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EGCG Bioactivity, Oral Bioavailability, and Delivery-System Strategies: A Narrative Review

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Abstract

Epigallocatechin-3-gallate (EGCG) is one of the most widely studied catechins with a high abundance in green tea. It has a variety of potential biological activities such as antioxidant, anti-inflammatory, antitumor, metabolic regulation, and neuroprotection. However, the pronounced in vitro biological activity of EGCG has not been fully translated into in vivo effectiveness. Its practical application is limited by factors such as physicochemical instability, gastrointestinal degradation, limited intestinal absorption, extensive metabolism, and food-matrix effects, collectively contributing to low oral bioavailability. Based on the available literature, this article reviews the major biological activities, bioavailability limitations and delivery-system optimization strategies of EGCG. Human pharmacokinetic studies indicate considerable interindividual variability and limited systemic exposure following oral administration of EGCG. Delivery systems such as nanoemulsions, liposomes, protein- and polysaccharide-based nanoparticles have demonstrated the potential to improve EGCG stability, protection during gastrointestinal transit, and bioaccessibility. However, most of this evidence is derived from in vitro digestion models and animal experiments. Some animal studies further suggest that these delivery systems may enhance systemic exposure and related biological effects, but improvements in formulation performance or bioaccessibility do not necessarily translate into increased bioavailability in humans. Human pharmacokinetic validation, clinical evidence, and long-term safety data remain limited. Future research should therefore prioritize standardized evaluation methods, human bioavailability studies, long-term safety assessment, and scalable manufacturing using food-grade materials to facilitate the translation of EGCG delivery technologies into practical nutritional and pharmaceutical applications.

Keywords

epigallocatechin-3-gallate, green tea, biological activities, bioavailability, delivery systems

1. Introduction

Green tea has received wide attention because it is rich in a variety of biologically active plant compounds, among which catechins are considered to be an important component of green tea to exert health-related effects. Epigallocatechin-3-gallate (EGCG) is one of the most deeply studied catechins with a high abundance in green tea. In recent years, a large number of in vitro, animal and some human studies have found that EGCG has multiple potential biological activities, including scavenging reactive oxygen species, modulating oxidative stress, modulating inflammatory responses, modulating tumor cell proliferation and apoptosis, regulating glucose and lipid metabolism and exerting neuroprotective effects [1-7]. Therefore, EGCG has considerable

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potential as a functional food ingredient and pharmacologically active compound. However, there is still a significant gap between the biological activity of EGCG and its in vivo effectiveness. EGCG is susceptible to oxidation and degradation by factors such as temperature, light, oxygen, and pH. After oral administration, it also needs to go through complex processes such as gastrointestinal digestion, intestinal absorption, and intestinal and hepatic metabolism, which collectively limit systemic exposure and oral bioavailability [8,11].

A substantial body of literature addresses EGCG bioactivity, bioavailability constraints and delivery-system engineering, yet critical research gaps persist. First, much bioactivity evidence originates from cell and animal experiments. It remains unclear whether in-vitro effective concentrations can be attained physiologically within human circulation. Second, poor oral bioavailability arises from interconnected physicochemical and physiological processes spanning stability, gastrointestinal transit, absorption and metabolism. Many publications examine a single step in isolation rather than considering the full in-vivo cascade. The food matrix further affects the release and absorption of EGCG, adding to the complexity of its in-vivo performance [12]. Third, various delivery-system platforms have been reported; however, studies often rely primarily on formulation metrics such as particle size and encapsulation efficiency. Whether favourable formulation metrics translate into improved systemic exposure in humans remains unclear. Moreover, the lack of standardized evaluation criteria across delivery platforms limits the ability to link pre-clinical findings with human outcomes.

Against this background, this narrative review the current understanding of EGCG's biological activities, identifies the major barriers to its oral bioavailability, and compares the performance of existing delivery-system approaches. It further evaluates key translational bottlenecks and identifies directions for future research. Two core review questions guide this work: (1) Which physicochemical and physiological factors most strongly limit the oral bioavailability of EGCG? and (2) To what extent do current delivery systems improve stability, bioaccessibility, and systemic exposure, and what evidence supports translation to humans?

