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Nano Micro Biosystems

Online ISSN: 2980-8057

Novel formulations of ellagic acid for the improvement of antimicrobial, antioxidant, anticancer, antidiabetic, and neuroprotective applications

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ARTICLE INFO

Mini-review paper

Article history:
Received: 05 Mar 2023
Revised: 01 Apr 2023
Accepted: 02 Apr 2023
ePublished: 05 Apr 2023

Keywords:
Ellagic acid, Antidiabetic activity, Anticancer activity, Reticuloendothelial system, Metastatic melanoma, Neuroprotective activity

ABSTRACT

The application of bioactive compounds in combination with conventional drugs can improve therapeutic activities. Various therapeutic activities involve antimicrobial, antioxidant, anticancer, antidiabetic, and neuroprotective properties for ellagic acid and its derivatives such as 3,3′-di-O-methyl ellagic acid. For example, ellagic acid has been proclaimed to be effective in the regression of various kinds of tumors, involving but not limited to lung cancer, colorectal carcinoma, esophageal cancer, metastatic melanoma, hepatocellular carcinoma, tongue cancer, breast cancer, bladder cancer, endometrial carcinoma, and prostate cancer. However, ellagic acid has a hydrophobic or lipophilic property that leads to low circulation in the reticuloendothelial system (RES) or bioavailability. This mini-review discusses various formulations of ellagic acid considering therapeutic activities based on their bulk and nano aspects.

DOI: https://doi.org/10.22034/nmbj.2023.388479.1015

1. Introduction

Various therapeutic applications have been reported for herbal phenols and polyphenols [1-3]. Ellagic acid ($C_{14}H_6O_8$) is a polyphenol isolated from various plant species such as *Rosa rugosa* [4], *Rubus chamaemorus* [5], *Rubus ursinus*×*Rubus idaeus* [6], *Rubus allegheniensis* [7], and *Rubus fruticosus* [8] (Figure 1). These plant species containing ellagic acid can be applied to green synthesize metal or metal oxide nanoparticles (NPs). This ability may have resulted from ellagic acid's reducing and stabilizing properties [8].

Hydrophobic or lipophilic property is ellagic acid's main disadvantage, resulting in bioavailability or low circulation in the reticuloendothelial system [9].

According to the above introduction, this mini-review has attempted to explain and discuss the therapeutic activities of ellagic acid and its derivatives considering both bulk and nano aspects of formulations.

2. Antimicrobial activity

Derivatives of ellagic acid, 3,3′-di-O-methyl ellagic acid, isolated from the root bark of *Afzelia Africana*, had antibacterial effects on pathogenic fungi, Gram-negative, and Gram-positive bacteria. *Streptococcus mutans*, *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans* 1, methicillin-resistant *S. aureus* (MRSA), *Bacillus subtilis*, *Klebsiella pneumonia*, and *Pseudomonas aeruginosa* showed the sensitivity upon treatment by 3,3′-di-O-methyl ellagic acid as the minimum inhibitory concentration (MIC_{50}: the lowest amount of the antibacterial agent at which 50% of the bacteria are inhibited) values of 5.5, 8.3, 0.5, 3.6, 5.9, 2.7, 7.7, and 7.7 mg/mL, respectively [10]. Green synthesis of metal and metal oxide NPs has increased the biocompatibility of these NPs, significantly [11]. Reducing and stabilizing the properties of ellagic acid available in *Rubus fruticosus* L. and *Rubus idaeus* L. extracts can lead to the biosynthesis of silver (Ag) NPs. Biosynthesized AgNPs at 50 ppm by *R. fruticosus*

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and *R. idaeus* showed ~40% and ~99% bacterial inactivation against the dental pathogen of *Candida albicans*, respectively. Growth of *Enterococcus faecalis*, another dental pathogen, was inhibited by 50 ppm of AgNPs synthesized by *R. fruticosus* and *R. idaeus* with values of ~25% and ~89%, respectively [8].

