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Exploring the Therapeutic Properties of Ellagic Acid Nanoclusters - A Review

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ABSTRACT

Ellagic acid (EA) is a natural polyphenol and dilactone of hexahydroxydiphenic acid (HHDP), primarily found as ellagitannins in plants like pomegranates, raspberries, grapes, nuts, and strawberries. Its molecular structure consists of a gallic acid dimer linked by two lactone bonds. EA is produced through the hydrolysis of ellagitannins and geraniin and is a major bioactive compound in pomegranates, exhibiting strong antioxidant, anti-diabetic, anti-cancer, antiparasitic, and organ-protective properties.

However, EA's low water solubility limits its absorption and therapeutic potential. To enhance its bioactivity and bioavailability, various nanoparticle formulations and microspheres have been developed. Recent in vitro and in vivo studies indicate that EA nanoparticles (EA-NPs) offer improved antioxidant effects, mitigate oxidative stress, detoxify, and inactivate DNA and RNA viruses. EA-NPs have also shown benefits in reducing diabetes complications and preventing lung, prostate, and pancreatic cancers. Additionally, EA-loaded microspheres exhibit inhibitory effects on *Babesia* species and *Theileria equi*, while EA nanoparticle formulations combined with chemotherapeutics show promise in breast cancer therapy. This review explores EA nanoparticle formulations and their recent therapeutic advancements.

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Introduction

Ellagic acid was discovered in 1831 by Braconnot, who named it "acide ellagique" [1]. Ellagic acid (EA) (Figure. 1), 2,3,7,8-tetrahydroxy-chromeno[5,4,3-cde] chromene-5,10-dione (molecular formula $C_{14}H_6O_8$) is a naturally occurring polyphenolic and powerful bioactive and highly thermostable (350°C melting point) molecule with 302 $gmol^{-1}$ of molecular weight. The structure of EA contains a lipophilic domain represented by four rings and it has four phenolic groups with two lactones which represent its hydrophilic domain [2].

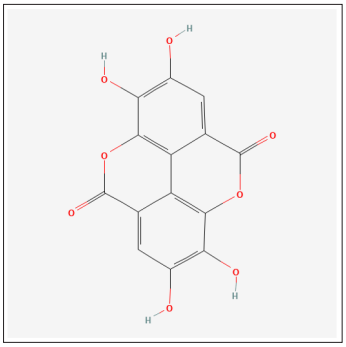

Figure 1: Ellagic Acid

Sources of EA

The presence of EA in plants was not widely known until the 20th century. Being part of the tannin family, EA is widely present in vegetables, fruits, oak, seeds and nuts [3] (Table 1). EA is one of the abundant phenolic acids in pomegranate juice (Punica granatum L.) [4]. In plant cells, EA is present in the bound form i.e., EA glycosides and ellagitannins (ET). EA glycosides contain sugar residues such as glucose, xylose, arabinose, or rhamnose. Upon hydrolysis, both ellagitannins and EA glycosides release EA, a process that occurs in various plants as well as in the digestive systems of humans and herbivorous animals [5]. For a long time, plants containing high amounts of EA have been identified as traditional medicine in Chinese medicine and Ayurveda [6].

Table 1: Some Sources of Ellagic Acid

Part	Common name	Scientific name	Reference
Fruit	Blackberry	*Rubus ursinus*	[7]
	Red raspberry	*Rubus idaeus*	[8]
	Strawberry	*Fragaria ananassa*	[8].
	Hipberry	*Rosa Canina*	[9]
	Plum	*Terminalia ferdinandiana*	[10]

	Cranberries	*Vaccinium subg. Oxycoccus*	[11]
	Pomegranate	*Punica granatum*	[12]
	Guava	*Psidium guajava L.*	[13]
	Black currants	*Ribes nigrum*	[14]
	Boysenberries	*Rubus ursinus × Rubus idaeus*	[15]
	Cloudberries	*Rubus chamaemorus*	[11]
Wood	Spanish oak	*Quercus pyrenaica*	[16]
	Chestnut oak	*Quercus prinus*	[17]
	White oak	*Quercus alba*	[17]
	Java plum bark	*Syzygium cumini*	[18]
	Mousedeer Plant bark	*Anisophyllea dichostyla R. Br.*	[19]
	Brazil nuts bark	*Bertholletia excelsa*	[20]
	Beka bark	*Oroxylum indicum*	[21]
Leaves	Eucalyptus	*Eucalyptus globulus*	[22]
Seeds and nuts	Walnuts	*Juglans nigra*	[7]
	Longan seed	*Dimocarpus longan*	[23]
	Manger kernel	*Mangifera indica*	[23]
	Pecan kernel	*Carya illinoinensis*	[24]
	Chestnut	*Castanea sativa*	[25]
	Heartnut	*Juglans ailantifolia*	[26]
	Brazil nuts	*Bertholletia excelsa*	[27]
	Peanuts	*Arachis hypogaea*	[28]
	Cashews	*Anacardium occidentale*	[29]
	Pistachio	*Pistacia vera L.*	[30]
	Pine nuts	*Pinus pinea*	[31]
	Almonds	*Prunus dulcis*	[32]
	Persian walnuts	*Juglans regia*	[26]

ETs can be categorized into monomeric, oligomeric, and polymeric types based on the number of hexahydroxydiphenic acid (HHDP) groups in the molecule [33,34]. Monomeric ETs consist of a single HHDP group attached to a glucoside core [33]. These monomeric ETs often undergo polymerization to form dimers, oligomers, and polymers, where the units are linked via C-O-C bonds [33,35] Table 2.

Table 2: Types of Ellagitannins

ET type	Examples
Monomeric ETs	Nupharin A, Geraniin, Tellimagrandin II, Punicalagin, Eugeniin, Davidiin, Casuarictin, Corilagin
Dimeric ETs	Sanguiin
Oligomeric ETs	Agrimoniin, Nupharin E, Nupharin C, Hirtellin A
C-glycosidic ETs	Vescalagin, Castalagin, Casuarinin, Stachyurin

Biosynthesis of EA

EA is mainly formed through the oxidation and dimerization of gallic acid derivatives. Gallic acid is synthesized via the shikimate pathway where 3-dehydroshikimate is converted to gallic acid through dehydrogenation. Depending on the species, this step can also occur via the polyketide pathway. Following this, gallic acid is esterified with glucose to form β-glucogallin, which forms serves as a building block to form larger polyphenolic compounds called Ellagitannins. Oxidative coupling between galloyl residues leads to the formation of HHDP units, which are characteristic structures of ETs [36].

Most ETs hydrolyze to produce EA, a process facilitated by the breakdown of HHDP groups into EA under acidic or enzymatic conditions. This characteristic is common among monomeric, oligomeric, and some polymeric ETs, as the HHDP groups are a defining feature of these compounds. However, C-glycosidic ellagitannins, such as vescalagin and castalagin, are structurally distinct due to their C-glycosidic linkages, which render them more resistant to hydrolysis. While they can release EA under certain conditions, their hydrolysis is generally more challenging compared to other types of ETs [37].

Extraction of EA from Natural Sources

EA content varies significantly across different fruits, nuts, and seeds, influenced by the extraction methods used. In fruits, berries such as raspberries and cane berries show a wide range of ellagic acid content, from 2.63 to 90 mg/g, with extraction methods like solid-liquid extraction, and sonication [38] [39]. Pomegranate has notably high concentrations in its peels, mesocarps, and juice, with values reaching up to 81.23 mg/g and 2071 mg/L in the juice, extracted through methods like pressurized water, stirring, and solid-liquid extraction [40-42]. Strawberries, blackberries, and boysenberries tend to have lower levels, with some extractions yielding up to 17.92 mg/g [43-45]. Nuts and seeds such as pecan kernels exhibit wide variation depending on the preparation, ranging from 20.96 to 86.21 mg/g [23,24,46]. while mango kernel and longan seed contain relatively low ellagic acid levels (0.031–1.18 mg/g) [24].

The efficiency of EA extraction is influenced by factors such as the type of plant material, the part analyzed, and the specific extraction conditions. Alcohol-based solvents, particularly when acidified, have proven to be the most effective, especially when paired with techniques like vortexing and sonication [47]. In many studies, aqueous methanol in varying concentrations has been favoured as the extraction solvent. This preference is attributed to the high polarity of these solvents, which significantly enhances the yield of extracted compounds [48]. To further optimize the recovery of EA, some researchers employ multi-solvent extraction strategies. For example, Määttä-Riihinen et al. used ethyl acetate for the initial extraction, followed by methanol to process the remaining

solid residue, showcasing a methodical approach to maximize EA recovery [8]. This combination of advanced techniques and strategic solvent use underscores the importance of tailoring the extraction protocol to the specific characteristics of the plant material and the desired compound.

Technical applications of EA

Research on EA has been highly interdisciplinary, with a significant focus on its medicinal and nutritional benefits. However, its applications extend beyond these areas, encompassing various other fields as well. It has been identified as an efficient chelating agent for metal ions by Zhang et al. and Przewloka et al., further enhancing its potential in environmental and industrial applications [49,50]. Reitze et al. expanded on EA's chemical versatility, synthesizing a range of innovative polymer precursors, which could open new possibilities in material science [51]. In recent years, EA has garnered attention for its use as a chemical sensor, with researchers demonstrating its ability to detect nitrobenzene and selectively identify copper ions in aqueous solutions, highlighting its promise for environmental monitoring and analytical applications [52] [53]. Additionally, Goriparti et al. showed that EA could serve as a high-capacity electrode material for lithium-ion batteries, suggesting its relevance in energy storage technologies [54]. Grape et al. explored EA in the creation of biocompatible bismuth ellagate metal-organic frameworks (MOFs), underlining its role in the development of bioinspired microporous materials for advanced applications [55]. Additionally, Vilela et al. demonstrated that chitosan/ellagic acid films exhibit UV-light protection, homogeneity, and flexibility, positioning them as effective materials for active food packaging [56]. These diverse studies collectively highlight the versatile technical applications of ellagic acid in areas ranging from environmental management to material science and energy storage.

