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REVIEW ARTICLE

A thorough assessment on the recent pharmacological and therapeutic potential of ellagic acid

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Abstract

This review comprehensively examines the pharmacological and therapeutic potential of ellagic acid (EA). A systematic literature search was conducted in PubMed and Google Scholar, employing keywords related to EA's biological sources, derivatives and efficacy focusing on studies published up to February 2025. Inclusion criteria encompassed original research and mechanistic reviews in English, while editorials, non-English publications and studies lacking direct EA focus or sufficient data were excluded. EA, a dietary polyphenol, exhibits potent antioxidant and anti-inflammatory activities, demonstrating therapeutic potential across various disease areas. Mechanistically, EA modulates key signalling pathways like NF-κB, MAPK and Nrf2/ARE, impacting cellular processes such as apoptosis, oxidative stress and inflammation. Preclinical studies highlight EA's efficacy in combating cancer (inhibiting tumor growth and metastasis), cardiovascular diseases (ameliorating mitochondrial dysfunction and oxidative stress), neurodegenerative disorders (enhancing neuronal viability and reducing neuroinflammation), diabetes (improving glucose homeostasis), liver and kidney pathologies (reducing fibrosis and oxidative damage) and fertility (modulating reproductive hormones and sperm protection). Additionally, EA demonstrates cytoprotective and anti-ulcer effects, protecting against cellular damage and gastric mucosa injury. EA presents a promising therapeutic agent with diverse pharmacological activities. Its ability to modulate multiple signalling pathways and exert protective effects against various pathologies underscores its potential. Further studies will validate efficacy, optimize delivery and explore synergistic effects, ultimately translating preclinical findings into effective clinical applications.

Keywords: anticancer; ellagic acid; nephroprotective; neuroprotective; pharmacological

Introduction

Ellagic acid (EA), a ubiquitous dietary polyphenol found in various fruits (e.g., strawberries, raspberries, pomegranates) and nuts (e.g., walnuts), has garnered significant scientific attention over the past five years, primarily due to accumulating evidence of its pleiotropic pharmacological properties and therapeutic potential (1-3). This heightened interest stems not only from its established antioxidant, anti-inflammatory and antineoplastic activities, but also from its potential applications in the prophylaxis and treatment of a diverse range of pathologies, including hepatic disorders (4). The bioavailability of ellagic acid is modulated by its release from ellagitannins, such as punicalagins, abundant in pomegranates (5). Furthermore, the bioactivity of ellagic acid is potentiated by its capacity to attenuate oxidative damage targeting critical biomolecules, including lipids, amino acids and guanosine, thereby conferring cytoprotective effects (6). Recent pharmacological investigations indicate that ellagic acid represents a promising avenue for therapeutic development across a broad spectrum of disease states.

Structure of Ellagic acid (Fig. 1), a dilactone of dihydroxybenzoic acid, features a central aromatic ring system adorned with hydroxyl groups, which contribute significantly to its observed antioxidant activity (7, 8). The molecular structure of ellagic acid is characterized by the presence of two benzene rings linked by two lactone groups, which confers it a unique polyphenolic nature (9). This structural configuration is responsible for the diverse biological properties of ellagic acid, including its potent antioxidant and free radical scavenging capabilities. As a dimeric derivative of gallic acid, ellagic acid can occur either in its free form or as a complex within ellagitannins in a variety of plant-based sources, such as berries, pomegranates, grapes, walnuts and certain edible mushrooms (10, 11). Various studies reveal that the total ellagic acid content in these plant sources can range from 5.6 mg per 100 g of fresh muscadine grape wine to 10.2 mg per 100 g of fresh muscadine grape juice (12). Ellagic acid in pomegranate (*Punica granatum*, Lythraceae) (13) juice and extract are found predominantly in the form of punicalagins, which are the major ellagitannins in pomegranate (14).

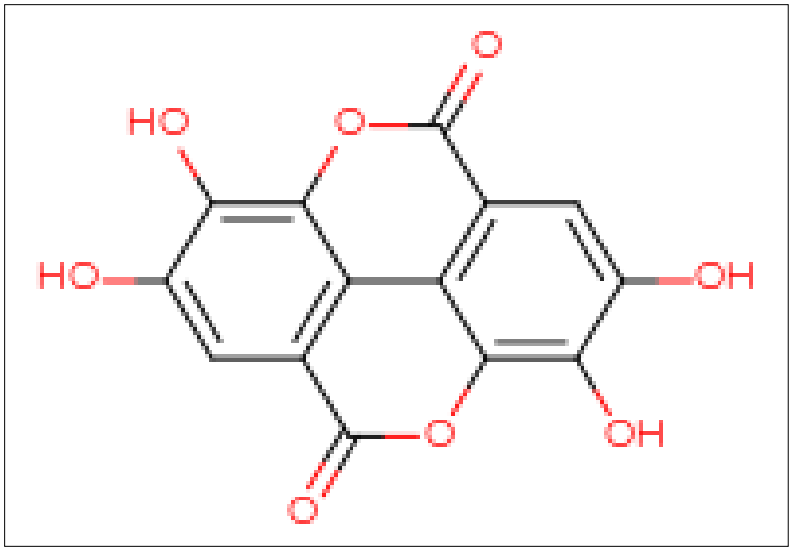

Fig. 1. Structure of ellagic acid.

