NANOPARTICLE

Review Article

A Comprehensive Review on Pharmacological Activities of Ellagic Acid and its Applications

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ABSTRACT

Ellagic acid is a potent antioxidant with a unique chemical structure contributing to its wide range of biological activities. Its presence in various fruits and vegetables makes it an important dietary component for promoting health and preventing disease. Understanding its structure helps appreciate its role in various physiological processes and potential therapeutic applications. The primary source of production is the hydrolysis of ellagitannins, which are a broadly distributed category of secondary metabolites. Ellagic Acid is garnering interest because of its notable antioxidant, and anti-inflammatory, characteristics. Ellagic Acid has been extensively documented for its anticancer, cardioprotective, hepatoprotective, and neuroprotective effects. This review examines the health-enhancing properties of Ellagic Acid and explores the potential mechanisms through which it contributes to health maintenance. Additionally, it emphasizes analytical techniques for ellagic acid measurement and determining Ellagic acid with spectrophotometric methods. It summarizes existing literature regarding the therapeutic potential of this polyphenolic compound in addressing various human diseases.

Keywords: Ellagic Acid, Analytical Techniques, Polyphenolic Compounds, Spectrophotometric Methods

INTRODUCTION

Ellagic acid (EA) is a polyphenolic compound known for its strong anti-inflammatory, anti-cancer, and antioxidant qualities. Several fruits and plants contain EA, which has been thoroughly researched for its potential to treat complex illnesses like cancer, heart disease, and neurological disorders. EA has been shown in numerous studies published in respectable journals, including Oxidative Medicine and Cellular Longevity and Antioxidants, to play a part in lowering

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oxidative stress, regulating inflammatory pathways, and bolstering physiological defenses. Notwithstanding its encouraging pharmacological characteristics, EA's limited aqueous solubility, quick metabolism, and poor bioavailability have all impeded its clinical translation.

The limitations of EA have been the subject of numerous studies that have looked into a variety of delivery systems, such as oral formulations and simple extractions. These methods have demonstrated some promise, but they are unable to deliver consistent therapeutic results, especially in applications that require long-term stability or targeted delivery. Consequently, it is imperative to cultivate novel approaches that can enhance the therapeutic effectiveness of EA while overcoming its inherent constraints.

This work offers a novel method for functionalizing EA (Ellagic Acid) with nanomaterials using modern nanotechnology. EA's stability, bioavailability, and targeted delivery are enhanced by this integration, enabling precise and regulated therapeutic applications. This study explores the synergistic potential of EA-nanoparticle conjugates in a range of biomedical applications, such as drug delivery, bioimaging, and antioxidant therapies, in contrast to earlier research that mostly concentrated on the standalone properties of EA.

This work is novel in that it addresses important gaps in the clinical applications of EA by methodically optimizing nanomaterial platforms to maximize its potential. This research sets a new standard for the use of natural compounds in precision medicine by overcoming the drawbacks of previous studies and offering long-lasting and incredibly successful therapeutic solutions for difficult health issues.

SOURCES OF EA

Ellagic Acid [EA] shows traits that are indicative of an amphiphilic molecule. Ellagic acid is classified as 2,3,7,8-tetrahydroxy-1-benzopyrano[5,4,3-cd] benzopyran-5,10-dione by the IUPAC. Its structure consists of four hydroxyl groups and a planar biphenyl lipophilic region joined by two lactone rings. These elements form a hydrophilic section together with the lactone groups. Since the hydrophilic part of the EA molecule has donor sites (–OH) and acceptor sites (lactone) for hydrogen bonds, it is essential to the biological action of the compound [1]. Under physiological conditions, the phenolic hydroxyl groups can separate, producing negatively charged phenolate ions. Ellagic acid (EA) can be found in plant cells in two forms: free and covalently bound, where it forms ellagitannins and EA glycosides. The chemical reactivity, solubility, and bioavailability of these substances vary.

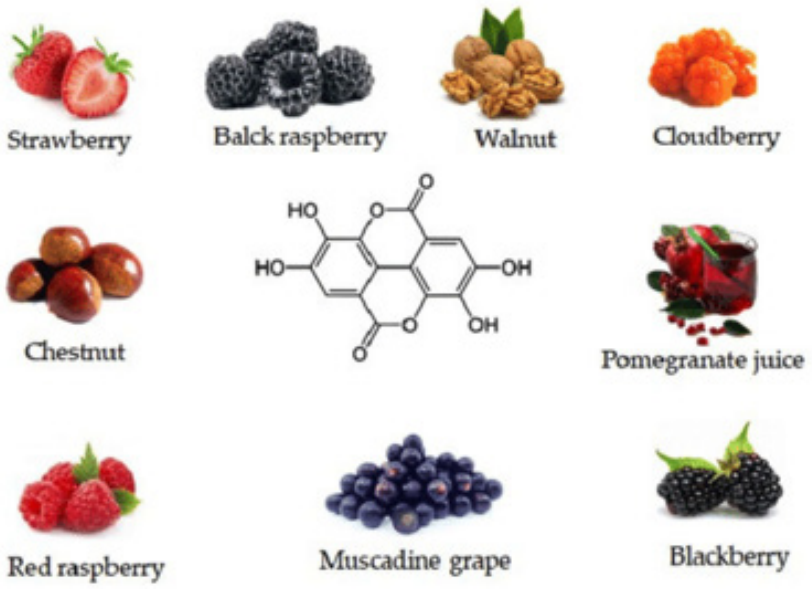

Figure 1. Structure and main foods that contain Ellagic Acid.

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Because of the diverse biological effects of ellagic acid (EA), edible plants (Figure 1) [2] that contain its hydrolyzable derivatives like ellagitannins are important sources of EA that are safe for human consumption. These plants are functional foods, which can improve health and lower disease risk. Studies reveal that many medicinal plant species used in traditional medicine worldwide, such as Ayurveda and TCM, are abundant in ellagitannins and EA. Few plant species are known to contain very high levels of ellagitannins and their derivatives, however, these species are essential natural sources of ellagic acid (EA) for human diets [1]. Interestingly, fruits are the main source of high ellagitannin and EA levels.

The proportion of EA bound to free forms varies significantly among plant species. Furthermore, the percentage of unbound EA may vary according to the analytical techniques used to evaluate it [3]. Although some research suggests that free EA makes up only a small portion of the entire EA pool in plants, other studies suggest that this proportion may account for as much as 50% of the total content. Interestingly, almost 70.6% of the entire EA pool is found in the fruits of Terminalia Ferdinandiana Exell, also referred to as the Kakadu plum, with most of that pool residing in its free form. Strawberries, on the other hand, are said to have a far smaller percentage of free EA, with an estimated 7.4% of their total composition.

The bark and wood of several tree species, such as those belonging to the genus Quercus, Eucalyptus, and Castanea, are known to contain notably high concentrations of ellagic acid (EA). Therefore, there is a chance for the industrial extraction of EA from byproducts from the pomegranate husk and other juice production, as well as from residues from the forestry and wood-processing industries.

DETERMINATION OF EA

Spectrophotometric Methods

Using UV spectroscopy, ellagic acid can be measured by creating a stock solution and locating its absorption maxima, which are typically located at 277 nm. This particular wavelength is then used to assess different dilutions. The method has been verified for linearity, accuracy, and precision, and it follows Lambert-Beer's law within a certain concentration range. This method is a reliable way to identify ellagic acid in a variety of samples, guaranteeing accurate and timely measurement as well as good recovery rates. This technique is valued for its accuracy and ability to handle diverse sample types efficiently [3].

High -Performance Liquid Chromatography (HPLC)

High-Performance Liquid Chromatography (HPLC) is an accurate method for measuring ellagic acid in a variety of sample types. This procedure uses a reversed-phase C18 column in conjunction with a mobile phase that is typically made up of acetonitrile and water with an acid modifier added. Ellagic acid is separated when samples are added to the HPLC system based on how well it binds to the stationary phase in the column. This method is widely used for its accuracy in quantifying ellagic acid in fruits, wines, and other plant-based materials [4].

Ultra -High -Performance Liquid Chromatography (UHPLC)

The sophisticated method referred to as Ultra-High-Performance Liquid Chromatography (UHPLC) is employed for the analysis of ellagic acid across diverse materials. In contrast to conventional High-Performance Liquid Chromatography (HPLC), this technique utilizes a C18 column in conjunction with a high-pressure system, thereby enhancing both the resolution and the speed of the analytical process [4]. The mobile phase generally consists of acetonitrile and water, often supplemented with formic acid. A common detection approach is tandem mass spectrometry (MS/MS), which employs electrospray ionization (ESI) to achieve high levels of sensitivity and specificity. This method is effective for quantifying ellagic acid in complex matrices like wines and plant extracts, ensuring accurate and reproducible results [5].

Gas Chromatography-Mass Spectrometry (GC-MS)

With gas chromatography-mass spectrometry (GC-MS), ellagic acid can be effectively measured. This analytical method entails vaporizing the sample and then using a gas chromatograph to separate its constituent parts. The mass spectrometer ionizes and analyzes the chemicals after they have been separated, providing detailed information about their molecular makeup and structure. GC-MS is very useful for identifying and measuring ellagic acid in complex matrices like food products and plant extracts because of its excellent sensitivity and specificity. This method is particularly useful for its ability to identify and measure trace amounts of ellagic acid with high accuracy [6,7].

Liquid Chromatography-Mass Spectrometry (LC-MS/MS)

Liquid Chromatography-Mass Spectrometry (LC-MS/MS) is a sophisticated analytical technique that combines liquid chromatography (LC) with mass spectrometry (MS) to

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precisely measure and identify substances like ellagic acid. In this procedure, ellagic acid is successfully separated from other components of the sample by liquid chromatography, and its identity and concentration are determined by mass spectrometry, which evaluates the mass-to-charge ratio. This method's remarkable sensitivity and specificity make it very useful for examining complex biological and environmental samples [6]. LC-MS/MS is widely used in pharmaceutical, environmental, and food industries for its accuracy and ability to handle diverse sample types [7].

