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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].

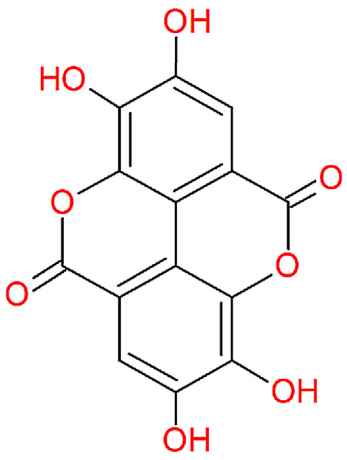

Fig. 1. Chemical structure of ellagic acid ($C_{14}H_6O_8$).

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Table 1
Plant extracts containing of ellagic acid.

Botanical name	Part used	Extract	Pharmacological activities	References
Barringtonia racemosa	Leaves and stems	Aqueous	Antioxidant	[307]
Carya illinoinensis	Kernels and shells	Aqueous	Antioxidant and antihyperlipidemic	[308,309]
Chrozophora senegalensis	Leaves	Aqueous	Antimalarial	[310]
Cistus laurifolius	Leaves	Ethanol	Antioxidant and antidiabetic	[311,312]
Cochlospermum angolensis	Bark	Aqueous and hydromethanol	Antioxidant and antidepressant	[313]
Decalepis hamiltonii	Roots	Aqueous	Antioxidant	[314]
Delonix elata	Stem bark	Ethanol	Antihepatotoxic	[315]
Dimocarpus longan	Seeds	Ethanol and methanol	Antioxidant, antifungal and antimicrobial	[19,316–318]
Emblica officinalis, syn Phyllanthus emblica	Hulls and fruit	Ethanol, methanol and ethyl acetate	Antioxidant, antihepatotoxic, anti-inflammatory, antidiabetic and anticarcinogenic	[319–325]
Eucalyptus globulus	Bark, stem, leaves and fruit	Aqueous	Antioxidant	[326–328]
Euphorbia supina	Herb	Methanol	Antioxidant	[61]
Ficus glomerata	Fruit	Ethyl acetate	Antioxidant and gastroprotector	[329,330]
Gentiana scabra	Rhizomes	Aqueous	Antihepatotoxic	[99]
Geranium carolinianum	Aerial	Aqueous, ethanol and ethyl acetate	Anti-hepatitis B virus	[293,331]
Geum rivale	Aerial	Methanol	Not determined	[332]
Irvingia gabonensis	Seeds	Hydromethanol	Not determined	[333]
Lagerstroemia speciosa	Leaves and stem	Ethanol	Antidiabetic, antihyperuricemic and anti-human immunodeficiency virus (HIV)	[334–337]
Macrosiphonia longiflora	Xylipodium	Hydroethanol	Anti-inflammatory	[338]
Mangifera indica	Fruit	Ethanol	Antioxidant	[19,339]
Moringa oleifera	Leaves, fruit and seeds	Aqueous and ethyl acetate	Antioxidant	[340–342]
Myrciaria dubia	Fruit	Hydromethanol	Antioxidant	[343]
Polygonum chinense	Aerial	Ethanol	Anti-diarrheal	[344]
Psidium friedrichsthalianum	Fruit	Ethyl acetate	Antioxidant and anti-inflammatory	[161]
Punica granatum	Husk, fruit, seeds	Aqueous, ethanol, methanol, acetic acid	Antioxidant, anti-inflammatory, anticarcinogenic, antidiabetic, antinociceptive, antibacterial, antifungal and anti-hepatitis C virus	[40,299,345–352]
Rubus parvifolius	Whole plant	n-butanol	Antihepatotoxic	[353]
Sebastiania chamaelea	Whole plant	Aqueous	Antimalarial	[310]
Tamarix aphylla	Leaves and stem	Ethyl acetate	Not determined	[354]
Terminalia chebula	Fruit	Aqueous, methanol	Antioxidant, anticarcinogenic, antibacterial and anti-hepatitis C virus	[300,355–358]
Thespesia lampas	Roots	Ethanol	Antioxidant and antihepatotoxic	[359,360]
Trapa taiwanensis	Fruit	Aqueous	Antihepatotoxic	[361]
Vitis rotundifolia	Fruit	Methanol	Antioxidant and anticarcinogenic	[362–364]
Woodfordia fruticosa	Flowers	Methanol	Antioxidant, anti-inflammatory, antibacterial, antifibrotic and anti-asthmatic	[102,365,366]

2.2. Pharmacological activities

EA has been reported to possesses antimutagenic [39], antigenotoxic [40,41], anti-apoptotic [42–44], anticarcinogenic [45], antibacterial [46], antiviral [47], antimalarial [48], antiallergic [49], anti-inflammatory [50,51], antiatherogenic [52]; antidiabetic [20,53], antiepileptic [54], antidepressant [55], antianxiety [56], neuroprotective [57], pneumoprotective [58], nephroprotective [59], cardioprotective [60] and hepatoprotective activities [61]. Recently, it has been shown that urolithins are not only potent antioxidants [62,63], but that also have anti-inflammatory [64,65], anticarcinogenic [66–69], antimalarial [70], antidiabetic [71] and antiaromatase properties [72].

2.3. Molecular targets

EA exerts its beneficial effects by regulating multiple pathways including: (i) activation of the antioxidant response through the nuclear erythroid 2-related factor 2 (Nrf2) [73,74]; (ii) inhibition of proinflammatory agents, such as cyclooxygenase (COX-2) and cytokines by nuclear factor-kappa B (NF-κB) [51,75]; (iii) alteration of several growth factors expression, as the platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β), hepatic growth factor (HGF) [76,77]; (iv) depletion of adhesion molecules, like vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) among others [78]; (v) modulation of several cell survival/cell-cycle genes such as cyclin D1 and E, p21, B-cell lymphoma 2 (Bcl-2), Bcl-2-associated X protein (Bax) [79,80], tumor suppressors (p53, DUSP6, Fos), oncogenes (K-Ras, c-Myc) [81]; (vi) regulation of kinases, like mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3-K), glycogen synthase kinase 3 beta (GSK-3β) [82–84] (Fig. 2).

2.4. Antioxidant properties of EA

Liver damage in most cases involves oxidative stress and is characterized by a progressive evolution from steatosis to chronic hepatitis, fibrosis, cirrhosis and hepatocellular carcinoma. Hepatocytes are equipped with molecular machinery that controls the level of oxidative stress and maintains the balance between prooxidant and antioxidant agents [6,85]. However, under conditions which promote oxidative stress, endogenous machinery may not

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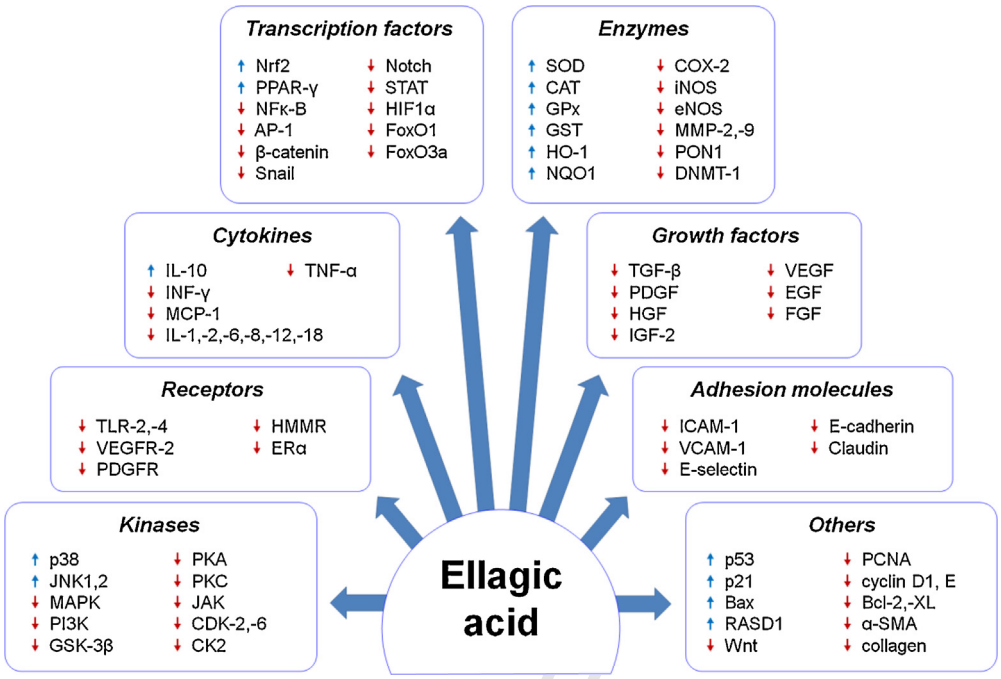