In the nutraceutical sector, its potent antioxidant capacity facilitates its incorporation into dietary supplements, where it is marketed for its potential to mitigate oxidative stress and inflammatory responses. Within the cosmetic industry, ellagic acid's ability to inhibit melanogenesis underpins its utilization in skincare formulations designed to address hyperpigmentation, while its antioxidant attributes confer protective effects against free radical-induced cutaneous damage. Furthermore, research is exploring its application in active food packaging, leveraging its antioxidant and antimicrobial characteristics to enhance product shelf life and impede microbial spoilage (15). Additionally, agricultural studies are examining ellagic acid's capacity to augment plant stress tolerance and photosynthetic efficiency, potentially enhancing crop resilience in adverse environmental conditions, as the *in vivo* generated metabolites of ellagic acid have been shown to possess comparable or even greater antioxidant activity than the parent compound (16).

The present review aims to provide a comprehensive overview of the pharmacological and therapeutic potential of ellagic acid based on the research conducted in recent years.

Materials and Methods

A comprehensive electronic literature search was conducted in PubMed and Google Scholar to identify relevant studies published up to February 2025. The search strategy employed a combination of keywords pertaining to the biological sources of ellagic acid (EA), its derivatives and EA itself, as well as keywords related to its molecular, biochemical, pharmacological and therapeutic efficacy. The search was limited to English-language publications. Furthermore, the reference lists of the retrieved articles were manually reviewed to identify additional, potentially non-indexed, relevant studies.

Inclusion criteria

The inclusion criteria for this review encompass original research articles, including *in vitro*, *in vivo* and clinical studies, as well as review articles that provide significant mechanistic insights. The focus of the selected studies was on the biological sources, chemical properties, pharmacological activities and therapeutic potential of ellagic acid and its derivatives. Additionally, studies investigating the molecular mechanisms underlying the action of ellagic acid is also included. Research exploring the effects of ellagic acid on various health conditions, including cancer, cardiovascular diseases, neurodegenerative disorders, diabetes, liver and kidney pathologies, fertility and hormonal regulation, as well as ulcers and cryoprotection, were also shortlisted.

Exclusion criteria

The exclusion criteria for this review encompass publications that do not align with the study's scope and methodological consistency. Editorials, letters to the editor and conference abstracts were excluded unless they contained significant original data. Additionally, publications in languages other than English will were considered. Studies that did not directly examine the effects of ellagic acid, as well as those focused solely on its chemical synthesis or extraction without evaluating its biological activity, were not considered. Research in which ellagic acid is not the primary focus of the investigation was also ignored. Studies with insufficient data for analysis or those with irretrievable data was omitted to ensure the reliability and validity of the review findings.

Therapeutic and pharmacological potential

Anti-inflammatory potential

Ellagic acid has demonstrated potent anti-inflammatory properties in a variety of *in vitro* and *in vivo* studies (17). Its anti-inflammatory mechanisms involve the modulation of key signalling pathways, such as the nuclear factor-kappa B and mitogen-activated protein kinase cascades, which play pivotal roles in the regulation of inflammatory responses (18). Ellagic acid has been shown to inhibit the production of pro-inflammatory mediators, including nitric oxide, prostaglandin E2 and various cytokines, in cell-based models of inflammation (19). Furthermore, ellagic acid's capacity to suppress the activation of transcription factors like NF-κB and downregulate the expression of inflammatory enzymes, such as inducible nitric oxide synthase and cyclooxygenase-2, has been extensively documented (20). In another study anti-

inflammatory properties were explored wherein ellagic acid effectively attenuated inflammation-induced joint damage in a murine model of osteoarthritis, suggesting its potential therapeutic applications in the management of inflammatory joint disorders (21). Anti-inflammatory studies of Ellagic acid in comparison with other natural polyphenols like resveratrol and curcumin indicate its superior potency in inhibiting inflammatory mediators like PGE2, NO and cytokines like IL-6 and TNF-α (22). Reports have also indicated the role of ellagic acid as key anti-inflammatory agent at the molecular level in modulating key signalling pathways like NF-κB, MAPK and PI3K/Akt which are central to inflammatory processes (11, 23, 24).