Capillary Electrophoresis (CE)

Using charge and size as key factors, capillary electrophoresis (CE) is a successful technique for separating and analyzing ellagic acid. By containing ellagic acid inside a thin capillary tube that is exposed to an electric field, this method works. CE is especially well-suited for examining complex biological and environmental samples because of its remarkable sensitivity and resolution. CE is particularly useful for analyzing small sample volumes and provides rapid, efficient separation of ellagic acid from other components [3]. It is widely used in 3.7 pharmaceutical, environmental, and food industries for its precision and versatility [8].

Fluorescence Spectroscopy

Fluorescence spectroscopy uses ellagic acid's natural fluorescence properties to perform extremely sensitive examinations of the substance. This technique detects the light that ellagic acid emits when activated at certain wavelengths, enabling precise quantification even at low quantities. It is particularly useful for the analysis of biological and environmental samples because of its remarkable sensitivity and quick processing speed. Fluorescence spectroscopy is widely applied in pharmaceutical, food, and environmental industries for detecting and quantifying ellagic acid, offering a non-destructive and efficient analytical approach [9].

Nuclear Magnetic Resonance (NMR) Spectroscopy

Nuclear magnetic resonance (NMR) spectroscopy, which makes use of the magnetic properties of the acid's nuclei, is an effective method for studying ellagic acid. This method provides a thorough understanding of ellagic acid's molecular dynamics, structure, and environment. By using a powerful magnetic field to capture nuclear spin interactions, NMR makes precise identification and quantification possible. This method is highly valuable in the pharmaceutical, environmental, and food industries for its ability to provide comprehensive structural insights and high-resolution data [10].

TLC (Thin-Layer Chromatography)

With Thin-Layer Chromatography (TLC), ellagic acid analysis can be carried out successfully and economically. Using this technique, ellagic acid is separated on a glass or plastic plate that has been lightly covered with a stationary phase, most often silica gel. It is possible to isolate ellagic acid based on its affinity for the stationary phase by applying the sample as a spot and allowing a solvent (mobile phase) to ascend through the layer via capillary action. This method is useful for qualitative and semi-quantitative analysis, providing rapid results and requiring minimal sample preparation [11]. TLC is widely used in pharmaceutical, environmental, and food industries for its simplicity and efficiency [8].

Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) and High-Performance Liquid Chromatography (HPLC) are well known for their accuracy, sensitivity, and efficiency when analyzing complex compounds. Although it requires a derivatization procedure, gas chromatography-mass spectrometry (GC-MS) is very useful for examining volatile ellagic acid derivatives. For many assays, spectrophotometric techniques are quick and affordable, but they might not be accurate enough for trace-level analysis. Every analytical approach has pros and downsides of its own, so when choosing one, it's critical to take into account things like sample complexity, sensitivity requirements, and available equipment.

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Table1. Methods of Analysis to Determine Ellagic Acid

Analytical Technique	Description	Sensitivity	Sample Types	Advantages	References
High-Performance Liquid Chromatography (HPLC)	UV detection in chromatographic separation	High	Plant extracts and bodily fluids	High reproducibility and accuracy	[11]
Liquid Chromatography-Mass Spectrometry (LC-MS)	Mass detection combined with HPLC for accurate quantification	Very high	Urine, tissue samples, and plasma	High specificity and sensitivity	[11]
Capillary Electrophoresis (CE)	Separation by electrophoresis according to size and charge	Moderate	Plant extracts and herbal formulations	Low usage of solvents	[12]
Spectrophotometry (UV-Vis)	Utilizing absorbance measurement for quantification	Moderate	Plant extracts and food	Easy and economical	[13]
Nuclear Magnetic Resonance (NMR)	Structural elucidation using magnetic resonance	Moderate	Pure compounds, formulations	Detailed structural information	[14]
Thin Layer Chromatography (TLC)	Compound separation using UV detection on a solid support	Moderate	Crude plant materials and herbal extracts	economical and easy to use	[15]
Fluorescence Spectroscopy	Fluorescent characteristics for identification	High	foods, tissues, and plant extracts.	Real-time monitoring and sensitive detection	[16]
Ultra-High-Performance Liquid Chromatography (UHPLC)	chromatographic method with high resolution and faster throughput	Very High	Plant extracts and bodily fluids	Higher resolution and a quicker analysis time	[17,18]
Gas Chromatography-Mass Spectrometry (GC-MS)	Mass spectrometry in conjunction with chromatographic separation	High	Plant extracts and essential oils	Higher sensitivity and accuracy	[7]

NANOMATERIALS AND ELLAGIC ACID DOPING

Ellagic acid (EA) is a polyphenolic molecule with potent anti-inflammatory, anticancer, and antioxidant qualities. Doping nanomaterials with ellagic acid improves both their biocompatibility and bioactivity. For instance, ellagic acid-functionalized gold nanoparticles (EA-AuNPs) exhibit excellent reactive oxygen species (ROS)-scavenging activity and high dispersion, making them effective in biomedical applications like myocardial infarction treatment [19]. Additionally, EA-AuNPs demonstrate high bactericidal efficacy against multi-drug-resistant bacteria and can disperse biofilms, offering a promising alternative to traditional antibiotics [9]. Because of their enhanced functionality and therapeutic potential, ellagic acid-doped nanomaterials are highly valuable in the pharmaceutical, environmental, and medical fields.

TYPES OF NANOMATERIALS COMMONLY USED WITH ELLAGIC ACID

Metal Oxide Nanoparticles

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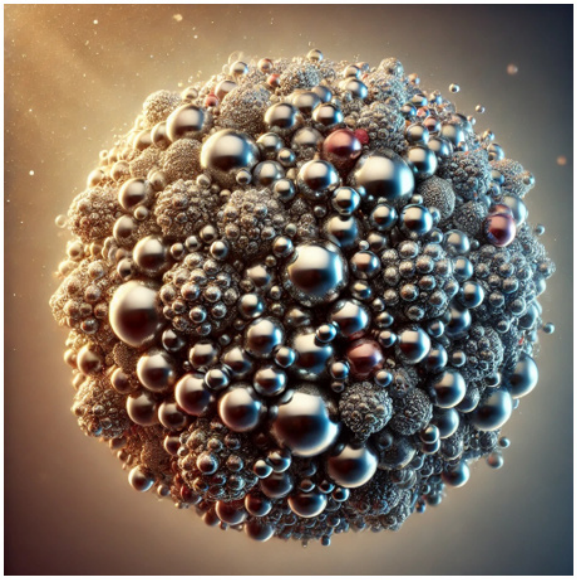

Figure 2. Metal oxide particles.

Ellagic acid can be used to functionalize metal oxide nanoparticles, improving their bioactivity and biocompatibility. Ellagic acid-modified zinc oxide nanoparticles in (Figure 2) (ZnO NPs) have improved antibacterial, photolytic, antioxidant, and UV-blocking capabilities. These altered nanoparticles may also be used in a variety of therapeutic procedures including drug delivery. These nanomaterials are effective in biomedical applications, such as combating multi-drug-resistant bacterial infections and reducing inflammation [20]. The synergistic impact of ellagic acid with metal oxides, including zinc oxide (ZnO), greatly increases the usefulness of these nanomaterials in the pharmaceutical, medical, and environmental domains. Their enhanced functionality, medicinal potential, and photoprotective qualities are the reasons for this improvement.

Metal Nanoparticles

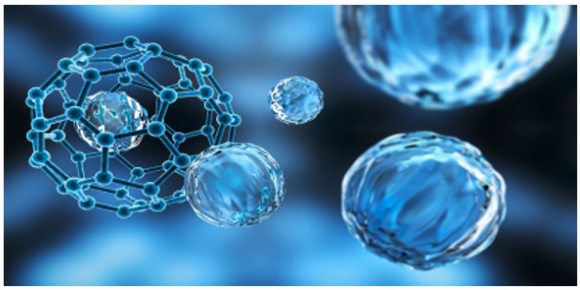

Figure 3. Metal Nanoparticles.

A synergistic effect is produced when ellagic acid is combined with metal oxides (Figure 3)[21], including zinc oxide (ZnO), gold (Au), silver (Ag), and platinum (Pt). These nanoparticles have a lot of promise for use in biomedical applications, especially in the management of bacterial infections that are resistant to drugs and the reduction of inflammation. For instance, ellagic acid-modified AuNPs show high bactericidal efficacy and the ability to disperse biofilms [22]. Additionally, these nanoparticles are used in treating myocardial infarction due to their excellent reactive oxygen species (ROS)-scavenging activity [23]. The addition of ellagic acid to metal nanoparticles greatly improves their therapeutic uses and functioning, making them extremely advantageous in the environmental, medicinal, and pharmaceutical fields. Ellagic acid serves as a capping and reducing agent during the creation of these nanoparticles, forming biocompatible nanostructures with enhanced therapeutic qualities.

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Carbon-Based Nanomaterials

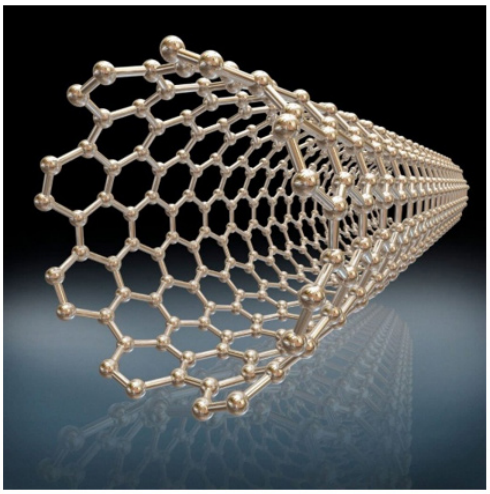

Figure 4. Carbon Nanotubes.

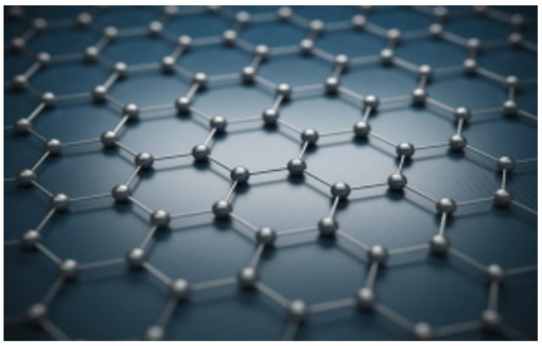

Figure 5. Graphene.

