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Review

Ellagic acid: Pharmacological activities and molecular mechanisms involved in liver protection

Wylly Ramsés García-Niño*, Cecilia Zazueta

Department of Cardiovascular Biomedicine, National Institute of Cardiology "Ignacio Chávez", Juan Badiano No. 1, Section XVI, 14080, D.F., Mexico

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ABSTRACT

Traditional drugs or therapies rarely have effects on regression of chronic liver diseases, which result in many cases from sustained oxidative stress. In recent years, ellagic acid (EA) has gained attention due to its multiple biological activities and several molecular targets. This is the first review focused on the pharmacological properties and on the molecular mechanisms activated by EA in terms of liver protection. EA possesses antioxidant, antihepatotoxic, antisteatosic, anticholestatic, antifibrogenic, antihepatocarcinogenic and antiviral properties that improves the hepatic architectural and functions against toxic and pathological conditions. The molecular mechanisms that EA activates include the scavenging of free radicals, regulation of phase I and II enzymes, modulation of proinflammatory and profibrotic cytokines synthesis, the regulation of biochemical pathways involved in the synthesis and degradation of lipids as well as the maintenance of essential trace elements levels. EA also inhibits hepatic stellate cells and mast cells activation, the proliferation of transformed cells, as well as viral replication by increasing antioxidant response, induction of apoptosis, downregulation of genes involved in cell cycle and angiogenesis, and stimulation of cellular immune response. Despite the enormous therapeutic potential of EA as an innovative pharmacological strategy, the number of phase I and II trials in patients is scarce, precluding its clinical application. In these sense, the use of new delivery systems that enhances EA bioavailability would improve the results already obtained. Also it remains to be determined if treatment with urolithins instead of EA would represent a better strategy in hepatic disease treatment.

Contents

* Corresponding author. Tel.: +52 55 5573 2911; fax: +52 55 5573 0926.
E-mail address: wramsesgarcia@gmail.com (W.R. García-Niño).

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1. Introduction

The liver is the largest internal organ of the body, about 2% of body weight in the adult, which accounts to approximately 1400 g in females and 1800 g in males. The liver receives blood supply from both the hepatic artery and the portal vein [1], and is composed by hepatocytes (that occupy almost 80% of total liver volume and perform the majority of liver functions), sinusoidal endothelial cells, Kupffer cells and hepatic stellate cells (HSC) [2]. This organ takes up nutrients, acting as store or provider to other organs, metabolizes a wide variety of nutrients and xenobiotics and serves as an excretory organ for bile pigments, cholesterol, bacterial products, and drugs [3,4]. In consequence, this organ is highly susceptible to the effects of toxins [5]. Oxidative stress is one of the central mechanisms involved in the pathogenesis and progression of liver diseases, which results from an imbalance between the action of pro-oxidant agents and the cellular antioxidant defenses [6,7]. In general these pro-oxidants are referred as reactive oxygen species (ROS), including superoxide radical ($O_2^{\bullet -}$), hydroxyl radical ($HO^{\bullet}$), hydrogen peroxide (H_2O_2), nitric oxide ($NO^{\bullet}$) and peroxynitrite ($ONOO^{\bullet}$) [8]. Therefore, the use of natural antioxidants instead of conventional treatments has emerged as an alternative strategy to prevent or attenuate liver injury [9–12]. The term antioxidant refers to any substance that delays, prevents or removes oxidative damage of easily oxidizable biomolecules, among them lipids, proteins and DNA [13,14]. The hepatoprotective properties of secondary metabolites of many plants and their extracts have been associated with its antioxidant properties [15–17]. In consequence, many of them have been proposed as therapeutic agents or adjuvants in the treatment of liver disease [18,19]. Particularly, recent studies have demonstrated that EA (a naturally occurring polyphenolic compound) possesses exceptional pharmacological properties against liver toxicity and disease. Thus, the purpose of this paper is to review scientific evidence regarding to the hepatoprotective effect of EA, since this issue has not been analyzed in depth and because in view of current basic knowledge, this compound has potential to be evaluated in medical treatments or as a food supplement to prevent or reduce liver injury caused by toxicity or disease.

2. Ellagic acid chemistry

EA (2,3,7,8-tetrahydroxy[1]-benzopyranol[5,4,3-cde]benzopyran-5,10-dione) was discovered in 1831 by Braconnot [20] (Fig. 1). It is a highly thermostable molecule (melting point of 350 °C), with a molecular weight of 302.197 g mol^{-1}, slightly soluble in water, alcohol, and ether, but soluble in caustic potash [21]. Structurally, presents four rings representing the lipophilic domain, four phenolic groups and two lactones, which form hydrogen-bonds sides and act as electron acceptors respectively, and that represent the hydrophilic domain [22].

EA is a naturally occurring polyphenolic compound which is found in many fruits, nut galls and plant extracts in the forms of hydrolysable tannins called ellagitannins (Table 1) such as raspberries, strawberries, grapes, pomegranate, black currants, camu-camu, mango, guava, walnuts, almonds, longan seeds and green tea [23–25].

2.1. Absorption, biodistribution, metabolism, and excretion

Ellagitannins and EA bioavailability is low in human [26] and animal models [27–29] due to their hydrophobic nature. Hydrolysis of ellagitannins release EA under physiological conditions, which is moderately absorbed and metabolized by gut microbiota to urolithins (dibenzopyran-6-one metabolites) through remotion of one of the two lactone groups and subsequent decarboxylation, and dehydroxylation reactions [30]. Urolithin D, urolithin C, urolithin A and urolithin B are sequentially produced and absorbed in the intestine, as their lipophilicity increased [31]. The amount of ellagitannins and EA in the systemic circulation and peripheral tissues is almost negligible, whereas urolithins and their conjugates can reach concentrations at the micromolar level [32]. Furthermore, EA and its metabolites are subjected to phase II reactions including glucuronidation, sulfation and methylation that occurs in the wall of the large intestine and/or post-absorption in the liver [33–35]. It has been described the presence of urolithin A, urolithin B and dimethyl-EA-glucuronide in peripheral plasma, as well as glucuronides and methyl glucuronides of EA, urolithin A, C, and D in bile (enterohepatic circulation) [36]. Regarding tissue distribution of urolithins and their conjugates, urolithin A accumulates in prostate, intestinal, and colon tissues, whereas urolithin A glucuronide was primarily detected in liver and kidney tissues from mice [37]. EA-derived metabolites, mainly urolithin A and B are excreted through the urine; EA and EA-O-glucuronide urinary excretion in humans is <1% of intake [38], whereas urolithin A is the main metabolite detected in feces in both pigs and humans [27,35].

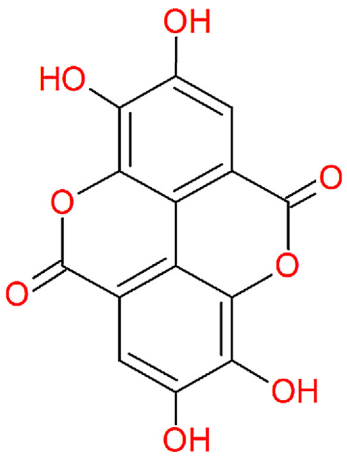

Fig. 1. Chemical structure of ellagic acid ($C_{14}H_6O_8$).

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