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Review Article

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

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ABSTRACT

Cancer and oxidative stress are closely linked disease processes that greatly affect morbidity and death worldwide. When there is too much Reactive Oxygen Species (ROS) and not enough natural antioxidant defences, lipids, proteins, and nucleic acids become damaged by oxidative stress. This makes cancer grow and spread. Plant-based polyphenols have garnered significant attention as natural regulators of oxidative stress and cancer-related pathways. Ellagic acid, a polyphenolic dilactone originating from ellagitannins, has been recognized as a bioactive molecule with significant therapeutic potential. This study looks at ellagic acid from medicinal plants in great detail, focusing on its antioxidant and anticancer properties. A critical analysis of its chemical composition, biosynthetic origin, modes of action, therapeutic significance, and constraints concerning bioavailability and clinical applicability is provided. A thorough evaluation of published experimental and preclinical investigations was performed to evaluate the chemical, physicochemical, biosynthetic, and biological characteristics of ellagic acid. A thorough literature search was carried out to find pertinent peer-reviewed publications published upto 2025 utilizing electronic databases such as PubMed, Scopus, and Web of Science. Ellagic acid is found in many fruits and medicinal plants, such as berries, pomegranates, almonds, and woody tissues. It can be found in free form or by ellagitannin hydrolysis. It has high antioxidant properties because it can pick up free radicals, bind to metal ions, stop lipid peroxidation, and boost the activity of antioxidant enzymes that are already in the body. It also has broad-spectrum anticancer effects by stopping angiogenesis, stopping inflammatory signalling, causing cell cycle arrest and death, and stopping tumours from spreading and invading other tissues. However, its therapeutic usefulness is restricted by its low solubility in water, low oral bioavailability, and fast metabolism. Ellagic acid is a potential natural antioxidant and chemopreventive agent. It has a lot of promise for future cancer therapy development since it changes oxidative stress and a number of cancer-related signalling pathways.

Keywords: Anticancer activity, Antioxidant activity, Bioavailability, Chemoprevention, Ellagic acid, Ellagitannins, Medicinal plants, Natural products, Oxidative stress, Polyphenols.

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INTRODUCTION

Two of the most important and interrelated global health issues of the twenty-first century are oxidative stress and cancer. An imbalance between the generation of Reactive Oxygen Species (ROS) and biological systems' ability to neutralise these reactive intermediates through antioxidant defences is the cause of oxidative stress. Overproduction of ROS can harm vital biomolecules including proteins, lipids, and nucleic acids, which can eventually result in cellular malfunction and the advancement of illness. An increasing amount of data links oxidative stress to the aetiology of many chronic illnesses, such as diabetes, inflammatory diseases, cancer, cardiovascular diseases, and neurological problems. Global health data show that cancer is still one of the top causes of morbidity and death globally, and that its prevalence is expected to increase dramatically as a result of variables related to lifestyle, environmental exposure, ageing, and population expansion. Because cancer is complex and involves oxidative damage, chronic inflammation, epigenetic changes, and genetic abnormalities, there is an urgent need for safe, efficient

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prevention and treatment approaches (Zhang *et al.*, 2023; Zhu *et al.*, 2022; Shakeri *et al.*, 2018; Aishwarya *et al.*, 2021).

Although there is no denying that traditional cancer treatment methods like surgery, radiation, and chemotherapy have increased patient survival rates, they are frequently linked to drawbacks such poor selectivity, systemic toxicity, drug resistance, and unfavourable side effects. These disadvantages have sparked a lot of interest in alternative and complementary methods, especially those that use natural ingredients. In this regard, chemicals produced from medicinal and nutritional plants have drawn a lot of interest due to their possible use as an adjuvant cancer treatment and in preventing illness. Due in great part to their redox-modulating and antioxidant qualities, polyphenols are a varied family of secondary plant metabolites that display a broad variety of biological activities (Alfei *et al.*, 2019; Lu *et al.*, 2023; Mohammadinejad *et al.*, 2022; Zeb *et al.*, 2018).

Fruits, vegetables, herbs, spices, and medicinal plants that have long been utilised in a variety of medical systems are rich sources of plant-derived polyphenols. These substances have been shown to alter enzyme activity, scavenge free radicals, chelate metal ions, and control intracellular signalling pathways that are essential for cell survival, proliferation, and death. Diets high in plant foods high in polyphenols are consistently linked to a lower risk of chronic illnesses, including several forms of cancer, according to epidemiological research. Plant polyphenols are particularly appealing as chemopreventive and therapeutic agents because, in contrast to manufactured antioxidants, they frequently have pleiotropic actions, affecting several biological targets at once (Maleki *et al.*, 2023; Yoganathan *et al.*, 2021; García-Niño *et al.*, 2022; Jaman and Sayeed, 2018).

One such naturally occurring polyphenolic substance that has gained a lot of pharmacological attention is ellagic acid. Ellagitannins, a family of hydrolysable tannins that are extensively found in the plant world, are frequently hydrolysed to produce ellagic acid, a dilactone that is chemically generated from hexahydroxydiphenic acid. Since its discovery in the nineteenth century as a component of gall nuts and oak bark, ellagic acid has been found in a wide range of nutritional sources and medicinal plants, such as nuts, pomegranates, berries, and several medicinal herbs. Strong antioxidant activity and the capacity to interact with a variety of biological targets are conferred by its stiff polyphenolic structure, which is typified by many hydroxyl groups and aromatic rings (Kharat *et al.*, 2020; Kaczmarek-Szczepańska *et al.*, 2024).

Beyond its antioxidant properties, ellagic acid has many other biological uses. The anti-inflammatory, antibacterial, hepatoprotective, cardioprotective, and neuroprotective properties of ellagic acid have been shown in preclinical research. Its increasing recognised as a powerful anticancer drug is especially significant. According to experimental data, ellagic acid can stop the cell cycle, cause programmed cell death, prevent tumour invasion and metastasis, and decrease the growth of cancer cells. Modification of important molecular pathways implicated in carcinogenesis, such as inflammatory mediators, carcinogenic signalling cascades, oxidative stress response pathways, and proteins linked to apoptosis, mediates these effects. Furthermore, ellagic acid has demonstrated the capacity to specifically target cancer cells while preserving healthy cells, which is a very desirable characteristic in the creation of anticancer drugs (Yang *et al.*, 2023; Ahlawat *et al.*, 2020; Bai *et al.*, 2022; Javaid *et al.*, 2021; Adedara *et al.*, 2023).

The fact that ellagic acid comes from medicinal plants that have been utilised for ages is another significant feature. Thus, ellagic acid's medicinal value crosses the gap between conventional wisdom and contemporary scientific verification. However, there is still no therapeutic use for ellagic acid, even though a great deal of *in vitro* and *in vivo* research has shown its pharmacological potential. Its development as a therapeutic drug has been limited by issues such quick metabolism, low oral bioavailability, poor water solubility, and heterogeneity in biological response. To get over these restrictions and improve its clinical usefulness, formulation science advancements including nano-delivery technologies and structural alteration are being intensively investigated (Al-Shar'I *et al.*, 2021; Diao *et al.*, 2022).

The objective of the review is to provide a contemporary and systematic overview of ellagic acid sourced from medicinal plants, highlighting its anti-cancer and antioxidant characteristics. The specific goals of this review are to: (i) talk about oxidative stress and cancer in relation to global health; (ii) stress the importance of plant-derived polyphenols in preventing disease; (iii) explain the chemical makeup and biological importance of ellagic acid; and (iv) critically evaluate the experimental data that currently supports its anticancer and antioxidant properties. The goal of this study is to help the growing interest in ellagic acid as a potential natural chemical for preventing and treating cancer by filling in the gaps in what is already known and confirming what is already known. It also intends to get more people to do research on how to use ellagic acid in medicine.

Physicochemical Properties and Chemical Nature of Ellagic Acid

Ellagic acid is a polyphenolic dilactone that occurs naturally and is a kind of hydrolysable tannin. It is the dilactone form of hexahydroxydiphenic acid, with a molecular weight of 302.19 g/mol and the formula $C_{14}H_6O_8$. The molecule is made up of two fused aromatic rings with two lactone moieties and four phenolic hydroxyl groups (Zeb *et al.*, 2018; Yoganathan *et al.*, 2021).

This structural arrangement gives the molecule significant redox activity because the conjugated aromatic system encourages charge delocalisation and the phenolic hydroxyl groups easily give up hydrogen atoms and transfer electrons. These traits help explain why ellagic acid is such a potent antioxidant. Additionally, the

planar aromatic structure facilitates interactions with regulatory proteins and nucleic acids, offering a molecular explanation for its documented pro-apoptotic and antiproliferative activities in cancer cells (García-Niño *et al*., 2022).

Origin of Biosynthesis

A structurally complicated subclass of hydrolysable tannins found in many medicinal plants, ellagitannins are biosynthetically related to ellagic acid. The majority of ellagic acid is found in plants as a latent metabolite, produced by the conversion of ellagitannins during plant metabolism, processing, or digestion, in contrast to many phenolic compounds that are directly synthesised and maintained in free form.

One or more Hexahydroxydiphenoyl (HHDP) groups esterified to a central glucose or polyol core are what define ellagannins. Galloyl groups obtained from the shikimate-phenylpropanoid pathway undergo oxidative coupling to form these HHDP moieties. Enzymatic esterification processes during plant growth bind HHDP units to glucose's hydroxyl groups, producing a variety of structurally distinct ellagitannins, including monomers, dimers, and oligomers (Wang *et al*., 2023; Kumar *et al*., 2024).

When the ester bonds in ellagitannins are hydrolytically broken, ellagic acid is produced. Endogenous plant enzymes, acidic environments, heat treatment, or microbial activity can all start this process. Free HHDP units are liberated upon hydrolysis; however, these intermediates are chemically unstable and quickly undergo intramolecular lactonization, resulting in the thermodynamically stable end product of ellagic acid. Because it transforms the very reactive HHDP structure into the distinctive dilactone framework of ellagic acid, this spontaneous cyclisation step is essential (Ceci *et al*., 2020).

Enzymatic hydrolysis occurs in the gastrointestinal system when ellagitannins from dietary and medicinal plant sources are consumed by humans. The gut bacteria may either partially absorb the produced ellagic acid or further metabolise it into urolithins, which are thought to be important contributors to systemic biological effects. Therefore, ellagitannins serve as both controlled-release reservoirs of ellagic acid and its downstream metabolites as well as precursors (Wang *et al*., 2022).

Crucially, the observed variation in ellagic acid concentration across plant species, plant sections, and processing conditions may be explained by the biosynthetic link between ellagic acid and ellagitannins. Plant maturity, environmental stress, drying, fermentation, and extraction parameters are some of the factors that have a significant impact on the degradation of ellagitannin and, in turn, the production of ellagic acid. Understanding this biosynthesis route is crucial from a pharmacognostic standpoint in order to improve the therapeutic potential of medicinal plants high in ellagitannin, standardise herbal formulations, and optimise extraction techniques.