Fig. 2. Ellagic acid upregulates (↑) or downregulates (↓) several molecular targets. Nuclear erythroid 2-related factor 2 (Nrf2); peroxisome proliferator-activated receptor gamma (PPAR-γ); nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB); activator protein 1 (AP-1); signal transducer and activator of transcription (STAT); hypoxia-inducible factor 1 alpha (HIF-1); forkhead box protein O (FoxO); superoxide dismutase (SOD); catalase (CAT); glutathione peroxidase (GPx); glutathione-*S*-transferase (GST); heme oxygenase-1 (HO-1); NAD(P)H:quinone oxidoreductase 1 (NQO1); cyclooxigenase 2 (COX-2); inducible nitric oxide synthase (iNOS); endothelial nitric oxide synthase (eNOS); matrix metalloproteinase (MMP); paraoxonase-1 (PON1); DNA methyltransferase 1 (DNMT-1); interleukin-10 (IL-10); interferon gamma (IFN-γ); monocyte chemoattractant protein 1 (MCP-1); tumor necrosis factor alpha (TNF-α); transforming growth factor beta (TGF-β); platelet-derived growth factor (PDGF); hepatocyte growth factor (HGF); insulin-like growth factor 2 (IGF-2); vascular endothelial growth factor (VEGF); endothelial growth factor (EGF); fibroblast growth factor (FGF); Toll-like receptor (TLR); hyaluronan-mediated motility receptor (HMMR); estrogen receptor alpha (ERα); intercellular adhesion molecule-1 (ICAM-1); vascular cell adhesion molecule-1 (VCAM-1); c-Jun NH(2)-terminal kinase (JNK); mitogen-activated protein kinase (MAPK); phosphoinositide 3-kinase (PI3-K); glycogen synthase kinase 3 beta (GSK-3β); protein kinase A (PKA); protein kinase C (PKC); janus kinase (JAK); cyclin-dependent kinase (CDK); casein kinase 2 (CK2); dexamethasone-induced Ras-related protein 1 (RASD1); proliferating cell nuclear antigen (PCNA); alpha smooth muscle actin (α-SMA).

be sufficient and dietary antioxidants may be required to maintain optimal cellular functions [86].

EA has demonstrated scavenging activity against a variety of ROS. The four hydroxyl and two lactone functional groups act respectively as hydrogen bond acceptors and donors, enabling EA to scavenge $O_2^{\bullet -}$, $HO^{\bullet}$, H_2O_2 and $ONOO^{\bullet}$ [87–89]. On the other hand, EA exerts indirect protective effect against oxidative stress in hepatic cells by upregulation of Nrf2 and downregulation of Kelch-like ECH-associated protein 1 (Keap1), which modulates the induction of phase I and phase II detoxifying enzymes [74,90,91]. Nrf2 is a redox-sensitive transcription factor considered the master antioxidant response regulator in the cell. Under basal conditions is bound to its repressor Keap1 in the cytoplasm, which promotes its ubiquitination and subsequent degradation by the proteosomal pathway [92–94]. Low levels of ROS or electrophiles induce the oxidation or covalent modification of cysteine residues contained in Keap1 decreasing its affinity to Nrf2 and releasing it for nuclear translocation. Also, the release of Nrf2 from its inhibitor requires its phosphorylation at Ser-40 by kinases such as extracellular-signal-regulated kinases (ERK), protein kinase C (PKC) and PI3-K [95]. Once translocated into nucleus, Nrf2 forms a heterodimer with small Maf protein that binds to the antioxidant responsive elements (ARE) or to the electrophile responsive elements (EpRE), regulating the expression of genes that encode antioxidant and cytoprotective enzymes [96–98]. Barch et al. [99] determined that lactone groups in the EA molecule are the portions required for induction of phase II enzymes, but it has not been determined if EA could induce Nrf2 phosphorylation *via* upstream kinases PI3K/Akt and MAPK [83,84]. In particular, EA increases reduced glutathione (GSH) levels through upregulation of GSH synthetase, glutamate-cysteine ligase catalytic subunit (GCLC) and glutamate-cysteine ligase regulatory subunit (GCLR) [100]. Also, EA induces the expression of NADPH:quinone oxidoreductase 1 (NQO1), heme oxygenase-1 (HO-1) [73,101–103], superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione-*S*-transferase (GST) [74,104,105] (Fig. 3).

2.5. Antihepatotoxic properties of EA

Hepatotoxicity refers to liver dysfunction or liver damage associated with exposure to drugs or xenobiotics [106]. Clinical symptoms of liver damage are jaundice, swollen and tender liver; whereas biochemical alterations include elevated levels of hepatic enzymes in the blood and loss of enzymatic activities in the liver. Under histological examination, common findings are fatty degeneration and necrosis of central hepatocytes, destruction of intracellular organelles, fibrosis and cirrhosis [107]. Hepatotoxicity may result not only of the combined action of the primary compound and reactive metabolites, but from the immunologically-mediated response which impact on hepatocytes, biliary epithelial cells and/or liver vasculature [5]. Reactive metabolites include epoxides, quinones, free radicals, ROS and unstable conjugates which can directly react with proteins, nucleic acids and lipids [108]. At respect, EA has shown hepatoprotective effects in murine models against a variety of agents that disrupt the function or the architectural structure of liver (Table 2).

2.5.1. Alcohol

Excessive alcohol intake is a major public health challenge worldwide [109]. Alcohol affects every organ system in the body

