisms of action of TF3-derived metabolites and systematically comparing their pharmacological profiles with the parent compound will help define the *in vivo* functional positioning of TF3 and provide a theoretical rationale for developing more targeted and accessible delivery strategies.

3. Biological activities of TF3

TF3 has been reported to exhibit a variety of biological activities, including antioxidant, anti-inflammatory, antimicrobial, antiviral and anticancer properties. These characteristics suggest that TF3 may contribute to the modulation of multiple disease processes (12,13,50-52). Numerous studies have indicated that the pleiotropic activities of TF3 support its potential relevance to neurodegenerative

disorders, periodontal diseases, viral pathogenesis and cancer. Furthermore, available evidence suggests that TF3 influences key disease-associated pathways, including the canonical inflammatory and stress signaling axes (NF- κ B and MAPK), antioxidant defense systems [nuclear factor erythroid 2-related factor 2 (Nrf2)/Kelch-like ECH-associated protein 1 (Keap1)], virus replication-associated proteases [such as 3C-like protease (3CLpro) and non-structural protein 2b-non-structural protein 3 (NS2B-NS3)], and multiple receptor tyrosine kinases and their downstream signaling cascades [such as EGFR and platelet-derived growth factor receptor (PDGFR)] (50,53-55).

Antioxidant properties of TF3. Tea is widely regarded as a natural antioxidant, largely attributable to the redox-active properties of its polyphenols (56). Studies have shown that catechins possess substantial antioxidant capacity, enabling the inhibition of free-radical generation, direct scavenging of reactive species and chelation of transition metal ions, thereby limiting lipid peroxidation *in vitro* and *in vivo* (57,58). Theaflavins, formed through the oxidation of epicatechin, are also considered to exhibit antioxidant potential, as they can reduce intracellular reactive oxygen species (ROS) and mitigate hydroxyl radical-induced DNA damage (59). Among the four major theaflavins in black tea, TF3 exhibits the highest scavenging activity against hydrogen peroxide and

2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals. TF1 scavenges superoxide anion radicals, whereas TF2B can scavenge singlet oxygen and hydrogen peroxide, and attenuate hydroxyl radical-induced DNA damage (9). These findings suggest that galloylated theaflavins display stronger scavenging activity against hydroxyl and DPPH radicals than their non-galloylated counterparts.

Oxidative stress can induce neuronal apoptosis via excessive generation of ROS, such as superoxide anions and hydroxyl radicals and is widely implicated in the pathogenesis of neurodegenerative diseases (60). TF3 has been reported to suppress oxidative stress by modulating oxidase activity and to exert neuroprotective effects in pheochromocytoma PC12 cells, primarily through the inhibition of oxidase activity, which reduces cell apoptosis (60). Additionally, TF3 promotes the dissociation of Nrf2 from Keap1, induces Nrf2 phosphorylation and facilitates its nuclear translocation, where Nrf2 binds to the antioxidant response element and initiates transcription of heme oxygenase-1, superoxide dismutases, glutathione (GSH) peroxidase and catalases (61).

However, it has been indicated that TF3 exhibits cell type-dependent effects, yielding divergent outcomes in malignant tumor cells compared with normal cells. For instance, in normal GN46 fibroblasts, TF3 exerts antioxidant effects; at 250 μ M, it promotes intracellular GSH synthesis by activating δ -glutamylcysteine synthetase and GSH synthetase. By contrast, in oral squamous cell carcinoma HSC-2 cells, TF3 (250–500 μ M) induces apoptosis by disrupting redox homeostasis and antioxidant defenses, resulting in decreased GSH levels and caspase-3 activation, which subsequently leads to poly (ADP-ribose) polymerase cleavage (56). Concurrently, TF3 induces apoptosis primarily via activation of the intrinsic mitochondrial pathway, integrating oxidative stress signaling, Bcl-2 family regulation, and caspase cascade activation (5,62). The detailed process is shown in Fig. 4A.

In summary, TF3 may function as an antioxidant that contributes to the prevention and management of neurodegenerative diseases and osteoporosis through regulation of cellular oxidative stress (60,63). Conversely, in cancer models, TF3 can disrupt redox homeostasis by promoting excessive ROS generation and activating apoptosis signaling pathways, thereby acting as an inducer of oxidative stress-mediated apoptosis (64). Taken together, these observations underscore the potential of TF3 in modulating redox-related pathways relevant to human health.

Anti-inflammatory properties of TF3. Inflammation is a protective response of biological systems to external stimuli and serves as an essential mediator of host defense. However, dysregulated or uncontrolled inflammation can result in chronic, low-grade inflammatory states, ultimately contributing to the development of multisystem diseases (65). Lipopolysaccharide (LPS), a component of the outer membrane of Gram-negative bacteria, can stimulate macrophages and circulating monocytes to release pro-inflammatory cytokines, leading to transient immune activation characterized by elevated levels of TNF- α , IL-1 β and IL-6 (66,67). TF3 reduces the levels of these cytokines by inhibiting phosphorylation of p38 MAPK and JNK, as well as by suppressing the nuclear translocation of NF- κ B (p65) in LPS-treated RAW 264.7

macrophages (68). TF3 also alleviates LPS-induced acute lung injury in mice (69).

Another study has demonstrated that oral administration of TF3 (5 mg/kg; oral gavage) notably improved trinitrobenzene sulfonic acid (TNBS)-mediated colitis by reducing the mRNA and protein levels of IL-12, IFN- γ , TNF- α and inducible nitric oxide synthase in the colonic mucosa. Additionally, TF3 markedly inhibited TNBS-induced NF- κ B nuclear localization and cytoplasmic I κ B kinase activity, while preserving the stability of the NF- κ B inhibitor I κ B α in colonic tissues and activated macrophages (10,70). IL-6 contributes to bone resorption and is positively associated with periodontal disease progression. TF3 suppresses TNF superfamily member 14 (TNFSF14)-induced IL-6 production, attenuates TNFSF14 receptor expression, and blocks activation of ERK and NF- κ B in human gingival fibroblasts (71) (Fig. 4B).

In summary, these findings suggest that TF3 exerts anti-inflammatory effects predominantly through the inhibition of both NF- κ B and MAPK activation thereby supporting its potential as a therapeutic candidate for inflammation-related disorders.

Antimicrobial properties of TF3. TF3 has been reported to exhibit bactericidal activity. The 2-methyl-D-erythritol-4-phosphate terpene biosynthesis pathway is needed for the survival of most bacteria and numerous human pathogens, rendering it a potential target for the identification of novel antimicrobial agent (72). Deoxy-D-xylulose-5-phosphate reductoisomerase (DXR) is a validated antimicrobial target within this pathway (73). Among the four major theaflavins in black tea, TF1, which lacks a GA ester side chain, exhibits the lowest inhibitory activity against DXR (IC₅₀ >100 mM), whereas the other three theaflavins, each containing at least one GA ester side chain, show stronger inhibition (IC₅₀=14.9–29.2 mM). Docking simulations further indicate that TF3 interacts more strongly with DXR than other theaflavins, owing to additional hydrogen bonding and close contact at the binding interface. This observation not only helps explain the stronger DXR inhibitory activity of TF3 relative to TF1 but also underscores the contribution of organic acid ester side chains to the antimicrobial activity of theaflavins (12). Furthermore, TF3, as a natural antimicrobial agent, exhibits antibacterial and sporicidal activities, including disruption of bacterial membranes, inhibition of metabolic activity and suppression of spore germination via binding to key spore-associated proteins. Accordingly, TF3 may have utility not only against common bacterial pathogens but also as a complementary strategy for infections involving antibiotic-resistant bacteria (74).

Metallo- β -lactamases (MBLs) are β -lactam resistance determinants produced by a range of Gram-negative bacteria and are major contributors to the increasing resistance to β -lactam antibiotics (75). It has been shown that certain pathogens, such as *Staphylococcus aureus*, can acquire resistance to β -lactam antibiotics by producing β -lactamases that hydrolyze the amide bond of the β -lactam ring. Various β -lactam anti-infective regimens have been developed for methicillin-resistant *S. aureus*, including penicillin- β -lactamase inhibitor combinations, and first-, second- and third-generation cephalosporins. TF3 reduces the minimum inhibitory