Physicochemical properties

Although ellagic acid has promise bioactivity, its pharmacological effectiveness is limited by its unfavourable physicochemical characteristics. It is less soluble in water and more soluble in polar organic solvents including ethanol, dimethyl sulfoxide, and methanol. Oral absorption and systemic bioavailability are severely limited by this poor water solubility. at acidic circumstances, ellagic acid has a moderate level of chemical stability; nevertheless, it is vulnerable to destruction at alkaline pH, extended thermal exposure, and photolytic conditions. With many ionisable phenolic groups and pKa values reported to be between 6.5 and 7.5, the chemical partially ionises at physiological pH. Although ellagic acid's hydroxyl and carbonyl functions make it naturally polar, its pharmacokinetic profile is further limited by strong intermolecular hydrogen bonding and aromatic stacking, which lower membrane permeability (Shakeri *et al*., 2018; Ni *et al*., 2023).

Physicochemical Properties of Ellagic Acid

Ellagic Acid Bioactivity-Related Factors

A number of interconnected variables that affect ellagic acid's stability, absorption, metabolic destiny, and interactions with molecular targets all have an impact on its biological activity. Despite ellagic acid's potent antioxidant and anticancer qualities *in vitro*, physical and biological limitations frequently restrict its effectiveness *in vivo*. Translating its pharmacological potential into therapeutic applications requires a thorough comprehension of these elements (Liu *et al*., 2023, Kiasalari *et al*., 2021; Evtyugin *et al*., 2020).

Dissolution Behaviour and Solubility

One of the most important things that affects how well ellagic acid works is that it doesn't dissolve well in water. Because it doesn't dissolve well, it doesn't dissolve in gastrointestinal fluids, which makes it harder for the body to absorb it via the intestinal epithelium. Ellagic acid has a poor solubility, which means that the effective concentration that is accessible at systemic and cellular targets is lower than it may be, even if it has a high intrinsic activity.

Absorption and Bioavailability

Ellagic acid does not get absorbed well when taken by mouth since it doesn't easily pass through membranes and doesn't dissolve well. It is hard to passively diffuse across biological membranes because it may form many hydrogen bonds, has a planar aromatic structure, and is very polar. As a result, just a little quantity of ellagic acid that is eaten gets into the bloodstream without being destroyed.

Microbiota in the Gut and Changes in Metabolism

The gut microbiota's ability to change ellagic acid is a big part of what makes it bioactive. After you eat them, gut bacteria turn ellagitannins and ellagic acid into urolithins. These are better at being absorbed, have a greater lipophilicity, and stay in the body longer. variances in the makeup of the gut microbiota cause big variances in how much urolithin is made, which in turn impacts how each person's body reacts. Urolithins are often credited with in vivo anticancer properties instead of ellagic acid.

Chemical Stability and the Environment

The pH, oxidative conditions, temperature, and exposure to light all impact how stable ellagic acid is. Acidic environments keep things relatively stable, whereas alkaline ones make things break down and become less active. Also, heat processing and being in the sun for a long time might make it less efficient as an antioxidant. These parts are very important when it comes to processing, extracting, formulating, and storing food.

Source, how it was taken out, and how it was processed

The quantity and activity of ellagic acid depend a lot on the plant source and the amount of ellagitannin. Ellagitannin profiles are affected by where they are grown, what species they are, what parts of the plant they are in, and how mature they are. The extraction methods (types of solvent, temperature, pH, and time) also change how well hydrolysis works and how pure it is, which changes how living things work.

Interaction with metal ions and biomolecules

Ellagic acid easily interacts with proteins, enzymes, metal ions, and nucleic acids since it is made up of several different types of polyphenols. Metal chelation makes antioxidants work better by stopping oxidative processes that are caused by metals. However, too much protein binding might make free medications less available. Depending on the physiological state, these interactions might make biological reactions stronger or weaker.

Distribution inside cells and absorption by cells

The level of bioactivity of ellagic acid is also affected by where it is found inside cells and how cells take it in. Limited membrane transport and active efflux mechanisms can lower the amount of substances inside cells. After being taken in by the cell, ellagic acid may go to certain organelles, where it can change the balance of redox, send signals for apoptosis, and control the cell cycle.

Dosage Form and Drug Delivery System

The formulation technique has a big role in boosting bioactivity. Sometimes, traditional dosage formulations can't get around problems with solubility and permeability. Modern techniques such solid dispersions, liposomes, polymeric carriers, and nanoparticles have showed promise in making ellagic acid more soluble, stable, targeted, and effective against cancer. Ellagic acid's bioactivity is determined by a complex interplay of solubility, absorption, metabolism, stability, biological interactions, and formulation characteristics. These limitations must be overcome through microbiota-targeted methods, optimised extraction, and novel delivery systems in order to maximise its antioxidant and anticancer potential *in vivo*.

Sources of Ellagic Acid in Nature

Ellagic acid is a naturally occurring polyphenolic compound that is widely distributed across the kingdom of plants. The majority of the time, it can be found free or as part of complex hydrolysable tannins known as ellagitannins, which hydrolyse to form ellagic acid. Medicinal plants high in ellagic acid have attracted a lot of scientific attention due to their significant antioxidant qualities and their application in the prevention and treatment of cancer (Table 1). Environmental conditions, processing methods, plant species, and plant component all significantly affect the amount of ellagic acid (Rahimi *et al*., 2024; Nyamba *et al*., 2021).

Medicinal Plants Rich in Ellagic Acid

Many plant materials used in cooking and medicine are natural sources of ellagic acid. These sources have long been used in traditional medicine, and science has now verified their health-promoting properties (Wang *et al*., 2025; Abdelkader *et al*., 2020).

Fruits (e.g., Berries, Pomegranate)

One of the best food sources of ellagic acid is fruit. Large quantities, mostly in the form of ellagitannins, are found in berries such blueberries, cranberries, blackberries, raspberries, and strawberries. With significant quantities in the peel, arils, and juice, pomegranates are regarded as one of the most powerful sources. The ellagic acid and its metabolites, which neutralise reactive oxygen species and prevent the growth of cancer cells, are primarily responsible for the antioxidant and anticancer properties linked to these fruits.

Leaves, Bark, Seeds, and Roots

Apart from fruits, ellagic acid is also present in inedible plant parts like leaves, bark, seeds, and roots. Species such as oak and eucalyptus tree barks are particularly good sources of ellagitannin due to their high concentration. Pulp usually has lower numbers than seeds and peels, which serve as tissues that protect against oxidative damage and microbial attack. A protective secondary metabolite called ellagic acid builds up in the leaves of many medicinal plants, increasing their therapeutic efficiency.

Traditional Medicinal Plants

Ellagic acid is found in large quantities in a variety of plants that are used in traditional medicine, including traditional

Parameter	Description
Chemical name	Ellagic acid
Molecular formula	$C_{14}H_6O_8$
Molecular weight	302.19 g/mol
Chemical class	Polyphenolic dilactone (hydrolyzable tannin derivative)
Solubility	Poorly soluble in water; soluble in methanol, ethanol, DMSO
pKa	~6.5-7.5 (phenolic hydroxyl groups)
Polarity	Moderate to high
Stability	Stable in acidic conditions; sensitive to light, heat, and alkaline pH
Bioavailability	Low (enhanced via microbial metabolism to urolithins)

Chinese medicine, Ayurveda, and herbal remedies. Historically, these herbs have been used to treat inflammation, infections, gastrointestinal problems, and tumours. By demonstrating that ellagic acid contributes significantly to their anti-inflammatory, anti-cancer, and antioxidant properties, recent phytochemical research validates their continued use in herbal formulations and nutraceuticals.

Distribution in Different Plant Parts

The physiological function of each tissue in a plant greatly influences the non-uniform distribution of ellagic acid. Comparative research shows that:

- Because ellagic acid acts as a protective antioxidant against environmental stresses, its concentrations are often higher in peels, rinds, and exterior layers.
- Because of their function in defence and structural integrity, seeds and bark frequently exhibit higher amounts than interior tissues.
- Moderate levels are found in leaves, which assist defence against oxidative damage and UV radiation.
- Although they typically have lesser quantities, fruit pulp and roots nonetheless provide a substantial nutritional contribution.

When choosing the right plant materials for extraction, formulation, and therapeutic application, this tissue-specific dispersion is crucial. Optimising extraction techniques and increasing the yield of bioactive ellagic acid for use in pharmaceutical and nutraceutical applications is also made easier with an understanding of these differences (Table 2) (Castellacci and Bergonzi, 2025).

Extraction, Isolation, and Quantification of Ellagic Acid

Extraction, separation, and measurement are all important steps in figuring out how ellagic acid works in the body and how it may be used as a therapy. Ellagic acid is present in medicinal plants either in its free form or, more commonly, as a result of ellagitannin hydrolysis. So, the extraction efficiency depends on the plant source, the section of the plant used, the polarity of the solvent, the extraction conditions, and the pretreatment methods. To ensure optimal recovery, purity, and reproducibility particularly for antioxidant and anticancer research suitable extraction and analytical methodologies are essential (Rostami *et al.*, 2022; Neamatallah *et al.*, 2020).

Methods of Extracting Ellagic Acid

There are two primary sorts of ways to get ellagic acid: old-fashioned ways and newer, more advanced ways. Modern techniques are more efficient, use less solvent, and keep bioactivity better, but traditional methods are still popular since they are easy to use and cheap (Kawasaki *et al.*, 2024; Hagihara *et al.*, 2022; Fan *et al.*, 2022; Saribas *et al.*, 2023; Kubota *et al.*, 2019; Lin *et al.*, 2019; Arab *et al.*, 2019).

Common Methods of Extraction

Heat-assisted mass transfer and solvent diffusion are the two main ideas behind classic extraction procedures. These methods are often used in both large-scale extraction and early phytochemical investigations.

The process of maceration

Maceration is one of the easiest and most common ways to get rid of ellagic acid in medicinal plants. This procedure requires soaking plant material in a suitable solvent, which is commonly methanol, ethanol, acetone, or a mix of these, for a lengthy period at room temperature. The solvent dissolves ellagic acid and other polyphenols by getting into the plant tissues during maceration.

Maceration has a number of drawbacks while being simple to execute and requiring no complex equipment. These include a longer extraction time, a decreased extraction efficiency, and the potential for sensitive phytoconstituents to degrade as a result of extended exposure to light and oxygen. Notwithstanding these limitations, maceration is nevertheless helpful for early screening investigations and thermolabile chemicals.

Soxhlet Extraction

Soxhlet extraction is a common technique for continuously extracting ellagic acid from dried plant sources. This method allows for the complete extraction of polyphenolic compounds by washing the plant powder with boiling solvent over and over again.

In general, Soxhlet extraction makes more ellagic acid than maceration, especially when it comes to plant matrices that are high in ellagitannins. But heating for a long time can use more solvent and break down some heat-sensitive compounds. This method also takes a long time and isn't as good for the environment, which makes it less useful for big or environmentally friendly extraction processes.