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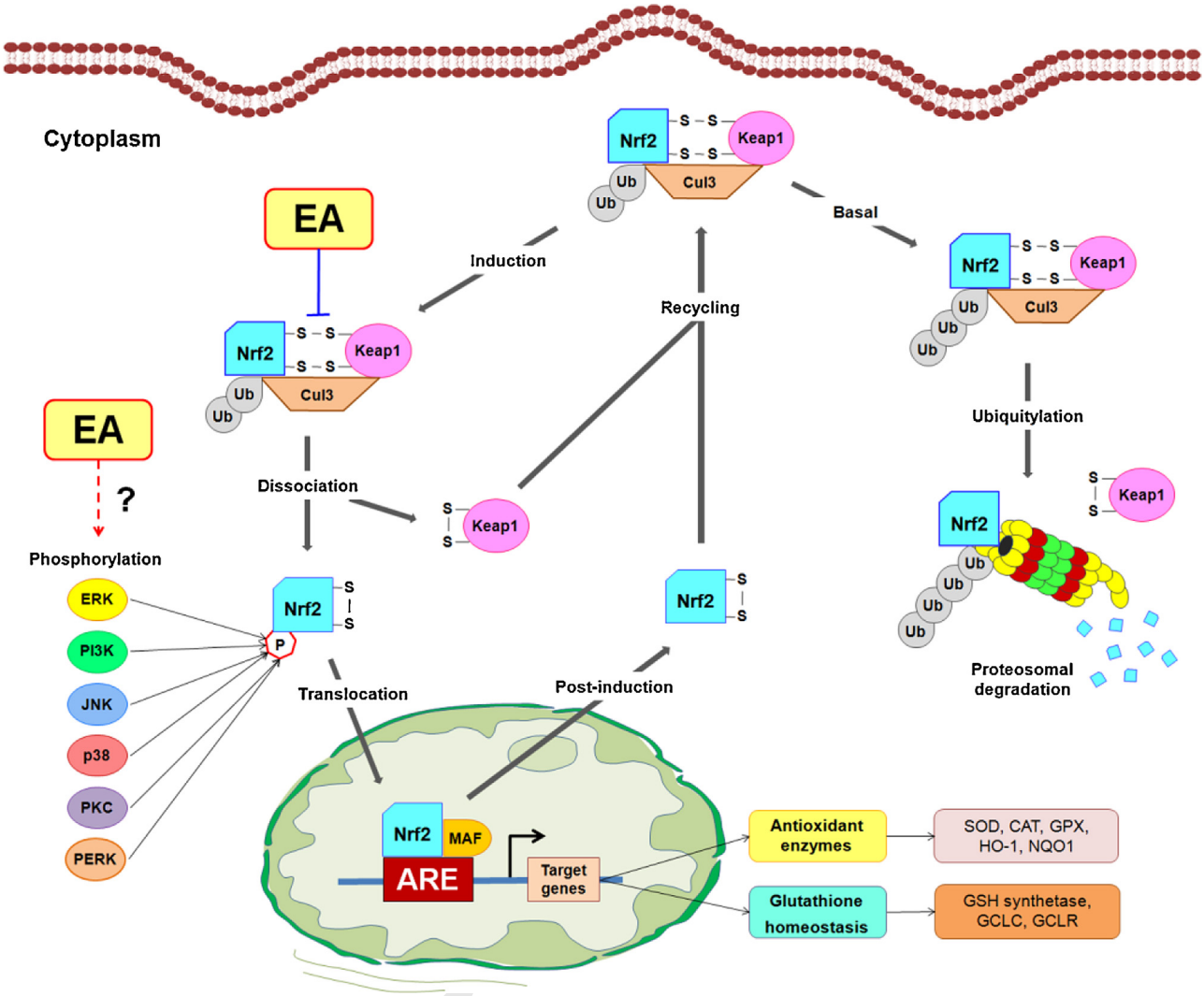

Fig. 3. Ellagic acid (EA) increases antioxidant response through the transcriptional activation of nuclear erythroid 2-related factor 2 (Nrf2). Nrf2 under basal conditions, is bound to its repressor Kelch-like ECH-associated protein 1 (Keap1) in the cytoplasm. Keap1 serves as an adaptor protein between Nrf2 and the cullin-3 (Cul3) complex, leading to ubiquitylation of Nrf2 and subsequent degradation by the 26S proteasome. EA interacts with cysteine residues contained in Keap1 decreasing its affinity to Nrf2, releasing it for nuclear translocation. On the other hand, EA could induce Nrf2 phosphorylation at Ser-40 through the activation of kinases, such as extracellular-signal-regulated kinases (ERK), phosphoinositide 3-kinase (PI3-K), c-Jun NH(2)-terminal kinase (JNK), protein kinase C (PKC), protein kinase RNA-like endoplasmic reticulum kinase (PERK) and p38. Once translocated into nucleus, Nrf2 binds to the antioxidant responsive elements (ARE) regulating the expression of genes that encode antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx); heme oxygenase- 1 (HO-1); NADPH:quinone oxidoreductase 1 (NQO1), as well as enzymes involved in glutathione (GSH) homeostasis such as GSH synthetase, glutamate-cysteine ligase catalytic subunit (GCLC) and glutamate-cysteine ligase regulatory subunit (GCLR).

causing a variety of disorders [110] and particularly in liver has been associated with a spectrum of diseases, from steatosis and steatohepatitis to cirrhosis and hepatocellular carcinoma [111,112]. EA inhibits alcohol-induced liver cell damage increasing the antioxidant levels, scavenging free radicals and stabilizing cell membranes [113–115]. Also, it has been reported that EA protects hepatocytes by regulating the activity of cytochrome P450 (CYP450) enzymes, decreasing the activation of numerous xenobiotics to toxic metabolites and in consequence, diminishing oxidative stress [116–118]. Another reports indicate that EA has anti-inflammatory properties, by reducing the expression of proinflammatory and pro-fibrogenic cytokines like interleukins (IL-1α, IL-6, IL-8), tumor necrosis factor alpha (TNF-α) and TGF-β, which are involved in alcohol-induced inflammation and fibrosis [111,119]. As TGF-β reduces the expression of alcohol dehydrogenase 1 (ADH1) [120], which along with aldehyde dehydrogenase (ALDH) are the principal enzymes responsible of ethanol metabolism, it follows that EA could reduce liver damage and steatosis associated with chronic alcohol consumption, although this possibility has not been demonstrated.

2.5.2. Carbon tetrachloride (CCl_4)

CCl_4 is widely used to assess liver damage and the effect of hepatoprotective agents [121,122]. CCl_4 is metabolized by CYP450 in the endoplasmic reticulum of hepatic cells producing the unstable free radicals trichloromethyl (CCl_3•) and trichloromethyl peroxyl (CCl_3O_2•) [123] that stimulates Kupffer cells to produce ROS, leading to lipid peroxidation and subsequently to centrilobular hepatic necrosis, inflammation and fibrosis [124–126]. EA attenuates free radicals production by normalizing the activity of CYP450 [127], improving the antioxidant and cytoprotective responses and preserving the structural integrity of liver cells [128–130]. Recently, it was reported that natural extracts containing EA have antifibrotic activities, as reduction in the formation of fibrotic septa was observed in liver from rats treated chronically with CCl_4 [131].

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Table 2
Ellagic acid protective effects against toxins-induced liver damage.

Hepatotoxin	Animal model	Ellagic acid hepatoprotection			References
		Biochemical	Antioxidant	Histological	
Alcohol	Wistar rats	↓ GGT ↓ ALP	↓ TBARS ↓ Hydroperoxides ↓ NO• ↓ Protein carbonylation ↑ Vitamin C and E ↑ GSH ↑ SOD and CAT activities	↓ Sinusoidal dilatation ↓ Portal inflammation ↓ Thickening of blood vessels ↓ Steatosis ↓ Necrosis ↓ Fibrosis	[86,87,237,367]
Carbon tetrachloride	Rats Swiss albino mice	↓ AST ↓ ALT ↓ ALP ↓ Bilirubin ↓ Hydroxyproline	↓ MDA ↑ GSH ↑ SOD, CAT and GPx activities	↓ Fatty infiltration ↓ Portal inflammation ↓ Centrizonal necrosis ↓ Fibrosis	[98–101,368]
Cisplatin	Sprague-Dawley rats	ND	↓ MDA ↑ GSH ↑ GPx and CAT activities	↓ Hepatocellular necrosis ↓ Karyomegaly ↓ Kupffer cell activation ↓ Bile duct proliferation	[108]
Concanavalin A	Balb/c mice	↓ AST ↓ ALT	↑ GSH	↓ Apoptotic hepatocytes ↓ Necrosis ↓ Fulminant hepatitis	[44,123]
Cyclosporine A	Wistar rats	↓ AST ↓ ALT ↓ ALP ↓ LDH ↓ Bilirubin	↓ TBARS ↓ Hydroperoxides ↑ Vitamin C and E ↑ GSH ↑ SOD, CAT and GST activities	↓ Sinusoidal dilatation	[130]
D-Galactosamine and lipopolysacharide	Balb/c mice	↓ AST ↓ ALT	↓ MDA ↑ Nrf2 ↑ HO-1	↓ Portal inflammation ↓ Inflammatory cell infiltration ↓ Necrosis	[75]
Isoniazid and rifampicin	Wistar rats	↓ AST ↓ ALT ↓ ALP ↓ Bilirubin	ND	Normalize liver weight ↓ Histological alterations	[144]
Mercury	Wistar rats	↓ AST ↓ ALT ↓ ALP ↓ LDH ↓ Bilirubin ↓ Cholesterol ↑ Albumine	↓ MDA ↑ GSH ↑ SOD, CAT and GPx activities	↓ Hypertrophy of hepatocytes ↓ Disorientation of the liver cords ↓ Multinucleated cells ↓ Swelling ↓ Necrosis	[162,163]
Paracetamol	Swiss albino mice	↓ AST ↓ ALT ↓ ALP	↓ MDA ↑ GSH ↑ CAT activity	Normalize liver weight ↓ Steatosis ↓ Hydropic degeneration ↓ Centrizonal necrosis ↓ Inflammatory cell infiltration	[179]

Gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), thiobarbituric acid reactive substances (TBARS), nitric oxide (NO•), malondialdehyde (MDA), reduced glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione-*S*-transferase (GST), heme oxygenase-1 (HO-1), nuclear erythroid 2-related factor 2 (Nrf2), not determined (ND).