Anticancer properties

The anticancer potential of ellagic acid has been well-documented in a wide range of cancer types, including breast, prostate, colon, pancreatic and liver cancer (3, 16). Experimental evidence supports the role of ellagic acid in targeting key hallmarks of cancer, including cell proliferation (Fig. 2), angiogenesis, apoptosis evasion, immune evasion, inflammation and genomic instability (25). Studies have found that one molecule of ellagic acid can potentially bind to one molecule of HTf, mediated by the involvement of hydrogen bonds and van der Waals forces, as supported by molecular docking simulations. These findings suggest that ellagic acid may exhibit promising antimetastatic activity against H358 lung cancer cells, as well as an ideal binding affinity to a drug carrier protein model (26). A report on liver cancer found that EA exhibits radio-sensitizing effects, inhibits inflammatory pathways and modulates the tumor microenvironment, offering potential therapeutic benefits against hepatocellular carcinoma (27). Ellagic acid has been shown to inhibit the proliferation and migration of pancreatic cancer cells by modulating the expression of key cell cycle regulators and apoptosis-related proteins (24). Ellagic acid treatment was found to diminish the stem-like traits in cancer cells, thereby decreasing the survival and self-renewal capacity of ovarian and lung cancer stem-like cells. Furthermore, EA treatment constrained the populations of lung and ovarian CSLCs identified by the CD133+ and CD44+CD117+ markers, respectively (28). Furthermore, ellagic acid has been reported to induce cell cycle arrest and apoptosis in cervical cancer cells by regulating the signal transducer and activator of transcription 3 signalling pathway (29). Anti-cancer properties of ellagic acid have also been documented in prostate cancer cells, where it inhibited cell growth and induced apoptosis by targeting the STAT3 signalling pathway (30). Ellagic acid role in breast cancer has been well studied, where it has been shown to suppress proliferation, migration and invasion of breast cancer cells by modulating the expression of matrix metalloproteinases and the epithelial-mesenchymal transition (31). Ellagic acid has been found to inhibit tumor growth in human pancreatic cancer cell xenografted mice and to induce cell apoptosis in human bladder cancer cells through endoplasmic reticulum stress- and mitochondria-dependent signalling pathways (29). Ellagic acid showed significant potency on bladder cancer TSGH8301 cells by inducing apoptosis via activation of endoplasmic reticulum stress- and mitochondria-dependent signalling pathways (32). Another study revealed that ellagic acid as a potent agent for suppressing tumor growth in human pancreatic cancer cell xenografted mice (24). Reports are also available indicating ellagic acid potentiates the differentiation of human leukemia cells and presented an anti -angiogenesis activity in breast cancer (33). Effect of ellagic acid on neuroblastoma cells exhibited decreased cell viability, induced cell cycle arrest in the G1 phase and promoted cell apoptosis by modulating the expression of cell cycle- and apoptosis-related proteins (34). Role of ellagic acid on thyroid cancer cells revealed the inhibition of cell proliferation, migration and invasion by regulating the expression of epithelial-mesenchymal transition markers and matrix metalloproteinases (35).

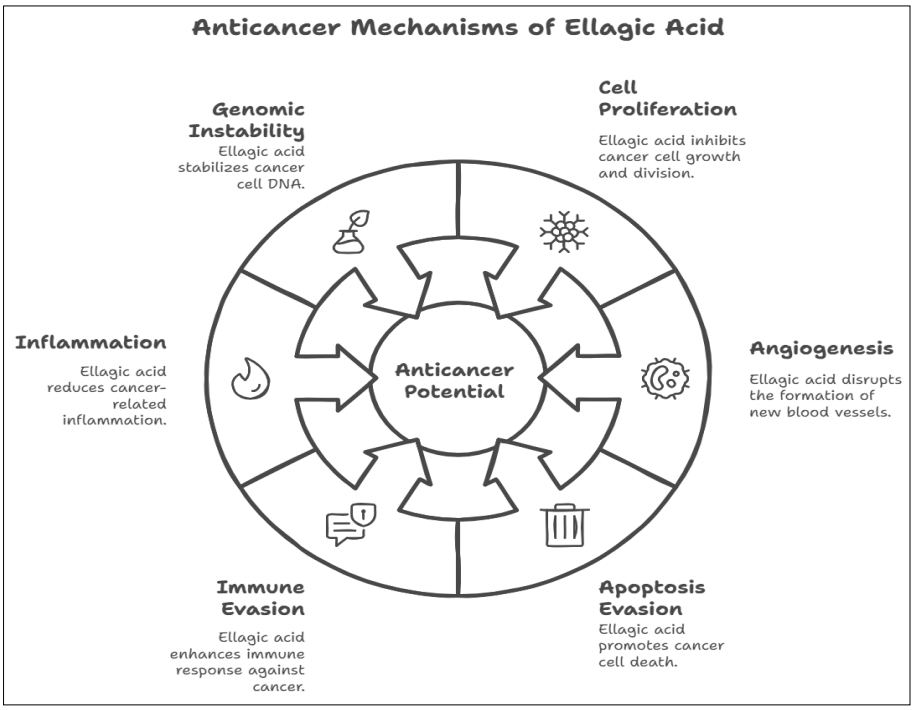

Fig. 2. Diagrammatic representation details the diverse biological activities of ellagic acid associated with cancer amelioration.