Contemporary Methods of Extraction

The drawbacks of traditional extraction procedures have been addressed by the development of modern approaches. While keeping ellagic acid's structural integrity, these methods improve extraction efficiency, shorten processing times, and use less solvent.

Ultrasound-Assisted Extraction (UAE)

Ultrasound-assisted extraction uses high-frequency ultrasonic vibrations to break down plant cell walls through a process called cavitation. This process makes it simpler for solvents to get into cells and for intracellular compartments to let go of ellagic acid. There are a lot of benefits to using UAE instead of traditional techniques, including as needing less solvent, taking less time to extract, and getting more out of the extraction. It works exceptionally effectively to keep the antioxidant and anticancer effects of phenolic compounds like ellagic acid while getting them out. The UAE is becoming more and more popular for phytochemical and medicinal research since it works well and is good for the environment.

Microwave-Assisted Extraction (MAE)

In order to facilitate effective cell wall breakage and improved mass transfer, microwave-assisted extraction uses microwave radiation to quickly heat the solvent and plant matrix. MAE offers excellent ellagic acid recovery while drastically cutting down on extraction time and solvent usage. For the extraction of polyphenols encased in intricate plant matrix, this method works particularly well. However, in order to prevent ellagic acid breakdown, careful optimisation of microwave power, temperature, and exposure duration is required. For medicinal plant research, MAE is regarded as a very effective and environmentally friendly extraction method when used appropriately.

For fundamental research, traditional extraction procedures like maceration and Soxhlet extraction are still useful, but contemporary approaches like ultrasound-assisted and microwave-assisted extraction provide greater sustainability, efficiency, and reproducibility. Choosing the right extraction technique is essential for optimising ellagic acid output and guaranteeing its successful assessment in research on antioxidants and anticancer agents.

Ellagic Acid Purification and Isolation

To get ellagic acid in a chemically pure state, it needs to be separated and cleaned from medicinal plant extracts. This is necessary for structural characterisation, biological evaluation, and formulation development. Ellagic acid is often found in free form or released from ellagitannins after hydrolysis, therefore isolating it generally involves hydrolysis, solvent separation, and chromatographic purification. The choice of procedure depends on the intended purpose, the complexity of the extract, and the plant source (Elseweidy *et al.*, 2022; Peng *et al.*, 2023; Wu *et al.*, 2025; Raj *et al.*, 2024; Al-Hoshary and Zalzala, 2023).

Hydration of Ellagitannins

Ellagic acid is mostly present in medicinal plants as a structural element of ellagitannins, rather than as a free molecule. Because of this, an initial phase of acidic or enzymatic breakdown often releases ellagic acid. Acid hydrolysis usually uses diluted mineral acids like hydrochloric or sulphuric acid under strict heating conditions. When the plant extract or ellagitannin-rich fraction is refluxed with aqueous acid, ester connections are broken and ellagic acid is released. To stop the breakdown or polymerisation of phenolic compounds, the acid content, temperature, and time must be carefully adjusted. Following hydrolysis, insoluble residues are filtered out of the mixture by cooling it down, and then ellagic acid is recovered by solvent extraction.

Table 1: Comparison of Ellagic Acid with Selected Dietary Polyphenols.

Polyphenol	Molecular Weight (g/mol)	Water Solubility	Major Biological Activities	Bioavailability
Ellagic acid	302.19	Poor	Antioxidant, anticancer, chemopreventive	Low
Gallic acid	170.12	High	Antioxidant, antimicrobial	Moderate
Quercetin	302.24	Poor	Antioxidant, anti-inflammatory, anticancer	Low
Resveratrol	228.24	Poor	Antioxidant, cardioprotective, anticancer	Low
Catechin	290.27	Moderate	Antioxidant, cardioprotective	Moderate

Table 2: Tissue-wise distribution of ellagic acid in plant parts, showing relative content, predominant forms, biological roles, representative sources, and pharmacological significance.

Relative Ellagic Acid Content	Predominant Form	Physiological / Biological Role	Representative Examples	Pharmacological & Practical Significance
Very High	Ellagitannins → Ellagic acid	Protection against UV radiation, pathogens, oxidative stress	Pomegranate peel, strawberry skin, raspberry skin	Major source for antioxidant and anticancer extracts; agro-waste valorization
High	Free ellagic acid and ellagitannins	Protection of genetic material and lipids during dormancy	Walnut seeds, raspberry seeds	High antioxidant potential; used in nutraceutical formulations
Very High	Ellagitannins	Structural defense, antimicrobial protection	Oak bark, chestnut bark	Industrial source of ellagic acid; traditional medicinal use
Moderate	Ellagitannins	Photoprotection, redox balance, defense against herbivores	Pomegranate leaves, medicinal herb leaves	Contributes to antioxidant and anti-inflammatory activity
Low to Moderate	Mostly free ellagic acid	Minor antioxidant protection	Pomegranate arils, berry pulp	Important dietary source despite lower concentration
Low to Variable	Ellagitannins (species-dependent)	Defense against soil pathogens	Selected medicinal roots	Limited use; species-specific relevance
Moderate to High	Ellagitannins	Protection against oxidation and pests	Chestnut shells, walnut shells	Sustainable source for extraction; high polyphenol yield
Low to Moderate	Free ellagic acid	Protection during reproductive phase	Flowering medicinal plants	Minor contributor; supportive antioxidant role

Solvent-Solvent partitioning

A common first purification process after extraction and hydrolysis is liquid-liquid partitioning. By isolating ellagic acid from highly polar and non-polar contaminants, this method lowers the complexity of the extraction. Following suspension in water, the crude extract is progressively separated using organic solvents with varying degrees of polarity, including n-hexane, chloroform, ethyl acetate, and n-butanol. Ellagic acid preferentially concentrates in solvents that are fairly polar, especially ethyl acetate. This fractionation process improves ellagic acid enrichment before chromatographic purification.

Column Chromatography

To separate ellagic acid from enriched fractions, one of the most often used methods is open-column chromatography. Usually, silica gel is utilised as the stationary phase, and solvent systems like ethyl acetate-methanol, chloroform-methanol, or ethyl acetate-formic acid-water are used as the mobile phases. Increasing solvent polarity is used to progressively elute the enhanced fraction once it has been put onto the column. Thin-Layer Chromatography is used to quantify and track fractions (TLC). Colour reactions using phenolic detection reagents, Rf values, and UV fluorescence are used to identify fractions that contain ellagic acid. Reduced pressure is used to combine and concentrate these fractions.

Preparative Thin-Layer Chromatography (PTLC)

Preparative TLC is a useful purification technique for handling tiny amounts of extract. Using this method, the enriched fraction is applied as a band on silica gel-coated preparative TLC plates. Under UV light, the ellagic acid band is visible on plates that have been created using solvent solutions that have been optimised. Following scraping of the relevant silica gel zone, ellagic acid is recovered by solvent extraction, filtering, and solvent evaporation. PTLC is helpful for laboratory-scale separation and offers excellent purity, despite its restricted scalability.

High-Performance Liquid Chromatography (HPLC)

The most dependable method for high-purity isolation is thought to be preparative or semi-preparative HPLC. Mobile phases for reverse-phase columns (usually C18) are made of water-acetonitrile or water-methanol systems and are frequently acidified with acetic or formic acid. Because of its superior resolution, repeatability, and purity, HPLC is especially well-suited for isolating ellagic acid for pharmacological and mechanistic investigations. Retention time is used to collect the isolated compound, and spectroscopic methods are used to confirm it.

Re-crystallization

Recrystallisation is frequently used to achieve the final purification of ellagic acid, improving chemical purity and eliminating trace contaminants. Commonly used solvents include aqueous

alcohols, methanol, ethanol, and acetone. A heated solvent is used to dissolve the partly purified ellagic acid, which is then allowed to cool and crystallise gradually. Under vacuum, the resultant crystals are filtered, cleaned, and dried. It is very effective to recrystallise since ellagic acid is not very soluble in cold solvents.

Identity and Purity Verification

Using a variety of analytical methods, the identification and purity of the extracted ellagic acid are verified, including:

Chromatography using thin layers (single spot)

- Utilising HPLC purity profiling.
- Using UV-visible spectroscopy (which shows distinctive absorption maxima).
- Lactone groups and phenolic OH infrared spectroscopy.
- (^{1}H and ^{13}C NMR) Nuclear magnetic resonance.

Mass spectrometry

By using these methods, the isolated compound's structural validity and fitness for antioxidant and anticancer assessments are guaranteed. Ellagic acid is isolated and purified using a methodical process that combines solvent partitioning, hydrolysis, chromatographic separation, and recrystallisation. For pharmacological research, high purity and repeatability are crucial, and advanced chromatographic methods like preparative HPLC offer both. Maintaining the biological activity of ellagic acid while optimising production requires careful consideration of the separation parameters.

Methods of Analysis for Ellagic Acid

For ellagic acid's antioxidant and anticancer activity to be assessed, precise identification, measurement, and structural confirmation are necessary. Because of its poor water solubility and polyphenolic composition, sensitive and specific analytical methods are needed. For both qualitative and quantitative examination of ellagic acid in crude extracts, purified fractions, and formulated systems, a variety of spectroscopic and chromatographic techniques have been used. Nuclear Magnetic Resonance (NMR), LC-MS, HPLC, and UV-visible spectroscopy are the most popular methods among them (Wang *et al.*, 2025; Duckworth *et al.*, 2023; Türkmen *et al.*, 2022; Kaur *et al.*, 2021).

High-Performance Liquid Chromatography (HPLC)

To determine the amount of ellagic acid in extracts from medicinal plants, high-performance liquid chromatography is the most popular and reliable technique. HPLC's high sensitivity, reproducibility, and selectivity make it suitable for routine analytical and quality control trials. Ellagic acid is frequently analysed using reverse-phase HPLC systems with C_{18} columns. Commonly employed as mobile phases include water and organic solvents such as acetonitrile or methanol. Often, phosphoric or formic acid is added to these solvents to improve peak shape and resolution. Using UV or diode-array detectors, ellagic acid is frequently detected due to its strong absorption at wavelengths between 254 and 280 nm, which is caused by its aromatic rings. Ellagic acid in intricate plant matrices can be properly measured by HPLC, which also allows for the simultaneous analysis of related phenolic compounds. Limit of Detection (LOD), Limit of Quantification (LOQ), linearity, accuracy, and precision are among the method validation criteria that are routinely specified to guarantee analytical dependability.