2.5.3. Cisplatin

Cisplatin [*cis*-diamminedichloroplatinum (II)] is one of the most widely used antineoplastic agents in the treatment of solid tumors and hematological malignancies [132,133]. However, its clinical use is limited due to its toxic side effects which are associated with increased oxidative stress, leading to nephrotoxicity, neurotoxicity, ototoxicity and hepatotoxicity [134–136]. EA increases the viability of hepatocytes in cisplatin-induced damage acting as ROS scavenger and by maintaining the antioxidant enzyme levels [137]. However, it is not known if EA effects are mediated through Nrf2 activation and/or if this antioxidant has impact on mitochondrial dysfunction that is involved in cisplatin-induced hepatotoxicity [138–140]. On the other hand, EA confers protection against cisplatin-induced damage in organs like kidney [59,141,142], heart [137], testis and also in spermatozoa [143,144].

2.5.4. Concanavalin A (ConA)

ConA is a lectin derived from *Canavalia ensiformis* seeds, with polyclonal T-cell mitogenic properties, that induces selective liver failure in mice that resembles viral hepatitis, autoimmune hepatitis and other immune-mediated liver diseases in humans [145,146]. In this model, hepatic damage results from increase in proinflammatory cytokines [147,148] and elevated ROS levels [149–151]. EA avoids ConA-induced hepatitis by downregulating the expression of Toll like receptors-2 and -4 (TLR-2, TLR-4), proteins involved in MAPK/NF-κB signaling pathways and proinflammatory cytokines, like TNF-α, IL-1β and IL-6 [61]. Furthermore, it has been described

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that EA prevented from necrosis and apoptosis after ConA injury by ameliorating oxidative stress and preserving mitochondrial function [152].

2.5.5. Cyclosporine A (CsA)

CsA is a potent immunosuppressor widely used in transplant surgery and in treatment of several autoimmune diseases [153]. Nevertheless, it affects kidney, heart and liver function [154]. Although, the mechanisms by which CsA causes hepatic injury are not clear, several reports have suggested that ROS overproduction and depletion of hepatic antioxidant system underlie in CsA toxicity [155,156]. CsA hepatotoxicity is characterized by cholestasis, hyperbilirubinemia, hypoproteinemia, increased alkaline phosphatase and elevated transaminases, inhibition of protein synthesis and de-regulation in lipid secretion in both human and experimental animals [157,158]. EA protective potential against CsA-induced hepatic dysfunction has been related with ROS scavenger properties and with its capacity to increase the antioxidant response [159,160]. Also, EA attenuates hyperbilirubinemia, maintains the normal architecture of liver tissue, confers protection in CsA-induced nephrotoxicity [161,162], in cardiotoxicity [160], as well as in testicular and spermatozoa damage [24].

2.5.6. D-Galactosamine (D-GalN) and lipopolysacharide (LPS)

D-GalN is a hepatotoxic agent metabolized exclusively in hepatocytes, which reduces the intracellular pool of uracil nucleotides, thus inhibiting the synthesis of RNA and proteins. The administration of D-GalN combined with a low dose of LPS develops lethal liver injury, which resembles the biochemical and metabolic changes observed in fulminant hepatic failure [163,164]. D-GalN injury is characterized by increased NF-κB nuclear translocation, augmented expression of the inducible nitric oxide synthase (iNOS), TNF-α, interferon gamma (IFN-γ), IL-1β, IL-6, IL-12, and IL-18 and downregulation of Nrf2, NQO1, HO-1, and GSTα expression [165]. In this model, EA and other polyphenols protect liver through the activation of Nrf2, and suppressing the NF-κB pathway [103,166,167]. In addition, studies *in vitro* suggested that urolithins are implied in the anti-inflammatory effects of EA [168–170].

2.5.7. Rifampicin and isoniazid

Tuberculosis treatment with combined therapy of rifampicin and isoniazid frequently causes liver injury in humans [171]. Rifampicin induces conjugated hyperbilirubinemia by inhibiting the major bile salt exporter pump, the basolateral Na^+/taurocholate cotransporting polypeptide (NTCP) [172,173]. On other hand, isoniazid is directly or indirectly metabolized to acetyl hydrazine and hydrazine by N-acetyltransferase (NAT) and amidohydrolase. These metabolites are oxidized in liver by CYP450 monooxygenases generating electrophilic intermediates and free radicals that have been pointed out as the causative hepatotoxins in liver damage [174,175]. Analysis of both biochemical and histological markers, indicates that EA protects from isoniazid-rifampizine-induced liver toxicity maintaining the plasma membrane integrity of hepatocytes [176]. However, information on the EA mechanisms related with attenuation of hyperbilirubinemia are still controversial, as it is not known if this compound interferes with NTCP inhibition, or if prevents the formation of isoniazid metabolites that inhibit the enzymatic activity of NAT or amidohydrolase, as has been observed in other models [177–179]. Neither is known if EA directly reduces the generation of free radicals or acts indirectly, activating Nrf2.

2.5.8. Mercury (Hg)

Hg is a toxic and hazardous metal that may exist in the environment [180,181]. Exposure to mercurial compounds induces hepatotoxicity associated with oxidative stress [182–185], generating hepatocellular defects like hepatomegaly, centrilobular hepatic steatosis [186,187], decrease in the synthesis of hepatic coagulation factors [188–192] and diminution in the activity of metabolic enzymes [193]. EA reduces mercuric chloride damage, avoiding the generation of oxidative stress and diminishing the possibility of damage to liver cells [194,195]. Besides, EA might act chelating Hg^{2+}, as it chelates other divalent ions such as Ni^{2+}, Zn^{2+}, Fe^{2+} and Cu^{2+} [196–199]. On the other hand, EA protects the functional and structural integrity of mitochondria and endoplasmic reticulum [152,200], which are main targets of mercury toxicity [201,202].

2.5.9. Paracetamol

Paracetamol (acetaminophen), 4-hydroxyacetanilide, is one of the most widely used drugs, due to its analgesic and antipyretic properties [203]. Though safe at therapeutic doses, it may cause acute liver failure at overdoses, being a main cause of death or transplantation in countries like UK and USA [204–206]. Acetaminophen overdose causes a multitude of interrelated biochemical reactions in hepatocytes including oxidative stress, covalent modification and oxidation of proteins, lipid peroxidation, mitochondrial dysfunction and centrilobular necrosis [207–210]. EA, not only ameliorates acetaminophen-induced liver injury contending against oxidative stress, but also prevents the formation of reactive metabolites that inhibits the activity of CYP2E1 (cytochrome P450, family 2, subfamily E, polypeptide 1) [211]. Paracetamol binds covalently to DNA, induces DNA single-strand breaks (SSBs) and inhibits the replicative and repair synthesis of DNA [212,213]. Although experimental evidence is lacking, EA might counteract DNA damage, as previously demonstrated in N-nitrosodiethylamine and cyclophosphamide induced damage [40,214]. In both models EA restores many of the hallmarks of genotoxicity to normal levels.

2.6. Antisteatosic properties of EA

Steatosis or fatty liver refers to an excessive accumulation of triglycerides and subsequent formation of lipid droplets in the cytoplasm of hepatocytes [215,216]. Fatty liver is most often attributed to the effects of alcohol excess, obesity, diabetes, or drugs, and is usually divided into alcoholic fatty liver disease (AFLD) and non-alcoholic fatty liver disease (NAFLD) [217,218]. When steatosis of the liver is further accompanied by inflammation, the condition is termed steatohepatitis, that is associated with the development of fibrosis and even cirrhosis [219,220]. Steatosis and related complications induced by alcohol [115], paracetamol [211] and CCl_4 [127] are reduced with EA administration by the mechanisms previously discussed.

