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EXPLORING ELLAGIC ACID AS A HEPATOPROTECTIVE AGENT: FROM MECHANISTIC PATHWAYS TO THERAPEUTIC APPLICATIONS

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ABSTRACT

Ellagic acid (EA), a naturally occurring polyphenolic compound found in various fruits and nuts, has emerged as a promising hepatoprotective agent due to its potent antioxidant, anti-inflammatory, antifibrotic, and anticancer properties. Chronic liver diseases such as non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD), fibrosis, and hepatocellular carcinoma are driven by oxidative stress, inflammation, mitochondrial dysfunction, and hepatocyte apoptosis. EA exerts hepatoprotective effects by scavenging reactive oxygen species (ROS), upregulating Nrf2/HO-1 signaling, suppressing NF-κB-mediated inflammation, stabilizing mitochondrial membranes, and modulating apoptosis pathways. However, EA's poor water solubility, limited gastrointestinal absorption, and rapid metabolism severely restrict its bioavailability. Recent advancements in Nano nanoformulations, such as liposomes, phytosomes, and nanoparticles, have shown promise in improving its pharmacokinetic profile. Moreover, gut microbiota-derived metabolites, particularly urolithin A, are believed to mediate many of EA's systemic effects, although interindividual variability in microbial composition influences therapeutic outcomes. In addition to its hepatoprotective activity, EA demonstrates anticancer potential by targeting cell cycle regulators and pro-survival pathways, and offers dermatoprotective benefits through photo protection, anti-tyrosinase activity, and wound healing enhancement. While preclinical studies consistently validate EA's efficacy, further clinical trials and microbiome-personalized approaches are essential to fully translate its potential into therapeutic application. This review comprehensively explores the pharmacological mechanisms, bioavailability challenges, and future directions for EA in liver disease and beyond.

KEYWORDS: Ellagic acid, hepatoprotection, bioavailability, liver disease, nano-formulations.

INTRODUCTION

Chronic liver diseases such as viral hepatitis, alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), fibrosis, cirrhosis, and hepatocellular carcinoma represent a significant and growing global health challenge, causing over two million deaths annually. These conditions are primarily underpinned by persistent oxidative stress, inflammation, metabolic disturbances, and exposure to various toxins and infections. Unfortunately, current pharmacological treatments are often insufficient, delivering limited efficacy and, in some cases, causing adverse effects. Therefore, identifying safer and more effective hepatoprotective agents remains a priority. Ellagic acid (EA) is a natural polyphenolic compound prevalent in pomegranates, berries, nuts, and seeds. Chemically, it is classified as a dilactone derived from hexahydroxydiphenic acid and is notable for its potent antioxidant, anti-inflammatory, antifibrotic, antiviral, and immunomodulatory properties (Zhang et al., 2024; Qiu et al., 2021). Despite its promising pharmacological profile, EA suffers from poor solubility and limited oral absorption. Its therapeutic effectiveness is further hampered by rapid metabolism via gut microbiota into

urolithins, which may partly mediate its systemic effects (Zhang et al., 2024; Li et al., 2023). EA's clinical utility is impeded by its pharmacokinetic constraints. It exhibits poor water solubility and rapid first-pass metabolism. However, gut bacterial conversion to urolithins enhances bioavailability and may play a central role in mediating its health benefits (Zhang et al., 2025; Li et al., 2023). To improve EA's therapeutic efficacy, researchers are developing novel nano- and micro-encapsulated formulations aimed at increasing solubility, metabolic stability, and liver targeting (Ciesielski et al., 2022; Qiu et al., 2021). Oxidative stress plays a pivotal role in hepatic damage, spawning lipid peroxidation, mitochondrial damage, and cell death. EA exhibits strong antioxidant capabilities by both direct free radical scavenging and induction of the Nrf2/HO-1 pathway. In vitro studies in HepG2 cells under hyperglycaemic stress showed EA restored antioxidant enzymes (SOD, HO-1, NQO1) through miR-223-mediated downregulation of Keap1, thereby activating Nrf2 (Qiu et al., 2021). In vivo, EA significantly reduced oxidative damage by elevating Nrf2 and HO-1 expression in cisplatin-induced liver injury in mice (Zhang et al., 2024). Similar outcomes including reduced malondialdehyde and enhanced antioxidant enzyme activity were also observed in NAFLD models following EA supplementation (Qiu et al., 2021; Ioannidis et al., 2021). Chronic hepatic inflammation drives disease progression through mediators like TNF-α, IL-1β, IL-6, and the NF-κB pathway. EA suppresses these inflammatory signals, as demonstrated in various models: it attenuated cytokine release and improved histopathology in acrylamide-challenged rats (Ioannidis et al., 2021); reduced NF-κB activation and systemic IL-6 in cisplatin-treated mice (Zhang et al., 2024); and diminished pro-inflammatory markers in ALD models, correlating with enhanced antioxidant defenses (Liu et al., 2022; Qiu et al., 2021). Persistent fibrosis stems from unrestrained inflammation and extracellular matrix deposition. In CCl_4- and bile duct-ligated (BDL) rodent models, EA reduced fibrosis markers, collagen deposition, and fibrogenic cytokines (TGF-β1, TNF-α) (Nasir et al., 2021; Liu et al., 2022). EA also safeguards mitochondria against apoptosis: in Con A-induced acute liver injury, EA preserved membrane potential and curtailed cell death (Nasir et al., 2021). Recent studies implicate pyroptosis a lytic, pro-inflammatory type of cell death via caspase-1/gasdermin D in ischemia–reperfusion liver injury. EA pre-treatment in murine models significantly reduced caspase-1 and GSDMD activation, diminishing the release of IL-1β and IL-18 and mitigating inflammatory damage (Liu et al., 2022). Hepatic lipid accumulation is central to NAFLD/NASH. In C57BL/6J mice, dietary EA reduced total cholesterol and LDL while increasing HDL levels. Mechanistically, EA downregulated lipogenesis (ACC) while upregulating fatty acid oxidation genes (CPT1B, PPARα). These lipid improvements corresponded with enhanced Nrf2-ARE activity and bolstered antioxidant defenses (Qiu et al., 2021; Ioannidis et al., 2021). The gut–liver axis profoundly influences hepatic health, especially in alcohol-induced injury. EA preserved intestinal tight junction proteins, normalized CYP2E1 expression, and reduced oxidative stress markers. These effects correlated with lower endotoxin translocation and diminished ALT/pro-inflammatory cytokine levels comparable to silymarin treatment (Liu et al., 2022).

Sources and Chemistry of Ellagic Acid

Ellagic acid (EA) is a naturally occurring phenolic compound widely distributed in fruits, vegetables, and nuts. Its richest dietary sources include pomegranates (*Punica granatum*), strawberries (*Fragaria* × *ananassa*), raspberries (*Rubus idaeus*), blackberries, grapes, walnuts, almonds, and oak-aged beverages like wine and whiskey (Landete et al., 2011; Seeram et al., 2005). EA exists either in free form or more commonly as ellagitannins hydrolyzable tannins that yield EA upon acid or enzymatic hydrolysis. In plant matrices, EA is typically bound to glucose and gallic acid in the form of ellagitannins, such as punicalagin (from pomegranate), geraniin, and vescalagin. Upon ingestion, ellagitannins are hydrolyzed in the upper gastrointestinal tract to release free EA, which is then metabolized by gut microbiota into bioactive derivatives known as **urolithins** (Tomás-Barberán et al., 2017).

Table 1: Natural Dietary Sources of Ellagic Acid and Their Estimated Ellagic Acid Content.

Source	Ellagic Acid Form	Estimated Content (mg/100g)
Pomegranate juice	Punicalagin (ET)	40–70
Strawberries	Free EA + ETs	20–30
Raspberries	Sanguiin H-6 (ET)	30–60
Walnuts	ETs (e.g., vescalagin)	40–60
Almonds	Free EA	5–15

Chemical Structure

Chemically, ellagic acid is a polyphenolic dilactone formed by oxidative coupling of two gallic acid units, resulting in a biaryl tetrahydroxy compound with two lactone rings. Its molecular formula is $C_{14}H_6O_8$**,** and it has a molecular weight of 302.19 g/mol. The structure contains four hydroxyl groups and two lactone groups, which contribute to its strong antioxidant capacity**,** as these groups participate in electron donation and free radical neutralization. EA's poor aqueous solubility (~9.7 µg/mL) and instability at neutral or basic pH are key challenges to its pharmaceutical development (Hsu et al., 2007).