Ellagic acid-modified carbon-based nanomaterials, especially graphene and carbon nanotubes, show enhanced bioactivity and biocompatibility. These nanomaterials show notable effectiveness in several medicinal applications, including medication administration, antioxidant therapy, bioimaging, and managing bacterial infections resistant to many drugs. For instance, ellagic acid-modified graphene in (Figure 5) shows improved antioxidant properties, while ellagic acid-functionalized carbon nanotubes in (Figure 4) demonstrate high bactericidal efficacy [24]. Because of their enhanced functionality and therapeutic potential, ellagic acid-doped carbon-based nanomaterials are highly valuable in the pharmaceutical, environmental, and medical industries. Carbon-based materials can be functionalized with EA to improve their biocompatibility and biological system interaction.

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Polymeric Nanoparticles

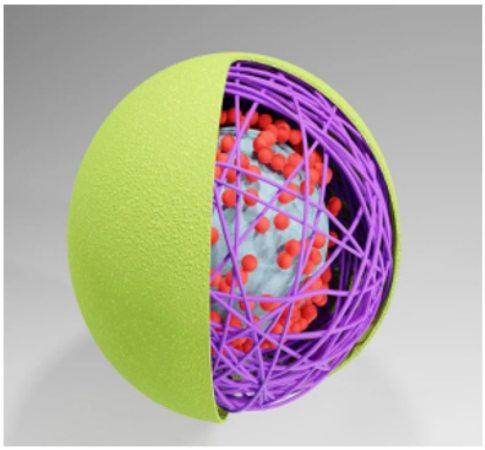

Figure 6. Polymeric Nanoparticles.

The bioavailability and therapeutic effectiveness of ellagic acid are improved by polymeric nanoparticles in (Figure 6)[25] that encapsulate it, such as those made of alginate, chitosan, poly(lactide-co-glycolide) (PLGA), or polycaprolactone (PCL). These nanoparticles improve oral bioavailability, promote wound healing, increase antioxidant capacity, and show anticancer properties. For instance, ellagic acid-loaded PLGA nanoparticles have shown potential in preventing cyclosporine A-induced nephrotoxicity [26]. These nanoparticles are being used more and more in cancer therapy because of their higher cell absorption capabilities and lethal effects on cancer cells. A promising approach for a range of biomedical applications is the integration of ellagic acid into polymeric nanoparticles.

Silica Nanoparticles (SiO_2)

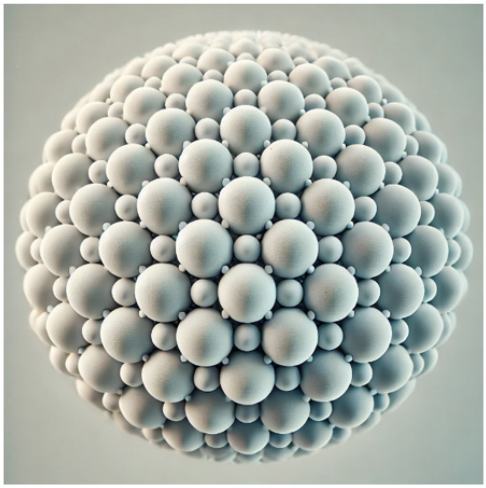

Figure 7. Silica Nanoparticles.

Because of their improved biocompatibility and bioactivity, ellagic acid-functionalized silica nanoparticles in (Figure 7) [27](SiO_2 NPs) show great promise for a range of applications [28]. In the fields of drug delivery, antioxidant therapy, and the avoidance of bacterial infections resistant to several drugs, these nanoparticles show great promise. In particular, ellagic acid-modified SiO_2 nanoparticles exhibit exceptional antioxidant properties and possible therapeutic uses [29]. They are also appropriate for application in environmental remediation and biological imaging due to their large surface area and simplicity of functionalization. A promising approach for a range of pharmacological, environmental, and therapeutic uses is the combination of ellagic acid and silica nanoparticles.

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Table 2. Comparison of Ellagic Acid (EA) – Nanomaterials systems and their Applications

Nanomaterial System	Properties	Applications	Advantages	References
Carbon-Based Nanomaterials(CNTs)	Excellent conductivity and a large surface area	Biosensors, cancer treatment, and drug delivery	High biocompatibility and drug-loading capability	[30]
Metal Nanoparticles (e.g., gold , silver)	High reactivity and adjustable optical characteristics	Antimicrobial agents and anticancer therapy	Surface plasmon resonance and high stability	[31]
Metal oxide Nanoparticles (e.g., ZnO, TiO2)	Photocatalysis and antimicrobial properties	Cancer treatment, antimicrobials, and antioxidants	ROS production and high biocompatibility	[32]
Mesoporous Silica Nanoparticles (MSNs)	Variable pore size and large pore volume	Gene therapy and medication delivery	High stability and regulated medication release	[33]
Polymeric Nanoparticles	Biodegradable, adjustable release characteristics	anti-inflammatory and medication administration	Polymers that are biocompatible and adaptable	[34]

Methods of Doping Nanomaterials with Ellagic Acid

Ellagic acid doping of nanomaterials entails adding EA either during or after the nanomaterials' synthesis. Here are a few typical techniques:

In-Situ Synthesis (Co-Precipitation)

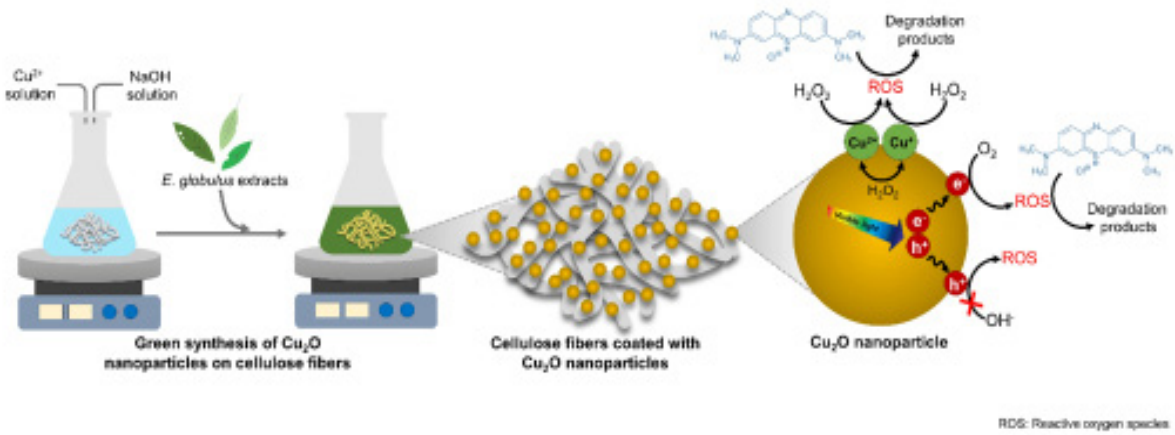

Figure 8. Copper Oxide Nanoparticle preparation by using In-situ Synthesis.

Co-precipitation or in-situ synthesis is an effective method for doping nanomaterials with ellagic acid. With this method, nanoparticles can be generated and functionalized simultaneously in a single step. Usually, ellagic acid and metal salts are dissolved in a solvent, and then a precipitating agent is added to help the nanoparticles form. By incorporating ellagic acid molecules into the nanoparticle framework, this synthesis technique enhances the biocompatibility and bioactivity of the particles [35]. This technique is frequently used to create metal and metal oxide nanoparticles, such as zinc, gold, or silver oxide nanoparticles [36] in (Figure 8) [37]. Antioxidant treatments, drug delivery systems, and the management of bacterial infections resistant to many drugs are among the possible uses. The co-precipitation method is used because it is easy to use, economical, and produces high-quality nanomaterials. Additionally, the green manufacturing of nanoparticles is made possible by ellagic acid's inherent stabilizing and reducing properties.

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Surface Functionalization or Adsorption

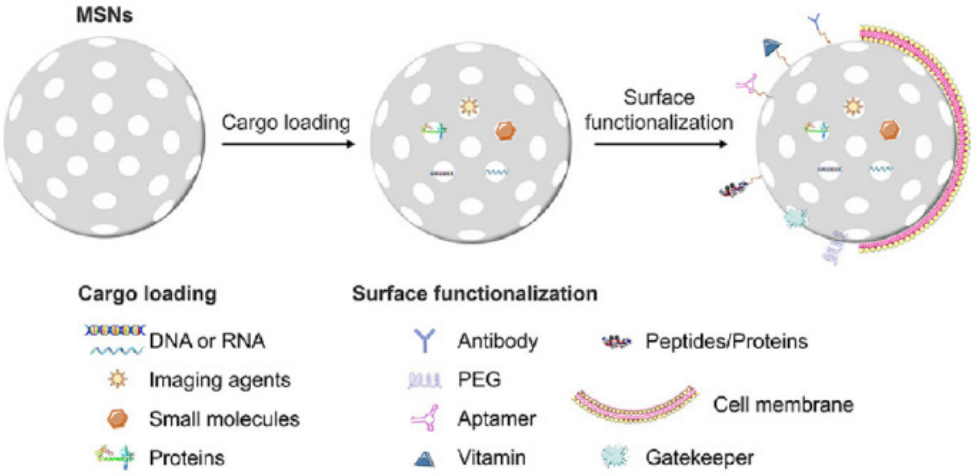

Figure 9. Doping of Nanoparticle by Surface Functionalization.

The process known as surface functionalization or adsorption doping involves attaching ellagic acid molecules to the surfaces of nanoparticles to improve the characteristics of nanomaterials. Physical adsorption techniques or chemical bonding are usually used in this process in the (Figure 9) [38]. Ellagic acid-modified nanoparticles exhibit improved antioxidant activity, increased biocompatibility, and improved therapeutic efficacy. For instance, ellagic acid-modified gold nanoparticles (EA-AuNPs) show high bactericidal efficacy and the ability to disperse biofilms, making them effective against multi-drug-resistant bacteria [39]. The stability and bioavailability of therapeutic drugs are greatly improved by ellagic acid, which makes these nanoparticles essential parts of drug delivery systems. Enhancing the performance and adaptability of nanomaterials for a range of uses, such as environmental remediation, medicines, and biomedical imaging, requires the functionalization process. This method has several benefits, especially when altering nanoparticles meant for drug delivery or sensors. Among its notable advantages are its ease of use, versatility for many kinds of interactions, both covalent and non-covalent, and the possibility of post-synthesis alterations.