Pharmacological Effects of EA

As research continues, the potential health benefits and therapeutic applications of simple ellagitannins, including their role in plant defence, are being increasingly recognized. EA has been notified to possess robust antioxidant activity against ROS (reactive oxygen species) in a cell-based assay. EA is not only a potent antioxidant, but it is also reported to have anticarcinogenic, anti-apoptotic, anti-inflammatory, antiviral, antibacterial, antidiabetic, cardioprotective and neuroprotective properties (Figure 2) [58-66].

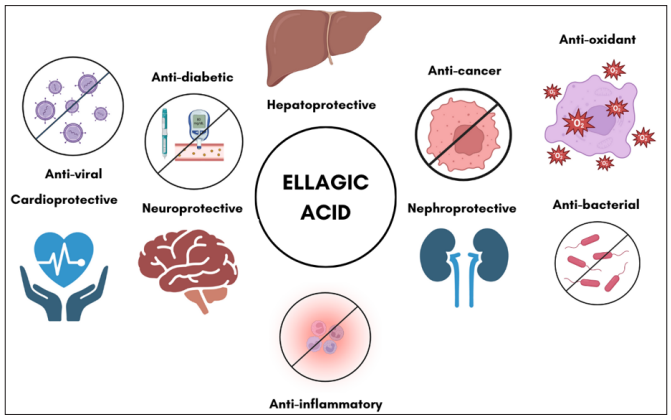

Figure 2: Pharmacological Properties of EA (Image source - Biorender)

Hseu et al. reported that ellagic EA protects human keratinocytes from UVA-induced oxidative stress and apoptosis by enhancing cell viability, reducing ROS and DNA damage, and modulating Nuclear erythroid 2-related factor 2 (Nrf2) gene signalling. Its protective effects are linked to increased expression of antioxidant enzymes like Heme Oxygenase-1 (HO-1) and Superoxide dismutase (SOD) [67]. El-Shitany et al. reported that EA effectively reduces carrageenan-induced inflammation by inhibiting pro-inflammatory markers like Cyclooxygenase (COX-2), Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), Malondialdehyde (MDA), and Nitric oxide (NO), while boosting antioxidant levels (GSH) and anti-inflammatory cytokines (IL-10). Its protective effects involve modulation of oxidative stress, cytokine release, and COX-2 expression [61]. Han et al. observed that EA inhibited the mRNA expression of β-defensin2, an antimicrobial peptide commonly associated with psoriasis lesions. Additionally, they reported that EA reduced the mRNA expression of specific inflammatory cytokines and chemokines, including CXC motif chemokine ligand 8 (CXCL8) and CC motif chemokine ligand 20 (CCL20) in HaCaT human keratinocyte [68].

Chung et al. reported that EA inhibits ovarian carcinoma cell proliferation by inducing G1 phase arrest, caspase-3-mediated apoptosis, and restoring anoikis through modulation of key molecular pathways. It also enhances the efficacy of chemotherapy, suggesting its potential as a chemo preventive and therapeutic agent for ovarian cancer [69]. Umesalma et al. reported that EA inhibits colon cancer progression in a 1,2-dimethyl hydrazine (DMH) induced rat model by suppressing the phosphoinositide-3-kinase (PI3K)/ Protein kinase B (Akt) pathway, modulating B-cell lymphoma 2 (Bcl-2) family proteins, and activating Bcl-2-associated X protein (Bax) and caspase-3 to promote apoptosis. These findings highlight EA's potential as a chemo preventive agent against colon carcinoma [70]. Gonzalez-Sarrias et al. reported that its colonic metabolites, urolithin-A and -B, inhibit colon cancer cell growth by arresting the cell cycle and modulating mitogen-activated protein kinase (MAPK) signalling and cell cycle-related genes. These findings highlight their potential as dietary chemo preventive agents targeting key processes in colon cancer development [71].

Yu et al. reported that EA suppresses IL-1β-induced oxidative stress, nuclear translocation of NF-κB, and expression of adhesion molecules like vascular cell adhesion molecule-1 (VCAM-1) and endothelial leukocyte adhesion molecule (E-selectin) in human umbilical vein endothelial cells (HUVEC), reducing monocyte adhesion. These anti-inflammatory effects highlight EA's potential in preventing atherosclerosis [72]. Kullappan et al. reported that EA exhibited the strongest binding affinity (-9.9 kcal/mol) and the highest stability in complexes with Zika virus NS3 helicase, making it a promising inhibitor for viral RNA synthesis and genome replication. ADMET analysis confirmed its nontoxic and non-carcinogenic properties, emphasizing its therapeutic potential [73].

Ellagic acid wields its benignant effects by controlling multiple pathways which include antioxidant, anti-inflammatory, and anti-cancer properties. Its ability to modulate key molecular pathways such as Nrf2 signalling, PI3K/Akt, MAPK, and NF-κB, as well as its role in enhancing antioxidant enzyme expression, reducing oxidative stress, and promoting apoptosis, underscores its therapeutic potential. These findings suggest that EA is a promising natural compound for the prevention and treatment of various diseases, including cancer, atherosclerosis, and inflammatory conditions.

Bioavailability of EA

The bioavailability of ETs is low in humans. This may be due

to their large size and high polarity [74]. When hydrolysed, they release EA which is also poorly bioavailable due to their hydrophobic nature [75]. The high number of hydrogen bond donors and acceptors in ellagic acid, combined with its polar structure, makes it less likely to passively diffuse through lipid membranes, which is essential for drug absorption. While it doesn't fit Lipinski's criteria for oral bioavailability, it may still be biologically active and useful in non-oral formulations or for specific biological targets [76]. In humans, EA is typically absorbed through the stomach or small intestine [35]. The hydrolysis of ETs to release EA occurs in the small intestine, where the pH is neutral to slightly basic. This pH environment also facilitates the absorption of EA. While no specific transporters for EA uptake in the gut epithelium have been identified, it is believed to be absorbed via passive diffusion driven by a concentration gradient [77]. Once absorbed, EA is metabolized by the gut microbiota into urolithins [78]. Initially, one of the lactone rings of EA is opened, followed by the removal of a carboxyl group to form urolithin D. Urolithin D then undergoes dihydroxylation, losing one, two, or three hydroxyl groups, resulting in the formation of urolithin C, urolithin A/ isourolithin A, and urolithin B, respectively, each being more bioavailable than the other (Figure 3) [79].

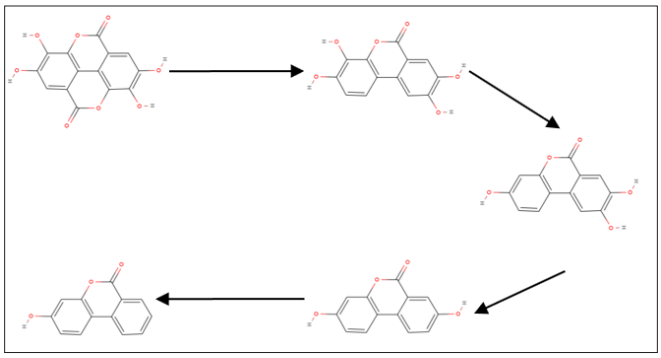

Figure 3: Gut Metabolism of EA

Furthermore, pharmacokinetic studies of EA have shown significant inter-individual variability. Additionally, González-Sarrías et al concluded that increasing the intake of EA does not enhance its bioavailability, with plasma concentrations rarely exceeding nanomolar levels in humans [80]. In contrast, urolithins can reach bloodstream concentrations at the micromolar level [81]. Since the conversion of EA to its metabolites occurs in vivo, discrepancies between in vitro and in vivo results regarding its bioavailability are inevitable [82]. In vitro studies frequently indicate high solubility and stability for EA, suggesting favourable absorption profiles [83]. However, these models lack critical physiological factors such as enzymatic activity, gut microbiota metabolism, and interactions with other dietary components, which are integral to the in vivo environment [84]. As a result, in vitro absorption rates often overestimate EA's actual bioavailability. Conversely, in vivo studies consistently report significantly lower bioavailability, as outlined previously. These differences highlight the need for a deeper understanding of EA's bioavailability mechanisms and the development of innovative strategies to enhance it.

Ellagic Acid Nanoparticle Formulations and Microspheres

EA due to its hydrophobic nature is insoluble in water resulting in lower bioavailability and bioactivity, poor absorption and quick elimination from our body. Because of this, its molecular effects and therapeutic edge are restricted as most of the clinical drugs are orally administered [85]. This led to the development of advanced delivery systems such as Nanoparticle formulations and Microspheres to overcome their hydrophobicity and to enhance their bioavailability and bioactivity [86].

● Chitosan-Coated Ellagic Acid Nanoparticles

Ellagic acid is loaded into chitosan nanoparticles and EANP@CS (Chitosan-coated ellagic acid nanoparticles) were prepared using sodium triphosphate (STP) as a gelatin agent. Chitosan is a Chitin-derived polymer compound, frequently used in enzyme loading and drug conduction carriers. Chitosan nanoparticles exhibit a positive surface charge which gives significant confluence to negatively charged biological membranes and site-specific site targeting. As a result, Chitosan nanoparticles are referred more specifically to the target cells as a drug-coated material to enhance drug release. Transmission electron micrographs of ellagic acid encapsulated chitosan nanoparticles (EANP@CS) revealed that EANP@CS are spherical in shape with average size of 20 to 62 nm [85].