Stability and Solubility Challenges

Ellagic acid (EA) faces significant pharmaceutical limitations due to its physicochemical properties. It is relatively unstable in alkaline environments and highly susceptible to oxidative degradation, which can compromise its therapeutic efficacy. Moreover, EA exhibits poor water solubility and low intestinal permeability, categorizing it under Biopharmaceutical Classification System (BCS) Class IV. These factors collectively contribute to its poor oral bioavailability. Once absorbed, EA undergoes extensive phase II metabolism mainly glucuronidation and methylation resulting in rapid excretion via urine and feces (González-Sarrías et al., 2015). These metabolic pathways further reduce its systemic concentration, limiting its therapeutic effectiveness. To address these challenges, recent pharmaceutical advancements have explored the use of nanoparticle formulations, liposomal encapsulation, and phytosome-based carriers. These innovative delivery systems aim to enhance the solubility, stability, and permeability of EA, thereby improving its pharmacokinetic profile and bioavailability. Additionally, co-administration with bioenhancers or use of polymeric carriers has shown promise in optimizing EA's clinical potential.

Metabolism to Urolithins

The gut microbiota plays a crucial role in the metabolic transformation of ellagic acid (EA) into a series of bioactive compounds known as urolithins, primarily urolithins A, B, C, and D. This microbial bioconversion is essential for the biological activity of EA, as the parent compound itself exhibits limited systemic bioavailability. Among these metabolites, urolithin A is the most prominent and well-studied. It demonstrates markedly improved pharmacokinetic properties, including higher bioavailability, better cellular uptake, and a longer plasma half-life compared to native EA. Importantly, urolithin A retains the antioxidant and anti-inflammatory properties of EA and, in some cases, even enhances them. Studies have shown that it exerts beneficial effects on mitochondrial function, cellular senescence, and autophagy, particularly in hepatic and muscle tissues. These effects suggest a strong link between EA intake and systemic health benefits, mediated predominantly through its microbial metabolites. The variability in urolithin production among individuals largely dependent on gut microbiota composition also highlights the importance of personalized nutrition and microbiome profiling. Overall, the transformation of EA to urolithins is a pivotal step that significantly influences its therapeutic potential and underscores the role of gut microbiota in modulating polyphenol efficacy (Tomás-Barberán et al., 2017).

Pharmaceutical Limitations

Despite its extensive pharmacological potential, ellagic acid (EA) faces multiple pharmaceutical limitations that hinder its effective therapeutic use. One of the most significant challenges is its low oral bioavailability, which is primarily attributed to its poor water solubility and limited intestinal permeability. Additionally, EA undergoes rapid metabolism and clearance from systemic circulation, reducing its biological half-life and overall therapeutic efficacy. Another important constraint is its chemical instability at neutral and alkaline pH, which further compromises its absorption and bioactivity in the gastrointestinal tract. To overcome these barriers, pharmaceutical research has focused on developing innovative delivery systems that can enhance EA's solubility, stability, and absorption. Approaches such as cyclodextrin inclusion complexes**,** liposomal formulations, and nanotechnology-based systems including nanoparticles and phytosomes have shown encouraging results in improving the pharmacokinetic properties of EA, thereby increasing its therapeutic potential (Ciesielski et al., 2022).

Table 2: Natural Dietary Sources of Ellagic Acid, Their Forms, and Estimated Content.

Source	Ellagic Acid Form	Estimated Content (mg/100g)	Reference
Pomegranate juice	Punicalagin (ET)	40–70	Seeram et al., 2005
Strawberries	Free EA + ETs	20–30	Landete et al., 2011
Raspberries	Sanguiin H-6 (ET)	30–60	Landete et al., 2011
Walnuts	ETs (e.g., vescalagin)	40–60	Tomás-Barberán et al., 2017
Almonds	Free EA	5–15	González-Sarrías et al., 2015

Table 3: Recent reports on EA presence as a major constituent of medicinal plants and their cumulative pharmacological effect as reported with other phytochemical constituents (for the period from 2018 to 2024).

Sr. no	Medicinal Plant name	Plant family	Part used	Pharmacological effect	References
1	Chrozophora oblongifolia	Euphorbiaceae	Root	Anti-cancer	(Shendge et al., 2018)
2	Clerodendrum Viscosum	Lamiaceae	Leaf	Ameliorates iron-overload induced hepatotoxicity	(Süntar et al., 2020)
3	Cornus mas L.	Cornaceae	Fruit	Prevents ulcerative colitis	(Prabha et al., 2019)
4	Hopea parviflora	Dipterocarpaceae	Stem bark	Anti-inflammatory	(Zhang et al 2020)
5	Mentha	Lamiaceae	Whole	Anti-diabetic	(Zhao et al 2019)

	pulegiumL		plant		
6	Lagerstroemia speciosa	Lythraceae	Leaf	Anti-diabetic	(Moharram et al 2018)
7	Myrciaria cauliflora	Myrtaceae	Bark, wood	Anti-inflammatory	(Morikawa et al.,2018)
8	Pimenta racemosa	Myrtaceae	Leaf	Hepato protective and anti-inflammatory	(Anantpadma et al., 2018)
9	Potentilla anserina	Rosaceae	Whole plant	Hepatoprotective activity	(Yang et al., 2020)
10	Rhodiola rosea	Crassulaceae	Herbal	Inhibits viral entry	(Park, W. Y et al., 2019)
11	Rubus Chingii	Rosaceae	Fruit	Antioxidant	(Tan, Y. H., Shudo et al., 2019)
12	Rubuscoreanus	Rosaceae	Whole plant	Anti-obesity	(Brito, S. A et al., 2018)
13	Sanguisorba officinalis	Rosaceae	Whole plant	InducesG1cellcyclearrest	(Rummun et al., 2020)
14	Spondias Mombin	Anacardiaceae	Leaf	Anti-inflammatory	(P. Truchado et al., 2012)
15	Tamarix nilotica	Tamaricaceae	Leaf	Anti-cancer	(J.C. Espín et al 2007, G. Borges et al., 2007)
16	Terminalia bentzoë	Combretaceae	Leaf	Antioxidant and cell cycle arrest at G0/G1phase	(R. González-Barrio et al., 2011)

Absorption

Ellagic acid (EA) exhibits poor intestinal absorption primarily due to its low water solubility (approximately 9.7 µg/mL), high polarity, and its propensity to form insoluble complexes with dietary metal ions and proteins within the gastrointestinal tract (Hsu et al., 2007). Following oral administration, only a small fraction of free EA is absorbed through the small intestine, with the majority passing unabsorbed into the colon. Pharmacokinetic studies in rats have demonstrated that oral dosing with EA results in very low plasma concentrations. Peak plasma levels (Cmax) are typically reached within 1 to 2 hours post-ingestion, followed by a rapid decline, indicating limited systemic exposure (González-Sarrías et al., 2015). The low intestinal permeability of EA further supports its classification as a Biopharmaceutics Classification System (BCS) Class IV compound, characterized by both poor solubility and poor permeability (González-Sarrías et al., 2015; Tomas-Barberán et al., 2017).