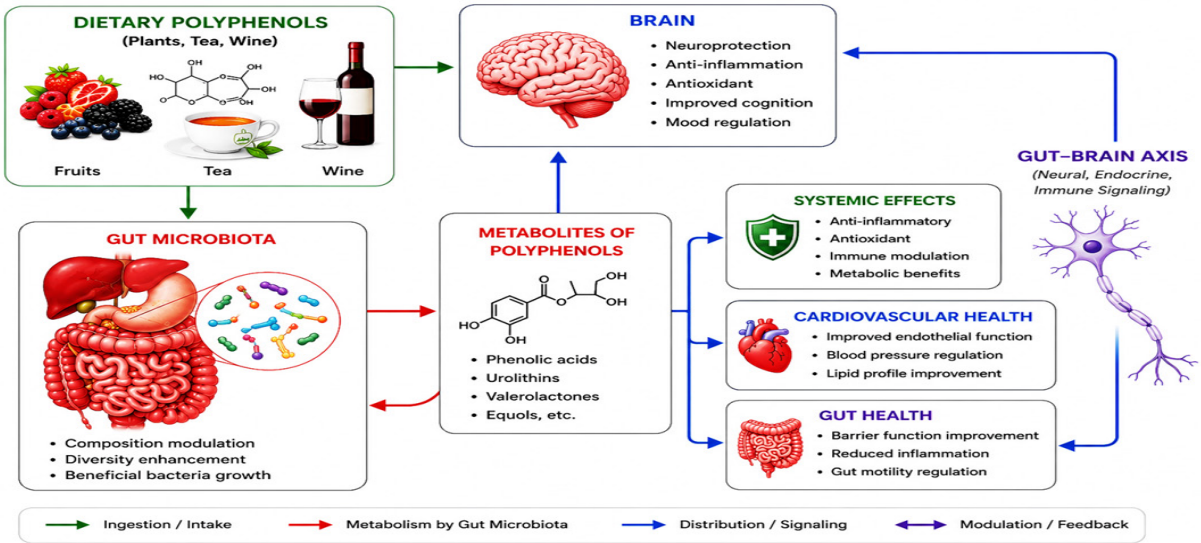

Figure 1: Schematic representation of dietary polyphenol intake and metabolism, illustrating the role of gut microbiota in biotransforming polyphenols into bioactive metabolites and their bidirectional interaction with the gut-brain axis, influencing systemic distribution and biological effects.

Liquid Chromatography-Mass Spectrometry (LC-MS)

The very sensitive and effective analytical technique known as liquid chromatography-mass spectrometry can be used to identify, confirm, and quantify ellagic acid, particularly in complex biological and plant matrices. In LC-MS, the molecular selectivity of mass spectrometry and the separation efficiency of liquid chromatography are combined. The reason ellagic acid is often examined in negative ionisation mode is because it contains acidic phenolic groups. The procedure provides molecular ion peaks and characteristic fragmentation patterns that enable clear chemical identification. LC-MS is particularly helpful for monitoring ellagic acid at trace levels and studying its metabolites, including urolithins generated during gut microbial metabolism. For studies including ellagic acid pharmacokinetics, bioavailability, and metabolomics, LC-MS is crucial due to its superior sensitivity and selectivity above HPLC-UV.

Visible and UV Spectroscopy (UV-vis)

UV-visible spectroscopy is a rapid and simple technique for the first identification and quantification of ellagic acid. The molecule has characteristic UV absorption maxima due to its conjugated aromatic structure. Ellagic acid often shows strong absorption bands about 254-280 nm, which correlate to π-π^* electrical transitions. UV-vis analysis is widely utilised in extraction, isolation, and fraction monitoring, particularly when chromatographic methods are not readily available. Even though UV-vis spectroscopy lacks the specificity required for analysis in complex mixtures, it can be useful for routine screening, assessing the purity of isolated compounds, and preliminary quantification when used in conjunction with standard calibration curves.

Nuclear Magnetic Resonance Spectroscopy (NMR)

Using nuclear magnetic resonance spectroscopy is a dependable way to validate and clarify the structure of ellagic acid. Comprehensive information about the compound's molecular structure, functional groups, and chemical landscape may be found in the NMR spectra of the proton (^{1}H) and carbon (^{13}C). While ^{13}C NMR spectra display signals associated with lactone carbonyl carbons and aromatic carbons, ^{1}H NMR spectra display unique signals related to hydroxyl groups and aromatic protons in ellagic acid. Advanced two-dimensional NMR techniques such as COSY, HSQC, and HMBC may be used to confirm structural relationships.

For isolating the extracted ellagic acid from structurally related polyphenols and verifying its purity, NMR spectroscopy is very important. Despite the need for more sophisticated equipment and somewhat larger sample quantities, NMR is still crucial for structural authentication. Complementary techniques are necessary for the analytical characterisation of ellagic acid. HPLC is the method of choice for routine quantification; LC-MS allows for high sensitivity and molecular confirmation; UV-vis spectroscopy ensures conclusive structural validation; and NMR spectroscopy offers rapid preliminary analysis. By combining these analytical methods, ellagic acid in medicinal plants may be accurately assessed and supported as a potent antioxidant and anti-cancer agent.

Metabolism and Bioavailability of Ellagic acid

Even though ellagic acid's antioxidant and anticancer properties have been well-established, its therapeutic use is severely constrained by its complicated metabolism and low bioavailability. Low water solubility, restricted intestinal absorption, and substantial biotransformation after oral administration are the characteristics of ellagic acid. To maximise its therapeutic uses, it is crucial to comprehend its absorption, metabolic destiny, and the function of gut bacteria.

Assimilation and Metabolic Change

When ellagic acid-rich meals or extracts from medicinal plants are consumed orally, the gastrointestinal system is where ellagic acid is mostly absorbed. Its polyphenolic composition, limited water solubility, and propensity to form compounds with food proteins and minerals, however, result in very low and extremely variable absorption (Figure 1). Ellagic acid is frequently found in plants as a ellagitannin component. In order to release free ellagic acid, ellagitannins are hydrolysed by acids in the stomach and by enzymes in the intestine during digestion. By passive diffusion, ellagic acid is only partially absorbed by the intestinal epithelium once it is released (Kyriakoudi *et al.*, 2024; Jun *et al.*, 2025; Gul *et al.*, 2022; Pieróg *et al.*, 2021; Lim *et al.*, 2019; Tan *et al.*, 2019; Kábelová *et al.*, 2021; Bodiga *et al.*, 2022).

Phase II metabolic changes, mostly conjugation events such glucuronidation and methylation in the intestinal wall and liver, occur after ellagic acid is absorbed. Compared to the original molecule, these conjugated metabolites may have changed or decreased biological activity, but they are more water soluble and circulate in plasma. However, most ingested ellagic acid is not absorbed and travels to the colon, where the gut flora further breaks it down.

Ellagic Acid Metabolism (Urolithin Production) and the Function of the Gut Microbiota

When it comes to ellagic acid's bioavailability and biological effects, the gut microbiota is crucial. In the colon, some intestinal microbes break down unabsorbed ellagic acid and ellagitannins to produce a class of low-molecular-weight substances called urolithins. Urolithins are made by a series of dehydroxylation and lactone ring modification processes. These include urolithin A, urolithin B, and their related derivatives. Compared to ellagic acid itself, these metabolites are more lipophilic and better absorbed, which increases their systemic availability. After absorption, urolithins mostly exist in plasma as conjugates of glucuronides or sulphates (Gorgisen *et al.*, 2020).

In vivo models, urolithins frequently outperform ellagic acid in terms of antioxidant, anti-inflammatory, and anticancer properties. However, because gut microbial makeup varies greatly across individuals, so does the ability to manufacture urolithins. The varied biological responses shown in human trials with diets high in ellagic acid can be partially explained by the different metabotypes that result from this inter-individual variability (Baradaran Rahimi *et al.*, 2020).

Limitations in Oral Bioavailability

The therapeutic efficacy of ellagic acid is severely limited due to its poor to moderate oral bioavailability, despite good *in vitro* results. There are several reasons for this restriction:

1. Low water solubility causes incomplete dissolution in gastrointestinal fluids.
2. Poor intestinal permeability results in limited passive diffusion across epithelial membranes.
3. Rapid conjugation and removal due to a high first-pass metabolism.
4. Because of dependence on gut flora, there is a high degree of inter-individual variability in systemic exposure.

Additionally, ellagic acid binds to metal ions and dietary macromolecules with a high affinity, reducing the quantity of free concentration that may be absorbed. As a result, unmetabolized ellagic acid plasma concentrations are often rather low following oral administration. To improve intestine absorption, stability, and solubility, several strategies have been proposed to overcome these problems. These consist of polymeric nanoparticles, lipid-based carriers, phospholipid complexes, and nanoformulations. These techniques are increasingly being researched to improve the therapeutic potential of ellagic acid in the treatment of antioxidants and cancer (Islam *et al.*, 2025; Cota and Patil, 2023; Altındağ *et al.*, 2021; Guo *et al.*, 2023; Zheng *et al.*, 2025).

Ellagic acid has a limited oral bioavailability due to its high metabolism and poor absorption. The significance of gut microbiota is shown by the significant role that microbial metabolites like urolithins play in influencing its biological function in vivo. Understanding these pharmacokinetic limitations is necessary to develop advanced delivery systems and increase the therapeutic potential of ellagic acid derived from medicinal plants.

Potential of Ellagic acid as an Antioxidant

Because of its potent antioxidant properties, ellagic acid, a naturally occurring polyphenolic molecule, has been the focus of much investigation (Figure 2). Its capacity to defend against oxidative stress-mediated illnesses like cancer, heart disease, neurological diseases, and inflammatory conditions depends on this function. Oxidative stress is caused by an imbalance between the body's antioxidant defence mechanisms and the generation of Reactive Oxygen and Nitrogen Species (ROS/RNS). Because it corrects this imbalance through a number of complementary antioxidant mechanisms, ellagic acid can function at different stages of oxidative damage (Peker and Elpek 2021).

Antioxidant Action Mechanisms

The unique chemical structure of ellagic acid, which is defined by a conjugated aromatic system and many phenolic hydroxyl groups, is thought to be responsible for its antioxidant properties. Because of these structural characteristics, ellagic acid may interact with lipid peroxides, metal ions, and free radicals in an efficient manner. Below is a discussion of the main processes underlying its antioxidant effect.

Radical Scavenging Without Charge

The main and most direct antioxidant mechanism of ellagic acid is free radical scavenging. Reactive nitrogen species, like nitric oxide, and reactive oxygen species, including superoxide anion, hydroxyl radical, and peroxyl radical, are very unstable compounds that can harm proteins, DNA, and lipids. By giving away hydrogen atoms or electrons, ellagic acid neutralises these reactive species and transforms them into more stable, non-reactive forms. Ellagic acid's four phenolic hydroxyl groups enable resonance stabilisation of the resultant phenoxyl radicals, which stops radical chain reactions from spreading. Because of this characteristic, ellagic acid is very good at halting oxidative cascades early on. Using common antioxidant tests including DPPH, ABTS, FRAP, and ORAC, a number of *in vitro* investigations have continuously shown that ellagic acid has a potent ability to scavenge radicals, frequently matching or surpassing that of well-known antioxidants. By reducing oxidative damage to cellular components, this free radical scavenging activity helps biological systems resist oxidative stress-induced cellular transformation and promote cytoprotection (Pardo-Peña *et al.*, 2023).