Sol-Gel Method

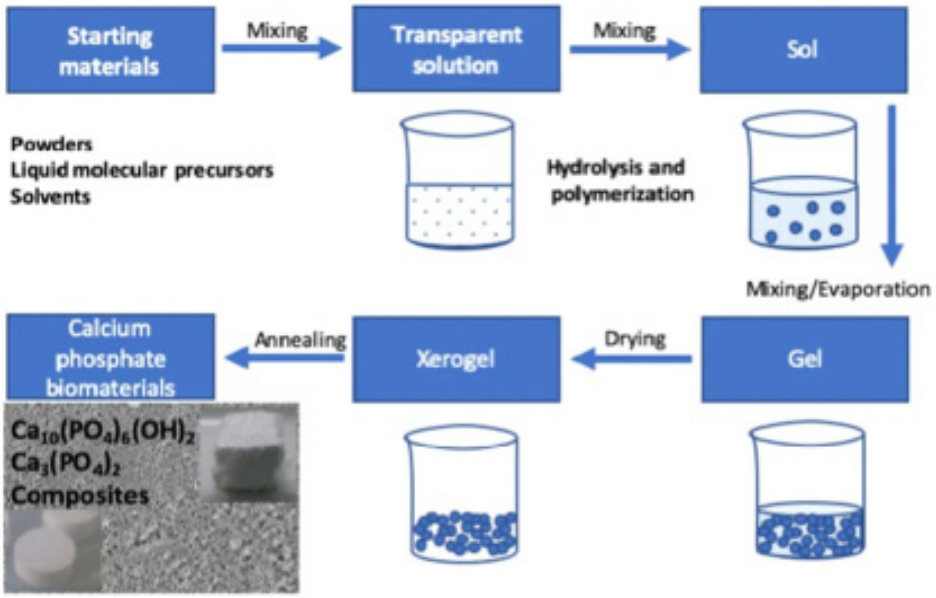

Figure 10. Doping of Nanoparticles by Sol-Gel method.

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The sol-gel method is a successful way to dope nanomaterials with ellagic acid. By turning a colloidal solution (sol) into a gel-like structure, this technique makes it easier to incorporate ellagic acid into the nanomaterial framework. To produce a gel, ellagic acid and metal alkoxides are usually first dissolved in a solvent, followed by polycondensation and hydrolysis reactions. The resulting gel is then dried and calcined to produce doped nanomaterials as shown in the (Figure 10) [40] with enhanced properties [41]. Ellagic acid-infused nanomaterials exhibit improved biocompatibility, increased therapeutic efficacy, and improved antioxidant qualities. Drug delivery, antioxidant therapy, and the avoidance of bacterial infections resistant to several drugs are among their uses [42]. The sol-gel approach, which is frequently used to create silica or titania nanoparticles, is favored because of its simple process, affordability, and ability to produce high-quality nanomaterials with exact surface and textural characteristics. This process produces extremely homogeneous nanoparticles, which makes it easier to accurately incorporate ellagic acid [43].

Green Synthesis

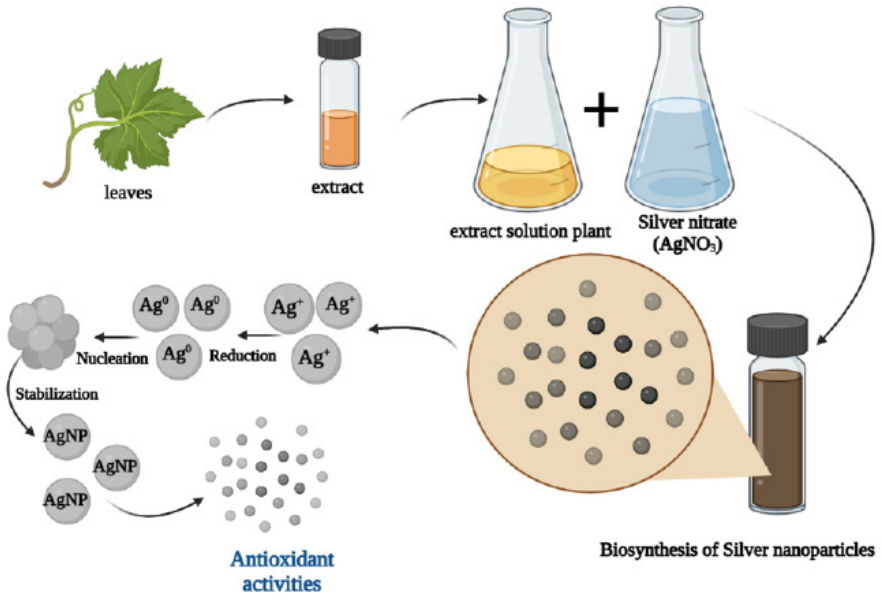

Figure 11. Doping of Nanoparticle by Green Synthesis.

Natural resources are used in environmentally friendly synthesis methods to incorporate ellagic acid into nanomaterials. Usually, plant extracts, microbes, or other biological agents are used in this green synthesis method in (Figure 11) [44] to reduce metal ions and create nanoparticles. Ellagic acid is added during this synthesis, which aids in the process as a whole. The method's cost-effectiveness, sustainability, and lack of harmful chemicals make it especially beneficial for applications in the biomedical and environmental domains [45,46]. Ellagic acid-enriched nanomaterials produced using this environmentally friendly process exhibit enhanced biocompatibility, antioxidant qualities, and therapeutic efficacy. Drug delivery, antioxidant therapy, and the avoidance of bacterial infections resistant to several drugs are among their possible uses. Because of its ease of use, safety for the environment, and capacity to yield superior nanomaterials with desired properties, this synthesis method is recommended.

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Electrochemical Deposition

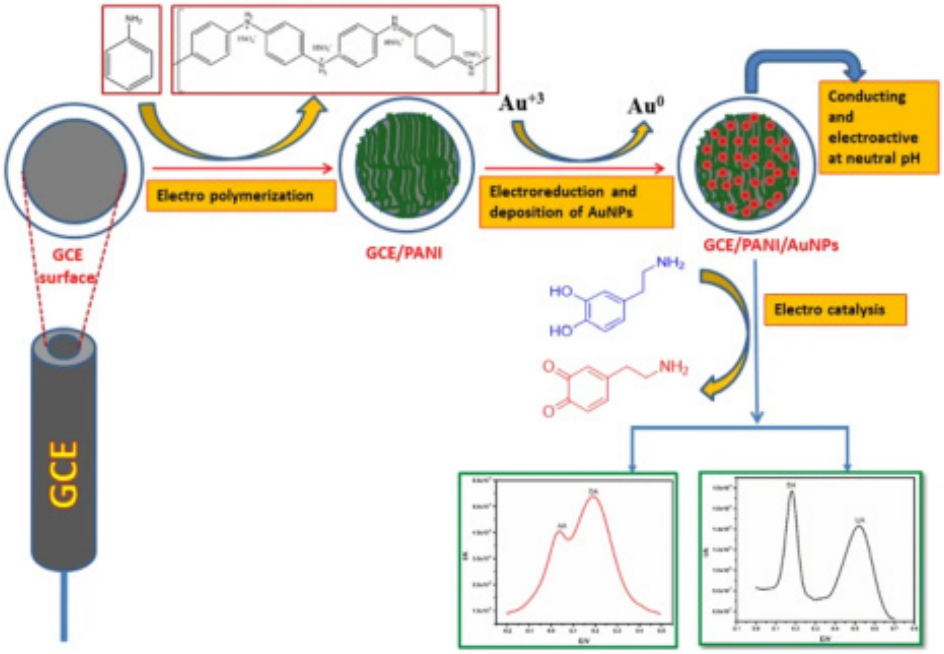

Figure 12. Doping of Nanoparticle by Electrochemical Deposition.

The process of electrochemical deposition is a useful method for ellagic acid doping of nanomaterials. By reducing metal ions from an electrolyte solution onto a conductive substrate with the help of an applied electric field, this technique makes it easier to include ellagic acid during the deposition phase as shown in (Figure 12) [47]. By precisely controlling the nanoparticles' size, distribution, and shape, this procedure enhances their biocompatibility and bioactivity. Ellagic acid-functionalized nanoparticles have improved antioxidant properties, making them appropriate for use in drug delivery systems, antioxidant therapy, and the fight against bacterial infections resistant to several drugs [48]. The synthesis of superior nanomaterials with consistent characteristics and little aggregation is another advantage of this method. The electrochemical deposition approach is widely used in the pharmaceutical, medical, and environmental sectors because of its ease of use, affordability, and ability to create nanomaterials with exceptional functionality.

Applications of Ellagic Acid-Doped Nanomaterials

Drug Delivery

Nanomaterials enhanced with ellagic acid function as efficient drug delivery vehicles, increasing the bioavailability of ellagic acid and other medicinal substances [49]. For example, in the context of cancer treatment, polymeric nanoparticles containing ellagic acid can enable controlled release mechanisms.

Antioxidant and Anti-inflammatory Agents

When metal oxide nanoparticles like ZnO and TiO_2 are doped with ellagic acid, their antioxidant properties are greatly enhanced, making them ideal for usage in cosmetic and biomedical applications [50].

Biomedical Imaging and Theranostics

Ellagic acid-conjugated gold nanoparticles show great promise in imaging methods including photoacoustic imaging and photothermal treatment [49].

Environmental Sensing and Remediation

When carbon-based materials like graphene are combined with ellagic acid, they can function as efficient biosensors for the detection of heavy metals and other environmental pollutants [32].

Photocatalysis and UV Protection

In addition to improving UV protection, adding metal oxide nanoparticles and ellagic acid to sunscreen formulations may also speed up the photocatalytic breakdown of environmental contaminants [51].