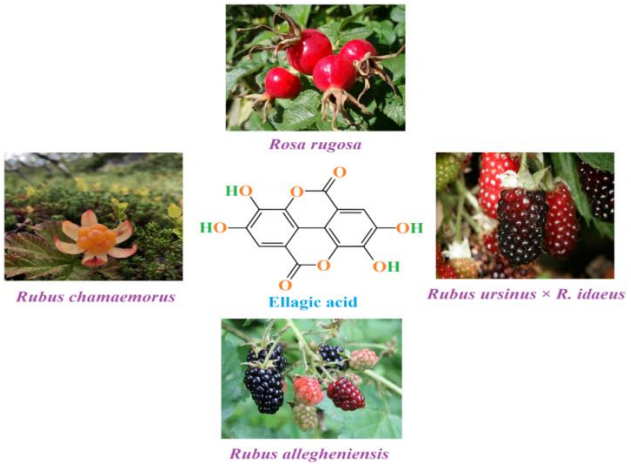

Fig. 1. Four main fruits contain a high level of ellagic acid.

Ellagic acid can form a complex with β-cyclodextrin and (2-hydroxypropyl)-β-cyclodextrin due to increasing antimicrobial and antioxidant activities [12]. Additionally, loading of ellagic acid on graphene oxide at a concentration of 5 mg/ml exhibited enhanced antibacterial effects on *Proteus mirabilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, methicillin-resistant *Staphylococcus aureus* (MRSA), and *S. aureus* by inhibition zone diameters of 3.07, 2.77, 2.5, 3.3, 2.87, and 2.97, respectively. Antibacterial activity against these bacteria for ellagic acid was lower at values of 1.65, 1.6, 0, 1.5, 0, and 0, respectively [13].

3. Anticancer activity

In inflammatory and cancer diseases, there is a high expression of sphingosine kinase 1 (SphK1) [14]. Ellagic acid can bind to ATP-binding pocket of this enzyme and reduce its catalytic activity in lung cancer cell lines [15]. Another enzyme with a critical role in the cancer metabolism is pyruvate dehydrogenase kinase 3 (PDK3) [16]. This enzyme can phosphorylate pyruvate dehydrogenase complex and hinder the entry of pyruvate for its catabolism into the tricarboxylic (TCA) cycle. Based on in silico study, ellagic acid showed the inhibition of the kinase activity of PDK3 by the lower binding energy of −7.9 kcal/mol compared to capsaicin, ursolic acid, limonin, vanillin, citral, DL-α-Tocopherol acetate, and simvastatin with values of −6.6, −7.6, −7.7, −6.0, −6.6, −7.4, and −7.2 kcal/mol, respectively [17]. One of the major clinical challenges in the chemotherapy of cancers is emerging of multidrug resistance in various cancer cells [18]. Drug efflux (expelling drug out of the cells) by ATP binding cassette (ABC) transporters mainly P-glycoprotein (P-gp) is the main drug resistance mechanism of cancer cells [19]. Urolithins can be produced by the gut microbiota from ellagitannins and ellagic acid. These natural compounds showed the blocking activity of drug efflux transporter in breast cancer [20]. A plethora of nanocarriers, specifically lipid nanoparticles has been presented for formulations of therapeutic agents [21]. Loading of the ellagic acid by apamin-functionalized emulsomes exhibited a significant apoptotic effect by increasing the expression of tumor necrosis factor-α (TNF-α) in breast cancer cells compared to the free ellagic acid [22].

4. Neuroprotective and anti-aging effects

Alzheimer's disease (AD) is the common age-related neurodegenerative disorder, dementia, characterized by irreversible and progressive loss of neurons. Deposition of amyloid beta (A β) and tau proteins can form plaques around brain cells and form tangles within brain cells [23]. Aβ oligomers can interact with various receptors such as the N-methyl-D-aspartic acid receptor (NMDAR), the receptor for advanced glycation end product (RAGE), paired immunoglobulin-like receptor B (PirB), the low-density lipoprotein receptor-related protein (LRP), metabotropic glutamate receptors (mGluR5), α subunit-containing nicotinic acetylcholine receptor (α7nAChR), ephrin type-B receptor 2 (EphB2), scavenger receptor A-1 (SCARA-1), and microglia receptors to producing hyperphosphorylated tau, reactive oxygen species, and inflammatory response [24]. By increasing SOD mRNA expression, Ellagic acid can modulate the decrease in entorhinal cortex (ERC) thickness, caused by neurotoxicity and caspase-3-mediated apoptosis resulting from the amyloid precursor protein. Ellagic acid also reduced