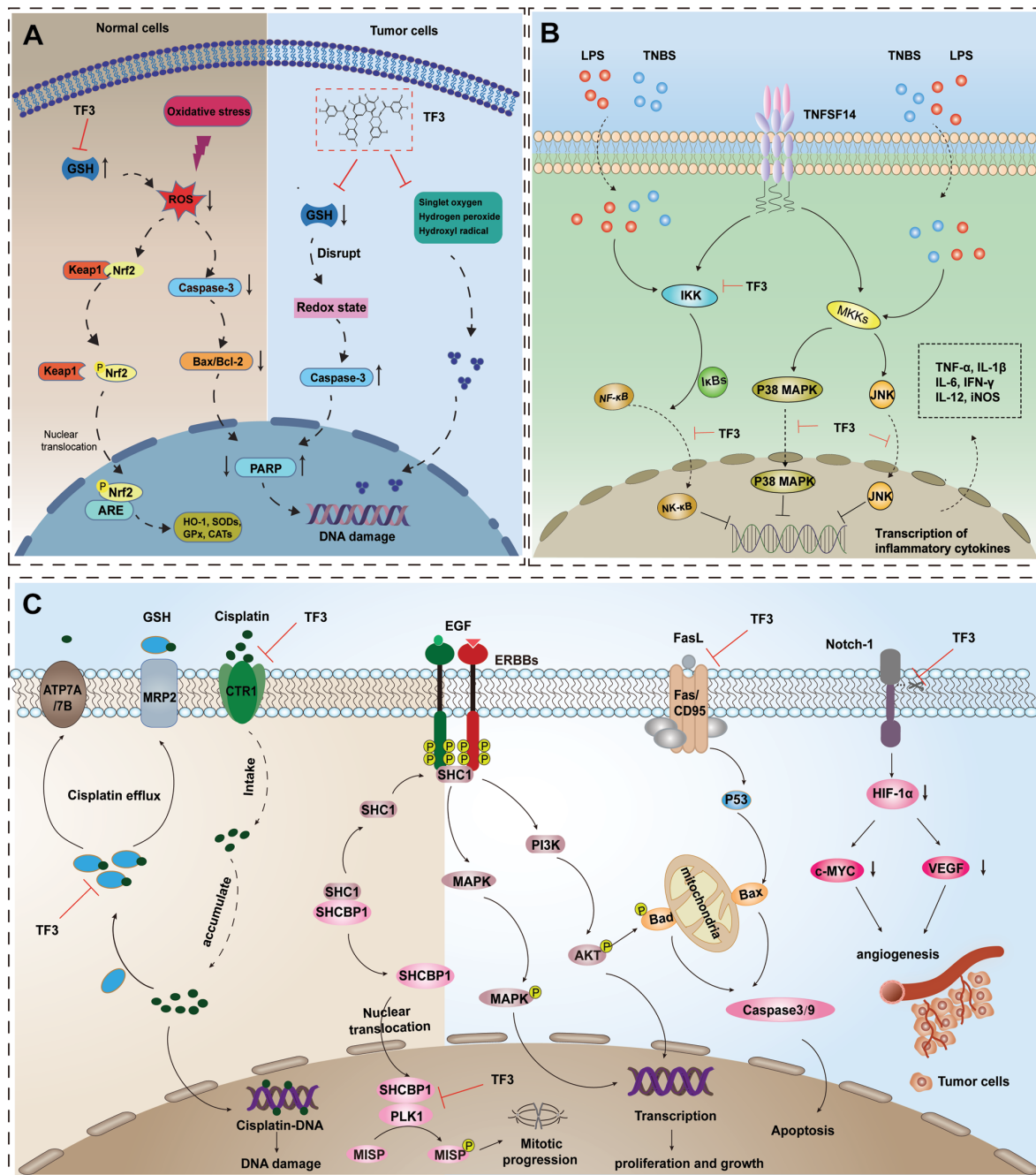


Figure 4. Schematic illustration of the molecular mechanisms of TF3 in antioxidant defense, inflammation suppression and tumor inhibition. (A) Antioxidant mechanism of TF3. In normal cells, TF3 markedly decreases ROS levels by promoting the dissociation of Nrf2 from Keap1 inducing Nrf2 phosphorylation, and facilitating its translocation into the nucleus to interact with ARE, which initiates transcription of HO-1, SODs, GPx and CATs. In cancer cells, TF3 decreases GSH levels, disrupts redox homeostasis and activates caspase-3, resulting in increased PARP cleavage (cleaved PARP $\uparrow$) and apoptosis. By contrast, in normal cells, TF3 maintains redox balance and reduces PARP cleavage (cleaved PARP $\downarrow$). (B) Anti-inflammatory mechanism of TF3. TF3 reduces the levels of pro-inflammatory cytokines TNF- α , IL-1 β and IL-6 by suppressing the activation of MAPK, JNK and NF- κ B. (C) Antitumor mechanism of TF3. TF3 decreases GSH levels to reduce efflux relaxation of cisplatin and improve the expression of copper CTR1, which heightens the sensitivity of ovarian cancer cells to cisplatin. When EGF activates HER2, SHC1 dissociates from SHCBP1 and is recruited by HER2 to activate the classical MAPK and PI3K signaling pathways. Dissociated SHCBP1 enters the nucleus and interacts with PLK1, which promotes phosphorylation of the mitotic protein MISP to regulate mitosis. TF3 attenuates tumor cell-induced angiogenesis by suppressing the cleavage of Notch-1 and subsequently decreasing HIF-1 α , c-Myc and VEGF expression. TF3, theaflavin-3,3'-digallate; ROS, reactive oxygen species; GSH, glutathione; ARE, antioxidant response element; HO-1, heme oxygenase-1; SODs, superoxide dismutases; GPx, GSH peroxidase; CATs, catalases; PARP, poly(ADP-ribose) polymerase; CTR1, copper transporter 1; SHC1, Src homology 2 domain-containing transforming protein 1; SHCBP1, Shc SH2-domain binding protein 1; PLK1, polo-like kinase 1; MISP, mitotic spindle positioning protein; HIF-1 α , hypoxia-inducible factor 1 α ; TNBS, 2,4,6-trinitrobenzenesulfonic acid; MKK, mitogen-activated protein kinase kinase; Keap1, Kelch-like ECH-associated protein 1; Nrf2, nuclear factor erythroid 2-related factor 2; LPS, lipopolysaccharide; TNFSF14, TNF superfamily member 14; ATP7A/7B, ATPase copper transporting α/β ; FasL, Fas ligand; MRP2, resistance-associated protein 2; P, phosphorylated.

concentration of β -lactam antibiotics against the *S. aureus* BAA1717 strain by 4- or 8-fold (fractional inhibitory

concentration index=0.313 or 0.188, respectively), whereas TF3 alone exhibits weak antibacterial activity. Additionally,

TF3 provides marked protection against MBL-mediated hydrolysis of nitrocefin (76). Its inhibitory effects on three distinct MBL variants suggest broad-spectrum inhibitory potential (76). TF3 also inhibits the production, secretion and activity of α -hemolysin (Hla), alleviates Hla-associated immune responses and skin injury, and protects the skin barrier, thereby supporting its future development as a potential MBL-targeting adjunct (77).

TF3 also exhibits potential oral health benefits. Research has suggested that it enhances the antibacterial effects of antimicrobial agents against periodontal disease by inhibiting the secretion of IL-8 and while increasing the secretion of β -defensins in oral epithelial cells (78). Furthermore, theaflavins inhibit the proliferation of *Streptococcus mutans*, showing protective effects against dental caries *in vitro*. The underlying mechanism involves reducing the formation of biofilm matrices containing glucans and extracellular DNA (eDNA) (79). TF3 also attenuates the expression of genes encoding glucosyltransferases [including Glucosyltransferase B (gtfB), gtfC and gtfD], thereby potentially lowering *S. mutans*-associated cariogenicity. Furthermore, TF3 reduces eDNA formation in *S. mutans* biofilms by negatively regulating genes involved in cell autolysis and membrane vesicle-associated components, such as lysis-related gene A (lrgA), lrgB and packaging enzyme A (80,81). Another study has indicated that TF3 inhibits *S. mutans* biofilm formation by suppressing enolase, lactate dehydrogenase, F-type ATPase and proline dehydrogenase activity. Additionally, TF3 exerts antimicrobial activity against *Listeria monocytogenes* by disrupting the cell membrane, altering the membrane potential and fluidity, and inhibiting biofilm maturation. These actions position TF3 as a natural antimicrobial candidate with potential applications in food-surface disinfection and prevention of bacterial contamination (51). Furthermore, TF3 specifically interferes with quorum sensing pathways, including the gelatinase (GelE) and serine protease (SprE) system, as well as the protein translocation channel SecY, and membrane protein functions, effectively inhibiting biofilm formation by *Enterococcus faecalis* rather than relying solely on bactericidal activity. Accordingly, TF3 may represent a safe and feasible natural strategy for preventing or adjunctively managing *E. faecalis*-associated root canal infections, endocarditis and urinary tract infections (82).

In conclusion, TF3 exerts antimicrobial effects by targeting enzymes related to bacterial survival and resistance (such as DXR, MBLs, enolase, lactate dehydrogenase, F-type ATPase and Hla), disrupting cell membranes and inhibiting spore germination. Furthermore, when combined with antibiotics, TF3 can enhance antibacterial efficacy. Taken together, TF3 may have translational potential as a natural antimicrobial agent or adjunct.

Antiviral properties of TF3. Human coronaviruses are major causes of upper respiratory tract diseases in both animals and humans. Severe acute respiratory syndrome coronavirus (SARS-CoV) is the etiological agent of SARS (83,84); in the absence of widely effective, specific therapeutics for SARS-CoV and given the continuing need for antiviral drug development, identifying inhibitors targeting the SARS-CoV main protease

has become particularly important. 3CLpro of SARS-CoV has been identified as a promising drug target (54). Among 720 natural product compounds, 3-iso-theaflavin-3-gallate, tannic acid and TF3 were identified as potential inhibitors of 3CLpro, exhibiting potent inhibitory effects at concentrations <10 mM (16). Another study investigating FDA-approved antiviral drugs for coronavirus disease 2019 (COVID-19) and SARS-CoV-2 proteases (covering 1,129 antiviral drug ligands, 459 antimalarial drug ligands and 110 plant-specific drugs) demonstrated that lopinavir, amoxicillin and TF3 exhibited the highest docking scores. The predicted protease-inhibitor complexes were then validated through 20-nsec molecular dynamics simulations, which showed plausible conformational changes during binding and favorable affinity for the main protease binding site (85).

The RNA-dependent RNA polymerase (RdRp) involved in SARS-CoV-2 replication provides another potential antiviral target (86,87). Multiple studies have shown that plant-derived polyphenols can inhibit the RdRp of RNA viruses. Using a polyphenol database, several polyphenols were screened and evaluated for their potential in treating COVID-19 by binding to RdRp (88). Molecular docking experiments indicated that EGCG, TF1, TF2A, TF2B, TF3, hesperidin, quercetin and kaempferol can bind to the dynamic catalytic pocket of SARS-CoV-2 RdRp. Furthermore, binding free energy estimates derived from 150-nsec molecular dynamics simulations suggested that EGCG, TF2A, TF2B and TF3 adopt relatively stable binding conformations with RdRp (84). Additionally, TF3 has been reported to bind to the SARS-CoV-2 SARS-Unique Domain, blocking its interactions with guanine quadruplex RNA and host proteins, thereby inhibiting viral replication and protein translation (89). Overall, these bioactive compounds exhibit broad antiviral activity against COVID-19 and have been proposed to display favorable pharmacokinetic characteristics (90).

Regarding other viruses, theaflavins can block HIV-1 envelope glycoprotein-mediated membrane fusion, preventing HIV-1 entry into target cells and thereby exerting anti-HIV-1 activity (91). TF3 may block the interaction between the HIV-1 envelope glycoprotein and the target cell membrane by binding to a highly conserved hydrophobic pocket within the central trimeric helical structure formed by the N-terminal heptad repeat of glycoprotein 41 (91). Furthermore, research has indicated that TF3 is a potent inhibitor of the flavivirus NS2B-NS3 heterodimeric serine protease. TF3 binds to the Zika virus (ZIKV) protease, thereby impairing viral maturation and replication. TF3 can also prevent viral polyprotein cleavage in ZIKV-infected cells or in cells expressing only the NS2B-NS3 protease. Docking simulations suggest that TF3 interacts with several key residues within the ZIKV protease cleavage cavity (11). Finally, TF3 inhibits herpes simplex virus (HSV) activity under neutral or acidic conditions. HSV is a major cause of genital ulcers. When combined with lactic acid, TF3 inactivates HSV in low-pH environments, such as liquid semen and cervicovaginal fluids (92).

In summary, these studies suggest that TF3 interacts with multiple viral enzymes and domains, and can inhibit the activity of SARS-CoV-2, HIV-1, ZIKV and HSV, supporting its potential as a candidate antiviral agent.

Anticancer properties of TF3. Over the past five decades, the understanding of the bioactive effects of phytochemicals in suppressing tumor initiation and progression has progressively expanded (93). A substantial body of evidence indicates that polyphenolic compounds derived from black tea exhibit anticancer activity against lung, liver, gastric, breast and ovarian cancer (13,94-96).

Ovarian cancer is one of the most common and lethal gynecological malignancies (97). Due to low rates of early detection and the development of resistance to first-line chemotherapeutic agents, the prognosis remains poor, with a global 5-year survival rate of ~30% around the year 2000 (97). Ovarian cancer stem cells, characterized by differentiation, self-renewal and metastatic capacity, are key contributors to recurrence and drug resistance. Notably, TF3 exhibits lower cytotoxicity toward normal ovarian cells than toward cancer cells, and suppresses the viability of the ovarian cancer cell lines A2780/CP70 and OVCAR3 by modulating the Wnt/ β -catenin signaling pathway (98). Another study has reported that TF3 reduced c-Myc, hypoxia-inducible factor 1 α and VEGF expression by inhibiting Notch-1 cleavage, thereby attenuating OVCAR-3-induced angiogenesis in human umbilical vein endothelial cells and chick chorioallantoic membrane models (13,99) (Fig. 4C). Several studies have also shown that TF3 suppresses tumor progression by activating apoptosis-related signaling. TF3 in combination with ascorbic acid activates caspase-3 and caspase-9 via the MAPK pathway, inducing apoptosis in esophageal cancer Eca-109 cells and lung adenocarcinoma SPC-A-1 cells (98,100,101). Furthermore, TF3 regulates the ratio of pro- and anti-apoptotic proteins through Chk2 phosphorylation, initiating intrinsic apoptosis in a p53-independent manner and inducing extrinsic apoptosis in ovarian cancer by upregulating death receptor expression. TF3 also promotes G₀/G₁ cell cycle arrest by enhancing p27 expression, thereby modulating ovarian cancer cell cycle progression (102).