Recently, Yoshimura et al. [221] reported that EA recovered liver function and reduced the pathological conditions associated with steatosis in a KK-A^y mouse model which develops obesity and hyperglycemia at an earlier stage. In these combined model of obesity/type 2 diabetes, EA administration diminished the accumulation of free fatty acids (FFA) in the liver observed both in obesity [222,223] and in type 2 diabetes [224,225] improving obesity-induced dyslipidemia. Besides, EA increased high density lipoprotein (HDL) cholesterol in serum and prevented from triglycerides accumulation in liver by regulating lipogenesis and β-oxidation. Hepatic β-oxidation provides ketone bodies (acetoacetate and β-hydroxybutyrate) by progressive shortening of two-carbon-units of fatty acyl-CoA to the peripheral circulation, through an enzymatic system transcriptionally regulated by the peroxisome proliferator–activated receptor-alpha (PPAR-α) [226,227]. PPAR-α is a ligand-activated transcription factor that upregulates many genes involved in fatty acid utilization [228–230]. Recent studies have shown that EA upregulates liver PPAR-α increasing the expression of genes involved in cholesterol synthesis and transport, in fatty acid synthesis, in fatty acid

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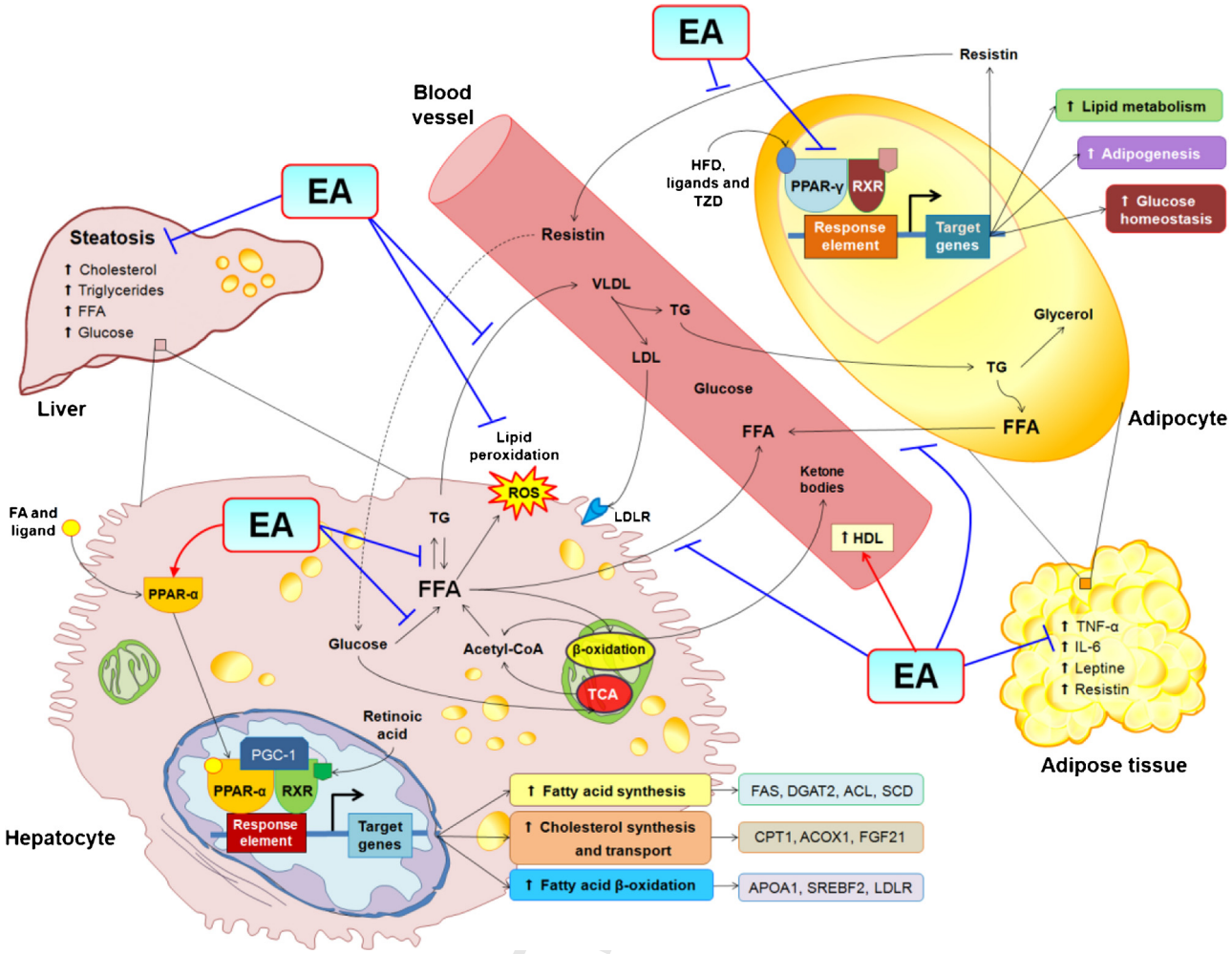

Fig. 4. Molecular mechanisms involved in the antisteatosic effects of ellagic acid (EA). EA recovered liver function and reduced the pathological conditions associated with steatosis. It diminishes the accumulation of free fatty acids (FFA), increases high density lipoprotein (HDL) cholesterol in serum and prevents from triglycerides (TG) accumulation in liver through upregulation of the peroxisome proliferator–activated receptor-alpha (PPAR-α), that increases the expression of genes involved in fatty acid synthesis, cholesterol synthesis/transport and fatty acid β-oxidation, *e.g.* fatty acid synthase (FAS), diacylglycerol acyltransferase-2 (DGAT2), ATP citrate lyase (ACL), stearoyl-CoA desaturase 1 (SCD), carnitine palmitoyltransferase 1 (CPT1), acylCoA oxidase 1 (ACOX1), fibroblast growth factor 21 (FGF21), apolipoprotein A (APOA1), sterol regulatory element binding transcription factor 2 (SREBF2) and low density lipoprotein receptor (LDLR). Also, EA downregulates the peroxisome proliferator-activated receptor-gamma (PPAR-γ) and genes involved in adipogenesis. EA prevented from metabolic deregulation associated with resistin secretion. Retinoid X receptor (RXR); PPAR coactivator-1 (PGC-1); tricarboxylic acid (TCA); very low density lipoprotein (VLDL); low density lipoprotein (LDL); low density lipoprotein receptor (LDLR); high fat diet (HFD); tumor necrosis factor alpha (TNF-α); interleukin-6 (IL-6).

β-oxidation and that also downregulates genes involved in adipogenesis [221,231,232] (Fig. 4).

On the other hand, it has been proposed that circulating inflammatory mediators manufactured and released by white adipose tissue are important in the development of steatosis and subsequent progression of liver disease and insulin resistance [233–235]. In particular, the adipokine resistin, which is secreted from adipocytes in rodents influences adipogenesis, increases triglyceride synthesis and suppress mitochondrial fatty acid β-oxidation, resulting in the accumulation of intracellular lipids in adipocytes [236,237]. EA prevented metabolic disturbances associated with steatosis development in both KK-A^{y} mice [221] and in ovariectomized mice which show high resistin levels in serum and elevated mRNA expression in white adipose tissue [238] (Fig. 4).

2.7. Anticholestatic properties of EA

Cholestatic liver diseases are the result of functional defects in bile formation at the level of the hepatocyte or that arises from impairment in bile secretion and flow at the bile duct level [239–241]. This condition is caused by genetic defects, toxins, or deregulations in the immune system that damage the bile ducts and cause accumulation of bile and liver tissue damage, followed by inflammation and fibrosis, and that may culminate in liver cirrhosis and hepatocellular or cholangiocellular cancer [242,243].