Cardioprotective effects

Ellagic acid has shown promising cardioprotective effects in both *in vitro* and *in vivo* studies, indicating its potential in preventing and managing cardiovascular diseases (Table 1). Its cardioprotective mechanisms involve the modulation of oxidative stress, inflammation and lipid metabolism, all of which are crucial factors in the development and progression of cardiovascular disorders (36). Reports have demonstrated that ellagic acid (EA) improves mitochondrial dysfunction and protects diabetic hearts. The mitochondrial tricarboxylic acid cycle regulates DNA 5-hydroxymethylcytosine levels by affecting the activity of 10-11 translocation enzymes. Therefore, it was hypothesized that ellagic acid prevents diabetic cardiac dysfunction by modulating DNA 5-hydroxymethylcytosine levels (37). Studies have demonstrated that oral administration of ellagic acid, a potent natural antioxidant, can ameliorate MI-induced left ventricular diastolic dysfunction in ovariectomized rats by attenuating the formation of reactive oxygen species. This reduction in oxidative stress is associated with decreased left ventricular diastolic dysfunction, thereby preventing the detrimental effects of estrogen deficiency in these rats (38). Accumulating evidence suggests that ellagic acid and its metabolites, the urolithins, may exert protective and therapeutic effects on cardiovascular diseases with a low risk of side effects. These compounds have the potential to regulate imbalances in lipid metabolism, suppress pro-inflammatory factor production, inhibit vascular smooth muscle cell proliferation, prevent cardiomyocyte apoptosis, improve endothelial cell function and modulate calcium homeostasis. These actions may contribute to the prevention and amelioration of various cardiovascular conditions, including atherosclerosis, hypertension, myocardial infarction, cardiac fibrosis, cardiomyopathy, cardiac arrhythmias and cardiotoxicities in experimental models. Several molecular pathways and signalling cascades, such as phosphatidylinositol 3-kinase/protein kinase B, mitogen-activated protein kinase, NF-κB, nuclear factor erythroid-2 related factor 2, sirtuin1, microRNAs and extracellular signal-regulated kinase, have been associated with the therapeutic effects of EA and urolithins on the cardiovascular system (36).

Neuroprotective effects of EA

Ellagic acid's neuroprotective effects have garnered considerable attention, suggesting its potential in preventing and managing neurodegenerative diseases (Fig. 3). Ellagic acid has the capacity to protect the brain against damages from oxidants and inflammatory agents following stroke to reduce neuronal mortality (39). Numerous studies have revealed that ellagic acid, a phenolic compound widely distributed in dicotyledonous plants, possesses potent anti-inflammatory and antioxidant properties. Additionally, evidence suggests that ellagic acid can enhance neuronal viability, mitigate neuronal defects and alleviate damage in neurodegenerative conditions such as Alzheimer's disease, Parkinson's disease and cerebral ischemia (Table 1). This paper provides a comprehensive review of the biochemical functions and neuroprotective effects of ellagic acid, highlighting its potential clinical applications (40).

Studies have reported that ellagic acid reduced the expression of glial fibrillary acidic protein and exhibited neuroprotective effects by mitigating hippocampal CA1 pyramidal neuron injury and also displayed reverse oxidative stress, apoptosis and neuroinflammatory processes, as well as its capacity to regulate AMPK and p-tau signalling (41). Another study revealed that administering EA orally significantly ameliorated post-surgical cognitive impairment in aged mice, as demonstrated by their improved performance on maze tests. This enhancement in behavioural outcomes of the EA-treated mice was associated with the rejuvenation of IGF-1 signalling, a reduction in oxidative stress markers in the hippocampus and an increase in the activity of antioxidant enzymes such as SOD and CAT. A decrease in microglia-driven neuroinflammation in the hippocampus, underscoring the antioxidant and anti-inflammatory properties of EA was also noted. Interestingly, when EA was administered concurrently with an IGF1R inhibitor, these benefits were abrogated, emphasizing the pivotal role of the IGF-1 pathway in the neuroprotective potential of EA (42, 43). The EA crystalline particles have demonstrated significant H_2O_2-related ROS scavenging capacity, high cellular uptake, excellent neuroprotective effects in PC12 cells, as well as high drug

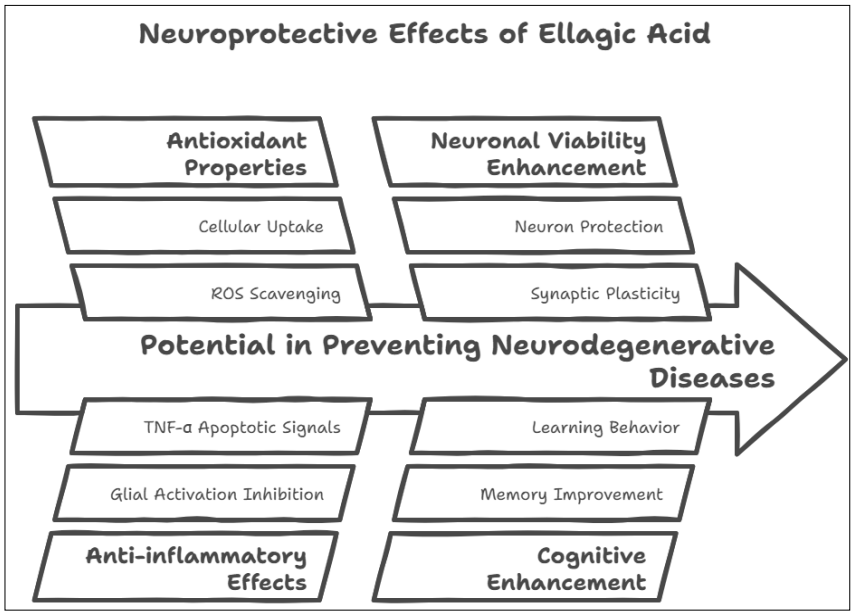

Fig. 3. The reported neuroprotective effects of ellagic acid, demonstrating its potential therapeutic applications.