Chelation of Metals

Through Fenton and Haber-Weiss reactions, transition metals like Iron (Fe^{2+}/Fe^{3+}) and Copper (Cu^{2+}) are important contributors to the production of very reactive hydroxyl radicals. These metal-catalyzed processes increase oxidative stress and encourage DNA damage, protein oxidation, and lipid peroxidation. Ellagic acid's molecular structure contains neighbouring hydroxyl and carbonyl functional groups, which contribute to its potent metal chelating capabilities. Ellagic acid inhibits the production of secondary reactive species by attaching to metal ions and preventing them from taking part in redox cycling. In pathological situations including inflammation, neurodegeneration, and cancer that are linked to metal ion excess, metal chelation is especially crucial. By this process, ellagic acid indirectly prevents

metal-induced cellular damage and mutagenesis in addition to lowering oxidative stress (Cheshomi *et al.*, 2021).

Lipid Peroxidation Inhibition

Polyunsaturated fatty acids in cell membranes are the focus of the damaging oxidative process known as lipid peroxidation, which causes membrane stiffness, integrity loss, and compromised cellular function. Free radicals start the process, which is then carried out by lipid peroxyl radicals to produce harmful byproducts such malondialdehyde and 4-hydroxynonenal. Lipid peroxidation is inhibited at several stages by ellagic acid. It stops the chain process by stabilising lipid peroxyl radicals, scavenging starting radicals, and chelating metal ions that catalyse lipid oxidation. According to experimental research, ellagic acid plays a crucial function in membrane protection by dramatically lowering lipid peroxidation indicators in both *in vitro* and *in vivo* settings. Ellagic acid helps to maintain cellular homeostasis and shields tissues from oxidative damage by maintaining membrane fluidity and inhibiting lipid oxidative breakdown. This process is especially important for avoiding oxidative damage linked to ageing, chronic inflammatory disorders, and carcinogenesis (Kaur *et al.*, 2021; Kyriakoudi *et al.*, 2024; Jun *et al.*, 2025; Gul *et al.*, 2022).

Effects of Integrated Antioxidants

Ellagic acid has antioxidant properties because it can do more than one thing at once, such as chelate metals, stop lipid peroxidation, and scavenge free radicals. Ellagic acid can protect against oxidative stress in the short and long term since it works on many different targets. Moreover, by diminishing oxidative DNA damage, maintaining cellular redox homeostasis, and preventing chronic oxidative stress-induced signalling irregularities, these pathways collectively enhance its chemopreventive and anticancer properties (Pieróg *et al.*, 2021).

Ellagic acid has a lot of antioxidant potential since it can directly scavenge reactive species, chelate pro-oxidant metal ions, and stop lipid peroxidation. These activities represent the metabolic basis for the antioxidant and anticancer effects of ellagic acid, which comes from medicinal plants and is important for protecting biological systems from oxidative damage.

Ellagic Acid Antioxidant Studies *in vitro*

Ellagic acid's ability to scavenge free radicals and lower their levels is routinely tested *in vitro* antioxidant assays that are done in very controlled laboratory settings. These tests are quick, easy, and cheap ways to find out how well ellagic acid works with other popular antioxidants and to learn more about how it works as an antioxidant. Some of the most used *in vitro* assays are the DPPH, ABTS, FRAP, and ORAC tests. Each one is based on a distinct chemical principle and shows a different side of how antioxidants work (Guo *et al.*, 2023; Zheng *et al.*, 2025; Peker *et al.*, 2021; Pardo-Peña *et al.*, 2023; Cheshomi *et al.*, 2021; Chambers *et al.*, 2020).

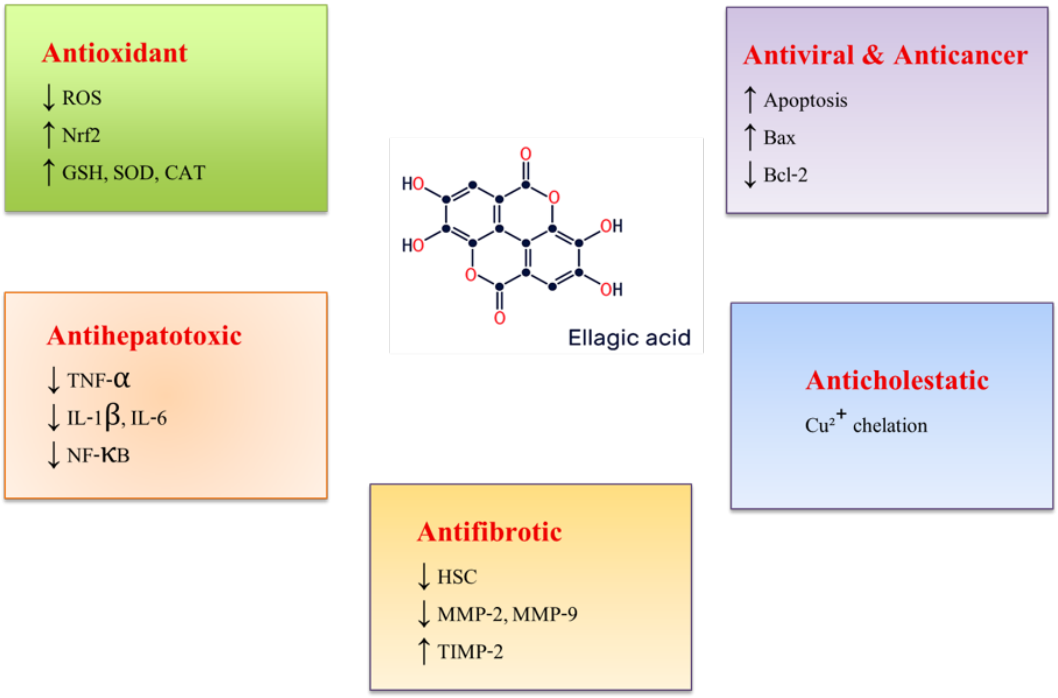

Figure 2: Schematic illustration of the pleiotropic pharmacological actions of ellagic acid, highlighting its antioxidant, antihepatotoxic, antifibrotic, anticholestatic, antiviral, and anticancer effects mediated through modulation of oxidative stress, inflammatory signaling, apoptosis, fibrogenic markers, and metal ion chelation.

DPPH Radical Scavenging Test

The DPPH (2,2-diphenyl-1-picrylhydrazyl) test is one of the most used ways to see how well ellagic acid can get rid of free radicals. DPPH is a stable, nitrogen-centered free radical that is a deep violet colour. It has a unique absorption maximum at 517 nm. When ellagic acid is introduced to the chemical system, it gives the DPPH radical hydrogen atoms or electrons, which makes it a pale yellow non-radical state. In addition to this decrease, there is a noticeable decline in absorbance, which is directly proportional to how well the molecule can scavenge radicals. Ellagic acid has a lot of phenolic hydroxyl groups that may stabilise free radicals via resonance, hence it always has a strong DPPH radical scavenging effect. To make it easier to compare the results with popular antioxidants like ascorbic acid or Trolox, they are frequently shown as percentage inhibition or IC_{50} values (Guo *et al.*, 2023).

Test for the decolorisation of ABTS radical cation

The ABTS (2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)) test measures how well ellagic acid can get rid of $ABTS^{+}$• radical cations. These cations are generated when ABTS is oxidised using the correct oxidising agent. The ABTS+• radical has a blue-green colour and is commonly measured at 734 nm. Adding ellagic acid to the radical cation makes it less powerful, which causes it to lose colour in proportion to how well the molecule works as an antioxidant.

One of the best things about the ABTS test is that it can be used to measure ellagic acid in a wide range of solvent systems and complex plant extracts. This is because it can be used to test both hydrophilic and lipophilic antioxidants. Ellagic acid's wide range of antioxidant properties is shown by how well it works to get rid of ABTS radicals. People often utilise Trolox Equivalent Antioxidant Capacity (TEAC) values to show their results (Neamatallah *et al.*, 2020).

FRAP Assay: The Power of Ferric Reducing Antioxidants

The FRAP test measures the acid's reducing power by looking at how well ellagic acid can change Ferric (Fe^{3+}) ions into Ferrous (Fe^{2+}) ions in an acidic environment. A specific ligand and the reduced ferrous ions form a coloured complex that makes a bright blue colour that can be detected using a spectrophotometer. FRAP assesses how well ellagic acid can provide electrons, which is different from radical scavenging tests, which measure how well it can neutralise radicals directly. Ellagic acid has a lot of polyphenols in it, which makes it easy for it to take part in redox reactions. This gives it a high ability to reduce ferric. The FRAP test is very useful for figuring out how well ellagic acid works as an antioxidant in plant extracts. It is often used with other tests for a full antioxidant profile because it doesn't look at thiol-based antioxidants or compounds that solely work by quenching radicals.

ORAC Test: Oxygen Radical Absorbance Capacity

The ORAC test checks how well ellagic acid can protect a fluorescent probe from oxidative damage caused by peroxyl radicals, which are one of the most important reactive oxygen species in the body. In this experiment, the heat breaks down an azo molecule, which makes peroxyl radicals. These radicals slowly make the probe's fluorescence fade. Ellagic acid stops this fluorescence degradation by taking up peroxyl radicals. The area under the curve that shows the fluorescence decline is used to figure out how much protection there is. ORAC is thought to be a physiologically relevant test since it assesses antioxidant activity against peroxyl radicals, which are typically linked to lipid peroxidation and oxidative stress in cells. Ellagic acid protects biological systems from oxidative damage quite well, as seen by its high ORAC values. Trolox equivalents are often used to show findings (Al-Hoshary and Zalzala, 2023; Wang *et al.*, 2025; Duckworth *et al.*, 2023; Türkmen *et al.*, 2022).

Comparative Importance of Assays for *in Vitro* Antioxidants

Every *in vitro* antioxidant test assesses a distinct antioxidant activity mechanism. ORAC represents peroxyl radical scavenging capacity, FRAP evaluates reducing power, while DPPH and ABTS tests mainly measure radical scavenging ability. Ellagic acid continuously performs well in each of these tests, demonstrating its multipurpose antioxidant properties. The significant antioxidant capacity of ellagic acid is convincingly demonstrated by *in vitro* antioxidant investigations employing DPPH, ABTS, FRAP, and ORAC tests. The substance exhibits effective oxidative damage prevention, reducing power, and free radical scavenging. These results support its ongoing research as a natural antioxidant generated from medicinal plants and provide the molecular foundation for its observed *in vivo* antioxidant and anticancer activities (Pieróg *et al.*, 2021).

In vivo Antioxidant Effects of Ellagic Acid

Important proof of ellagic acid's antioxidant effectiveness in physiological settings comes from in vivo investigations. In contrast to in vitro tests, which evaluate direct radical scavenging, *in vivo* studies show ellagic acid's systemic antioxidant effects, including how it interacts with metabolism, tissue distribution, and cellular defence systems. The potential of ellagic acid to alter endogenous antioxidant enzyme systems, which fortifies the body's natural defences against oxidative stress, is a key mechanism behind its in vivo antioxidant effect (Aishwarya *et al.*, 2021; Kubota *et al.*, 2019).