The anti-cholestatic properties of EA have been investigated in experimental biliary obstruction model by measuring liver injury markers and the levels of copper (Cu) and zinc (Zn) [244–248]. Cu is an essential trace element required for normal function of proteins, which is bound to specific amino acid residues in an active site [249–251]. However, its accumulation causes hepatitis, cholestasis, cirrhosis and ultimately death [252–254]. On the other hand, zinc is an essential trace element with catalytic, structural and regulatory properties, involved in antioxidant, anti-inflammatory, and antiapoptotic processes [255–257]. EA did not exerted anticholestatic effect in the experimental biliary obstruction model, since the level of biochemical markers in plasma such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and total bilirubin were not decreased. However, EA reduced Cu accumulation in the liver, which might avoid

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other toxic effects related with ROS production, GSH oxidation, lipid peroxidation [258–260] and mitochondrial injury [261,262].

2.8. Antifibrogenic properties of EA

Hepatic fibrosis is a wound healing process characterized by accumulation of extracellular matrix (ECM) proteins, especially collagen types I and III, proteoglycans, fibronectin and laminin in response to liver injury [263,264]. In acute injury, liver recovers completely without scarring or complication. However, under chronic injury the liver is changed into fibrotic state by the activation of HSC, excessive production of ECM and the aberrant activity of TGF-β1 that ultimately leads to cirrhosis and many complications like portal hypertension, liver failure and hepatocellular carcinoma [265–267]. Scarce information about the antifibrotic effects of EA exists in liver; however Buniatian [268] demonstrated that this compound reduces the activation process at moderate concentrations (6 μg/ml) in HSC cultures, preventing HSC change from quiescent cells to activated myofibroblast-like cells, although it is worth mentioning that EA increased the activation of HSC at higher concentrations (30 μg/ml). On the other hand, EA regulate the expression of proteins related with fibrogenesis and fibrolysis which are upregulated in liver diseases. These proteins include specialized zinc-dependent enzymes such as matrix metalloproteinases-2 and -9 (MMP-2, MMP-9) that degrades ECM, and tissue inhibitor of metalloproteinases-2 (TIMP-2) [269].

Other profibrogenic factors, such as TGF-β1 and PDGF are overexpressed during the activation in HSC, in Kupffer cells, in infiltrating circulating monocytes, in activated and aggregated platelets and in damaged hepatocytes [270,271]. Analysis of current literature indicates that both cytokines increase activation, proliferation and chemotaxis through c-Jun N-terminal kinase-dependent Smad2/3 phosphorylation in HSC [266]. At respect, it has been observed that EA attenuates pancreatic inflammation and fibrosis by inhibiting the expression of TGF-β and PDGF as well as by blocking the signaling pathways downstream in pancreatic stellate cells (PSC) both *in vivo* and *in vitro* [272,273]. Since, PSC resemble morphologic, functional and gene expression characteristics in HSC [274], it could be speculated that EA might diminish fibrosis in HSC through a similar mechanism. In addition, clinical and experimental data suggest that oxidative stress and lipid peroxidation might be one of the common pathways leading to HSC activation that perpetuate fibrosis [275,276]. Thus, the antioxidant properties of EA could also participate in preventing HSC activation.

2.9. Antihepatocarcinogenic properties of EA

Hepatocellular carcinoma (HCC) is a malignant tumor arising from the hepatocytes [277]. HCC is a major public health problem worldwide and usually represents a late complication of chronic progressive liver disease [278,279]. Cirrhosis has been considered as the most widespread and unifying condition for the development of HCC, due to continuous liver cell turnover and consequent accumulation of genetic alterations, activation of cellular oncogenes, as well as inactivation of tumor suppressor genes and DNA repair genes [280,281]. The main risk factors include chronic infection by hepatitis B virus (HBV) and hepatitis C virus (HCV), alcohol abuse, aflatoxins, NAFLD, obesity, hemochromatosis and several genotoxic and nongenotoxic chemical carcinogens [282–284]. HCC treatment may involve surgical resection, liver transplantation, local ablative therapies, including radiofrequency ablation (RFA), percutaneous ethanol injection, and transcatheter arterial chemoembolization (TACE), chemotherapy, hormonotherapy and immunotherapy [285,286]. However, this is prohibitively expensive for many patients and benefits are limited [287]. For this reason, new chemopreventive strategies that decrease or delay the onset of HCC are being evaluated [288]. In this respect, EA has shown chemopreventive effects in rodent models of oral [105,289,290], esophagic [291,292], mammary [293,294], lung [295], prostatic [296], intestinal [297] and colon cancer [298,299]. Besides, the antiproliferative activity of both EA and urolithins on several tumor cell lines has been clearly demonstrated Table 3 [79,300–303]. In contrast, the evidence of anti-hepatocarcinogenic effects of EA is still contradictory (Table 3). EA has demonstrated to prevent the hepatic tumor promoting activity of chemical carcinogens, such as N-2-fluorenylacetamide (FAA) [304] or benzo[a]pyrene (BP) [305]. Recently, a couple of studies were published supporting that EA could be a promising agent against chemical-induced HCC. Srigopalram et al. [306] demonstrated that EA restrains abnormal proliferation of hepatocytes by the stimulation of apoptosis and regulating the permeabilization of the mitochondrial outer membrane. Apoptosis is a type of cell death tightly controlled by extrinsic stimuli through cell surface death receptors or by intrinsic stimuli *via* the mitochondrial signaling pathway, giving as a result the activation of proteases termed caspases that cleave a variety of cellular targets, resulting in morphological changes, mitochondrial permeability transition pore (mPTP) opening, release of cytochrome c, degradation of genomic DNA, and thereby, phagocytic removal of the apoptotic cell [307,308]. Besides, EA downregulates the expression of Bcl-2, an important cell survival and cell death regulator that inhibits apoptosis, along with upregulation of Bax, which functions as a proapoptotic factor that inhibits cell survival. In addition, EA inhibited cell proliferation downregulating cyclin D1 and cyclin E1, molecules required for the entry into and completion of S phase, leading to the arrest in the G_1 phase of the cell cycle [309]. On the other hand, EA attenuated hepatic inflammation by downregulating NF-κB expression and avoiding mast cell activation which contribute to primary inflammatory responses in the early phase of acute liver injury [310].

EA showed anti-angiogenic activity, in other words the capacity to inhibit the formation of new blood vessels. This fact, is very important since tumor-associated vessels promote tumor growth by providing oxygen and nutrients and favor tumor metastasis by facilitating tumor cell entry into the circulation [311]. As described previously, EA downregulated the expression of MMP-2 and MMP-9, well known mediators of tissue remodeling, neo-angiogenesis and metastasis by cleaving endothelial cell-cell adhesions [312]. On the other hand, Hussein and Khalifa [214] presented data that EA protected hepatocytes from HCC-induced liver injury by suppressing abnormal proliferation of early preneoplastic lesions and increasing the antioxidant response what in consequence attenuated DNA fragmentation.

Conversely, some reports indicate that EA has only partial preventive effects [313] or even, that promote increased hepatocarcinogenesis in models in which 2-amino-3-methylimidazo[4,5-f]quinoline (IQ) [314] or 3,3′,4,4′-tetrachlorobiphenyl (PCB-77) [315] were used as inductors. This dual effect of EA could be consequence of different treatment doses and schedules that induced higher toxicity and increased incidence of liver adenomas and carcinomas [316]. In this respect, it is known that metabolic bioactivation of procarcinogens could generate more reactive metabolites capable of binding to macromolecules and generating free radicals and ROS that lead to chromosomal aberrations [108].

2.10. Antiviral properties of EA: anti-hepatitis B and C virus

Hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infections constitute a significant health burden because in the long-term, these can lead to fibrosis, cirrhosis and HCC [317,318]. HCC due to HBV and HCV may be an indirect result of enhanced hepatocyte turnover that take place in an effort to replace infected cells that

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Table 3
Biological effects of ellagic acid against chemical hepatocarcinogenesis in experimental models.