● β-CD EA Microspheres

β-CD EA microspheres are prepared using β-cyclodextrin (β-CD) as a coating material of EA. β-cyclodextrin (β-CD), a cyclodextrin glucose transferase-derived cyclic oligosaccharide with seven glucose monomers form inclusion compounds. Here β-cyclodextrin (β-CD) acts as a host where Ellagic acid as a guest gets accommodated (host-guest interaction) resulting in the formation of an inclusion complex. Scanning electron microscopy (SEM) study revealed that β-CD EA microsphere complexes are spherical with a size of 6.12 ± 3.27 µm [87].

Antioxidant Mechanism of Ellagic Acid Nanoparticles

Recent studies have explored the antioxidant properties of EA in various forms, demonstrating its potential to mitigate oxidative stress in different biological contexts [88] (Table 3). One study highlighted the effectiveness of chitosan-coated ellagic acid nanoparticles (EANP@CS), derived from pomegranate, in reducing the harmful effects of sodium nitrite toxicity in rats. The treatment resulted in significant reductions in serum nitric oxide levels, liver and kidney nitric oxide levels, and liver NOS activity. In addition, liver Gpx and catalase activity were notably increased, while hepatic DNA fragmentation was significantly reduced, with a decrease in DNA damage from 43.32% in the sodium nitrite-intoxicated group to 27.30% in the EANP@CS-treated group [85]. This finding is further supported by studies on different formulations of EA. For example, EA has been intercalated into layered double hydroxide (LDH) nanoparticles, enhancing its bioavailability and antioxidant effects. These hybrid materials demonstrated significant antioxidant activity, measured by DPPH and CuPRAC assays, indicating their potential in scavenging free radicals [89]. In a similar vein, ellagic acid-loaded nanostructured lipid carriers (NLCs) prepared from various lipid compositions, including NLC-EA1 and NLC-EA2, were shown to manage high antioxidant activity with minimal toxicity to human keratinocyte cells. NLC-EA1 exhibited less cytotoxicity than NLC-EA2, further emphasizing the promise of lipid-based EA formulations for antioxidant therapies [90].

Table 3: Ellagic Acid Nanoparticles Exhibiting Antioxidant Mechanism

Sl no.	Nanoparticle type	Highlighted results	Reference
1	Chitosan-coated EA nanoparticles (EANP@CS)	Reduced nitric oxide levels, increased liver Gpx and catalase activity, reduced DNA damage (43.32% → 27.30%).	[85]
2	EA-Layered Double Hydroxide (LDH) Nanoparticles	Improved bioavailability; strong antioxidant activity (DPPH, CuPRAC assays).	[89]
3	Ellagic Acid-Loaded Nanostructured Lipid Carriers (NLCs)	High antioxidant activity; NLC-EA1 less cytotoxic than NLC-EA2.	[90]
4	Ellagic Acid-Loaded PEG-Chitosan Nanoparticles (EA@PCS)	Mitigated oxidative stress, apoptosis; synergistic effect, low cytotoxicity.	[91]
5	Ellagic Acid Nanoformulation (NEL) with Metformin	Enhanced testicular antioxidant capacity, reduced diabetic damage.	[92]
6	Ellagic acid crystalline particles	Significant H_2O_2 related ROS scavenging ability in PC12 cells	[93]
7	Ellagic acid - modified gold nanoparticles (EA-AuNPs)	EA-AuNPs targeted bacteria, reduced IL-6, and boosted IL-10, showing antimicrobial and anti-inflammatory potential.	[94]
8	Ellagic acid loaded zein nanoparticles	EA-loaded zein NP demonstrated potential against free radicals and infections by Gram-positive and Gram-negative bacteria.	[95]

Other studies have also highlighted the role of EA-loaded nanoparticles in combating oxidative stress in specific models. For example, Ellagic Acid Loaded PEG-Chitosan Nanoparticles (EA@PCS) demonstrated significant antioxidant activity in human neuroblastoma cells, mitigating rotenone-induced oxidative stress and apoptosis. The combination of EA with a chitosan nanoparticle carrier was found to be less cytotoxic than when EA or chitosan were used separately, suggesting a synergistic protective effect [91]. Furthermore, an investigation into the antioxidant effects of EA in combination with metformin (MET) revealed promising results in alleviating testicular damage induced by diabetes. EA nanoformulation (NEL) significantly enhanced antioxidant capacity in the testes, with NEL and MET co-treatment showing the best outcome in restoring oxidative balance and reducing lipid peroxidation [92]. Together, these studies underscore the versatility of EA, particularly in nanoparticle form, for combating oxidative stress and its potential therapeutic applications in various diseases and conditions.

Detoxifying and Hepatoprotective Mechanism

Recent studies have highlighted the protective potential of EA nanoparticles in mitigating chemical-induced toxicity, particularly in liver and kidney models. One study demonstrated the ability of EA nanoparticles, prepared using the emulsion solvent diffusion technique to enhance bioavailability, in alleviating cisplatin (CISP)-induced hepatotoxicity in rats. Pre-treatment with EA nanoparticles resulted in significant reductions in liver function enzymes such as ALT, AST, and ALP, which are markers of liver damage. Additionally, oxidative stress markers like malondialdehyde (MDA) and nitric oxide (NO) levels were notably decreased, while liver glutathione (GSH) levels were significantly increased, indicating improved liver function. Immunohistochemical analyses further showed a decrease in apoptotic markers such as BAX and Bcl-2, highlighting the protective effect of EA nanoparticles in preventing liver cell apoptosis induced by CISP [96].

This hepatoprotective effect is supported by another study in which chitosan-coated EA nanoparticles (EANP@CS) were used to treat rats intoxicated with sodium nitrite (NaNO2). Results revealed that EANP@CS treatment significantly reduced serum urea levels, a marker of kidney dysfunction, as well as liver AST levels, compared to the NaNO2 intoxicated group. These findings emphasize the nephroprotective and hepatoprotective effects of EA nanoparticles, suggesting their potential to counteract oxidative stress and organ damage induced by toxic chemicals like cisplatin and sodium nitrite [85]. Collectively, these studies suggest that ellagic acid nanoparticles offer dual protection for both the liver and kidneys, providing a promising approach to ameliorating toxicity-induced damage.

Inactivates RNA, DNA Viruses

Currently, the entire world is recovering from the COVID-19 pandemic, emerging from the new coronavirus SARS-CoV 2 along with its various mutants has severely affected numerous lives and economic systems across the globe. Till now no clinically approved drug has been developed for this disease. In a recent study, a hybrid Ellagic acid nanoformulation was developed and tested across various cell lines. In this study, Ellagic acid is prepared as inorganic-organic hybrid nanoformulation by using inorganic functionalized zinc oxide nanoparticles (ZnO NPs) where organic Ellagic acid is loaded via covalent interactions and the effect of this hybrid nanoformulation on cell lines such as human coronavirus 229E (HCoV-229E) (RNA viruses) and human adenovirus type 7 (Ad-7) (DNA viruses) were determined. The Antiviral Evaluation of Ellagic acid hybrid nanoformulation treated Ad-7 (DNA virus) and HCoV-229E (RNA viruses) cell lines have shown lower IC50 4.1 µg/mL and 6.6 µg/mL respectively along with a better therapeutic index of 51.7 and 75.7 respectively compared to the control (ZnO NPs) group. Moreover, this hybrid nanoformulation showed direct inactivation of HCoV-229E with a percentage inhibition of > 60%. This result suggests that this hybrid nanoformulation is potentially secure and a cost-effective possible therapeutic strategy for COVID-19 [97].

Antiparasitic Activities of Ellagic Acid

A recent study investigated the antiparasitic effects of EA on *Theileria equi* (in vitro) and four Babesia species, including *B. bovis*, *B. bigemina*, *B. divergens*, and *B. caballi* (in vitro), as well as *Babesia microti* in mice (in vivo). In this study, EA was formulated into microspheres using β-cyclodextrin (β-CD), referred to as β-CD EA microspheres, and into APSP EA nanoparticles using an antisolvent precipitation method with a syringe pump. The formulations were then evaluated for their effects on Babesia species and *T. equi* in vitro, and *B. microti*

in vivo. In vitro growth-inhibition assays showed that β-CD EA microspheres significantly inhibited the growth of all Babesia species and *T. equi*, with the APSP EA nanoparticles showing lower IC50 (half-maximal inhibitory concentration) values than the β-CD EA microspheres. In vivo, APSP EA nanoparticles reduced peak parasitemia of *B. microti* by 68.1% at a concentration of 70 mg/kg, and when combined with atovaquone (AQ), APSP EA nanoparticles exhibited an enhanced chemotherapeutic effect compared to the nanoparticles alone. These results suggest that ellagic acid in both microspheres and nanoparticle formulations holds promise as an effective antiparasitic therapy [98].

Inhibition of Adipogenic Differentiation

A recent study prepared Chitosan/alginate-ellagic acid microspheres and evaluated their effects on the murine preadipocyte cell line 3T3-F442A. These microspheres demonstrated a dose-dependent inhibitory effect on preadipocyte proliferation. Oil Red O staining of the 3T3-F442A adipocytes indicated that Chitosan/alginate-ellagic acid microspheres effectively inhibited adipogenesis, the process by which preadipocytes differentiate into adipocytes, in a dose-dependent manner. To explore the underlying molecular mechanisms, the study assessed the mRNA expression of C/EBPα (CCAAT/enhancer-binding protein alpha) and PPARγ (peroxisome proliferator-activated receptor gamma) using qPCR analysis. The results showed that the Chitosan/alginate-ellagic acid microspheres significantly downregulated the expression of C/EBPα and PPARγ, leading to the inhibition of both preadipocyte proliferation and adipogenic differentiation [99].