Metabolism by Gut Microbiota

Due to its poor solubility and limited permeability in the upper gastrointestinal (GI) tract, a substantial proportion of orally ingested ellagic acid (EA) and its precursors, notably ellagitannins, bypass absorption in the stomach and small intestine and arrive largely unmetabolized in the colon. Within the colonic environment, these compounds undergo extensive biotransformation mediated by gut microbiota, resulting in the formation of a distinct group of low-molecular-weight metabolites known as urolithins, including urolithins A, B, C, and D. The metabolic pathway begins with the hydrolysis of ellagitannins into free EA, followed by stepwise microbial catabolism involving lactone-ring cleavage, decarboxylation, and dehydroxylation. This transformation typically proceeds from urolithin D to urolithin C, then urolithin A**,** and finally urolithin B, depending on microbial enzyme activity and substrate availability (Tomas-Barberán et al., 2017). These urolithins possess greater intestinal permeability, enhanced systemic bioavailability, and improved metabolic stability compared to parent EA. As a result, urolithins are considered the primary circulating and bioactive forms responsible for the systemic antioxidant, anti-inflammatory, and hepatoprotective effects attributed to EA. Emerging evidence suggests that urolithin A, in particular, exhibits potent biological effects, including mitochondrial biogenesis, anti-aging properties, and cytoprotective activities in hepatic and other tissues. Urolithins also demonstrate favorable pharmacokinetic profiles, including longer half-lives, increased tissue distribution, and stronger affinity for plasma proteins, facilitating their sustained activity in vivo. Crucially, the conversion of EA to urolithins is highly individual-dependent, governed by the composition and enzymatic capabilities of the host's gut microbiota. Individuals are categorized into three microbiota-driven metabotypes**.**

- **Metabotype A**: Produces primarily urolithin A
- **Metabotype B**: Produces both urolithin A and urolithin B
- **Metabotype 0**: Produces negligible or no detectable urolithins

This interindividual variability introduces significant heterogeneity in the pharmacodynamic response to EA, meaning that therapeutic efficacy may vary dramatically between individuals with different microbial profiles (Selma et al., 2014). Consequently, personalized nutrition and pharmacology approaches potentially involving microbiome modulation via prebiotics, probiotics, or tailored formulations are increasingly recognized as essential for optimizing EA-based interventions.

Bio-distribution

Following their microbial transformation in the colon, urolithins metabolites of ellagic acid (EA) enter the systemic circulation primarily in conjugated forms, such as glucuronides and sulfates. These conjugates have been detected in various tissues, including the liver, colon, prostate, kidney, and plasma, indicating their capacity for widespread distribution throughout the body. Animal studies have demonstrated tissue-specific accumulation of urolithins, with particularly high concentrations observed in the liver and colon. This selective biodistribution provides mechanistic evidence supporting the therapeutic potential of EA, especially in hepatic and gastrointestinal disorders. The liver, a central organ in detoxification and metabolic regulation, benefits from the antioxidant and anti-inflammatory properties of urolithins. Meanwhile, the colon being the site of their microbial conversion experiences direct exposure to their local effects. As a result, the biodistribution profile of urolithins enhances the pharmacological efficacy of EA and reinforces its relevance in the prevention and treatment of liver and colon-related diseases (González-Sarrías et al., 2015).

Excretion

Ellagic acid (EA) and its downstream microbial metabolites are primarily eliminated from the body via both fecal and urinary routes, reflecting their distinct absorption and metabolic pathways. A significant fraction of orally administered EA and ellagitannins due to their poor aqueous solubility, low membrane permeability, and susceptibility to hydrolysis is not absorbed in the upper gastrointestinal tract. Instead, this unabsorbed portion passes through the digestive system and is largely excreted in feces, representing a major route of elimination for unmetabolized EA (Cerdá et al., 2004). In contrast, EA-derived microbial metabolites, particularly urolithins, exhibit markedly improved absorption characteristics. Once formed in the colon, urolithins are efficiently absorbed across the intestinal barrier, where they undergo phase II metabolism, including glucuronidation and sulfation, primarily in the liver. These conjugated forms are then excreted through the renal pathway, appearing in urine within 24 to 48 hours following EA ingestion, with peak urinary concentrations generally observed between 6 to 12 hours post-consumption. This biphasic elimination pattern highlights the delayed but sustained bioavailability of urolithins compared to native EA (González-Sarrías et al., 2015).

Pharmacokinetic studies have consistently demonstrated that the oral bioavailability of free EA is exceedingly low, typically less than 10%, due to limited dissolution in gastrointestinal fluids and inefficient epithelial transport. In contrast, the bioavailability of urolithins is significantly higher, attributable to their increased lipophilicity, better membrane permeability, and prolonged systemic retention. Urolithins exhibit greater tissue distribution and stronger binding to plasma proteins, further enhancing their pharmacodynamic potential and enabling their detection in peripheral tissues such as the liver, colon, and brain (González-Sarrías et al., 2015). These findings underscore the critical role of microbial transformation in the pharmacokinetic fate and systemic bioactivity of EA. While the parent compound exhibits limited systemic exposure, its microbial metabolites particularly urolithin A serve as the principal bioactive entities responsible for the antioxidant, anti-inflammatory, and hepatoprotective actions observed in vivo. Accordingly, the evaluation of EA-based therapies must consider not only the pharmacokinetics of the parent compound but also the metabolic conversion efficiency and interindividual variability in urolithin production, which directly influence therapeutic outcomes.

Table 4: Summary of ADME Properties of Ellagic Acid.

Parameter	Details	Reference
Absorption	Low solubility & permeability; poor GI absorption	Hsu et al., 2007
Metabolism	Converted by colonic bacteria to urolithins A, B, C, D	Tomas-Barberán et al., 2017
Biodistribution	Urolithins distribute to liver, kidney, colon, and plasma	González-Sarrías et al., 2015
Excretion	EA in feces; urolithins in urine (mainly as glucuronides and sulfates)	Cerdá et al., 2004

Pharmacological activities

According to reports, EA has Antimutagenic (Wood *et al.*, 1982) Antigenotoxic (Agil *et al.*, 2022) Anti-apoptotic (Abdel-Daim *et al.*, 2020) Anticarcinogenic (Zhang *et al.*, 2014) Antibacterial (Polce *et al.*, 2022) Antiviral (Ayhanci *et al.*, 2021) Antimalarial (Seo *et al.*, 2020) Antiallergic (Goswami *et al.*, 2014) Anti-inflammatory (Mohan *et al.*, 2022) Antiatherogenic (Alshammari *et al.*, 2022) Antidiabetic (Niu *et al.*, 2022) Antiepileptic (Girish *et al.*, 2020) Antidepressant (Mousavi *et al.*, 2023) Anti-inflammatory (Tomás-Barberán *et al.*, 2017) Anticarcinogenic (González-Sarrías *et al.*, 2016) Antimalarial (Seo *et al.*, 2020) Antidiabetic (Singh *et al.*, 2021) Antiaromatase (Larrosa *et al.*, 2006) Anti-hyperlipidemic (Nunez-Sanchez *et al.*, 2014) Molecular targets (Piwowarski *et al.*, 2017) Antianxiety (Mousavi *et al.*, 2023) Neuroprotective (Ramesh *et al.*, 2021) Pneumoprotective (Sánchez-González *et al.*, 2020) Nephroprotective (Abdel-Daim *et al.*, 2020) Cardioprotective (Polce *et al.*, 2022) Hepatoprotective (Singh *et al.*, 2013) Strong antioxidant (Mohan *et al.*, 2022).

Bioavailability of EA

Ellagic acid (EA), despite its well-documented therapeutic potential, is significantly limited in clinical use due to its poor oral bioavailability. Several factors contribute to this issue, including its poor aqueous

solubility, low permeability across the intestinal epithelium, and extensive first-pass metabolism. Additionally, interactions with dietary components and variations in gastrointestinal pH further hinder its absorption and systemic availability (González-Sarrías et al., 2015; Hsu et al., 2007). Upon oral administration, a large proportion of free EA either remains unabsorbed or is excreted unchanged through feces. As a result, only trace concentrations of EA are detected in plasma, even after ingestion of EA-rich foods or supplements. This limited systemic exposure suggests that the biological effects attributed to EA may be more strongly linked to its gut-derived metabolites, such as urolithins, rather than the parent compound itself (Seeram et al., 2004). Overcoming these pharmacokinetic barriers remains a major focus of current pharmaceutical research.