These studies suggest that TF3 inhibits ovarian cancer-related malignant phenotypes and may represent a candidate therapeutic agent. Notably, TF3 has been investigated as an adjuvant to cisplatin in advanced ovarian cancer and exhibits synergistic cytotoxicity in A2780/CP70 and OVCAR3 cells (103). Subsequent study has further indicated that TF3 enhances cisplatin-induced DNA damage by promoting intracellular accumulation of platinum (Pt) and formation of DNA-Pt adducts, thereby attenuating cisplatin resistance. Additionally, TF3 decreases GSH levels to reduce cisplatin efflux and increases copper transporter 1 expression, consequently enhancing ovarian cancer cell sensitivity to cisplatin (104). Multidrug resistance-associated protein 2 [MRP2; gene name ATP-binding cassette (ABC)C2], a member of the ABC transporter family, plays a critical role in the development of cisplatin resistance. Accumulating *in vitro* and *in vivo* evidence has demonstrated that MRP2 promotes tumor cell resistance through multiple mechanisms, including the regulation of cisplatin efflux, glutathione (GSH) conjugation metabolism, and intracellular platinum accumulation (68).

Mutations in the p53 tumor suppressor gene contribute to tumorigenesis and progression, with ~50% of malignant tumors harboring p53 mutations (105). Theaflavins activate the death receptor FAS, a member of the TNF receptor family

involved in programmed cell death, and inhibit the phosphorylated (p-)Akt/p-Bad cell survival pathway, thereby promoting apoptosis in p53-mutant breast cancer cells. Furthermore, theaflavins enhance the p53/ROS/p38 MAPK positive feedback loop and suppress the pro-migratory proteases MMP-2 and MMP-9, thereby inhibiting migration in human breast cancer cells (106,107). Additionally, TF3 inhibits the proliferation of androgen-responsive prostate cancer LNCaP cells by suppressing androgen receptor expression, thereby reducing androgen-mediated prostate-specific antigen and fatty acid synthase levels (108). Furthermore, TF3 induces apoptosis and cell cycle arrest in prostate cancer cells by activating the protein kinase C δ /acid sphingomyelinase signaling pathway, which is dependent on 67 kDa laminin receptor expression, thereby inhibiting cancer cell proliferation. Notably, TF3 exhibits low cytotoxicity in normal prostate cells and selectivity toward cancer cells, supporting its potential as a candidate for anti-prostate cancer therapy (109).

In addition, the study has suggested that TF3 can inhibit receptor tyrosine kinase activity and downstream signaling. In NIH3T3 fibroblasts and human squamous carcinoma A431 cells, TF3 notably inhibits the autophosphorylation of EGFR and PDGFR, mediated by EGF and PDGF, respectively (55). Accordingly, TF3 can attenuate EGFR interactions and downstream mitogenic signaling (110). Overexpression of fatty acid synthase in human breast cancer MCF-7 cells has been reported to further amplify EGF stimulation. TF3 restricts fatty acid synthase activity at both the protein and mRNA level, thereby limiting lipid synthesis and proliferation in MCF-7 cells (111).

Furthermore, overactivation of the Src homology 2 domain-containing transforming protein 1 (SHC1)/Shc SH2-domain binding protein 1 (SHCBP1)/polo-like kinase 1 (PLK1) signaling axis is implicated in gastric cancer resistance to HER2-targeted agents such as trastuzumab, and has been described as a non-canonical downstream pathway of HER2. Upon EGF-driven activation of HER2, SHC1 dissociates from SHCBP1 and binds to HER2, thereby activating the canonical MAPK and PI3K pathways. Released SHCBP1 translocates into the nucleus and interacts with PLK1, and thereby facilitating mitotic progression in gastric cancer cells. Notably, TF3 inhibits formation of the SHCBP1-PLK1 complex, promotes its dissociation and suppresses this signaling cascade (112). Combination treatment with TF3 and trastuzumab has been reported to enhance therapeutic efficacy against gastric cancer *in vitro* and *in vivo* (112).

TF3 inhibits osteosarcoma cell proliferation and promotes apoptosis by increasing ROS levels, inducing DNA damage, activating caspase signaling and perturbing cell-cycle progression. These mechanisms support TF3 as a candidate anticancer compound for osteosarcoma and provide a theoretical rationale for its further evaluation in osteosarcoma therapy (14). TF3 also inhibits nasopharyngeal carcinoma (NPC) cell proliferation, migration and invasion through multiple mechanisms, including the induction of apoptosis, suppression of metastasis-related signaling pathways, and metabolomics analyses indicate that TF3 modulates metabolic pathways in NPC cells. TF3-associated apoptosis, metabolic reprogramming and regulation of key pathways support further investigation as a natural compound for NPC intervention (113).

In conclusion, TF3 exerts anticancer effects across multiple tumor types, including ovarian cancer, esophageal cancer, lung cancer, gastric cancer, breast cancer, prostate cancer, osteosarcoma and NPC, by promoting apoptosis, inducing cell cycle arrest, and modulating receptor tyrosine kinase signaling and downstream pathways (93-96,110,112). Additionally, TF3 may serve as an adjuvant or sensitizer in combination with conventional chemotherapeutic agents to enhance anticancer efficacy.

Other biological functions of TF3

Antidiabetic and cardiovascular protective effects. Diabetes is a major global health burden and is frequently accompanied by cardiovascular complications, which represent the leading cause of death among patients with diabetes (114). Increasing evidence suggests that TF3 exerts multitarget antidiabetic effects by improving insulin sensitivity, regulating hepatic glucose metabolism and promoting pancreatic β -cell regeneration (19,115). By coordinately modulating glucose homeostasis and insulin signaling pathways, TF3 has been proposed to have potential as a natural antidiabetic agent (19).

Chronic hyperglycemia is associated with impaired angiogenesis, persistent inflammation and defects in collagen synthesis, resulting in delayed wound healing and an increased risk of diabetic foot ulcers (116). Notably, TF3, particularly when formulated as a nanoparticles hydrogels (TFDG NPS@hydrogels), has been reported to accelerate wound healing in diabetic models by suppressing chronic inflammation, enhancing extracellular matrix remodeling, promoting angiogenesis and activating the TGF- β 1/SMAD3 signaling pathway (20).

In diabetic cardiomyopathy, hyperglycemic conditions are associated with downregulation of connexin 43 (Cx43) expression and impairment of cardiomyocyte autophagy, thereby increasing susceptibility to arrhythmias (117). TF3 has been reported to mitigate these pathological alterations by activating AMP-activated protein kinase (AMPK) signaling, restoring Cx43 expression and improving autophagic flux (118,119). Additionally, TF3 alleviates diabetes-associated liver and kidney dysfunction by modulating oxidative stress and regulating the circ-ITCH (circular RNA itchy E3 ubiquitin protein ligase)/Nrf2 pathway, and enhances the therapeutic effects of metformin, thereby supporting its potential as an adjunctive strategy for diabetic complications (120).

Protection against osteoporosis and arthritis. Osteoporosis is characterized by excessive bone resorption and impaired bone formation (121). Evidence indicates that TF3 inhibits osteoclast differentiation, polarization and bone-resorptive activity by suppressing receptor activator of NF- κ B ligand-induced ERK signaling (17). Furthermore, TF3 inhibits the migration and differentiation of osteoclast precursor cells by reducing the expression and activity of matrix metalloproteinases (MMP-2 and MMP-9) (122).

In an inflammatory bone loss model, TF3 has been reported to alleviate titanium particle-induced bone resorption and to maintain bone integrity (17). Under conditions of estrogen deficiency and inflammation, TF3 has been shown to enhance osteoblast function, increase bone mass and suppress inflammatory responses by activating osteogenic signaling pathways such as the MAPK, Wnt/ β -catenin and bone morphogenetic protein/Smad signaling pathways (61).

In addition to osteoporosis, TF3 modulates immune responses in arthritis by promoting M2 macrophage polarization and inhibiting M1 polarization, while also regulating autophagy. Collectively, these actions reduce inflammation and ameliorate joint damage, suggesting that TF3 may represent a candidate for the management of chronic inflammatory bone diseases such as rheumatoid arthritis (18).

Hepatoprotective effects in fatty liver diseases. Non-alcoholic fatty liver disease is driven by dysregulated lipid metabolism, oxidative stress, inflammation and disruption of the gut-liver axis, which collectively promote progression toward fibrosis and cirrhosis (123). TF3 has been reported to attenuate hepatic lipid accumulation and liver injury by regulating the fatty acid desaturase 1/peroxisome proliferator-activated receptor δ /fatty acid binding protein 4 axis and modulating gut microbiota composition, thereby restoring lipid metabolic homeostasis in non-alcoholic fatty liver disease models (15).

Similarly, alcoholic liver disease is associated with acetaldehyde toxicity, oxidative stress, inflammation, activation of hepatic stellate cells and lipid metabolic disturbances (124). TF3 has been reported to exert hepatoprotective effects by coordinately engaging antioxidant, anti-inflammatory, anti-fibrotic mechanisms, as well as modulating the gut-liver axis through suppression of hepatic TLR4/NF- κ B signaling, thereby alleviating liver injury and limiting fibrotic progression (53). Taken together, these findings support TF3 as a candidate natural agent for the prevention and management of fatty liver diseases.

Other biological functions of TF3. In addition to metabolic and bone-related disorders, TF3 has been reported to exhibit a range of other biological activities. TF3 demonstrates anti-allergic effects by inhibiting the expression of pro-inflammatory cytokines (such as IL-12, IFN- γ and TNF- α) and preserving systemic antioxidant capacity in allergy models (125). TF3 also exerts anti-obesity effects by inhibiting fatty acid synthesis, enhancing fatty acid oxidation and regulating lipid metabolism-related signaling pathways (such as the AMPK, sterol regulatory element-binding protein-1c, acetyl-CoA carboxylase and carnitine palmitoyltransferase 1 signaling pathways) (58,126-128).

TF3 also exhibits protective effects against atherosclerosis by improving lipid profiles, reducing inflammation and oxidative stress, and reprogramming metabolic homeostasis associated with plaque stabilization (21). In neurodegenerative disease models, TF3 improves learning and memory deficits through antioxidant mechanisms, by enhancing cholinergic neurotransmission (including increased acetylcholine levels and acetylcholinesterase inhibition) and regulating glutamatergic signaling, as well as activation of the Nrf2 pathway, thereby supporting a potential role in delaying brain aging and cognitive decline (22). A summary of these biological functions is shown in Table I.

4. Delivery, dosage and safety research progress of TF3

Application of delivery systems in enhancing TF3 bioavailability. Despite TF3 having been reported to exhibit pharmacological activities, including antioxidant, anti-inflammatory and anticancer effects, its low bioavailability and

Table I. Possible biofunctions of theaflavin-3,3'-digallate in cell and animal models.