oxidative stress and restored episodic memory in AD rat models [25]. Furthermore, ellagic acid can prevent Aβ induced neurotoxicity in SH-SY5Y neuroblastoma cells by promoting Aβ aggregation into fibrils with significant oligomer loss [26]. Ellagic acid metabolite also inhibits the hyperphosphorylation of tau and improves learning and memory deficits in APP/PS1 transgenic mice model of Alzheimer's disease [27]. Parkinson's disease (PD) is a neurodegenerative disease characterized by α synuclein aggregation in dopaminergic neurons resulting in neuronal death [28]. It is indicated that a polyphenolic compound, ellagic acid can inhibit α-synuclein aggregation and reduce cytotoxicity [29]. In addition, ellagic acid was shown to reduce rotenone-elicited ROS and reactive nitrogen species (RNS) in PC12 cells [30].

5. Antiobesity and Antidiabetic activity

Finding effective antiobesity and antidiabetic drugs without side effects is a critical challenge for treating obesity and diabetes. By non-competitive inhibiting activity, ellagic acid isolated from pomegranate peel extract exhibited IC_{50} values of 369.83 and 672.81 μg/mL against α-amylase and lipase, respectively. In addition, a molecular docking study showed the binding energies of − 6.87 and − 8.54 kcal/mol toward lipase and α-amylase, respectively. Van der Waals forces and hydrogen were the two main bonds for the interaction of ellagic acid with both enzymes [31]. In a comparative study, glucoside tricetin 4′-O-β-glucopyranoside, tricetin, luteolin, ellagic acid, and granatin B isolated from the flowers of *Punica granatum* were evaluated against the α-glucosidase activity. Tricetin showed a significant α-glucosidase inhibitory activity comparable to the other ellagitannins, flavones, and antidiabetic drug acarbose. Hydroxyl groups on the flavone molecule can increase its inhibition towards lipase, α-glucosidase, and α-amylase activities [32].

6. Conclusions

The application of natural metabolites in complex with conventional drugs can synergize therapeutic activities. Ellagic acid has hydrophobic or lipophilic properties as a significant limitation for clinical formulation. Novel formulations in micro and nano scales can increase the therapeutic activity of ellagic acid. Loading of the ellagic acid by apamin-functionalized emulsomes showed the significant apoptotic effect in breast cancer cells. Encapsulation in NPs and loading of these metabolites on NPs are the main strategies for an effective formulation. In the case of antiobesity and antidiabetic activities, hydroxyl groups on the ellagic acid can enhance its inhibition towards enzymes of lipase, α-glucosidase, and α-amylase.

Study Highlights

- Ellagic acid has hydrophobic or lipophilic properties as a significant limitation for clinical formulation.
- Novel formulations in micro and nano scales can augment the therapeutic activity of ellagic acid.
- Loading of the ellagic acid by apamin-functionalized emulsomes showed a significant apoptotic effect in breast cancer cells.

Abbreviations

ABC: ATP binding cassette
AD: Alzheimer's disease
EphB2: Ephrin type-B receptor 2
LRP: The low-density lipoprotein receptor-related protein
mGluR5: Metabotropic glutamate receptors
MRSA: Methicillin-resistant *S. aureus*
NMDAR: N-methyl-D-aspartic acid receptor
NPs: Nanoparticles
P-gp: P-glycoprotein
PirB: Paired immunoglobulin-like receptor B
RAGE: The receptor for advanced glycation end product
SCARA-1: Scavenger receptor A-1
SphK1: Sphingosine kinase 1
TCA: Tricarboxylic
TNF-α: Tumor necrosis factor-α
α7nAChR: α subunit containing nicotinic acetylcholine receptor

Funding

This work was not supported by any institutes.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with animals or human participants performed by any of the authors.

Author Contributions

Both authors: conceptualization, writing the first draft, and revising the manuscript.

Acknowledgements

Declared none.

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HOW TO CITE THIS ARTICLE:
Ahmadi S, Javid H. Novel formulations of ellagic acid for the improvement of antimicrobial, antioxidant, anticancer, antidiabetic, and neuroprotective applications. Nano Micro Biosystems. 2023;2(1):31-35.doi: https://doi.org/10.22034/nmbj.2023.388479.1015