Pharmacokinetics and Absorption Limitations

Ellagic acid (EA) is categorized as a Biopharmaceutics Classification System (BCS) Class IV compound, a group known for poor water solubility and low intestinal permeability. These properties present major challenges for its oral bioavailability and therapeutic application. After oral administration, EA's absorption is largely confined to the upper gastrointestinal tract, but even there, uptake remains inefficient. As a result, plasma concentrations stay extremely low, even when high doses of EA or EA-rich extracts are consumed (Hsu et al., 2007). Human pharmacokinetic studies have shown that the maximum plasma concentration (Cmax) of EA after ingestion of pomegranate juice is less than 100 ng/mL, with a short plasma half-life of approximately 1.5 hours or less (Seeram et al., 2004). Preclinical studies in rats report similar findings, where peak plasma concentrations occur within 1 to 2 hours post-administration, followed by a rapid decline. These observations confirm EA's rapid systemic clearance and further underscore the need for formulation strategies to improve its pharmacokinetic profile.

Role of Gut Microbiota in Enhancing Bioavailability

A significant portion of ellagic acid's (EA) systemic biological activity is now understood to arise not from the parent compound itself, but from its gut microbial metabolites, collectively known as urolithins. These compounds are more lipophilic, possess greater intestinal permeability, and exhibit improved bioavailability compared to EA. Urolithins have been detected in plasma and tissues for extended durations following ingestion, indicating their sustained presence and activity in the body. Among them, urolithin A has received the most scientific attention due to its favorable pharmacokinetic profile and robust biological effects. It has demonstrated superior anti-inflammatory, antioxidant, and cytoprotective properties in various experimental models when compared to EA, supporting the idea that these microbial derivatives are largely responsible for the systemic pharmacological benefits associated with EA intake (Tomas-Barberán et al., 2017).

Interindividual Variability in Bioavailability

The conversion of EA to urolithins depends on the composition of the individual's gut microbiota. Some individuals are efficient converters ("metabotype A or B"), while others are "non-converters" (metabotype 0), and thus show low systemic exposure to urolithins even with the same dietary intake (Selma et al., 2014). This results in significant interindividual differences in EA bioavailability and therapeutic response.

Strategies to Improve Bioavailability

Table 5: Several advanced delivery systems have been developed to address EA's poor bioavailability.

Formulation	Mechanism of Improvement	Outcome
Cyclodextrin Complexes	Improves water solubility	3–5x increase in dissolution rate (Hsu et al., 2007)
Liposomes	Enhances membrane permeability	Better tissue penetration
Nanoparticles	Increases solubility and surface area	Higher plasma retention (Ciesielski et al., 2022)
Phytosomes	Phospholipid-based vesicles improving absorption	Significant rise in bioactive urolithins

To overcome the limitations posed by ellagic acid's (EA) poor oral bioavailability, a range of advanced drug delivery systems have been developed and are currently under preclinical and early clinical evaluation. Cyclodextrin inclusion complexes have shown promise by significantly enhancing EA's aqueous solubility, resulting in a three- to five-fold increase in its dissolution rate (Hsu et al., 2007). Liposomal formulations, by encapsulating EA within lipid bilayers, facilitate better membrane permeability and improve tissue penetration. Nanoparticles, particularly those engineered from biocompatible polymers, offer increased solubility and surface area, leading to higher plasma retention and improved systemic exposure (Ciesielski et al., 2022). Phytosomes, which involve the complexation of EA with phospholipids, enhance its gastrointestinal absorption and contribute to a substantial rise in the generation of bioactive urolithins. These delivery strategies represent promising approaches to maximize the therapeutic potential of EA by overcoming its inherent pharmacokinetic barriers.

Table 6: Key Bioavailability Parameters of EA.

Parameter	Details	Reference
Absorption	Low solubility & permeability; poor GI absorption	Hsu et al., 2007
Metabolism	Converted by colonic bacteria to urolithins A, B, C, D	Tomas-Barberán et al., 2017
Biodistribution	Urolithins distribute to liver, kidney, colon, and plasma	González-Sarrías et al., 2015
Excretion	EA in feces; urolithins in urine (mainly as glucuronides and sulfates)	Cerdá et al., 2004

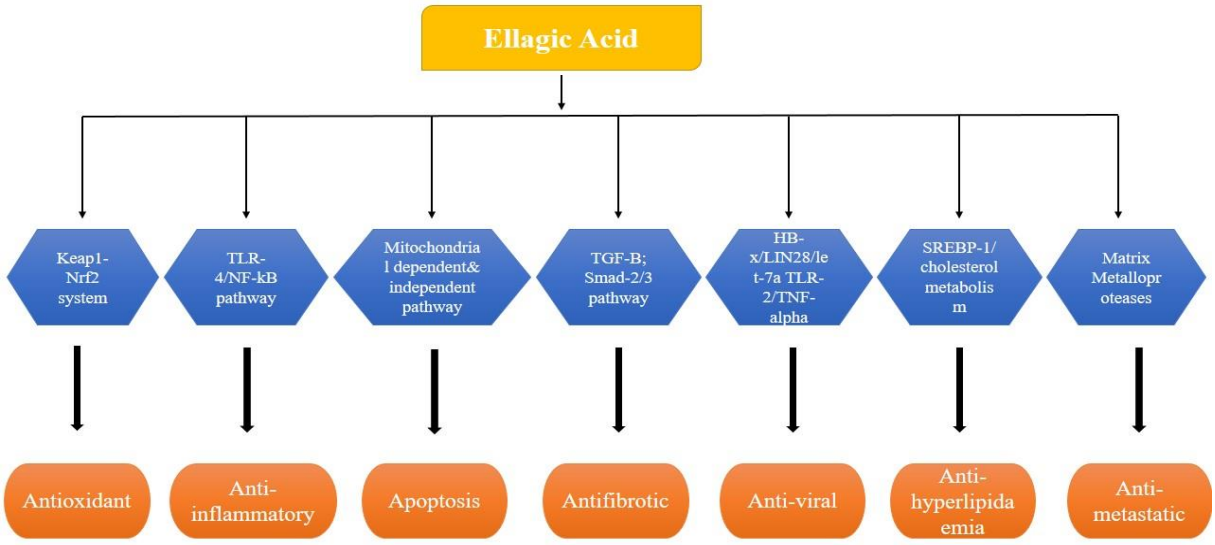

Figure 1: Salient pharmacological features of EA elicited by regulation of key signalling pathways to combat liver disease.

Antioxidant properties of EA

Ellagic acid (EA) is a potent natural antioxidant known for its significant free radical scavenging, lipid peroxidation inhibition, and enzyme-regulating properties. These antioxidant actions are central to its hepatoprotective mechanisms, particularly in the context of liver disorders where oxidative stress plays a major role (Zhang et al., 2024; Qiu et al., 2021). Reactive oxygen species (ROS), including superoxide (O_2^-), hydroxyl radicals (•OH), and hydrogen peroxide (H_2O_2), are key contributors to the pathogenesis of liver diseases such as non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD), hepatic fibrosis, and drug-induced liver injury (DILI). These ROS can cause oxidative damage to lipids, proteins, and DNA, ultimately leading to hepatocyte death and inflammation. One of the primary antioxidant mechanisms of EA involves direct scavenging of free radicals. EA's polyphenolic hydroxyl groups donate hydrogen atoms or electrons to neutralize ROS. Its unique molecular structure, consisting of four hydroxyl groups and two lactone rings, allows for resonance stabilization of the phenoxyl radical, thereby enhancing its radical-scavenging efficiency (Hsu et al., 2007). In vitro studies using DPPH and ABTS assays have demonstrated that EA possesses strong, dose-dependent radical scavenging activity, often comparable to standard antioxidants such as ascorbic acid and quercetin (Landete et al., 2011). In addition to direct scavenging, EA plays a critical role in inhibiting lipid peroxidation a chain reaction where ROS attack polyunsaturated fatty acids in cellular membranes. This process compromises membrane integrity and contributes to cell death. Experimental studies in animal models have shown that EA administration significantly reduces malondialdehyde (MDA) levels, a well-established marker of lipid peroxidation, particularly in liver tissues subjected to oxidative insults from agents like doxorubicin, acetaminophen, or carbon tetrachloride (CCl_4) (Nasir et al., 2021; Zhang et al., 2024). EA also exerts indirect antioxidant effects by modulating intracellular defense pathways, particularly through the activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling cascade. Nrf2 is a key transcription factor that binds to antioxidant response elements (ARE) in the promoter regions of several phase II detoxifying and antioxidant enzyme genes. These include heme oxygenase-1 (HO-1), superoxide dismutase (SOD), catalase (CAT), and NAD (P)H quinone oxidoreductase 1 (NQO1). Studies in diabetic rat models and HepG2 cells have shown that EA enhances the nuclear translocation of Nrf2 and upregulates the expression of HO-1 and NQO1, leading to a restored redox balance and reduced oxidative liver damage (Qiu et al., 2021; Zhang et al., 2024). Furthermore, EA contributes to the maintenance of mitochondrial integrity, a vital aspect of its antioxidant function. Mitochondria are both generators and targets of ROS in hepatocytes. EA has been shown to preserve mitochondrial membrane