Hepatocarcinogen Dose, administration pathway	Animal model	Ellagic acid		References
		Dose, administration pathway	Biological effects	
FAA 200 ppm, diet	ACI/N rats	400 ppm, diet	↓ Number of GGT positive liver foci ↓ Incidence and multiplicity of adenomas and carcinomas	[271]
BP 0.3 mg l^{-1} in drinking water	Balb/c mice	500 mg kg^{-1} b.w., i.p.	↓ Hepatic CYP450 levels ↓ AHH and 7-ethoxycumarin-o-deethylase activities ↑ GST activity	[272]
IQ 100 mg kg^{-1} b.w., i.g.	Rats	1%, diet	No reduction on the number of GST-P positive liver foci	[281]
NDEA 100 mg kg^{-1} b.w., i.p. MNU 20 mg kg^{-1} b.w., i.p. DMH 40 mg kg^{-1} b.w., s.c. BBN 0.05% in drinking water DHPN 0.1% in drinking water	F344 rats Multi-organ Carcinogenesis	1%, diet	↑ Number of GST-P positive liver foci ↓ Incidence and number of adenomas in the lung ↓ Incidence and number of adenomas and carcinomas in the small intestine	[283]
2-NP 100 mg kg^{-1} b.w., i.p.	F344 rats	20 and 100 mg kg^{-1} b.w., orally	↓ 8-OH-dG formation in the liver nuclear DNA No reduction on ALT and AST activities	[280]
PCB-77 300 μmol kg^{-1} b.w., i.p.	Sprague-Dawley rats	0.4%, diet	↑ Number of GST-P positive liver foci ↓ Size of the foci	[282]
NDEA 0.01% in drinking water	Wistar rats	30 mg kg^{-1} b.w., oral	↑ Cell shrinkage, apoptotic bodies, chromatin condensation and mitochondrial swelling ↓ Density of mast cells ↓ NF-κB, cyclin-D1, cyclin-E1, MMP-2, and MMP-9 expression ↓ PCNA-positive nuclei ↓ Bcl-2 expression ↑ Bax, cyt c and caspase-9 expression	[273]
NDEA 200 mg kg^{-1} b.w., i.p.	Wistar rats	50 mg kg^{-1} b.w., oral	↓ ALT, AST, ALP and total bilirubin ↓ Tumor markers arginase and L-fucosidase ↑ G6PD ↑ GPx, GGT and GST activities ↑ GSH and total proteins	[182,369]

N-2-fluorenylacetamide (FAA), benzo[a]pyrene (BP), 2-amino-3-methylimidazo[4,5-f]quinoline (IQ), N-nitrosodiethylamine (NDEA), N-methylnitrosourea (MNU), 1-2,dimethylhydrazine (DMH), N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN), 2,2′-dihydroxy-di-n-propylnitrosamine (DHPN), 3,3′,4,4′-tetrachlorobiphenyl (PCB-77), gamma-glutamyl transpeptidase (GGT), cytochrome P450 (CYP450), aryl hydrocarbon hydroxylase (AHH), placental glutathione-*S*-transferase (GST-P), 8-hydroxy-deoxyguanosine (8-OH-dG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), glucose-6-phosphate dehydrogenase (G6PD), glutathione peroxidase (GPx), glutathione-*S*-transferase (GST), reduced glutathione (GSH), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), matrix metalloproteinase (MMP), proliferating cell nuclear antigen (PCNA), B-cell lymphoma 2 (Bcl-2), Bcl-2-associated X protein (Bax) cytochrome c (cyt c), body weight (b.w.), intragastric (i.g.), intraperitoneal (i.p.), subcutaneous (s.c.).

have been immunologically attacked and in which opportunities for oncogenic mutation occur [319]. HBV is a small double-stranded circular virus (3.2 kb in length), consisting of an incomplete plus DNA strand of variable length and a full-length minus strand that presents all the coding information organized in four open reading frames (ORF). This ORF encode the viral proteins, hepatitis B core antigen (HBcAg) or nucleocapside protein, the soluble and secreted hepatitis B e antigen (HBeAg), a reverse transcriptase/DNA polymerase (Pol), the viral envelope proteins which express hepatitis B surface antigen (HBsAg) and the hepatitis B x protein (HBx) [320,321]. Replication of the viral genome occurs *via* an RNA pregenomic (pgRNA) that binds to HBV polymerase (Pol). Pol initiates pgRNA encapsidation and reverse transcription inside the capsid. Matured, relaxed circular DNA (rc-DNA) containing nucleocapsids can be recycled to the nucleus, or be secreted *via* interaction with the envelope proteins as progeny virions [322].

In the search of new selective antiviral agents, EA has revealed potential activities against HBV infection (Fig. 5A). Pathak et al. [323] identified that EA inhibits the HBx-induced transcriptional activation for replication of the virus. HBx is a multifunctional regulator of cellular signal transduction and transcription pathways and has a critical role in HBV replication and as a cofactor of carcinogenesis [324]. Additional studies have shown experimental evidence that EA reduces HBsAg and HBeAg secretion in HBV-infected cells and suggested that this compound could be forming unstable complexes with glycoproteins of the viral envelope [325,326]. Although EA failed in blocking HBV Pol activity and HBV replication, it showed immunoregulatory effects in HBeAg transgenic mice. EA effectively reduced the production of HBeAg and its accumulation in serum, blocked the inhibitory effects on the immune tolerance caused by HBeAg, restored B-cells to produce anti-HBeAg immunoglobulins, maintained the activation and proliferation of T-helper cells (Th1, Th2 or Th0 cell subsets), increased the cytotoxic T lymphocytes (CTL) response and stimulated IL-4 and INF-γ production in lymphocytes isolated from HBeAg transgenic mice [327].

HCV is an enveloped single-stranded RNA virus (9.6 kb in length), consisting of a large ORF. RNA viral genome is translated by ribosomes bound to the endoplasmic reticulum into a polyprotein that is processed co- and post-translationally into a single