A, Antioxidant					
First author/s, year	Study type	Experimental models and techniques	Isolation methods of TFs	Target or signaling pathway	(Refs.)
Schuck <i>et al.</i> , 2008	<i>In vitro</i>	HSC-2 cells and GN46 fibroblasts under H ₂ O ₂ -induced oxidative damage	Solvent extraction	GSH↓, oxidative stress↑ and activation of caspase-3 to cleave PARP	(56)
Lin <i>et al.</i> , 2000	<i>In vitro</i>	HL-60 cells; oxidative stress assay; intracellular ROS detection using DCF-DA	Solvent extraction after decaffeination by chloroform	Xanthine oxidase ↓	(59)
B, Anti-inflammatory					
First author/s, year	Study type	Experimental models	Isolation methods of TFs	Target or signaling pathway	(Refs.)
Hosokawa <i>et al.</i> , 2010	<i>In vitro</i>	HGFs and tissue samples from patients with inflamed gingiva	Purchased from Nagara Science Co., Ltd	TNFSF14-induced ERK, JNK and NF-κB activation ↓	(71)
Ukil <i>et al.</i> , 2006; Pan <i>et al.</i> , 2000	<i>In vivo</i>	Mice with TNBS-induced colitis	Solvent extraction	Reduced levels of TNF-α, IL-12, IFN-γ and iNOS; decreased nuclear translocation of NF-κB and cytosolic IKK activity, with preservation of IκBα	(10,70)
Wu <i>et al.</i> , 2017	<i>In vitro/ in vivo</i>	U937 human leukemia cells, LO-2 hepatocytes, and RAW 264.7 macrophages; mouse model of acute lung injury	Purchased from Chinese Academy of Sciences	p-c-JNK and p-p38 MAPK ↓, and TNF-α, IL-1β and IL-6 ↓	(69)
C, Antibacterial					
First author/s, year	Study type	Experimental models	Isolation methods of TFs	Target or signaling pathway	(Refs.)
Hui <i>et al.</i> , 2016	<i>In vitro</i>	HPLC and docking experiment	Purchased from Chengdu Biopurify Phytochemicals, Ltd.	DXR ↓	(12)
Teng <i>et al.</i> , 2019	<i>In vitro</i>	Nitrocefin assay; checkerboard and time-kill assays to evaluate antibacterial synergy; molecular docking analysis	Purchased from Dalian Meilun Biology Technology Co., Ltd	Metallo-β-lactamase activity ↓	(76)
Lombardo Bedran, <i>et al.</i> , 2015	<i>In vitro</i>	OBA-9 human oral epithelial cell line and checkerboard technique	Purchased from Niagen Bioscience	IL-8 ↓ and hBD secretion ↑	(78)
Wang <i>et al.</i> , 2019	<i>In vitro</i>	<i>Streptococcus mutans</i> UA159 and biofilm formation and biofilm dispersion assays	Purchased from Chengdu Biopurify, Ltd.	gtfB, gtfC and gtfD encoding glucosyltransferases ↓, and holo-like proteins lrgA, lrgB and srtA ↓	(81)
D, Antiviral					
First author/s, year	Study type	Experimental models	Isolation methods of TFs	Target or signaling pathway	(Refs.)
Cui <i>et al.</i> , 2020	<i>In vitro</i> (Zika virus)	Fluorescence-based screening assay and molecular docking studies	Obtained from the TargetMol Chemicals Inc.	NS2B-NS3	(11)

Table I. Continued.

D, Antiviral					
First author/s, year	Study type	Experimental models	Isolation methods of TFs	Target or signaling pathway	(Refs.)
Chen <i>et al</i> , 2005	<i>In vitro</i> (SARS-CoV)	HPLC proteolytic assay; fluorogenic substrate peptide assay	Gifted from Dr Yu-Chih Liang, School of Medical Technology, Taipei Medical University	3C-like protease ↓	(16)
Singh <i>et al</i> , 2021	<i>In vitro</i> (SARS-CoV)	Molecular docking studies, molecular dynamics simulations and ADMET studies	Not described	RNA-dependent RNA polymerase	(90)
Liu <i>et al</i> , 2005	<i>In vitro</i> (HIV-1)	MT-2 cells, CEM cells and normal diploid human lung fibroblast cells (MRC-5); computer-aided molecular docking	Obtained from MicroSource Discovery Systems, Inc.	Gp41	(91)
Isaacs and Xu, 2013	<i>In vitro</i> (HSV)	Vero and CV-1 cells	Not described	Inactivation of HSV	(92)
E, Anticancer					
First author/s, year	Study type	Experimental models	Isolation methods of TFs	Target or signaling pathway	(Refs.)
Gao <i>et al</i> , 2016	<i>In vitro</i> (ovarian cancer)	HUVEC tube formation assay, chick chorioallantoic membrane assay and ELISA	Purified by semi-preparative HPLC	Inhibiting Notch-1 cleavage, c-Myc, HIF-1α and VEGF ↓, and Akt/mTOR/p70S6K/4E-BP1 ↓	(13)
Pan <i>et al</i> , 2018	<i>In vitro</i> (ovarian cancer)	Cell viability assay, tumor sphere formation assay, ALDH assay and ALDH-based sorting	Purified by semi-preparative HPLC	Caspase-3 and -7 ↑, and Wnt/β-catenin ↓	(98)
Gao <i>et al</i> , 2013	<i>In vitro</i> (lung and esophageal cancer)	SPC-A-1 human lung adenocarcinoma cells and Eca-109 human esophageal carcinoma cells	Purified by semi-preparative HPLC	Caspases-3/9 ↑ and MAPK ↑	(101)
Gao <i>et al</i> , 2019	<i>In vitro</i> (ovarian cancer)	Hoechst 33342 staining assay and caspase-glo assay	Purified by semi-preparative HPLC	Phosphorylation of Chk2 ↑ and p27 ↑	(102)
Pan <i>et al</i> , 2018	<i>In vitro</i> (ovarian cancer)	Determined by inductively coupled plasma mass spectrometry and GSH assay	Purified by semi-preparative HPLC	GSH ↓ and CTR1 ↑	(104)
Lahiry <i>et al</i> , 2010	<i>In vitro</i> (breast cancer)	Flow cytometry and co-immunoprecipitation	Purchased from MilliporeSigma	Fas death receptor/caspase-8 ↑ and p-Akt/p-Bad ↓	(106)
Adhikary <i>et al</i> , 2010	<i>In vitro</i> (breast cancer)	Assessment of ROS and coimmunoprecipitation	Purchased from MilliporeSigma	p53/ROS/p38MAPK ↑, and MMP-2 and MMP-9 ↓	(107)
Lee <i>et al</i> , 2004	<i>In vitro</i> (prostate cancer)	5α-reductase assay and ELISA	Not described	Androgen receptor ↓ and fatty acid synthase ↓	(108)
Shi <i>et al</i> , 2021	<i>In vitro</i> and <i>in vivo</i> (gastric cancer)	Molecular docking and SPR technology	Purchased from Shandong Topscience Biotech Co., Ltd.	SHCBP1 ↓	(112)

Table I. Continued.

F, Anti-high glucose					
First author/s, year	Study type	Experimental models	Isolation methods of TFs	Target or signaling pathway	(Refs.)
Shen <i>et al.</i> , 2019	<i>In vitro</i>	Tandem mCherry-GFP-LC3 fluorescence detection and dye transfer assay	Purchased from Shanghai Aladdin Biochemical Technology Co., Ltd.	Cx43 ↑ and AMPK ↑	(119)
G, Anti-osteoporosis					
First author/s, year	Study type	Experimental models	Isolation methods of TFs	Target or signaling pathway	(Refs.)
Hu <i>et al.</i> , 2017	<i>In vitro/</i> <i>in vivo</i>	Micro-computed tomography scanning and resorption pit assay	Purchased from MilliporeSigma	Bone destruction ↓ and ERK ↓	(17)
Oka <i>et al.</i> , 2012	<i>In vitro/</i> <i>in vivo</i>	Osteoclast formation assay and gelatin zymography	Purchased from Wako Pure Chemical Industries, Ltd.	MMP-2 and MMP-9 ↓	(122)
H, Antiallergic					
First author/s, year	Study type	Experimental models	Isolation methods of TFs	Target or signaling pathway	(Refs.)
Yoshino <i>et al.</i> , 2010	<i>In vitro/</i> <i>in vivo</i>	Mouse type IV allergic model; determination of antioxidant activities	Supplied by Unilever Japan KK	Antioxidant activity ↑, and IL-12, IFN-γ and TNF-α ↓	(125)

GSH, glutathione; HPLC, high-performance liquid chromatography; ROS, reactive oxygen species; DXR, deoxy-D-xylulose-5-phosphate reductoisomerase; iNOS, inducible nitric oxide synthase; HGF, human gingival fibroblasts; hBD, human β-defensin; NS2B-NS3, non-structural protein 2b-non-structural protein 3; ALDH, aldehyde dehydrogenase; SHCB1, Src homology 2 domain-containing transforming binding protein 1; SPR, surface plasmin resonance; ICP-MS, inductively coupled mass spectrometry; TNBS, trinitrobenzene sulfonic acid; 4E-BP1, eukaryotic translation initiation factor 4E-binding protein 1; AMPK, AMP-activated protein kinase; Chk2, checkpoint kinase 2; CTR1, copper transporter 1; Cx43, connexin 43; GFP, green fluorescent protein; Gp41, glycoprotein 41; H₂O₂, hydrogen peroxide; HIF-1α, hypoxia-inducible factor 1α; HSV, herpes simplex virus; p-, phosphorylated; SARS-CoV, severe acute respiratory syndrome coronavirus; TNFSF14, TNF superfamily member 14; ADMET, absorption, distribution, metabolism, excretion, and toxicity; DCF-DA, dichlorofluorescein diacetate; lrgA, lysis-related gene A; SrtA, sortase A; gtfB, glucosyltransferase B.

limited stability in practical settings restrict broader application in functional foods and dietary supplements (129,130). Accordingly, several advanced delivery systems have been developed to improve the physicochemical properties and pharmacokinetic behavior of TF3, thereby enhancing its biological performance and expanding its potential utility in food and medical contexts.

Common delivery systems include nanoemulsions, liposomes, protein complex co-precipitates and polysaccharide-based microgels (131-133). Among these, nanoemulsions, due to their small droplet size, favorable dispersibility and thermal stability, have been reported to improve TF3 solubility and stability in aqueous media. By forming a protective interfacial layer that limits oxidation and enzymatic degradation, nanoemulsions can prolong the gastrointestinal residence

time of TF3 and thereby improve oral bioavailability (134). Liposomes, with a membrane-mimetic architecture, can protect TF3 from acidic conditions and enzymatic degradation in the gastrointestinal tract, facilitate trans-epithelial transport, and enhance stability and systemic exposure. In addition, liposomes can modulate TF3 release kinetics, enabling sustained-release or targeted-release profiles. Protein complex co-precipitation systems generate stable complexes by associating TF3 with casein or whey protein via electrostatic, hydrophobic and hydrogen-bond interactions. This approach not only improves TF3 dispersibility in liquid foods but also leverages gastric proteolysis to delay release, thereby reducing premature degradation and facilitating absorption in the small intestine. Polysaccharide-based microgels (such as chitosan, sodium alginate and pectin microgels) exhibit

pH responsiveness, biodegradability and mucoadhesive properties, enabling controlled TF3 release under varying gastrointestinal conditions and potentially enhancing tissue targeting (132). Furthermore, alginate can form gel shells through Ca^{2+} -mediated crosslinking to encapsulate TF3 for colon-targeted release, whereas chitosan can increase adhesion to the intestinal mucosa via electrostatic interactions, thereby improving transepithelial transport efficiency (135).

Through the design of these delivery systems, TF3 degradation in the gastrointestinal environment can be attenuated, its solubility and absorption enhanced, and its release profile and targeting behavior optimized. Notably, TF3-loaded nanoparticles and hydrogel formulations have been reported to improve therapeutic outcomes in preclinical models, thereby supporting the feasibility of delivery-driven enhancement (134,135). Furthermore, nanocarrier systems enable TF3 to be delivered in a controlled manner to specific tissues, such as tumors, inflammatory sites or metabolically active organs (136,137). Functionalized nanoparticles can further improve cellular uptake and reduce off-target effects, thereby creating opportunities for the translational development of TF3 in cancer, inflammation and metabolic diseases (29).

In summary, well-designed delivery systems not only improve the stability and bioavailability of TF3 in the gastrointestinal tract but also enhance therapeutic performance through targeted delivery. Future research should focus on the safety and biocompatibility of carrier materials, rigorous validation of delivery efficiency and industrial scalability to facilitate the translation of TF3 into nutritional medicine and personalized nutrition.