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PRECLINICAL PHARMACOLOGICAL EVALUATIONS OF ELLAGIC ACID

A brief overview of the experimental evidence demonstrating the advantages of EA consumption in reducing inflammation and oxidative stress, as well as its potential applications in the treatment of various cancers, metabolic syndrome, and the liver and central nervous system (CNS). It is explained in the (Figure 13)

Figure 13. Biological effects of Ellagic acid.

Ellagic Acid and Oxidative Stress: Insights into Its Protective Mechanisms

Ellagic acid's potent antioxidant properties make it important for reducing oxidative stress. A discrepancy between the body's ability to use antioxidants to combat reactive oxygen species (ROS) and the production of ROS causes oxidative stress, which damages cells. This imbalance is linked to the onset of several illnesses, such as cancer, heart problems, neurological conditions, and aging.

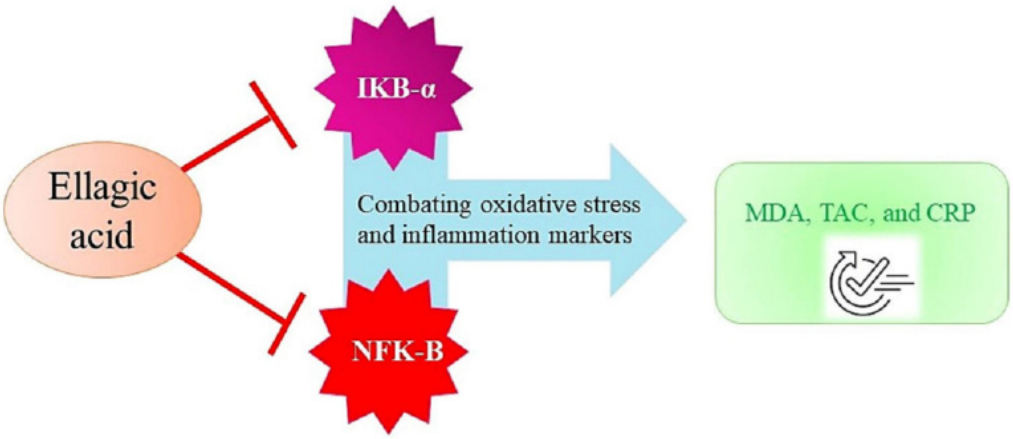

Figure 14. Pathway of Oxidative Stress of Ellagic Acid.

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Free Radical Scavenging

Reactive oxygen species (ROS) that seriously oxidatively damage proteins, lipids, and DNA include superoxide anions (O_2^-), hydroxyl radicals (OH•), and peroxyl radicals (ROO•). Ellagic acid (EA) efficiently neutralizes these ROS. By stabilizing these radicals and minimizing cellular damage, it functions as a donor of hydrogen or electrons. Important biological molecules are kept intact by this mechanism [52].

Inhibition of Lipid Peroxidation

Free radicals attack polyunsaturated fatty acids in cell membranes, causing lipid peroxidation, a destructive chain reaction that kills cells. By neutralizing lipid radicals and preserving membrane integrity, ellagic acid stops this process [53].

Chelation of Metal Ions

Transition metals including iron (Fe^{2+}) and copper (Cu^{2+}), which catalyze the Fenton and Haber-Weiss processes that produce ROS, are chelated by ellagic acid. Oxidative stress is decreased by EA's binding of these metals, which stops them from taking part in processes that produce ROS [54].

Activation of Antioxidant Defense Systems

Ellagic acid increases the expression of natural antioxidant enzymes such as glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD). In order to detoxify ROS and stop oxidative damage, these enzymes are essential [55].

Inhibition of ROS-Producing Enzymes

By blocking important ROS-producing enzymes including xanthine oxidase and NADPH oxidase, ellagic acid lowers ROS levels in the cellular environment and lessens oxidative damage [56].

Modulation of Signaling Pathways

Ellagic acid activates Nrf2 from Figure 14 [57], a transcription factor that triggers the production of antioxidant proteins, hence modulating oxidative stress-sensitive pathways. Additionally, it suppresses NF-κB, which lowers inflammation brought on by oxidative damage [58].

Protection Against DNA Damage

Ellagic acid prevents DNA strand breaks and mutations by neutralizing ROS and blocking their interaction with DNA, which helps to prevent cancer and other degenerative disorders [59,60].

Mitochondrial Protection

The main locations for ROS generation are mitochondria. By scavenging ROS and preserving mitochondrial integrity, ellagic acid maintains mitochondrial function, which is crucial for cellular energy production and survival [61,62].

Health Implications of Ellagic Acid in Oxidative Stress

Cardiovascular Protection

Atherosclerosis and other cardiovascular diseases are primarily caused by oxidative stress. By inhibiting lipid peroxidation, lowering inflammation, and improving endothelial function, ellagic acid lessens these effects and protects the heart and blood vessels [63].

Cancer Prevention

Carcinogenesis is linked to oxidative stress through mechanisms like DNA damage and persistent inflammation. By scavenging free radicals, chelating metals, and modifying signaling pathways, ellagic acid demonstrates potential anticancer properties by halting the development and spread of tumors [64].

Neuroprotection

The brain's high oxygen consumption and lipid content make it especially susceptible to oxidative stress. By protecting neurons from oxidative damage, ellagic acid has shown neuroprotective effects. This may be helpful in the treatment of neurodegenerative diseases like Parkinson's and Alzheimer's [65].

Anti-Aging Effects

Because oxidative stress damages cellular structures, it quickens the aging process. By scavenging reactive oxygen species (ROS) and encouraging cellular repair processes, ellagic acid has the potential to slow down the aging process. This is particularly important for skin health because ellagic acid has been shown to stop UV-induced oxidative stress from breaking down collagen [66].

Diabetes Management

Oxidative stress plays a significant role in the development of complications like neuropathy, nephropathy, and retinopathy

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in people with diabetes. Ellagic acid decreases oxidative damage and increases insulin sensitivity, which helps manage diabetes and its complications [67].

Liver Protection

Oxidative stress can cause liver diseases like fatty liver, cirrhosis, and fibrosis, and the liver is essential for the body's detoxification process. Ellagic acid has been demonstrated to prevent hepatotoxicity by lowering oxidative damage and liver inflammation [67].

ANTI-INFLAMMATORY PROPERTIES OF ELLAGIC ACID AND THEIR CONSEQUENCES FOR RELATED DISEASES

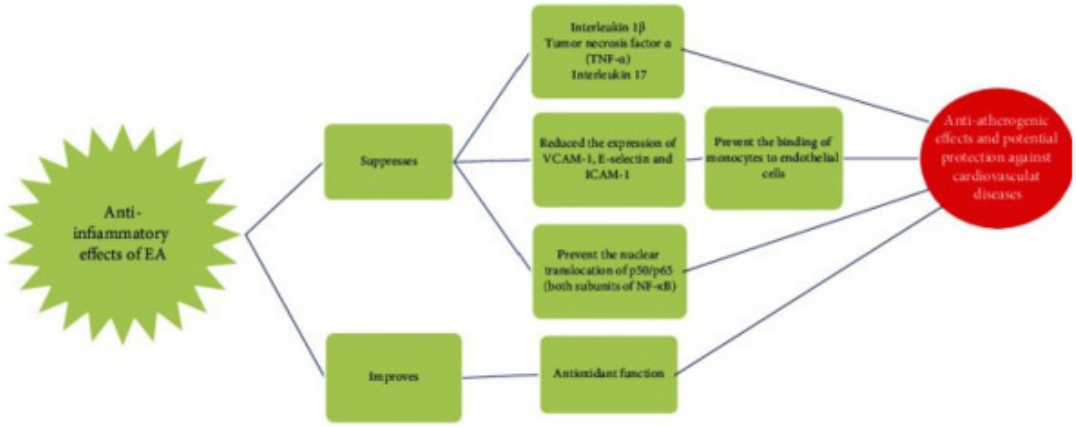

Figure 15. Anti-inflammatory effects of ellagic acid and its consequences in cardiovascular disease.

Pro-inflammatory cytokine inhibition

Important pro-inflammatory cytokines like TNF-α from Figure 15 [69], IL-6, IL-1β, and IL-8 are inhibited by ellagic acid (EA). Because they coordinate the recruitment of immune cells and trigger inflammatory pathways, these cytokines are essential to the inflammatory response. Numerous pathogenic illnesses, such as autoimmune diseases, cardiovascular diseases, and neurodegenerative disorders, are linked to chronic elevations of these cytokines. EA considerably reduces chronic inflammation by controlling cytokine generation, and it may also be used to treat inflammatory diseases [70].

Repression of the NF-κB Route

One of the main systems that controls the production of genes linked to inflammation, such as adhesion molecules, cytokines, and chemokines, is the NF-κB pathway. Many inflammatory illnesses are linked to NF-κB activation. EA has been demonstrated to efficiently reduce the expression of these inflammatory genes by blocking NF-κB activation. EA aids in lowering inflammation and associated cellular reactions by blocking this mechanism [71].

COX and LOX Enzyme Inhibition

Pro-inflammatory mediators including prostaglandins and leukotrienes, which are important in inflammation, are synthesized by the enzymes cyclooxygenase (COX) and lipoxygenase (LOX). Due to EA's inhibition of COX-2 and 5-LOX, fewer inflammatory mediators are produced. In inflammatory bowel disease (IBD), arthritis, and other chronic inflammatory illnesses, this inhibition may be helpful [72,73].

Blocking Inflammasome Activity

One important pro-inflammatory cytokine, IL-1β, is activated and matured in large part by NLRP3 inflammasomes. EA's anti-inflammatory properties are further enhanced by its demonstrated ability to prevent NLRP3 inflammasome activation. In rheumatoid arthritis and other inflammatory illnesses, EA helps regulate inflammation by blocking the release of IL-1β [74].

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Consequences for Related Diseases

Cardiovascular Diseases

Atherosclerosis is a disorder where plaque accumulation thickens the arterial walls. One of the main causes of this condition is chronic inflammation. Ellagic acid may help prevent or slow the development of atherosclerosis and other cardiovascular diseases by lowering inflammation and oxidative stress [49].

Metabolic Disorders (e.g., Type 2 Diabetes, Obesity)

A key component of metabolic diseases including type 2 diabetes and obesity is persistent low-grade inflammation. Ellagic acid has demonstrated promise in lowering inflammation in adipose tissue, enhancing insulin sensitivity, and preventing complications from diabetes [75].

