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Ellagic Acid from Medicinal Plants: A Review on Its Antioxidant and Anticancer Potential

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ABSTRACT
Ellagic acid (EA) is a naturally occurring polyphenolic dilactone produced by hydrolysis of ellagitannins and is abundant in pomegranate, berries, walnuts and several medicinal plants. Preclinical research over the last two decades has demonstrated EA's strong antioxidant activity and multimodal anticancer effects—inducing cell-cycle arrest and apoptosis, modulating key signaling pathways (NF-κB, PI3K/Akt, p53, TGF-β/Smad), inhibiting metastasis and angiogenesis, and synergizing with chemotherapeutics in some models. Clinical data remain limited and are complicated by EA's low oral bioavailability and extensive gut-microbial metabolism to urolithins, which themselves may mediate many systemic effects. This review summarizes current knowledge on EA's sources, chemistry, antioxidant actions, anticancer mechanisms, formulation strategies to improve bioavailability, preclinical and clinical evidence, safety, and future research directions.

I. INTRODUCTION

Polyphenols from medicinal plants are intensively investigated for cancer prevention and adjuvant therapy. Among them, ellagic acid (EA) has attracted sustained interest because it arises from widely consumed foods (pomegranate, raspberries, strawberries, walnuts) and from medicinal-plant ellagitannins, and because of a growing preclinical literature reporting antioxidant, anti-inflammatory, and antineoplastic effects. This review integrates chemical, mechanistic, pharmacokinetic, formulation, and translational data to provide an up-to-date perspective.

1. Chemistry, natural sources and extraction

EA is the dilactone of hexahydroxydiphenic acid and is generated by hydrolysis of ellagitannins in plant tissues. Major dietary and medicinal sources include Punicagranatum (pomegranate), various raspberries and blackberries, strawberries, walnuts, certain oak woods and tree barks, and several traditional medicinal herbs. Extraction methods vary (aqueous/organic solvents, hydrothermal processes); analytical quantification typically uses HPLC-MS. Plant matrix and processing (juice, peel, seed) dramatically influence EA yields.

2. Antioxidant properties and biochemical activities

EA's chemical structure (multiple phenolic hydroxyls and lactone rings) enables radical scavenging and metal-chelating actions, and it can upregulate endogenous antioxidant enzymes (SOD, catalase, glutathione peroxidase) while lowering markers of oxidative damage in multiple in vitro and in vivo models. These antioxidant actions are central to its cytoprotective and chemopreventive effects, but under some experimental conditions EA or its metabolites may also act as a pro-oxidant to trigger cancer cell death.

3. Anticancer mechanisms — overview

Preclinical studies indicate that EA exerts antitumor activity through several complementary mechanisms:

- **Cell cycle arrest and apoptosis:** EA has been reported to induce G0/G1 or G2/M arrest and to activate intrinsic (mitochondrial) and extrinsic apoptotic pathways in breast, colon, prostate, liver, gastric and pancreatic cancer cell lines.
- **Modulation of signaling pathways:** EA inhibits pro-survival and inflammatory pathways including NF-κB and PI3K/Akt, while promoting tumor suppressor pathways such as p53. In colorectal and gastric cell models EA also modulates TGF-β/Smadsignaling.
- **Anti-metastatic and anti-angiogenic effects:** EA reduces migration, invasion, matrix

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metalloproteinase expression and angiogenic factors in multiple models, suggesting it can limit metastatic potential.

- **Oxidative stress modulation and DNA damage:** EA both reduces oxidative DNA damage in healthy cells and, in cancer cells, can increase ROS and DNA damage leading to apoptosis—context and dose matter.

These multimodal effects support EA's potential both as a chemopreventive agent and as an adjuvant to standard chemotherapy in preclinical studies.

4. Pharmacokinetics, metabolism and bioavailability

EA shows poor aqueous solubility and limited oral bioavailability. After ingestion of ellagitannin-rich foods, the gut microbiota hydrolyzeellagitannins to EA and subsequently transform EA into gut-derived metabolites called **urolithins** (notably urolithin A), which are better absorbed and likely act as major systemic effectors attributed to dietary EA. Interindividual differences in microbiota ("urolithinmetabotypes") lead to variable systemic exposure to urolithins, complicating translation from cell models to humans. Strategies to overcome low bioavailability include prodrugs, nanocarriers, and complexation with cyclodextrins or TPGS micelles.