Safety evaluation and human dosage conversion of TF3. In advancing TF3 as an active ingredient in functional foods or dietary supplements, systematic evaluation of its safety profile and feasible human intake levels is essential. Existing evidence suggests that TF3, as a constituent derived from traditional tea, is supported by a favorable safety background (138). The US FDA has classified tea and its major polyphenolic constituents as 'GRAS', providing preliminary assurance for food-related applications of TF3 (139). However, systematic toxicological studies specifically focused on TF3 remain limited, particularly regarding chronic toxicity and target organ safety under long-term, high-dose exposure.

An *in vivo* study reported no overt adverse effects within commonly used experimental dose ranges. In a single preclinical study comprising several animal experiments, TF3 was administered orally at ~20 and 40 mg/kg body weight for several weeks in C57BL/6 mice (6-8 weeks old, 20-25 g), no notable changes in body weight, abnormal behavior or pathological damage to major organs were observed (69). Although TF3 appears to be well tolerated in short-term animal studies, most available investigations have primarily focused on pharmacodynamic outcomes, and comprehensive toxicological evaluations remain limited.

Converting efficacious doses from animal experiments to feasible human intake levels is a key step in assessing the nutritional applicability of TF3. Using the commonly applied body surface area-based conversion approach, a 5 mg/kg dose in mice corresponds to ~0.4 mg/kg in humans; thus, an adult weighing 60 kg would require an estimated intake of ~24 mg

TF3 per day to achieve comparable exposure (140,141). By contrast, TF3 typically accounts for 0.20-0.54% (1.99 to 5.39 mg/g) of the dry weight of black tea, and a single serving (~2 g tea leaves) provides <11 mg TF3 (134). Therefore, routine tea consumption alone is unlikely to reach intake levels associated with bioactivity in animal models. This gap suggests that TF3 may be more suitably delivered via functional food fortification, nutritional supplements or optimized delivery systems rather than relying exclusively on conventional tea consumption. In this context, incorporation of the aforementioned delivery strategies may improve TF3 stability and bioavailability, potentially enabling biological effects at lower practical intake levels and thereby enhancing feasibility and safety for population-level use.

In conclusion, although existing studies support an acceptable short-term safety profile for TF3, the long-term safety threshold and generalizability to broader populations require further systematic investigation. Future studies should include multi-dose, extended-duration and multi-species *in vivo* toxicology assessments, complemented by human intervention studies, to define safe intake ranges and functional dose intervals for TF3. This evidence will be essential for standardized application in functional foods and nutritional medicine.

5. Metabolic mechanisms and clinical translation of TF3

Efficacy comparison and mechanistic differences between TF3 and its metabolites. A key issue in the clinical translation of TF3 is whether its biological effects are primarily mediated by the intact parent compound or by degradation products and gut microbiota-derived metabolites, such as GA and PG. This question is particularly relevant given the chemical instability of TF3 and limited systemic exposure following oral administration.

A pharmacokinetic study indicated that TF3 exhibits low oral absorption and undergoes extensive gastrointestinal biotransformation, resulting in markedly low concentrations in plasma and peripheral tissues (43). By contrast, GA and PG are low-molecular-weight phenolic compounds that are more readily absorbed and can achieve higher systemic concentrations (142,143). Accordingly, GA and PG may constitute principal bioactive species downstream of TF3, notably contributing to its *in vivo* effects.

Mechanistically, TF3 and its metabolites display both overlapping and distinct modes of action. TF3 has been described primarily as a pleiotropic modulator of oxidative stress, inflammatory signaling pathways (such as the NF- κ B, MAPK and Nrf2 signaling pathways) and receptor tyrosine kinases (63,70). By contrast, GA and PG have been reported to exert more consistent cytotoxic and pro-oxidant effects in tumor cells, inducing apoptosis through mitochondrial dysfunction, caspase activation and suppression of NF- κ B signaling (144,145).

Despite these observations, direct head-to-head comparisons of TF3 and its metabolites under standardized experimental conditions remain scarce. The absence of such comparative analyses constitutes a major knowledge gap and complicates interpretation of the relative contributions of TF3 and its metabolites to *in vivo* efficacy.

Potential for combination therapy and clinical translation pathways of TF3. Given the multitarget regulatory properties of TF3, it appears well suited for combination-based therapeutic strategies. Preclinical studies have reported that TF3 enhances the efficacy of chemotherapeutic agents (such as cisplatin) by promoting intracellular drug accumulation and reducing GSH-mediated drug efflux, thereby increasing tumor cell susceptibility to apoptosis (103,104). In the antimicrobial field, TF3 has been reported to restore β -lactam antibiotic activity by inhibiting MBLs, supporting its potential role as an adjunct to antibiotic therapy (76). Collectively, these findings suggest that TF3 may be more effective as a synergistic modulator than as a standalone intervention.

Future translational research should prioritize standardized comparisons of TF3 and its metabolites at physiologically relevant doses. Key steps include formulation-dependent pharmacokinetic characterization, systematic safety evaluation and disease-specific efficacy validation. Given the long history of TF3 dietary exposure, it may be particularly amenable to development as a nutraceutical, functional food ingredient or adjunct therapeutic agent. Accordingly, a metabolism-informed translational roadmap that integrates delivery strategies with combination regimens may facilitate the progression of TF3 from experimental studies to clinical application.

6. Conclusion and future prospects

TF3 has been proposed to serve a role in the prevention and management of human diseases, particularly in cancer-related contexts. As a major theaflavin component in black tea, TF3 exhibits a broad spectrum of reported bioactivities, including antioxidant, anti-inflammatory, antiviral, anticancer and anti-allergic effects. With respect to antitumor activity, TF3 has been reported to display comparatively low cytotoxicity toward normal cells while inhibiting tumor cells, supporting its potential translational relevance. In addition, TF3 may act synergistically with conventional chemotherapeutic agents, such as cisplatin and trastuzumab, thereby enhancing therapeutic responsiveness.

However, despite numerous *in vitro* and *in vivo* studies describing multiple biological functions of TF3, translational development continues to face several challenges. First, most available evidence is derived from cellular and animal models, whereas systematic clinical validation remains limited, precluding robust assessment of efficacy and long-term safety in human populations. Second, the experimental doses used in numerous studies exceed those achievable through routine tea consumption, and feasible intake levels, safety thresholds and human metabolic characteristics remain insufficiently defined, thereby constraining the practical development of TF3 as a functional food ingredient or dietary supplement. Notably, some studies rely on specific disease models or target overexpression systems, and stable therapeutic effects under complex pathological conditions have not been confirmed, limiting generalizability. Furthermore, as a natural product, TF3 is chemically labile, readily degradable and challenging to obtain at high purity, posing challenges for product standardization, scalability and industrial translation. Although delivery strategies (such as nanoemulsions, liposomes and microcapsules) have been explored to improve stability and

bioavailability, most remain at an early stage and lack clinical validation and large-scale implementation.

In light of these considerations, future research should prioritize the following areas: i) Detailed characterization of TF3 metabolism and degradation mechanisms, including stability testing across pHs, solvents and temperatures, together with delineation of its metabolic fate in the human gastrointestinal tract; ii) clarification of pharmacological differences between TF3 and its major metabolites across disease models, with identification of core active species and key molecular targets to inform rational delivery optimization; iii) systematic toxicology and pharmacokinetic investigations using multi-dose, extended-duration and multi-species designs, complemented by human intervention trials to define safe intake ranges and functional dose intervals; and iv) development of standardized, scalable and cost-efficient TF3 formulations to improve accessibility and sustainability in functional foods and clinical nutrition.

In conclusion, TF3 is a natural bioactive molecule with multitarget regulatory potential and an apparently favorable short-term tolerability profile, and it may have value for therapeutic development. Future efforts should emphasize mechanistic elucidation, formulation optimization and evidence-based clinical research to support translation from experimental studies to real-world disease intervention, thereby contributing to the development of natural product-derived therapeutics and precision nutrition strategies.

Acknowledgements

Not applicable.

Funding

This study was supported by the National Key Research and Development Program of China (grant no. 2022YFA1305000 to J.G.), the Fundamental Research Funds for the Central Universities (grant no. lzujbky-2023-ey11 to J.G.), the National Natural Science Foundation of China (grant no. 32200426 to J.G.), the Major Science and Technology Projects of Gansu Province (grant no. 25ZDFA003 to J.G.), the Talents Program of the Lanzhou University Second Hospital (grant no. yjrck-yqdj-2022-02 to J.G.).

Availability of data and materials

Not applicable.

Authors' contributions

TM and SZ contributed to the conception and design of the review and drafted the main text of the manuscript. SZ and MX were involved in data collection, literature analysis and interpretation of the data, and prepared the figures and table. JG and ZM made substantial contributions to the conceptual framework of the review, critically revised the manuscript for important intellectual content and provided expert input on data interpretation. All authors participated in manuscript revision, read and approved the final version to be published and agreed to be accountable for all aspects of the work.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