Table 1. Data summarizing the pharmacological and therapeutic effects of ellagic acid

Therapeutic area	Effects of ellagic acid (EA)	Key mechanisms
Anti-inflammatory	Inhibits pro-inflammatory mediators (NO, PGE2, cytokines); suppresses NF-κB and MAPK activation; attenuates joint damage in osteoarthritis	Modulation of NF-κB, MAPK and PI3K/Akt signalling pathways
Anticancer	Inhibits cell proliferation, angiogenesis and metastasis; induces apoptosis and cell cycle arrest; modulates tumor microenvironment; reduces cancer stem cell traits	Targeting key hallmarks of cancer, including cell cycle regulation, apoptosis pathways (STAT3) and expression of matrix metalloproteinases
Cardioprotective	Reduces oxidative stress; improves mitochondrial function; regulates lipid metabolism; prevents cardiomyocyte apoptosis and fibrosis; improves endothelial function	Modulation of oxidative stress, inflammation, lipid metabolism and signalling pathways (PI3K/Akt, MAPK, NF-κB, Nrf2, SIRT1)
Neuroprotective	Protects against oxidative damage and neuroinflammation; enhances neuronal viability; mitigates neurodegenerative conditions (Alzheimer's, Parkinson's); improves cognitive function	Antioxidant and anti-inflammatory effects; regulation of AMPK, p-tau, IGF-1, CREB, Dnm-1 and synaptophysin signalling
Anti-diabetic	Improves glucose homeostasis; enhances insulin sensitivity; modulates lipid levels; reduces oxidative stress; improves mitochondrial function	Enhancing insulin secretion; regulating glucose transporter 4; modulating lipid levels; reducing oxidative stress; upregulating uncoupling protein 1
Hepatoprotective	Reduces hepatic stress response, inflammation and fibrosis; upregulates Nrf2; attenuates CDDP-induced liver dysfunction; modulates tumor microenvironment in HCC	Upregulation of Nrf2/HO-1 signalling; downregulation of NF-κB; modulation of TGF-α, TGF-β and VEGF expression
Nephroprotective	Mitigates kidney damage and dysfunction; protects against oxidative stress and histopathological abnormalities; regulates TGF-β/Smad signalling; activates SIRT1 and NRF2	Antioxidant and anti-inflammatory properties; regulation of TGF-β/Smad, SIRT1 and NRF2 signalling pathways; mitochondrial protection
Cytoprotective	Protects against cellular damage from various toxicants and stressors; protects against DNA injury and oxidative stress; protects lens epithelial cells	Modulation of Nrf2/ARE signalling; normalization of lipid metabolism; reduction of oxidative stress and inflammatory mediators
Fertility enhancement	Ameliorates testicular impairment; improves semen quality; benefits premature ovarian insufficiency; protects sperm from oxidative damage	Modulating testosterone synthesis, germ cell proliferation and oxidative stress; regulating androgen and estrogen receptors; reducing ROS
Hormonal regulation	Modulates androgen and estrogen receptor signalling; regulates hormones of the hypothalamic-pituitary-gonadal axis; improves follicular development and oocyte quality in PCOS	Effects on LH, FSH, progesterone and estrogen levels; modulation of miRNA-21 expression; improvement of ovarian morphology
Anti-ulcer	Protects gastric mucosa; promotes ulcer healing; reduces oxidative stress and inflammation in colitis; regulates ROS/NLRP3 pathway	Antioxidant and anti-inflammatory effects; regulation of the ROS/NLRP3 and Nrf2/HO-1 pathways; increase in mucus production; improvement of gut microbiome balance

loading and blood-brain barrier permeability, suggesting great potential for treating oxidative stress-mediated Alzheimer's disease (44). Ellagic acid has demonstrated potent anti-inflammatory effects by inhibiting astroglial activation, modulating FAIM-L expression and protecting against TNF-α-induced apoptotic signals. Furthermore, the neuromodulatory properties of EA have been attributed to its regulation of CREB levels, Dnm-1 expression and synaptophysin levels, ultimately enhancing long-term potentiation and synaptic plasticity. Additionally, EA has induced beneficial cytological and behavioral changes, improving both long-term and short-term spatial memory as well as associative learning behavior in animal models, underscoring its cognitive enhancement potential (45). Ellagic acid has demonstrated high potency to mitigate neuronal oxidative stress and related pathologies, including Parkinson's disease (46).