Antidiabetic Mechanism of Ellagic Acid Nanoparticles

Diabetes mellitus (DM) is a metabolic disorder characterized by elevated blood glucose levels, arising either from underproduction of insulin (Type-1 DM) or impaired insulin action (Type-2 DM). Type-1 DM is largely genetic, while Type-2 DM is primarily driven by lifestyle factors and is more manageable. Both types can lead to acute complications such as hyperglycemia, hypoglycemia, and diabetic ketoacidosis, as well as chronic complications including retinopathy, nephropathy, neuropathy, cardiovascular diseases (CVD), and Alzheimer's disease, all of which are associated with increased oxidative stress from elevated blood glucose. Recent studies have investigated potential therapeutic approaches involving ellagic acid (EA), a potent antioxidant, to alleviate some of these complications.

One such study developed ellagic acid nanoparticles (NEA) encapsulated with zinc oxide and evaluated their effects on two key enzymes, aldose reductase and α-glucosidase. Aldose reductase plays a critical role in the development of diabetic complications via the polyol pathway, generating reactive oxygen species (ROS), while α-glucosidase accelerates glucose absorption from dietary carbohydrates. In vitro tests showed that NEA significantly inhibited both enzymes at a concentration of 0.4%, demonstrating its potential to mitigate oxidative stress and prevent secondary diabetes complications, suggesting that NEA may be an effective therapeutic strategy [100].

Moreover, another study assessed the protective effects of EA, an ellagic acid nanoformulation (NEL), and metformin (MET) on testicular damage induced by high-fat diet (HF) and streptozotocin (STZ)-induced diabetes in rats. NEL combined with MET significantly improved fasting blood glucose (FBG) levels, testicular weight, and histopathological markers, preserving germ cell layers and seminiferous tubules. In contrast, diabetic rats treated with EA alone or MET alone showed less significant improvements. These results suggest that NEL, particularly when combined with MET, effectively prevents male reproductive damage due to diabetes, underscoring the potential of EA-based formulations in restoring organ functions affected by diabetes [101].

Furthermore, a study examined ellagic acid nanoparticles (Ella NPs) alone and in combination with metformin (a common antidiabetic medication) for their effects on Type-2 diabetes in HFD/STZ-induced rats. Results showed that Ella NPs in combination with metformin not only significantly reduced blood glucose levels but also helped preserve the function of pancreatic beta cells, crucial for insulin production. The study also found a notable improvement in body weight and plasma lipid profiles in the combined treatment group compared to the diabetic controls, suggesting that Ella NPs, especially in synergy with metformin, could serve as a potent antidiabetic agent, improving glucose metabolism and reducing the risk of cardiovascular disease [102].

These studies interrelate in showing that ellagic acid, in various nanoparticle forms, offers significant antioxidant and therapeutic potential for managing diabetes and its complications, particularly when combined with conventional antidiabetic drugs such as metformin.

Anticancer Mechanism

Cancer is a major global health concern, with an estimated 17 million diagnoses in 2018 and a predicted rise to 27.5 million new cases by 2040, as reported by the International Agency for Research on Cancer. The key risk factors for cancer include smoking, unhealthy diets, sedentary lifestyles, and infections, and this burden is expected to increase substantially due to population growth and aging [103]. In recent studies, ellagic acid (EA), a potent antioxidant, has emerged as a promising anticancer agent, demonstrating anticancer potential across various cancer types when delivered through innovative nanoformulations.

One such study investigated the anticancer effects of EA delivered as solid lipid nanoparticles (SLNs) in human prostate cancer (PC3) cells. EA-loaded SLNs displayed enhanced drug release, particularly in lower pH and higher temperature conditions, and exhibited a dose-dependent antiproliferative effect in PC3 cells. MTT assays showed a lower IC50 value for EA-loaded SLNs compared to EA alone, indicating increased potency. Moreover, apoptosis induction, confirmed by DAPI staining and upregulation of pro-apoptotic Bax mRNA (2.39-fold increase), supports the efficacy of EA-loaded SLNs. These findings suggest that EA-loaded SLNs can overcome the therapeutic limitations of EA and serve as a potential therapeutic strategy for prostate cancer [104]. In yet another study, EA was combined with lipoic acid (ALA) and fluvastatin (FLV) in nanostructured lipid carriers (NLCs) and tested against prostate cancer (PC-3) cells. The combination of EA, ALA, and FLV NLCs showed a significant increase in caspase-3 activity, an apoptotic marker, compared to EA, ALA, and FLV alone. The combination also reduced cell viability more effectively, with a lower IC50 value, suggesting that EA in combination with ALA and FLV in NLCs holds promise as an enhanced therapeutic approach for prostate cancer treatment [105].

Additionally, EA has been investigated for its effectiveness in lung cancer (A549 cells), using lactoferrin–chondroitin sulfate nanocomplexes to deliver both EA and doxorubicin (DOX), a chemotherapeutic agent. This inhalable nanocomplex showed improved cytotoxicity and enhanced drug accumulation in A549 cells. In vivo studies in mice revealed significant reductions in lung tumor weight and tumor biomarkers such as VEGF and Ki-67,

confirming the potential of EA-DOX inhalable nanocomplexes as a promising targeted therapy for lung cancer [106].

Furthermore, in the treatment of tongue squamous carcinoma (SAS) cells, a synergistic therapy combining EA with microRNA 125 (miR-125), which regulates mitochondrial dysfunction, demonstrated enhanced anticancer activity. EA and miR-125 nanoformulations targeted mitochondria and cellular metabolism, effectively reducing tumor growth in SAS cells. This combination offers a new therapeutic strategy targeting mitochondrial dysfunction, a key metabolic alteration in cancer cells [107].

These studies illustrate the growing potential of EA in cancer therapy, particularly when formulated in combination with other bioactive compounds in nanoparticle forms. The synergistic effects seen in various cancer cell lines highlight the advantages of nanomedicine in enhancing drug delivery, improving therapeutic efficacy, and minimizing side effects, thus offering promising strategies for the treatment of several types of cancer.

In Breast Cancer Therapy

Breast cancer remains one of the most prevalent and deadly cancers among women worldwide. In 2020, it surpassed lung cancer as the most frequently diagnosed cancer, with an estimated 2.3 million new cases (11.7% of all cancer cases) and 684,996 deaths globally [108]. Recent research has focused on enhancing the efficacy of ellagic acid (EA), a bioactive compound with potent anticancer properties, through novel nanoparticle formulations. These studies have shown that combining EA with other anticancer agents in nanoparticle forms can significantly improve therapeutic outcomes against breast cancer.

One such study involved the preparation of EA encapsulated in chitosan nanoparticles coated with Tween 80 (EA-chitosan-NPs) to assess its therapeutic effects on breast cancer. In vitro, cytotoxicity tests on MCF-7 breast cancer cells revealed that EA-chitosan-NPs significantly inhibited cell proliferation, with a lower IC50 value (30.55 µg/ml) compared to uncoated EA-NPs (36.64 µg/ml) and free EA (39.55 µg/ml). The in vivo results in mice bearing Ehrlich Ascites Carcinoma (EAC) tumours also demonstrated that EA-chitosan-NPs effectively caused tumour regression (73%) after 28 days, which was notably higher than the tumour regression seen with uncoated EA-NPs (48%) and free EA (51%). Histopathological analyses revealed more significant tumour necrosis and fewer prominent nuclei in the EA-chitosan-NPs treated group, indicating a potent antitumor efficacy. This study suggests that EA-loaded chitosan nanoparticles may be a promising approach for breast cancer treatment in the future [109].

Another study evaluated EA encapsulated in Schizophyllan and Chitin nanoparticles (EA/SPG-NP and EA/Ch-NP) to enhance its bioavailability and therapeutic effects against MCF-7 cells. Both formulations showed significant inhibition of cell proliferation in a dose-dependent manner, with lower IC50 values compared to free EA, further supporting the potential of nanoparticle-based delivery systems for breast cancer therapy [110].

In a different approach, EA was combined with the cytotoxic drug Pemetrexed (PMT) and encapsulated in Lactoferrin-coupled mesoporous silica nanoparticles (Lf-MSNPs) to explore a synergistic effect against MCF-7 cells. The dual-loaded EA+PMT MSNPs showed enhanced inhibition of cancer cell proliferation with an IC50 of 14 µg/ml, significantly more effective than EA-loaded MSNPs (IC50 = 20 µg/ml), highlighting the therapeutic benefit of combining EA with other chemotherapeutic agents [111].

In another study, EA was combined with paclitaxel (PTX), a widely used anticancer drug, and encapsulated in N-iso-propylacrylamide-polyethylene glycol acrylate (NIPAAm-PEG) polymeric nanoparticles. The EA+PTX loaded nanoparticles showed superior inhibition of cell growth in MCF-7 cells compared to PTX-loaded nanoparticles alone. The combination of EA and PTX in these polymeric nanoparticles resulted in better inhibition with a lower IC50 of 45 µg/ml compared to PTX alone (80 µg/ml) [112].

Collectively, these studies underscore the potential of EA nanoparticle formulations as a potent therapeutic strategy for breast cancer, particularly when combined with established chemotherapeutic agents like Pemetrexed and Paclitaxel. The use of nanoparticle carriers not only enhances the bioavailability and targeted delivery of EA but also improves its synergistic effect with other anticancer agents, making these combination therapies highly promising for effective breast cancer treatment.