Neurodegenerative Diseases (e.g., Alzheimer's Disease, Parkinson's Disease)

A major contributing factor to the development of neurodegenerative illnesses like Parkinson's and Alzheimer's is neuroinflammation. Ellagic acid may have neuroprotective benefits by lowering oxidative stress and modifying inflammatory pathways in the brain [76].

Cancer

Chronic inflammation is closely linked to the development and progression of various cancers. Ellagic acid has demonstrated anti-tumor properties in vitro and in vivo, partially due to its ability to inhibit inflammatory pathways involved in tumor growth and metastasis [65].

Gastrointestinal Disorders (e.g., IBD, Ulcerative Colitis)

Chronic inflammation of the gastrointestinal tract is a hallmark of inflammatory bowel diseases (IBD), which include Crohn's disease and ulcerative colitis. Because it improves the function of the intestinal barrier and reduces inflammation, ellagic acid may help reduce symptoms [77].

Arthritis

Inflammatory joint conditions include osteoarthritis and rheumatoid arthritis. Ellagic acid may lessen joint inflammation and delay the course of disease by inhibiting inflammatory mediators.

Ellagic acid is a promising natural substance for the prevention and treatment of a number of diseases linked to inflammation because of its anti-inflammatory qualities. Its therapeutic potential is enhanced by its mechanisms of action, which include antioxidant effects, NF-κB pathway suppression, and inhibition of inflammatory cytokines. The available data shows that it has potential as an adjuvant treatment for inflammatory illnesses, even though more clinical research is required to completely understand its safety and efficacy in people [78].

POSSIBLE THERAPEUTIC AND CHEMOPREVENTIVE APPLICATIONS OF EA IN CANCER

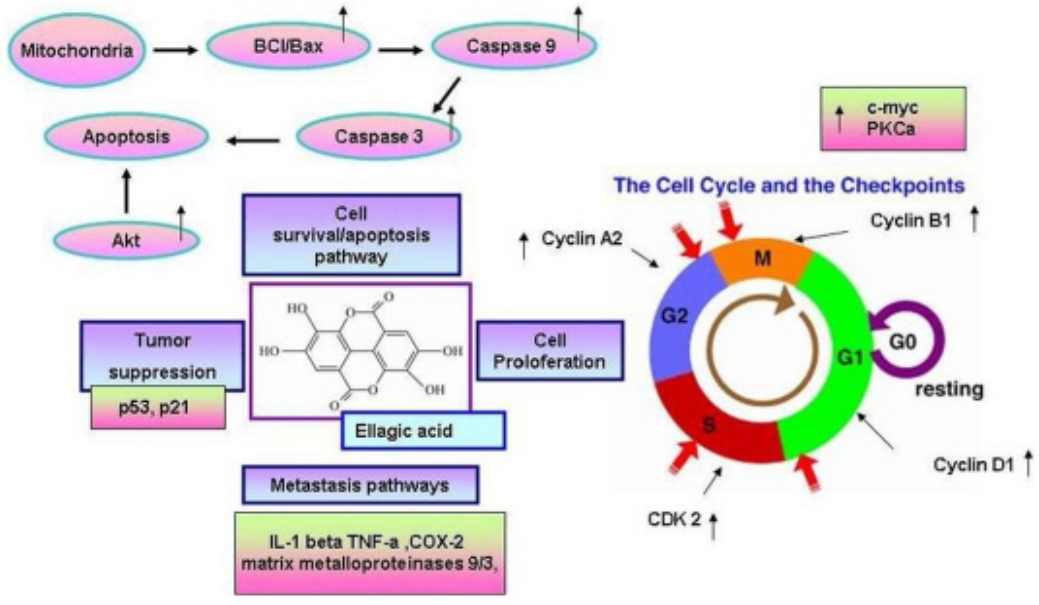

Figure 16. Anticancer effects of Ellagic acid and its metabolites.

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Because of its pro-apoptotic, anti-inflammatory, antioxidant, and anti-proliferative qualities, ellagic acid (EA) has drawn interest as a potentially useful substance for cancer treatment and chemoprevention. Because of its natural occurrence and safety profile, EA which is present in many fruits, but particularly in pomegranates and berries is particularly attractive for use in cancer research.

Antioxidant Activity

Strong antioxidant ellagic acid aids in the removal of free radicals and reactive oxygen species (ROS). One of the main causes of carcinogenesis is DNA damage, which is exacerbated by these extremely reactive chemicals. EA prevents mutations that might result in unchecked cell proliferation, a defining feature of cancer progression, by lowering oxidative stress [79].

Anti-inflammatory Effects

A known risk factor for cancer is chronic inflammation. EA decreases the production of pro-inflammatory cytokines such TNF-α, IL-6, IL-1β, and IL-8 by downregulating inflammatory pathways, especially by blocking the NF-κB pathway. This control of inflammation aids in reducing the tumor-promoting milieu that encourages the growth of cancer [64,80].

Pro-apoptotic Effects

In order to eradicate cancerous cells, ellagic acid causes apoptosis, or programmed cell death, in a variety of cancer cell lines. EA initiates a number of apoptotic mechanisms: EA suppresses the Akt signaling pathway, which is implicated in the survival and proliferation of cells. EA causes the death of cancer cells by focusing on this pathway [65,80,81]. Protein kinase C (PKC) isoforms, which are essential for controlling apoptosis, are modulated by EA.

Cell Cycle Arrest: EA stops cancer cells from multiplying and moving through the cell cycle by stopping the cell cycle, especially in the G0/G1 phase from Figure 6 [82].

ROS Production: EA causes cancer cells to produce more ROS, which leads to oxidative stress and apoptosis.

DNA Damage: EA has the ability to harm the DNA of cancer cells, which triggers the apoptotic process that destroys the harmed cells.

Cell Proliferation Inhibition

EA stops the growth of cancer cells in a number of ways:

Mitochondrial Dysfunction: EA causes mitochondrial dysfunction, which lowers energy generation and stops cancer cells from respiring, therefore preventing them from proliferating. Signaling Pathway Inhibition: EA efficiently stops the growth of cancer cells by blocking important signaling channels for cell division, including the Akt, Wnt/β-catenin, [62,83] and PI3K pathways.

Angiogenesis Reduction: By preventing the production of new blood vessels, angiogenesis, EA restricts the amount of oxygen and nutrients that tumors can receive [15,84].

Antimetastatic Characteristics

Ellagic acid stops cancer cells from spreading to other parts of the body because of its anti-metastatic qualities. EA obstructs multiple stages of metastasis:

EA inhibits the invasion of the extracellular matrix (ECM), which is a critical stage in the metastatic process of cancer cells [65,85].

Angiogenesis Inhibition: EA prevents new blood vessels from growing, which denies tumors the oxygen and nutrition they need to spread.

Modulation of Signaling Pathways: EA disrupts the PI3K, Wnt/β-catenin, and Akt pathways, which are essential for the migration and dissemination of cancer cells [86].

Inhibition of Angiogenesis

The process of creating new blood vessels, known as angiogenesis, promotes the growth of tumors. Angiogenesis is inhibited by ellagic acid by:

VEGFR-2 Pathway Inhibition: To stop tumor-induced angiogenesis, EA inhibits the vascular endothelial growth factor receptor (VEGFR-2) pathway.

Zinc-Chelation: Angiogenesis requires zinc, which EA lowers in availability by acting as a zinc chelator.

Inhibition of Matrix Metalloproteinase (MMP): EA inhibits MMP-2, an enzyme involved in the breakdown of extracellular matrix (ECM), a crucial stage in angiogenesis [87].

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Applications for Chemoprevention

The term "chemoprevention" describes the use of synthetic or natural materials to stop cancer. EA is essential for avoiding DNA damage, blocking the activation of carcinogens, and enhancing detoxification pathways:

Preventing DNA damage

EA shields DNA from oxidative damage and inhibits the production of carcinogenic oxidative DNA adducts like 8-oxodeoxyguosine (8-oxodG) [65].

Preventing the Activation of Carcinogens

Pro-carcinogens, or compounds that become carcinogenic following metabolic activation, are prevented from activating by EA. EA may reduce the risk of cancer by preventing these carcinogens from activating [15].

Improvements to Detoxification Routes

EA increases detoxification enzymes like glutathione S-transferases and quinone reductases, which aid in the detoxification of carcinogens, by activating the Nrf2 pathway [65].

Estrogen Receptor Modulation

Because EA has anti-estrogenic properties and binds to estrogen receptors, particularly ERα, it may be used to treat hormone-dependent malignancies like breast cancer [65].

Therapeutic Uses for Particular Cancers

Breast Cancer

When it comes to stopping the growth of breast cancer cells, especially those that are estrogen receptor-positive (ER+), EA has demonstrated encouraging results. By altering estrogen receptors, preventing angiogenesis, and triggering apoptosis in breast cancer cells, it has anti-proliferative effects [65].

Prostate Cancer

According to studies, EA may slow the progression of prostate cancer by suppressing PSA (prostate-specific antigen) levels, lowering androgen receptor activity, and inhibiting the proliferation of prostate cancer cells. Additionally, it exhibits anti-angiogenic properties that inhibit the growth of tumors [65].

Colon Cancer

Studies have shown that EA may slow the progression of prostate cancer by reducing androgen receptor activity, inhibiting the proliferation of prostate cancer cells, and suppressing PSA (prostate-specific antigen) levels. It also has anti-angiogenic qualities that prevent tumors from growing [65].

Lung Cancer

Because EA inhibits the bioactivation of environmental carcinogens like tobacco smoke, it may be able to prevent or treat lung cancer, which is frequently caused by these carcinogens. By encouraging apoptosis and preventing cell cycle progression, EA has demonstrated promise in slowing the growth of lung cancer cells [65].

Skin Cancer

As one of the main causes of skin cancer, UV-induced DNA damage to skin cells is lessened by EA's photoprotective qualities. Additionally, it inhibits angiogenesis, which is essential for the progression of melanoma, and stops the growth of melanoma cells [65].