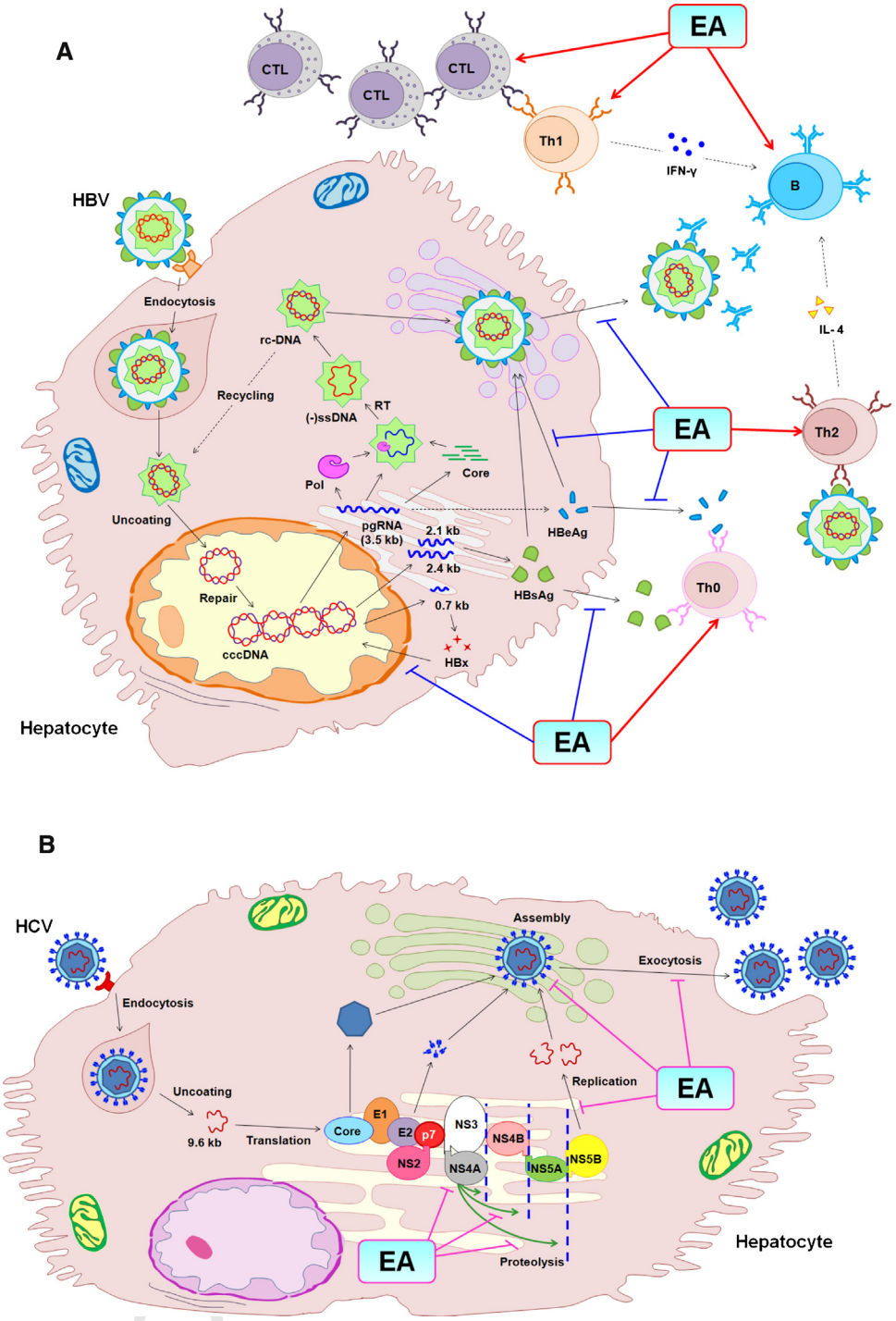

Fig. 5. Molecular mechanisms involved in the antiviral effects of ellagic acid (EA). (A) Anti-hepatitis B activity. HBV infects hepatocytes trough an endocytotic process, the nucleocapsids are released into the cytoplasm and the relaxed circular (rc)-DNA virus is converted into covalently closed circular DNA (cccDNA). This minichromosome encode the viral proteins hepatitis B core antigen (HBcAg), hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), a reverse transcriptase/DNA polymerase (Pol), hepatitis B surface antigen (HBsAg) and the hepatitis B x protein (HBx). EA reduces both HBsAg and HBeAg secretion, inhibits the HBx-induced transcriptional activation for replication of the virus. Also, EA reduces the production of HBeAg, restores B-cells ability to produce anti-HBeAg immunoglobulins, maintains the activation and proliferation of T-helper cells (Th), increases the cytotoxic T lymphocytes (CTL) response and, stimulates interleukin-4 (IL-4) and interferon gamma (INF-γ) production. (B) Anti-hepatitis C activity. Once HCV infects liver cells, the single-stranded RNA is translated into a single polypeptide, which is subsequently cleaved by viral and host proteases into three structural proteins, termed core, envelope 1 (E1), and E2, and seven non-structural proteins named p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B. EA inhibits NS3/4A protease interacting with the unconventional zinc-binding site present in the core region of the enzyme and blocking its activity. In this way, EA may inhibit the proteolytic processing of NS4B/5A and NS5A/5B junctions and by this mean diminish NS5B activity and HCV RNA levels.

polypeptide, which is subsequently cleaved by viral and host proteases into three structural proteins, termed core, envelope 1 (E1) and E2, and seven non-structural proteins named p7, NS2, NS3, NS4A, NS4B, NS5A and NS5B [328,329]. p7 connects the replication complexes and the core proteins to the glycoproteins E1 and E2. NS2 is a membrane-associated cysteine protease that interacts with E1, E2 and p7 complex and promotes the migration of the E1E2 heterodimer to the site of virus assembly. NS3

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possesses helicase and NTPase activities and along with its cofactor NS4A, conform the major viral protease. NS4B and NS5A are essential components of the viral replicase, whereas NS5B is the RNA-dependent RNA polymerase [330,331].

Recently, the antiviral activity of EA against HCV was described (Fig. 5B). Reddy et al. [332] and Ajala et al. [333] simultaneously demonstrated that EA inhibits NS3/4A protease activity *in vitro*, suggesting that EA interacts with the unconventional Zn-binding site present in the core region of the enzyme, blocking its activity. In this way, EA may inhibit the proteolytic processing of NS4B/5A and NS5A/5B junctions and by this mean diminish NS5B activity and HCV RNA levels, preventing from HCV-induced hepatocarcinogenesis. However, it is necessary to develop further studies on EA-induced antiviral mechanisms, as well as identify its effects on new viral targets, before proposing this compound as an alternative therapy to conventional antiviral drugs.

3. Future perspectives

To date information of the pharmacological properties of EA in the context of hepatoprotection is very limited; therefore it is important to extend the knowledge about the action mechanisms of this flavonoid and to perform additional preclinical studies *in vitro* and *in vivo* models. Also, it is worth mentioning that the effects of EA and pomegranate juice (containing EA) are being evaluated in phase I, II and III clinical trials (ClinicalTrials.gov Identifier: NCT00455416; NCT02263378; NCT01916239), though these studies are focused mainly on its anticarcinogenic activity [66,334,335] and in hyperpigmentation disorders treatment [336–338]. These pioneer studies might be a breakthrough in the search for natural compounds with beneficial activities to humans and serve as a basis in the near future to begin tests seeking to prevent, reduce or eliminate liver damage caused by the exposure to xenobiotics or disease. New delivery systems that are being explored in the field of cancer research to improve the bioavailability and bioactivity of EA, such as EA/chitosan formulations [339–341], nanoparticles [342–344,161], niosomes [345], microspheres [346], polymeric implants [293] and adjuvants [347], might be also evaluated in hepatic pathologic models.

Finally, as it has been suggested that urolithins, may be the molecules responsible for the biological effects exerted by EA treatment [31], it is necessary to develop more investigation to identify the potential effects of these compounds in liver disease.

4. Concluding remarks

EA, a naturally occurring polyphenolic compound, shows several potential pharmacological properties mainly associated with their ability to modulate the cell redox changes. EA prevents liver toxicity induced by alcohol, CCl_4, cisplatin, ConA, CsA, d-Gal/LPS, isoniazid and rifampicin, Hg and paracetamol by mechanisms related with free radicals scavenging, chelation of divalent ions, modulation of CYP450 enzymes activity, upregulation of Nrf2 and downregulation of NF-κB and proinflammatory cytokines. Antisteatosic properties of EA entail the upregulation of PPAR-α, downregulation of PPAR-γ, inhibition of lipid peroxidation and adipokine secretion. Data about the anticholestatic potential of EA are scarce; however it has been reported that EA reduce Cu accumulation and Cu-induced oxidative stress. Besides, EA decreases liver fibrosis by inhibiting ROS production and the activation of HSC; it also downregulates MMP-2, MMP-9 and TIMP-2. On the other hand, EA shows protective properties against chemical hepatocarcinogenesis *via* several mechanisms: increase of the antioxidant response, inhibition of transformed cells proliferation, induction of apoptosis, regulation of mPTP opening, inhibition of mast cell activation, upregulation of Bax and downregulation of Bcl-2, cyclin D1, cyclin E1, NF-κB, MMP-2 and MMP-9. In addition, EA prevents HCC due to its antiviral activity against HBV and HCV by blocking viral replication and stimulating cellular immune response.

Although the hepatoprotective properties of EA are still matter of intensive investigation, it is also necessary to develop preclinical studies along with phase I and II clinical trials aimed to evaluate the pharmacological potential of EA and of its metabolites, either in combination with medical treatments (to increase their efficacy and to counteract side effects) or as a food supplement to prevent liver damage associated with toxicity or disease. Also, evaluate the efficacy of delivery systems that improve EA bioavailability in pathologic conditions is a major issue. On the other hand, the recognition of relevant biological activities from urolithins and their possible implications in liver protection needs to be explored.

Conflict of interest

The authors do not have any conflict of interest with the content of the manuscript.

Uncited references

[370–411].

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