potential, prevent mitochondrial swelling, inhibit cytochrome c release, and block the initiation of apoptosis under oxidative stress conditions (Nasir et al., 2021). These effects help sustain cellular viability and enhance overall hepatocellular resistance to oxidative damage. When compared to standard antioxidants, EA displays comparable or even superior efficacy. It has demonstrated similar radical-scavenging potential to quercetin and gallic acid in various assays (Landete et al., 2011), and in some rodent studies, has surpassed the antioxidant effects of vitamin C in preventing liver lipid peroxidation (Qiu et al., 2021). These findings underscore EA's promise as a therapeutic candidate for managing oxidative stress-associated liver diseases.

Table 7: Antioxidant Actions of EA – Mechanisms and Markers.

Mechanism	Biomarker/Effect	Reference
ROS scavenging	↓ DPPH, ABTS radicals	Landete et al., 2011
Lipid peroxidation inhibition	↓ MDA levels	Nasir et al., 2021
Nrf2 activation	↑ Nrf2, HO-1, NQO1, SOD	Zhang et al., 2024
Mitochondrial protection	↓ Cyt c release, ↑ MMP stabilization	Nasir et al., 2021
Indirect antioxidant response	Upregulation of endogenous enzymes	Qiu et al., 2021

Anti-Inflammatory
Properties of Ellagic Acid

Chronic inflammation plays a central role in the progression of various liver diseases, including non-alcoholic steatohepatitis (NASH), alcoholic liver disease, and drug-induced hepatotoxicity. The inflammatory response is largely mediated by cytokine production, activation of transcription factors such as nuclear factor-kappa B (NF-κB), and the mitogen-activated protein kinase (MAPK) pathways, which collectively sustain hepatic injury, promote immune cell infiltration, and contribute to fibrosis. In this context, ellagic acid (EA), a naturally occurring polyphenolic compound, has garnered attention for its potent anti-inflammatory effects, which significantly contribute to its hepatoprotective potential. Through both direct inhibition of inflammatory mediators and modulation of intracellular signaling pathways, EA mitigates liver inflammation and helps preserve hepatic function (Qiu et al., 2021; Zhang et al., 2024). One of the principal anti-inflammatory actions of EA involves the suppression of pro-inflammatory cytokines. Cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β) are major contributors to hepatic inflammation, promoting hepatocyte necrosis and attracting inflammatory cells to liver tissues. EA has been shown to significantly downregulate the expression and serum levels of these cytokines in various rodent models of liver injury, including those induced by doxorubicin, carbon tetrachloride (CCl_4), and lipopolysaccharide (LPS) (Nasir et al., 2021; Derosa et al., 2020). This suppression of cytokine production is associated with reduced inflammatory cell infiltration and attenuation of liver tissue damage, underscoring EA's role in regulating the hepatic inflammatory microenvironment.

The NF-κB signaling pathway is a central regulator of the inflammatory cascade in liver disease. In its inactive form, NF-κB is sequestered in the cytoplasm by its inhibitor, IκB-α. Upon stimulation by inflammatory triggers, IκB-α is phosphorylated and degraded, allowing NF-κB to translocate to the nucleus, where it promotes the transcription of numerous genes involved in inflammation, apoptosis, and immune responses. EA has been demonstrated to interfere with this pathway at multiple levels. It blocks the phosphorylation and degradation of IκB-α, thereby preventing the nuclear translocation of the NF-κB p65 subunit. As a result, the transcription of NF-κB-dependent inflammatory genes is significantly reduced. Studies involving LPS or toxin-exposed hepatic tissues revealed that EA treatment leads to a marked inhibition of NF-κB activation, which correlates with reduced expression of pro-inflammatory mediators and a decrease in liver injury (Zhang et al., 2024; Qiu et al., 2021). In addition to inhibiting NF-κB, EA modulates the MAPK signaling pathway, another crucial pathway implicated in liver inflammation. The MAPK family includes extracellular signal-regulated kinases (ERK1/2), c-Jun N-terminal kinases (JNK), and p38 MAPKs, all of which are activated in response to oxidative stress and inflammatory stimuli. These kinases regulate gene expression, cytokine production, and cell survival mechanisms during inflammation. EA has been shown to suppress the phosphorylation of ERK1/2, JNK, and p38 MAPK in hepatotoxicity models, thereby inhibiting downstream signaling events that lead to the amplification of inflammatory responses (Calegari et al., 2018). By modulating these signaling cascades, EA effectively blunts immune cell activation and reduces the release of pro-inflammatory cytokines, contributing to an overall anti-inflammatory effect in hepatic tissue.

Another critical aspect of EA's anti-inflammatory mechanism involves the downregulation of inflammatory enzymes such as cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS). COX-2 is responsible for the synthesis of pro-inflammatory prostaglandins, while iNOS produces high levels of nitric oxide (NO), a reactive molecule that exacerbates oxidative and inflammatory damage. Overexpression of COX-2 and iNOS is commonly observed in inflamed liver tissues, where they contribute to cellular injury and fibrosis. EA treatment significantly reduces the expression of both COX-2 and iNOS, leading to decreased levels of prostaglandin E2 (PGE2) and nitric oxide. This enzymatic downregulation plays a key role in mitigating inflammation-induced hepatic damage

(Derosa et al., 2020). The anti-inflammatory effects of EA are further supported by histopathological evidence. Liver tissue sections from animals treated with EA consistently show marked improvements in structural integrity compared to untreated controls. Common histological findings include reduced leukocyte infiltration, diminished sinusoidal congestion, and preservation of normal hepatic architecture. These tissue-level observations corroborate biochemical and molecular findings, affirming that EA confers robust protection against inflammation-induced liver damage (Nasir et al., 2021; Calegari et al., 2018).

Table 8: Anti-Inflammatory Mechanisms of Ellagic Acid.

Mechanism	Effect	Reference
↓ TNF-α, IL-6, IL-1β	Suppression of cytokine production	Nasir et al., 2021
Inhibits NF-κB	Blocks IκB-α degradation and p65 nuclear translocation	Zhang et al., 2024
↓ COX-2 and iNOS	Reduces prostaglandin and nitric oxide generation	Derosa et al., 2020
↓ MAPK signaling (ERK, JNK, p38)	Inhibits inflammation-related kinase activity	Calegari et al., 2018
Histological improvement	Lower inflammatory cell infiltration in liver tissues	Qiu et al., 2021

In summary, ellagic acid exhibits comprehensive anti-inflammatory effects that significantly contribute to its hepatoprotective properties. It modulates pro-inflammatory cytokine production, inhibits key inflammatory signaling pathways such as NF-κB and MAPK, suppresses the expression of pro-inflammatory enzymes like COX-2 and iNOS, and preserves liver histology in experimental models of hepatic inflammation. These actions highlight EA's therapeutic potential in managing inflammation-driven liver disorders such as NASH, alcoholic liver disease, and drug-induced hepatotoxicity. As evidence from both in vivo and in vitro studies continues to accumulate, EA emerges as a promising natural compound for future development in the treatment of chronic liver inflammation.