- Newman DJ and Cragg GM: Natural products as sources of new drugs from 1981 to 2014. *J Nat Prod* 79: 629-661, 2016.
- Varghese R and Dalvi YB: Natural products as anticancer agents. *Curr Drug Targets* 22: 1272-1287, 2021.
- Chen ZM and Lin Z: Tea and human health: Biomedical functions of tea active components and current issues. *J Zhejiang Univ Sci B* 16: 87-102, 2015.
- Burdock GA and Carabin IG: Generally recognized as safe (GRAS): History and description. *Toxicol Lett* 150: 3-18, 2004.
- Abudurehman B, Yu X, Fang D and Zhang H: Enzymatic oxidation of tea catechins and its mechanism. *Molecules* 27: 942, 2022.
- He HF: Research progress on theaflavins: Efficacy, formation, and preparation. *Food Nutr Res* 61: 1344521, 2017.
- Murakami S, Takahashi S, Muguruma H, Osakabe N, Inoue H and Ohsawa T: Polyphenol analysis in black tea with a carbon nanotube electrode. *Anal Sci* 35: 529-534, 2019.
- Wu YY, Li W, Xu Y, Jin EH and Tu YY: Evaluation of the antioxidant effects of four main theaflavin derivatives through chemiluminescence and DNA damage analyses. *J Zhejiang Univ Sci B* 12: 744-751, 2011.
- Sang S, Lambert JD, Ho CT and Yang CS: The chemistry and biotransformation of tea constituents. *Pharmacol Res* 64: 87-99, 2011.
- Ukil A, Maity S and Das PK: Protection from experimental colitis by theaflavin-3,3'-digallate correlates with inhibition of IKK and NF-kappaB activation. *Br J Pharmacol* 149: 121-131, 2006.
- Cui X, Zhou R, Huang C, Zhang R, Wang J, Zhang Y, Ding J, Li X, Zhou J and Cen S: Identification of theaflavin-3,3'-digallate as a novel Zika virus protease inhibitor. *Front Pharmacol* 11: 514313, 2020.
- Hui X, Yue Q, Zhang DD, Li H, Yang SQ and Gao WY: Antimicrobial mechanism of theaflavins: They target 1-deoxy-D-xylulose 5-phosphate reductoisomerase, the key enzyme of the MEP terpenoid biosynthetic pathway. *Sci Rep* 6: 38945, 2016.
- Gao Y, Rankin GO, Tu Y and Chen YC: Theaflavin-3, 3'-digallate decreases human ovarian carcinoma OVCAR-3 cell-induced angiogenesis via Akt and Notch-1 pathways, not via MAPK pathways. *Int J Oncol* 48: 281-292, 2016.
- Law YY, Hsieh YH, Hsieh YS, Lee YH, Tang CL, Lee CY, Yang SF, Chu SC and Chen PN: Theaflavin-3,3'-digallate triggers apoptosis in osteosarcoma cells via the caspase pathway. *J Cancer* 16: 2567-2577, 2025.
- Zhou C, Zhang W, Lin H, Zhang L, Wu F, Wang Y, Yu S, Peng X, Cheng W, Li M, *et al*: Effect of theaflavin-3,3'-digallate on leptin-deficient induced nonalcoholic fatty liver disease might be related to lipid metabolism regulated by the Fads1/PPAR δ /Fabp4 axis and gut microbiota. *Front Pharmacol* 13: 925264, 2022.
- Chen CN, Lin CP, Huang KK, Chen WC, Hsieh HP, Liang PH and Hsu JT: Inhibition of SARS-CoV-2-like protease activity by theaflavin-3,3'-digallate (TF3). *Evid Based Complement Alternat Med* 2: 209-215, 2005.
- Hu X, Ping Z, Gan M, Tao Y, Wang L, Shi J, Wu X, Zhang W, Yang H, Xu Y, *et al*: Theaflavin-3,3'-digallate represses osteoclastogenesis and prevents wear debris-induced osteolysis via suppression of ERK pathway. *Acta Biomater* 48: 479-488, 2017.
- Zhang L, Li W, Hou Z, Wang Z, Zhang W, Liang X, Wu Z, Wang T, Liu X, Peng X, *et al*: Theaflavin-3,3'-digallate ameliorates collagen-induced arthritis through regulation of autophagy and macrophage polarization. *J Inflamm Res* 16: 109-126, 2023.
- Zhou H, Wu Y, Kim E, Pan H, He P, Li B, Chen YC and Tu Y: Simultaneous tests of theaflavin-3,3'-digallate as an anti-diabetic drug in human hepatoma G2 cells and Zebrafish (*Danio rerio*). *Nutrients* 13: 4379, 2021.
- Dong X, Miao J, Wu L, Kong Z, Liu Z, Jia D, Zhai Q, Zhang D and Xu Y: Diabetic wound healing breakthrough: theaflavin-3, 3'-digallate nanoparticles@hydrogel activates the TGF- β 1/SMAD3 pathway. *Phytomedicine* 141: 156617, 2025.
- Cen K, Huang Y, Xie Y, Zhang R, Cai Q, Zou L, Xiang Q, Yang C and Liu Y: Theaflavin-3,3'-digallate stabilizes vulnerable plaques by reprogramming metabolic homeostasis in neovascularization via HK2/TIGAR. *Phytomedicine* 145: 157014, 2025.
- Cao Y, Zhang Y, Jia Z, Jia H, Sun Y, Yuan H, Bian Y, Xu B, Fu J and Qin F: Theaflavin-3,3'-digallate ameliorates learning and memory impairments in mice with premature brain aging induced by D-galactose. *Physiol Behav* 261: 114077, 2023.
- Pan SY, Nie Q, Tai HC, Song XL, Tong YF, Zhang LJ, Wu XW, Lin ZH, Zhang YY, Ye DY, *et al*: Tea and tea drinking: China's outstanding contributions to the mankind. *Chin Med* 17: 27, 2022.
- Cabrera C, Artacho R and Gimenez R: Beneficial effects of green tea-a review. *J Am Coll Nutr* 25: 79-99, 2006.
- Lin JK: Cancer chemoprevention by tea polyphenols through modulating signal transduction pathways. *Arch Pharm Res* 25: 561-571, 2002.
- Tanaka T and Matsuo Y: Production mechanisms of black tea polyphenols. *Chem Pharm Bull (Tokyo)* 68: 1131-1142, 2020.
- Takemoto M and Takemoto H: Synthesis of theaflavins and their functions. *Molecules* 23: 918, 2018.
- Leung LK, Su Y, Chen R, Zhang Z, Huang Y and Chen ZY: Theaflavins in black tea and catechins in green tea are equally effective antioxidants. *J Nutr* 131: 2248-2251, 2001.
- Lei S, Xie M, Hu B, Zhou L, Sun Y, Saeeduddin M, Zhang H and Zeng X: Effective synthesis of theaflavin-3,3'-digallate with epigallocatechin-3-O-gallate and epicatechin gallate as substrates by using immobilized pear polyphenol oxidase. *Int J Biol Macromol* 94 (Pt A): 709-718, 2017.
- Xiao J and Högger P: Stability of dietary polyphenols under the cell culture conditions: Avoiding erroneous conclusions. *J Agric Food Chem* 63: 1547-1557, 2015.
- Jhoo JW, Lo CY, Li SM, Sang SM, Ang CYW, Heinze TM and Ho CT: Stability of black tea polyphenol, theaflavin, and identification of theanaphthoquinone as its major radical reaction product. *J Agric Food Chem* 53: 6146-6150, 2005.
- Krupkova O, Ferguson SJ and Wuerz-Kozak K: Stability of (-)-epigallocatechin gallate and its activity in liquid formulations and delivery systems. *J Nutr Biochem* 37: 1-12, 2016.
- Shingai Y, Fujimoto A, Nakamura M and Masuda T: Structure and function of the oxidation products of polyphenols and identification of potent lipoxygenase inhibitors from Fe-catalyzed oxidation of resveratrol. *J Agric Food Chem* 59: 8180-8186, 2011.
- Wang M, Xu J, Han T and Tang L: Effects of theaflavins on the structure and function of bovine lactoferrin. *Food Chem* 338: 128048, 2021.
- Lipinski CA, Lombardo F, Dominy BW and Feeney PJ: Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliv Rev* 46: 3-26, 2001.
- Henning SM, Aronson W, Niu Y, Conde F, Lee NH, Seeram NP, Lee RP, Lu J, Harris DM, Moro A, *et al*: Tea polyphenols and theaflavins are present in prostate tissue of humans and mice after green and black tea consumption. *J Nutr* 136: 1839-1843, 2006.
- Mulder TP, van Platerink CJ, Wijnand Schuyt PJ and van Amelsvoort JM: Analysis of theaflavins in biological fluids using liquid chromatography-electrospray mass spectrometry. *J Chromatogr B Biomed Sci Appl* 760: 271-279, 2001.
- Fan Y, Lei Z, Huang J, Su D, Ni D and Chen Y: Effect and mechanism of theaflavins on fluoride transport and absorption in caco-2 cells. *Foods* 12: 1487, 2023.
- Selma MV, Espín JC and Tomás-Barberán FA: Interaction between phenolics and gut microbiota: Role in human health. *J Agric Food Chem* 57: 6485-6501, 2009.
- Chen H, Parks T A, Chen X, Gillitt ND, Jobin C and Sang S: Structural identification of mouse fecal metabolites of theaflavin 3,3'-digallate using liquid chromatography tandem mass spectrometry. *J Chromatogr A* 1218: 7297-7306, 2011.
- Chen H, Hayek S, Rivera Guzman J, Gillitt ND, Ibrahim SA, Jobin C and Sang S: The microbiota is essential for the generation of black tea theaflavins-derived metabolites. *PLoS One* 7: e51001, 2012.