2. Literature Review

Antioxidant and anti-inflammatory activities are well-documented biological effects of EGCG. Its antioxidant activity is not limited to isolated in-vitro systems; studies use human skin tissue have demonstrated that EGCG can attenuate UV-induced oxidative stress [2]. EGCG regulates reactive oxygen species (ROS) homeostasis, oxidative-stress signaling, and endogenous antioxidant defence pathways through both direct and indirect mechanisms. It also regulates inflammatory mediators including TNF-α, IL-1β, IL-6, COX-2 and iNOS in pre-clinical injury models [3]. Beyond regulating inflammatory signalling cascades, recent animal work indicates EGCG may alleviate inflammation partially through restoring host microbial composition [4]. Pre-clinical tumour-model work demonstrates capacity to suppress proliferation and induce apoptosis in malignant cell lines. Notably, anti-tumour activity of EGCG appears dependent on disease progression stage, with observable effects in early-stage rather than late-stage experimental prostate cancer [5]. However, the clinical relevance of these findings remains uncertain. For example, the concentration of EGCG used in some antitumor studies is much higher than the plasma concentration that can usually be achieved after oral administration by the human body, so whether the significant antitumor effect observed in vitro has practical clinical significance still needs to be further verified. These findings highlight the need to interpret bioactivity together with achievable systemic exposure.

Existing human pharmacokinetic investigations confirm detectable plasma EGCG post-oral intake, though systemic exposure is modulated by dosage, administration schedule, food co-ingestion and inter-individual variation [8-10]. Oral EGCG reaches peak plasma concentration rapidly yet demonstrates short half-life and extensive phase-II biotransformation, with substantial inter-individual variation in measured pharmacokinetic profiles [8]. Repeated-dose studies further illustrate how dosing regimen shapes circulating EGCG levels alongside safety considerations [9]. Dose-exposure relationships are non-linear under repeated oral administration in healthy volunteers [10]. Food intake markedly suppresses EGCG oral bioavailability; AUC values under fasting conditions can be several-fold higher compared with co-administration with food matrices [11]. Complex food systems also alter EGCG release during digestion, creating disconnect between intrinsic compound activity and realised bioaccessibility [12]. EGCG suffers gastrointestinal degradation; intestinal epithelial barriers constrain absorption; absorbed EGCG undergoes extensive glucuronidation, sulfation and

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methylation, collectively lowering circulating concentrations of parent compound [8]. These sequential physicochemical and physiological processes together determine its low oral bioavailability.

To counteract these bottlenecks, diverse delivery-system strategies have been explored. Nanoemulsions enhance EGCG dispersibility and gastrointestinal bioaccessibility, accompanied by elevated in-vivo AUC in rodent models [13]. Protein- and polysaccharide-based nanoparticles confer physicochemical stabilization through hydrogen-bonding, hydrophobic and electrostatic intermolecular interactions [14-16]. Bilayer-modified nanoliposomes improve EGCG stability and in-vitro bioavailability under simulated digestive environments [17]. Collectively, available data suggest delivery-system encapsulation can ameliorate formulation-level stability. Heterogeneity in starting materials, fabrication workflows, EGCG loading dose and outcome metrics across studies prevents definitive identification of universally superior platforms.

Three major gaps remain in the current literature. First, a large number of studies focus on in vitro digestion, bioaccessibility and cell experiments. There are relatively few studies that can really prove that the delivery system improves the pharmacokinetic parameters of human EGCG [8]. Second, many studies take "high encapsulation efficiency", "small particle size" or "good stability" as the main basis for the success of the delivery system, but there is no simple linear relationship between these preparation indicators and the final human bioavailability. Third, the lack of unified evaluation standards between different delivery systems makes it difficult to directly compare the research results horizontally. Future investigations should assess the complete fate cascade: gastrointestinal degradation, absorption, metabolism and systemic exposure, rather than focusing solely on preparation optimization.