Hepatoprotective Effects of Ellagic Acid: Evidence from Experimental Models

Liver diseases such as drug-induced liver injury (DILI), non-alcoholic steatohepatitis (NASH), alcoholic liver disease, and fibrosis are multifactorial conditions characterized by a convergence of oxidative stress, chronic inflammation, mitochondrial dysfunction, and hepatocellular apoptosis. These interconnected pathophysiological processes contribute to the progression of liver damage, culminating in fibrosis and hepatic failure if left unchecked. Given this complexity, therapeutic agents with multi-target capabilities are of significant interest. Ellagic acid (EA), a naturally occurring polyphenolic compound, has demonstrated a broad spectrum of pharmacological actions including antioxidant, anti-inflammatory, anti-apoptotic, and mitochondrial-stabilizing effects that collectively underpin its hepatoprotective potential (Nasir et al., 2021; Zhang et al., 2024). Evidence from animal models has provided robust support for the hepatoprotective activity of EA. In a well-established model of doxorubicin (DOX)-induced hepatotoxicity, EA significantly mitigated liver injury caused by this anthracycline chemotherapeutic agent. DOX is known to provoke oxidative liver damage through the excessive generation of reactive oxygen species (ROS), lipid peroxidation, inflammation, and mitochondrial dysfunction. EA administration in DOX-challenged rats resulted in a marked reduction in serum liver enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and bilirubin, which are indicators of hepatocellular leakage and damage. In parallel, hepatic malondialdehyde (MDA) levels a key marker of lipid peroxidation were significantly decreased, while levels of glutathione (GSH), superoxide dismutase (SOD), and catalase were restored, indicating a potent antioxidant response. Furthermore, EA effectively reduced pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), suggesting anti-inflammatory activity. Histological analysis of liver tissues demonstrated preservation of hepatic architecture, reduced necrosis, and diminished inflammatory infiltrates. Mechanistically, these protective effects were attributed to the activation of the Nrf2/HO-1 signalling pathway and the concurrent inhibition of NF-κB, highlighting EA's ability to modulate both oxidative stress and inflammation (Zhang et al., 2024).Similar hepatoprotective effects have been observed in models of liver injury induced by methotrexate (MTX) and carbon tetrachloride (CCl_4), both of which cause hepatocellular damage via oxidative and inflammatory mechanisms. In these models, EA administration led to reduced hepatocyte necrosis and apoptosis, attenuation of oxidative stress, and significant histopathological improvements. Liver sections from EA-treated animals showed preserved architecture, minimal ballooning of hepatocytes, and reduced leukocyte infiltration, further confirming the compound's anti-inflammatory and anti-apoptotic actions (Nasir et al., 2021; Calegari et al., 2018). The hepatoprotective efficacy of EA is further supported by consistent modulation of key biochemical parameters in various experimental settings. A summary of these changes across multiple hepatotoxicity models illustrates the compound's multifaceted mechanisms.

Table 9: Biochemical and Inflammatory Parameters Modulated by Ellagic Acid (EA).

Parameter	Effect of EA	Significance
ALT, AST, ALP	↓ Levels	Reduced hepatocellular leakage
MDA	↓ Lipid peroxidation marker	Antioxidant effect
GSH, SOD, Catalase	↑ Levels	Enhances antioxidant defense
TNF-α, IL-6, IL-1β	↓ Cytokine expression	Anti-inflammatory action

(References: Nasir et al., 2021; Qiu et al., 2021)

In addition to its effects on oxidative stress and inflammation, EA plays a critical role in protecting against mitochondrial dysfunction and apoptosis, particularly in models of drug-induced hepatotoxicity. Mitochondria are not only major sites of ROS production but also central regulators of apoptosis. Damage to mitochondrial membranes results in the dissipation of mitochondrial membrane potential (MMP), the release of cytochrome c into the cytosol, and the activation of caspases, particularly caspase-3, which executes the apoptotic program. EA has been shown to stabilize MMP, thereby preventing mitochondrial swelling and cytochrome c release. It also suppresses caspase-3 activation, effectively blocking the downstream apoptotic cascade. These protective actions are vital in maintaining hepatocyte viability and preventing liver function deterioration in response to toxic insults (Qiu et al., 2021).

Table 10: Mechanistic Insights into the Hepatoprotective Effects of Ellagic Acid (EA).

Mechanism	Effect	Reference
↓ Oxidative stress	↓ MDA, ↑ SOD, GSH, CAT	Nasir et al., 2021
↓ Inflammation	↓ TNF-α, IL-6, IL-1β; Inhibition of NF-κB	Qiu et al., 2021
↑ Antioxidant pathways	Nrf2/HO-1 pathway activation	Zhang et al., 2024
↓ Apoptosis	↓ Caspase-3, preserved mitochondrial potential	Calegari et al., 2018
Histopathological protection	Reduced necrosis, preserved hepatocyte integrity	Nasir et al., 2021

Collectively, these findings from diverse animal models underscore the robust hepatoprotective capacity of ellagic acid. Its ability to restore antioxidant defences, reduce inflammation, preserve mitochondrial integrity, and inhibit apoptosis provides a strong rationale for its further exploration as a therapeutic candidate for liver diseases. The consistency of EA's protective effects across different models of liver injury reinforces its translational potential. Future studies should explore its pharmacokinetics, bioavailability, and efficacy in clinical settings to fully harness its benefits in managing hepatic disorders.

Anticancer Potential of Ellagic Acid: Cytotoxic, Molecular, and Synergistic Mechanisms

Ellagic acid (EA), a naturally occurring polyphenol, has demonstrated remarkable anticancer properties in various preclinical models. Both in vitro and in vivo studies have confirmed its potent cytotoxic and antiproliferative effects across a wide spectrum of cancer types. Unlike many traditional chemotherapeutic agents that non-selectively target both healthy and malignant cells, EA shows preferential toxicity toward cancer cells while sparing normal tissues, highlighting its therapeutic promise with potentially lower side effect profiles (Umesalma et al., 2020; Larrosa et al., 2006). This selective action is thought to be mediated by EA's unique polyphenolic structure, which enables it to modulate key cellular pathways implicated in tumor development and progression, including those governing proliferation, apoptosis, angiogenesis, and metastasis. In vitro investigations have consistently demonstrated EA's ability to exert dose-dependent cytotoxicity across multiple human cancer cell lines. These include HepG2 (liver), MCF-7 (breast), PC-3 (prostate), HT-29 (colon), and A549 (lung) cells. The mechanisms underlying its cytotoxicity involve several hallmark anticancer activities: arrest of cell cycle progression particularly at G1 or G2/M checkpoints induction of DNA fragmentation, depolarization of the mitochondrial membrane, and activation of caspase-dependent apoptosis. In HepG2 liver cancer cells specifically, EA has been shown to significantly decrease cell viability while promoting apoptosis through downregulation of anti-apoptotic proteins such as Bcl-2 and survivin, and upregulation of pro-apoptotic mediators like Bax and caspase-9. These findings indicate that EA primarily engages the intrinsic (mitochondrial) apoptotic pathway, leading to PARP cleavage and irreversible cellular damage (Huang et al., 2015; Lee-Chang et al., 2011).

Beyond cell culture models, EA's anticancer efficacy has been corroborated in various animal studies. In N-nitrosodiethylamine (NDEA)-induced hepatocellular carcinoma (HCC) models in rats, EA administration resulted in a significant reduction in tumour incidence and multiplicity. Levels of alpha-fetoprotein (AFP), a clinical biomarker for HCC, were markedly decreased, indicating reduced tumour activity. Histopathological evaluations further revealed preservation of normal liver architecture and decreased nodular transformation, suggesting robust antitumor activity (Umesalma et al., 2020). Moreover, EA has demonstrated antiangiogenic properties by suppressing vascular endothelial growth factor (VEGF) expression. This leads to reduced neovascularization, which is critical for tumour growth and metastasis. Concurrently, EA inhibits matrix metalloproteinases MMP-2 and MMP-9, enzymes