Discussion

Ellagic acid, a polyphenolic compound with a unique structure featuring both lipophilic and hydrophilic domains, is a natural antioxidant that has gained considerable attention for its various pharmacological and therapeutic properties [113]. It is derived from the hydrolysis of ellagitannins, present in various plant sources such as pomegranates, raspberries, strawberries, and walnuts. This molecule demonstrates not only a broad range of medicinal benefits but also promises in diverse technical applications, such as in materials science and environmental monitoring.

EA's robust antioxidant activity is one of its most widely recognized benefits, particularly in protecting cells from oxidative stress. This protective effect extends beyond antioxidants to include anti-inflammatory, anticarcinogenic, and neuroprotective properties. EA's capacity to inhibit inflammatory pathways makes it an attractive candidate for the prevention and treatment of chronic conditions like cancer, cardiovascular diseases, and neurodegenerative disorders. Furthermore, EA has shown potential in synergizing with chemotherapy in ovarian cancer treatment, underscoring its value as both a chemo preventive and therapeutic agent.

Despite its promising pharmacological properties, EA faces a significant challenge of low bioavailability. Both EA and its precursor ellagitannins are poorly absorbed due to their large molecular size, polarity, and hydrophobic nature, which limit their effectiveness in vivo. The conversion of EA into bioactive urolithins by gut microbiota improves bioavailability, though the process varies among individuals due to differences in microbiota composition [114]. EA's therapeutic efficacy is constrained by rapid metabolism and limited systemic availability. Urolithins, the metabolites derived from EA, overcome many of these limitations due to their enhanced bioavailability, allowing for better systemic distribution. Among them, urolithin A has shown significant anti-inflammatory and antioxidant effects, as well as neuroprotective benefits and the ability to address metabolic disorders like type 2 diabetes and obesity. Compared to EA, urolithins are more effective at improving intestinal barrier function and preventing inflammation-induced barrier dysfunction. While both EA and urolithins share antioxidant and anti-inflammatory properties, urolithins are more versatile and potent in their therapeutic applications due to their superior bioavailability and broader pharmacological spectrum, particularly in treating metabolic and neurodegenerative disorders.

Recent advancements suggest that optimizing extraction and formulation methods could mitigate some of the bioavailability issues. Strategies such as employing methanol-based solvents, ultrasound-assisted extraction, and multi-solvent extraction systems have been effective in obtaining higher yields of EA from plant material. Additionally, improving the stability and solubility of EA formulations may enhance their potential for therapeutic applications. As a solution, advanced drug delivery systems, such as nanoparticle formulations and microspheres, have been explored to overcome these barriers and enhance the therapeutic efficacy of EA.

The development of chitosan-coated ellagic acid nanoparticles (EANP@CS) represents a promising approach to overcoming EA's poor solubility. Chitosan, a biocompatible and biodegradable polymer, offers several advantages, including improved drug loading, controlled release, and enhanced cellular uptake due to its positive surface charge, which enables effective interaction with negatively charged biological membranes. Transmission electron micrographs have revealed that these nanoparticles possess a spherical shape with an average size ranging from 20 to 62 nm, which contributes to their efficient penetration across biological barriers [85]. Additionally, the use of β-cyclodextrin (β-CD) to form EA-loaded microspheres enhances solubility by facilitating the formation of an inclusion complex. β-CD serves as a host molecule, accommodating EA as the guest, thereby stabilizing the hydrophobic drug. The resulting β-CD EA microspheres are spherical in shape and exhibit controlled release properties that further promote the bioavailability of EA [87]. This strategy of combining β-CD and EA ensures greater efficiency in drug delivery, which can be crucial for targeting diseases with oxidative stress-related pathophysiology, such as cancer and diabetes.

The incorporation of EA into nanoparticle formulations significantly enhances its antioxidant capacity. Various studies have demonstrated that EA-loaded nanoparticles, such as EANP@CS, effectively mitigate oxidative damage. One study highlighted the antioxidant activity of chitosan-coated EA nanoparticles in rats with sodium nitrite-induced toxicity, where the treatment reduced oxidative stress markers, including nitric oxide and DNA fragmentation, and boosted antioxidant enzyme activities like Gpx and catalase [85]. These findings are consistent with other reports showing that EA-loaded nanoparticles or hybrids (such as those with layered double hydroxides or lipid carriers) effectively scavenge free radicals and reduce oxidative stress, thereby demonstrating promising therapeutic potential for managing diseases linked to oxidative damage [89,90].

Moreover, EA's role in protecting against chemical-induced hepatotoxicity and nephrotoxicity has been established in several models. For instance, EA nanoparticles reduced liver damage and improved liver function in rats treated with the chemotherapy drug cisplatin [96]. The hepatoprotective and nephroprotective effects of EA-loaded nanoparticles are crucial for mitigating drug-induced organ toxicity, a common challenge in cancer therapies and other therapeutic treatments [115].

EA formulations have also shown promise in antiviral and antiparasitic treatments. The development of EA hybrid nanoformulations with zinc oxide nanoparticles demonstrated significant antiviral activity against both RNA and DNA viruses, including human coronavirus 229E and adenovirus type 7, providing a potential therapeutic avenue for managing viral infections such as COVID-19 [97]. In addition to its antiviral properties, EA-loaded nanoparticles have exhibited activity against parasitic infections, particularly against Babesia species and Theileria equi. Both in vitro and in vivo studies have demonstrated that EA-based formulations, including β-CD EA microspheres and APSP EA nanoparticles, reduce parasitemia and enhance chemotherapeutic effects when combined with other treatments like atovaquone [98]. These findings suggest that EA could be developed as a potent anti-parasitic agent through nanoparticle-based delivery systems.

The ability of EA to combat cancer has gained significant attention, with numerous studies exploring its anticancer effects when formulated into nanoparticles. EA-loaded nanoparticles have demonstrated enhanced bioavailability, improved tumor penetration, and a higher therapeutic index compared to free EA [116,117]. For example, EA encapsulated in solid lipid nanoparticles (SLNs) significantly inhibited the proliferation of cancer cells, induced apoptosis, and reduced tumor growth in animal models [104]. The synergistic effects of EA in combination with other anticancer agents, such as diindolylmethane and paclitaxel, further suggest that EA-loaded nanoparticles could serve as effective carriers for combination therapies, improving treatment outcomes and reducing side effects in cancer therapy [105,112]. EA formulations are also showing promise in the treatment of breast cancer. Recent research revealed that EA encapsulated in chitosan nanoparticles significantly inhibited the proliferation of MCF-7 breast cancer cells and induced tumor regression in a mouse model [109]. Moreover, combination therapies involving EA and other cytotoxic agents, such as pemetrexed or paclitaxel, delivered via nanoparticles, demonstrated synergistic anticancer effects with reduced IC50 values and enhanced therapeutic responses [111,112].

The antioxidant and anti-inflammatory effects of EA, particularly in nanoparticle form, offer great potential in alleviating complications of diabetes. EA nanoparticles have shown promise in inhibiting key enzymes involved in diabetic complications, such as aldose reductase and α-glucosidase, and may provide a viable strategy for managing oxidative stress and preventing secondary complications [100]. Furthermore, combination therapies involving EA and metformin have demonstrated protective effects on diabetic-induced testicular damage, offering a potential approach for managing male reproductive health in diabetes [102].

Conclusion

While EA shows great promise as a multi-functional bioactive compound with significant medicinal and technical benefits, overcoming its bioavailability limitations remains a key hurdle. Future research focusing on enhancing its absorption and systemic bioavailability, alongside its ongoing use in diverse fields, will determine its full potential as a therapeutic agent and functional material in technology. EA, especially when delivered through advanced nanoparticle formulations, offers significant therapeutic potential across a variety of biological contexts, including antioxidant defense, cancer treatment, antiviral and antiparasitic therapy, and the management of diabetes and its complications. Nanoparticle and microsphere-based delivery systems enhance the bioavailability, stability, and controlled release of EA, maximizing its therapeutic efficacy while minimizing side effects. Continued research into these advanced formulations holds promise for expanding the clinical applicability of ellagic acid in managing oxidative stress-related diseases and other chronic conditions.