42. Sun L, Su Y, Hu K, Li D, Guo H and Xie Z: Microbial-transferred metabolites of black tea theaflavins by human gut microbiota and their impact on antioxidant capacity. *Molecules* 28: 5871, 2023.
43. Liu Z, de Bruijn WJC, Bruins ME and Vincken JP: Microbial metabolism of theaflavin-3,3'-digallate and its gut microbiota composition modulatory effects. *J Agric Food Chem* 69: 232-245, 2021.
44. Choi KC, Lee YH, Jung MG, Kwon SH, Kim MJ, Jun WJ, Lee J, Lee JM and Yoon HG: Gallic acid suppresses lipopolysaccharide-induced nuclear factor-kappaB signaling by preventing RelA acetylation in A549 lung cancer cells. *Mol Cancer Res* 7: 2011-2021, 2009.
45. Lo C, Lai TY, Yang JH, Yang JS, Ma YS, Weng SW, Chen YY, Lin JG and Chung JG: Gallic acid induces apoptosis in A375. S2 human melanoma cells through caspase-dependent and -independent pathways. *Int J Oncol* 37: 377-385, 2010.
46. Giftson Senapathy J, Jayanthi S, Viswanathan P, Umadevi P and Nalini N: Effect of gallic acid on xenobiotic metabolizing enzymes in 1,2-dimethyl hydrazine induced colon carcinogenesis in Wistar rats-a chemopreventive approach. *Food Chem Toxicol* 49: 887-892, 2011.
47. Han YH, Kim SZ, Kim SH and Park WH: Pyrogallol inhibits the growth of lung cancer Calu-6 cells via caspase-dependent apoptosis. *Chem Biol Interact* 177: 107-114, 2009.
48. Kawada M, Ohno Y, Ri Y, Ikoma T, Yuugetu H, Asai T, Watanabe M, Yasuda N, Akao S, Takemura G, *et al.*: Anti-tumor effect of gallic acid on LL-2 lung cancer cells transplanted in mice. *Anticancer Drugs* 12: 847-852, 2001.
49. Ding Y, Chen B, Gao Z, Suo H and Xiao H: Pre-treated theaflavin-3,3'-digallate has a higher inhibitory effect on the HCT116 cell line. *Food Nutr Res* 61: 1400340, 2017.
50. Xu C, Ni S, Xu N, Yin G, Yu Y, Zhou B, Zhao G, Wang L, Zhu R, Jiang S and Wang Y: Theaflavin-3,3'-digallate inhibits erastin-induced chondrocytes ferroptosis via the Nrf2/GPX4 signaling pathway in osteoarthritis. *Oxid Med Cell Longev* 2022: 3531995, 2022.
51. Lin Y, Shen C, Zhao J, Wang C, Obara M, Maung AT, Morita M, Abdelaziz MNS, Masuda Y, Honjoh KI and Miyamoto T: Antibacterial effect and mechanism of theaflavin against *Listeria monocytogenes* and its application on apple skins. *J Food Sci* 89: 6653-6663, 2024.
52. Mhatre S, Srivastava T, Naik S and Patravale V: Antiviral activity of green tea and black tea polyphenols in prophylaxis and treatment of COVID-19: A review. *Phytomedicine* 85: 153286, 2021.
53. Tang MG, Xiong LG, Huang JA, Hara Y, Zhang S, Liu ZH and Liu AL: Theaflavin-3,3'-digallate prevents alcoholic liver injury by suppressing hepatic TLR4/NF- κ B signaling and modulating the gut-liver axis in mice. *J Nutr Biochem* 145: 110031, 2025.
54. Anand K, Ziebuhr J, Wadhvani P, Mesters JR and Hilgenfeld R: Coronavirus main proteinase (3CLpro) structure: Basis for design of anti-SARS drugs. *Science* 300: 1763-1767, 2003.
55. Liang YC, Chen YC, Lin YL, Lin-Shiau SY, Ho CT and Lin JK: Suppression of extracellular signals and cell proliferation by the black tea polyphenol, theaflavin-3,3'-digallate. *Carcinogenesis* 20: 733-736, 1999.
56. Schuck AG, Ausubel MB, Zuckerbraun HL and Babich H: Theaflavin-3,3'-digallate, a component of black tea: An inducer of oxidative stress and apoptosis. *Toxicol In Vitro* 22: 598-609, 2008.
57. Yang Z, Jie G, Dong F, Xu Y, Watanabe N and Tu Y: Radical-scavenging abilities and antioxidant properties of theaflavins and their gallate esters in H₂O₂-mediated oxidative damage system in the HPF-1 cells. *Toxicol In Vitro* 22: 1250-1256, 2008.
58. Luo XY, Takahara T, Hou J, Kawai K, Sugiyama T, Tsukada K, Takemoto M, Takeuchi M, Zhong L and Li XK: Theaflavin attenuates ischemia-reperfusion injury in a mouse fatty liver model. *Biochem Biophys Res Commun* 417: 287-293, 2012.
59. Lin JK, Chen PC, Ho CT and Lin-Shiau SY: Inhibition of xanthine oxidase and suppression of intracellular reactive oxygen species in HL-60 cells by theaflavin-3,3'-digallate, (-)-epigallocatechin-3-gallate, and propyl gallate. *J Agric Food Chem* 48: 2736-2743, 2000.
60. Zhang J, Cai S, Li J, Xiong L, Tian L, Liu J, Huang J and Liu Z: Neuroprotective effects of theaflavins against oxidative stress-induced apoptosis in PC12 Cells. *Neurochem Res* 41: 3364-3372, 2016.
61. Ge G, Yang S, Hou Z, Gan M, Tao H, Zhang W, Li W, Wang Z, Hao Y, Gu Y and Geng D: Theaflavin-3,3'-digallate promotes the formation of osteoblasts under inflammatory environment and increases the bone mass of ovariectomized mice. *Front Pharmacol* 12: 648969, 2021.
62. Pan MH, Liang YC, Lin-Shiau SY, Zhu NQ, Ho CT and Lin JK: Induction of apoptosis by the oolong tea polyphenol theasinensin A through cytochrome c release and activation of caspase-9 and caspase-3 in human U937 cells. *J Agric Food Chem* 48: 6337-6346, 2000.
63. Ai Z, Wu Y, Yu M, Li J and Li S: Theaflavin-3, 3'-Digallate Suppresses RANKL-induced osteoclastogenesis and attenuates ovariectomy-induced bone loss in mice. *Front Pharmacol* 11: 803, 2020.
64. He T, Lin X, Yang C, Chen Z, Wang L, Li Q, Ma J, Zhan F, Wang Y, Yan J and Quan Z: Theaflavin-3,3'-digallate plays a ROS-mediated dual role in ferroptosis and apoptosis via the MAPK pathway in human osteosarcoma cell lines and xenografts. *Oxid Med Cell Longev* 2022: 8966368, 2022.
65. Mantovani A, Allavena P, Sica A and Balkwill F: Cancer-related inflammation. *Nature* 454 436-444, 2008.
66. Goodman RB, Pugin J, Lee JS and Matthay MA: Cytokine-mediated inflammation in acute lung injury. *Cytokine Growth Factor Rev* 14: 523-535, 2003.
67. Tiwari MM, Brock RW, Megyesi JK, Kaushal GP and Mayeux PR: Disruption of renal peritubular blood flow in lipopolysaccharide-induced renal failure: Role of nitric oxide and caspases. *Am J Physiol Renal Physiol* 289: F1324-F1332, 2005.
68. Wen X, Buckley B, McCandlish E, Goedken MJ, Syed S, Pelis R, Manautou JE and Aleksunes LM: Transgenic expression of the human MRP2 transporter reduces cisplatin accumulation and nephrotoxicity in MRP2-null mice. *Am J Pathol* 184: 1299-1308, 2014.
69. Wu Y, Jin F, Wang Y, Li F, Wang L, Wang Q, Ren Z and Wang Y: In vitro and in vivo anti-inflammatory effects of theaflavin-3,3'-digallate on lipopolysaccharide-induced inflammation. *Eur J Pharmacol* 794: 52-60, 2017.
70. Pan MH, Lin-Shiau SY, Ho CT, Lin JH and Lin JK: Suppression of lipopolysaccharide-induced nuclear factor-kappaB activity by theaflavin-3,3'-digallate from black tea and other polyphenols through down-regulation of IkappaB kinase activity in macrophages. *Biochem Pharmacol* 59: 357-367, 2000.
71. Hosokawa Y, Hosokawa I, Ozaki K, Nakanishi T, Nakae H and Matsuo T: Tea polyphenols inhibit IL-6 production in tumor necrosis factor superfamily 14-stimulated human gingival fibroblasts. *Mol Nutr Food Res* 54 (Suppl 2): S151-S158, 2010.
72. Keylor MH, Matsuura BS and Stephenson CR: Chemistry and biology of resveratrol-derived natural products. *Chem Rev* 115: 8976-9027, 2015.
73. Singh N, Chev   G, Avery MA and McCurdy CR: Targeting the methyl erythritol phosphate (MEP) pathway for novel antimalarial, antibacterial and herbicidal drug discovery: Inhibition of 1-deoxy-D-xylulose-5-phosphate reductoisomerase (DXR) enzyme. *Curr Pharm Des* 13: 1161-1177, 2007.
74. Yussof A, Cammalleri B, Fayemiwo O, Lopez S and Chu T: Antibacterial and sporicidal activity evaluation of theaflavin-3,3'-digallate. *Int J Mol Sci* 23: 2153, 2022.
75. Boyd SE, Livermore DM, Hooper DC and Hope WW: Metallo- β -Lactamases: Structure, function, epidemiology, treatment options, and the development pipeline. *Antimicrob Agents Chemother* 64: e00397, 2020.
76. Teng Z, Guo Y, Liu X, Zhang J, Niu X, Yu Q, Deng X and Wang J: Theaflavin-3,3'-digallate increases the antibacterial activity of β -lactam antibiotics by inhibiting metallo- β -lactamase activity. *J Cell Mol Med* 23: 6955-6964, 2019.
77. Goc A, Sumera W, Rath M and Niedzwiecki A: Inhibition of α -hemolysin activity of *Staphylococcus aureus* by theaflavin 3,3'-digallate. *PLoS One* 18: e0290904, 2023.
78. Lombardo Bedran TB, Morin MP, Palomari Spolidorio D and Grenier D: Black tea extract and its theaflavin derivatives inhibit the growth of periodontopathogens and modulate interleukin-8 and β -defensin secretion in oral epithelial cells. *PLoS One* 10: e0143158, 2015.
79. Kong J, Xia K, Su X, Zheng X, Diao C, Yang X, Zuo X, Xu J and Liang X: Mechanistic insights into the inhibitory effect of theaflavins on virulence factors production in *Streptococcus mutans*. *AMB Express* 11: 102, 2021.
80. Nakahara K, Kawabata S, Ono H, Ogura K, Tanaka T, Ooshima T and Hamada S: Inhibitory effect of oolong tea polyphenols on glycosyltransferases of *Streptococcus*. *Appl Environ Microbiol* 59: 968-973, 1993.