involved in extracellular matrix degradation and tumor cell invasion, underscoring its potential to impede metastatic spread (Larrosa et al., 2006). At the molecular level, EA's antitumor effects are attributed to its ability to modulate several oncogenic signaling pathways. One prominent mechanism involves inhibition of nuclear factor-kappa B (NF-κB), a transcription factor that promotes cancer progression through the regulation of genes involved in inflammation, proliferation, and resistance to apoptosis. EA has been found to block NF-κB activation, thereby suppressing inflammatory signaling cascades that contribute to tumor survival and aggressiveness. Additionally, EA interferes with the phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway, a crucial axis in cellular survival and metabolism, which is often upregulated in various cancers. By downregulating this pathway, EA limits tumour cell proliferation and enhances susceptibility to apoptosis. Furthermore, EA inhibits the Wnt/β-catenin signaling pathway, which plays a pivotal role in cellular differentiation, growth, and metastasis. Finally, EA has been shown to activate the tumour suppressor protein p53, which is essential for DNA repair, cell cycle regulation, and programmed cell death. The multi-targeted action of EA across these signalling axes supports its broad-spectrum anticancer activity (Lei et al., 2021). In addition to its direct antitumor effects, EA has demonstrated synergistic activity when combined with conventional chemotherapeutic agents. Studies have shown that EA enhances the cytotoxic effects of doxorubicin in both liver and breast cancer models, as well as potentiates the action of cisplatin in ovarian and colon cancers. It also improves the efficacy of 5-fluorouracil in colorectal cancer therapy. This synergy not only increases tumour cell kill rates but also allows for reduced dosages of chemotherapeutic drugs, thereby minimizing adverse side effects. Moreover, EA's intrinsic antioxidant and anti-inflammatory properties provide added protection to non-cancerous tissues, reducing off-target toxicity and improving overall treatment outcomes (Umesalma et al., 2020; Lei et al., 2021).

Table 11: Anticancer Mechanisms of Ellagic Acid (EA) and Their Cellular Outcomes.

Mechanism	Outcome	Reference
Mitochondrial apoptosis	↑ Caspase-3, ↓ Bcl-2, ↑ Bax	Huang et al., 2015
Cell cycle arrest	G1/G2 phase arrest, ↓ Cyclin D1	Lee-Chang et al., 2011
Antiangiogenic activity	↓ VEGF, ↓ CD31, ↓ MMP-2/9	Larrosa et al., 2006
Inhibition of PI3K/Akt/mTOR	↓ Tumor growth and proliferation	Lei et al., 2021
Enhancement of chemotherapy	↑ Efficacy of doxorubicin and 5-FU	Umesalma et al., 2020

In summary, ellagic acid emerges as a compelling candidate in cancer therapy due to its multifaceted mechanisms of action, encompassing antiproliferative, pro-apoptotic, antiangiogenic, antimetastatic, and chemosensitizing effects. Its ability to modulate key molecular pathways relevant to cancer biology further reinforces its potential as a standalone agent or an adjuvant to existing chemotherapies. Further clinical studies are warranted to validate its efficacy and safety in human populations and to explore optimal delivery methods for improved bioavailability and therapeutic impact.

Dermatoprotective Properties of Ellagic Acid

The skin, serving as the body's primary barrier against environmental insults, is consistently exposed to factors such as ultraviolet (UV) radiation, oxidative stress, microbial agents, and pollutants. These aggressors contribute to a range of dermatological conditions, including premature aging, hyperpigmentation, inflammation, collagen degradation, and skin cancers. Natural antioxidants have garnered significant attention in skin therapeutics, and ellagic acid (EA) a polyphenolic compound abundantly found in fruits like pomegranates, strawberries, and various nuts, has emerged as a promising agent with extensive dermato-protective properties. EA's protective role in skin health can be attributed to its antioxidant, anti-inflammatory, photo protective, anti-tyrosinase, and wound-healing activities (Lim et al., 2019; Kim et al., 2010). One of the most compelling aspects of EA in dermatology is its photo protective capability against UVB radiation, which is known to induce DNA damage, promote reactive oxygen species (ROS) formation, and accelerate photo aging. Studies have shown that EA significantly reduces UVB-induced oxidative stress in dermal fibroblasts by attenuating ROS production. Furthermore, EA inhibits the expression of matrix metalloproteinase-1 (MMP-1), an enzyme that degrades type I collagen, thereby preventing structural damage to the dermal extracellular matrix. In a human skin equivalent model, EA application led to reduced wrinkle formation, lipid peroxidation, and inflammatory cytokine levels such as IL-6 and TNF-α after UV exposure, indicating that it preserves skin elasticity and integrity under phototoxic stress (Lim et al., 2019). This photoprotective function highlights EA's potential in cosmetic formulations aimed at preventing UV-induced skin damage.

In addition to its role in photo aging, EA has shown significant promise in the treatment of pigmentary disorders. The compound exhibits strong anti-tyrosinase activity, which is critical in the regulation of melanin biosynthesis. In melanocyte cultures, EA effectively inhibited tyrosinase activity and suppressed the expression of microphthalmia-associated transcription factor (MITF), a transcriptional regulator of melanogenic enzymes. This dual inhibition leads to a substantial reduction in melanin content. Moreover, in vivo studies on UV-irradiated guinea pig models have demonstrated

that topical application of EA markedly reduces skin pigmentation, thereby suggesting its therapeutic utility in hyperpigmentation disorders such as melasma and age spots (Kim et al., 2010). Given its natural origin and efficacy, EA presents an attractive alternative to synthetic depigmenting agents, many of which pose safety concerns. Another critical aspect of EA's dermatological benefit lies in its anti-aging effects. Aging skin is characterized by reduced collagen content and increased activity of collagen-degrading enzymes such as MMP-1 and MMP-9. EA has been found to inhibit both these enzymes, while concurrently upregulating type I procollagen expression. These actions serve to maintain dermal collagen levels, improve skin texture, and delay the visible signs of aging, especially in individuals with chronic UV exposure (Lim et al., 2019; Park et al., 2011). The ability of EA to preserve the extracellular matrix enhances its value as an anti-aging compound in skincare. Beyond its photoprotective and anti-aging functions, EA also exhibits notable antimicrobial and wound healing properties. It promotes keratinocyte migration, a key step in re-epithelialization during wound repair. Additionally, EA enhances angiogenesis and accelerates wound contraction, thereby shortening the overall healing time. These effects are particularly valuable in managing chronic wounds and ulcers. Furthermore, EA's antimicrobial activity has been reported against common skin pathogens such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*, making it useful in preventing secondary infections during wound healing (Marquez-Curtis et al., 2019). These combined effects position EA as a potent agent in topical formulations for both therapeutic and preventive skincare.

Table 12: Dermatological Benefits of Ellagic Acid.

Skin Effect	Mechanism/Outcome	Reference
Photoprotection	↓ UVB-induced ROS, MMP-1, inflammation	Lim et al., 2019
Skin lightening	↓ Tyrosinase, ↓ MITF, ↓ Melanin synthesis	Kim et al., 2010
Anti-aging	↑ Collagen I, ↓ MMP-1 and MMP-9	Park et al., 2011
Wound healing	↑ Cell migration, angiogenesis	Marquez-Curtis et al., 2019
Antibacterial	Inhibits skin pathogens	Marquez-Curtis et al., 2019

In summary, ellagic acid provides comprehensive dermato-protection through multiple biological mechanisms. It safeguards skin from photodamage, inhibits melanin production, slows collagen degradation, and promotes wound healing. These effects are mediated via modulation of oxidative stress, inflammatory cytokines, proteolytic enzymes, and melanogenic pathways. Given its efficacy and safety profile, EA represents a valuable component in the development of cosmeceuticals and dermatological therapeutics targeting a range of skin conditions from aging and hyperpigmentation to microbial infections. Continued research, particularly clinical trials in human subjects, is essential to fully elucidate its potential and optimize its application in skincare regimens.