References

1. Law DJ (1922) Synthetic tannins: Their synthesis, industrial products and application. By Georg Grasser. Translated by F. G. A. Enna. Pp. vi+143. (London: Crosby Lockwood and Son. 1922.) Price 12s. net. Journal of the Society of Chemical Industry 41: R141–R141.
2. Sepulveda L, Ascacio A, Rodriguez-Herrera R, Aguilera-Carbo A, Aguilar CN (2012) ChemInform Abstract: Ellagic Acid: Biological Properties and Biotechnological Development for Production Processes. ChemInform. https://onlinelibrary.wiley.com/doi/abs/10.1002/chin.201250260.
3. Derosa G, Maffioli P, Sahebkar A (2016) Ellagic Acid and Its Role in Chronic Diseases. In: Gupta SC, Prasad S, Aggarwal BB, editors. Anti-inflammatory Nutraceuticals and Chronic Diseases [Internet]. Cham: Springer International Publishing 473-479.
4. Amakura Y, Okada M, Tsuji S, Tonogai Y (2000) Determination of phenolic acids in fruit juices by isocratic column liquid chromatography. J Chromatogr A 891: 183-188.
5. Lee JH, Johnson JV, Talcott ST (2005) Identification of Ellagic Acid Conjugates and Other Polyphenolics in Muscadine Grapes by HPLC-ESI-MS. J Agric Food Chem 53: 6003-6010.
6. Cui Q, Du R, Anantpadma M, Schafer A, Hou L, et al. (2018) Identification of Ellagic Acid from Plant Rhodiola rosea L. as an Anti-Ebola Virus Entry Inhibitor. Viruses 10: 152.
7. Daniel EM, Krupnick AS, Heur YH, Blinzler JA, Nims RW, et al. (1989) Extraction, stability, and quantitation of ellagic acid in various fruits and nuts. Journal of Food Composition and Analysis 2: 338-349.
8. Määttä Riihinen KR, Kamal Eldin A, Törrönen AR (2004) Identification and Quantification of Phenolic Compounds in Berries of Fragaria and Rubus Species (Family Rosaceae). J Agric Food Chem 52: 6178–6187.
9. Diamanti J, Mazzoni L, Balducci F, Cappelletti R, Capocasa F, et al. (2014) Use of Wild Genotypes in Breeding Program Increases Strawberry Fruit Sensorial and Nutritional Quality. J Agric Food Chem 62: 3944-3953.
10. Konczak I, Maillot F, Dalar A (2014) Phytochemical divergence in 45 accessions of Terminalia ferdinandiana (Kakadu plum). Food Chemistry151: 248-256.
11. (2025) Proanthocyanidins and hydrolysable tannins: occurrence, dietary intake and pharmacological effects - Smeriglio - 2017 - British Journal of Pharmacology - Wiley Online Library. https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bph.13630.
12. Fischer UA, Carle R, Kammerer DR (2011) Identification and quantification of phenolic compounds from pomegranate (Punica granatum L.) peel, mesocarp, aril and differently produced juices by HPLC-DAD–ESI/MSn. Food Chemistry 127: 807-821.
13. Liu X, Yan X, Bi J, Wu X, Liu J, et al. (2020) Identification of phenolic compounds and antioxidant activity of guava dehydrated by different drying methods. Drying Technology 38:987-1000.
14. Flores G, Ruiz del Castillo ML (2015) Variations in ellagic acid, quercetin and myricetin in berry cultivars after preharvest methyl jasmonate treatments. Journal of Food Composition and Analysis 39: 55-61.
15. Ryu J, Kwon SJ, Jo YD, Choi HI, Kang KY, et al. (2017) Fruit Quality and Chemical Contents of Hybrid Boysenberry (Rubus ursinus) Lines Developed by Hybridization and Gamma Irradiation. Plant Breeding and Biotechnology 5: 228-236.
16. Alañón ME, Castro Vázquez L, Díaz-Maroto MC, Hermosín Gutiérrez I, Gordon MH, et al. (2011) Antioxidant capacity and phenolic composition of different woods used in cooperage. Food Chemistry 129: 1584-1590.
17. Lei Z, Jervis J, Helm RF (2001) Use of Methanolysis for the Determination of Total Ellagic and Gallic Acid Contents of Wood and Food Products. J Agric Food Chem 49: 1165-1168.
18. Simões Pires CA, Vargas S, Marston A, Ioset JR, Paulo MQ, et al. (2009) Ellagic Acid Derivatives from Syzygium cumini Stem Bark: Investigation of their Antiplasmodial Activity. Natural Product Communications 4: 1934578X0900401012.
19. Khallouki F, Haubner R, Hull WE, Erben G, Spiegelhalder B, et al. (2007) Isolation, purification and identification of ellagic acid derivatives, catechins, and procyanidins from the root bark of Anisophyllea dichostyla R. Br. Food and Chemical Toxicology 45: 472-485.
20. Silva FMA da, Hanna ACS, Souza AA de, Silva FA da, Canhoto OMF, et al. (2019) Integrative Analysis Based on HPLC-DAD-MS/MS and NMR of Bertholletia excelsa Bark Biomass Residues:Determination of Ellagic Acid Derivatives. J Braz Chem Soc 30: 830-836.
21. Zaveri M, Jain AK (2008) Quantification of Baicalein, Chrysin, Biochanin-A and Ellagic Acid in Root Bark of Oroxylum indicum by RPHPLC with UV Detection. Eurasian Journal of Analytical Chemistry 3: 245-257.
22. Liu Z, Chen Z, Han F, Kang X, Gu H, et al. (2016) Microwave-assisted method for simultaneous hydrolysis and extraction in obtaining ellagic acid, gallic acid and essential oil from Eucalyptus globulus leaves using Brönsted acidic ionic liquid [HO3S(CH2)4mim]HSO4. Industrial Crops and Products 81: 152-161.
23. Soong YY, Barlow PJ (2006) Quantification of gallic acid and ellagic acid from longan (Dimocarpus longan Lour.) seed and mango (Mangifera indica L.) kernel and their effects on antioxidant activity. Food Chemistry 97: 524-530.
24. Gong Y, Pegg RB (2017) Separation of Ellagitannin-Rich Phenolics from U.S. Pecans and Chinese Hickory Nuts Using Fused-Core HPLC Columns and Their Characterization. J Agric Food Chem 65: 5810-5820.
25. Gonçalves B, Borges O, Costa HS, Bennett R, Santos M, et al. (2010) Metabolite composition of chestnut (Castanea sativa Mill.) upon cooking: Proximate analysis, fibre, organic acids and phenolics. Food Chemistry 122: 154-160.
26. Li, Tsao R, Yang R, Liu C, Zhu H, et al. (2006) Polyphenolic Profiles and Antioxidant Activities of Heartnut (Juglans ailanthifolia Var. cordiformis) and Persian Walnut (Juglans regia L.). J Agric Food Chem 54: 8033-8040.
27. John JA, Shahidi F (2010) Phenolic compounds and antioxidant activity of Brazil nut (Bertholletia excelsa). Journal of Functional Foods 2: 196-209.
28. Win M, Abdul Hamid A, Baharin B, Anwar F, Mc S, et al. (2011) Phenolic compounds and antioxidant activity of peanut's skin, hull, raw kernel and roasted kernel flour. Pakistan Journal of Botany 43: 1635-1642.
29. Chandrasekara N, Shahidi F (2011) Effect of Roasting on Phenolic Content and Antioxidant Activities of Whole Cashew Nuts, Kernels, and Testa. J Agric Food Chem 59: 5006-5014.
30. Tomaino A, Martorana M, Arcoraci T, Monteleone D, Giovinazzo C, et al. (2010) Antioxidant activity and phenolic profile of pistachio (Pistacia vera L., variety Bronte) seeds and skins. Biochimie 92: 1115-1122.
31. Faiqa Zulfqar, Muhammad F Akhtar, Ammara Saleem, Bushra Akhtar, Ali Sharif (2020) Chemical characterization, antioxidant evaluation, and antidiabetic potential of Pinus gerardiana (Pine nuts) extracts. Journal of Food Biochemistry: https://onlinelibrary.wiley.com/doi/10.1111/jfbc.13199.