3. Methodology

This narrative review applies a structured literature search combined with narrative synthesis to organize primary studies concerning EGCG bioactivity, oral-bioavailability barriers and delivery-system technologies, so as to address the two core questions outlined above. PubMed, Web of Science, Scopus, and Google Scholar were queried, with PubMed prioritized for medically relevant records. Search term combinations were constructed thematically corresponding to each sub-topic, covering EGCG biological function, human pharmacokinetics under single and repeated dosing, food-matrix influences, and diverse carrier-based delivery platforms.

Literature screening mainly focused on three domains: EGCG biological activity, factors constraining oral bioavailability, and delivery-system optimization. The included studies mainly include human trials, animal experiments, in vitro experiments and primary studies of different EGCG delivery systems [13-17]. Publications indexed in PubMed from high-impact journals received priority screening. For bioavailability-relevant content, studies reporting pharmacokinetic endpoints (Cmax, AUC, Tmax, half-life) in humans or animals were targeted, including investigations describing dose-exposure responses and food-matrix interference [8-12]. For delivery-system research, extracted readouts encompassed particle dimension, encapsulation efficiency, physicochemical stability, bioaccessibility, release behaviour and observed in-vivo exposure outcomes.

Records were grouped thematically. For delivery-system publications, carrier materials, preparation techniques and evaluation indicators were further compared. Due to the obvious differences in experimental models, dosages, drug administration methods and bioavailability evaluation methods in different studies, this paper mainly adopts a narrative synthesis method. Findings were organized qualitatively by study type, by which bioavailability bottleneck each intervention aimed to mitigate, and by hierarchy of pre-clinical versus human evidence. Special attention was paid to distinguishing improvements observed at the formulation stage from measurable shifts in in-vivo systemic exposure.

4. Evidence Synthesis

Synthesized primary-study evidence indicates that EGCG exhibits broad bioactivity, with antioxidant, anti-inflammatory, and anti-tumor pre-clinical evidence being most abundant [1-5]. Research additionally covers metabolic regulation in obesity models, neuroprotection following cerebral injury and microbiota-modulating effects [4,6,7]. Despite variability across experimental set-ups, most pre-clinical work confirms EGCG can interfere with multiple cellular signalling cascades. Nevertheless, translation of in-vitro bioactivity to

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physiological effect is constrained by multi-layered bioavailability barriers originating from both compound properties and human physiological conditions.

Human pharmacokinetic evidence demonstrates orally administered EGCG can enter systemic circulation, yet attained parent-compound concentrations remain low and highly variable depending on dose, food matrix and inter-individual physiology [8-11]. Intestinal and hepatic phase-II metabolism will further reduce circulating intact EGCG [8]. Food composition strongly modulates exposure, demonstrating that external environmental factors during gastrointestinal transit can greatly alter realised systemic levels [11,12]. Poor oral bioavailability therefore emerges as a cumulative outcome spanning chemical instability in gut luminal conditions, limited epithelial uptake and rapid metabolic transformation.

Various delivery systems have been developed to address specific barriers to EGCG during gastrointestinal transit and systemic absorption. Nanoemulsions may improve the dispersion and gastrointestinal of EGCG [13], while protein- and polysaccharide-based nanoparticles can enhance its structural stability through non-covalent interactions, including hydrogen bonding, hydrophobic interactions, and electrostatic interactions [14-16]. Liposomes may provide additional protection through their lipid bilayer structure. Accordingly, these systems differ in their primary functions: some formulations mainly improve physicochemical stability, while others focus on gastrointestinal protection, sustained release, or enhanced in-vitro bioaccessibility. However, direct cross-study comparisons remain challenging because studies use different carrier materials, preparation methods, EGCG doses, experimental models, and evaluation metrics. Notably, improvements in bioaccessibility observed in vitro or enhanced systemic exposure observed in animal studies cannot be assumed to translate into reliable improvements in systemic bioavailability in humans [17].