Anti-diabetic effects of EA

Ellagic acid has emerged as a promising therapeutic agent for diabetes, demonstrating multifaceted effects on glucose homeostasis, insulin sensitivity and pancreatic function. Multiple studies have shown that ellagic acid could be a potent compound for treating various disorders, including diabetes, hypertension and hyperlipidemia, through diverse mechanisms (Table 1). These mechanisms include increasing insulin secretion, enhancing insulin receptor substrate protein 1 expression, regulating glucose transporter 4 and modulating levels of triglycerides, total cholesterol, low-density lipoprotein and high-density lipoprotein. Additionally, ellagic acid has demonstrated the ability to attenuate tumor necrosis factor-alpha, interleukin-6, reactive oxygen species, malondialdehyde and oxidative stress in related tissues. Furthermore, ellagic acid has been shown to ameliorate mitochondrial function, upregulate uncoupling protein 1 and regulate blood levels of nitrate/nitrite, as well as vascular relaxations in response to acetylcholine and sodium nitroprusside (47). Several meta-analyses of preclinical and clinical trials from 2002 to 2022 have found that ellagic acid and ellagitannins possess antidiabetic properties and can improve diabetes management. The current body of evidence generally indicates improvements in diabetes biomarkers with EA and ET interventions. Specifically, EA and ETs have been shown to significantly reduce fasting glucose levels, total cholesterol and low-density lipoprotein in preclinical trials, significantly increase high-density lipoprotein in clinical trials and significantly reduce glycated hemoglobin (HbA1c) levels (48). A study found that eight weeks of supplementation with ellagic acid at 180 mg/day reduced blood sugar, insulin, insulin resistance and Fetuin-A levels, while increasing SIRT1 in patients with type 2 diabetes. These results support the notion that polyphenol antioxidants, such as EA, can play an important role in managing diabetes by helping to control the condition and potentially reducing the need for medications (49). Ellagic acid has been found to reduce oxidative stress, which is a crucial element in the development of type 2 diabetes and its vascular complications (50). Ellagic acid affects insulin, glycogen, phosphatases, aldose reductase, sorbitol accumulation, advanced glycation end-product formation and resistin secretion, which may explain its effects on metabolic syndrome and diabetes (51).

Hepatoprotective potential

Ellagic acid has garnered significant attention for its hepatoprotective properties, demonstrating efficacy against a spectrum of liver disorders and injuries. Studies have shown that EA treatment significantly reduced hepatic stress response, inflammatory cell infiltration and hepatic fibrosis in mice. *In vitro* and *in vivo* mechanistic investigations revealed that EA's protective effects were mediated by the upregulation of nuclear factor erythroid 2-related factor 2. EA promoted the translocation of Nrf2 from the cytosol to the nucleus and the finding that Nfe2l2 shRNA and inhibition of Nrf2 by ML385 reversed the EA-induced hepatoprotective effects in TiO2 NP-exposed hepatocytes and mice underscores the crucial role of the Nrf2 pathway (52). Other results revealed that CDDP treatment resulted in liver dysfunction, oxidative stress and caspase activation, which were effectively attenuated by EA cotreatment in a dose-dependent manner. Furthermore, EA supplementation significantly downregulated the CDDP exposure-induced protein and mRNA expression of NF-κB, IL-1β, TNF-α and IL-6 but further upregulated the protein and mRNA expression of Nrf2 and HO-1. Molecular docking analysis revealed strong interactions between EA and the NF-κB or Keap1 proteins (53). Another study reported that EA effectively reduced biomarkers and restored the altered liver structure. At the mRNA level, EA downregulated the expression of TGF-α, TGF-β and VEGF, while restoring p53 expression. This led to an increase in apoptotic cells stained for caspase3 and a decrease in CD44-positive hepatic cancer stem cells. Studies have shown that EA was able to modulate the tumor microenvironment in an HCC rat model, ultimately targeting the HCSCs (54). A study also found that chronic administration of EA ameliorates hepatic damage and steatosis in STZ-induced T1DM rats, primarily through its hypoglycemic and antioxidant effects, as well as by activating AMPK (55).

Nephroprotective properties

Ellagic acid's nephroprotective effects have been investigated through extensive research, with promising results indicating its potential in mitigating kidney damage and dysfunction. Ellagic acid has been shown to protect against diabetic nephropathy by regulating the transcription and activation of Nrf2 (56). Studies indicate that ellagic acid administration protects the kidneys against mitochondrial dysfunction, oxidative stress and histopathological abnormalities induced by ifosfamide. Collectively, the results demonstrate that EA plays a protective role against ifosfamide-induced nephrotoxicity through its mitochondrial protective and antioxidant properties (57). Furthermore, studies have found that EA-enriched Hibiscus leaf extract regulates the TGF-β/Smad signalling pathway, leading to reduced renal mesangial cell injury and fibrosis in hypertensive nephropathy. This provides a new mechanistic understanding of ellagic acid's nephroprotective properties (58). Ellagic acid has been shown to protect against cyclophosphamide-induced renal damage in rats (59). A study demonstrated that the administration of ellagic acid led to a significant improvement in renal function biomarkers compared to the rats with acute kidney injury. This was accompanied by notable reductions in tumor necrosis factor-α levels and increases in interleukin-10 levels observed in blood samples.

Additionally, the improvement in histopathological indices observed in the rats that received ellagic acid confirmed its nephroprotective effects (60). Ellagic acid has been shown to reduce the progression of morphological transformations and concomitantly suppress the expression of renal fibrotic and epithelial-mesenchymal transition-related proteins, both *in vitro* and *in vivo*. These findings suggest that EA plays a role in suppressing renal fibrogenesis, indicating its promising potential in the management of chronic kidney disease (61). Another study found that treatment with ellagic acid significantly increased the levels of antioxidant enzymes and reduced malondialdehyde concentration. Moreover, EA administration remarkably upregulated the mRNA and protein levels of SIRT1 and NRF2, as well as deacetylated the NRF2 protein. Additionally, EA-treated rats exhibited improved kidney function and histopathological scores, suggesting that ellagic acid exerts protective effects on aged kidneys by activating the SIRT1 and NRF2 signalling pathways (62).