Endogenous Antioxidant Defence System and Oxidative Stress

An imbalance between the production of Reactive Oxygen Species (ROS) and the body's natural antioxidant defences' ability to neutralize them results in oxidative stress. A well-coordinated

network of enzymatic and non-enzymatic antioxidants provides antioxidant protection in biological systems. Superoxide Dismutase (SOD), Catalase (CAT), Glutathione Peroxidase (GPx), and Glutathione Reductase (GR) are important enzymatic antioxidants. Reduced Glutathione (GSH), vitamins, and polyphenols are examples of non-enzymatic antioxidants. This defence mechanism is overpowered by excessive ROS production in a number of clinical diseases, including cancer, diabetes, neurodegeneration, and inflammation. This results in DNA damage, protein oxidation, and lipid peroxidation. According to in vivo research, ellagic acid efficiently reverses these mechanisms by lowering oxidative damage indicators and re-establishing the balance of antioxidant enzymes (Rahimi Naiini *et al*., 2024).

Superoxide Dismutase (SOD) modulation

The first line of enzymatic protection against oxidative stress is superoxide dismutase, which catalyses the transformation of superoxide anions into molecular oxygen and hydrogen peroxide. SOD activity is frequently markedly decreased in animal models exposed to oxidative stress, such as chemically induced toxicity, carcinogenesis, or inflammation. It has been demonstrated that ellagic acid administration dramatically increases SOD activity in plasma and tissues, such as the liver, kidney, brain, and tumour tissues. This improvement makes it easier to effectively detoxify superoxide radicals, which stops oxidative cascades from occurring later. The importance of ellagic acid in bolstering early-stage antioxidant defence is shown by the increase of SOD activity after treatment (Duckworth *et al*., 2023; Liu *et al*., 2023).

Increased Activity of Catalase (CAT)

In order to stop the buildup of this potentially dangerous oxidant, catalase is essential for breaking down hydrogen peroxide into water and oxygen. According to in vivo research, oxidative stressors are linked to decreased catalase activity, which results in cellular damage caused by hydrogen peroxide. Catalase activity has been shown to be restored or increased by ellagic acid treatment, especially in hepatic and renal tissues. Ellagic acid helps preserve redox equilibrium and guards against oxidative damage to cellular constituents by encouraging the effective elimination of hydrogen peroxide. Given that persistent oxidative stress plays a role in the development and spread of tumours, this impact is particularly pertinent to cancer prevention (Türkmen *et al*., 2022).

Glutathione Reductase (GR) and Glutathione Peroxidase (GPx) Regulation

An essential part of intracellular antioxidant defence is the glutathione system. Using reduced Glutathione (GSH) as a substrate, glutathione peroxidase catalyses the reduction of hydrogen peroxide and lipid hydroperoxides, whereas glutathione reductase restores GSH from its oxidised state. It has been repeatedly shown in in vivo experimental models that ellagic acid maintains intracellular GSH levels via increasing GPx and GR activity. Under oxidative stress, this glutathione redox cycle reinforcement is essential for preserving overall cellular integrity and shielding cellular membranes from lipid peroxidation.

Preservation of Lower Glutathione (GSH) Levels

One important non-enzymatic antioxidant that scavenges free radicals directly and acts as a cofactor for antioxidant enzymes is reduced glutathione. GSH is usually depleted as a result of oxidative stress, which compromises cellular defences. GSH levels in a variety of tissues have been demonstrated to be considerably raised or restored by ellagic acid administration. Improved recycling through glutathione reductase, decreased oxidative consumption, or increased glutathione synthesis might all be responsible for this impact. GSH level maintenance is especially crucial for detoxification procedures and defence against oxidative damage brought on by carcinogens (Peng *et al*., 2023).

Decrease in Oxidative Stress Indicators

Apart from modifying enzymes, ellagic acid efficiently lowers oxidative stress indicators in vivo. After ellagic acid therapy, studies consistently show lower levels of Malondialdehyde (MDA) and other lipid peroxidation products. Reduced membrane lipid degradation and enhanced cellular stability are shown by lower levels of these markers. Ellagic acid's systemic antioxidant properties have also been confirmed by its association with decreased oxidative DNA damage and protein carbonyl concentration (Baradaran Rahimi *et al*., 2020; Islam *et al*., 2025).

Mechanism of Enzyme Modulation

It is thought that ellagic acid's capacity to alter endogenous antioxidant enzymes involves controlling redox-sensitive transcription factors and signalling pathways that control the expression of antioxidant genes. Instead of only serving as a temporary radical scavenger, ellagic acid encourages adaptive activation of antioxidant defences by reducing oxidative stress and preserving cellular redox equilibrium. By regulating endogenous antioxidant enzymes such as SOD, catalase, GPx, and GR while preserving decreased glutathione levels, ellagic acid has strong protective benefits, as in vivo antioxidant studies unequivocally show. Together, these activities lower oxidative stress indicators, safeguard cellular macromolecules, and enhance ellagic acid's chemoprotective and anticancer properties. The importance of ellagic acid as a physiologically potent antioxidant obtained from medicinal plants is highlighted by the improvement of intrinsic antioxidant defence mechanisms (Elseweidy *et al*., 2022).

Potential of Ellagic acid as an Anticancer Agent

A promising polyphenol generated from plants, ellagic acid has strong anticancer potential. Several characteristics of cancer, such as unchecked cell proliferation, resistance to apoptosis,

invasion, metastasis, and angiogenesis, are targeted by ellagic acid, according to a wealth of experimental data from *in vitro* and in vivo investigations. Ellagic acid is particularly appealing for cancer prevention and adjuvant therapy because, in contrast to traditional cytotoxic drugs, it uses multi-targeted molecular pathways to produce its anticancer effects (Guo *et al.*, 2023; Zheng *et al.*, 2025; Peker *et al.*, 2021; Pardo-Peña *et al.*, 2023).

Anticancer Molecular Mechanisms of Action

By altering a number of intracellular signalling pathways implicated in tumour growth, cell survival, and proliferation, ellagic acid has anticancer properties. Together, these intricately linked processes help to inhibit the growth of tumours and the development of cancer.

Cause of Apoptosis

Programmed cell death, or apoptosis, is a strictly controlled process that is necessary to get rid of damaged or aberrant cells. The capacity of ellagic acid to specifically cause apoptosis in cancer cells while preserving healthy cells is one of its most important anticancer strategies. Both the internal (mitochondrial) and extrinsic (death receptor-mediated) apoptotic pathways are triggered by ellagic acid. In the intrinsic process, cytochrome c is released into the cytosol when ellagic acid alters the potential of the mitochondrial membrane. Apoptotic cell death is the final outcome of this process, which also activates caspase-9 and downstream effector caspases like caspase-3. Furthermore, by upregulating pro-apoptotic proteins (like Bak and Bax) and downregulating anti-apoptotic proteins (such Bcl-2 and Bcl-xL), ellagic acid alters the expression of proteins that regulate apoptosis. This change in the ratio of Bax to Bcl-2 promotes apoptosis in the mitochondria. Additionally, it has been demonstrated that ellagic acid promotes chromatin condensation and DNA fragmentation, two characteristics of apoptotic cell death (Gorgisen *et al.*, 2020; Baradaran Rahimi *et al.*, 2020; Islam *et al.*, 2025; Cota and Patil, 2023; Altındağ *et al.*, 2021; Guo *et al.*, 2023).

Arrest in the Cell Cycle

One characteristic that distinguishes cancer cells is their unchecked cell cycle development. By causing cell cycle arrest at certain checkpoints, ellagic acid inhibits the growth of cancer cells and has potent anticancer effects. According to experimental research, depending on the kind of cancer cell and the dosage employed, ellagic acid can stop the cell cycle at the G0/G1, S, or G2/M stages. The control of important cell cycle-related proteins, including as cyclins, Cyclin-Dependent Kinases (CDKs), and CDK inhibitors, mediates this pause. Ellagic acid upregulates CDK inhibitors like p21 and p27 while downregulating cyclins like cyclin D1 and cyclin B1. Consequently, the retinoblastoma protein's phosphorylation is suppressed, which stops the cell cycle from progressing to later stages. Prolonged cell cycle arrest strengthens apoptotic signaling's anticancer effects by sensitising cancer cells to it (Pieróg *et al.*, 2021).

Anti-Metastatic and Anti-Proliferative Impacts

By inhibiting the signalling pathways that support the development and survival of cancer cells, ellagic acid has strong anti-proliferative properties. It lowers the expression of proteins involved in cellular proliferation and disrupts growth factor-mediated signalling. In addition to preventing proliferation, ellagic acid severely hinders the migration and invasion of cancer cells, two processes that are essential for metastasis. It lowers the production and activity of Matrix Metalloproteinases (MMPs), which are the enzymes that break down the basement membrane and extracellular matrix. Ellagic acid prevents tumour cells from invading nearby tissues and distant organs by blocking MMPs. Additionally, ellagic acid affects the Epithelial-Mesenchymal Transition (EMT), a process linked to a higher risk of metastasis. By preserving epithelial properties and inhibiting mesenchymal indicators, ellagic acid helps to lessen the tendency of cancer cells to spread.

Anti-Angiogenic Properties

The development of new blood vessels, or angiogenesis, is necessary for tumour growth, metastasis, and nutrition delivery. Ellagic acid limits the growth of tumours by having strong anti-angiogenic actions. Vascular Endothelial Growth Factor (VEGF) and other pro-angiogenic mediators are among the important angiogenic factors whose expression is suppressed by ellagic acid. Endothelial cell migration, proliferation, and tube formation—all essential processes in angiogenesis—are disrupted by ellagic acid's inhibition of VEGF signalling. Furthermore, ellagic acid lowers inflammation and oxidative stress in the tumour microenvironment, two factors that are

Table 3: Anticancer Effects of Ellagic Acid on Specific Cancer Types.

Cancer Type	Major Anticancer Effects	Key Mechanisms
Breast cancer	Inhibition of proliferation and metastasis	Apoptosis induction, cell cycle arrest, MMP inhibition
Prostate cancer	Growth suppression and chemoprevention	Oxidative stress reduction, apoptosis, anti-angiogenic effects
Colon cancer	Tumor growth inhibition and prevention	Apoptosis, anti-inflammatory action, oxidative damage reduction
Lung cancer	Suppression of tumor progression	Antioxidant activity, apoptosis, anti-metastatic effects
Skin cancer	Photoprotection and chemoprevention	UV-induced oxidative stress reduction, DNA protection, apoptosis

Table 4: Role of Ellagic Acid in Cancer Prevention.