Three consistent patterns have emerged from the preclinical evidence base. First, most encapsulation strategies improve the physicochemical stability of EGCG under laboratory storage and simulated gastrointestinal digestive conditions. Second, nanoformulation frequently improve the measured in-vitro bioaccessibility of EGCG, but these in-vitro outcomes cannot reliably predict pharmacokinetic performance in humans. Third, empirical evidence from human trials quantifying delivery system-driven improvements in systemic exposure to EGCG remains limited [8]. Overall, current preclinical evidence supports delivery systems as conceptually promising approaches; however, based on the available published evidence, no single carrier platform has been validated to consistently improve thee bioavailability of EGCG in humans. Detailed comparative parameters for included delivery-system studies are summarised in Appendix Table 1.

Table 1: Comparison of Selected EGCG Delivery Systems and Their Bioavailability-Related Outcomes

Carrier type	Study model	EGCG dose	Particle size /Encapsulation efficiency	Bioaccessibility	Cmax/AUC	Key findings & limitations	Reference
Nanoemulsion	In vitro simulated gastrointestinal digestion; in vivo rat model	Not explicitly reported (tea-polyphenol formulation for oral administration)	~99 nm / Not reported	Significantly improved compared with aqueous EGCG	Elevated plasma AUC in rat model vs. free EGCG	Enhances EGCG dispersion and digestive-phase protection; improves systemic exposure in rat model. Limitation: No human pharmacokinetic validation; stability concerns during long-term storage	[13]
Casein-glucosamine protein nanoparticles	In vitro characterization; in vivo rat arthritis model	Not explicitly reported	Not reported / Not reported	Not measured	Not measured	Enhanced anti-arthritic therapeutic efficacy in animal model. Limitation: Incomplete physicochemical characterization; no human pharmacokinetic data	[14]
Zein-gum arabic composite nanoparticles	In vitro simulated gastrointestinal digestion	0.5 mg/mL	187.4 nm / 76.4%	Improved after simulated gastrointestinal digestion	Not measured	Stabilizes EGCG against gastrointestinal degradation via non-covalent interactions. Limitation: Purely in vitro study; no in vivo	[15]

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Carrier type	Study model	EGCG dose	Particle size /Encapsulation efficiency	Bioaccessibility	Cmax/AUC	Key findings & limitations	Reference
						animal or human systemic exposure data	
Gum arabic-maltodextrin polysaccharide nanoparticles	In vitro prostate cancer cell assay	Not explicitly reported	~200–300 nm / Not reported	Not determined	Not measured	Demonstrated chemopreventive potential against prostate cancer cell lines. Limitation: No digestion or in vivo pharmacokinetic evaluation; lack of human-relevant data	[16]
ε-Polylysine/sodium alginate bilayer-modified nanoliposomes	In vitro simulated gastrointestinal digestion	0.2 mg/mL	143.8 nm / 84.7%	Enhanced in vitro bioavailability under simulated gastrointestinal conditions	Not measured	Bilayer coating greatly improves EGCG stability against gastric and intestinal degradation. Limitation: Purely in vitro study; no animal or human systemic exposure results	[17]

5. Discussion and Translational Implications

Synthesized evidence shows contemporary EGCG research is less limited by documentation of in-vitro bioactivity than by the challenge of translating pre-clinical potency to real-world physiological effect. A large number of cell-based assays show EGCG can regulate oxidative stress, inflammation, oncogenic pathways and metabolic homeostasis [1-7]. Still, without sufficient gastrointestinal resilience and adequate systemic exposure after oral ingestion, these favourable in-vitro observations may not materialize within human physiology [8,11]. Human studies further reveal that dose selection, repeated administration and co-ingested food components all shape actual circulating EGCG concentrations [9-12]. Research emphasis has therefore gradually shifted from cataloguing bioactivity toward strategies mitigating oral-bioavailability limitations, fuelling delivery-system development.