Cytoprotective efficacy

EA has demonstrated marked cytoprotective properties across various cell types and tissues, suggesting its potential as a broad-spectrum protective agent against cellular damage and dysfunction (Table 1). A study provides further insights into the cytoprotective potential of ellagic acid against heavy metal-induced neurotoxicity and oxidative stress, suggesting the beneficial effects of consuming EA-rich foods (34). Ellagic acid protects human lens epithelial cells from oxidative stress-induced damage (63). The cytoprotective activity of ellagic acid has been demonstrated against a variety of toxicants and stressors (64). Ellagic acid protected cells against DNA injury induced by free radicals and it can prevent the traumatic brain injury (65). Ellagic acid has been reported to exhibit remarkable protective properties against a variety of toxicants. Its protective effects were primarily mediated through the normalization of lipid metabolism, oxidative stress and inflammatory mediators, such as tumor necrosis factor-α, interleukin-6 and IL-1β (66) In terms of molecular mechanisms, ellagic acid's cytoprotective effects often involve the modulation of key signalling pathways, such as the Nrf2/ARE pathway, which plays a critical role in cellular defence against oxidative stress (62).

Ellagic acid and fertility

Ellagic acid has been investigated for its potential to improve fertility and reproductive health in both males and females, with studies suggesting that it may counteract the adverse effects of various factors on reproductive function (Fig. 4). A report found that ellagic acid ameliorates heat-induced testicular impairment by modulating testosterone synthesis, germ cell proliferation and oxidative stress. These effects could be mediated through the regulation of androgen and estrogen receptors (67). Researchers investigated the effects of a commercially available combined compound containing ellagic acid and *Annona muricata* on semen quality in patients with HR-HPV infection. The study found that this therapy was associated with a significant reduction in the persistence of HPV DNA in the seminal fluid (68). Ellagic acid has been shown to have beneficial effects on premature ovarian insufficiency, as evidenced by decreased levels of cholesterol, triglycerides, follicle-stimulating hormone and luteinizing hormone, coupled with increased levels of estrogen (69). Another group evaluated the effect of ellagic acid on rabbit sperm traits after freezing and thawing. Semen samples collected from New Zealand White rabbit males were cryopreserved in a BotuCrio freezing medium supplemented with different concentrations of EA using the manual slow freezing procedure. After thawing, sperm motility parameters were assessed by CASA. Additionally, the researchers evaluated sperm viability, apoptosis, acrosome integrity, intracellular reactive oxygen species and mitochondrial activity using flow cytometry. The results showed that adding EA to the freezing medium at all tested concentrations led to a significant reduction ($P < 0.05$) in intracellular ROS in the frozen-thawed sperm cells. However, this antioxidant effect was not reflected in the motility parameters. Interestingly, semen supplemented with 1.5 mM EA also yielded a lower proportion of apoptotic cells compared to the control group. In conclusion, EA supplementation of the semen extender demonstrated its antioxidative properties, which helped protect spermatozoa against oxidative damage during the cryopreservation process (70). A report has shown that DBP (Phthalate) causes oxidative damage by increasing the malondialdehyde level and decreasing antioxidant parameters, leading to increased abnormal sperm rate, decreased sperm motility and

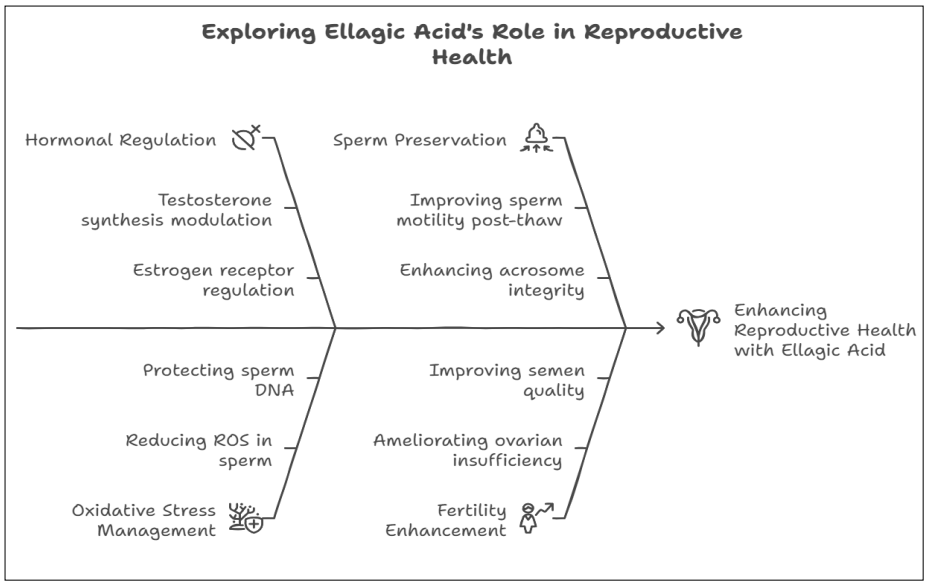

Fig. 4. Visual representation of research findings related to ellagic acid's effects on reproductive capacity.

concentration and histopathological damage. However, the antioxidant activity of ellagic acid has been found to inhibit this damage (64, 71). Another group suggests ellagic acid as a suitable molecule to protect sperm DNA from oxidative stress, with a potentially significant translational impact on the management of male infertility (72). *In vitro* combination of ascorbic and ellagic acids in sperm oxidative damage inhibition was examined. The use of antioxidants to reduce oxidative stress contributes to the improvement in reproductive function (73).