Aspect of Cancer Prevention	Mechanism of Action of Ellagic Acid	Molecular/ Cellular Targets	Preventive Outcome
Initiation phase inhibition	Scavenging of ROS and RNS	Superoxide, hydroxyl radicals, nitric oxide	Reduced oxidative mutations
Inhibition of carcinogen activation	Suppression of phase I enzymes	Cytochrome P450 enzymes	Reduced formation of reactive carcinogens
Enhancement of detoxification	Induction of phase II enzymes	Glutathione-S-transferase, UDP-glucuronyl transferase	Increased elimination of carcinogens
Anti-inflammatory action	Reduction of chronic inflammation	Pro-inflammatory mediators	Suppression of tumor promotion
Regulation of cell proliferation	Control of abnormal cell growth	Cell cycle regulatory proteins	Prevention of clonal expansion
Induction of apoptosis	Elimination of damaged cells	Pro- and anti-apoptotic proteins	Removal of pre-malignant cells
Antioxidant enzyme modulation	Strengthening endogenous defense	SOD, CAT, GPx, GSH	Sustained redox homeostasis
Protection against DNA damage	Prevention of oxidative DNA lesions	DNA bases, chromosomal integrity	Reduced mutagenesis
Inhibition of angiogenesis	Limitation of blood vessel formation	Angiogenic mediators	Restricted tumor nourishment
Anti-metastatic potential	Suppression of invasion and migration	Extracellular matrix-degrading enzymes	Prevention of malignant progression
Maintenance of genomic stability	Support of DNA repair mechanisms	DNA repair enzymes	Long-term cancer risk reduction

known to encourage angiogenesis. When oxidative stimuli and angiogenic signalling are inhibited together, blood vessel creation is compromised, which eventually deprives tumours of oxygen and nutrition. Through a variety of molecular pathways, such as apoptosis induction, cell cycle arrest, metastasis and proliferation inhibition, and angiogenesis suppression, ellagic acid has strong anticancer action. Ellagic acid's promise as a natural chemopreventive and therapeutic agent is highlighted by these complimentary activities, which allow it to target cancer progression at different stages. Ellagic acid is a viable option for additional research in cancer prevention and adjuvant anticancer therapy because of its multi-targeted mechanism of action and minimal toxicity (Peng *et al.*, 2023; Wu *et al.*, 2025).

Impact of Ellagic acid on Particular Cancer Types

In experimental animals, ellagic acid has shown broad-spectrum anticancer efficacy against a variety of cancer types (Table 3). Modification of oxidative stress, apoptosis, cell cycle control, inflammation, angiogenesis, and pathways linked to metastasis influence its effects (Figure 3). Depending on the tumour microenvironment, metabolic variables, and tissue-specific signalling pathways, ellagic acid's anticancer effectiveness differs depending on the kind of cancer. Experimental data supports its effects on major malignancies, which are summarised in the next subsections (Islam *et al.*, 2025; Cota and Patil, 2023; Altındağ *et al.*, 2021; Guo *et al.*, 2023).

Breast Cancer

In terms of ellagic acid action, breast cancer is among the most researched cancer forms. By altering both estrogen-dependent and estrogen-independent pathways, ellagic acid has potent anti-proliferative and pro-apoptotic effects on breast cancer cell lines. By triggering intrinsic apoptotic pathways and causing cell cycle arrest, often at the G0/G1 or G2/M phase, ellagic acid suppresses the development of cancer cells. It modifies the expression of proteins that regulate apoptosis, reducing anti-apoptotic proteins and boosting pro-apoptotic factors. Furthermore, ellagic acid inhibits inflammatory signalling and oxidative stress, both of which are known to accelerate the growth of breast tumours. Through the inhibition of matrix metalloproteinases and disruption of the epithelial-mesenchymal transition, ellagic acid has been demonstrated to impede the migration and invasion of breast cancer cells. These outcomes point to ellagic acid's possible function in halting the spread and recurrence of breast cancer.

Prostate Cancer

Ellagic acid exhibits notable growth-inhibitory and chemopreventive effects in models of prostate cancer. Ellagic

acid modulates androgen signalling, oxidative stress, and chronic inflammation, all of which are directly linked to the evolution of prostate cancer. By causing apoptosis and cell cycle arrest, which are frequently accompanied by mitochondrial malfunction and caspase activation, ellagic acid prevents the growth of prostate cancer cells. Additionally, it lessens oxidative DNA damage, which is a major factor in the development of prostate cancer. Furthermore, ellagic acid inhibits inflammation linked to tumours and tampers with angiogenic signalling, which helps to slow the growth and spread of tumours. These results provide credence to ellagic acid's possible application as a dietary chemopreventive therapy for prostate cancer.

Colon cancer

Colon cancer is a pertinent target for ellagic acid management since it is closely associated with oxidative stress, inflammation, and dietary variables. In colon cancer cells, ellagic acid and its gut microbial metabolites have strong anti-proliferative and pro-apoptotic actions. By causing cell cycle arrest and triggering apoptotic signalling pathways, ellagic acid suppresses the development of colon cancer cells. Additionally, it contributes to chemoprevention by lowering oxidative DNA damage and lipid peroxidation in colon tissues. Additionally, by preventing the breakdown of extracellular matrix, ellagic acid inhibits the invasion of cancer cells and lowers inflammatory mediators implicated in colon carcinogenesis. The usefulness of ellagic acid in preventing colon cancer is further enhanced by its capacity to act locally in the gastrointestinal system.

Lung Cancer

High levels of oxidative stress and aggressive metastatic behaviour are hallmarks of lung cancer. In lung cancer models, ellagic acid has demonstrated encouraging anticancer benefits, especially through its anti-inflammatory and antioxidant properties. Ellagic acid inhibits the advancement of the cell cycle and induces apoptosis, which decreases the growth of lung cancer cells. Additionally, it inhibits signalling pathways triggered by oxidative stress that support tumour development and survival. Ellagic acid has been shown to prevent lung cancer cells from migrating and invading in experimental animals, suggesting that it may have anti-metastatic properties. Ellagic acid helps to inhibit the growth of lung tumours by lowering oxidative damage and altering signalling pathways that promote tumour growth.

Skin Cancer

The development of skin cancer is closely linked to oxidative stress, DNA damage, and inflammation brought on by Ultraviolet (UV) radiation. In models of skin cancer, ellagic acid has significant photoprotective and chemopreventive benefits. By scavenging free radicals and boosting natural antioxidant defences, ellagic acid shields skin cells from UV-induced oxidative damage. It lessens DNA damage, prevents aberrant cell division, and encourages damaged or altered skin cells to undergo apoptosis. Additionally, ellagic acid inhibits angiogenic factors and inflammatory mediators that contribute to the formation of skin tumours. These characteristics demonstrate its potential application in dietary and topical skin cancer prevention techniques.

Numerous cancer types, including those of the breast, prostate, colon, lung, and skin, are significantly inhibited by ellagic acid. Its capacity to target several cancer-related pathways, including inflammation, angiogenesis, oxidative stress, apoptosis, and metastasis, highlights its promise as a broad-spectrum natural anticancer drug. These results lend credence to the idea that ellagic acid may be used to prevent cancer and as a supplement to traditional cancer treatments.

Role of Ellagic Acid in Cancer Prevention

Prior to the onset of clinically observable illness, cancer prevention aims to inhibit or postpone the beginning, development, and advancement of carcinogenesis. A polyphenol produced from nutritional and medicinal plants, ellagic acid has drawn a lot of interest as a natural chemopreventive agent (Table 4). Long-term antioxidant, anti-inflammatory, and gene-regulatory effects rather than immediate cytotoxicity are what give it its preventative potential. Because it protects against DNA damage, modulates important signalling pathways, and has chemopreventive properties, ellagic acid can be interpreted as having a function in preventing cancer.

Mechanisms of Ellagic Acid Chemoprevention

Chemoprevention is the process of preventing cancer at different stages by using natural or synthetic chemicals. Ellagic acid has multi-stage chemopreventive action, meaning it works at the beginning, middle, and end stages of the formation of cancer. Ellagic acid neutralises reactive oxygen and nitrogen species that lead to DNA mutations and lowers oxidative stress during the beginning stage. It stops carcinogenic intermediates from forming by chelating metal ions and scavenging free radicals. Additionally, by blocking phase I enzymes that activate pro-carcinogens and boosting phase II detoxifying enzymes, ellagic acid reduces carcinogen bioactivation via modulating the activity of xenobiotic-metabolizing enzymes.

The well-known cause of tumour promotion, chronic inflammation, is suppressed by ellagic acid during the promotion stage. Both prolonged cell proliferation and the synthesis of inflammatory mediators are inhibited. Ellagic acid inhibits angiogenesis, invasion, and metastasis throughout the progression stage, which stops malignant transformation and tumour growth. A crucial prerequisite for chemopreventive drugs meant for long-term use is that ellagic acid exhibits these actions without seriously harming healthy cells (Elseweidy *et al.*, 2022; Peng *et al.*, 2023; Wu *et al.*, 2025; Raj *et al.*, 2024; Al-Hoshary and Zalzala, 2023).

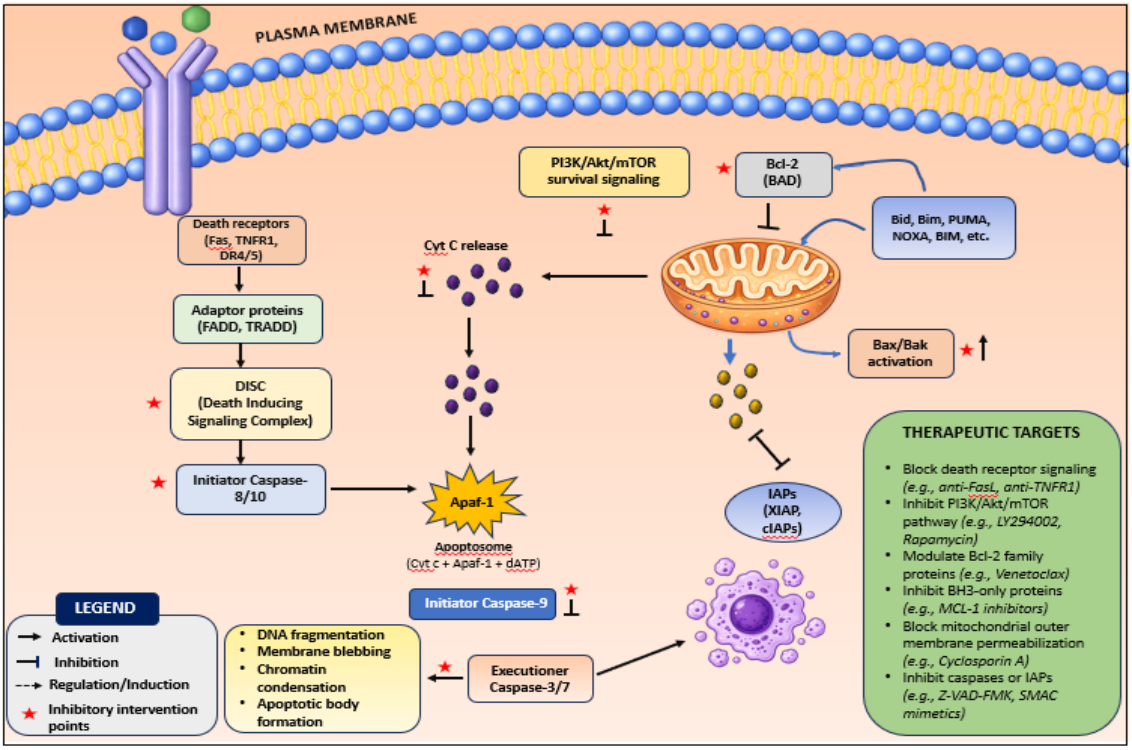

Figure 3: Schematic depiction of apoptosis signaling pathways, illustrating the interplay between death receptor-mediated (extrinsic) signaling and mitochondrial (intrinsic) pathways, including DISC formation, cytochrome c release, PI3K/Akt/mTOR modulation, Bcl-2 family regulation, caspase activation, and execution of apoptotic cell death.