Different delivery systems are engineered to address distinct bioavailability bottlenecks. Improvements in formulation characteristics, enhanced in-vitro bioaccessibility, and gains in systemic bioavailability represent three separate levels of outcome; positive results at one level do not guarantee corresponding benefits will appear at another level. Nanoemulsions improve dispersion and digestive-phase protection [13]; protein-polysaccharide nanoparticle systems stabilize EGCG against chemical degradation via intermolecular binding [14-16]. Modified nanoliposomes strengthen resistance against gastrointestinal degradation [17]. No universal superior carrier exists; suitability depends upon which specific bioavailability bottleneck requires mitigation. If chemical degradation during storage and gastrointestinal transit represents the main constraint, stabilization-focused encapsulation is appropriate.

A pervasive methodological shortcoming within existing literature is treating favourable formulation metrics as surrogate proof of improved human biological performance. High encapsulation efficiency, small particle size and good storage stability reflect progress at the preparation level and cannot substitute for human pharmacokinetic endpoints such as AUC or Cmax [8]. Future work should deploy multi-tiered evaluation workflows integrating formulation characterization, simulated gastrointestinal digestion including food-matrix contexts, bioaccessibility testing, cellular uptake, animal pharmacokinetics and ultimately human investigation.

Further translational obstacles persist. Most datasets derive from in-vitro and animal experiments, with large inter-study heterogeneity hindering cross-platform comparison. Practical barriers include carrier-material long-term safety profiles, scalable industrial manufacture, shelf-life stability and production expenditure [13,15]. Beyond the development of novel carrier systems, greater priority should be given to human pharmacokinetic evaluation, safety monitoring, and the use of food-grade, industrially scalable materials to facilitate the translation of EGCG delivery technologies from laboratory research to nutritional and pharmacological applications.

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Taken together, multiple physicochemical and physiological factors collectively limit the oral bioavailability of EGCG. Degradation in gastrointestinal fluids, limited intestinal absorption, and rapid phase-II metabolism in the intestine and liver reduce the circulating levels of intact EGCG, while food-matrix effects and inter-individual variability further contribute to differences in systemic exposure [8-12]. Although existing delivery-system strategies can effectively improve the physicochemical stability and in-vitro bioaccessibility of EGCG under experimental conditins, conclusive evidence demonstrating a sustainable improvement in systemic EGCG bioavailability in humans remains lacking. Promising pre-clinical observations cannot be directly extrapolated to oral performance in humans, highlighting a critical gap between formulation-level improvement and physiological efficacy under real-world [13-17].

6. Conclusion

This narrative review examined the key factors limiting the oral bioavailability of EGCG and evaluated the current performance of available delivery-system technologies. Overall, pre-clinical primary-study evidence supports broad antioxidant, anti-inflammatory, anti-tumour, metabolic-regulatory and neuroprotective bioactivity for green-tea-derived EGCG.

Its oral efficacy is constrained by interconnected physicochemical and physiological barriers. Luminal gastrointestinal degradation, limited intestinal absorption, and metabolic transformation in the intestine and liver collectively reduce circulating of intact EGCG. Food matrix further interferes with EGCG release and absorption within the digestive tract. Simply raising administered EGCG dosage cannot fully overcome these multi-step utilization constraints, motivating interest in protective delivery-system technologies.

Nanoemulsions, protein- or polysaccharide-based nanoparticles, and modified liposomes can improve EGCG stability and bioaccessibility under simulated gastrointestinal digestion conditions to varying degrees. Some animal studies have also reported increased tissue exposure following encapsulation. Nevertheless, most supporting evidence comes from in-vitro and animal-model experiments. Study conditions and measured endpoints differ widely across publications; improved formulation-level parameters and in-vitro bioaccessibility do not equate to confirmed enhanced systemic exposure for humans.

The key evidence boundaries should be acknowledged. Direct human pharmacokinetic data quantifying delivery system-mediated improvements in EGCG bioavailability remain limited. Further research should prioritize the establishing of multi-level evaluation pipelines, human-relevant pharmacokinetic testing, long-term safety evaluation, and validation of real-world performance. Only through a comprehensive evidence chain spanning formulation development, preclinical evaluation, and human studies can it be determined whether delivery-system encapsulation can reliably unlock EGCG's intrinsic biological potential for human nutritional or pharmacological application.

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Conflicts of Interest

The authors declare no conflict of interest.

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