32. Milbury PE, Chen CY, Dolnikowski GG, Blumberg JB (2006) Determination of Flavonoids and Phenolics and Their Distribution in Almonds. J Agric Food Chem 54: 5027-5033.
33. Aguilera Carbo A, Augur C, Prado Barragan LA, Favela Torres E, Aguilar CN (2008) Microbial production of ellagic acid and biodegradation of ellagitannins. Appl Microbiol Biotechnol 78: 189-199.
34. Aires A (2020) Tannins: Structural Properties, Biological Properties and Current Knowledge. BoD – Books on Demand 150.
35. Lipińska L, Klewicka E, Sójka M (2014) The structure, occurrence and biological activity of ellagitannins: a general review. Acta Scientiarum Polonorum Technologia Alimentaria 13: 289-299.
36. Ishikura N, Hayashida S, Tazaki K (1984) Biosynthesis of gallic and ellagic acids with14C-labeled compounds inAcer andRhus leaves. Bot Mag Tokyo 97: 355-367.
37. Jourdes M, Pouységu L, Deffieux D, Teissedre PL, Quideau S (2013) Hydrolyzable Tannins: Gallotannins and Ellagitannins. In: Ramawat KG, Mérillon JM, editors. Natural Products: Phytochemistry, Botany and Metabolism of Alkaloids, Phenolics and Terpenes [Internet]. Berlin, Heidelberg: Springer 1975-2010.
38. Wada L, Ou B (2002) Antioxidant Activity and Phenolic Content of Oregon Caneberries. J Agric Food Chem50: 3495-3500.
39. Bradish CM, Yousef GG, Ma G, Perkins Veazie P, Fernandez GE (2015) Anthocyanin, Carotenoid, Tocopherol, and Ellagitannin Content of Red Raspberry Cultivars Grown under Field or High Tunnel Cultivation in the Southeastern United States. https://journals.ashs.org/jashs/view/journals/jashs/140/2/article-p163.xml.
40. Romani A, Campo M, Pinelli P (2012) HPLC/DAD/ESI-MS analyses and anti-radical activity of hydrolyzable tannins from different vegetal species. Food Chemistry 130: 214-221.
41. Masci A, Coccia A, Lendaro E, Mosca L, Paolicelli P, et al. (2016) Evaluation of different extraction methods from pomegranate whole fruit or peels and the antioxidant and antiproliferative activity of the polyphenolic fraction. Food Chemistry 202: 59-69.
42. Çam M, Hışıl Y (2010) Pressurised water extraction of polyphenols from pomegranate peels. Food Chemistry 123: 878-885.
43. Gasperotti M, Masuero D, Guella G, Palmieri L, Martinatti P, et al. (2013) Evolution of Ellagitannin Content and Profile during Fruit Ripening in Fragaria spp. J Agric Food Chem 61: 8597-8607.
44. Van de Velde F, Pirovani ME, Drago SR (2018) Bioaccessibility analysis of anthocyanins and ellagitannins from blackberry at simulated gastrointestinal and colonic levels. Journal of Food Composition and Analysis 72: 22-31.
45. Williams DJ, Edwards D, Pun S, Chaliha M, Sultanbawa Y (2014) Profiling ellagic acid content: The importance of form and ascorbic acid levels. Food Research International 66: 100-116.
46. Malik NS, Perez JL, Lombardini L, Cornacchia R, Cisneros Zevallos L, et al. (2009) Phenolic compounds and fatty acid composition of organic and conventional grown pecan kernels. Journal of the Science of Food and Agriculture 89: 2207-2213.
47. Mantzourani C, Kakouri E, Palikaras K, Tarantilis PA, Kokotou MG (2024) Urolithins and Their Precursors Ellagic Acid and Ellagitannins: Natural Sources, Extraction and Methods for Their Determination. Separations 11: 174.
48. Markom M, Hasan M, Daud WRW, Singh H, Jahim JM (2007) Extraction of hydrolysable tannins from Phyllanthus niruri Linn.: Effects of solvents and extraction methods. Separation and Purification Technology 52: 487-496.
49. Zhang NZ, Chen YY (1988) Synthesis of Macroporous Ellagitannic Acid Resin and Its Chelating Properties for Metal Ions. Journal of Macromolecular Science: Part A – Chemistry 25: 1455-1462.
50. Przewloka SR, Shearer BJ (2002) The Further Chemistry of Ellagic Acid II. Ellagic Acid and Water-Soluble Ellagates as Metal Precipitants 56:13-19.
51. Reitze JD, Przewloka SR, Shearer BJ (2001) The Further Chemistry of Ellagic Acid: I. Synthesis of Tetramethylellagic Acid and Associated Polymer Precursors 55: 171-175.
52. Wang H, Xu X, Lee C, Johnson C, Sohlberg K, et al. (2012) Highly Selective Sensing of Nitroaromatics Using Nanomaterials of Ellagic Acid. J Phys Chem C 116: 4442-4448.
53. Gonçalves SSL, Rudnitskaya A, Sales AJM, Costa LMC, Evtuguin DV (2020) Nanocomposite Polymeric Materials Based on Eucalyptus Lignoboost® Kraft Lignin for Liquid Sensing Applications. Materials 13: 1637.
54. Goriparti S, Harish MNK, Sampath S (2013) Ellagic acid – a novel organic electrode material for high-capacity lithium-ion batteries. Chem Commun 49: 7234-7236.
55. Grape ES, Flores JG, Hidalgo T, Martínez-Ahumada E, Gutiérrez-Alejandre A, et al. A Robust and Biocompatible Bismuth Ellagate MOF Synthesized Under Green Ambient Conditions. J Am Chem Soc 142: 16795-16804.
56. Vilela C, Pinto RJB, Coelho J, Domingues MRM, Daina S, et al. (2017) Bioactive chitosan/ellagic acid films with UV-light protection for active food packaging. Food Hydrocolloids 73: 120-128.
57. Malini P, Kanchana G, Rajadurai M (2011) Antibiabetic Efficacy of Ellagic Acid in StreptozotocinInduced Diabetes Mellitus in Albino Wistar Rats 4.
58. Li TM, Chen GW, Su CC, Lin JG, Yeh CC, et al. (2005) Ellagic Acid Induced p53/p21 Expression, G1 Arrest and Apoptosis in Human Bladder Cancer T24 Cells. Anticancer Research 25: 971-979.
59. Khanduja KL, Avti PK, Kumar S, Mittal N, Sohi KK, et al. (2006) Anti-apoptotic activity of caffeic acid, ellagic acid and ferulic acid in normal human peripheral blood mononuclear cells: A Bcl-2 independent mechanism. Biochimica et Biophysica Acta (BBA) - General Subjects 1760: 283-289.
60. Ou HC, Lee WJ, Lee SD, Huang CY, Chiu TH, et al. (2010) Ellagic acid protects endothelial cells from oxidized low-density lipoprotein-induced apoptosis by modulating the PI3K/Akt/eNOS pathway. Toxicology and Applied Pharmacology 248: 134-143.
61. El Shitany NA, El Bastawissy EA, Eldesoky K (2014) Ellagic acid protects against carrageenan-induced acute inflammation through inhibition of nuclear factor kappa B, inducible cyclooxygenase and proinflammatory cytokines and enhancement of interleukin-10 via an antioxidant mechanism. International Immunopharmacology 19: 290-299.
62. Park SW, Kwon MJ, Yoo JY, Choi HJ, Ahn YJ (2014) Antiviral activity and possible mode of action of ellagic acid identified in Lagerstroemia speciosa leaves toward human rhinoviruses. BMC Complementary and Alternative Medicine 14: 171.
63. Abuelsaad ASA, Mohamed I, Allam G, Al Solumani AA (2013) Antimicrobial and immunomodulating activities of hesperidin and ellagic acid against diarrheic Aeromonas hydrophila in a murine model. Life Sciences 93: 714-722.

64. Da Silva Pinto M, De Carvalho JE, Lajolo FM, Genovese MI, Shetty K (2010) Evaluation of Antiproliferative, Anti-Type 2 Diabetes, and Antihypertension Potentials of Ellagitannins from Strawberries (Fragaria × ananassa Duch.) Using In Vitro Models. Journal of Medicinal Food 13: 1027-1035.
65. Kannan MM, Quine SD (2013) Ellagic acid inhibits cardiac arrhythmias, hypertrophy and hyperlipidaemia during myocardial infarction in rats. Metabolism - Clinical and Experimental 62: 52-61.
66. Kwak HM, Jeon SY, Sohng BH, Kim JG, Lee JM, et al. (2005) β-Secretase(BACE1) inhibitors from pomegranate (Punica granatum) husk. Arch Pharm Res 28: 1328-1332.
67. Hseu YC, Chou CW, Senthil Kumar KJ, Fu KT, Wang HM, et al. (2012) Ellagic acid protects human keratinocyte (HaCaT) cells against UVA-induced oxidative stress and apoptosis through the upregulation of the HO-1 and Nrf-2 antioxidant genes. Food and Chemical Toxicology 50: 1245-1255.
68.
69. Han YJ, Chung HS, Hwang HS (2024) Ellagic acid suppresses β-defensin2 antimicrobial peptide and CCL20 chemokine in psoriasis-like HaCaT human keratinocyte. Adv Tradit Med (ADTM). https://doi.org/10.1007/s13596-024-00814-6.
70. Chung YC, Lu LC, Tsai MH, Chen YJ, Chen YY, et al. (2013) The Inhibitory Effect of Ellagic Acid on Cell Growth of Ovarian Carcinoma Cells. Evidence-Based Complementary and Alternative Medicine 2013: 306705.
71. Umesalma S, Sudhandiran G (2011) Ellagic acid prevents rat colon carcinogenesis induced by 1, 2 dimethyl hydrazine through inhibition of AKT-phosphoinositide-3 kinase pathway. European Journal of Pharmacology 660: 249-258.
72. González Sarrías A, Espín JC, Tomás Barberán FA, García Conesa MT (2009) Gene expression, cell cycle arrest and MAPK signalling regulation in Caco-2 cells exposed to ellagic acid and its metabolites, urolithins. Molecular Nutrition & Food Research 53: 686-698.
73. Yu YM, Wang ZH, Liu CH, Chen CS (2007) Ellagic acid inhibits IL-1β-induced cell adhesion molecule expression in human umbilical vein endothelial cells. British Journal of Nutrition 97: 692-698.
74. Kullappan M, Benedict BA, Rajajagadeesan A, Baskaran P, Periadurai ND, et al. (2022) Ellagic Acid as a Potential Inhibitor against the Nonstructural Protein NS3 Helicase of Zika Virus: A Molecular Modelling Study. BioMed Research International 2022: 2044577.
75. Whitley AC, Stoner GD, Darby MV, Walle T (2003) Intestinal epithelial cell accumulation of the cancer preventive polyphenol ellagic acid—extensive binding to protein and DNA. Biochemical Pharmacology 66: 907-915.
76. Truchado P, Larrosa M, García Conesa MT, Cerdá B, Vidal Guevara ML, et al. (2012) Strawberry Processing Does Not Affect the Production and Urinary Excretion of Urolithins, Ellagic Acid Metabolites, in Humans. J Agric Food Chem 60: 5749-5754.
77. Cosme P, Rodríguez AB, Espino J, Garrido M (2020) Plant Phenolics: Bioavailability as a Key Determinant of Their Potential Health-Promoting Applications. Antioxidants 9: 1263.
78. González Barrio R, Borges G, Mullen W, Crozier A (2010) Bioavailability of Anthocyanins and Ellagitannins Following Consumption of Raspberries by Healthy Humans and Subjects with an Ileostomy. J Agric Food Chem58: 3933-3939.
79. Espín JC, Larrosa M, García Conesa MT, Tomás Barberán F (2013) Biological significance of urolithins, the gut microbial ellagic Acid-derived metabolites: the evidence so far. Evid Based Complement Alternat Med 2013: 270418.
80. García-Villalba R, Beltrán D, Espín JC, Selma MV, Tomás-Barberán FA (2013) Time Course Production of Urolithins from Ellagic Acid by Human Gut Microbiota. J Agric Food Chem 61: 8797-8806.
81. González Sarrías A, García Villalba R, Núñez Sánchez MÁ, Tomé Carneiro J, Zafrilla P, et al. (2015) Identifying the limits for ellagic acid bioavailability: A crossover pharmacokinetic study in healthy volunteers after consumption of pomegranate extracts. Journal of Functional Foods 19: 225-235.
82. Cerdá B, Tomás-Barberán FA, Espín JC (2005) Metabolism of Antioxidant and Chemopreventive Ellagitannins from Strawberries, Raspberries, Walnuts, and Oak-Aged Wine in Humans: Identification of Biomarkers and Individual Variability. J Agric Food Chem 53: 227-235.
83. Tomás Barberan FA, Espín JC, García-Conesa MT (2009) Bioavailability and Metabolism of Ellagic Acid and Ellagitannins. In: Chemistry and Biology of Ellagitannins [Internet]. World Scientific 273-297.
84. Vattem D, Shetty K (2005) Biological Functionality of Ellagic Acid: A Review. Journal of Food Biochemistry 29: 234-266.
85. Kawabata K, Yoshioka Y, Terao J (2019) Role of Intestinal Microbiota in the Bioavailability and Physiological Functions of Dietary Polyphenols. Molecules 24: 370.
86. EL Barky AR, Mohamed TM, Ali EMM (2020) Detoxifying and antioxidant effect of ellagic acid nano particles in rats intoxicated with sodium nitrites. Applied Biological Chemistry 63: 47.
87. Gu W, Kong R, Qi S, Cheng X, Cai X, et al. (2024) Sono-assembly of ellagic acid into nanostructures significantly enhances aqueous solubility and bioavailability. Food Chemistry 1: 442: 138485.
88. Wang H, Zhang Y, Tian Z, Ma J, Kang M, et al. (2017) Preparation of β-CD-Ellagic Acid Microspheres and Their Effects on HepG2 Cell Proliferation. Molecules 22: 2175.
89. Abe LT, Lajolo FM, Genovese MI (2010) Comparison of phenol content and antioxidant capacity of nuts. Food Sci Technol 30: 254-259.
90. Muráth S, Szerlauth A, Sebők D, Szilágyi I (2020) Layered Double Hydroxide Nanoparticles to Overcome the Hydrophobicity of Ellagic Acid: An Antioxidant Hybrid Material. Antioxidants.9: 153.
91. Singh Hallan S, Sguizzato M, Pavoni G, Baldisserotto A, et al. (2020) Ellagic Acid Containing Nanostructured Lipid Carriers for Topical Application: A Preliminary Study. Molecules 25: 1449.
92. Ahlawat J, Neupane R, Deemer E, Sreenivasan ST, Narayan M (2020) Chitosan–Ellagic Acid Nanohybrid for Mitigating Rotenone-induced Oxidative Stress. ACS Appl Mater Interfaces. 12: 18964-18977.
93. Harakeh S, Qari M, Rajeh N, Ali S, El-Shitany N, et al. (2022) Ellagic acid nanoparticles attenuate oxidative stress and testicular damage in high fat Diet/Streptozotocin-Induced diabetic rats. Journal of King Saud University - Science. 34: 101720.
94. Ha W, Ma R, Kang JY, Iradukunda Y, Shi YP (2024) Green and shape-tunable synthesis of ellagic acid crystalline particles by tannic acid for neuroprotection against oxidative stress. Biomater Sci 12: 3610-3621.
95. Wang Y, Wu F, Li Y, Wang S, Ren Y, et al. (2024) Ellagic acid-modified gold nanoparticles to combat multi-drug-resistant bacterial infections in vitro and in vivo. Mater Horiz 11: 4781-4790.
96. Tavares W de S, Pena GR, Martin Pastor M, Sousa FFO de (2021) Design and characterization of ellagic acid-loaded zein nanoparticles and their effect on the antioxidant and