81. Wang S, Wang Y, Wang Y, Duan Z, Ling Z, Wu W, Tong S, Wang H and Deng S: Theaflavin-3,3'-digallate suppresses biofilm formation, acid production, and acid tolerance in streptococcus mutans by targeting virulence factors. *Front Microbiol* 10: 1705, 2019.
82. Wang S, Deng S and Wang Y: Theaflavin-3,3'-digallate effectively attenuates biofilm formation by *Enterococcus faecalis* via the targeting of specific quorum sensing pathways. *Microb Pathog* 193: 106739, 2024.
83. Latif AA and Mukaratirwa S: Zoonotic origins and animal hosts of coronaviruses causing human disease pandemics: A review. *Onderstepoort J Vet Res* 87: e1-e9, 2020.
84. Gogoi M, Borkotoky M, Borchetia S, Chowdhury P, Mahanta S and Barooah AK: Black tea bioactives as inhibitors of multiple targets of SARS-CoV-2 (3CLpro, PLpro and RdRp): A virtual screening and molecular dynamic simulation study. *J Biomol Struct Dyn* 40: 7143-7166, 2022.
85. Peele KA, Potla Durthi C, Srihansa T, Krupanidhi S, Ayyagari VS, Babu DJ, Indira M, Reddy AR and Venkateswarulu TC: Molecular docking and dynamic simulations for antiviral compounds against SARS-CoV-2: A computational study. *Inform Med Unlocked* 19: 100345, 2020.
86. Elfiky AA: Novel guanosine derivatives against Zika virus polymerase in silico. *J Med Virol* 92: 11-16, 2020.
87. Elfiky AA and Azzam EB: Novel guanosine derivatives against MERS CoV polymerase: An in silico perspective. *J Biomol Struct Dyn* 39: 2923-2931, 2021.
88. Ahmed-Belkacem A, Guichou JF, Brillet R, Ahnou N, Hernandez E, Pallier C and Pawlotsky JM: Inhibition of RNA binding to hepatitis C virus RNA-dependent RNA polymerase: A new mechanism for antiviral intervention. *Nucleic Acids Res* 42: 9399-9409, 2014.
89. Qin B, Li Z, Tang K, Wang T, Xie Y, Aumonier S, Wang M, Yuan S and Cui S: Identification of the SARS-unique domain of SARS-CoV-2 as an antiviral target. *Nat Commun* 14: 3999, 2023.
90. Singh S, Sk MF, Sonawane A, Kar P and Sadhukhan S: Plant-derived natural polyphenols as potential antiviral drugs against SARS-CoV-2 via RNA-dependent RNA polymerase (RdRp) inhibition: An in-silico analysis. *J Biomol Struct Dyn* 39: 6249-6264, 2021.
91. Liu S, Lu H, Zhao Q, He Y, Niu J, Debnath AK, Wu S and Jiang S: Theaflavin derivatives in black tea and catechin derivatives in green tea inhibit HIV-1 entry by targeting gp41. *Biochim Biophys Acta* 1723: 270-281, 2005.
92. Isaacs CE and Xu W: Theaflavin-3,3'-digallate and lactic acid combinations reduce herpes simplex virus infectivity. *Antimicrob Agents Chemother* 57: 3806-3814, 2013.
93. Barboza JR, Pereira FAN, Vasconcelos CC, de Sousa Ribeiro MN and Lopes AJO: Molecular mechanisms of action and chemosensitization of tumor cells in ovarian cancer by phytochemicals: A narrative review on pre-clinical and clinical studies. *Phytother Res* 37: 2484-2512, 2023.
94. Chung FL: The prevention of lung cancer induced by a tobacco-specific carcinogen in rodents by green and black tea. *Proc Soc Exp Biol Med* 220: 244-248, 1999.
95. Wen S, Sun L, An R, Zhang W, Xiang L, Li Q, Lai X, Huo M, Li D and Sun S: A combination of Citrus reticulata peel and black tea inhibits migration and invasion of liver cancer via PI3K/AKT and MMPs signaling pathway. *Mol Biol Rep* 47: 507-519, 2020.
96. Kim TL, Jeong GH, Yang JW, Lee KH, Kronbichler A, van der Vliet HJ, Grosso G, Galvano F, Aune D, Kim JY, *et al*: Tea consumption and risk of cancer: An umbrella review and meta-analysis of observational studies. *Adv Nutr* 11: 1437-1452, 2020.
97. Mizuno T, Suzuki N, Makino H, Furui T, Morii E, Aoki H, Kunisada T, Yano M, Kuji S, Hirashima Y, *et al*: Cancer stem-like cells of ovarian clear cell carcinoma are enriched in the ALDH-high population associated with an accelerated scavenging system in reactive oxygen species. *Gynecol Oncol* 137: 299-305, 2015.
98. Pan H, Kim E, Rankin GO, Rojanasakul Y, Tu Y and Chen YC: Theaflavin-3, 3'-digallate inhibits ovarian cancer stem cells via suppressing Wnt/ β -Catenin signaling pathway. *J Funct Foods* 50: 1-7, 2018.
99. Gao Y, Rankin GO, Tu Y and Chen YC: Inhibitory effects of the four main theaflavin derivatives found in black tea on ovarian cancer cells. *Anticancer Res* 36: 643-651, 2016.
100. Li W, Wu JX and Tu YY: Synergistic effects of tea polyphenols and ascorbic acid on human lung adenocarcinoma SPC-A-1 cells. *J Zhejiang Univ Sci B* 11: 458-464, 2010.
101. Gao Y, Li W, Jia L, Li B, Chen YC and Tu Y: Enhancement of (-)-epigallocatechin-3-gallate and theaflavin-3,3'-digallate induced apoptosis by ascorbic acid in human lung adenocarcinoma SPC-A-1 cells and esophageal carcinoma Eca-109 cells via MAPK pathways. *Biochem Biophys Res Commun* 438: 370-374, 2013.
102. Gao Y, Yin J, Tu Y and Chen YC: Theaflavin-3,3'-digallate suppresses human ovarian carcinoma OVCAR-3 cells by regulating the checkpoint kinase 2 and p27 kipl pathways. *Molecules* 24: 673, 2019.
103. Pan H, Li J, Rankin GO, Rojanasakul Y, Tu Y and Chen YC: Synergistic effect of black tea polyphenol, theaflavin-3,3'-digallate with cisplatin against cisplatin resistant human ovarian cancer cells. *J Funct Foods* 46: 1-11, 2018.
104. Pan H, Kim E, Rankin GO, Rojanasakul Y, Tu Y and Chen YC: Theaflavin-3,3'-digallate enhances the inhibitory effect of cisplatin by regulating the copper transporter 1 and glutathione in human ovarian cancer cells. *Int J Mol Sci* 19: 117, 2018.
105. Hollstein M, Sidransky D, Vogelstein B and Harris CC: p53 mutations in human cancers. *Science* 253: 49-53, 1991.
106. Lahiry L, Saha B, Chakraborty J, Adhikary A, Mohanty S, Hossain DM, Banerjee S, Das K, Sa G and Das T: Theaflavins target Fas/caspase-8 and Akt/pBad pathways to induce apoptosis in p53-mutated human breast cancer cells. *Carcinogenesis* 31: 259-268, 2010.
107. Adhikary A, Mohanty S, Lahiry L, Hossain DM, Chakraborty S and Das T: Theaflavins retard human breast cancer cell migration by inhibiting NF-kappaB via p53-ROS cross-talk. *FEBS Lett* 584: 7-14, 2010.
108. Lee HH, Ho CT and Lin JK: Theaflavin-3,3'-digallate and penta-O-galloyl-beta-D-glucose inhibit rat liver microsomal 5alpha-reductase activity and the expression of androgen receptor in LNCaP prostate cancer cells. *Carcinogenesis* 25: 1109-1118, 2004.
109. Sun L, Wen S, Li Q, Lai X, Chen R, Zhang Z, Cao J and Sun S: Theaflavin-3,3'-di-gallate represses prostate cancer by activating the PKC δ /aSMase signaling pathway through a 67 kDa laminin receptor. *Food Funct* 13: 4421-4431, 2022.
110. Mizuno H, Cho YY, Zhu F, Ma WY, Bode AM, Yang CS, Ho CT and Dong Z: Theaflavin-3, 3'-digallate induces epidermal growth factor receptor downregulation. *Mol Carcinog* 45: 204-212, 2006.
111. Yeh CW, Chen WJ, Chiang CT, Lin-Shiau SY and Lin JK: Suppression of fatty acid synthase in MCF-7 breast cancer cells by tea and tea polyphenols: A possible mechanism for their hypolipidemic effects. *Pharmacogenomics* 3: 267-276, 2003.
112. Shi W, Zhang G, Ma Z, Li L, Liu M, Qin L, Yu Z, Zhao L, Liu Y, Zhang X, *et al*: Hyperactivation of HER2-SHCBP1-PLK1 axis promotes tumor cell mitosis and impairs trastuzumab sensitivity to gastric cancer. *Nat Commun* 12: 2812, 2021.
113. Wan C, Hu X, Yang P, Li M, Nisar MF, Zhou Z, Gan Y, Cai Y and Liu Z: Screening of theaflavins that inhibit proliferation of nasopharyngeal carcinoma cells through metabolomics approaches. *Food Sci Nutr* 13: e70642, 2025.
114. Macpherson H, Formica M, Harris E and Daly RM: Brain functional alterations in type 2 Diabetes-A systematic review of fMRI studies. *Front Neuroendocrinol* 47: 34-46, 2017.
115. Cai X, Liu Z, Dong X, Wang Y, Zhu L, Li M and Xu Y: Hypoglycemic and lipid lowering effects of theaflavins in high-fat diet-induced obese mice. *Food Funct* 12: 9922-9931, 2021.
116. Burgess JL, Wyant WA, Abdo Abujamra B, Kirsner RS and Jozić I: Diabetic wound-healing science. *Medicina (Kaunas)* 57: 1072, 2021.
117. Desplantez T: Cardiac Cx43, Cx40 and Cx45 co-assembling: involvement of connexins epitopes in formation of hemichannels and Gap junction channels. *BMC Cell Biol* 18 (Suppl 1): 3, 2017.
118. Li X, Yu L, Gao J, Bi X, Zhang J, Xu S, Wang M, Chen M, Qiu F and Fu G: Apelin ameliorates high glucose-induced downregulation of connexin 43 via AMPK-Dependent pathway in neonatal rat cardiomyocytes. *Aging Dis* 9: 66-76, 2018.
119. Shen Z, Chen Q, Jin T, Wang M, Ying H, Lu J, Wang M, Zhang W, Qiu F, Jin C, *et al*: Theaflavin 3,3'-digallate reverses the downregulation of connexin 43 and autophagy induced by high glucose via AMPK activation in cardiomyocytes. *J Cell Physiol* 234: 17999-18016, 2019.

120. Fu H, He J, Li C and Chang H: Theaflavin-3,3'-digallate protects liver and kidney functions in diabetic rats by up-regulating Circ-ITCH and Nrf2 signaling pathway. *J Agric Food Chem* 72: 14630-14639, 2024.
121. Rachner TD, Khosla S and Hofbauer LC: Osteoporosis: Now and the future. *Lancet* 377: 1276-1287, 2011.
122. Oka Y, Iwai S, Amano H, Irie Y, Yatomi K, Ryu K, Yamada S, Inagaki K and Oguchi K: Tea polyphenols inhibit rat osteoclast formation and differentiation. *J Pharmacol Sci* 118: 55-64, 2012.
123. Qu Z, Liu C, Li P, Xiong W, Zeng Z, Liu A, Xiao W, Huang J, Liu Z and Zhang S: Theaflavin promotes myogenic differentiation by regulating the cell cycle and surface mechanical properties of C2C12 cells. *J Agric Food Chem* 68: 9978-9992, 2020.
124. Sussman NL and Lucey MR: Alcohol and alcoholic liver disease. *Clin Liver Dis* 23: xiii-xiv, 2019.
125. Yoshino K, Yamazaki K and Sano M: Preventive effects of black tea theaflavins against mouse type IV allergy. *J Sci Food Agric* 90: 1983-1987, 2010.
126. Lin CL, Huang HC and Lin JK: Theaflavins attenuate hepatic lipid accumulation through activating AMPK in human HepG2 cells. *J Lipid Res* 48: 2334-2343, 2007.
127. Zhang W, An R, Li Q, Sun L, Lai X, Chen R, Li D and Sun S: Theaflavin TF3 relieves hepatocyte lipid deposition through activating an AMPK signaling pathway by targeting Plasma Kallikrein. *J Agric Food Chem* 68: 2673-2683, 2020.
128. Chen G, Yuan H, Zhang L, Zhang J, Li K and Wang X: Pancreatic lipase immobilization on cellulose filter paper for inhibitors screening and network pharmacology study of anti-obesity mechanism. *Talanta* 280: 126750, 2024.
129. Yang CS, Wang X, Lu G and Picinich SC: Cancer prevention by tea: Animal studies, molecular mechanisms and human relevance. *Nat Rev Cancer* 9: 429-439, 2009.
130. Chen D, Milacic V, Chen MS, Wan SB, Lam WH, Huo C, Landis-Piwowar KR, Cui QC, Wali A, Chan TH and Dou QP: Tea polyphenols, their biological effects and potential molecular targets. *Histol Histopathol* 23: 487-496, 2008.
131. Mozafari MR, Johnson C, Hatziantoniou S and Demetrios C: Nanoliposomes and their applications in food nanotechnology. *J Liposome Res* 18: 309-327, 2008.
132. Rashidinejad A, Birch EJ, Sun-Waterhouse D and Everett DW: Delivery of green tea catechin and epigallocatechin gallate in liposomes incorporated into low-fat hard cheese. *Food Chem* 156: 176-183, 2014.
133. Han X, Niu X, Xu M, Feng R, Han Q, Liu B, Cheng Y, Yun S, Cheng F, Feng C and Cao J: Flammulina velutipes protein-Flammulina velutipes soluble polysaccharide-tea polyphenols particles stabilized Pickering emulsions for the delivery of β -carotene. *Int J Biol Macromol* 285: 138299, 2025.
134. Paiva L, Lima E, Motta M, Marcone M and Baptista J: Investigation of the azorean camellia sinensis processing conditions to maximize the theaflavin 3,3'-di-O-Gallate content as a potential antiviral compound. *Antioxidants (Basel)* 11: 1066, 2022.
135. Li H, Shen S, Yu K, Wang H and Fu J: Construction of porous structure-based carboxymethyl chitosan/sodium alginate/tea polyphenols for wound dressing. *Int J Biol Macromol* 233: 123404, 2023.
136. Davis ME, Chen ZG and Shin DM: Nanoparticle therapeutics: An emerging treatment modality for cancer. *Nat Rev Drug Discov* 7: 771-782, 2008.
137. Kenchegowda M, Rahamathulla M, Hani U, Begum MY, Guruswamy S, Osmani RAM, Gowrav MP, Alshehri S, Ghoneim MM, Alshlowi A and Gowda DV: Smart nanocarriers as an emerging platform for cancer therapy: A review. *Molecules* 27: 146, 2021.
138. Chacko SM, Thambi PT, Kuttan R and Nishigaki I: Beneficial effects of green tea: A literature review. *Chin Med* 5: 13, 2010.
139. Hara Y: Tea catechins and their applications as supplements and pharmaceuticals. *Pharmacol Res* 64: 100-104, 2011.
140. Reagan-Shaw S, Nihal M and Ahmad N: Dose translation from animal to human studies revisited. *FASEB J* 22: 659-661, 2008.
141. Nair AB and Jacob S: A simple practice guide for dose conversion between animals and human. *J Basic Clin Pharm* 7: 27-31, 2016.
142. Pimpão RC, Ventura MR, Ferreira RB, Williamson G and Santos CN: Phenolic sulfates as new and highly abundant metabolites in human plasma after ingestion of a mixed berry fruit purée. *Br J Nutr* 113: 454-463, 2015.
143. Shahrzad S, Aoyagi K, Winter A, Koyama A and Bitsch I: Pharmacokinetics of gallic acid and its relative bioavailability from tea in healthy humans. *J Nutr* 131: 1207-1210, 2001.
144. Ji BC, Hsu WH, Yang JS, Hsia TC, Lu CC, Chiang JH, Yang JL, Lin CH, Lin JJ, Suen LJ, *et al*: Gallic acid induces apoptosis via caspase-3 and mitochondrion-dependent pathways in vitro and suppresses lung xenograft tumor growth in vivo. *J Agric Food Chem* 57: 7596-7604, 2009.
145. Han YH, Moon HJ, You BR, Kim SZ, Kim SH and Park WH: Propyl gallate inhibits the growth of HeLa cells via caspase-dependent apoptosis as well as a G1 phase arrest of the cell cycle. *Oncol Rep* 23: 1153-1158, 2010.



Copyright © 2026 Ma et al. This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.