Pharmacokinetic Challenges and Enhancement Strategies of Ellagic Acid

Despite ellagic acid's (EA) broad pharmacological potential including antioxidant, anti-inflammatory, anticancer, and hepatoprotective properties its clinical application is significantly hindered by poor pharmacokinetics. EA is a polyphenolic compound known for its low water solubility, minimal gastrointestinal permeability, rapid metabolism, and extensive excretion. These characteristics result in low systemic bioavailability, posing a major obstacle to its therapeutic translation (González-Sarrías et al., 2015; Seeram et al., 2004). As a result, even when administered in high oral doses, EA achieves minimal plasma concentrations, limiting its effectiveness in vivo. According to the Biopharmaceutics Classification System (BCS), EA falls under Class IV, which includes compounds with both low aqueous solubility and poor intestinal permeability. Following oral administration, only a small fraction of free EA is absorbed in the gastrointestinal tract. Human studies evaluating EA absorption from natural sources such as pomegranate juice report peak plasma concentrations below 100 ng/mL, with a rapid time to peak concentration (Tmax) of approximately one hour and a relatively short elimination half-life of under two hours (Hsu et al., 2007; Seeram et al., 2004). These pharmacokinetic traits limit the time and concentration window during which EA can exert its biological effects.

Interestingly, a substantial portion of EA's systemic activity is not directly attributable to the parent compound but instead to its metabolites, particularly urolithins. Once EA reaches the colon, gut microbiota converts it into a family of more bioavailable derivatives, including urolithins A, B, C, and D. These metabolites are more lipophilic, readily absorbed into systemic circulation, and exhibit improved stability and tissue distribution. Among them, urolithin A has demonstrated the most potent biological activity, and its presence in plasma and tissues suggests a key role in mediating EA's therapeutic outcomes (Tomas-Barberán et al., 2017). The conversion to urolithins extends EA's pharmacological window and offers a mechanistic explanation for its systemic effects despite poor absorption of the native compound. The distribution of EA itself is limited due to its low solubility and membrane permeability. However, its microbial metabolites, especially urolithins, have been detected in various organs, including the liver, kidneys, colon, and even the brain. These compounds exhibit a higher affinity for plasma proteins, enabling more extended circulation times and potentially contributing to

their therapeutic effects (González-Sarrías et al., 2015). This improved distribution pattern supports the view that EA's metabolites, rather than the parent compound, serve as the primary bioactive agents in vivo. In terms of excretion, EA is rapidly eliminated from the body. Studies in rodents indicate that over 90% of orally administered EA is excreted within 48 hours, mainly through feces. In humans, urolithin conjugates particularly glucuronides and sulfates are predominantly found in urine, reflecting the involvement of hepatic and renal clearance mechanisms (Selma et al., 2014). This rapid clearance further reduces the therapeutic window of native EA, highlighting the importance of strategies that either prolong retention or enhance its absorption. A notable challenge in EA pharmacokinetics is the substantial interindividual variability caused by differences in gut microbiota composition. Individuals can be categorized into distinct metabotypes based on their capacity to produce urolithins. Metabotype A individuals produce urolithin A, Metabotype B produce both urolithins A and B, while Metabotype 0 individuals do not generate urolithins at all. This variation significantly influences EA's systemic effects and underscores the need for personalized approaches in EA-based therapy (Selma et al., 2014). Such variability not only affects therapeutic outcomes but also complicates clinical study designs and dosage standardization. To overcome these pharmacokinetic limitations, several formulation strategies have been investigated. Cyclodextrin inclusion complexes are used to enhance EA's aqueous solubility by forming hydrophilic outer shells around the lipophilic core of the molecule. Liposomal and solid lipid nanoparticle (SLN) formulations aim to improve intestinal permeability and protect EA from early degradation. Phytosomes, composed of phospholipid complexes, have shown promise in enhancing membrane permeability and facilitating efficient intestinal absorption. Additionally, nanoemulsions have been developed to improve systemic circulation time and reduce rapid excretion. These advanced delivery systems have demonstrated significant improvements in EA bioavailability and tissue distribution in both preclinical and early-phase clinical studies (Ciesielski et al., 2022).

Table 13: Pharmacokinetic Properties of Ellagic Acid (EA).

Pharmacokinetic Parameter	Details	Reference
Solubility	~9.7 µg/mL in water	Hsu et al., 2007
Tmax (human plasma)	~1 hour post-oral administration	Seeram et al., 2004
Bioavailability	Very low (<1%); higher for urolithins	González-Sarrías et al., 2015
Half-life	<2 hours for EA; longer for urolithins	Seeram et al., 2004
Major metabolic route	Microbial biotransformation to urolithins	Tomas-Barberán et al., 2017
Excretion	Mainly fecal and urinary (as urolithin conjugates)	Selma et al., 2014

In conclusion, while ellagic acid holds considerable promise as a therapeutic agent across multiple disease states, its unfavourable pharmacokinetic profile represents a significant barrier to its clinical development. The limited absorption, rapid clearance, and interindividual variability in metabolism necessitate innovative delivery approaches and possibly the use of bioactive metabolites like urolithin A as surrogate therapeutic agents. Future research should continue to optimize nanoformulations and explore the pharmacodynamics of urolithins to fully harness EA's therapeutic potential.

Future Perspectives

To translate EA from bench to bedside, several critical challenges must be addressed through a combination of technological innovation, personalized medicine, and translational research.

- **Development of Advanced Drug Delivery Systems**: Modern pharmaceutical technologies such as solid lipid nanoparticles (SLNs), liposomes, Nano emulsions, and phytosomes are essential to improve EA's pharmacokinetic profile. These systems enhance solubility, protect against premature metabolism, and promote targeted delivery, thereby improving therapeutic outcomes in liver disease, cancer, and dermatological conditions.
- **Conducting Well-Powered Clinical Trials**: Rigorous, randomized, placebo-controlled human studies are needed to validate the preclinical efficacy of EA. These trials should assess both EA and its urolithin metabolites in a variety of conditions, including non-alcoholic steatohepatitis (NASH), drug-induced liver injury (DILI), hepatocellular carcinoma (HCC), and photoaging-related skin disorders. Standardized dosing regimens, pharmacokinetic profiling, and safety evaluations should be incorporated into clinical trial designs.
- **Microbiome-Guided Personalization**: Given the variability in gut microbiota-mediated urolithin production, future strategies should include metabotype profiling to stratify patients based on their ability to metabolize EA. Personalized dosing or prebiotic/probiotic co-administration may be used to enhance urolithin production in low-producing individuals, increasing the clinical effectiveness of EA supplementation.
- **Combination Therapy Strategies**: Exploring the synergistic potential of EA with established chemotherapeutics, hepatoprotective agents, or cosmeceuticals can lead to more effective and less toxic therapeutic regimens. For instance, combining EA with doxorubicin may enhance anticancer efficacy while protecting against cardiotoxicity and hepatotoxicity.

- **Long-Term Safety and Toxicology Studies**: Although EA is generally regarded as safe, its chronic use in therapeutic doses requires thorough evaluation. Toxicokinetic and toxicodynamic studies in animal models and humans are necessary to rule out organ-specific toxicities, drug interactions, or cumulative adverse effects with prolonged administration.
- **Regulatory and Commercialization Efforts**: Regulatory approval processes for EA-based formulations must be streamlined through collaboration between academia, industry, and regulatory bodies. Additionally, efforts should be made to develop standardized extracts and validated biomarkers for monitoring therapeutic response.

CONCLUSION

Ellagic acid stands out as a promising natural compound with a strong foundation of preclinical evidence supporting its therapeutic potential across multiple domains, including hepatology, oncology, and dermatology. Its multi-targeted mechanisms of action such as scavenging reactive oxygen species (ROS), inhibiting inflammatory mediators, preserving mitochondrial function, modulating apoptosis, and regulating oncogenic signaling pathways highlight its value as a versatile pharmacological agent. Nonetheless, the successful clinical application of EA is contingent upon overcoming significant pharmacokinetic and translational hurdles. The emergence of gut microbial metabolites like urolithin A as potent bioactives redefines the therapeutic landscape of EA, emphasizing the need for personalized and microbiome-aware treatment strategies. Looking ahead, a multidisciplinary approach integrating pharmaceutical sciences, microbiome research, systems biology, and clinical pharmacology is essential to unlock the full therapeutic potential of ellagic acid. If these challenges are addressed, EA could evolve from a dietary polyphenol to a clinically effective agent with applications spanning chronic liver disease, cancer, skin disorders, and beyond. In conclusion, ellagic acid represents a compelling example of how natural compounds, when supported by modern science and innovative delivery systems, can offer valuable solutions to some of today's most pressing medical challenges.

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