Hormonal regulation by Ellagic acid

EA's potential in hormonal regulation extends to its ability to modulate hormone synthesis, metabolism and receptor activity, which has implications for various endocrine-related conditions. Studies on the hormonal effects of ellagic acid has proven that it can modulate both androgen and estrogen receptor signalling. In a rat model, ellagic acid treatment reduced LH levels and restored follicular development, particularly enhancing the growth of primordial and graafian follicles, along with modulating miRNA-21 expression. Furthermore, ellagic acid exhibited positive effects on ovarian morphology, including decreased theca layer thickness, increased oocyte diameter and improvements in antral and preovulatory follicles (Fig. 3). These findings suggest the potential of ellagic acid in addressing follicular development and oocyte quality in PCOS (74). Ellagic acid mitigated letrozole-induced PCOS by decreasing the levels of serum LH, testosterone and insulin while increasing the levels of FSH and progesterone (75). Ellagic acid regulates hormones of hypothalamic-pituitary-gonadal axis and improves follicular development and oocyte quality in PCOS rats (76).

Anti-ulcer properties

Recent studies have shed light on the anti-ulcer potential of ellagic acid, highlighting its ability to protect the gastric mucosa and promote ulcer healing. It has been demonstrated that ellagic acid can protect the gastric mucosa against damage induced by various ulcerogenic agents, such as non-steroidal anti-inflammatory drugs and ethanol. A study found that ellagic acid improved the health of the colon in mice with ulcerative colitis. EA reduced oxidative stress, inflammation and tissue damage in the colon. The study showed that EA regulated the ROS/NLRP3 pathway, which is involved in UC. Additionally, EA helped restore the balance of gut bacteria that was disrupted in UC, reducing harmful bacteria and increasing beneficial ones. These findings suggest that EA could be a valuable therapy for managing ulcerative colitis by reducing inflammation and oxidative stress and improving the gut microbiome (77). A study demonstrated that Gallic acid and an FY capsule exhibited gastroprotective effects against ethanol-induced gastric ulcers in rats. The underlying mechanism may involve the Nrf2/HO-1 antioxidative pathway, ultimately playing an anti-apoptotic role by regulating the expression of Bax, Bcl-2 and Caspase-3 (78). Pre-treatment with the FY capsule significantly reduced gastric ulcer inflammation, necrosis and hemorrhage, as evidenced by both gross and histological examination (79). In another study, ellagic acid exhibited gastroprotective activity against ethanol-induced gastric ulcers, as evidenced by a reduction in ulcer index and an increase in mucus production (80).

Conclusion

In conclusion, ellagic acid (EA) demonstrates a multifaceted pharmacological profile, supported by extensive preclinical investigations. Its potent anti-inflammatory properties, mediated through modulation of NF-κB and MAPK signalling, underscore its potential in managing inflammatory disorders. Furthermore, EA exhibits significant antineoplastic activity across diverse cancer types, targeting key oncogenic pathways and cellular processes, including cell proliferation, apoptosis and angiogenesis. Cardioprotective effects of EA are attributed to its ability to mitigate oxidative stress, inflammation and lipid dysregulation, thus offering potential therapeutic benefits in cardiovascular diseases. Neuroprotective effects, evidenced by its capacity to ameliorate oxidative damage and neuroinflammation, suggest its relevance in neurodegenerative conditions. EA's anti-diabetic potential is highlighted by its modulation of glucose homeostasis and insulin sensitivity. Moreover, EA demonstrates hepatoprotective and nephroprotective effects, primarily through the Nrf2/ARE signalling pathway, safeguarding against toxicant-induced organ damage. Its cytoprotective efficacy extends across various cell types, protecting against oxidative stress and DNA damage. EA's role in reproductive health is notable, with evidence indicating its ability to modulate hormonal balance and improve fertility parameters in both male and female subjects. Additionally, its anti-ulcer properties, particularly in inflammatory bowel disease, are attributed to its regulation of oxidative stress and the gut microbiome. While these preclinical findings are promising, further clinical trials are imperative to validate EA's efficacy and safety in human subjects. Future research should focus on optimizing dosage, delivery methods and investigating synergistic interactions with existing therapies to fully realize EA's therapeutic potential.

Authors' contributions

RCJ is extensively involved in collections of recent findings and integrating them. JK is part of data collection and designing the manuscript. CGL is participating in designing the paper and figures and references. SPS is participated in provided the theme, designing the article and figures. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest: Authors do not have any conflict of interest to declare.

Ethical issues: None

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