5. Delivery systems and formulation strategies

To address solubility and delivery challenges, researchers have tested EA-loaded nanoparticles, liposomes, polymeric micelles (e.g., TPGS micelles), and gold nanoparticle conjugates. These approaches often improve cellular uptake, prolong circulation, enhance tumor accumulation, and boost anticancer potency in animal models. Such formulation work also aims to deliver EA in combination with chemotherapeutic agents for synergistic effects (e.g., with sorafenib in HCC models).

6. Preclinical evidence by cancer type

- **Breast cancer:** In vitro and animal studies show reduced proliferation, induction of apoptosis, and suppression of metastatic phenotypes.
- **Colorectal cancer:** EA and urolithins inhibit proliferation and migration; modulation of Wnt/β-catenin and TGF-β pathways reported.
- **Hepatocellular carcinoma:** EA reduces tumor growth and can enhance effects of sorafenib in murine models.
- **Gastric and pancreatic cancer:** EA induces apoptosis and suppresses NF-κBsignaling in several studies.

While in vitro and in vivo animal models are abundant and largely consistent on EA's antitumor potential, species differences and pharmacokinetic issues must be recognized when extrapolating to humans.

7. Clinical evidence and human studies

Human clinical data specifically isolating EA's effects are limited. Most human research evaluates pomegranate extracts or ellagitannin-rich foods rather than purified EA, making it difficult to attribute benefits solely to EA. A small number of randomized trials and pilot studies have investigated pomegranate products or EA supplements for prostate, colorectal, and metabolic conditions, with mixed but sometimes promising outcomes; however, high-quality, large-scale oncology trials of purified EA are lacking. Recent clinical trials are expanding to metabolic and liver-disease endpoints but oncology remains largely preclinical.

8. Safety and toxicity

Preclinical toxicology studies indicate a relatively favorable safety profile at doses effective in animal models; however, very high doses may cause gastrointestinal or hepatic effects in some systems. Because EA is a component of foods traditionally consumed by humans, its acute toxicity is low, but formal chronic safety data for pharmacologic doses are relatively sparse. Interactions with chemotherapeutic agents—both beneficial and adverse—need careful assessment in controlled clinical studies.

9. Challenges and knowledge gaps

- **Bioavailability and microbiome dependency:** EA's conversion to urolithins by gut microbiota is central to systemic activity; variability in microbiota causes interindividual differences in response.
- **Attribution in complex extracts:** Studies using whole fruit/juice/extracts confound EA-specific effects with other polyphenols (punicalagins, anthocyanins).
- **Limited clinical oncology trials:** Despite robust preclinical literature, clinical oncology evidence for purified EA is scarce.

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- **Dose optimization and safety for long-term use:** Pharmacologic dosing regimens and long-term safety remain to be defined.

10. Future directions and recommendations

1. **Standardized formulations**: Develop and test standardized, well-characterized EA or urolithin formulations with improved pharmacokinetics (nanocarriers, prodrugs).
2. **Microbiome-stratified trials:** Include microbiome profiling and urolithinmetabotyping in human studies to identify responders and tailor interventions.
3. **Mechanistic clinical studies:** Small, mechanism-focused human trials (pharmacokinetics, biomarker modulation, target engagement) should precede large efficacy trials.
4. **Combination therapy evaluation:** Preclinical synergy with chemotherapeutics (e.g., sorafenib) merits controlled clinical assessment to determine safety and efficacy in combination regimens.

II. CONCLUSION

Ellagic acid is a bioactive plant-derived polyphenol with well-documented antioxidant and pleiotropic anticancer activities in vitro and in animal models. Its translation into clinical oncology is constrained by low bioavailability, dependence on gut microbial metabolism to active urolithins, and a paucity of high-quality human trials using purified EA. Advances in delivery systems, microbiome-informed clinical designs, and rigorous mechanism-centric human studies are required to determine whether EA or its metabolites can become useful chemopreventive agents or adjuvants in cancer therapy.

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