Potential Combination Therapy

Synergistic Impact of Chemotherapy

The effectiveness of conventional chemotherapeutic agents can be improved by EA. For example, EA has demonstrated synergistic effects when combined with medications such as doxorubicin and cisplatin, improving cancer cell death while lowering toxicity to healthy cells [15].

Breaking Through Chemoresistance

Chemotherapy-resistant cancer cells are common. EA is a useful adjunct therapy in the treatment of cancer because it has been demonstrated to reverse chemoresistance in a variety of cancers by modifying drug transporters and important signaling pathways [87].

Ellagic acid has a lot of promise as a cancer treatment and chemo-preventive agent. It is a versatile compound for research and possible clinical application because it can target several hallmarks of cancer, including reducing angiogenesis, promoting apoptosis, inhibiting proliferation, and preventing metastasis. Preclinical research yields encouraging results, but additional clinical trials are required to determine its safety and effectiveness in people.

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ELLAGIC ACID'S NEUROPROTECTIVE PROPERTIES

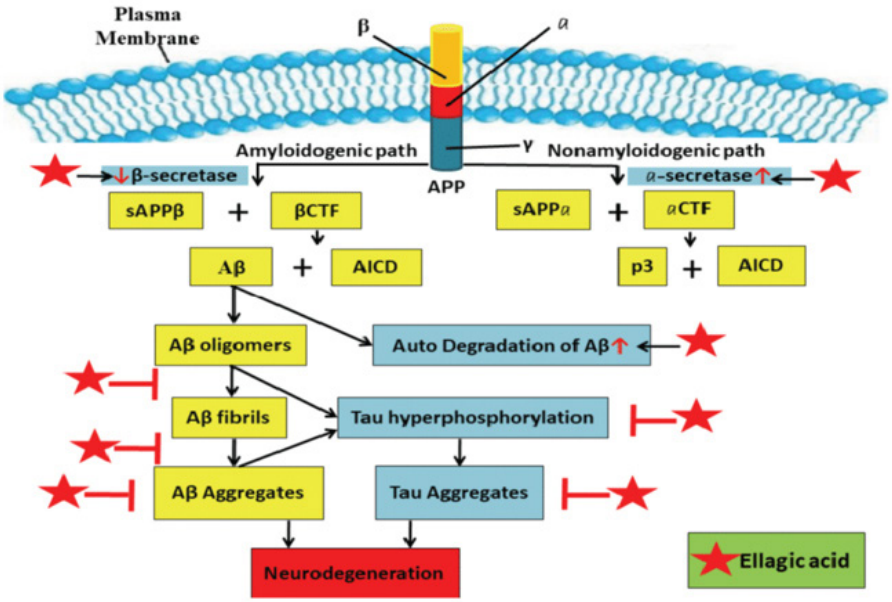

Figure 17. Neuroprotective effects of Ellagic acid.

Mechanisms of Antioxidants

Neuronal damage and neurodegenerative illnesses are significantly influenced by oxidative stress, which happens when the body's antioxidant defense capacity is exceeded by the formation of reactive oxygen species (ROS). Strong antioxidant ellagic acid prevents oxidative damage to neurons by neutralizing ROS. Additionally, it stimulates the production of endogenous antioxidants such superoxide dismutase (SOD), glutathione peroxidase, and catalase. EA maintains the integrity of the neuronal membrane by lowering lipid peroxidation, which is essential for sustaining cell signaling and function [88,89].

Reduction of Inflammation

A prevalent characteristic of neurodegenerative illnesses including Parkinson's and Alzheimer's is neuroinflammation. When microglia and astrocytes are activated, pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 are produced. Ellagic acid prevents the activation of inflammatory cells and decreases the release of these cytokines. Furthermore, EA modifies the NF-κB pathway, a crucial regulator of inflammation in the brain, and suppresses the expression of inflammatory enzymes including COX-2 and iNOS [90,91].

Neuroprotective and Anti-apoptotic Properties

One of the main characteristics of neurodegenerative disorders is apoptosis, or programmed cell death. By controlling the Bax/Bcl-2 ratio, which controls the mitochondrial apoptotic pathway, EA has anti-apoptotic effects. It stops cytochrome c from being released from mitochondria, which inhibits caspase-3 activation. Furthermore, EA stimulates the PI3K/Akt pathway, which improves neuronal repair and cell survival [92].

Protection of Mitochondria

A common feature of many neurodegenerative diseases is mitochondrial dysfunction. By lessening oxidative damage to mitochondrial proteins and DNA, ellagic acid contributes to mitochondrial protection. Additionally, it maintains the potential of the mitochondrial membrane, which is necessary for the synthesis of ATP and the survival of cells [93].

Decrease in the Production of Amyloid Plaques

The hallmark of Alzheimer's disease (AD) is the presence of amyloid-beta (Aβ) from Fig.17 [94] plaques. Amyloid-beta peptides combine to produce these plaques, which lead to neurotoxicity, oxidative stress, and inflammation. Ellagic acid has been demonstrated to inhibit Aβ peptide aggregation, which lowers plaque development and lessens the neurotoxicity that goes along with it. EA also promotes

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autophagy, a biological mechanism that helps the brain rid itself of damaged proteins like amyloid-beta. EA may reduce the cognitive impairment frequently seen in Alzheimer's disease by lowering the load of amyloid plaques [89,95].

Excitotoxicity Inhibition

Excitotoxicity is the result of overstimulation of neurons by the neurotransmitter glutamate, which causes calcium overload and sets off a series of events that result in oxidative damage and neuronal death. Excitotoxicity plays a role in the damage of neurons in conditions like epilepsy and stroke. By preventing calcium from entering neurons and restricting excessive glutamate release, ellagic acid lessens excitotoxicity. Even in the face of excitotoxic challenges, this protective activity aids in preserving the integrity and functionality of neurons [89,96].

Initiation of signaling pathways that confer neuroprotection

Several important cellular signaling pathways that shield neurons from harm are modulated by ellagic acid:

Nrf2/ARE Pathway: Heme oxygenase-1 (HO-1) and other detoxifying and antioxidant enzymes are expressed more when EA activates the Nrf2 transcription factor. This mechanism is essential for boosting antioxidant defense and shielding neurons from oxidative damage.

The mitogen-activated protein kinase (MAPK) pathway, which controls how cells react to stress, inflammation, and injury, is another pathway that EA affects. EA increases neuronal survival and lessens cellular damage by modifying this mechanism [97,98].

Promotion of Neurogenesis and Synaptic Plasticity

For learning, memory, and brain repair, neurogenesis—the process of producing new neurons—and synaptic plasticity—the capacity of synapses to become stronger or weaker over time—are essential. It has been demonstrated that ellagic acid stimulates neurogenesis, which helps heal brain areas harmed by neurodegenerative illnesses. By boosting the expression of brain-derived neurotrophic factor (BDNF), a protein necessary for neuron survival, differentiation, and growth, EA also improves synaptic plasticity [99].

Strategies for Safeguarding Against Ischemic Brain Injury

Lack of oxygen causes oxidative stress, inflammation, and energy loss in neurons in ischemia diseases like stroke. Because it inhibits neuronal death, preserves mitochondrial integrity, and reduces infarct size, ellagic acid has shown neuroprotective effects in ischemic brain injury. EA also reduces pro-inflammatory cytokine levels, which further lessens damage, and aids in protecting the blood-brain barrier (BBB), which may be weakened during ischemia [100].

Potential Uses in Neurodegenerative Disorders

Because of its neuroprotective qualities, ellagic acid may be used to treat and prevent a number of neurodegenerative illnesses:

Alzheimer's Disease: EA is a promising treatment for AD since it lowers oxidative stress, amyloid plaque production, and neuroinflammation [101].

Parkinson's Disease: Because EA has anti-inflammatory, anti-apoptotic, and antioxidant properties, it helps protect dopaminergic neurons, which are harmed in Parkinson's disease.

Stroke: By lowering oxidative damage, inflammation, and neuronal death, EA enhances recovery following an ischemic stroke [89,73].

Ellagic Acid's Cardioprotective Mechanisms

Ellagic acid has drawn a lot of attention for its possible cardioprotective benefits in addition to its neuroprotective qualities. The benefits of ellagic acid for the cardiovascular system are mostly attributed to its anti-inflammatory, anti-hypertensive, lipid-lowering, antioxidant, and anti-atherogenic properties. A thorough analysis of ellagic acid's cardioprotective benefits may be found below.

Antioxidant Properties

Atherosclerosis and myocardial infarction are two cardiovascular diseases (CVDs) that are significantly influenced by oxidative stress. As a strong antioxidant, ellagic acid scavenges free radicals and increases the activity of antioxidant enzymes such as SOD, glutathione peroxidase, and catalase. In experimental models of myocardial ischemia-reperfusion injury, EA has been demonstrated to lower ROS generation, limiting oxidative damage to cardiac tissues [102,103].

Anti-Inflammatory properties

One of the main causes of atherosclerosis and other CVDs is chronic inflammation. Ellagic acid suppresses NF-κB signaling,

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which controls genes linked to inflammation, and reduces levels of pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β). EA aids in preventing the development of plaque in arteries by lowering vascular inflammation [104].

Protection of Cardiomyocytes and Anti-Apoptotic Mechanisms

Apoptosis is a major contributing factor to heart failure and ischemic heart disease, and ellagic acid shields cardiomyocytes from it. EA decreases cell death brought on by ischemia and oxidative stress by upregulating anti-apoptotic proteins like Bcl-2 and downregulating pro-apoptotic proteins like Bax and caspase-3 [105,106].

Effects that Counteract Atherogenesis

Ellagic acid stops LDL cholesterol from oxidizing, which is a crucial stage in the formation of atherosclerotic plaques. Additionally, it raises HDL cholesterol while lowering LDL, total, and triglyceride levels. The development of atherosclerotic plaques is lessened by this improvement in lipid profiles [107,108,109].

Blood Pressure Management (Effects of Antihypertensive Agents)

The main ways that ellagic acid reduces hypertension are via enhancing endothelial function and boosting the synthesis of nitric oxide (NO), a vasodilator that lowers blood pressure. In animal models of hypertension, studies have shown that EA dramatically lowers both the systolic and diastolic blood pressure [110,111].