Alteration of Carcinogenesis-Related Signalling Pathways

Ellagic acid is essential for preventing cancer because it modulates several cell signalling pathways that control oxidative stress, inflammation, cell division, apoptosis, and survival. The development of cancer frequently results in dysregulation of several mechanisms. Ellagic acid inhibits inflammation-related and redox-sensitive pathways that encourage the development and spread of tumours. Through the preservation of cellular redox equilibrium, it stops the abnormal activation of transcription factors that lead to neoplastic transformation. Additionally, ellagic acid promotes cytoprotective signalling, which aids in DNA repair, antioxidant defence, and cellular homeostasis. Furthermore, ellagic acid ensures that damaged or mutant cells do not survive or multiply by modulating pathways that govern apoptosis and cell cycle regulation. The cellular environment is changed from a pro-carcinogenic state to a protective and homeostatic state by ellagic acid through the coordinated control of various signalling networks, which lowers the risk of cancer.

Guarding Against DNA Damage

One important beginning event in carcinogenesis is DNA damage. Base alterations, chromosomal instability, and DNA strand breaks can be caused by radiation, reactive oxygen species, environmental pollutants, and endogenous metabolic wastes. Ellagic acid is essential for shielding genetic material against harm of this kind. Through scavenging radicals before they interact with DNA, ellagic acid lessens oxidative DNA damages. Additionally, it prevents aldehydes that can create DNA adducts from being produced by lipid peroxidation. Additionally, ellagic acid stimulates DNA repair mechanisms and increases the activity of cellular antioxidant enzymes, which limits the accumulation of mutations.

Ellagic acid has been repeatedly demonstrated in experiments to lower levels of indicators linked to oxidative DNA damage, including oxidised nucleobases and strand breaks. In the long run, ellagic acid helps prevent cancer by disrupting the initial stages of carcinogenesis and maintaining genetic integrity.

By modulating signalling pathways linked to carcinogenesis, chemopreventive activities, and strong protection against DNA damage, ellagic acid contributes significantly to the prevention of cancer. Ellagic acid is a promising natural agent for long-term cancer prevention because of its capacity to function at several stages of cancer formation, low toxicity, and dietary availability. Its possible use in preventive dietary regimens and functional formulations targeted at lowering cancer risk is supported by a wealth of mechanistic research (Zheng *et al.*, 2025; Peker *et al.*, 2021; Pardo-Peña *et al.*, 2023; Cheshomi *et al.*, 2021; Chambers *et al.*, 2020).

FUTURE PERSPECTIVES

Ellagic acid should be studied in chemoprevention trials, with attention to selected design factors like chemical specificity and formulation capacity; if successful at preventing malignancy, focus could shift toward elucidating the biochemical base for cancer protection. Exploratory supplementation studies need to be replaced with well-designed, hypothesis-driven clinical trials with clearly defined endpoints designed to yield high-quality evidence. Promising targets of research lie in chemoprevention within susceptible populations, administration of ellagic acid as an adjunct to improve the therapeutic efficacy or tolerability of conventional treatments, and biomarker-centric assessment of response to treatment. In vivo discovery of a novel anticancer sy-basicity *in vitro* may allow to circumvent intestinal dexmedetomidine concentration, enteral fluid tolerance and stable antiplatelet effect. Adding validated surrogate biomarkers — so-called indicators of oxidative stress, inflammation, DNA damage and angiogenesis — will help establish biological activity as well as therapeutic relevance. Addressing the primary shortcoming of low oral bioavailability continues to be paramount; therefore, a two-pronged focus needs to be applied where structure-property optimization (e.g., prodrug and semi-synthetic strategies) should become integrated with delivery systems including lipid carriers, polymeric nanoparticles, and phospholipid complexes. similarly harmonized PK/PD endpoints will allow meaningful formulation comparisons. To elucidate on pleiotropic mechanisms and ensure the discovery of predictive biomarkers, systems-level investigations aided by omics technologies are warranted. Future approaches should incorporate gut microbiota-mediated variability for stratification of patients according to metabotype and give microbiome-based co-therapies.

CONCLUSION

Ellagic acid has evolved from a dietary polyphenol of interest, to a leading chemopreventive and anticancer tool with increasingly robust mechanistic support. Its pleiotropic biological activities—spanning oxidative stress, inflammation, apoptosis, cell cycle regulation and angiogenesis—highlight its therapeutic potential in oncology and integrative care. However, despite compelling preclinical evidence, clinical translation continues to be hampered by factors including poor oral bioavailability, intersubject variability in metabolism and lack of long-term data in humans. To fully unlock its therapeutic potential, a coordinated, multidisciplinary translational approach that encompasses chemistry and formulation science as well as systems biology and precision medicine is warranted. Ellagic acid has a realistic potential as either a chemopreventive or adjuvant agent in cancer treatment with robust clinical validation and rational optimization.

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ABBREVIATIONS

ABTS: 2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic Acid); **AP-1:** Activator Protein-1; **Bax:** Bcl-2-Associated X Protein; **Bcl-2:** B-cell Lymphoma 2; **CAT:** Catalase; **CDKs:** Cyclin-Dependent Kinases; **COSY:** Correlation Spectroscopy; **Cu^{2+}:** Copper Ion; **CYP450:** Cytochrome P450; **DMSO:** Dimethyl Sulfoxide; **DNA:** Deoxyribonucleic Acid; **Apaf-1:** Apoptotic Protease Activating Factor 1; **DISC:** Death-Inducing Signaling Complex; **DPPH:** 2,2-Diphenyl-1-picrylhydrazyl; **EMT:** Epithelial-Mesenchymal Transition; **Fe^{2+}:** Ferrous Ion; **Fe^{3+}:** Ferric Ion; **FRAP:** Ferric Reducing Antioxidant Power; **GPx:** Glutathione Peroxidase; **GR:** Glutathione Reductase; **GSH:** Reduced Glutathione; **HBV:** Hepatitis B Virus; **HCV:** Hepatitis C Virus; **HHDP:** Hexahydroxydiphenoyl; **HPLC:** High-Performance Liquid Chromatography; **HSQC:** Heteronuclear Single Quantum Coherence; **HMBC:** Heteronuclear Multiple Bond Correlation; **IL:** Interleukin; **IL-1β:** Interleukin-1 Beta; **IL-6:** Interleukin-6; **IL-12:** Interleukin-12; **LC-MS:** Liquid Chromatography-Mass Spectrometry; **LOD:** Limit of Detection; **LOQ:** Limit of Quantification; **MAE:** Microwave-Assisted Extraction; **MDA:** Malondialdehyde; **MMP:** Matrix Metalloproteinase; **MMP-2:** Matrix Metalloproteinase-2; **MMP-9:** Matrix Metalloproteinase-9; **NF-κB:** Nuclear Factor Kappa B; **NMR:** Nuclear Magnetic Resonance; **NO:** Nitric Oxide; **NQO1:** NAD(P)H Quinone Dehydrogenase 1; **ORAC:** Oxygen Radical Absorbance Capacity; **pKa:** Acid Dissociation Constant; **PPAR:** Peroxisome Proliferator-Activated Receptor; **PPAR-γ:** Peroxisome Proliferator-Activated Receptor Gamma; **PTLC:** Preparative Thin-Layer Chromatography; **RNS:** Reactive Nitrogen Species; **ROS:** Reactive Oxygen Species; **SOD:** Superoxide Dismutase; **TEAC:** Trolox Equivalent Antioxidant Capacity; **TIMP-2:** Tissue Inhibitor of Metalloproteinases-2; **TLC:** Thin-Layer Chromatography; **TNF-α:** Tumor Necrosis Factor Alpha; **UAE:** Ultrasound-Assisted Extraction; **UV-Vis:** Ultraviolet-Visible Spectroscopy; **VEGF:** Vascular Endothelial Growth Factor; **FADD:** Fas-Associated Protein with Death Domain; **FOXO3a:** Forkhead Box O3; **HSC:** Hepatic Stellate Cells; **NF-κB:** Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells; **RUNX3:** Runt-Related Transcription Factor 3; **STAT3:** Signal Transducer and Activator of Transcription 3; **TRADD:** TNFRSF1A-Associated via Death Domain; **UDP:** Uridine Diphosphate.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

R.T.: Conceptualization, literature survey, data curation, manuscript drafting, critical revision, and overall supervision of the review; M.D.I.A.-Z.: Literature search, validation of scientific content, and manuscript review; Y.G.B.: Data compilation, organization of references, and contribution to manuscript writing; G.T.: Methodological input, critical editing, and technical review of the manuscript; G.E.N.: Visualization, preparation of tables/figures, and literature support; K.J.N.: Scientific validation, language editing, and manuscript refinement; A.K.: Review of literature, data verification, and critical proofreading; K.Y.T.: Final review, supervision support, and approval of the manuscript. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

KEY FINDINGS

Ellagic Acid (EA) is a polyphenolic dilactone derived from ellagitannins, widely distributed as an important component of fruits and medicinal plants such as berries, pomegranate, almonds and woody tissues.

The review validates the role of oxidative stress in cancer initiation and progression, and EA has been shown to modulate this imbalance through its potent antioxidant activity.

EA demonstrates phytochemical characteristics such as the ability to scavenge free radicals, chelate metal ions, inhibit lipid peroxidation reaction and increase endogenous antioxidants.

Preclinical evidence shows that EA has broad-spectrum anticancer activity by inhibiting angiogenesis and inflammatory signaling, inducing cell cycle arrest and apoptosis, and suppressing tumor proliferation, invasion, and metastasis.

Although EA has promising therapeutic potential, its clinical translation is hampered by poor aqueous solubility, low oral bioavailability and rapid metabolism.

In summary, EA appears to be a potent natural antioxidant and chemopreventive phytoconstituent that holds strong potential for further development of anticancer modalities targeting oxidative stress-mediated pathways.

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