antibacterial activities. Journal of Molecular Liquids 341: 116915.

97. El-Shitany NAEA, Abbas AT, Ali SS, Eid B, Harakeh S, et al. (2019) Nanoparticles Ellagic Acid Protects Against Cisplatin-induced Hepatotoxicity in Rats Without Inhibiting its Cytotoxic Activity. International J of Pharmacology 15: 465-477.
98. AbouAitah K, Allayh AK, Wojnarowicz J, Shaker YM, Swiderska-Sroda A, et al. (2021) Nanoformulation Composed of Ellagic Acid and Functionalized Zinc Oxide Nanoparticles Inactivates DNA and RNA Viruses. Pharmaceutics 13: 2174.
99. Beshbishy AM, Batiha GES, Yokoyama N, Igarashi I (2019) Ellagic acid microspheres restrict the growth of Babesia and Theileria in vitro and Babesia microti in vivo. Parasites & Vectors 12: 269.
100. Ding C, Bi H, Wang D, Kang M, Tian Z, et al. (2025) Preparation of Chitosan/Alginate-ellagic Acid Sustained-release Microspheres and their Inhibition of Preadipocyte Adipogenic Differentiation. https://www.eurekaselect.com/article/100243.
101. Marella S, Hema K, Shameer S, Prasad TNVKV (2020) Nano-ellagic acid: inhibitory actions on aldose reductase and α-glucosidase in secondary complications of diabetes, strengthened by in silico docking studies. 3 Biotech 10: 439.
102. Harakeh S, Qari MH, Ramadan WS, Jaouni SKA, Almuhayawi MS, et al. (2020) A Novel Nanoformulation of Ellagic Acid is Promising in Restoring Oxidative Homeostasis in Rat Brains with Alzheimer's Disease. https://www.eurekaselect.com/article/112480.
103. Harakeh S, Almuhayawi M, Jaouni SA, Almasaudi S, Hassan S, et al. (2020) Antidiabetic effects of novel ellagic acid nanoformulation: Insulin-secreting and anti-apoptosis effects. Saudi Journal of Biological Sciences. 27: 3474-3480.
104. Mao JJ (2019) Introduction. The Cancer Journal 25: 305.
105. Hajipour H, Hamishehkar H, Rahmati yamchi M, Shanehbandi D, Ahmad SNS, et al. (2018) Enhanced Anti-Cancer Capability of Ellagic Acid Using Solid Lipid Nanoparticles (SLNs). Int J Cancer Manag. https://brieflands.com/articles/ijcm-9402#abstract.
106. Fahmy UA (2018) Augmentation of Fluvastatin Cytotoxicity Against Prostate Carcinoma PC3 Cell Line Utilizing Alpha Lipoic–Ellagic Acid Nanostructured Lipid Carrier Formula. AAPS PharmSciTech 19: 3454-3461.
107. Abd Elwakil MM, Mabrouk MT, Helmy MW, Abdelfattah EZA, Khiste SK, et al. (2018) Inhalable Lactoferrin–Chondroitin Nanocomposites for Combined Delivery of Doxorubicin and Ellagic Acid to Lung Carcinoma. Nanomedicine 13: 2015-2035.
108. Lo YL, Wang CS, Chen YC, Wang TY, Chang YH, et al. (2020) Mitochondrion-Directed Nanoparticles Loaded with a Natural Compound and a microRNA for Promoting Cancer Cell Death via the Modulation of Tumor Metabolism and Mitochondrial Dynamics. Pharmaceutics 12: 756.
109. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, et al. (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: A Cancer Journal for Clinicians 71: 209-249.
110. Kaur H, Ghosh S, Kumar P, Basu B, Nagpal K (2021) Ellagic acid-loaded, tween 80-coated, chitosan nanoparticles as a promising therapeutic approach against breast cancer: In-vitro and in-vivo study. Life Sciences 284: 119927.
111. Pirzadeh Naeeni S, Mozdianfard MR, Shojaosadati SA, Khorasani AC, Saleh T (2020) A comparative study on schizophyllan and chitin nanoparticles for ellagic acid delivery in treating breast cancer. International Journal of Biological Macromolecules 144: 380-388.
112. Ali OM, Bekhit AA, Khattab SN, Helmy MW, Abdel-Ghany YS, et al. (2020) Synthesis of lactoferrin mesoporous silica nanoparticles for pemetrexed/ellagic acid synergistic breast cancer therapy. Colloids and Surfaces B: Biointerfaces 188: 110824.
113. Suri S, Mirza MA, Anwer MK, Alshetaili AS, Alshahrani SM, et al. (2019) Development of NIPAAm-PEG acrylate polymeric nanoparticles for co-delivery of paclitaxel with ellagic acid for the treatment of breast cancer. Journal of Polymer Engineering 39: 271-278.
114. Golmei P, Kasna S, Roy KP, Kumar S (2024) A Review on Pharmacological Advancement of Ellagic Acid. Journal of Pharmacology and Pharmacotherapeutics 15: 93-104.
115. Cardona F, Andrés-Lacueva C, Tulipani S, Tinahones FJ, Queipo-Ortuño MI (2013) Benefits of polyphenols on gut microbiota and implications in human health. The Journal of Nutritional Biochemistry 24: 1415-1422.
116. Ríos JL, Giner RM, Marín M, Recio MC (2018) A Pharmacological Update of Ellagic Acid. Planta Medica 84: 1068-1093.
117. Mahmoudi A, Pour VZ, Salehzadeh A (2024) Cobalt oxide nanoparticles functionalized with glucose and conjugated to Ellagic acid (Co3O4@Glu-Ellagic acid NPs) induce apoptotic genes in HepG2, liver cancer cell line. Gene Reports 35: 101897.
118. Lin IC, Wu JY, Fang CY, Wang SC, Liu YW, et al. (2023) Absorption and Metabolism of Urolithin A and Ellagic Acid in Mice and Their Cytotoxicity in Human Colorectal Cancer Cells. Evidence-Based Complementary and Alternative Medicine 2023: 8264716.