Strategies for Safeguarding Against Myocardial Ischemia-Reperfusion Injury

Lack of oxygen causes oxidative stress, inflammation, and energy loss in neurons in ischemia diseases like stroke. Because it inhibits neuronal death, preserves mitochondrial integrity, and reduces infarct size, ellagic acid has shown neuroprotective effects in ischemic brain injury. EA also reduces pro-inflammatory cytokine levels, which further lessens damage, and aids in protecting the blood-brain barrier (BBB), which may be weakened during ischemia [89].

Prevention of Cardiac Hypertrophy

The abnormal growth of the heart muscle, known as cardiac hypertrophy, is frequently brought on by an increased workload in diseases including heart failure and hypertension. At first, hypertrophy might be compensatory, but if it persists, it can cause heart failure. It has been demonstrated that ellagic acid inhibits myocardial hypertrophy by:

Blocking Hypertrophic Signaling Pathways: EA inhibits the NFAT and ERK1/2 pathways, which are both implicated in the abnormal growth of cardiomyocytes [112].

Preventing Excessive Cardiomyocyte Proliferation: EA maintains heart function by regulating various signaling pathways, which stops the unchecked proliferation of heart muscle cells.

Effects on Thrombosis Prevention

The development of blood clots, known as thrombosis, can impair circulation and result in diseases including stroke and myocardial infarction (heart attack). Ellagic acid has anti-thrombotic qualities through:

Preventing Platelet Aggregation: EA lessens platelets' propensity to group together, which is an essential stage in the creation of clots.

Blocking Fibrinogen Activation: EA lowers the risk of thrombotic events by preventing fibrinogen, a protein implicated in clot formation, from becoming activated [113].

Mitigation of Cardiac Fibrosis

The aberrant buildup of extracellular matrix proteins in heart tissue is a hallmark of cardiac fibrosis, which can compromise heart function and result in heart failure. Following myocardial infarction and hypertension, this condition is prevalent. Heart fibrosis can be avoided or its progression slowed by ellagic acid by:

Decreased Fibroblast Activation: EA prevents fibroblasts, which are the cells that make fibrotic tissue, from becoming activated [114].

Reducing Fibrotic Markers: EA inhibits the expression of important molecules that contribute to the development of fibrosis, including collagen and TGF-β1 [115].

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EA'S BENEFICIAL EFFECTS ON LIPID AND GLUCOSE METABOLISM AS WELL AS ITS ABILITY TO PROTECT ORGANS

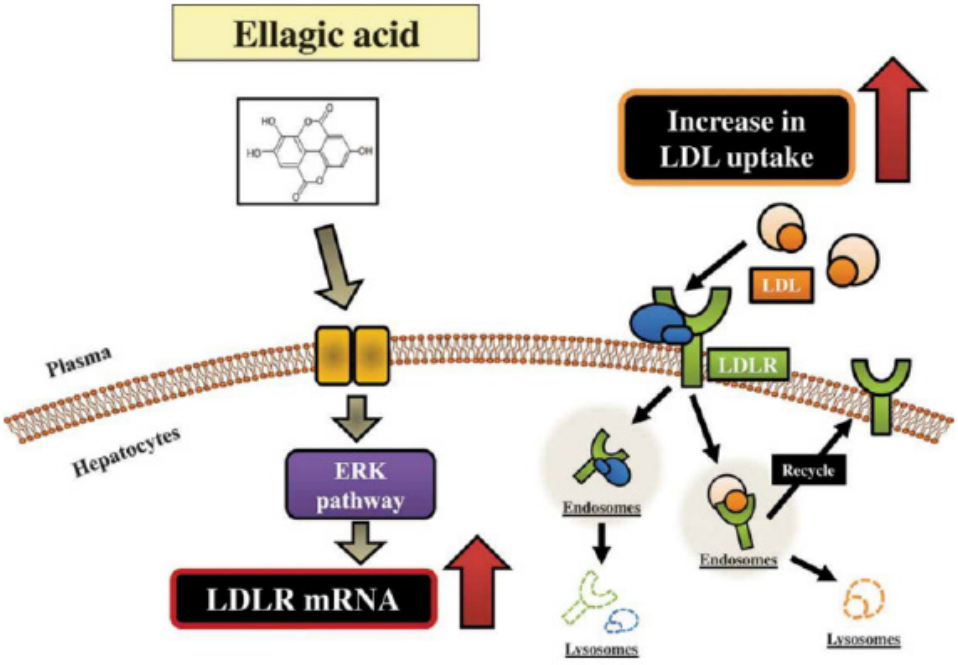

Figure 18. Ellagic acid induces an up-regulation of LDL receptor.

Effects of Glucose Metabolism

Enhances Insulin Sensitivity: By triggering important signaling pathways, including the AMP-activated protein kinase (AMPK) pathway, ellagic acid increases insulin sensitivity. AMPK is essential for controlling cellular energy balance, increasing insulin sensitivity, and improving glucose uptake. Elevated AMPK activity encourages glucose absorption in peripheral tissues, including muscle cells, and lowers blood glucose levels [116].

Lowers Blood Glucose Levels: By controlling the production of glucose transporters like GLUT4, which promotes glucose uptake in muscle cells, EA decreases fasting blood glucose levels. This control lowers blood glucose levels and improves glucose absorption [117,118].

Reduces Insulin Resistance: One of the main characteristics of type 2 diabetes and other metabolic diseases is insulin resistance. By reducing oxidative stress and inflammation, two major factors that contribute to insulin resistance, EA lowers insulin resistance. EA improves antioxidant defenses and decreases pro-inflammatory cytokines to restore insulin sensitivity [119].

Effects of Lipid Metabolism

Lowers Triglycerides and LDL (bad cholesterol): By blocking lipid production enzymes and encouraging the removal of lipids from the bloodstream, EA reduces the levels of LDL from Fig.18 [120] cholesterol and triglycerides. This effect enhances lipid profiles and helps prevent cardiovascular disorders.

Lowers Liver Lipid Accumulation: EA lowers the incidence of non-alcoholic fatty liver disease (NAFLD) and associated disorders by preventing lipid buildup in hepatocytes. It stops fat from accumulating in the liver and encourages lipid metabolism [121,122].

Controls Adipogenesis: EA controls adipogenesis, or the production of fat cells, by altering genes related to fat storage. This rule aids in controlling body weight and preventing obesity.

Protective Effects on Organs

Protects the Liver: By lowering oxidative stress and inflammation, which are crucial in liver disorders including fibrosis and NAFLD, EA protects the liver. By strengthening detoxification and lowering cholesterol buildup, it also enhances liver function [123].

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Kidney Protection: Elevated glucose levels and pollutants can cause oxidative stress and nephrotoxicity, which ellagic acid shields kidney cells from. It enhances kidney function and lowers inflammation [124].

Cardiovascular Protection: EA protects against cardiovascular illnesses by lowering cholesterol and preventing atherosclerosis. Its antioxidant qualities improve vascular health by lowering oxidative stress in blood vessels [125].

Neuroprotective Effects: By lowering inflammation and oxidative stress, two factors that significantly contribute to neurodegenerative disorders, EA shields the brain. Additionally, this neuroprotection might enhance cognitive function, particularly in diabetic individuals who frequently suffer from cognitive loss [92].

Anti-inflammatory and Antioxidant Properties

Strong anti-inflammatory and antioxidant properties of ellagic acid make it essential for avoiding harm to tissues and organs. EA shields cells from oxidative stress and chronic inflammation, two major causes of metabolic diseases, by neutralizing ROS and lowering pro-inflammatory cytokines [122,123].

Table 3. Pharmacological Activities of Ellagic acid

S.No.	Sources of Ellagic Acid	Yield of Ellagic Acid	The activity of Ellagic Acid from Source	Nanoparticles Used	References
1	Pomegranate (Punica granatum)	Peel: ~19-25 mg/g Juice: ~24 mg/L	Antioxidant Anti-inflammatory Anti-cancer	Chitosan nanoparticles PLGA nanoparticles	[126]
2	Green Tea (Camellia sinensis)	Leaf extract: ~1-3 mg/g	Anti-cancer, Cardioprotective	PLGA (poly-lactic-co-glycolic acid) nanoparticles	[127]
3	Grape (Vitis vinifera)	Seeds: ~5-15 mg/g	Anti-inflammatory, Cardioprotective, anticancer	Magnetic nanoparticles	[128]
4	Eucalyptus (Eucalyptus spp)	Leaves: ~5-10 mg/g	Antioxidant, antimicrobial	Carbon-based nanoparticles	[129]
5	Elderberry (Sambucus nigra)	Fruit: ~1-3 mg/g	Anti-viral, Antioxidant	Nano emulsion	[130]
6	Strawberries (Fragaria spp.)	150-200 mg/kg (fresh weight)	Antioxidant Anti-cancer Cardioprotective	Solid lipid nanoparticles PLGA nanoparticles	[131]
7	Blackberries (Rubus spp.)	~150 mg/kg (fresh weight)	Antioxidant Anti-diabetic Anti-inflammatory	Chitosan nanoparticles Lipid nanoparticles	[132]
8	Raspberries (Rubus idaeus)	~270-330 mg/kg (fresh weight)	Antioxidant Anti-cancer Anti-inflammatory	Lipid nanoparticles PLGA nanoparticles	[133]
9	Walnuts (Juglans regia)	~60-70 mg/kg (dry weight)	Cardioprotective Anti-cancer Neuroprotective	Chitosan nanoparticles PLGA nanoparticles	[134]
10	Oak (Quercus spp.)	~160 mg/kg (bark)	Antioxidant Anti-inflammatory Antimicrobial	Lipid nanoparticles Chitosan nanoparticles	[135]

CONCLUSION

Ellagic acid has important medicinal uses and is a promising Natural substance. Its stability by availability and targeted distribution are all improved by its encapsulation in nanomaterials or projects undertaken which maximizes its therapeutic potential. To analyze the presence and effectiveness of EA in nanoformulations, methods such as FTIR, UV visible spectroscopy, and HPLC-MS are invaluable. EA appears to have a bright future in animals based on these developments, particularly in anti-cancer anti-inflammatory neuroprotective, and hepatoprotective treatments. EA's potential in clinical applications must be fully realized through additional study on safety, efficacy, and large-scale production.

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None.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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